ANTHROP\C

Blind tests of Claude on unpublished total syntheses

The full routes for the targets from the Burns and Newhouse laboratories

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Author

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Overview

This write-up contains the nine route documents that three Claude models wrote for the three targets shared by Professor Noah Burns of Stanford and Professor Timothy Newhouse of Yale. Every page is shown exactly as the model produced it.

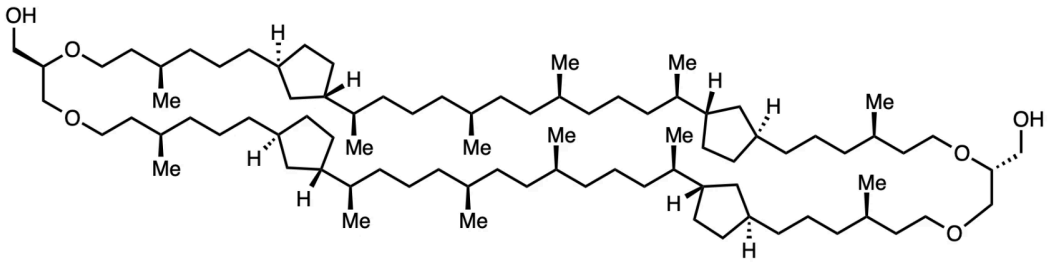
The professors saw the routes labeled only Model A, Model B and Model C. Model A is an earlier version of Claude Opus 5.5, Model B is an earlier version of Claude Mythos 5.2 and Model C is Claude Mythos 5.1.

For each target, every model received one image of the structure and the same prompt. The models had no internet, literature or reaction-database access, and their only tool was local code such as RDKit. Each model had one attempt. Nothing was edited, selected, or corrected. The letters A, B and C stand for the same three models throughout. None of the routes has been run in a laboratory, so all nine remain proposals.

Route document	Steps
GDGT-4 (Burns laboratory)	
Opus 5.5's route to GDGT-4	35
Mythos 5.2's route to GDGT-4	29
Mythos 5.1's route to GDGT-4	31
Triconnarin D (Newhouse laboratory)	
Opus 5.5's route to triconnarin D	31
Mythos 5.2's route to triconnarin D	27
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Bicyclic intermediate (Newhouse laboratory)	
Opus 5.5's route to the bicyclic intermediate	10
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GDGT-4 (Burns laboratory)

GDGT-4, a glycerol dialkyl glycerol tetraether, is a membrane lipid of archaea with a 68-membered macrocycle and 22 stereocenters. The Burns group has completed a synthesis that is not yet published.



[H][C@@]12CCC[C@H](CCO[C@H](CO)COCC[C@H](C)CCC[C@@](C3)([H])CC[C@]3([H])[C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@](CC4)([H])C[C@@]4([H])CCC[C@@H](C)CCOC[C@@H](CO)OCC[C@H](C)CCC[C@@](C5)([H])CC[C@]5([H])[C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@](CC2)([H])C1)C

The structure as Professor Burns drew it, in the image the models received.

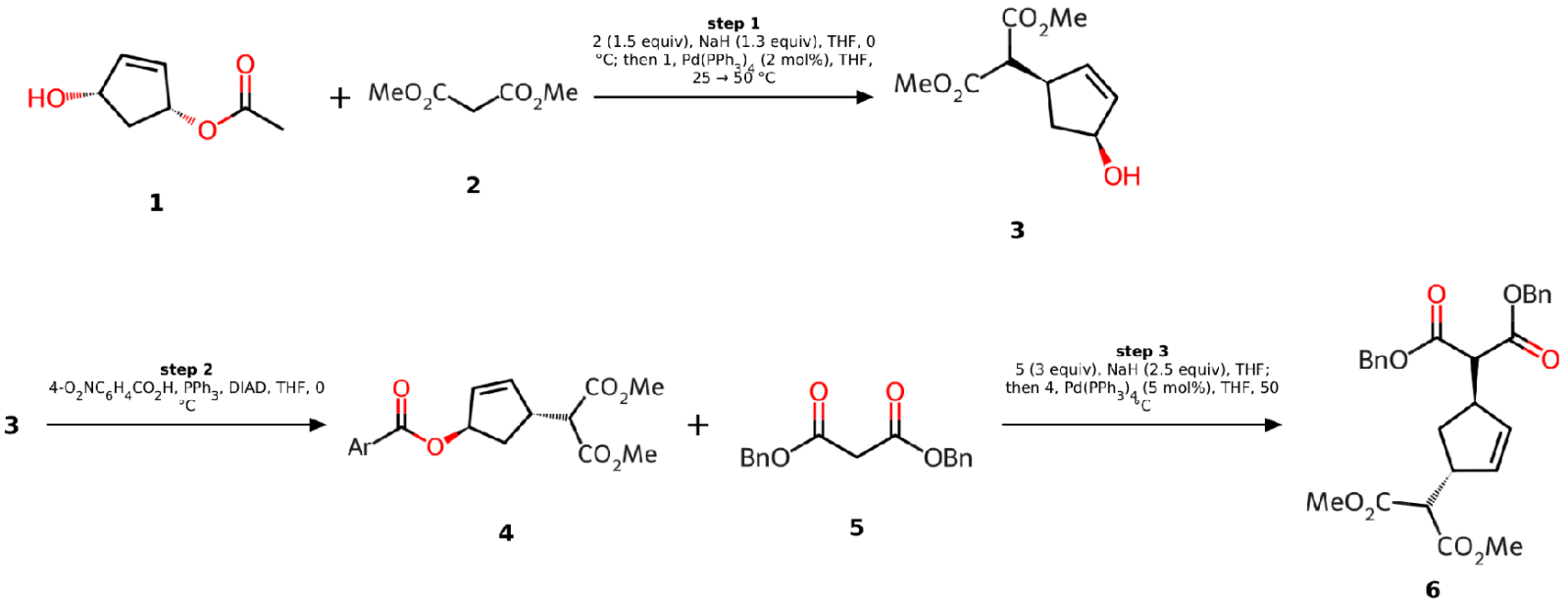
Route document	Steps
Opus 5.5's route to GDGT-4	35
Mythos 5.2's route to GDGT-4	29
Mythos 5.1's route to GDGT-4	31

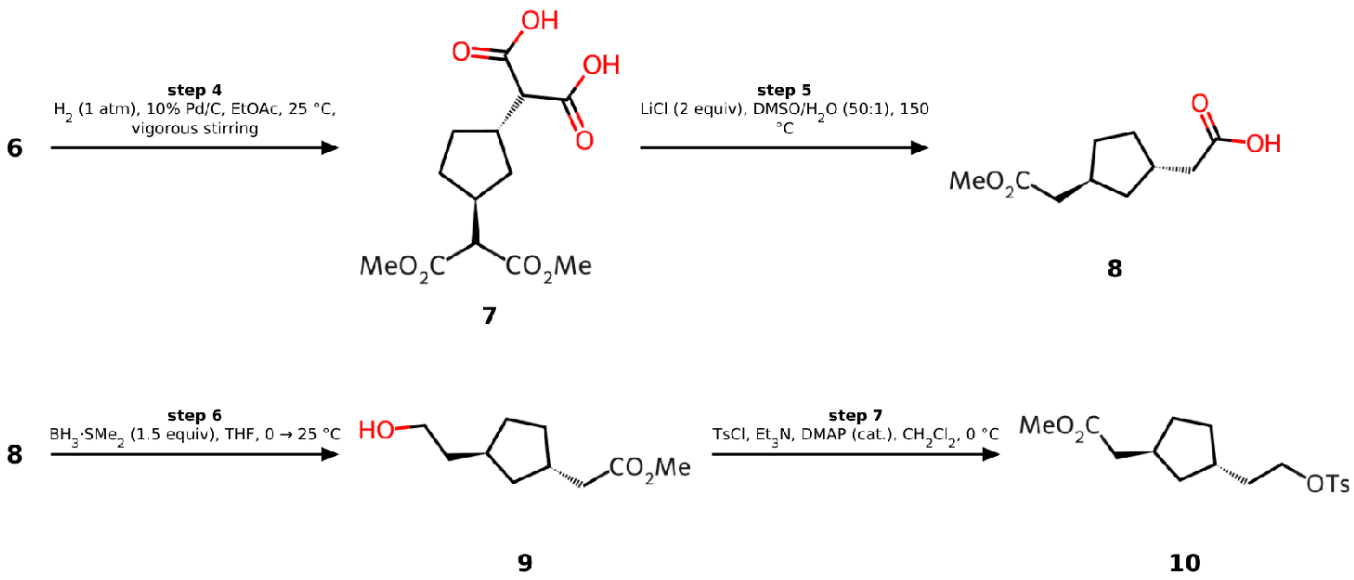
Proposed total synthesis of the C_{86} macrocyclic tetraether (GDGT-type) target — reaction scheme

Assumption: the drawn wedges make all four cyclopentanes trans (7S,10S in every half, so the molecule is C_2-symmetric), whereas the SMILES line under the drawing encodes two of them as cis (10R); I followed the drawing.

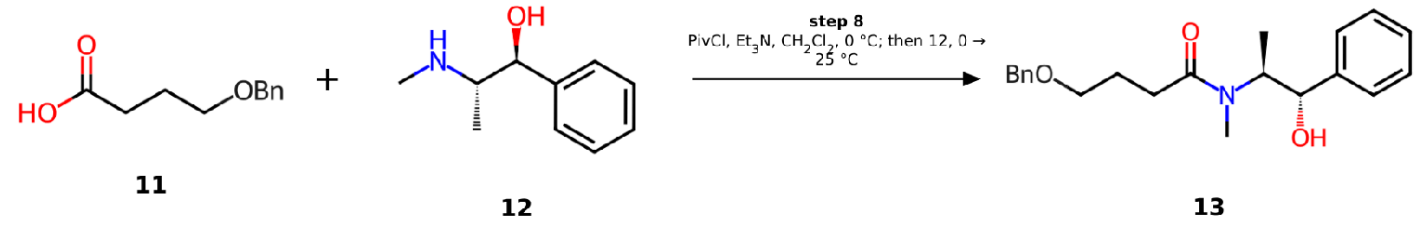
Abbreviations in the drawings: Ar = 4-$O_2NC_6H_4$; Bn = benzyl; Tr = trityl; Ts = tosyl; Ms = mesyl; Tf = triflyl. Reagents: DIAD = diisopropyl azodicarboxylate; LDA = lithium diisopropylamide; LAB = LiH_2NBH_3; NMP = N-methylpyrrolidinone; Hoveyda–Grubbs II = second-generation Hoveyda–Grubbs Ru catalyst; crossed double bonds = E/Z mixtures (removed later). Wedges/dashes show absolute configuration; all rings are trans-1,3-cyclopentanes.

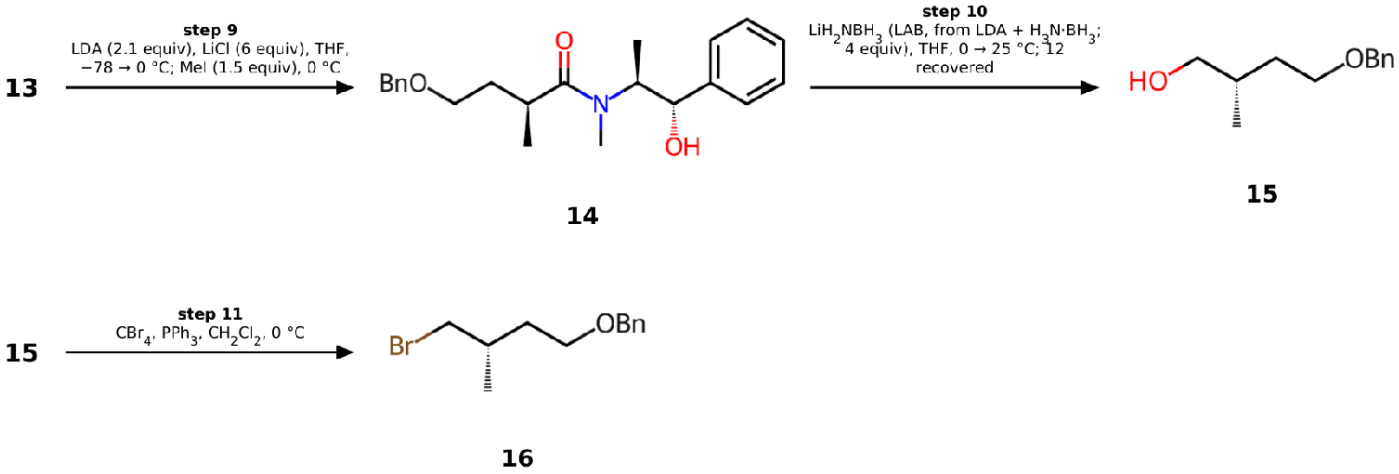
Scheme 1. The trans-1,3-cyclopentane core (C7 and C10 set); the longest linear sequence starts at 1



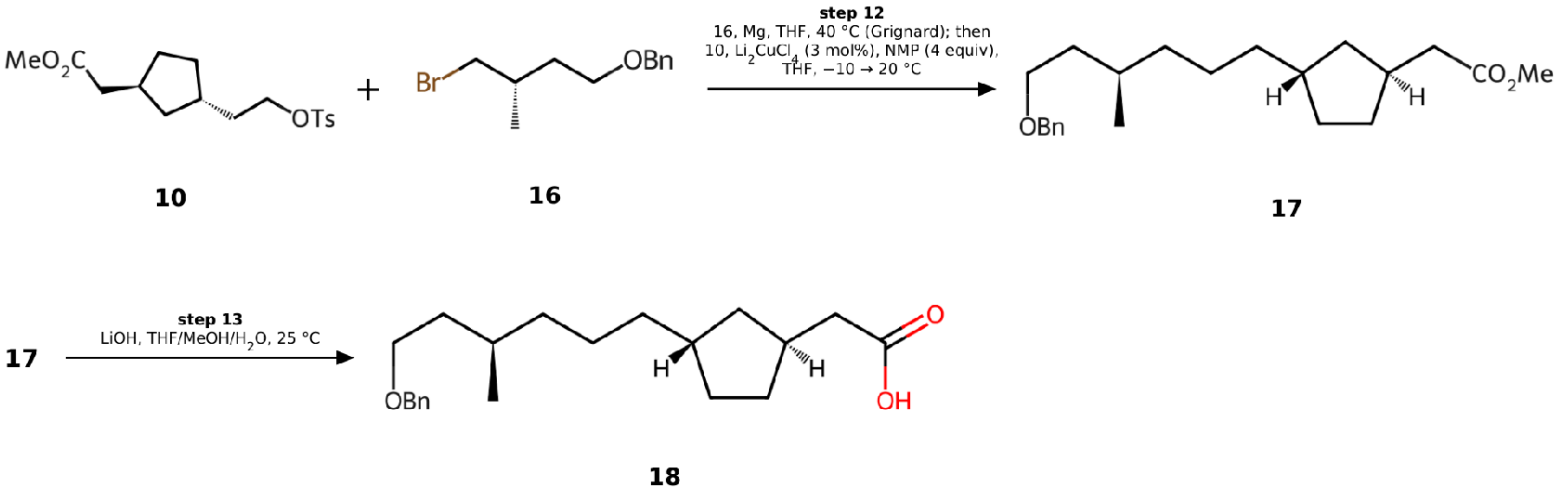


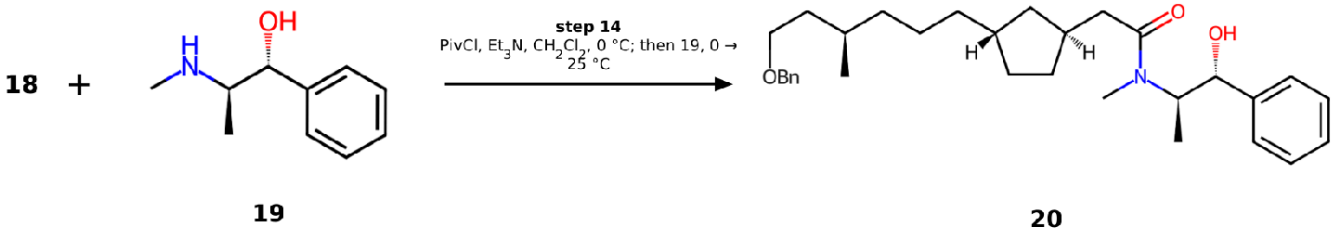
Scheme 2. C1–C4 fragment (C3 set by Myers methylation)





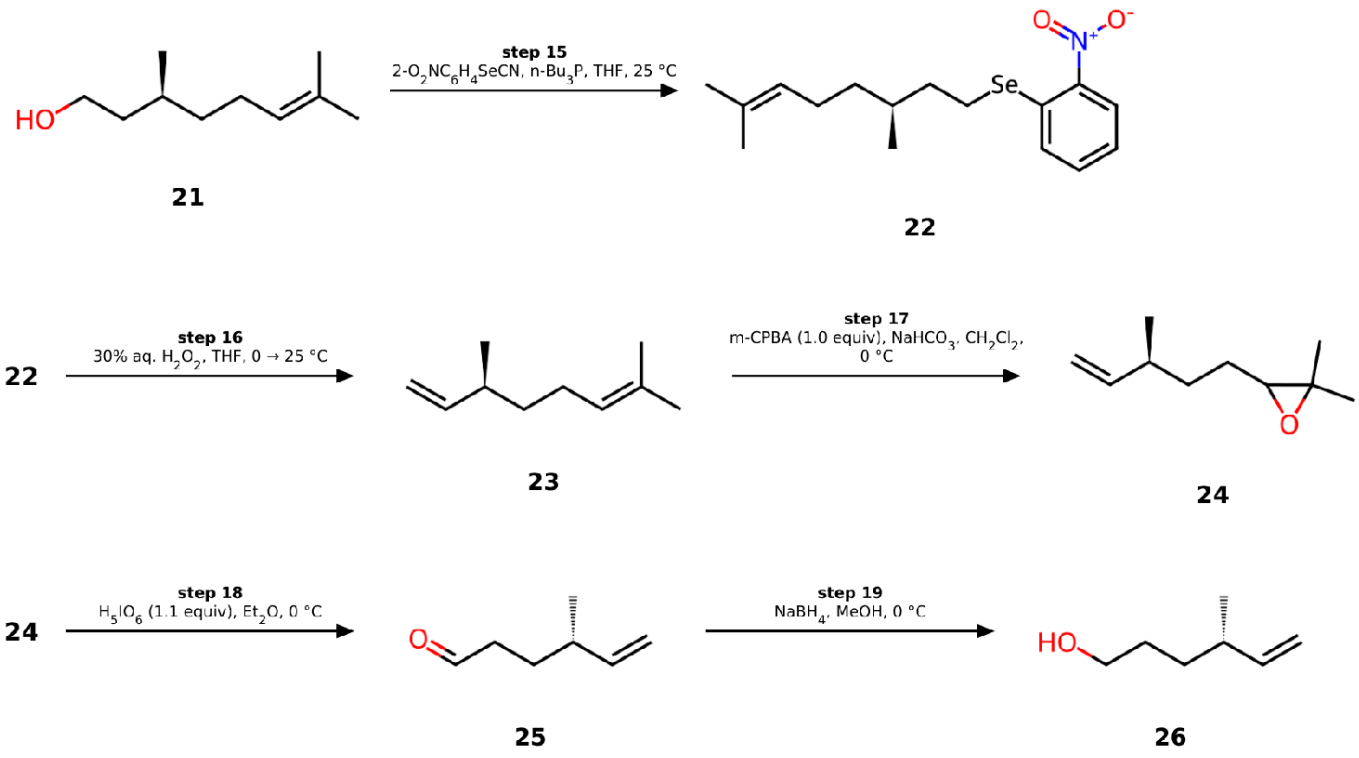
Scheme 3. C7 side chain (C4–C5 bond) and the C10-arm amide



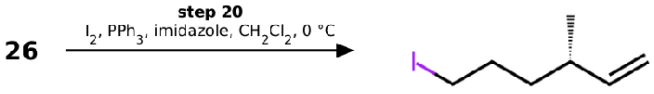


19 20

Scheme 4. C12–C17 fragment from (S)-citronellol (C15 from the chiral pool)

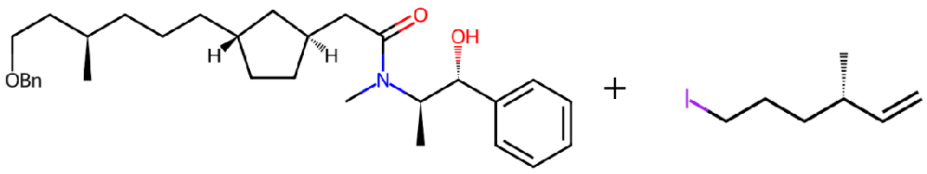


21 22 23 24 25 26



27

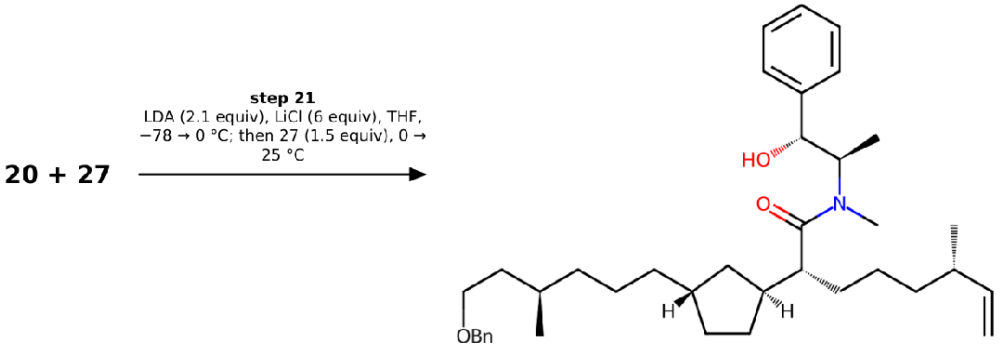
Scheme 5. C11 stereocentre (Myers alkylation) and the half-chain triflate 33



20

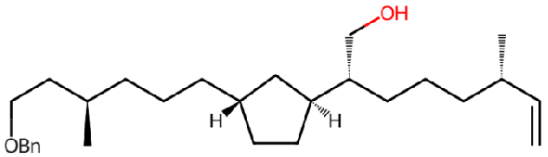
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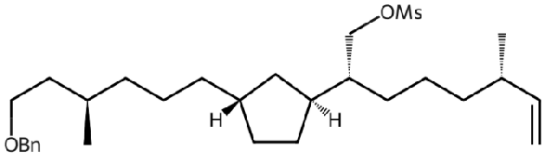
28

28 → **step 22**: LAB (4 equiv), THF, 25 → 40 °C; 19 recovered



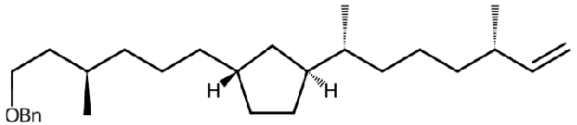
29

29 → **step 23**: MsCl, Et_3N, CH_2Cl_2, 0 °C



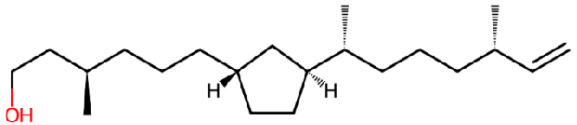
30

30 → **step 24**: $LiEt_3BH$ (3 equiv), THF, 65 °C

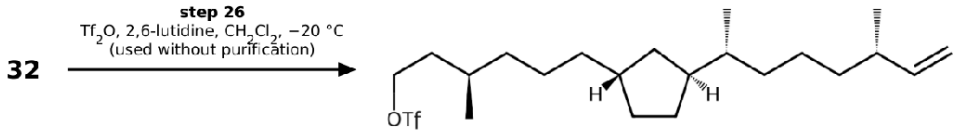


31

31 → **step 25**: Li, naphthalene (lithium naphthalenide), THF, −25 °C

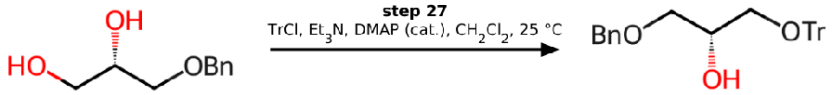


32

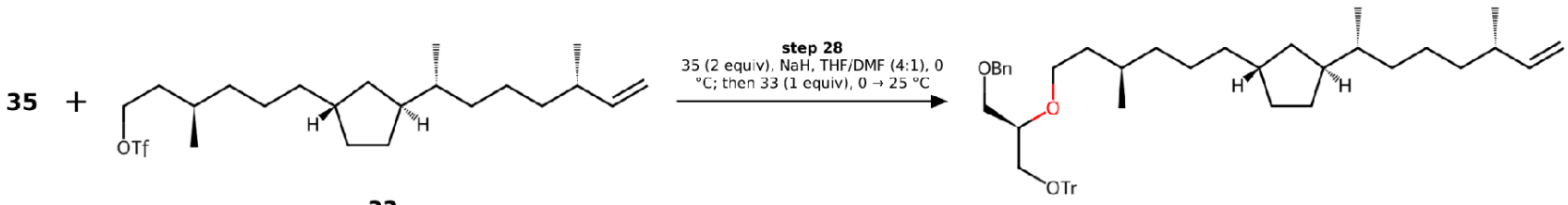


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Scheme 6. Glycerol unit and the first (sn-2) ether

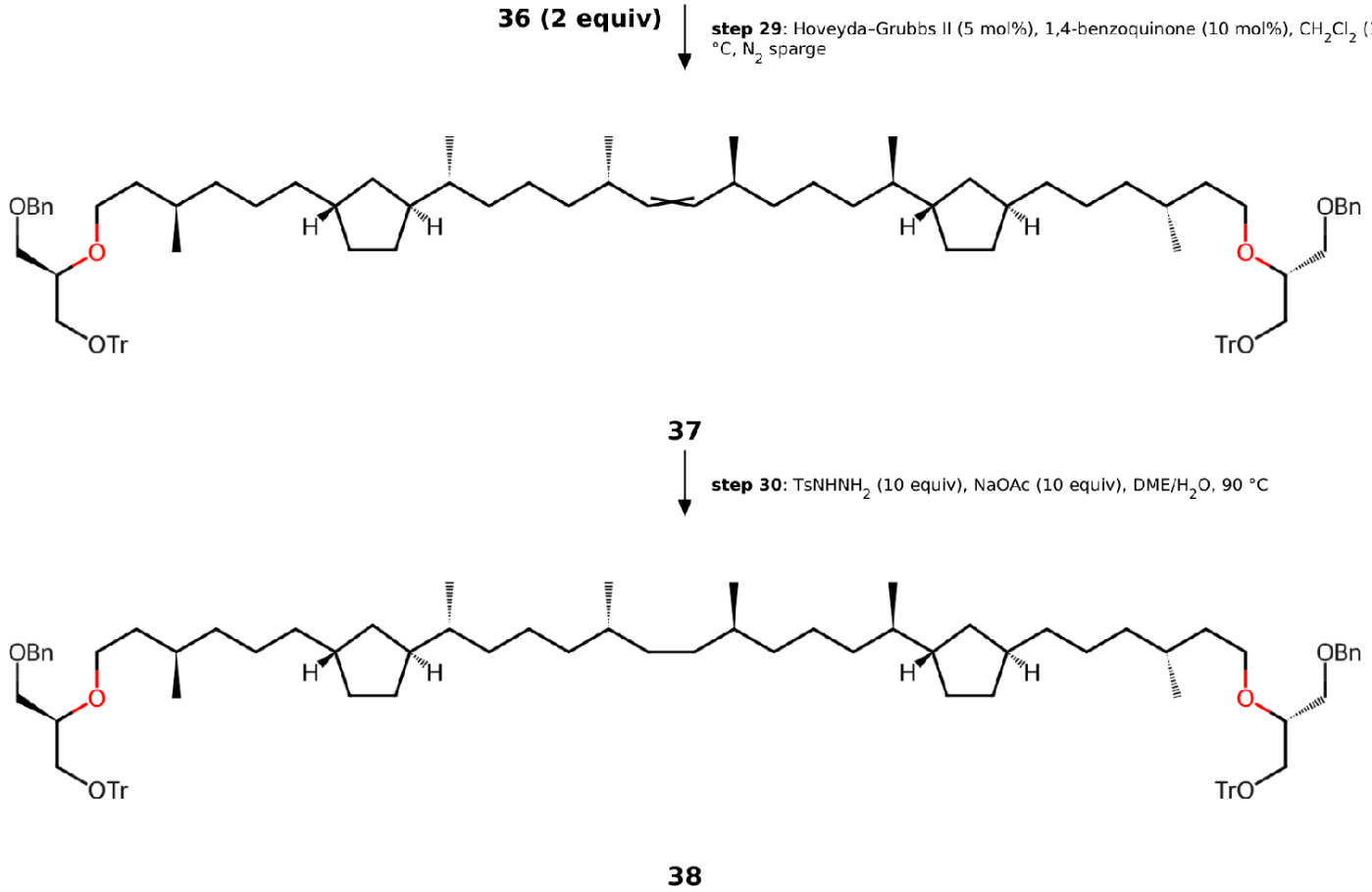


34 35

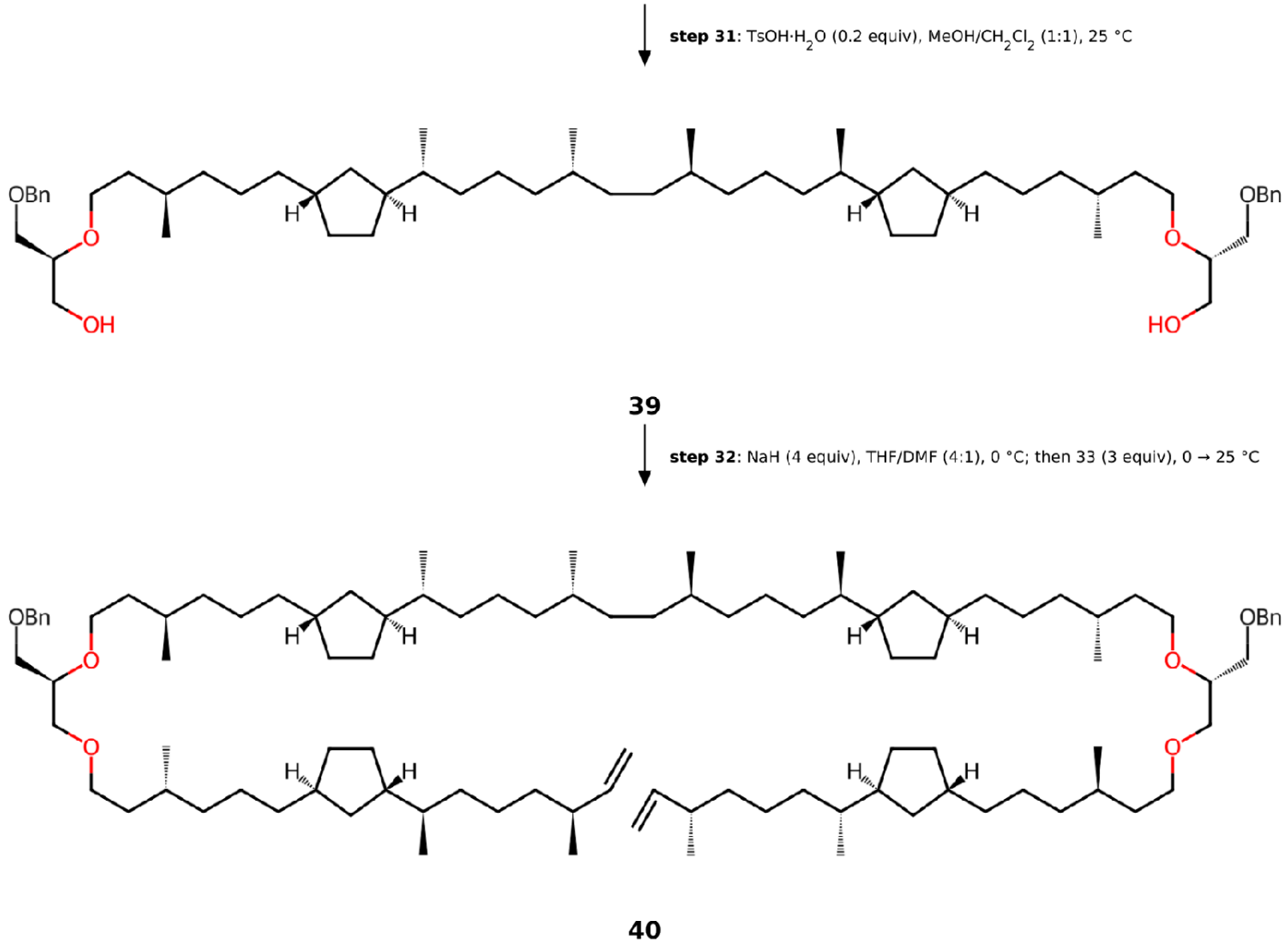


33 36

Scheme 7. First C40 chain by cross-metathesis (sn-2↔sn-2)

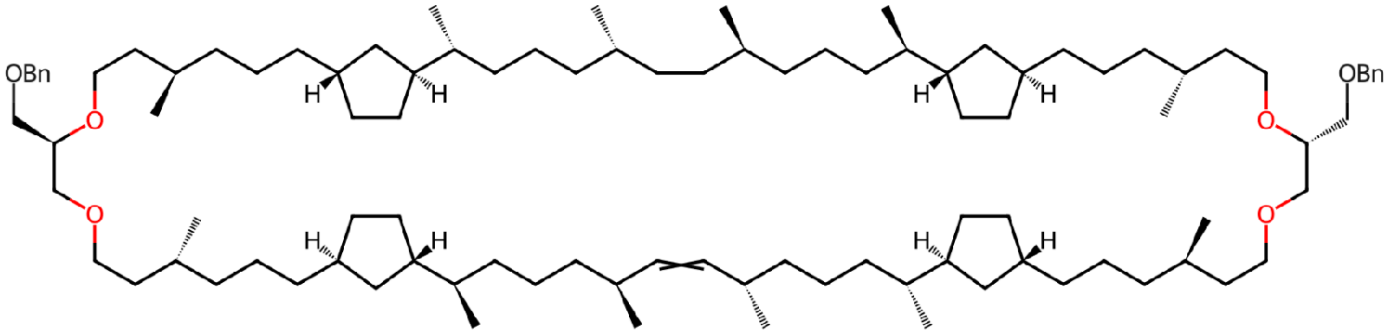


Scheme 7 (continued). sn-3 ethers



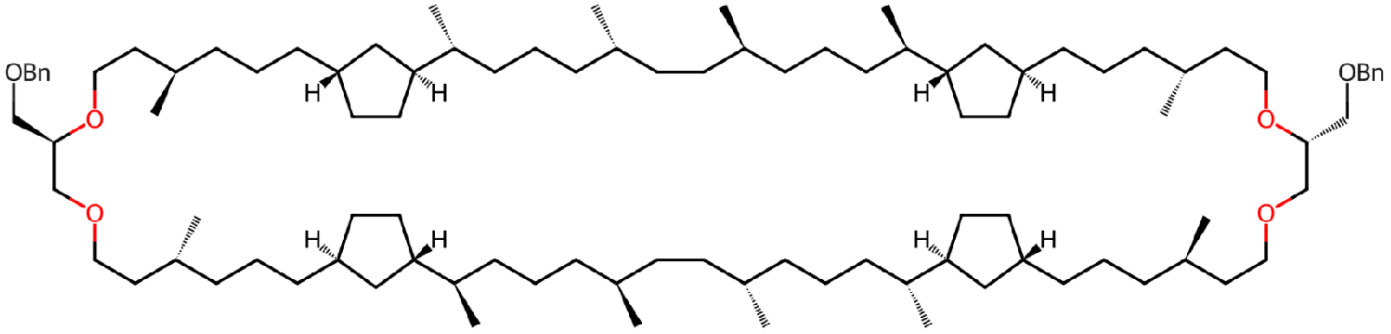
Scheme 8. Macrocyclisation by RCM (sn-3↔sn-3), reduction and deprotection

step 33: Hoveyda–Grubbs II (10 mol%, portionwise), 1,4-benzoquinone (20 mol%), toluene (0.5 mM), 80 °C



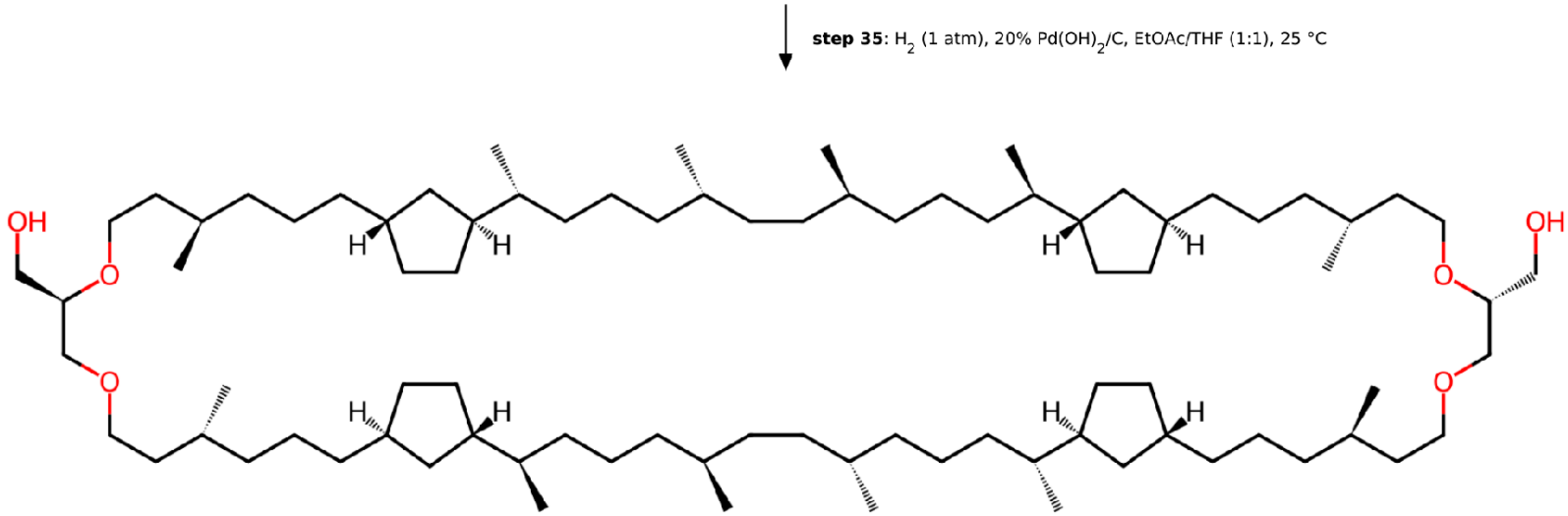
41

step 34: $TsNHNH_2$ (10 equiv), NaOAc (10 equiv), DME/H_2O, 90 °C



42

Scheme 8 (continued). Target



43 (target)

Retrosynthetic overview

1. 43 ⇒ remove the two sn-1 benzyl groups and saturate two C16=C16′ alkenes. The key C–C disconnections are the two C16–C16′ bonds in the middle of the two C_{40} chains: ring-closing metathesis (RCM) for the sn-3 chain and cross-metathesis (CM) for the sn-2 chain.

2. Each glycerol O–C1 bond ⇒ Williamson etherification of 1-O-benzyl-3-O-trityl-sn-glycerol (35) with one C_{21} half-chain triflate 33 (four copies). The sn-2 ethers are made and joined first; the sn-3 ethers are made last.

3. Half-chain 33 ⇒ C10–C11 bond (Myers alkylation of a cyclopentylacetamide with citronellol-derived iodide 27; the amide C=O becomes the C11 methyl) + C4–C5 bond (Cu-catalysed coupling with bromide 16, made by a Myers methylation).

4. Ring order: the trans-1,3-cyclopentane is made first, from cyclopentenol acetate 1, by Pd allylation (retention), Mitsunobu reaction (inversion), Pd allylation (retention) and hydrogenation. All four cyclopentanes are copies of this one building block, made before any chain is attached.

5. The 68-membered macrocycle is formed last: CM joins the first C_{40} chain (the product is still acyclic), then RCM of the two sn-3 chains closes the ring.

Assumption: the drawn wedges make all four cyclopentanes trans (7S,10S in every half, so the molecule is C_2-symmetric), whereas the SMILES line under the drawing encodes two of them as cis (10R); I followed the drawing.

Locants: each half-chain is numbered from the ether oxygen (C1) to C16 (biphytane numbering); its cyclopentane is C7, C8, C9, C10 plus C7a (the former C7 methyl, bonded to C10). In the target every half is 3R,7S,10S,11R,15S, and both glycerol C2 centres are R (2,3-di-O-alkyl-sn-glycerol, free sn-1 OH).

Route (forward direction)

Step 1

Reactants: 1 — (1R,4S)-4-hydroxycyclopent-2-en-1-yl acetate [= (1S,4R)-cis-4-acetoxycyclopent-2-en-1-ol] (commercial); **2** — dimethyl malonate (commercial)
Product: 3 — dimethyl 2-[(1R,4S)-4-hydroxycyclopent-2-en-1-yl]malonate (cis)
Conditions: 2 (1.5 equiv), NaH (1.3 equiv), THF, 0 °C; then 1, $Pd(PPh_3)_4$ (2 mol%), THF, 25 → 50 °C
Why: Pd(0) ionises the allylic acetate with inversion, and the soft malonate attacks the π-allyl anti to Pd, at the terminus remote from the OH. The net result is retention at C10, giving the cis product. Using preformed sodium malonate (no free NaH) avoids alkoxide-driven acetyl migration, which would racemise 1.

Step 2

Reactants: 3 — dimethyl 2-[(1R,4S)-4-hydroxycyclopent-2-en-1-yl]malonate (cis)
Product: 4 — (1R,4R)-4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopent-2-en-1-yl 4-nitrobenzoate (trans)
Conditions: 4-$O_2NC_6H_4CO_2H$, PPh_3, DIAD, THF, 0 °C
Why: The Mitsunobu S_N2 reaction inverts the carbinol carbon (future C7), so the new leaving group is trans to the malonate, ready for a second retentive substitution.

Step 3

Reactants: 4 — (1R,4R)-4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopent-2-en-1-yl 4-nitrobenzoate (trans); **5** — dibenzyl malonate (commercial)
Product: 6 — dibenzyl 2-[(1R,4R)-4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopent-2-en-1-yl]malonate (trans)
Conditions: 5 (3 equiv), NaH (2.5 equiv), THF; then 4, $Pd(PPh_3)_4$ (5 mol%), THF, 50 °C
Why: A second Tsuji–Trost substitution again goes with overall retention at the benzoate carbon, at the terminus remote from the existing substituent. It sets C7 and gives the trans-1,4-bis(malonate); the excess nucleophile outcompetes the acidic CH of 4.

Step 4

Reactants: 6 — dibenzyl 2-[(1R,4R)-4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopent-2-en-1-yl]malonate (trans)
Product: 7 — 2-[(1S,3S)-3-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopentyl]malonic acid (trans)
Conditions: H_2 (1 atm), 10% Pd/C, EtOAc, 25 °C, vigorous stirring
Why: Hydrogenolysis turns the benzyl esters into the malonic acid while the unhindered cis ring alkene is saturated. C7 and C10 are not alkene carbons, and fast H_2 uptake keeps Pd-mediated alkene migration negligible.

Step 5

Reactants: 7 — 2-[(1S,3S)-3-(1,3-dimethoxy-1,3-dioxopropan-2-yl)cyclopentyl]malonic acid (trans)
Product: 8 — 2-[(1S,3S)-3-(2-methoxy-2-oxoethyl)cyclopentyl]acetic acid (trans)
Conditions: LiCl (2 equiv), DMSO/H_2O (50:1), 150 °C
Why: In one pot, the malonic acid decarboxylates and the dimethyl malonate undergoes Krapcho dealkoxycarbonylation. This leaves one acid arm and one ester arm; the ring stereocentres are β to the carbonyls and cannot epimerise.

Step 6

Reactants: 8 — 2-[(1S,3S)-3-(2-methoxy-2-oxoethyl)cyclopentyl]acetic acid (trans)
Product: 9 — methyl 2-[(1S,3S)-3-(2-hydroxyethyl)cyclopentyl]acetate
Conditions: $BH_3{\cdot}SMe_2$ (1.5 equiv), THF, 0 → 25 °C
Why: Borane reduces carboxylic acids much faster than esters, so only the acid arm (future C6–C5) becomes a primary alcohol.

Step 7

Reactants: 9 — methyl 2-[(1S,3S)-3-(2-hydroxyethyl)cyclopentyl]acetate
Product: 10 — methyl 2-[(1S,3S)-3-{2-[(4-methylbenzenesulfonyl)oxy]ethyl}cyclopentyl]acetate
Conditions: TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C
Why: Routine tosylation of an unhindered primary alcohol activates C5 for the sp^3–sp^3 coupling; no stereocentre is involved.

Step 8

Reactants: 11 — 4-(benzyloxy)butanoic acid (commercial); **12** — (1S,2S)-(+)-pseudoephedrine (commercial)
Product: 13 — 4-(benzyloxy)-N-[(1S,2S)-1-hydroxy-1-phenylpropan-2-yl]-N-methylbutanamide
Conditions: PivCl, Et_3N, CH_2Cl_2, 0 °C; then 12, 0 → 25 °C
Why: The mixed pivalic anhydride acylates the pseudoephedrine nitrogen selectively, giving the Myers amide.

Step 9

Reactants: 13 — 4-(benzyloxy)-N-[(1S,2S)-1-hydroxy-1-phenylpropan-2-yl]-N-methylbutanamide
Product: 14 — (2S)-4-(benzyloxy)-N-[(1S,2S)-1-hydroxy-1-phenylpropan-2-yl]-N,2-dimethylbutanamide
Conditions: LDA (2.1 equiv), LiCl (6 equiv), THF, −78 → 0 °C; MeI (1.5 equiv), 0 °C
Why: MeI alkylates the (Z)-enolate on the face away from the lithium alkoxide (Myers model). With (S,S)-12 this sets the new centre as 2S (the future C3, which is R in the target), typically at ≥95:5 dr.

Step 10

Reactants: 14 — (2S)-4-(benzyloxy)-N-[(1S,2S)-1-hydroxy-1-phenylpropan-2-yl]-N,2-dimethylbutanamide
Product: 15 — (2S)-4-(benzyloxy)-2-methylbutan-1-ol
Conditions: LiH_2NBH_3 (LAB, from LDA + $H_3N{\cdot}BH_3$; 4 equiv), THF, 0 → 25 °C; 12 recovered
Why: LAB reduces pseudoephedrine amides directly to primary alcohols without epimerising the α-centre, and it releases the auxiliary.

Step 11

Reactants: 15 — (2S)-4-(benzyloxy)-2-methylbutan-1-ol
Product: 16 — benzyl (3S)-4-bromo-3-methylbutyl ether
Conditions: CBr_4, PPh_3, CH_2Cl_2, 0 °C
Why: Appel bromination occurs at the primary carbon; the stereocentre next to it keeps its configuration because no bond to it is broken.

Step 12

Reactants: 10 — methyl 2-[(1S,3S)-3-{2-[(4-methylbenzenesulfonyl)oxy]ethyl}cyclopentyl]acetate; **16** — benzyl (3S)-4-bromo-3-methylbutyl ether
Product: 17 — methyl 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}acetate
Conditions: 16, Mg, THF, 40 °C (Grignard); then 10, Li_2CuCl_4 (3 mol%), NMP (4 equiv), THF, −10 → 20 °C
Why: Cu-catalysed coupling of the primary Grignard reagent with the primary tosylate forms the C4–C5 bond by S_N2 at C5. The low-temperature, NMP-modified protocol leaves the methyl ester untouched, and no stereocentre is involved.

Step 13

Reactants: 17 — methyl 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}acetate
Product: 18 — 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}acetic acid
Conditions: LiOH, THF/MeOH/H_2O, 25 °C
Why: Saponification frees the acid; the α-carbon (future C11) is not yet a stereocentre and C10 is β, so nothing can epimerise.

Step 14

Reactants: 18 — 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}acetic acid; **19** — (1R,2R)-(−)-pseudoephedrine (commercial)
Product: 20 — 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-N-[(1R,2R)-1-hydroxy-1-phenylpropan-2-yl]-N-methylacetamide
Conditions: PivCl, Et_3N, CH_2Cl_2, 0 °C; then 19, 0 → 25 °C
Why: As in step 8, but with the (R,R)-auxiliary, which the Myers model requires to obtain the R configuration at C11.

Step 15

Reactants: 21 — (S)-(−)-citronellol [(3S)-3,7-dimethyloct-6-en-1-ol] (commercial)
Product: 22 — 1-{[(3S)-3,7-dimethyloct-6-en-1-yl]selanyl}-2-nitrobenzene
Conditions: 2-$O_2NC_6H_4SeCN$, n-Bu_3P, THF, 25 °C
Why: Under Grieco conditions, S_N2 at the primary carbon (future C17) gives the aryl selenide, well away from the C15 stereocentre.

Step 16

Reactants: 22 — 1-{[(3S)-3,7-dimethyloct-6-en-1-yl]selanyl}-2-nitrobenzene
Product: 23 — (3S)-3,7-dimethylocta-1,6-diene [(S)-β-citronellene]
Conditions: 30% aq. H_2O_2, THF, 0 → 25 °C
Why: The selenoxide eliminates (syn) toward the only β-CH_2, giving the terminal alkene; C15 is not involved and keeps its configuration.

Step 17

Reactants: 23 — (3S)-3,7-dimethylocta-1,6-diene [(S)-β-citronellene]
Product: 24 — 2,2-dimethyl-3-[(3S)-3-methylpent-4-en-1-yl]oxirane (about 1:1 at the oxirane CH; that centre is destroyed in step 18)
Conditions: m-CPBA (1.0 equiv), $NaHCO_3$, CH_2Cl_2, 0 °C
Why: The electron-rich trisubstituted alkene is epoxidised much faster than the vinyl group; the new oxirane centre does not matter because step 18 destroys it.

Step 18

Reactants: 24 — 2,2-dimethyl-3-[(3S)-3-methylpent-4-en-1-yl]oxirane (about 1:1 at the oxirane CH; that centre is destroyed in step 18)
Product: 25 — (4S)-4-methylhex-5-enal
Conditions: H_5IO_6 (1.1 equiv), Et_2O, 0 °C
Why: Periodic acid opens the epoxide and cleaves the diol, releasing acetone and the aldehyde. The stereocentre is γ to the carbonyl and cannot epimerise.

Step 19

Reactants: 25 — (4S)-4-methylhex-5-enal
Product: 26 — (4S)-4-methylhex-5-en-1-ol
Conditions: $NaBH_4$, MeOH, 0 °C
Why: The aldehyde is reduced chemoselectively; the alkene and the stereocentre are unaffected.

Step 20

Reactants: 26 — (4S)-4-methylhex-5-en-1-ol
Product: 27 — (3S)-6-iodo-3-methylhex-1-ene
Conditions: I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C
Why: Appel-type iodination gives an unbranched primary iodide, an ideal Myers electrophile (carbons C12–C17, with C15 S).

Step 21

Reactants: 20 — 2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-N-[(1R,2R)-1-hydroxy-1-phenylpropan-2-yl]-N-methylacetamide; **27** — (3S)-6-iodo-3-methylhex-1-ene
Product: 28 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-N-[(1R,2R)-1-hydroxy-1-phenylpropan-2-yl]-N,6-dimethyloct-7-enamide
Conditions: LDA (2.1 equiv), LiCl (6 equiv), THF, −78 → 0 °C; then 27 (1.5 equiv), 0 → 25 °C
Why: Myers alkylation of the (Z)-enolate, anti to the alkoxide, sets C11. With (R,R)-19 it gives the (2R)-amide, which becomes R at C11 once the carbonyl carbon is converted into the methyl group; the ring centres (β/γ) are unaffected.

Step 22

Reactants: 28 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-N-[(1R,2R)-1-hydroxy-1-phenylpropan-2-yl]-N,6-dimethyloct-7-enamide
Product: 29 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-6-methyloct-7-en-1-ol
Conditions: LAB (4 equiv), THF, 25 → 40 °C; 19 recovered
Why: As in step 10, the hindered α,α-disubstituted amide is reduced to the primary alcohol without epimerisation at C11.

Step 23

Reactants: 29 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-6-methyloct-7-en-1-ol
Product: 30 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-6-methyloct-7-en-1-yl methanesulfonate
Conditions: MsCl, Et_3N, CH_2Cl_2, 0 °C
Why: Mesylation activates the carbon that will become the C11 methyl; C11 itself is not touched.

Step 24

Reactants: 30 — (2R,6S)-2-{(1S,3S)-3-[(4R)-6-(benzyloxy)-4-methylhexyl]cyclopentyl}-6-methyloct-7-en-1-yl methanesulfonate
Product: 31 — benzyl (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl ether (half-chain C1–C17, 3R,7S,10S,11R,15S, C1-OBn, C16=C17 vinyl)
Conditions: $LiEt_3BH$ (3 equiv), THF, 65 °C
Why: Hydride S_N2 displacement at the primary, β-branched mesylate converts CH_2OMs into CH_3, which completes the R-C11 methyl stereocentre without breaking any bond to C11.

Step 25

Reactants: 31 — benzyl (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl ether (half-chain C1–C17, 3R,7S,10S,11R,15S, C1-OBn, C16=C17 vinyl)
Product: 32 — (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexan-1-ol
Conditions: Li, naphthalene (lithium naphthalenide), THF, −25 °C
Why: Reductive debenzylation leaves the terminal alkene intact (catalytic hydrogenolysis would reduce it).

Step 26

Reactants: 32 — (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexan-1-ol
Product: 33 — (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl trifluoromethanesulfonate
Conditions: Tf_2O, 2,6-lutidine, CH_2Cl_2, −20 °C (used without purification)
Why: This converts C1–OH into a very reactive primary triflate for the etherifications; no stereocentre is nearby.

Step 27

Reactants: 34 — 1-O-benzyl-sn-glycerol [(2S)-3-(benzyloxy)propane-1,2-diol] (commercial)
Product: 35 — 1-O-benzyl-3-O-trityl-sn-glycerol [(2R)-1-(benzyloxy)-3-(trityloxy)propan-2-ol]
Conditions: TrCl, Et_3N, DMAP (cat.), CH_2Cl_2, 25 °C
Why: The bulky trityl group caps the primary sn-3 OH selectively and leaves sn-2 OH free. C2 is untouched; its CIP label changes to R only because the priorities change.

Step 28

Reactants: 35 — 1-O-benzyl-3-O-trityl-sn-glycerol [(2R)-1-(benzyloxy)-3-(trityloxy)propan-2-ol]; **33** — (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl trifluoromethanesulfonate
Product: 36 — (2R)-1-(benzyloxy)-2-{[(3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl]oxy}-3-(trityloxy)propane (1-O-benzyl-3-O-trityl-sn-glycerol carrying the half-chain of 32 on O-2)
Conditions: 35 (2 equiv), NaH, THF/DMF (4:1), 0 °C; then 33 (1 equiv), 0 → 25 °C
Why: The secondary alkoxide is O-alkylated by the primary triflate (Williamson). The glycerol C2–O bond is not broken, so the sn configuration is retained; excess 35 is recovered.

Step 29

Reactants: 2 × **36** — (2R)-1-(benzyloxy)-2-{[(3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl]oxy}-3-(trityloxy)propane (1-O-benzyl-3-O-trityl-sn-glycerol carrying the half-chain of 32 on O-2)
Product: 37 — C_2-symmetric CM dimer of 36 (E/Z): two 1-O-benzyl-3-O-trityl-sn-glycerol units (C2 R) joined through their sn-2 oxygens by the 16,16′-didehydro C_{40} chain (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R; both cyclopentanes trans)
Conditions: Hoveyda–Grubbs II (5 mol%), 1,4-benzoquinone (10 mol%), CH_2Cl_2 (1 M) or neat, 40 °C, N_2 sparge
Why: Homodimerising CM of the α-branched terminal alkene, driven by high concentration and ethylene removal, joins the two sn-2 chains at C16–C16′. Benzoquinone suppresses Ru–H alkene migration, which could epimerise C15; the E/Z ratio is irrelevant.

Step 30

Reactants: 37 — C_2-symmetric CM dimer of 36 (E/Z): two 1-O-benzyl-3-O-trityl-sn-glycerol units (C2 R) joined through their sn-2 oxygens by the 16,16′-didehydro C_{40} chain (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R; both cyclopentanes trans)
Product: 38 — the saturated analogue of 37: sn-2,sn-2′-O,O′-(C_{40} chain)-bis(1-O-benzyl-3-O-trityl-sn-glycerol), chain configured as in 37
Conditions: $TsNHNH_2$ (10 equiv), NaOAc (10 equiv), DME/H_2O, 90 °C
Why: Diimide saturates the disubstituted alkene by concerted syn delivery of two H atoms, with no alkene migration, so C15/C15′ are safe. Removing this alkene also stops it from scrambling the second metathesis.

Step 31

Reactants: 38 — the saturated analogue of 37: sn-2,sn-2′-O,O′-(C_{40} chain)-bis(1-O-benzyl-3-O-trityl-sn-glycerol), chain configured as in 37
Product: 39 — the bis(1-O-benzyl-sn-glycerol) diol from 38 (both sn-3 CH_2OH free; glycerol C2 now labelled S by CIP, configuration unchanged)
Conditions: TsOH·H_2O (0.2 equiv), MeOH/CH_2Cl_2 (1:1), 25 °C
Why: Acidic methanolysis cleaves the trityl ethers selectively; the benzyl and dialkyl ethers survive.

Step 32

Reactants: 39 — the bis(1-O-benzyl-sn-glycerol) diol from 38 (both sn-3 CH_2OH free; glycerol C2 now labelled S by CIP, configuration unchanged); **33** — (3R)-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}-3-methylhexyl trifluoromethanesulfonate
Product: 40 — 39 with both sn-3 oxygens alkylated by the half-chain of 33 (each carrying a terminal C16=C17 vinyl group; glycerol C2 S by CIP)
Conditions: NaH (4 equiv), THF/DMF (4:1), 0 °C; then 33 (3 equiv), 0 → 25 °C
Why: Both primary sn-3 alkoxides are alkylated as in step 28, placing the second pair of half-chains on the sn-3 oxygens.

Step 33

Reactants: 40 — 39 with both sn-3 oxygens alkylated by the half-chain of 33 (each carrying a terminal C16=C17 vinyl group; glycerol C2 S by CIP)
Product: 41 — 68-membered macrocycle (E/Z at the sn-3 chain C16=C16′): two 1-O-benzyl-sn-glycerols joined sn-2↔sn-2 by the saturated C_{40} chain and sn-3↔sn-3 by its 16,16′-didehydro analogue; all chain centres as in 37; glycerol C2 S by CIP
Conditions: Hoveyda–Grubbs II (10 mol%, portionwise), 1,4-benzoquinone (20 mol%), toluene (0.5 mM), 80 °C
Why: High-dilution RCM joins the two sn-3 chains at C16–C16′ and closes the 68-membered ring. Because the sn-2 chains are already joined, only the sn-3↔sn-3 (parallel) connectivity of the target can form.

Step 34

Reactants: 41 — 68-membered macrocycle (E/Z at the sn-3 chain C16=C16′): two 1-O-benzyl-sn-glycerols joined sn-2↔sn-2 by the saturated C_{40} chain and sn-3↔sn-3 by its 16,16′-didehydro analogue; all chain centres as in 37; glycerol C2 S by CIP
Product: 42 — the saturated macrocycle: sn-1,sn-1′-di-O-benzyl derivative of the target (glycerol C2 S by CIP)
Conditions: $TsNHNH_2$ (10 equiv), NaOAc (10 equiv), DME/H_2O, 90 °C
Why: As in step 30: syn reduction without alkene migration keeps C15/C15′ intact.

Step 35

Reactants: 42 — the saturated macrocycle: sn-1,sn-1′-di-O-benzyl derivative of the target (glycerol C2 S by CIP)
Product: 43 — TARGET: the macrocyclic 2,3-di-O-alkyl-sn-glycerol tetraether with two (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R) trans,trans-bicyclic C_{40} chains (sn-2↔sn-2 and sn-3↔sn-3), free sn-1 OH, glycerol C2 (R); $C_{86}H_{164}O_6$
Conditions: H_2 (1 atm), 20% $Pd(OH)_2$/C, EtOAc/THF (1:1), 25 °C
Why: Hydrogenolysis removes the two sn-1 benzyl groups, the only reducible groups left, and frees the primary alcohols; no stereocentre is involved.

Changes after checking: I followed the drawn (all-trans) rings rather than the SMILES line. I also fixed the cyclopentenol enantiomer and every CIP label, including the (R,R) auxiliary for C11, by computation, and gave the aldehyde its own step (25). Finally, I added the diimide reductions (steps 30, 34), benzoquinone in both metatheses and preformed Na-malonate, so no step can epimerise C15 or C10 or scramble the connectivity.

Summary

Total steps: 35 (from commercial 1, 2, 5, 11, 12, 19, 21 and 34).

Longest linear sequence: 24 steps (1→3→4→6→7→8→9→10→17→18→20→28→29→30→31→32→33→36→37→38→39→40→41→42→43).

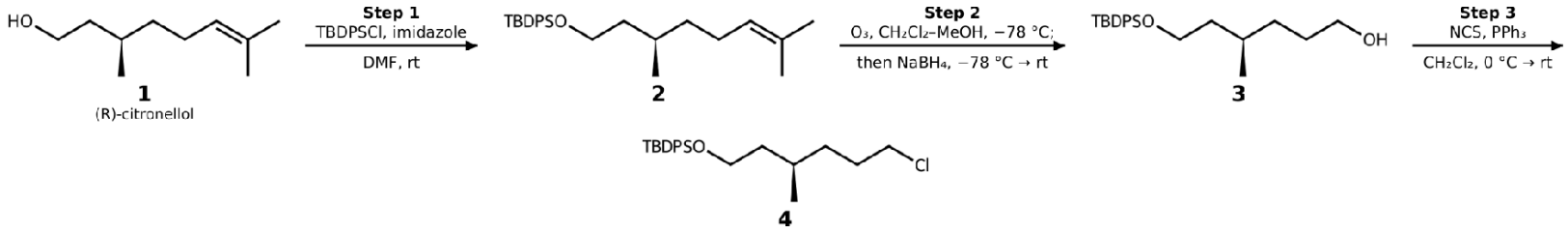
Three steps most likely to fail, each with one fallback:

1. **Step 33 (RCM between two α-branched vinyl groups closing the 68-membered ring)** — fallback: Close the ring by a [1+1] double Williamson etherification instead. Make the saturated C_{40} bis-triflate (CM dimer of 32, then diimide, then Tf_2O) and add it slowly at high dilution to the dianion of 39 (NaH, THF/DMF).
2. **Step 29 (intermolecular CM homodimerisation of the hindered alkene)** — fallback: First tether the two glycerols as an m-xylylene bis-ether (in place of the two benzyl groups), so that this C16–C16′ bond is also formed by RCM. The final hydrogenolysis (step 35) removes the tether.
3. **Step 12 (Cu-catalysed Grignard coupling next to a methyl ester)** — fallback: Use a Ni-catalysed alkyl–alkyl Negishi coupling instead: the iodide from 9 plus the organozinc from 16, $NiCl_2$·glyme/s-Bu-Pybox, DMA, 25 °C (ester-tolerant).

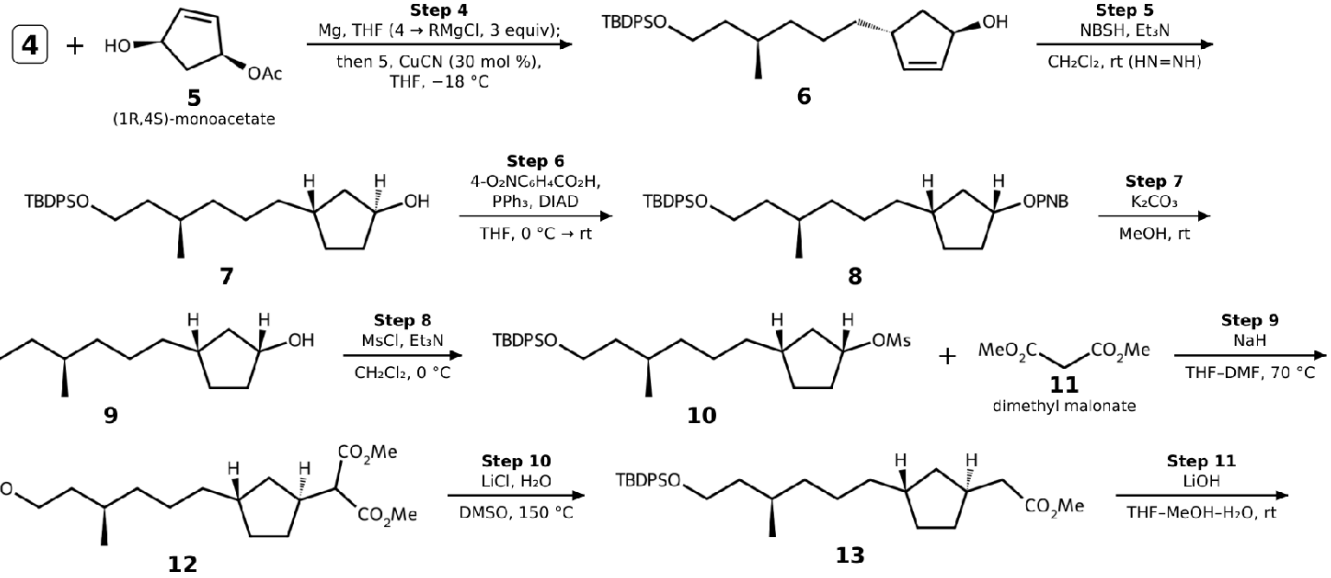
Total synthesis route to the target macrocyclic tetraether ($C_{86}H_{164}O_6$, 38)

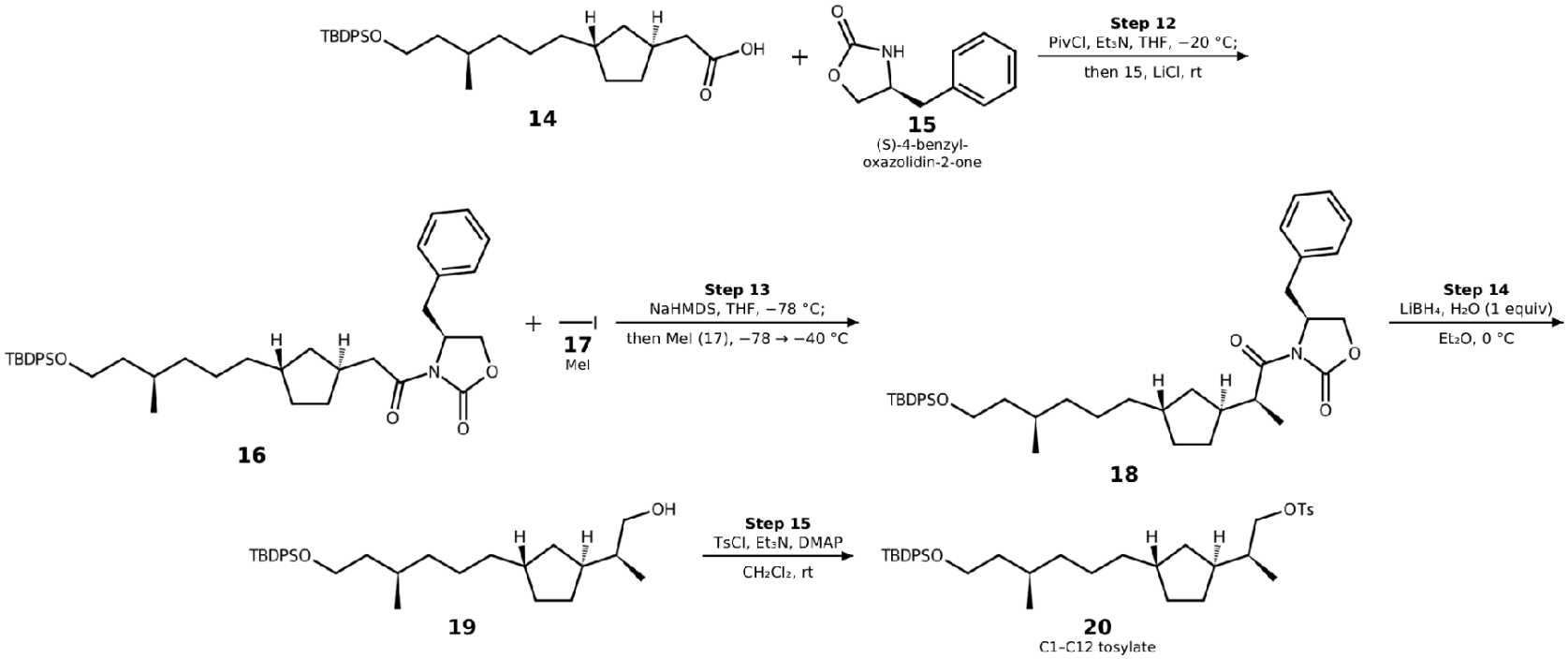
Reaction scheme. Numbers under the structures are the compound numbers used in the text; a boxed number is a compound drawn earlier in the scheme. Wedged/hashed bonds and the explicit ring hydrogens show the absolute configuration. Abbreviations: TBDPS = tert-butyldiphenylsilyl; PNB = 4-nitrobenzoyl; Ms = methanesulfonyl; Ts = 4-toluenesulfonyl; Tf = trifluoromethanesulfonyl; Bn = benzyl; Piv = pivaloyl; NCS = N-chlorosuccinimide; NBSH = 2-nitrobenzenesulfonylhydrazide; DIAD = diisopropyl azodicarboxylate; NaHMDS = sodium hexamethyldisilazide; TBAF = tetrabutylammonium fluoride; proton sponge = 1,8-bis(dimethylamino)naphthalene; HG-II = Hoveyda–Grubbs second-generation catalyst.

A. C1–C6 side chain: Grignard precursor 4 from (R)-citronellol (brings in C3)

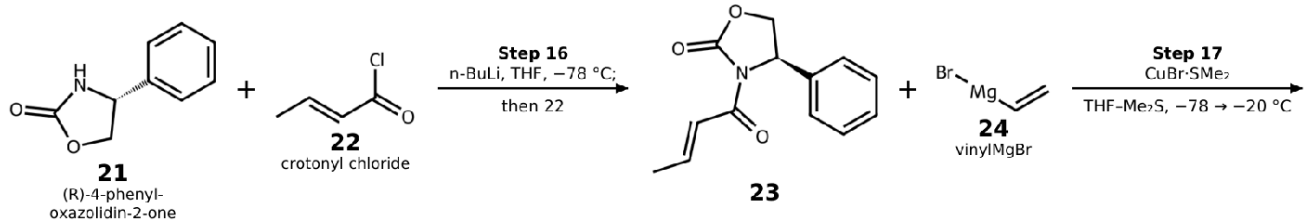


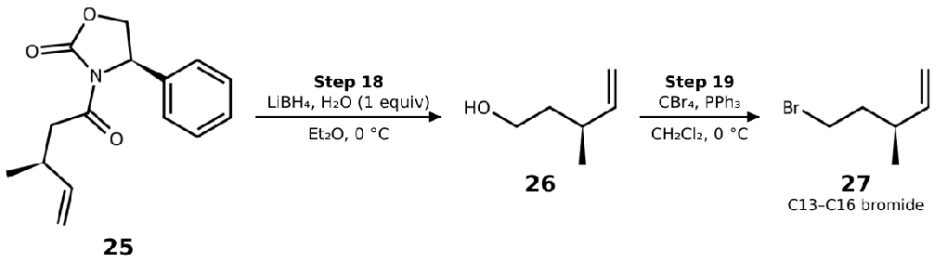
B. C1–C12 cyclopentane fragment 20 (C7 by anti-S_N2 cuprate substitution, C10 by Mitsunobu + malonate S_N2, C11 by Evans methylation)



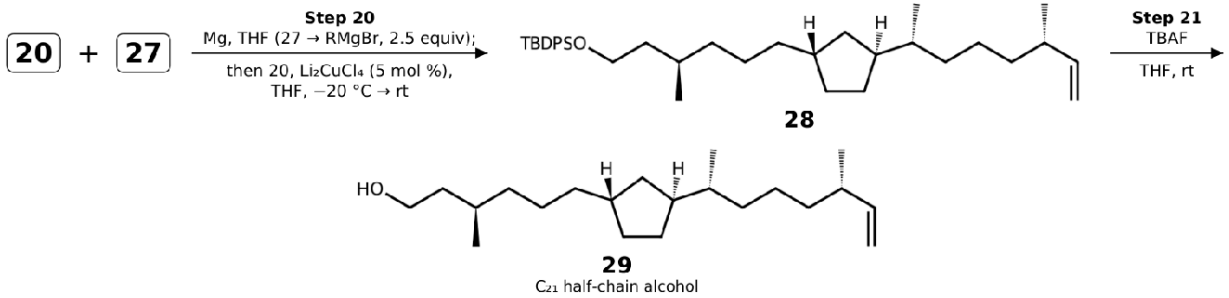


C. C13–C16 fragment 27 (C15 by auxiliary-controlled vinyl-cuprate addition)

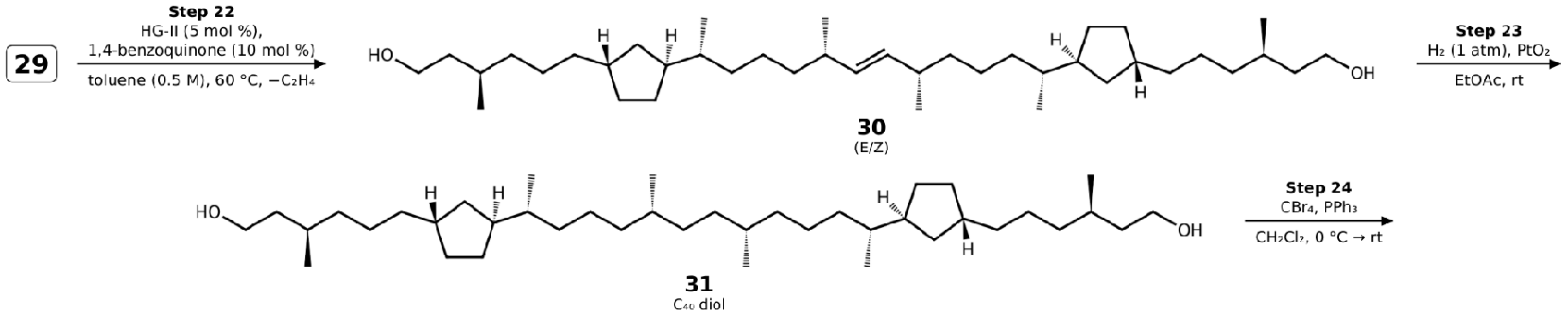


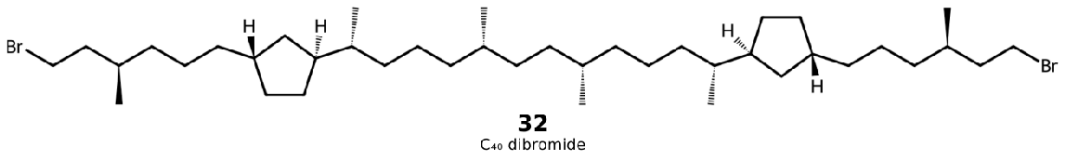


D. C_{21} half-chain alcohol 29 (the common building block, used four times)

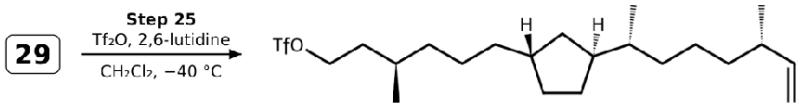


E. C_{40} chain (dibromide 32) by tail-to-tail self-metathesis of 29, and half-chain triflate 33



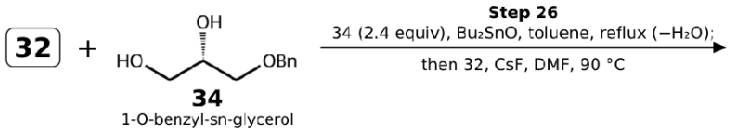


32
C_{40} dibromide

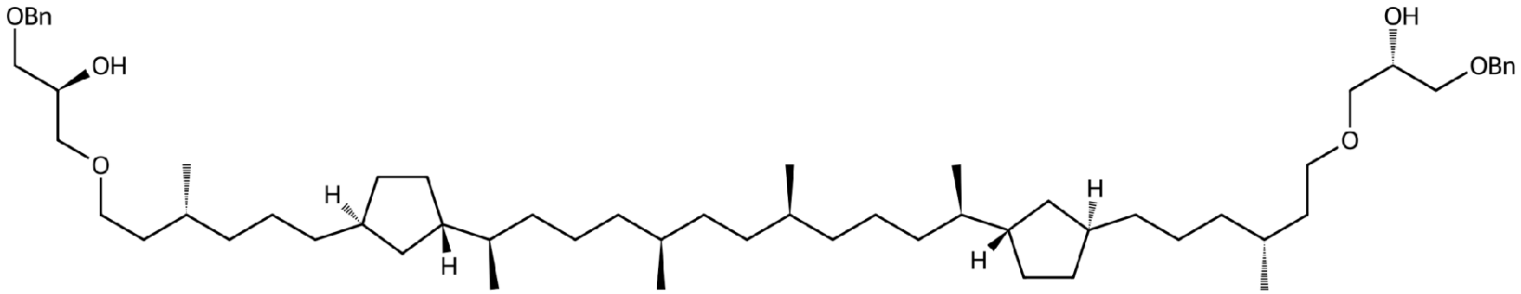


33
C_{21} triflate

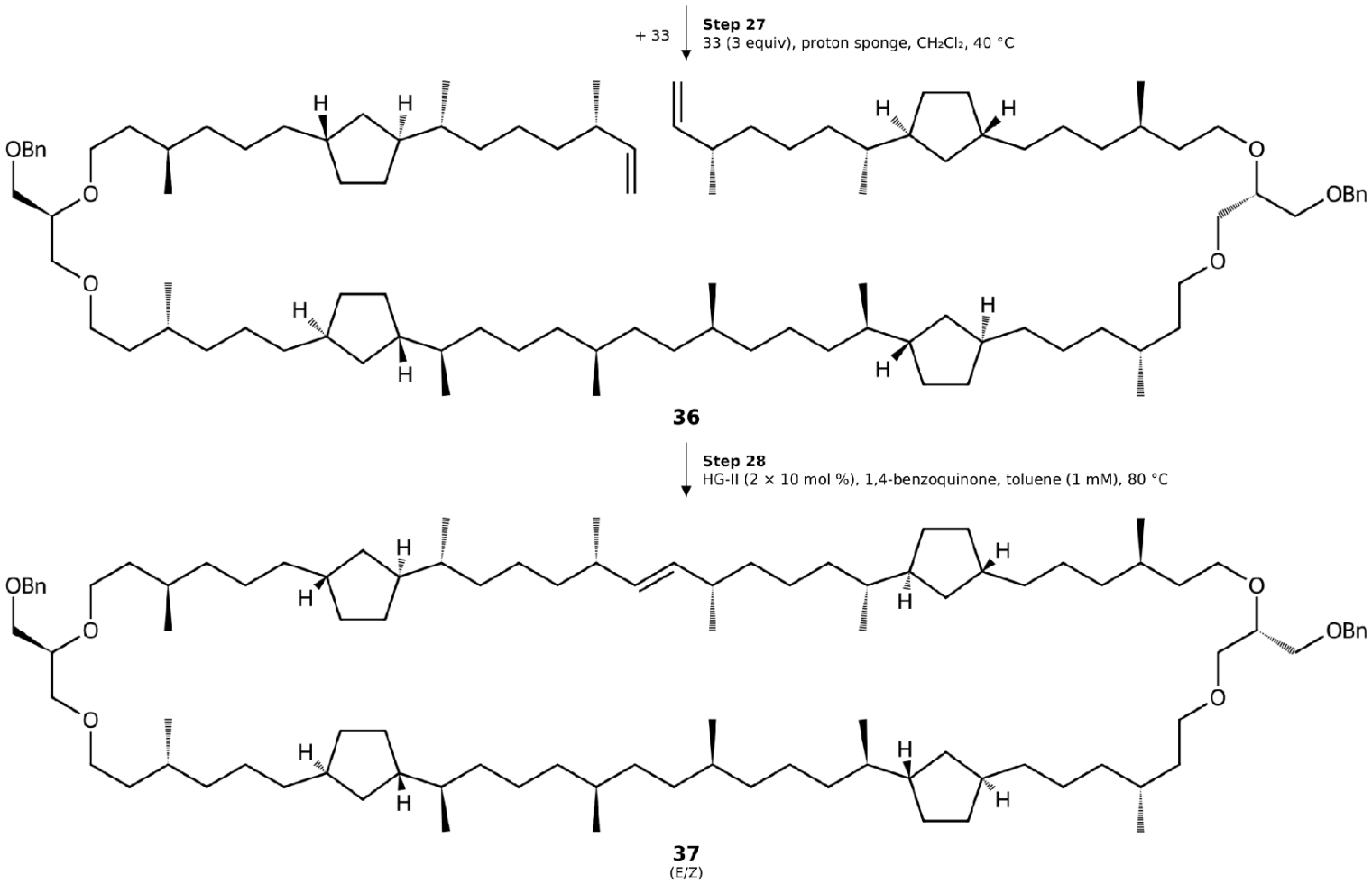
F. Assembly on two glycerols, ring-closing metathesis (the only ring-forming step) and global hydrogenation

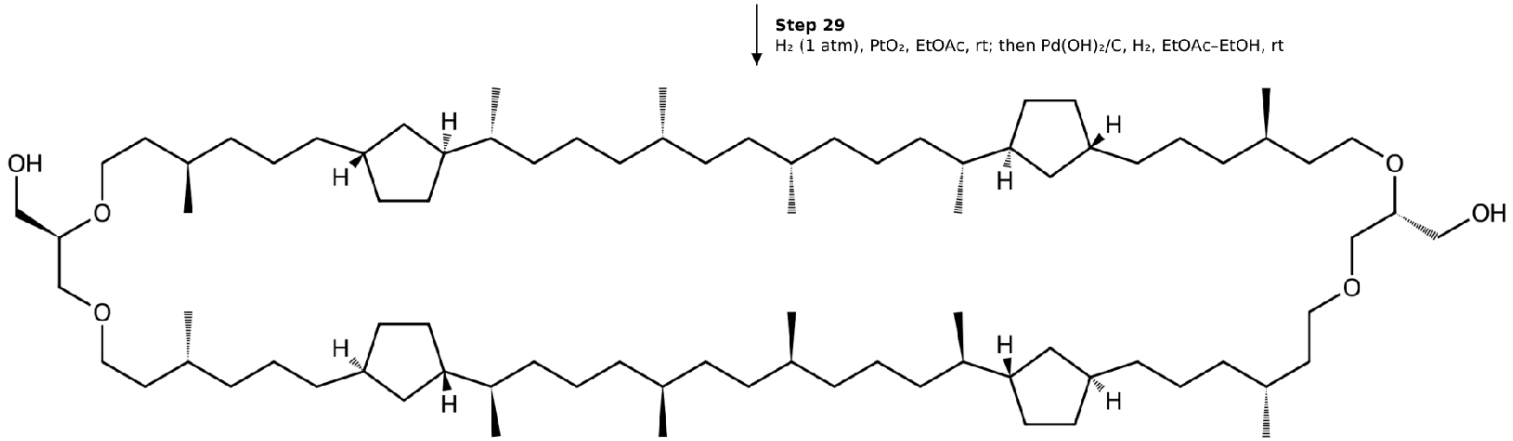


34
1-O-benzyl-sn-glycerol



35


+ 33
Step 27
33 (3 equiv), proton sponge, CH2Cl2, 40 °C
OBn
OBn
36
Step 28
HG-II (2 × 10 mol %), 1,4-benzoquinone, toluene (1 mM), 80 °C
OBn
OBn
37
(E/Z)



38
target

Where each of the 22 stereocentres of 38 is set, and why it survives

Stereocentre	Set in	How	Why it is not scrambled later
C3, C3′ (4 × in 38)	bought with (*R*)-citronellol 1	chiral pool	never next to a reacting centre
C7, C7′ (4 ×)	step 4	anti-S_N2 Cu-catalysed Grignard substitution of monoacetate 5 (inversion at the acetoxy carbon)	allylic only in 6; step 5 uses diimide (no alkene migration)
C10, C10′ (4 ×)	carbinol carbon of 5; steps 6 and 9	Mitsunobu inversion, then malonate S_N2 inversion (net retention, substituents end up trans)	β to the carbonyl in 12–18, not enolisable
C11, C11′ (4 ×)	step 13	Evans methylation, (*S*)-4-benzyl auxiliary, minor diastereomer removed	auxiliary removed reductively ($LiBH_4$), no epimerisation
C15, C15′ (4 ×)	step 17	vinyl-cuprate addition, (*R*)-4-phenyl auxiliary, recrystallised	allylic to a C=C in 25–30, 33, 36, 37: benzoquinone in the metatheses, PtO_2 (not Pd/C) for the reductions
glycerol C-2 (2 ×)	bought with 34	chiral pool (1-*O*-benzyl-*sn*-glycerol)	only O-alkylations; the C–O bonds at the stereocentre are never broken

Scheme legend: formula, molecular weight and isomeric SMILES of every numbered compound (the structures above were drawn from these SMILES)

No.	Formula	MW	Isomeric SMILES
1	C10H20O	156.3	CC(C)=CCC[C@@H](C)CCO
2	C26H38OSi	394.7	CC(C)=CCC[C@@H](C)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
3	C23H34O2Si	370.6	C[C@H](CCCO)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
4	C23H33ClOSi	389.1	C[C@H](CCCCl)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
5	C7H10O3	142.2	CC(=O)O[C@@H]1C=C[C@H](O)C1
6	C28H40O2Si	436.7	C[C@H](CCC[C@H]1C=C[C@H](O)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
7	C28H42O2Si	438.7	C[C@H](CCC[C@H]1CC[C@H](O)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
8	C35H45NO5Si	587.8	C[C@H](CCC[C@H]1CC[C@@H](OC(=O)c2ccc([N+](=O)[O-])cc2)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
9	C28H42O2Si	438.7	C[C@H](CCC[C@H]1CC[C@@H](O)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
10	C29H44O4SSi	516.8	C[C@H](CCC[C@H]1CC[C@@H](OS(C)(=O)=O)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
11	C5H8O4	132.1	COC(=O)CC(=O)OC
12	C33H48O5Si	552.8	COC(=O)C(C(=O)OC)[C@H]1CC[C@H](CCC[C@@H](C)CCO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)C1
13	C31H46O3Si	494.8	COC(=O)C[C@H]1CC[C@H](CCC[C@@H](C)CCO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)C1
14	C30H44O3Si	480.8	C[C@H](CCC[C@H]1CC[C@H](CC(=O)O)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
15	C10H11NO2	177.2	O=C1N[C@@H](Cc2ccccc2)CO1
16	C40H53NO4Si	640.0	C[C@H](CCC[C@H]1CC[C@H](CC(=O)N2C(=O)OC[C@@H]2Cc2ccccc2)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
17	CH3I	141.9	CI
18	C41H55NO4Si	654.0	C[C@H](CCC[C@H]1CC[C@H]([C@H](C)C(=O)N2C(=O)OC[C@@H]2Cc2ccccc2)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
19	C31H48O2Si	480.8	C[C@H](CCC[C@H]1CC[C@H]([C@H](C)CO)C1)CCO[Si](c1ccccc1)(c1ccccc1)C(C)(C)C
20	C38H54O4SSi	635.0	Cc1ccc(S(=O)(=O)OC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCO[Si](c3ccccc3)(c3ccccc3)C(C)(C)C)C2)cc1
21	C9H9NO2	163.2	O=C1N[C@H](c2ccccc2)CO1
22	C4H5ClO	104.5	C/C=C/C(=O)Cl
23	C13H13NO3	231.3	C/C=C/C(=O)N1C(=O)OC[C@H]1c1ccccc1
24	C2H3BrMg	131.3	C=[CH][Mg][Br]
25	C15H17NO3	259.3	C=C[C@@H](C)CC(=O)N1C(=O)OC[C@H]1c1ccccc1
26	C6H12O	100.2	C=C[C@@H](C)CCO
27	C6H11Br	163.1	C=C[C@@H](C)CCBr
28	C37H58OSi	547.0	C=C[C@@H](C)CCC[C@@H](C)[C@H]1CC[C@H](CCC[C@@H](C)CCO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)C1
29	C21H40O	308.6	C=C[C@@H](C)CCC[C@@H](C)[C@H]1CC[C@H](CCC[C@@H](C)CCO)C1
30	C40H76O2	589.0	C[C@@H](CCO)CCC[C@H]1CC[C@H]([C@H](C)CCC[C@H](C)C=C[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCO)C2)C1
31	C40H78O2	591.1	C[C@@H](CCO)CCC[C@H]1CC[C@H]([C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCO)C2)C1
32	C40H76Br2	716.9	C[C@@H](CCBr)CCC[C@H]1CC[C@H]([C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCBr)C2)C1
33	C22H39F3O3S	440.6	C=C[C@@H](C)CCC[C@@H](C)[C@H]1CC[C@H](CCC[C@@H](C)CCOS(=O)(=O)C(F)(F)F)C1
34	C10H14O3	182.2	OC[C@H](O)COCc1ccccc1
35	C60H102O6	919.5	C[C@H](CCC[C@H]1CC[C@H]([C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCOC[C@H](O)COCc3ccccc3)C2)C1)CCOC[C@H](O)COCc1ccccc1
36	C102H178O6	1500.5	C=C[C@@H](C)CCC[C@@H](C)[C@H]1CC[C@H](CCC[C@@H](C)CCO[C@@H](COCC[C@H](C)CCC[C@H]2CC[C@H]([C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]3CC[C@H](CCC[C@@H](C)CCOC[C@@H](COCc4ccccc4)OCC[C@H](C)CCC[C@H]4CC[C@H]([C@H](C)CCC[C@H](C)C=C)C4)C3)C2)COCc2ccccc2)C1
37	C100H174O6	1472.5	C[C@@H]1CCC[C@H]2CC[C@@H](C2)C[C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCOC[C@@H](COCc3ccccc3)OCC[C@H](C)CCC[C@H]3CC[C@@H](C3)[C@H](C)CCC[C@H](C)C=C[C@@H](C)CCC[C@@H](C)[C@H]3CC[C@H](CCC[C@@H](C)CCO[C@H](COCc4ccccc4)COCC1)C3)C2
38	C86H164O6	1294.3	C[C@@H]1CCC[C@H]2CC[C@@H](C2)[C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]2CC[C@H](CCC[C@@H](C)CCOC[C@@H](CO)OCC[C@H](C)CCC[C@H]3CC[C@@H](C3)[C@H](C)CCC[C@H](C)CC[C@@H](C)CCC[C@@H](C)[C@H]3CC[C@H](CCC[C@@H](C)CCO[C@H](CO)COCC1)C3)C2

Total synthesis route to the target macrocyclic tetraether ($C_{86}H_{164}O_6$, 38)

Retrosynthetic overview

1. 38 ⇐ (H_2: C=C reduction + 2 × O-benzyl hydrogenolysis) macrocyclic alkene 37 ⇐ (ring-closing metathesis, C16=C16′) acyclic diene 36. The 68-membered macrocycle is the only ring that is formed, and it is formed last.

2. 36 ⇐ two sn-2 O-alkylations of diol 35 with C_{21} triflate 33; 35 ⇐ regioselective (stannylene) sn-3 O-alkylation of 2 × 1-O-benzyl-sn-glycerol 34 with C_{40} dibromide 32.

3. C_{40} chain 32 ⇐ tail-to-tail self-metathesis / hydrogenation of the same C_{21} alcohol 29 (the C_2 symmetry means 29 is used four times).

4. 29 ⇐ Cu-catalysed sp^3–sp^3 coupling (C12–C13) of C1–C12 tosylate 20 with the Grignard of (S)-5-bromo-3-methylpent-1-ene 27 (C15 from an auxiliary-controlled vinyl-cuprate addition).

5. 20 ⇐ Evans methylation (C11) ⇐ malonate S_N2 with inversion (C10) ⇐ Mitsunobu inversion ⇐ anti-S_N2 Cu-catalysed Grignard substitution of monoacetate 5 (C7) with the (R)-citronellol-derived Grignard (C3). The four cyclopentanes are bought (as 5), not built.

Target, numbering and assumptions

Target 38: $C_{86}H_{164}O_6$ (MW 1294.3), 22 stereocentres, a 68-membered macrocycle (shortest path through the four trans-1,3-disubstituted cyclopentanes). Two identical, C_2-symmetric C_{40} chains (biphytane numbering: 3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R) bridge two (R)-configured glycerols (2,3-di-O-alkyl-sn-glycerol, free OH on C-1); one chain joins the two sn-2 oxygens, the other the two sn-3 oxygens ('parallel' arrangement).

Chain numbering used throughout (biphytane numbering): O–C1H_2–C2H_2–C3H(Me)–C4H_2–C5H_2–C6H_2–C7H(ring)–…–C10H(ring)–C11H(Me)–C12H_2–C13H_2–C14H_2–C15H(Me)–C16H_2–C16′H_2–…–C1′H_2–O; each cyclopentane = C7, C8, C9, C10 and C18 (C18 is the CH_2 that bridges C7 and C10).

• Assumption: The SMILES string and the drawing agree (checked with RDKit: same constitution, 22 defined stereocentres, all four rings trans-1,3); the SMILES was taken as the definition of the target.

• Assumption: Both enantiomers of cis-4-acetoxycyclopent-2-en-1-ol, citronellol, 4-substituted oxazolidin-2-ones and 3-(benzyloxy)propane-1,2-diol are catalogue chemicals and are treated as commercially available; ≥98% ee (R)-citronellol is assumed.

Route, step by step (forward direction)

Step 1

Reactants: **1** (R)-(+)-citronellol, (3R)-3,7-dimethyloct-6-en-1-ol (commercial)
Product: **2** (R)-tert-butyl[(3,7-dimethyloct-6-en-1-yl)oxy]diphenylsilane (TBDPS ether of 1)
Conditions: TBDPSCl, imidazole, DMF, rt
Why: Imidazole-catalysed silylation of the only OH; TBDPS is chosen because it survives every later operation (Grignard formation, Mitsunobu, NaH/malonate at 70 °C, Krapcho, LiOH, enolate chemistry, $LiBH_4$) and is removed by fluoride without touching a vinyl group; C3 (R) is carried in from citronellol.

Step 2

Reactants: **2** (R)-tert-butyl[(3,7-dimethyloct-6-en-1-yl)oxy]diphenylsilane (TBDPS ether of 1)
Product: **3** (4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexan-1-ol
Conditions: O_3, CH_2Cl_2–MeOH (4:1), −78 °C; then $NaBH_4$, −78 °C → rt
Why: Ozone cleaves the only C=C (electron-rich, trisubstituted) and $NaBH_4$ reduces the ozonide/aldehyde in situ to the C6 alcohol (the isopropylidene carbons leave as acetone); silyl ether and C3 are untouched.

Step 3

Reactants: **3** (4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexan-1-ol
Product: **4** (3R)-tert-butyl[(6-chloro-3-methylhexyl)oxy]diphenylsilane
Conditions: NCS, PPh_3, CH_2Cl_2, 0 °C → rt
Why: Appel-type chlorination of an unhindered primary alcohol under neutral conditions; the chloride is wanted because the Cu-catalysed substitution of step 4 is most regioselective with RMgCl.

Step 4

Reactants: **4** (3R)-tert-butyl[(6-chloro-3-methylhexyl)oxy]diphenylsilane; **5** (1R,4S)-cis-4-acetoxycyclopent-2-en-1-ol [= (1S,4R)-4-hydroxycyclopent-2-en-1-yl acetate; carbinol carbon R, acetoxy carbon S] (commercial)
Product: **6** (1R,4R)-4-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopent-2-en-1-ol (ring substituents trans)
Conditions: 4, Mg, THF, reflux (→ RMgCl, 3 equiv); then 5, CuCN (30 mol %), THF, −18 °C
Why: Kobayashi's CuCN-catalysed RMgCl substitution of the monoacetate (first equivalent deprotonates the OH) displaces acetate at the α-carbon (S_N2-type, 1,4 : 1,2 ≈ 9:1) strictly anti, so the side chain enters C7 with inversion and ends up trans to the hydroxyl (sets C7); under Cu catalysis at −18 °C the acetate carbonyl is not attacked.

Step 5
Reactants: **6** (1R,4R)-4-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopent-2-en-1-ol (ring substituents trans)
Product: **7** (1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentan-1-ol (trans)
Conditions: 2-$O_2NC_6H_4SO_2NHNH_2$ (NBSH), Et_3N, CH_2Cl_2, rt (diimide)
Why: Diimide saturates the unhindered cis ring alkene without the allylic C–O hydrogenolysis, allylic alcohol → ketone isomerisation or aryl reduction that heterogeneous catalysts can cause; no stereocentre is touched.

Step 6
Reactants: **7** (1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentan-1-ol (trans)
Product: **8** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl 4-nitrobenzoate (cis; OPNB)
Conditions: 4-$O_2NC_6H_4CO_2H$, PPh_3, DIAD, THF, 0 °C → rt
Why: Mitsunobu esterification of the secondary cyclopentanol proceeds with clean S_N2 inversion at C10, converting trans-7 into the cis ester so that the next (invertive) C–C bond formation delivers trans.

Step 7
Reactants: **8** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl 4-nitrobenzoate (cis; OPNB)
Product: **9** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentan-1-ol (cis)
Conditions: K_2CO_3, MeOH, rt
Why: Mild methanolysis cleaves only the activated nitrobenzoate (acyl–O cleavage, configuration retained); the primary TBDPS ether is stable to K_2CO_3/MeOH.

Step 8
Reactants: **9** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentan-1-ol (cis)
Product: **10** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl methanesulfonate (cis)
Conditions: MsCl, Et_3N, CH_2Cl_2, 0 °C
Why: Sulfonylation at oxygen (retention) puts a good leaving group on a cyclopentyl carbon, one of the secondary systems most amenable to S_N2.

Step 9
Reactants: **10** (1R,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl methanesulfonate (cis); **11** dimethyl malonate (commercial)
Product: **12** dimethyl 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}malonate (trans)
Conditions: 11 (3 equiv), NaH, THF–DMF (3:1), 70 °C
Why: Soft sodiomalonate displaces the cyclopentyl mesylate by S_N2 from the face opposite the leaving group (also the face anti to the cis C7 chain), so C10 is set with inversion and the two ring substituents become trans; E2 to the cyclopentene is the only competitor.

Step 10
Reactants: **12** dimethyl 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}malonate (trans)
Product: **13** methyl 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetate
Conditions: LiCl, H_2O, DMSO, 150 °C
Why: Krapcho dealkoxycarbonylation (Cl^- attack on OMe, loss of CO_2) removes one ester under neutral conditions; neither ring stereocentre is α to a carbonyl so nothing can epimerise, and the primary TBDPS ether tolerates LiCl/wet DMSO.

Step 11
Reactants: **13** methyl 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetate
Product: **14** 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetic acid
Conditions: LiOH, THF–MeOH–H_2O, rt
Why: Simple saponification at room temperature; TBDPS is stable to LiOH and there is no epimerisable centre.

Step 12
Reactants: **14** 2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetic acid; **15** (S)-4-benzyloxazolidin-2-one (commercial)
Product: **16** (4S)-4-benzyl-3-(2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetyl)oxazolidin-2-one
Conditions: PivCl, Et_3N, THF, −20 °C; then 15, LiCl, rt
Why: The mixed pivalic anhydride transfers only its unhindered acyl group to the LiCl/Et_3N-activated oxazolidinone, installing the (S)-benzyl auxiliary without strong base.

Step 13
Reactants: **16** (4S)-4-benzyl-3-(2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}acetyl)oxazolidin-2-one; **17** iodomethane (commercial)
Product: **18** (4S)-4-benzyl-3-[(2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propanoyl]oxazolidin-2-one
Conditions: NaHMDS, THF, −78 °C; then MeI (17), −78 → −40 °C
Why: NaHMDS gives the chelated (Z)-enolate whose face syn to the benzyl group is blocked, so MeI adds anti to benzyl and creates the C11 centre (2S in 18; dr ≈ 93:7, minor isomer removed by chromatography); the β ring centre C10 is not enolisable.

Step 14
Reactants: 18
(4S)-4-benzyl-3-[(2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propanoyl]oxazolidin-2-one
Product: 19 (2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propan-1-ol (C1–C12 fragment; C11 is S here only because CH_2OH outranks the ring, the geometry is that of 11R in the target)
Conditions: $LiBH_4$, H_2O (1 equiv), Et_2O, 0 °C
Why: $LiBH_4$ reduces the exocyclic imide carbonyl to the primary alcohol without epimerising the α-centre and releases auxiliary 15 for recovery; the silyl ether is inert.

Step 15
Reactants: 19 (2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propan-1-ol (C1–C12 fragment; C11 is S here only because CH_2OH outranks the ring, the geometry is that of 11R in the target)
Product: 20 (2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propyl 4-methylbenzenesulfonate (tosylate of 19)
Conditions: TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, rt
Why: Tosylation of the primary alcohol provides the electrophile for the Cu-catalysed coupling (β-branched primary tosylates are competent substrates).

Step 16
Reactants: 21 (R)-4-phenyloxazolidin-2-one (commercial); **22** (E)-but-2-enoyl chloride (crotonyl chloride, commercial)
Product: 23 (4R)-3-[(E)-but-2-enoyl]-4-phenyloxazolidin-2-one
Conditions: n-BuLi, THF, −78 °C; then 22
Why: The N-lithiated oxazolidinone is acylated cleanly by the acid chloride at −78 °C with retention of the (E)-alkene.

Step 17
Reactants: 23 (4R)-3-[(E)-but-2-enoyl]-4-phenyloxazolidin-2-one; **24** vinylmagnesium bromide (commercial, 1 M in THF)
Product: 25 (4R)-3-[(3S)-3-methylpent-4-enoyl]-4-phenyloxazolidin-2-one
Conditions: 24 (3 equiv), CuBr·SMe_2 (1.5 equiv), THF–Me_2S, −78 → −20 °C
Why: The vinyl cuprate adds 1,4 to the Mg-chelated syn-s-cis enoyl imide from the face anti to the 4-phenyl group (Hruby model), giving the (3S) adduct (dr ≥ 95:5, raised to > 99:1 by recrystallisation); this sets C15.

Step 18
Reactants: 25 (4R)-3-[(3S)-3-methylpent-4-enoyl]-4-phenyloxazolidin-2-one
Product: 26 (S)-3-methylpent-4-en-1-ol
Conditions: $LiBH_4$, H_2O (1 equiv), Et_2O, 0 °C
Why: Reductive removal of the auxiliary gives the primary alcohol and leaves the β-stereocentre and the vinyl group untouched; 21 is recovered; the volatile C_6 alcohol is isolated by careful distillation.

Step 19
Reactants: 26 (S)-3-methylpent-4-en-1-ol
Product: 27 (S)-5-bromo-3-methylpent-1-ene
Conditions: CBr_4, PPh_3, CH_2Cl_2, 0 °C
Why: Appel bromination of the primary alcohol under neutral conditions (the alkene is three bonds away, so no allylic transposition is possible) gives the Grignard precursor.

Step 20
Reactants: 20 (2S)-2-{(1S,3S)-3-[(4R)-6-(TBDPS-oxy)-4-methylhexyl]cyclopentyl}propyl 4-methylbenzenesulfonate (tosylate of 19); **27** (S)-5-bromo-3-methylpent-1-ene
Product: 28 tert-butyl{[(3R)-3-methyl-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}hexyl]oxy}diphenylsilane (C_{21} half-chain TBDPS ether)
Conditions: 27, Mg, THF (→ RMgBr, 2.5 equiv); then 20, Li_2CuCl_4 (5 mol %), THF, −20 °C → rt
Why: Cu-catalysed (Schlosser–Fouquet) coupling of a primary alkyl Grignard with a primary tosylate forms the C12–C13 sp^3–sp^3 bond; the cheap Grignard is the component used in excess, silyl ether and terminal alkene are inert, and no stereocentre is involved.

Step 21
Reactants: 28 tert-butyl{[(3R)-3-methyl-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}hexyl]oxy}diphenylsilane (C_{21} half-chain TBDPS ether)
Product: 29 (3R)-3-methyl-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}hexan-1-ol (C_{21} half-chain alcohol; biphytane numbering 3R,7S,10S,11R,15S, C16=CH_2)
Conditions: TBAF, THF, rt
Why: Fluoride cleaves the only silyl ether; the alkene is untouched.

Step 22
Reactants: **29** (3R)-3-methyl-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}hexan-1-ol (C_{21} half-chain alcohol; biphytane numbering 3R,7S,10S,11R,15S, C16=CH_2)
Product: **30** C_{40} alkene-diol: tail-to-tail dimer of 29, HO–C1…C16=C16′…C1′–OH (E/Z mixture), (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R)
Conditions: Hoveyda–Grubbs II (5 mol %), 1,4-benzoquinone (10 mol %), toluene (0.5 M), 60 °C, Ar sparge (−C_2H_4)
Why: Self-metathesis of the monosubstituted, allylically branched alkene with the robust HG-II catalyst (ethylene swept out) joins two halves tail-to-tail at C16=C16′ to give the C_2-symmetric C_{40} skeleton; benzoquinone suppresses the Ru–H alkene migration that would erode the allylic C15 centres; free OH is tolerated and E/Z is irrelevant.

Step 23
Reactants: **30** C_{40} alkene-diol: tail-to-tail dimer of 29, HO–C1…C16=C16′…C1′–OH (E/Z mixture), (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R)
Product: **31** C_{40} diol: 16,16′-saturated 30, (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R)-bis(trans-1,3-cyclopentane)biphytane-1,1′-diol
Conditions: H_2 (1 atm), PtO_2, EtOAc, rt
Why: Adams' catalyst reduces the disubstituted alkene with far less double-bond migration than Pd/C, protecting the two allylic C15/C15′ stereocentres; nothing else is reducible.

Step 24
Reactants: **31** C_{40} diol: 16,16′-saturated 30, (3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R)-bis(trans-1,3-cyclopentane)biphytane-1,1′-diol
Product: **32** C_{40} 1,1′-dibromide corresponding to diol 31 (same ten stereocentres)
Conditions: CBr_4, PPh_3, CH_2Cl_2, 0 °C → rt
Why: Double Appel bromination of the two primary alcohols under neutral conditions.

Step 25
Reactants: **29** (3R)-3-methyl-6-{(1S,3S)-3-[(2R,6S)-6-methyloct-7-en-2-yl]cyclopentyl}hexan-1-ol (C_{21} half-chain alcohol; biphytane numbering 3R,7S,10S,11R,15S, C16=CH_2)
Product: **33** trifluoromethanesulfonate (triflate) of 29
Conditions: Tf_2O, 2,6-lutidine, CH_2Cl_2, −40 °C (used crude)
Why: Low-temperature triflation of the primary alcohol with a hindered base; a primary alkyl triflate is needed to etherify the hindered sn-2 hydroxyl in step 27 and is used without purification; the alkene is inert.

Step 26
Reactants: **32** C_{40} 1,1′-dibromide corresponding to diol 31 (same ten stereocentres); **34** (S)-3-(benzyloxy)propane-1,2-diol (1-O-benzyl-sn-glycerol, commercial)
Product: **35** 3,3′-O-(C_{40}-1,1′-diyl)bis(1-O-benzyl-sn-glycerol): BnO–CH_2–CH(OH)–CH_2–O–[C_{40} chain of 31]–O–CH_2–CH(OH)–CH_2–OBn, both carbinol carbons S, both sn-2 OH free
Conditions: 34 (2.4 equiv), Bu_2SnO, toluene, reflux (−H_2O); then 32, CsF, DMF, 90 °C
Why: The dibutylstannylene acetal of the 1,2-diol is alkylated (CsF activation) selectively at the primary oxygen, so each end of the dibromide ends up on an sn-3 oxygen while both sn-2 hydroxyls stay free; the glycerol stereocentre is not touched and excess 34 is recovered.

Step 27
Reactants: **35** 3,3′-O-(C_{40}-1,1′-diyl)bis(1-O-benzyl-sn-glycerol): BnO–CH_2–CH(OH)–CH_2–O–[C_{40} chain of 31]–O–CH_2–CH(OH)–CH_2–OBn, both carbinol carbons S, both sn-2 OH free; **33** trifluoromethanesulfonate (triflate) of 29
Product: **36** acyclic tetraether diene: 35 in which each sn-2 oxygen carries the C_{21} alkenyl chain of 29 (two terminal CH(Me)–CH=CH_2 groups)
Conditions: 33 (3 equiv), 1,8-bis(dimethylamino)naphthalene (proton sponge), CH_2Cl_2, 40 °C
Why: Alkyl triflate/proton-sponge (the Aoki–Poulter archaeal-lipid conditions) etherifies the hindered secondary OH without forming an alkoxide, so there is no triflate elimination, benzyl migration or epimerisation.

Step 28
Reactants: **36** acyclic tetraether diene: 35 in which each sn-2 oxygen carries the C_{21} alkenyl chain of 29 (two terminal CH(Me)–CH=CH_2 groups)
Product: **37** macrocyclic alkene: 1,1′-di-O-benzyl ether of 16,16′-didehydro-38 (C16=C16′ in the sn-2/sn-2′ chain, E/Z mixture)
Conditions: Hoveyda–Grubbs II (2 × 10 mol %), 1,4-benzoquinone (20 mol %), toluene (1 mM), 80 °C, Ar sparge
Why: Only two alkenes are present, so RCM can give only one ring; at 1 mM the strain-free 68-membered ring (the only ring formed in the synthesis) closes in preference to oligomers, benzoquinone again prevents alkene migration, and E/Z is irrelevant.

Step 29

Reactants: 37 macrocyclic alkene: 1,1′-di-O-benzyl ether of 16,16′-didehydro-38 (C16=C16′ in the sn-2/sn-2′ chain, E/Z mixture)

Product: 38 target: the 68-membered glycerol dialkyl glycerol tetraether drawn in the question (both glycerol carbons R; each chain 3R,7S,10S,11R,15S,15′S,11′R,10′S,7′S,3′R)

Conditions: H_2 (1 atm), PtO_2, EtOAc, rt; then $Pd(OH)_2/C$, H_2 (1 atm), EtOAc–EtOH, rt

Why: Pt reduces the macrocyclic alkene without migration into the C15 centres, then Pearlman's catalyst hydrogenolyses both benzyl ethers; no other functional group is present, and the product is 38.

Checks that were run on the route (RDKit)

• Target parsed from the SMILES: $C_{86}H_{164}O_6$, 22 assigned stereocentres, ring sizes 68/5/5/5/5; both C_{40} chains and all four C_{21} halves are identical (canonical SMILES), both glycerols R, all rings trans.

• Every step was encoded as a reaction template and applied to the reactant structures; in all 29 steps the generated product is identical (canonical isomeric SMILES) to the numbered product, including the three invertive steps (4, 6, 9); the product of step 29 is identical to the target SMILES.

• cis/trans relationships on the ring were checked independently (meso test on the symmetrised ring): 5 cis, 6/7 trans, 8–10 cis, 12–20 trans, target rings trans. The new centres of steps 13 and 17 follow the Evans and Hruby models, cross-checked against the known (S)-benzyl-auxiliary allylation → (R) and (4R)-phenyl-auxiliary aryl-cuprate → (3S) outcomes.

• All structures in the scheme were drawn from the same stereo-SMILES that were used for the names, formulas and the reaction checks (legend table after the scheme).

What was changed after checking

Changed after checking: (i) the glycerol building block was corrected from the (R)- to the (S)-enantiomer of 3-(benzyloxy)propane-1,2-diol (1-O-benzyl-sn-glycerol) after the CIP/substructure check against the target; (ii) every C=C reduction next to a stereocentre (steps 5, 23, 29) was moved from H_2–Pd/C to diimide or PtO_2 ($Pd(OH)_2/C$ only afterwards for O-debenzylation) to avoid epimerisation by double-bond migration; (iii) a ring-closure-digit error in the SMILES used to draw 37 was fixed.

Closing summary

Total step count: 29 steps (steps 4 and 20 include the in-situ Grignard formation; 38 numbered compounds).

Longest linear sequence: 24 steps: 1 → 2 → 3 → 4 → 6 → 7 → 8 → 9 → 10 → 12 → 13 → 14 → 16 → 18 → 19 → 20 → 28 → 29 → 30 → 31 → 32 → 35 → 36 → 37 → 38.

The three steps most likely to fail, each with one fallback

1. Step 28 (macro-RCM of two allylically branched vinyl groups; slow initiation, oligomers, alkene migration). Fallback: cleave both vinyl groups of 36 (OsO_4/$NaIO_4$) to the C16/C16′ dialdehyde and close the ring by intramolecular McMurry coupling ($TiCl_3(DME)_{1.5}$, Zn–Cu, DME, reflux, syringe-pump addition) to the same alkene 37, the coupling precedented for the 72-membered archaeal tetraether macrocycle.

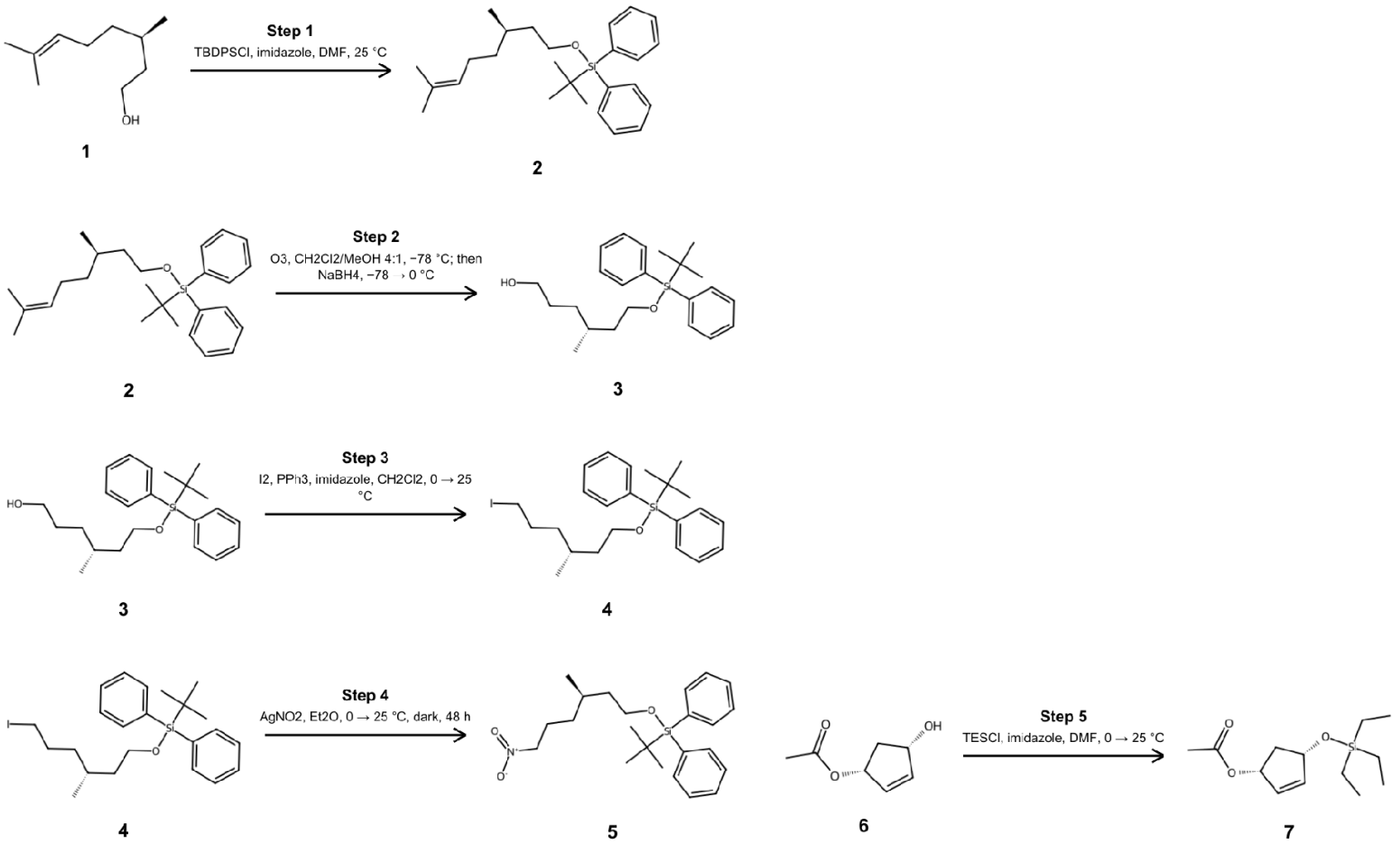
2. Step 9 (S_N2 of a secondary mesylate with malonate; E2 to the cyclopentene competes). Fallback: make the C10–C bond at the allylic stage instead: methyl carbonate of 6, $NaCH(CO_2Me)_2$, $Pd(PPh_3)_4$, THF (double inversion = net retention, giving the same trans isomer), then diimide reduction; this replaces steps 5–9.

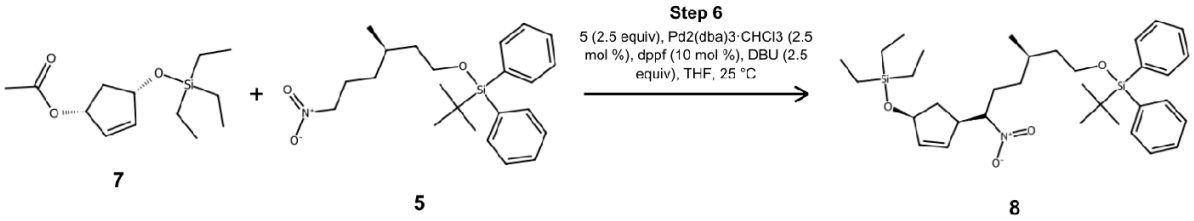
3. Step 26 (regioselective stannylene O-alkylation with an unactivated, lipophilic C_{40} dibromide; slow or incomplete bis-alkylation). Fallback: Williamson alkylation (NaH, DMF) of 1,2-O-isopropylidene-sn-glycerol [(S)-solketal] with 32, acidic removal of both acetonides and selective primary tritylation (TrCl, pyridine) to give the same sn-2-OH diol with Tr in place of Bn (Tr removed with acid after step 28/29).

Mythos 5.1's route to GDGT-4

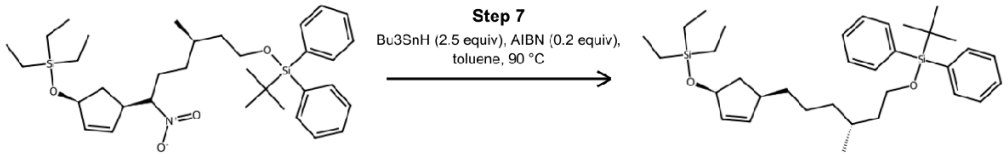
Proposed total synthesis of the target macrocyclic tetraether (GDGT-4 with four trans-cyclopentane rings): reaction scheme

Structures are drawn from the verified SMILES of every intermediate; wedges/dashes show absolute configuration. Compound numbers are given under each structure, conditions over each arrow. Compound 8 is a 1:1 mixture of epimers at the nitro-bearing carbon (no wedge drawn); all other stereocenters are single isomers.

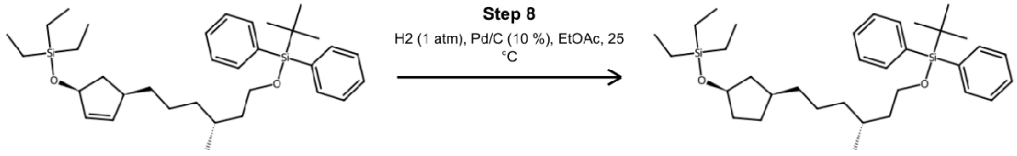




7 + 5 → 8



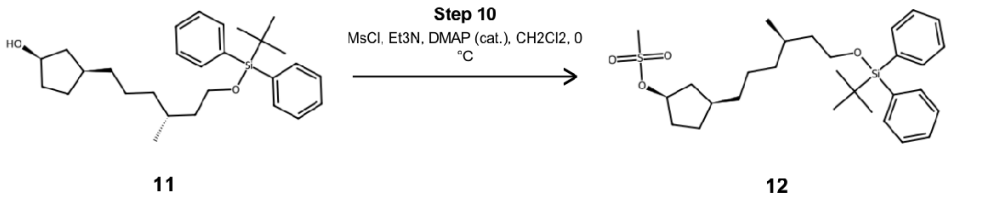
8 → 9



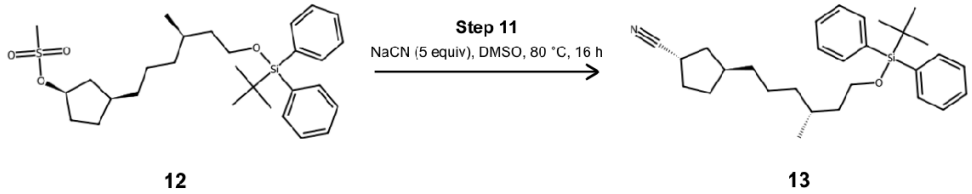
9 → 10



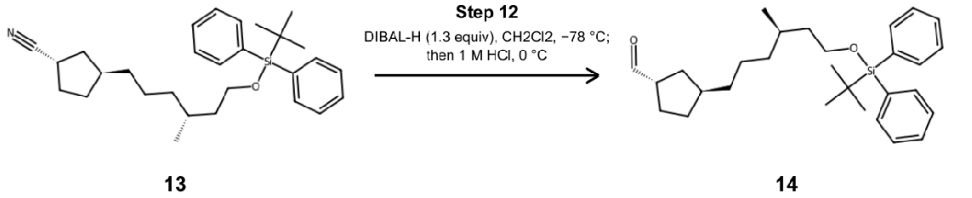
10 → 11



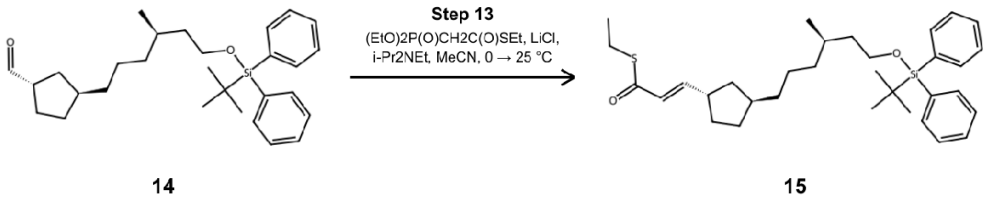
11 12



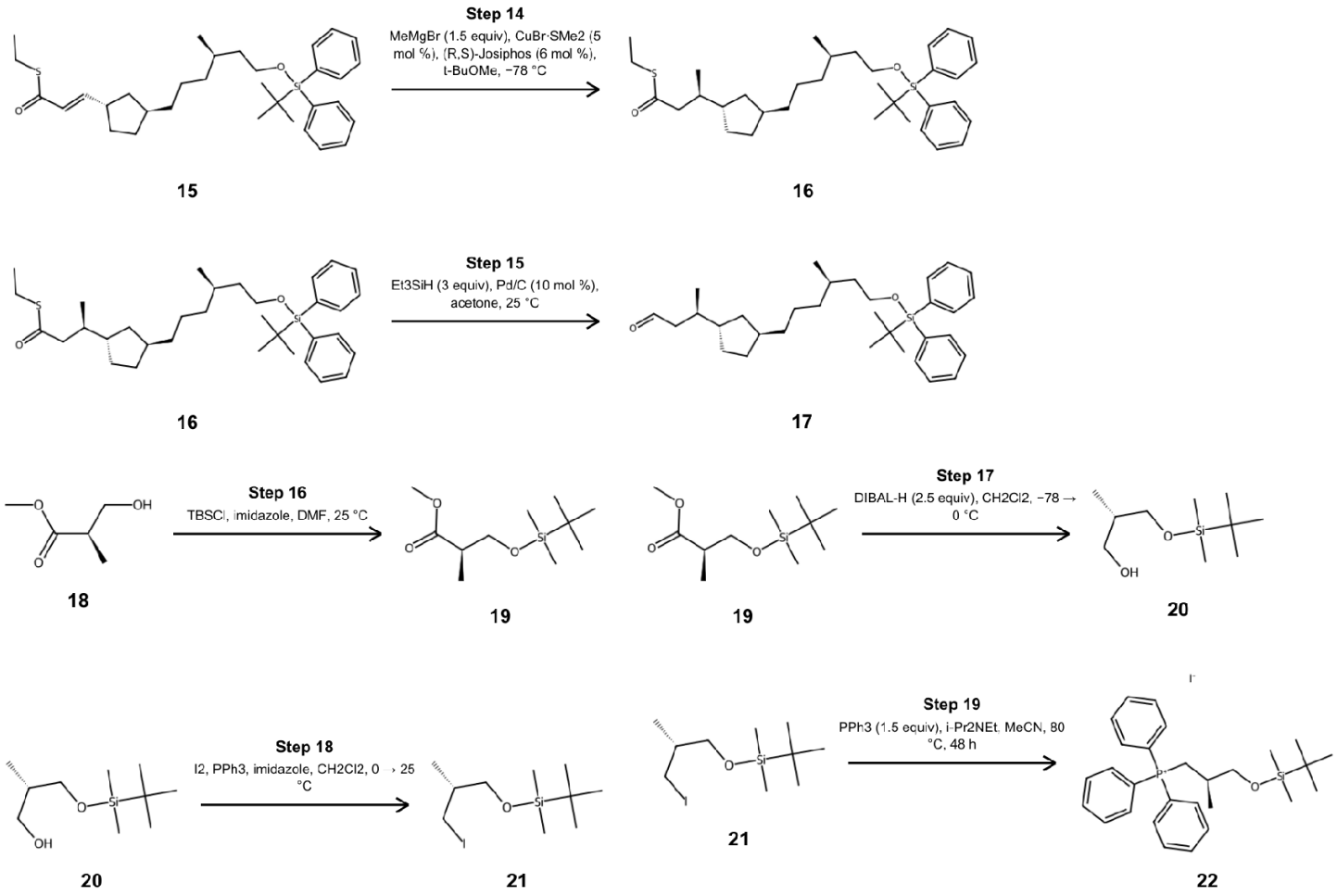
12 13

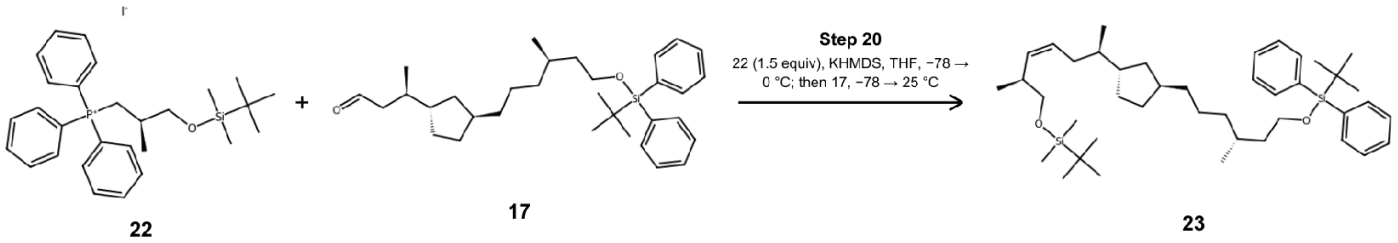


13 14



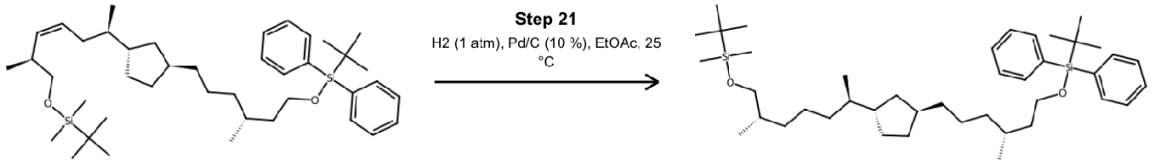
14 15


Step 14
MeMgBr (1.5 equiv), CuBr·SMe2 (5 mol %), (R,S)-Josiphos (6 mol %), t-BuOMe, −78 °C
15
16
Step 15
Et3SiH (3 equiv), Pd/C (10 mol %), acetone, 25 °C
16
17
Step 16
TBSCl, imidazole, DMF, 25 °C
18
19
Step 17
DIBAL-H (2.5 equiv), CH2Cl2, −78 → 0 °C
19
20
Step 18
I2, PPh3, imidazole, CH2Cl2, 0 → 25 °C
20
21
Step 19
PPh3 (1.5 equiv), i-Pr2NEt, MeCN, 80 °C, 48 h
21
22



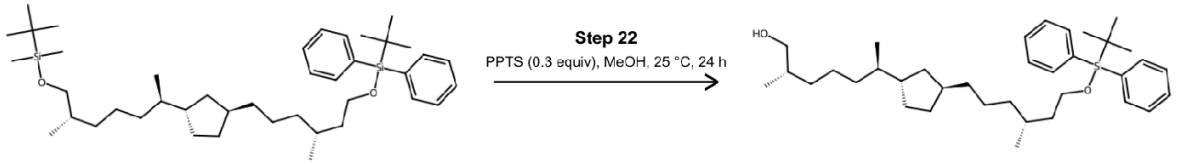
22 + 17 → 23

Step 20
22 (1.5 equiv), KHMDS, THF, −78 → 0 °C; then 17, −78 → 25 °C



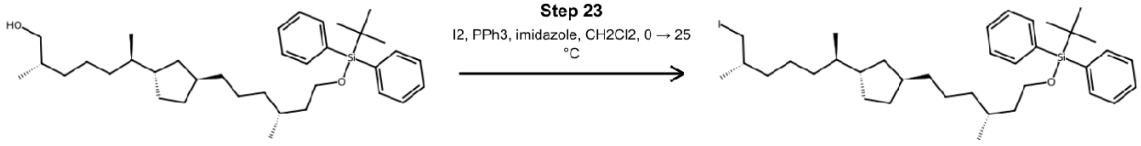
23 → 24

Step 21
H2 (1 atm), Pd/C (10 %), EtOAc, 25 °C



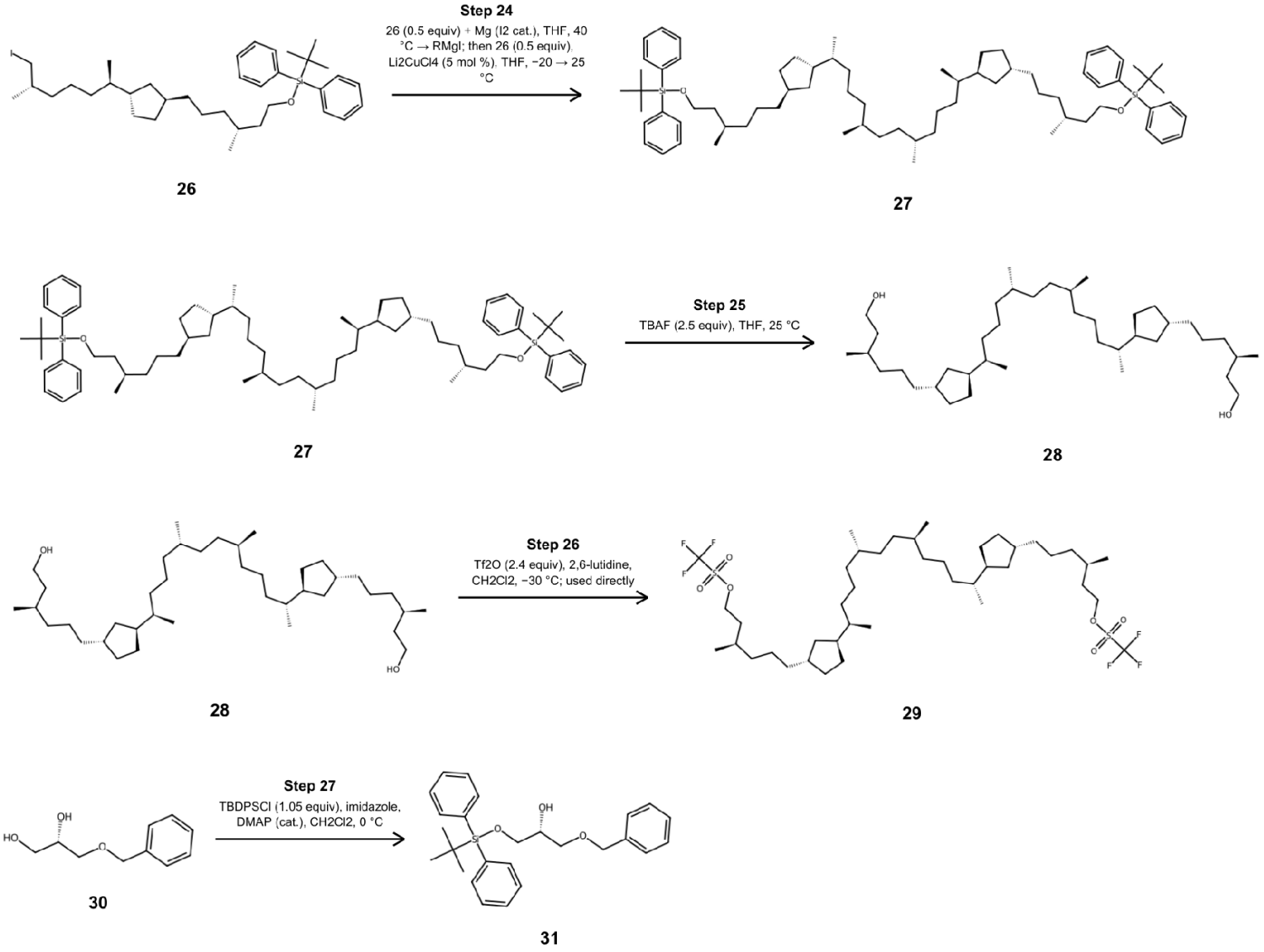
24 → 25

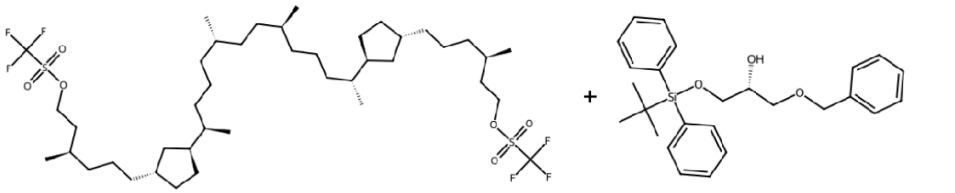
Step 22
PPTS (0.3 equiv), MeOH, 25 °C, 24 h



25 → 26

Step 23
I2, PPh3, imidazole, CH2Cl2, 0 → 25 °C


Step 24
26 (0.5 equiv) + Mg (I2 cat.), THF, 40 °C → RMgI; then 26 (0.5 equiv), Li2CuCl4 (5 mol %), THF, −20 → 25 °C
26
27
Step 25
TBAF (2.5 equiv), THF, 25 °C
27
28
Step 26
Tf2O (2.4 equiv), 2,6-lutidine, CH2Cl2, −30 °C; used directly
28
29
Step 27
TBDPSCl (1.05 equiv), imidazole, DMAP (cat.), CH2Cl2, 0 °C
30
31



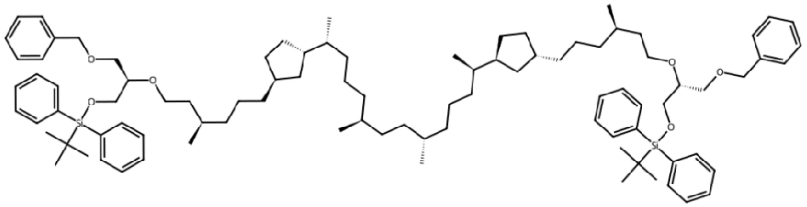
29

+

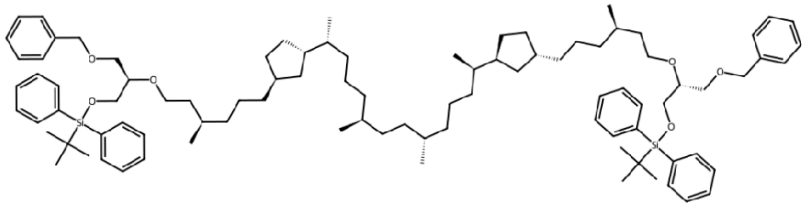
31

Step 28

31 (3 equiv), NaH (3 equiv), THF/DMF 4:1, 0 °C; then 29, 0 → 25 °C

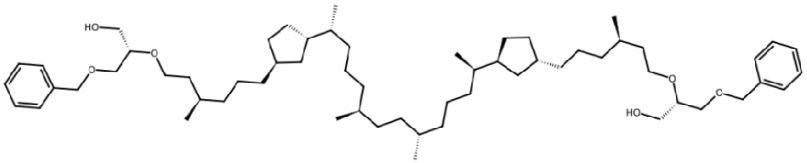


32

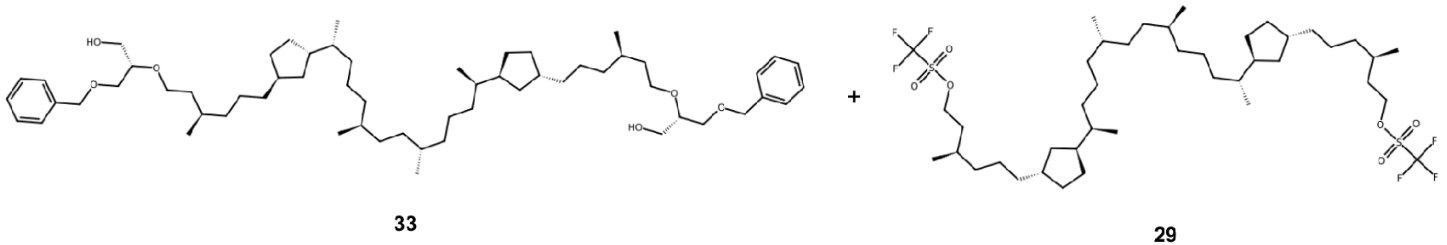


32

Step 29
TBAF (2.5 equiv), THF, 25 °C

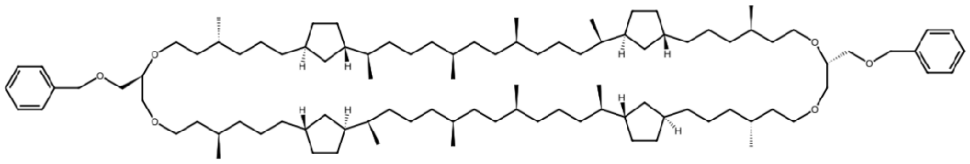


33

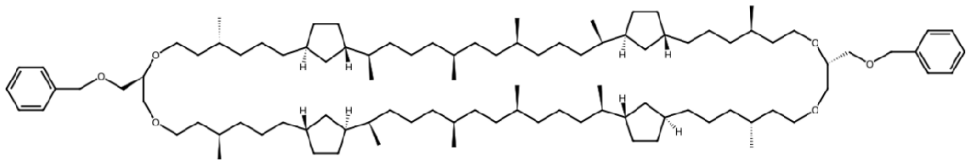


33 + 29

Step 30
NaH (10 equiv), THF/DMF 1:1, 60 °C; 33 + 29 (1:1) added by syringe pump over 12 h, final 1 mM

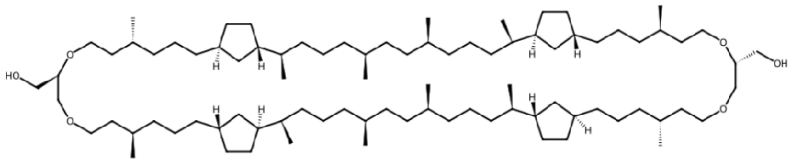


34



34

Step 31
H2 (1 atm), Pd(OH)2/C, EtOAc/EtOH 1:1, 25 °C



35

Retrosynthetic overview

1. The 72-membered tetraether is cut at its four C–O ether bonds into two identical C40 diols (biphytane-1,32-diols carrying two trans-1,3-cyclopentanes) and two 1-O-benzyl-sn-glycerol units; the macrocycle (the only ring formed in the forward direction) is closed last by a double Williamson etherification, the secondary (sn-2) oxygens intermolecularly and the primary (sn-3) oxygens intramolecularly, which delivers exactly the drawn parallel (sn-2/sn-2, sn-3/sn-3) regioisomer.

2. The C2-symmetric C40 diol is cut at the central C16–C17 bond into two identical C20 halves joined by a Cu-catalysed Tamura–Kochi coupling of a primary iodide with its own Grignard reagent.

3. The C20 half is cut at the two ring C–C bonds: C1–C6 comes from (R)-citronellol (as a nitroalkane nucleophile), the cyclopentane from the commercial (1S,4R)-cis-monoacetate of cyclopent-4-ene-1,3-diol, the C11 methyl from a Cu/Josiphos conjugate addition, and C14–C16 from the (R)-Roche ester.

4. The trans-1,3-cyclopentane is generated from the cis-monoacetate by a Pd-catalysed allylic substitution with net retention (C7) followed by an SN2 cyanide displacement with inversion (C10); both cyclopentane rings therefore exist from the start and no carbocycle is formed in the synthesis.

5. Ring-forming order: cyclopentanes present in the starting material → C40 chain (step 24) → linear bis-glycerol (step 28) → 72-membered macrocycle (step 30).

Assumption: the (R,S)-Josiphos ligand enantiomer is taken to deliver (R)-C11 in step 14; if the model substrate (S-ethyl oct-2-enethioate) shows the opposite sense, the (S,R)-ligand is used instead. The target as drawn is the parallel regioisomer (both secondary glycerol oxygens on one C40 chain), and the route is designed for exactly that isomer.

Numbered compounds

1 (R)-citronellol [(3R)-3,7-dimethyloct-6-en-1-ol]
2 tert-butyl{[(3R)-3,7-dimethyloct-6-en-1-yl]oxy}diphenylsilane [(R)-O-TBDPS-citronellol]
3 (4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexan-1-ol
4 tert-butyl{[(3R)-6-iodo-3-methylhexyl]oxy}diphenylsilane
5 tert-butyl{[(3R)-3-methyl-6-nitrohexyl]oxy}diphenylsilane (C1–C6 nitroalkane)
6 (1S,4R)-4-acetoxycyclopent-2-en-1-ol (cis-monoacetate of cyclopent-4-ene-1,3-diol, commercial)
7 (1R,4S)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-yl acetate
8 tert-butyl({(3R)-3-methyl-6-nitro-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (1:1 epimers at the nitro-bearing carbon; ring substituents cis)
9 tert-butyl({(3R)-3-methyl-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (cis)
10 tert-butyl({(3R)-3-methyl-6-[(1S,3R)-3-(triethylsilyloxy)cyclopentyl]hexyl}oxy)diphenylsilane (cis-1,3)
11 (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentan-1-ol (cis-1,3)
12 (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl methanesulfonate (cis-1,3)
13 (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbonitrile (trans-1,3)
14 (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbaldehyde (trans-1,3)
15 S-ethyl (2E)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]prop-2-enethioate
16 S-ethyl (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanethioate
17 (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanal
18 methyl (2R)-3-hydroxy-2-methylpropanoate [(R)-Roche ester, commercial]
19 methyl (2R)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropanoate
20 (2S)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropan-1-ol
21 tert-butyl[(2R)-3-iodo-2-methylpropoxy]dimethylsilane
22 [(2R)-3-(tert-butyldimethylsilyloxy)-2-methylpropyl]triphenylphosphonium iodide
23 tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,4Z,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylhept-4-en-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane
24 tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylheptan-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (complete C20 half, C1-OTBDPS / C16-OTBS)
25 (2S,6R)-6-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]-2-methylheptan-1-ol
26 tert-butyl({(3R)-6-[(1S,3S)-3-[(2R,6S)-7-iodo-6-methylheptan-2-yl]cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (C20 iodide)
27 1,32-bis[(tert-butyldiphenylsilyl)oxy] ether of diol 28 (C2-symmetric C40 chain)
28 (3R,7S,10S,11R,15S,18S,22R,23S,26S,30R)-3,11,15,18,22,30-hexamethyl-7,10:23,26-dimethanodotriacontane-1,32-diol (biphytane-1,32-diol with two trans-1,3-cyclopentane rings; C2-symmetric)
29 1,32-bis(trifluoromethanesulfonate) of diol 28
30 (S)-3-(benzyloxy)propane-1,2-diol [1-O-benzyl-sn-glycerol, commercial]
31 (2R)-1-(benzyloxy)-3-[(tert-butyldiphenylsilyl)oxy]propan-2-ol
32 bis(glycerol) diether: the C40 chain of 28 linked through both termini to the secondary (sn-2) oxygens of two units of 31 [1,32-bis{[(2R)-1-(benzyloxy)-3-(TBDPS-oxy)propan-2-yl]oxy} derivative of 28]
33 desilylated 32: 1,32-bis{[(2S)-1-(benzyloxy)-3-hydroxypropan-2-yl]oxy} derivative of 28 (two free primary OH)
34 1,1'-di-O-benzyl macrocyclic tetraether (di-O-benzyl ether of the target; 72-membered ring)

35 target: GDGT-4, the 72-membered glycerol dibiphytanyl glycerol tetraether with four trans-1,3-cyclopentane rings, (R,R)-glycerols, C86H164O6

Forward route

Step 1

Reactants: **1** (R)-citronellol [(3R)-3,7-dimethyloct-6-en-1-ol]
Product: **2** tert-butyl{[(3R)-3,7-dimethyloct-6-en-1-yl]oxy}diphenylsilane [(R)-O-TBDPS-citronellol]
Conditions: TBDPSCl, imidazole, DMF, 25 °C
Why: Silyl protection of the primary alcohol; the (R)-C3 stereocenter (target C3/C30) is taken from the chiral pool and is never touched again.

Step 2

Reactants: **2** tert-butyl{[(3R)-3,7-dimethyloct-6-en-1-yl]oxy}diphenylsilane [(R)-O-TBDPS-citronellol]
Product: **3** (4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexan-1-ol
Conditions: O3, CH2Cl2/MeOH 4:1, −78 °C; then NaBH4, −78 → 0 °C
Why: Ozonolysis cleaves the trisubstituted alkene and in situ borohydride reduction gives the primary alcohol, i.e. the complete C1–C6 fragment with its methyl branch.

Step 3

Reactants: **3** (4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexan-1-ol
Product: **4** tert-butyl{[(3R)-6-iodo-3-methylhexyl]oxy}diphenylsilane
Conditions: I2, PPh3, imidazole, CH2Cl2, 0 → 25 °C
Why: Appel iodination of an unhindered primary alcohol.

Step 4

Reactants: **4** tert-butyl{[(3R)-6-iodo-3-methylhexyl]oxy}diphenylsilane
Product: **5** tert-butyl{[(3R)-3-methyl-6-nitrohexyl]oxy}diphenylsilane (C1–C6 nitroalkane)
Conditions: AgNO2, Et2O, 0 → 25 °C, dark, 48 h
Why: Victor Meyer nitration of the primary iodide gives the nitroalkane (nitrite ester by-product separated); the nitro carbon becomes ring-attached C6, which carries no stereocenter in the target.

Step 5

Reactants: **6** (1S,4R)-4-acetoxycyclopent-2-en-1-ol (cis-monoacetate of cyclopent-4-ene-1,3-diol, commercial)
Product: **7** (1R,4S)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-yl acetate
Conditions: TESCl, imidazole, DMF, 0 → 25 °C
Why: Silylation of the allylic alcohol of the commercial cis-monoacetate; the acetate is kept as the leaving group for the palladium step.

Step 6

Reactants: **7** (1R,4S)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-yl acetate; **5** tert-butyl{[(3R)-3-methyl-6-nitrohexyl]oxy}diphenylsilane (C1–C6 nitroalkane)
Product: **8** tert-butyl({(3R)-3-methyl-6-nitro-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (1:1 epimers at the nitro-bearing carbon; ring substituents cis)
Conditions: 5 (2.5 equiv), Pd2(dba)3·CHCl3 (2.5 mol %), dppf (10 mol %), DBU (2.5 equiv), THF, 25 °C
Why: Tsuji–Trost allylation: Pd(0) ionizes the acetate anti to the C–O bond and the soft nitronate attacks the π-allyl anti to Pd, so the C–C bond forms with net retention (cis to OTES) at the terminus distal to the silyloxy group (Trost regiochemistry for 4-oxygenated cyclopentenyl esters); C7 is thereby fixed by the monoacetate and C6 is only a transient epimeric center.

Step 7

Reactants: **8** tert-butyl({(3R)-3-methyl-6-nitro-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (1:1 epimers at the nitro-bearing carbon; ring substituents cis)
Product: **9** tert-butyl({(3R)-3-methyl-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (cis)
Conditions: Bu3SnH (2.5 equiv), AIBN (0.2 equiv), toluene, 90 °C
Why: Ono radical denitration replaces the secondary nitro group by hydrogen and erases the transient C6 stereocenter without touching the ring.

Step 8

Reactants: **9** tert-butyl({(3R)-3-methyl-6-[(1R,4S)-4-(triethylsilyloxy)cyclopent-2-en-1-yl]hexyl}oxy)diphenylsilane (cis)
Product: **10** tert-butyl({(3R)-3-methyl-6-[(1S,3R)-3-(triethylsilyloxy)cyclopentyl]hexyl}oxy)diphenylsilane (cis-1,3)
Conditions: H2 (1 atm), Pd/C (10 %), EtOAc, 25 °C
Why: Hydrogenation of the ring alkene; both ring substituents are already in place so no stereocenter is created.

Step 9

Reactants: **10** tert-butyl({(3R)-3-methyl-6-[(1S,3R)-3-(triethylsilyloxy)cyclopentyl]hexyl}oxy)diphenylsilane (cis-1,3)
Product: **11** (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentan-1-ol (cis-1,3)
Conditions: PPTS (0.2 equiv), MeOH/CH2Cl2 1:1, 25 °C
Why: Mild acid cleaves the secondary TES ether selectively next to the primary TBDPS ether, unmasking the cis-1,3 alcohol.

Step 10

Reactants: **11** (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentan-1-ol (cis-1,3)
Product: **12** (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl methanesulfonate (cis-1,3)
Conditions: MsCl, Et3N, DMAP (cat.), CH2Cl2, 0 °C
Why: Mesylation without C–O cleavage keeps the cis configuration ready for displacement.

Step 11

Reactants: **12** (1R,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl methanesulfonate (cis-1,3)
Product: **13** (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbonitrile (trans-1,3)
Conditions: NaCN (5 equiv), DMSO, 80 °C, 16 h
Why: SN2 displacement by cyanide with Walden inversion converts the cis-1,3 relationship into the trans-1,3 relationship of the target (C7/C10); this is the single stereodefining event for C10.

Step 12

Reactants: **13** (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbonitrile (trans-1,3)
Product: **14** (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbaldehyde (trans-1,3)
Conditions: DIBAL-H (1.3 equiv), CH2Cl2, −78 °C; then 1 M HCl, 0 °C
Why: Reduction of the nitrile to the aldehyde via the aluminium imine; nothing else is reducible.

Step 13

Reactants: **14** (1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentane-1-carbaldehyde (trans-1,3)
Product: **15** S-ethyl (2E)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]prop-2-enethioate
Conditions: (EtO)2P(O)CH2C(O)SEt, LiCl, i-Pr2NEt, MeCN, 0 → 25 °C
Why: Masamune–Roush HWE with the thioester phosphonate gives the (E)-enethioate (>95:5) required for the conjugate addition.

Step 14

Reactants: **15** S-ethyl (2E)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]prop-2-enethioate
Product: **16** S-ethyl (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanethioate
Conditions: MeMgBr (1.5 equiv), CuBr·SMe2 (5 mol %), (R,S)-Josiphos (6 mol %), t-BuOMe, −78 °C
Why: Cu/Josiphos-catalysed conjugate addition of MeMgBr to the (E)-enethioate sets the C11 methyl stereocenter under catalyst control (Minnaard–Feringa deoxypropionate methodology, which tolerates γ-branching).

Step 15

Reactants: **16** S-ethyl (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanethioate
Product: **17** (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanal
Conditions: Et3SiH (3 equiv), Pd/C (10 mol %), acetone, 25 °C
Why: Fukuyama reduction converts the thioester into the aldehyde under neutral conditions, leaving the silyl ether and both stereocenters intact.

Step 16

Reactants: **18** methyl (2R)-3-hydroxy-2-methylpropanoate [(R)-Roche ester, commercial]
Product: **19** methyl (2R)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropanoate
Conditions: TBSCl, imidazole, DMF, 25 °C
Why: Silylation of the (R)-Roche ester; its stereocenter becomes target C15/C18.

Step 17

Reactants: **19** methyl (2R)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropanoate
Product: **20** (2S)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropan-1-ol
Conditions: DIBAL-H (2.5 equiv), CH2Cl2, −78 → 0 °C
Why: Ester reduction to the primary alcohol; the stereocenter is not involved.

Step 18

Reactants: **20** (2S)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropan-1-ol
Product: **21** tert-butyl[(2R)-3-iodo-2-methylpropoxy]dimethylsilane
Conditions: I2, PPh3, imidazole, CH2Cl2, 0 → 25 °C
Why: Appel iodination of the primary alcohol.

Step 19

Reactants: **21** tert-butyl[(2R)-3-iodo-2-methylpropoxy]dimethylsilane
Product: **22** [(2R)-3-(tert-butyldimethylsilyloxy)-2-methylpropyl]triphenylphosphonium iodide
Conditions: PPh3 (1.5 equiv), i-Pr2NEt, MeCN, 80 °C, 48 h
Why: SN2 of triphenylphosphine on the β-branched primary iodide gives the phosphonium salt (a known building block).

Step 20

Reactants: **22** [(2R)-3-(tert-butyldimethylsilyloxy)-2-methylpropyl]triphenylphosphonium iodide; **17** (3R)-3-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]butanal
Product: **23** tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,4Z,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylhept-4-en-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane
Conditions: 22 (1.5 equiv), KHMDS, THF, −78 → 0 °C; then 17, −78 → 25 °C
Why: Wittig olefination with the unstabilised ylide joins C13–C14 as the (Z)-alkene (geometry irrelevant, hydrogenated next); no stereocenter is touched.

Step 21

Reactants: **23** tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,4Z,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylhept-4-en-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane
Product: **24** tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylheptan-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (complete C20 half, C1-OTBDPS / C16-OTBS)
Conditions: H2 (1 atm), Pd/C (10 %), EtOAc, 25 °C
Why: Hydrogenation of the disubstituted alkene completes the C20 half with all five stereocenters set.

Step 22

Reactants: **24** tert-butyl({(3R)-6-[(1S,3S)-3-{(2R,6S)-7-[(tert-butyldimethylsilyl)oxy]-6-methylheptan-2-yl}cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (complete C20 half, C1-OTBDPS / C16-OTBS)
Product: **25** (2S,6R)-6-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]-2-methylheptan-1-ol
Conditions: PPTS (0.3 equiv), MeOH, 25 °C, 24 h
Why: Mild acid removes the primary TBS ether selectively in the presence of the primary TBDPS ether.

Step 23

Reactants: **25** (2S,6R)-6-[(1S,3S)-3-{(4R)-6-[(tert-butyldiphenylsilyl)oxy]-4-methylhexyl}cyclopentyl]-2-methylheptan-1-ol
Product: **26** tert-butyl({(3R)-6-[(1S,3S)-3-[(2R,6S)-7-iodo-6-methylheptan-2-yl]cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (C20 iodide)
Conditions: I2, PPh3, imidazole, CH2Cl2, 0 → 25 °C
Why: Appel iodination of the β-branched primary alcohol gives the coupling partner.

Step 24

Reactants: **26** tert-butyl({(3R)-6-[(1S,3S)-3-[(2R,6S)-7-iodo-6-methylheptan-2-yl]cyclopentyl]-3-methylhexyl}oxy)diphenylsilane (C20 iodide)
Product: **27** 1,32-bis[(tert-butyldiphenylsilyl)oxy] ether of diol 28 (C2-symmetric C40 chain)
Conditions: 26 (0.5 equiv) + Mg (I2 cat.), THF, 40 °C → RMgI; then 26 (0.5 equiv), Li2CuCl4 (5 mol %), THF, −20 → 25 °C
Why: Tamura–Kochi Cu-catalysed sp3–sp3 coupling of the Grignard with the iodide forms the central C16–C17 bond; because both partners are the same compound, cross- and homo-coupling converge on the single C2-symmetric C40 chain and no stereocenter is involved.

Step 25

Reactants: **27** 1,32-bis[(tert-butyldiphenylsilyl)oxy] ether of diol 28 (C2-symmetric C40 chain)

Product: **28** (3R,7S,10S,11R,15S,18S,22R,23S,26S,30R)-3,11,15,18,22,30-hexamethyl-7,10:23,26-dimethanodotriacontane-1,32-diol (biphytane-1,32-diol with two trans-1,3-cyclopentane rings; C2-symmetric)

Conditions: TBAF (2.5 equiv), THF, 25 °C

Why: Fluoride removes both TBDPS groups to give the C40 diol.

Step 26

Reactants: **28** (3R,7S,10S,11R,15S,18S,22R,23S,26S,30R)-3,11,15,18,22,30-hexamethyl-7,10:23,26-dimethanodotriacontane-1,32-diol (biphytane-1,32-diol with two trans-1,3-cyclopentane rings; C2-symmetric)

Product: **29** 1,32-bis(trifluoromethanesulfonate) of diol 28

Conditions: Tf2O (2.4 equiv), 2,6-lutidine, CH2Cl2, −30 °C; used directly

Why: Triflate activation of the two unhindered primary alcohols.

Step 27

Reactants: **30** (S)-3-(benzyloxy)propane-1,2-diol [1-O-benzyl-sn-glycerol, commercial]

Product: **31** (2R)-1-(benzyloxy)-3-[(tert-butyldiphenylsilyl)oxy]propan-2-ol

Conditions: TBDPSCl (1.05 equiv), imidazole, DMAP (cat.), CH2Cl2, 0 °C

Why: Selective silylation of the less hindered primary OH of (S)-1-O-benzylglycerol leaves the secondary OH free; the glycerol stereocenter (target C2 of each glycerol) comes from this commercial material.

Step 28

Reactants: **29** 1,32-bis(trifluoromethanesulfonate) of diol 28; **31** (2R)-1-(benzyloxy)-3-[(tert-butyldiphenylsilyl)oxy]propan-2-ol

Product: **32** bis(glycerol) diether: the C40 chain of 28 linked through both termini to the secondary (sn-2) oxygens of two units of 31 [1,32-bis{[(2R)-1-(benzyloxy)-3-(TBDPS-oxy)propan-2-yl]oxy} derivative of 28]

Conditions: 31 (3 equiv), NaH (3 equiv), THF/DMF 4:1, 0 °C; then 29, 0 → 25 °C

Why: Double Williamson etherification with excess secondary alkoxide converts both triflates; the bond is made at oxygen so the (R)-glycerol stereocenters are retained.

Step 29

Reactants: **32** bis(glycerol) diether: the C40 chain of 28 linked through both termini to the secondary (sn-2) oxygens of two units of 31 [1,32-bis{[(2R)-1-(benzyloxy)-3-(TBDPS-oxy)propan-2-yl]oxy} derivative of 28]

Product: **33** desilylated 32: 1,32-bis{[(2S)-1-(benzyloxy)-3-hydroxypropan-2-yl]oxy} derivative of 28 (two free primary OH)

Conditions: TBAF (2.5 equiv), THF, 25 °C

Why: Fluoride unmasks the two primary (sn-3) alcohols for the ring closure.

Step 30

Reactants: **33** desilylated 32: 1,32-bis{[(2S)-1-(benzyloxy)-3-hydroxypropan-2-yl]oxy} derivative of 28 (two free primary OH); **29** 1,32-bis(trifluoromethanesulfonate) of diol 28

Product: **34** 1,1'-di-O-benzyl macrocyclic tetraether (di-O-benzyl ether of the target; 72-membered ring)

Conditions: NaH (10 equiv), THF/DMF 1:1, 60 °C; 33 + 29 (1:1) added by syringe pump over 12 h, final 1 mM

Why: The first etherification is intermolecular and the second intramolecular, closing the 72-membered ring under pseudo-high dilution; all twenty-two stereocenters are untouched.

Step 31

Reactants: **34** 1,1'-di-O-benzyl macrocyclic tetraether (di-O-benzyl ether of the target; 72-membered ring)

Product: **35** target: GDGT-4, the 72-membered glycerol dibiphytanyl glycerol tetraether with four trans-1,3-cyclopentane rings, (R,R)-glycerols, C86H164O6

Conditions: H2 (1 atm), Pd(OH)2/C, EtOAc/EtOH 1:1, 25 °C

Why: Hydrogenolysis of the two benzyl ethers liberates the sn-1 hydroxymethyl groups and delivers the target.

Self-check

Changed after checking: the C16 protecting group was switched from PMB to TBS because PMB would not survive the Pd/C hydrogenation of step 21; the ring-alkene hydrogenation was moved before the mesylate/cyanide steps so the SN2 is done on a saturated cyclopentyl mesylate; and the starting-material enantiomers were fixed by CIP analysis of the target [(1S,4R)-monoacetate, (R)-Roche ester, (S)-1-O-benzylglycerol, (R)-citronellol] – the forward route was then rebuilt in silico and the last product is identical to the target (C86H164O6, all 22 stereocenters, both ring relationships trans).

Summary

Total steps: 31 (35 numbered compounds, 4 commercial chiral starting materials). Longest linear sequence: 25 steps, from (R)-citronellol (1) to the target (35).

Most likely to fail, with fallback:

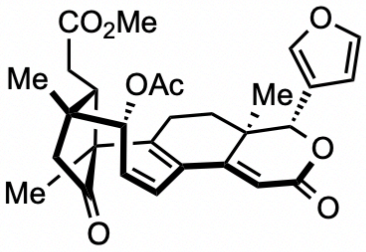
• Step 11 (cyanide SN2 on the cyclopentyl mesylate; E2 elimination competes): fallback – displace the corresponding triflate with Bu4NCN in MeCN at −40 → 0 °C, or use Mitsunobu cyanation (acetone cyanohydrin, DEAD, PPh3) of alcohol 11, both with inversion.

• Step 14 (Cu/Josiphos methyl addition next to the ring stereocenter; diastereoselectivity may erode): fallback – make the methyl ketone from nitrile 13 (MeMgBr, then hydrolysis), HWE to the (E)-β,β-disubstituted enoate and CuH/(R)-DTBM-SEGPHOS asymmetric conjugate reduction; or separate the C11 epimers of 17 by chromatography.

• Step 30 (72-membered double Williamson; oligomerisation and E2 lower the yield): fallback – convert 28 into the bis-iodide, use KH/18-crown-6 in THF at 60 °C with slow addition, or isolate the mono-etherified linear intermediate (excess 29) and cyclise it separately.

Triconnarin D (Newhouse laboratory)

Triconnarin D is a natural product with six stereocenters, three of them all-carbon quaternary centers. It has been made in the Newhouse laboratory, and that synthesis is not yet published.



methyl 2-((4*R*,4a*R*,7*S*,10*R*,14*S*,*Z*)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[*f*]isochromen-14-yl)acetate
Chemical Formula: $C_{29}H_{32}O_8$

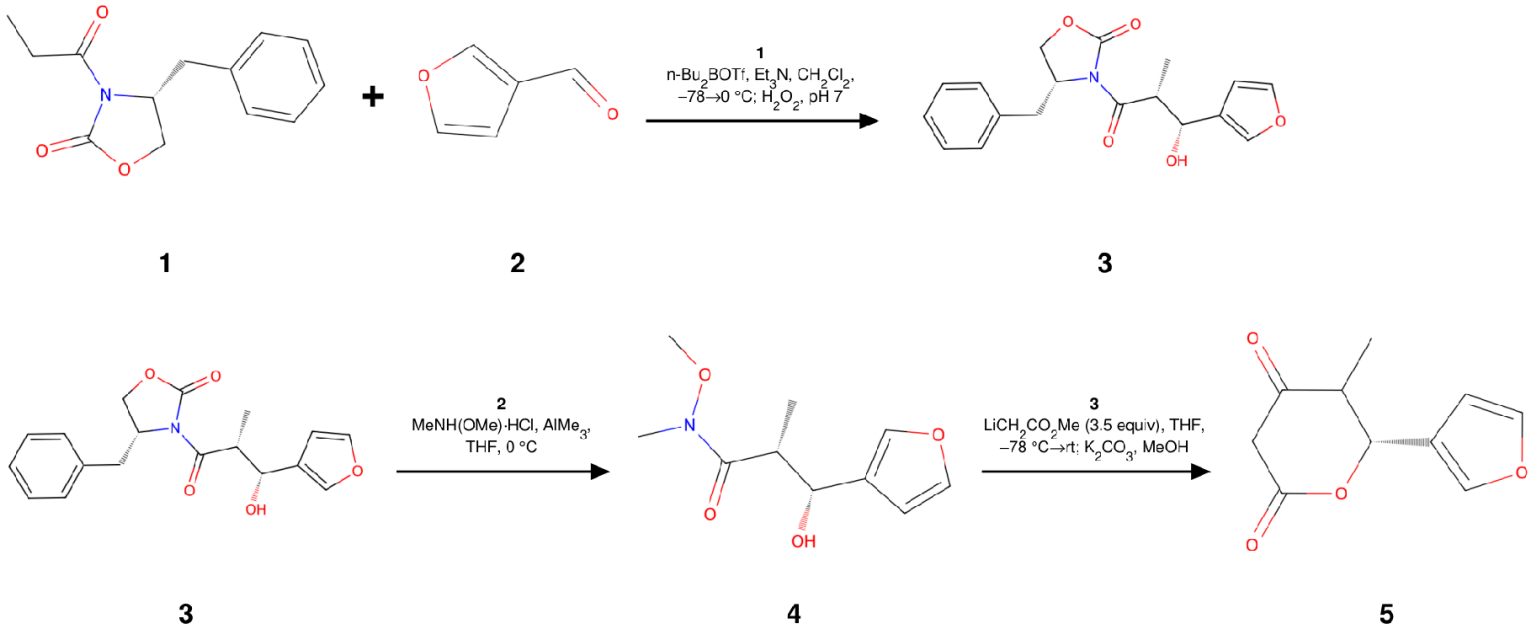
The drawing as Professor Newhouse sent it and as the models received it.

Route document	Steps
Opus 5.5's route to triconnarin D	31
Mythos 5.2's route to triconnarin D	27
Mythos 5.1's route to triconnarin D	29

Proposed total synthesis of methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate (37), $C_{29}H_{32}O_8$

Compound numbers are under the structures; the bold step number heads the conditions over each arrow. Wedges and hashes show absolute configuration; a plain bond at a stereocentre marks an epimer mixture (5 at C5, 17–20 at the carbinol carbon, 33 at C11). Atom labels such as C7, C11 or C13b follow the fused-ring numbering of the target name. TBS = t-BuMe$_2$Si, TBDPS = t-BuPh$_2$Si, TMS = Me$_3$Si, Tf = CF$_3$SO$_2$. The bridged compounds 33–37 are laid out differently from the supplied picture, so a few centres show a wedge where that picture has a hash (for example the 11-OAc); each drawing was checked to encode the configuration given by the CIP descriptors in the text and table (4R,4aR,7S,10R,11R,14S,Z for 37).

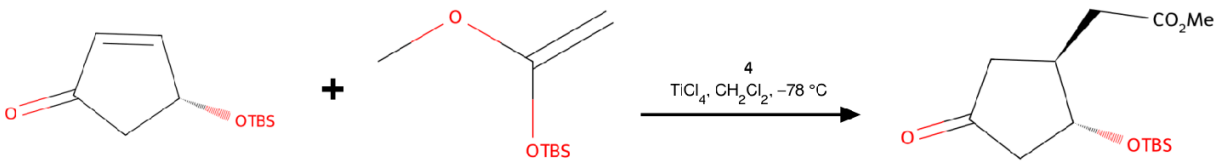
Fragment A: ring-D β-keto lactone



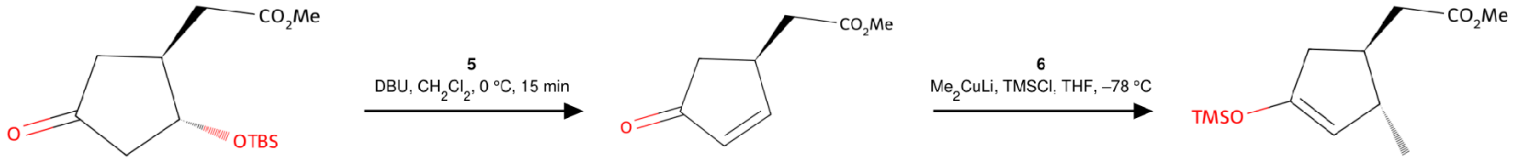
1 **2** **3**

3 **4** **5**

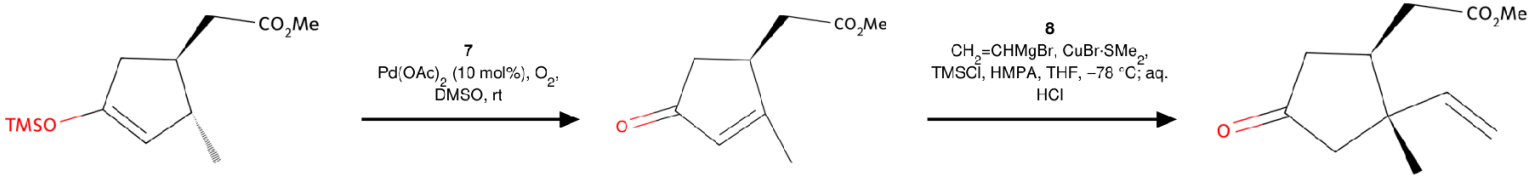
Fragment B: cyclopentane core (C14, then C10, then C7, each anti to the C14 side chain)



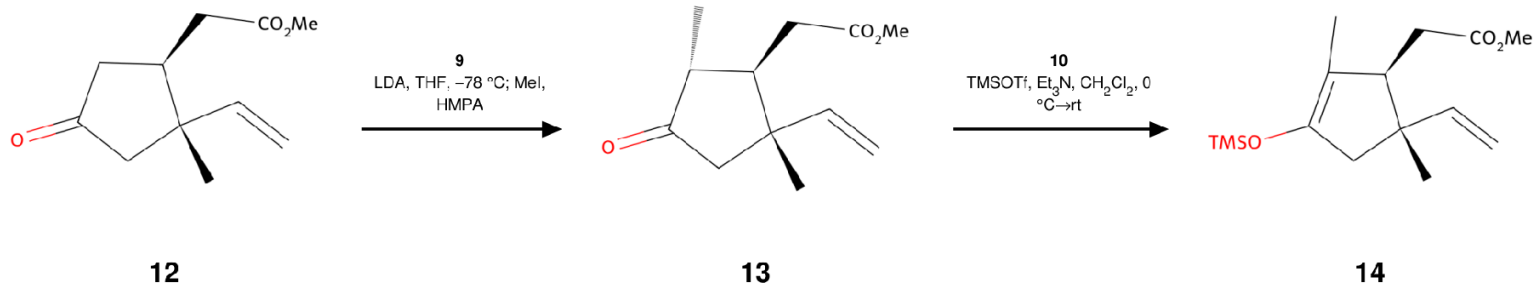
6 **7** **8**



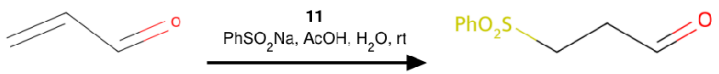
8 **9** **10**



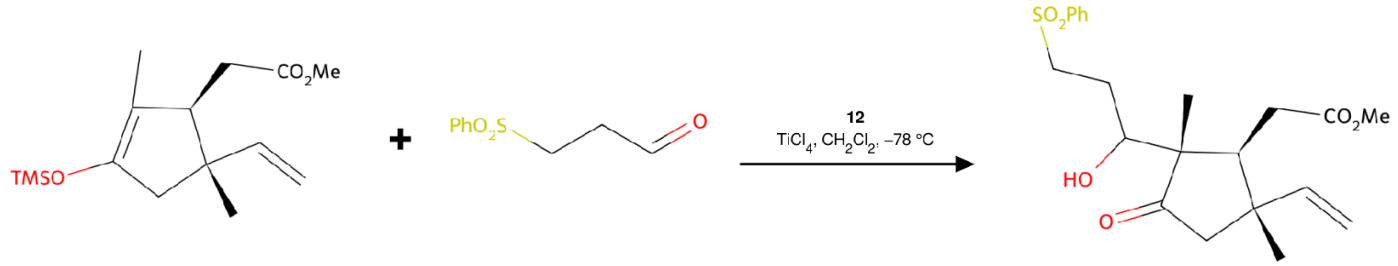
10 **11** **12**



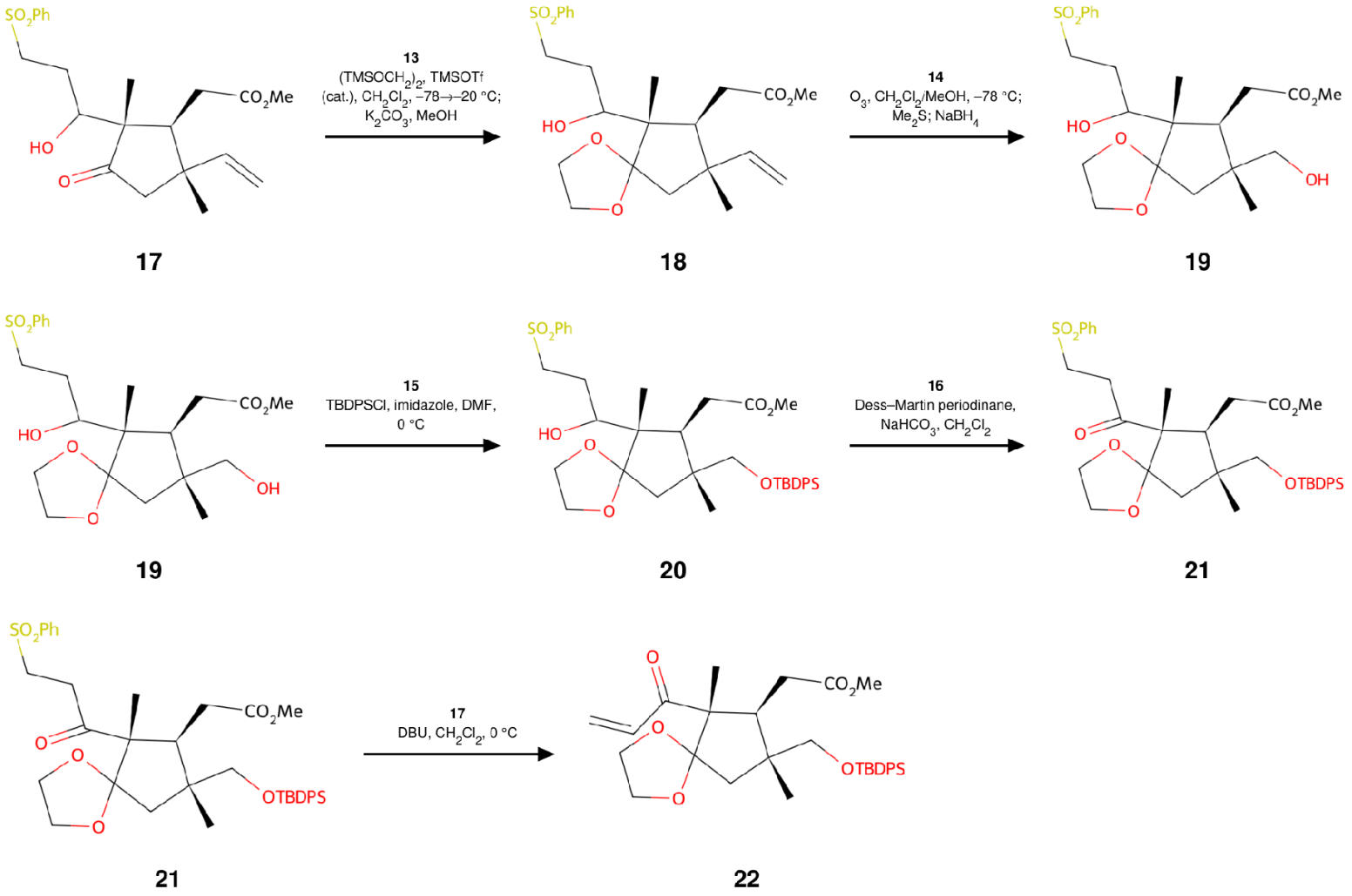
12 13 14



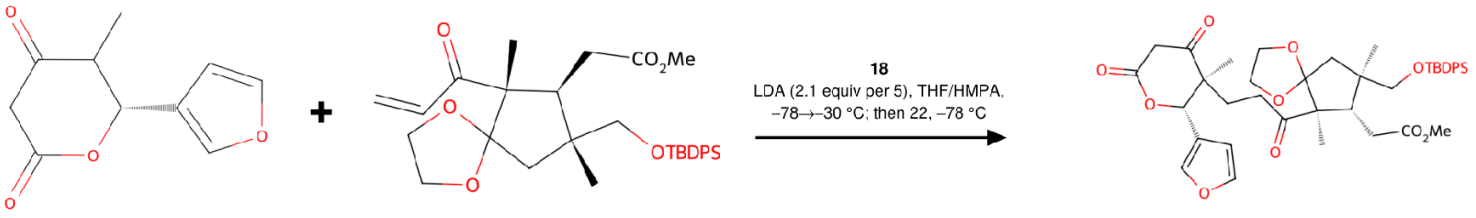
15 16



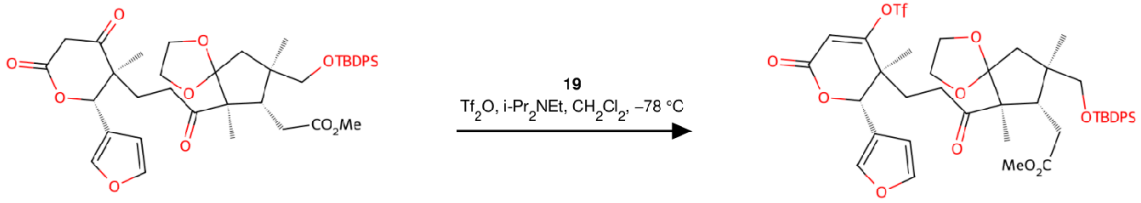
14 16 17


SO2Ph
CO2Me
HO
O
13
(TMSOCH2)2, TMSOTf
(cat.), CH2Cl2, −78→−20 °C;
K2CO3, MeOH
17
18
14
O3, CH2Cl2/MeOH, −78 °C;
Me2S; NaBH4
OH
19
15
TBDPSCl, imidazole, DMF,
0 °C
OTBDPS
20
16
Dess–Martin periodinane,
NaHCO3, CH2Cl2
21
17
DBU, CH2Cl2, 0 °C
22

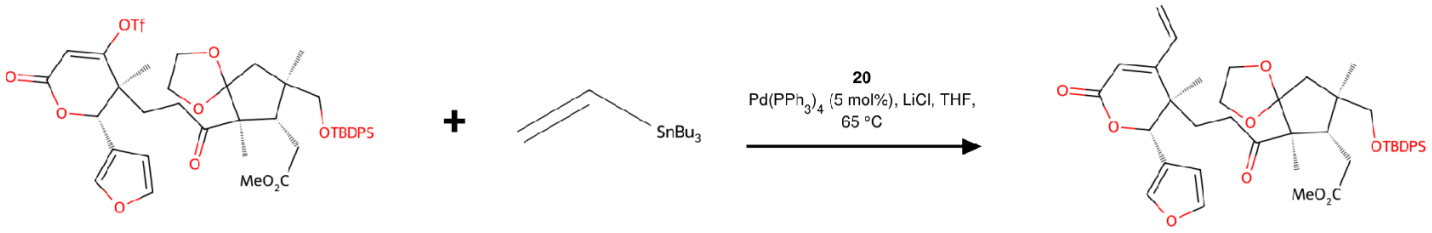
Coupling, ring C, eight-membered ring and end-game



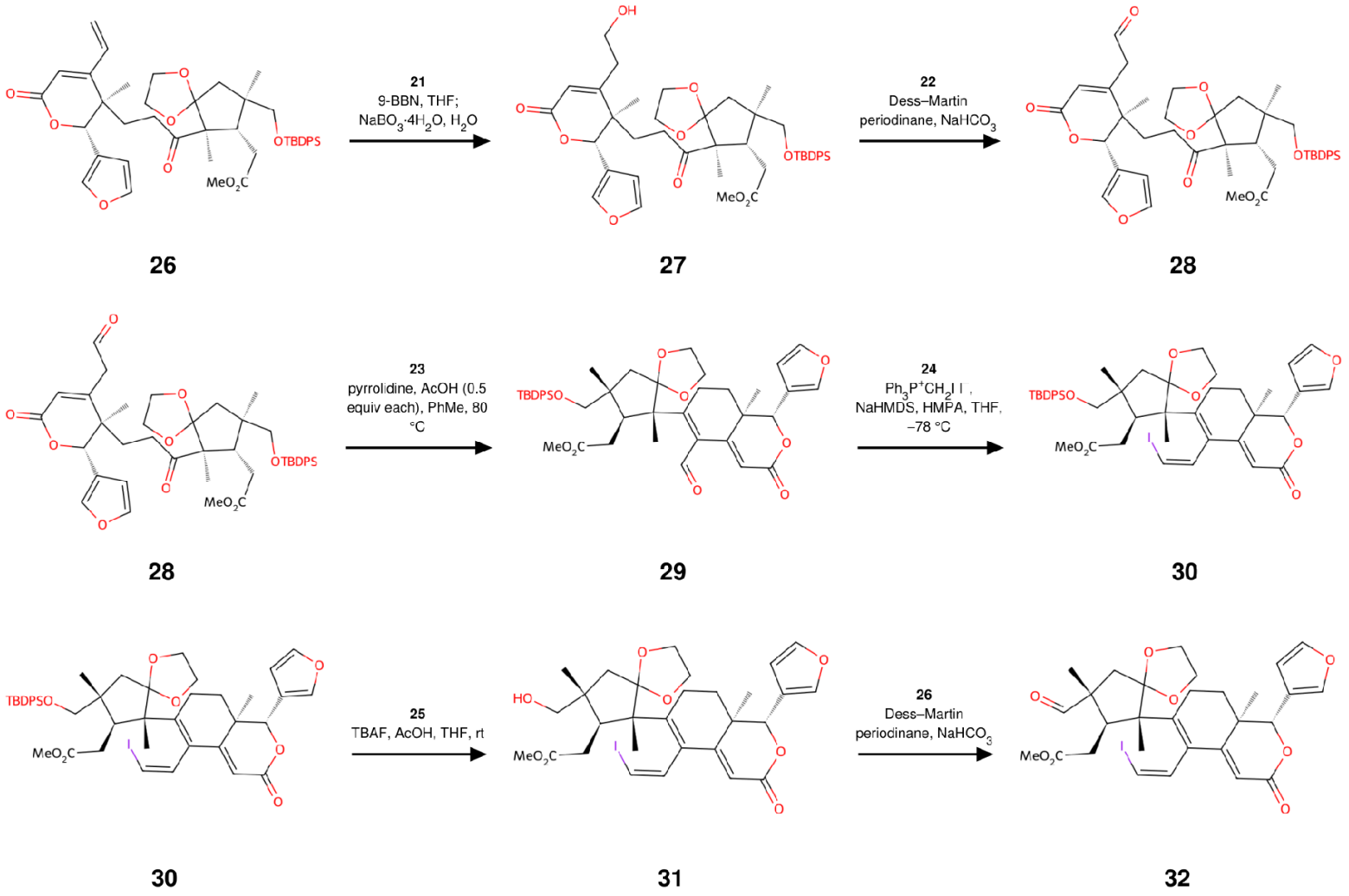
5 **22** **23**

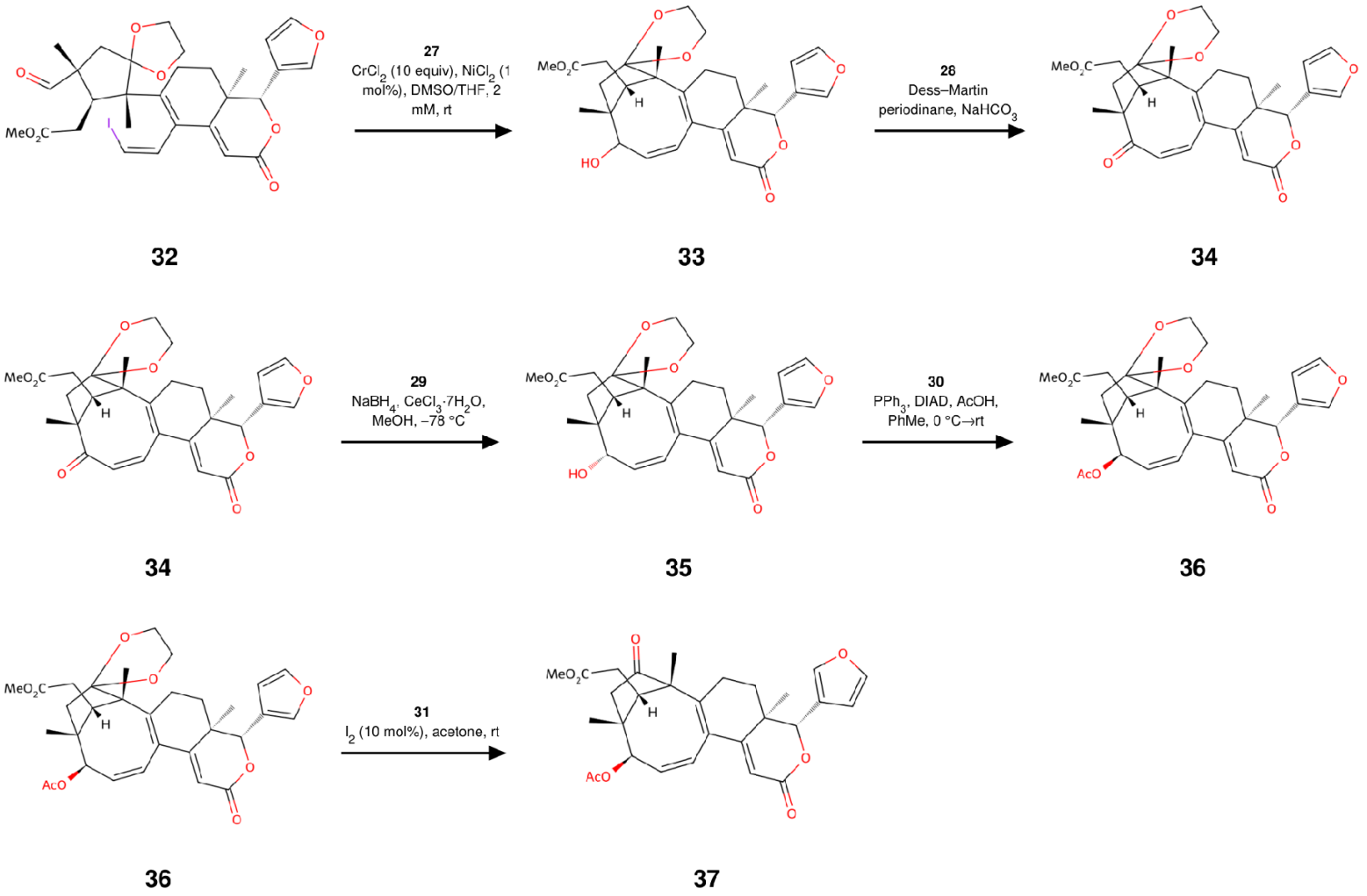


23 **24**



24 **25** **26**


21
9-BBN, THF;
NaBO3·4H2O, H2O
22
Dess–Martin
periodinane, NaHCO3
23
pyrrolidine, AcOH (0.5
equiv each), PhMe, 80
°C
24
Ph3P+CH2I I−,
NaHMDS, HMPA, THF,
–78 °C
25
TBAF, AcOH, THF, rt
26
Dess–Martin
periodinane, NaHCO3
OTBDPS
OH
TBDPSO
HO
MeO2C
26
27
28
28
29
30
30
31
32


27
CrCl2 (10 equiv), NiCl2 (1 mol%), DMSO/THF, 2 mM, rt
28
Dess–Martin periodinane, NaHCO3
29
NaBH4, CeCl3·7H2O, MeOH, –78 °C
30
PPh3, DIAD, AcOH, PhMe, 0 °C→rt
31
I2 (10 mol%), acetone, rt
32
33
34
34
35
36
36
37

Retrosynthetic overview

1. 37 ⇒ 36 ⇒ 35 ⇒ 34: unmask the C8 ketone last; make the 11R acetate by Mitsunobu inversion of the 11S alcohol that comes from face-selective reduction of the C11 ketone.

2. C11–C12 (intramolecular Nozaki–Hiyama–Kishi) ⇒ (Z)-dienyl iodide/aldehyde 32: the eight-membered bridge is closed last, across the cis-1,3 arms (C6a, C11) of the cyclopentane.

3. Ring C: C6a=C13a (intramolecular aldol condensation) and C13b–C13a (Stille vinylation of an enol triflate, then hydroboration–oxidation) ⇒ the 1,5-dicarbonyl compound 23.

4. C4a–C5 (γ-selective Michael addition of a β-keto-lactone dianion) ⇒ ring-D lactone 5 (from an Evans aldol of 3-furaldehyde) + vinyl ketone 22.

5. 22 is built from (R)-4-TBSO-cyclopentenone 6, setting C14, C10 and C7 in that order, each anti to the C14 side chain. Rings form in the order D, then C, then the eight-membered ring (the cyclopentane comes from 6; the C8 dioxolane is only a protecting group).

Assumptions

The name gives no descriptor for C11; it is assigned 11R from the hashed OAc in the drawing (OAc behind the page, C12 below, C10 to the left). All other descriptors (4R,4aR,7S,10R,14S,Z) are taken from the name.

Starting materials 1, 2, 6, 7, 15 and 25 are standard catalogue chemicals. Simple reagents (MeI, MeOAc, Me_2CuLi, vinylmagnesium bromide, $Ph_3P^+CH_2\,I^-$ and so on) are listed under Conditions and are not numbered.

The face selectivities claimed for steps 12, 29 and 30 rest on MMFF conformer searches with a simple steric probe (compounds 14 and 34), not on transition-state calculations.

Route (forward direction)

Fragment A: ring-D β-keto lactone 5

Step 1

Reactants: **1** (R)-4-benzyl-3-propanoyl-1,3-oxazolidin-2-one; **2** furan-3-carbaldehyde

Product: **3** (R)-4-benzyl-3-[(2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one

Conditions: n-Bu_2BOTf (1.1 equiv), Et_3N (1.3 equiv), CH_2Cl_2, –78 °C → 0 °C; then 2, –78 °C → 0 °C; pH 7 buffer, 30% H_2O_2, MeOH, 0 °C

Why: The (Z)-boron enolate reacts through a Zimmerman–Traxler chair with the aldehyde approaching away from the benzyl group (Evans syn aldol), so the (R)-auxiliary sets the future furyl carbinol C4 as R (and C2' as R).

Step 2

Reactants: **3** (R)-4-benzyl-3-[(2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one

Product: **4** (2R,3R)-3-(furan-3-yl)-3-hydroxy-N-methoxy-N,2-dimethylpropanamide

Conditions: MeNH(OMe)·HCl (3 equiv), $AlMe_3$ (3 equiv), THF, 0 °C

Why: The aluminium amide cleaves only the exocyclic imide C–N bond (auxiliary recovered) and tolerates the free β-OH; no stereocentre is touched.

Step 3

Reactants: **4** (2R,3R)-3-(furan-3-yl)-3-hydroxy-N-methoxy-N,2-dimethylpropanamide

Product: **5** (6R)-6-(furan-3-yl)-5-methyldihydro-2H-pyran-2,4(3H)-dione (C5 epimers; largely the 4-hydroxy-5,6-dihydro-2-pyrone enol)

Conditions: $LiCH_2CO_2Me$ (3.5 equiv, from MeOAc and LDA), THF, –78 °C → rt; then K_2CO_3, MeOH, rt; aq. HCl work-up

Why: The ester enolate turns the Weinreb amide into a δ-alkoxy β-keto ester that closes to the six-membered lactone; C6 (future C4) is retained, while the methyl-bearing C5 (future C4a) is epimerizable and is reset in step 18.

Fragment B: cyclopentane vinyl ketone 22

Step 4

Reactants: **6** (R)-4-[(tert-butyldimethylsilyl)oxy]cyclopent-2-en-1-one; **7** tert-butyl[(1-methoxyethenyl)oxy]dimethylsilane

Product: **8** methyl 2-[(1S,2R)-2-[(tert-butyldimethylsilyl)oxy]-4-oxocyclopentyl]acetate

Conditions: 7 (1.5 equiv), $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 °C; aq. $NaHCO_3$

Why: The Mukaiyama–Michael addition occurs anti to the C4-OTBS group, creating the future C14 stereocentre trans to OTBS.

Step 5

Reactants: **8** methyl 2-[(1S,2R)-2-[(tert-butyldimethylsilyl)oxy]-4-oxocyclopentyl]acetate

Product: **9** methyl 2-[(1S)-4-oxocyclopent-2-en-1-yl]acetate

Conditions: DBU (1.1 equiv), CH_2Cl_2, 0 °C, 15 min

Why: E1cB loss of $TBSO^-$ restores the enone; the ester-bearing centre takes no part, and a short, cold exposure to DBU avoids γ-deprotonation.

Step 6

Reactants: **9** methyl 2-[(1S)-4-oxocyclopent-2-en-1-yl]acetate

Product: **10** methyl 2-[(1S,2S)-2-methyl-4-[(trimethylsilyl)oxy]cyclopent-3-en-1-yl]acetate

Conditions: Me_2CuLi (1.5 equiv), TMSCl (3 equiv), THF, –78 °C

Why: The cuprate adds anti to the side chain and the enolate is trapped as a single silyl enol ether regioisomer; the new methyl-bearing centre is destroyed again in step 7.

Step 7

Reactants: **10** methyl 2-[(1S,2S)-2-methyl-4-[(trimethylsilyl)oxy]cyclopent-3-en-1-yl]acetate

Product: **11** methyl 2-[(1S)-2-methyl-4-oxocyclopent-2-en-1-yl]acetate

Conditions: $Pd(OAc)_2$ (10 mol%), O_2 (1 atm), DMSO, rt

Why: Saegusa-type oxidation of this regiodefined enol ether gives the 3-methyl enone (future C10 methyl) and leaves C14 untouched.

Step 8

Reactants: **11** methyl 2-[(1S)-2-methyl-4-oxocyclopent-2-en-1-yl]acetate

Product: **12** methyl 2-[(1S,2S)-2-ethenyl-2-methyl-4-oxocyclopentyl]acetate

Conditions: CH_2=CHMgBr (2 equiv), CuBr·SMe_2 (1 equiv), TMSCl, HMPA, THF, –78 °C; then 1 M HCl, THF

Why: The vinyl cuprate adds to the β,β-disubstituted enone anti to the neighbouring CH_2CO_2Me, creating quaternary C10 with the vinyl group (future C11) trans to the side chain, as the bridge requires.

Step 9

Reactants: **12** methyl 2-[(1S,2S)-2-ethenyl-2-methyl-4-oxocyclopentyl]acetate

Product: **13** methyl 2-[(1R,2S,5R)-2-ethenyl-2,5-dimethyl-4-oxocyclopentyl]acetate (the C5 configuration is irrelevant)

Conditions: LDA (1.05 equiv), THF, –78 °C; MeI (3 equiv), HMPA, –78 °C → –40 °C

Why: Kinetic deprotonation occurs at the α-CH_2 remote from quaternary C10 (future C7); the new methyl-bearing centre is epimerizable and is fixed in step 12.

Step 10

Reactants: **13** methyl 2-[(1R,2S,5R)-2-ethenyl-2,5-dimethyl-4-oxocyclopentyl]acetate (the C5 configuration is irrelevant)

Product: **14** methyl 2-[(1S,5S)-5-ethenyl-2,5-dimethyl-3-[(trimethylsilyl)oxy]cyclopent-2-en-1-yl]acetate

Conditions: TMSOTf (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C → rt

Why: Equilibrating silylation gives the more substituted (tetrasubstituted) enol ether toward C7.

Step 11
Reactants: **15** prop-2-enal (acrolein)
Product: **16** 3-(benzenesulfonyl)propanal
Conditions: $PhSO_2Na$ (1.2 equiv), AcOH, H_2O, rt
Why: Benzenesulfinate adds 1,4 to acrolein; the sulfone survives ozone and Lewis acids and later serves as a masked vinyl group.

Step 12
Reactants: **14** methyl 2-[(1S,5S)-5-ethenyl-2,5-dimethyl-3-[(trimethylsilyl)oxy]cyclopent-2-en-1-yl]acetate; **16** 3-(benzenesulfonyl)propanal
Product: **17** methyl 2-[(1S,2S,5S)-2-[3-(benzenesulfonyl)-1-hydroxypropyl]-5-ethenyl-2,5-dimethyl-3-oxocyclopentyl]acetate (carbinol epimers)
Conditions: 16 (1.3 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, –78 °C; quench with aq. $NaHCO_3$ at –78 °C
Why: The Mukaiyama aldol builds quaternary C7 from the face anti to the adjacent C14 side chain (the more open face in all low-energy MMFF conformers of 14, whose C10 carries only a small vinyl group), so the new C6a branch is trans to CH_2CO_2Me and cis to the future C11; the carbinol epimers do not matter.

Step 13
Reactants: **17** methyl 2-[(1S,2S,5S)-2-[3-(benzenesulfonyl)-1-hydroxypropyl]-5-ethenyl-2,5-dimethyl-3-oxocyclopentyl]acetate (carbinol epimers)
Product: **18** methyl 2-[(6S,7S,8S)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-ethenyl-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Conditions: $(TMSOCH_2)_2$ (3 equiv), TMSOTf (0.1 equiv), CH_2Cl_2, –78 °C → –20 °C; pyridine quench; then K_2CO_3, MeOH, rt
Why: Noyori conditions ketalize the hindered cyclopentanone without acid-promoted retro-aldol, and the carbinol O-TMS ether formed on the way is cleaved by K_2CO_3/MeOH.

Step 14
Reactants: **18** methyl 2-[(6S,7S,8S)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-ethenyl-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Product: **19** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-(hydroxymethyl)-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Conditions: O_3, CH_2Cl_2/MeOH (4:1), –78 °C; Me_2S; then $NaBH_4$, 0 °C
Why: Ozone cleaves the only alkene (the C10 vinyl group) and $NaBH_4$ reduces the aldehyde to the future C11 hydroxymethyl group; sulfone, ketal and ester are inert.

Step 15
Reactants: **19** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-(hydroxymethyl)-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Product: **20** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Conditions: TBDPSCl (1.1 equiv), imidazole, DMF, 0 °C
Why: The primary alcohol is silylated much faster than the neopentyl secondary carbinol.

Step 16
Reactants: **20** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)-1-hydroxypropyl]-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate (carbinol epimers)
Product: **21** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)propanoyl]-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate
Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt
Why: Buffered oxidation gives the C6a ketone; no stereocentre is formed.

Step 17

Reactants: **21** methyl 2-[(6S,7S,8R)-6-[3-(benzenesulfonyl)propanoyl]-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **22** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-6-(prop-2-enoyl)-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: DBU (1.5 equiv), CH_2Cl_2, 0 °C (crude 22 used at once)

Why: DBU triggers E1cB loss of benzenesulfinate from the β-sulfonyl ketone, unmasking the vinyl ketone Michael acceptor.

Coupling, ring C, the eight-membered ring and the end-game

Step 18

Reactants: **5** (6R)-6-(furan-3-yl)-5-methyldihydro-2H-pyran-2,4(3H)-dione (C5 epimers; largely the 4-hydroxy-5,6-dihydro-2-pyrone enol); **22** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6,8-dimethyl-6-(prop-2-enoyl)-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **23** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-4,6-dioxooxan-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: 5 (1.3 equiv), LDA (2.7 equiv), THF, HMPA, −78 °C → −30 °C (dianion); then 22, −78 °C; sat. NH_4Cl

Why: The dianion of 5 reacts at its terminal γ-carbon (C4a) from the face anti to the neighbouring furyl group, so the new C4a–C5 bond is trans to the furan and the C4a methyl is cis to it, as in the target.

Step 19

Reactants: **23** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-4,6-dioxooxan-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **24** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-[(trifluoromethanesulfonyl)oxy]-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: Tf_2O (1.1 equiv), i-Pr_2NEt (2.5 equiv), CH_2Cl_2, −78 °C

Why: The enolized β-keto lactone (a vinylogous acid) is triflated far faster than the hindered C6a ketone, and because C4a is quaternary the enol triflate can only form toward C1.

Step 20

Reactants: **24** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-[(trifluoromethanesulfonyl)oxy]-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate; **25** tributyl(ethenyl)stannane (vinyltributyltin)

Product: **26** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-4-ethenyl-2-(furan-3-yl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: 25 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), LiCl (3 equiv), THF, 65 °C

Why: The Stille coupling runs under neutral conditions and installs the vinyl group (future C13a–C13) at C13b without touching the lactone, ester, ketal or silyl ether.

Step 21

Reactants: **26** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-4-ethenyl-2-(furan-3-yl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **27** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-2-(furan-3-yl)-4-(2-hydroxyethyl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: 9-BBN (1.3 equiv), THF, 0 °C → rt; then $NaBO_3 \cdot 4H_2O$, H_2O/THF, rt

Why: 9-BBN adds to the terminal vinyl group of the diene with boron on the terminal carbon, and perborate oxidation gives the primary alcohol without hydrolysing the lactone or ester.

Step 22

Reactants: **27** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-2-(furan-3-yl)-4-(2-hydroxyethyl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **28** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-2-(furan-3-yl)-3-methyl-6-oxo-4-(2-oxoethyl)-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C

Why: Buffered oxidation gives aldehyde 28, which is used directly.

Step 23

Reactants: **28** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-{3-[(2R,3R)-2-(furan-3-yl)-3-methyl-6-oxo-4-(2-oxoethyl)-3,6-dihydro-2H-pyran-3-yl]propanoyl}-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **29** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-[(1R,8aR)-5-formyl-1-(furan-3-yl)-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: pyrrolidine (0.5 equiv), AcOH (0.5 equiv), PhMe (0.05 M), 80 °C

Why: The aldehyde-derived dienamine attacks the C6a ketone to close the fused six-membered ring C (attack through C1 would have to form a strained bridged ring), and dehydration gives the fully substituted, fully conjugated ring-C dienal, so no stereocentre is formed.

Step 24

Reactants: **29** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-[(1R,8aR)-5-formyl-1-(furan-3-yl)-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **30** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: $Ph_3P^+CH_2I\ I^-$ (2 equiv), NaHMDS (1.9 equiv), HMPA, THF, –78 °C (Stork–Zhao)

Why: Stork–Zhao iodomethylenation of the aldehyde is highly Z-selective and fixes the geometry of the future C12=C13 bond.

Step 25

Reactants: **30** methyl 2-[(6S,7S,8R)-8-{[(tert-butyldiphenylsilyl)oxy]methyl}-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **31** methyl 2-[(6S,7S,8R)-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-8-(hydroxymethyl)-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: TBAF (3 equiv), AcOH (3 equiv), THF, rt

Why: Acetic-acid-buffered fluoride removes the TBDPS group without harming the lactone or the ester.

Step 26

Reactants: **31** methyl 2-[(6S,7S,8R)-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-8-(hydroxymethyl)-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **32** methyl 2-[(6S,7S,8R)-8-formyl-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt

Why: Oxidation gives the neopentyl C11 aldehyde for the ring closure.

Step 27
Reactants: **32** methyl 2-[(6S,7S,8R)-8-formyl-6-[(1R,8aR)-1-(furan-3-yl)-5-[(Z)-2-iodoethenyl]-8a-methyl-3-oxo-1,7,8,8a-tetrahydro-3H-isochromen-6-yl]-6,8-dimethyl-1,4-dioxaspiro[4.4]nonan-7-yl]acetate

Product: **33** methyl 2-[(4R,4aR,7S,10R,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate (11R/11S mixture; the C8 ethylene ketal of 11-O-deacetyl-37)

Conditions: $CrCl_2$ (10 equiv), $NiCl_2$ (1 mol%), DMSO/THF (3:1), 0.002 M, rt, slow addition of 32

Why: The intramolecular Nozaki–Hiyama–Kishi reaction joins C12 to C11 at high dilution; it is selective for the aldehyde, keeps the Z alkene, and can close only because C6a and C11 are cis on the cyclopentane; C11 forms as an epimer mixture.

Step 28
Reactants: **33** methyl 2-[(4R,4aR,7S,10R,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate (11R/11S mixture; the C8 ethylene ketal of 11-O-deacetyl-37)

Product: **34** methyl 2-[(4R,4aR,7S,10R,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-4a,7,10-trimethyl-2,11-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt

Why: Oxidation converts both C11 epimers into a single ketone.

Step 29
Reactants: **34** methyl 2-[(4R,4aR,7S,10R,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-4a,7,10-trimethyl-2,11-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Product: **35** methyl 2-[(4R,4aR,7S,10R,11S,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Conditions: $NaBH_4$ (1.5 equiv), $CeCl_3{\cdot}7H_2O$ (1.5 equiv), MeOH, –78 °C

Why: Luche reduction delivers hydride 1,2 from the open face beside the C10 methyl (the other face lies under the one-carbon bridge, C14–H), which gives the 11S alcohol according to an MMFF steric analysis of 34.

Step 30
Reactants: **35** methyl 2-[(4R,4aR,7S,10R,11S,14S,Z)-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Product: **36** methyl 2-[(4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Conditions: PPh_3 (3 equiv), DIAD (3 equiv), AcOH (3 equiv), PhMe, 0 °C → rt

Why: The Mitsunobu displacement by acetate occurs with inversion, from the same open face, to give the 11R acetate; 11R is also the more stable C11 epimer (MMFF, ≈3.6 kcal/mol).

Step 31
Reactants: **36** methyl 2-[(4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-8,8-(ethane-1,2-diyldioxy)-4-(furan-3-yl)-4a,7,10-trimethyl-2-oxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate

Product: **37** methyl 2-[(4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl]acetate (the target)

Conditions: I_2 (10 mol%), acetone, rt

Why: Iodine-catalysed exchange with acetone removes the ketal under essentially neutral conditions that leave the furan, the allylic acetate and the dienoate intact; no stereocentre can epimerize (C7 is quaternary and C14 is β to the ketone).

Changed after checking: the C10 vinyl group is now kept until after the C7 aldol (using an ozone-stable sulfonyl aldehyde), because a C10 $CH_2OTBDPS$ group was predicted to block the required face at C7; C11 is now set by Luche reduction to 11S followed by Mitsunobu acetoxylation, because hydride delivery was predicted to give 11S; and an ethoxyvinyl Suzuki/acid-hydrolysis sequence was replaced by Stille vinylation, hydroboration and oxidation, because acid would remove the C8 ketal first.

Summary

Total step count: 31 (3 for fragment A; 14 for fragment B, including the one-step preparation of 16; 14 for the coupling and end-game).

Longest linear sequence: 27 steps, from 6 to 37 (steps 4–10, 12–31).

The three steps most likely to fail, with one fallback each

1. Step 27, the intramolecular Nozaki–Hiyama–Kishi closure of the bridged eight-membered diene ring. Fallback: close C12=C13 by ring-closing metathesis instead. Make the C13a vinyl group by $Ph_3P{=}CH_2$ olefination of 29 (in place of step 24), add vinylmagnesium bromide to the C11 aldehyde, then run Hoveyda–Grubbs II (PhMe, 80 °C, 1 mM); the ring can only give the Z alkene.

2. Step 23, the aldol condensation onto the very hindered C6a ketone that builds the fully substituted ring-C diene. Fallback: convert 28 into its TBS enol ether (TBSOTf, Et_3N), cyclize by an intramolecular Mukaiyama aldol (TBSOTf cat., CH_2Cl_2, –78 °C), and dehydrate the tertiary alcohol with the Burgess reagent.

3. Step 30, the Mitsunobu acetoxylation of a hindered, allylic neopentyl alcohol (elimination or S_N2' is possible). Fallback: equilibrate C11 through ketone 34 under Meerwein–Ponndorf–Verley/Oppenauer conditions (i-PrOH/acetone, catalytic aluminium biaryl-oxide, rt), which should favour 11R by ≈3.6 kcal/mol (MMFF), then acetylate (Ac_2O, DMAP, Et_3N).

Compound list (formula and stereodescriptor check)

Formula, MW and CIP descriptors were computed from the structures drawn in the scheme (RDKit, new CIP labeller). Descriptors are listed against the target locant of the corresponding atom; they can differ from the target's own descriptors because substituents change CIP priorities. "aux-C4" is C4 of the oxazolidinone. Compound 37 is identical (canonical SMILES) to the target built from the name.

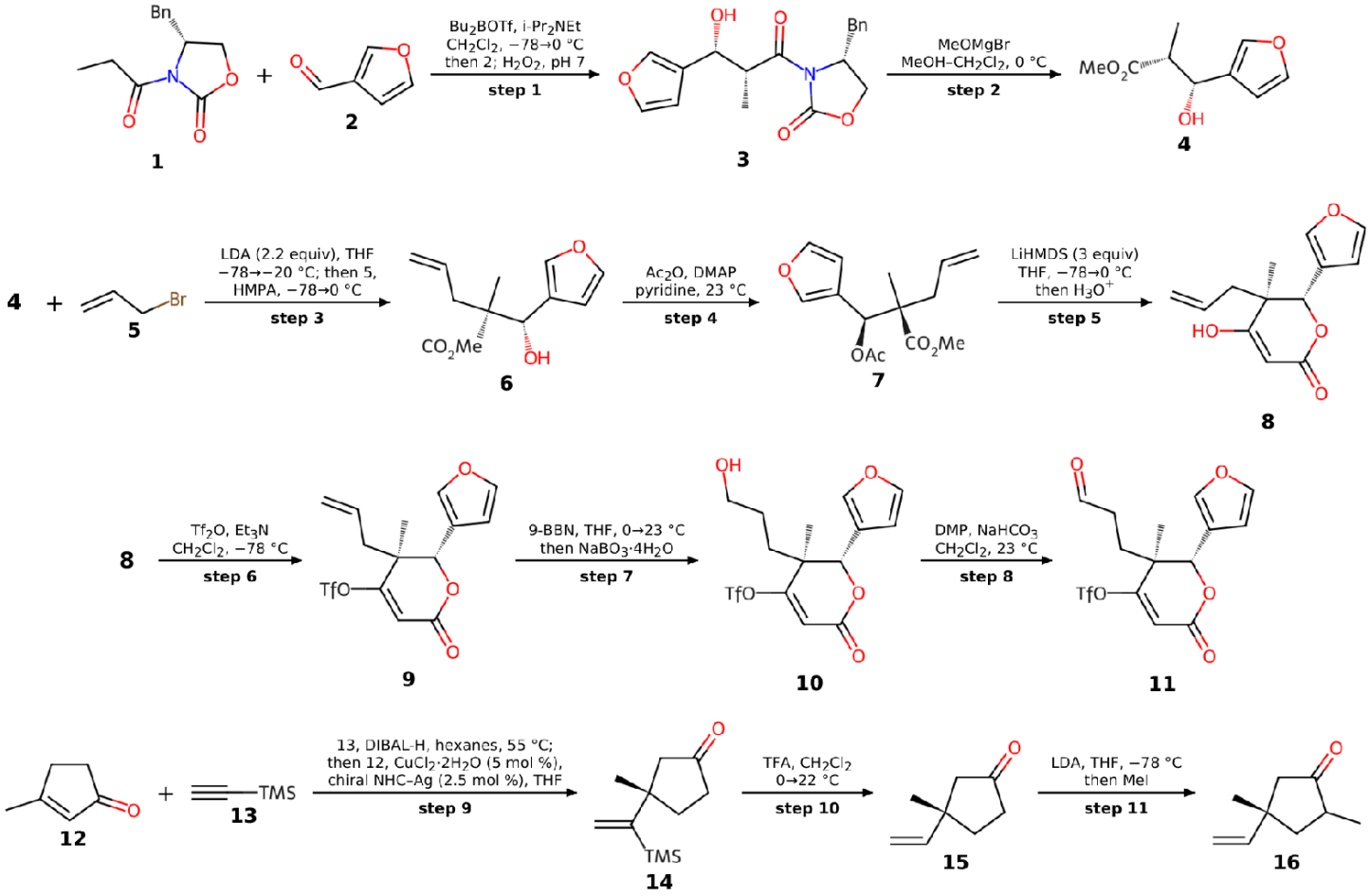
No.	Formula	MW	CIP descriptors (by target locant)	SMILES
1	$C_{13}H_{15}NO_3$	233.27	aux-C4 R	CCC(=O)N1C(=O)OC[C@H]1Cc1ccccc1
2	$C_5H_4O_2$	96.08	–	O=Cc1ccoc1
3	$C_{18}H_{19}NO_5$	329.35	aux-C4 R, C4 R, C4a R	C[C@@H](C(=O)N1C(=O)OC[C@H]1Cc1ccccc1)[C@@H](O)c1ccoc1
4	$C_{10}H_{15}NO_4$	213.23	C4 R, C4a R	CON(C)C(=O)[C@H](C)[C@@H](O)c1ccoc1
5	$C_{10}H_{10}O_4$	194.19	C4 R	CC1C(=O)CC(=O)O[C@H]1c1ccoc1
6	$C_{11}H_{20}O_2Si$	212.36	C10 R	CC(C)(C)[Si](C)(C)O[C@H]1C=CC(=O)C1
7	$C_9H_{20}O_2Si$	188.34	–	C=C(OC)O[Si](C)(C)C(C)(C)C
8	$C_{14}H_{26}O_4Si$	286.44	C10 R, C14 S	COC(=O)C[C@@H]1CC(=O)C[C@H]1O[Si](C)(C)C(C)(C)C
9	$C_8H_{10}O_3$	154.16	C14 S	COC(=O)C[C@H]1C=CC(=O)C1
10	$C_{12}H_{22}O_3Si$	242.39	C10 S, C14 S	COC(=O)C[C@@H]1CC(O[Si](C)(C)C)=C[C@H]1C
11	$C_9H_{12}O_3$	168.19	C14 S	COC(=O)C[C@@H]1CC(=O)C=C1C
12	$C_{11}H_{16}O_3$	196.25	C10 S, C14 S	C=C[C@]1(C)CC(=O)C[C@H]1CC(=O)OC
13	$C_{12}H_{18}O_3$	210.27	C7 R, C10 S, C14 R	C=C[C@]1(C)CC(=O)[C@H](C)[C@H]1CC(=O)OC
14	$C_{15}H_{26}O_3Si$	282.46	C10 S, C14 S	C=C[C@]1(C)CC(O[Si](C)(C)C)=C(C)[C@H]1CC(=O)OC
15	C_3H_4O	56.06	–	C=CC=O
16	$C_9H_{10}O_3S$	198.24	–	O=CCCS(=O)(=O)c1ccccc1
17	$C_{21}H_{28}O_6S$	408.52	C7 S, C10 S, C14 S	C=C[C@]1(C)CC(=O)[C@](C)(C(O)CCS(=O)(=O)c2ccccc2)[C@H]1CC(=O)OC
18	$C_{23}H_{32}O_7S$	452.57	C7 S, C10 S, C14 S	C=C[C@]1(C)CC2(OCCO2)[C@](C)(C(O)CCS(=O)(=O)c2ccccc2)[C@H]1CC(=O)OC
19	$C_{22}H_{32}O_8S$	456.56	C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO)CC2(OCCO2)[C@]1(C)C(O)CCS(=O)(=O)c1ccccc1
20	$C_{38}H_{50}O_6SSi$	694.96	C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(O)CCS(=O)(=O)c1ccccc1
21	$C_{33}H_{48}O_8SSi$	692.95	C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(=O)CCS(=O)(=O)c1ccccc1
22	$C_{32}H_{42}O_6Si$	550.77	C7 S, C10 R, C14 S	C=CC(=O)[C@]1(C)[C@@H](CC(=O)OC)[C@]1(C)(CC[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC12OCCO2
23	$C_{42}H_{52}O_{10}Si$	744.95	C4 S, C4a S, C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(=O)CC[C@]1(C)C(=O)CC(=O)O[C@H]1c1ccoc1
24	$C_{43}H_{51}F_3O_{12}SSi$	877.02	C4 S, C4a S, C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(=O)CC[C@]1(C)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]1c1ccoc1
25	$C_{14}H_{30}Sn$	317.11	–	C=[CH][Sn]([CH2]CCC)([CH2]CCC)[CH2]CCC

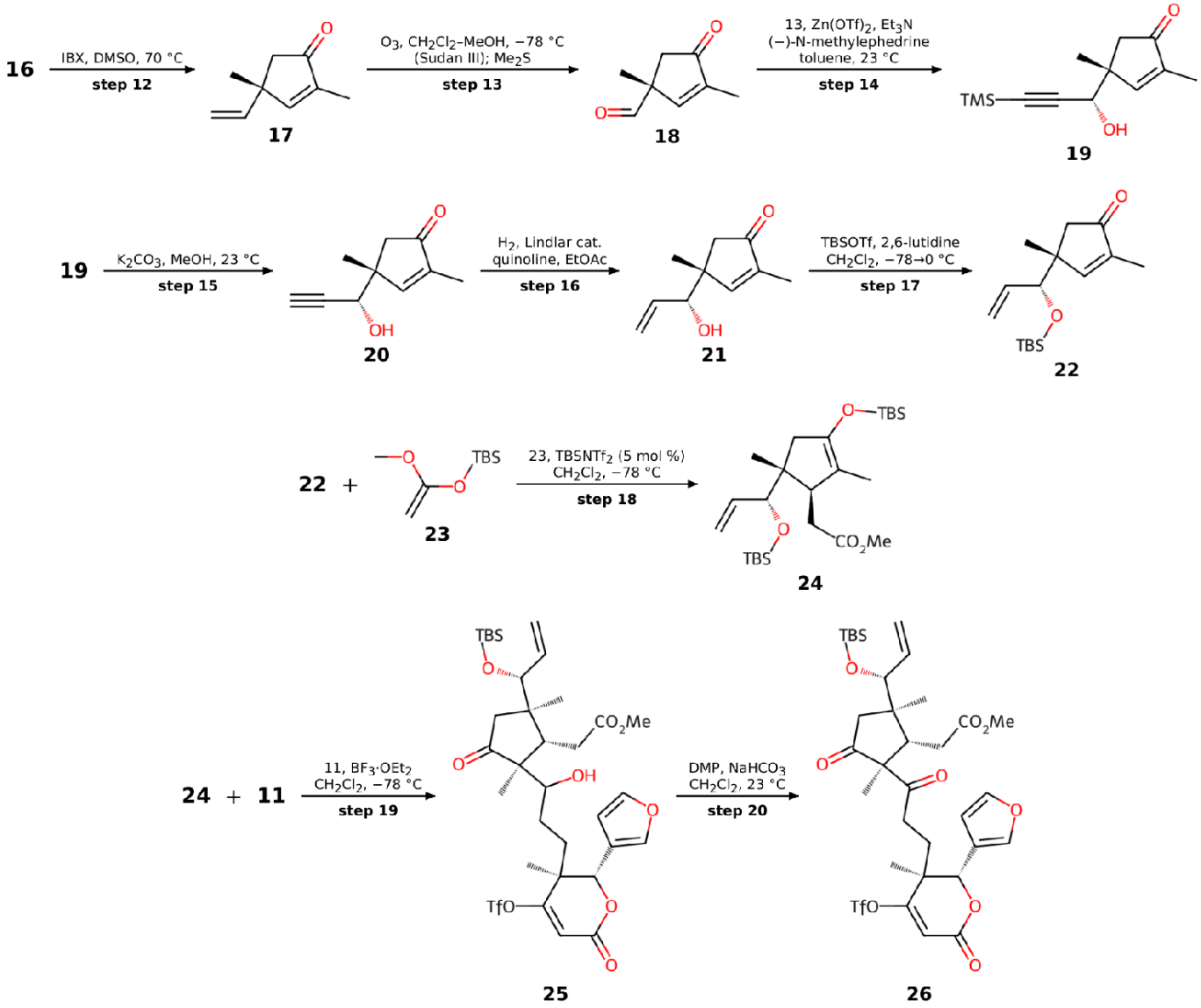
No.	Formula	MW	CIP descriptors (by target locant)	SMILES
26	$C_{44}H_{54}O_9Si$	754.99	C4 R, C4a R, C7 S, C10 R, C14 S	C=CC1=CC(=O)O[C@@H](c2ccoc2)[C@]1(C)CCC(=O)[C@]1(C)[C@@H](CC(=O)OC)[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC12OCCO2
27	$C_{44}H_{56}O_{10}Si$	773.01	C4 R, C4a R, C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(=O)CC[C@]1(C)C(CCO)=CC(=O)O[C@H]1c1ccoc1
28	$C_{44}H_{54}O_{10}Si$	770.99	C4 R, C4a R, C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C(=O)CC[C@]1(C)C(CC=O)=CC(=O)O[C@H]1c1ccoc1
29	$C_{44}H_{52}O_9Si$	752.98	C4 R, C4a R, C7 S, C10 R, C14 S	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C1=C(C=O)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
30	$C_{45}H_{53}IO_8Si$	876.90	C4 R, C4a R, C7 S, C10 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@](C)(CO[Si](c2ccccc2)(c2ccccc2)C(C)(C)C)CC2(OCCO2)[C@]1(C)C1=C(/C=C\I)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
31	$C_{29}H_{35}IO_8$	638.50	C4 R, C4a R, C7 S, C10 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@](C)(CO)CC2(OCCO2)[C@]1(C)C1=C(/C=C\I)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
32	$C_{29}H_{33}IO_8$	636.48	C4 R, C4a R, C7 S, C10 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@](C)(C=O)CC2(OCCO2)[C@]1(C)C1=C(/C=C\I)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
33	$C_{29}H_{34}O_8$	510.58	C4 R, C4a R, C7 S, C10 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@@]2(C)CC3(OCCO3)[C@]1(C)C1=C(/C=C\C2O)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
34	$C_{29}H_{32}O_8$	508.57	C4 R, C4a R, C7 S, C10 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@@]2(C)CC3(OCCO3)[C@]1(C)C1=C(/C=C\C2=O)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
35	$C_{29}H_{34}O_8$	510.58	C4 R, C4a R, C7 S, C10 R, C11 S, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@@]2(C)CC3(OCCO3)[C@]1(C)C1=C(/C=C\[C@@H]2O)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
36	$C_{31}H_{36}O_9$	552.62	C4 R, C4a R, C7 S, C10 R, C11 R, C14 S, C12=C13 Z	COC(=O)C[C@H]1[C@@]2(C)CC3(OCCO3)[C@]1(C)C1=C(/C=C\[C@H]2OC(C)=O)C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CC1
37	$C_{29}H_{32}O_8$	508.57	C4 R, C4a R, C7 S, C10 R, C11 R, C14 S, C12=C13 Z	COC(=O)C[C@@H]1[C@]2(C)C(=O)C[C@@]1(C)[C@H](OC(C)=O)/C=C\C1=C2CC[C@]2(C)C1=CC(=O)O[C@H]2c1ccoc1

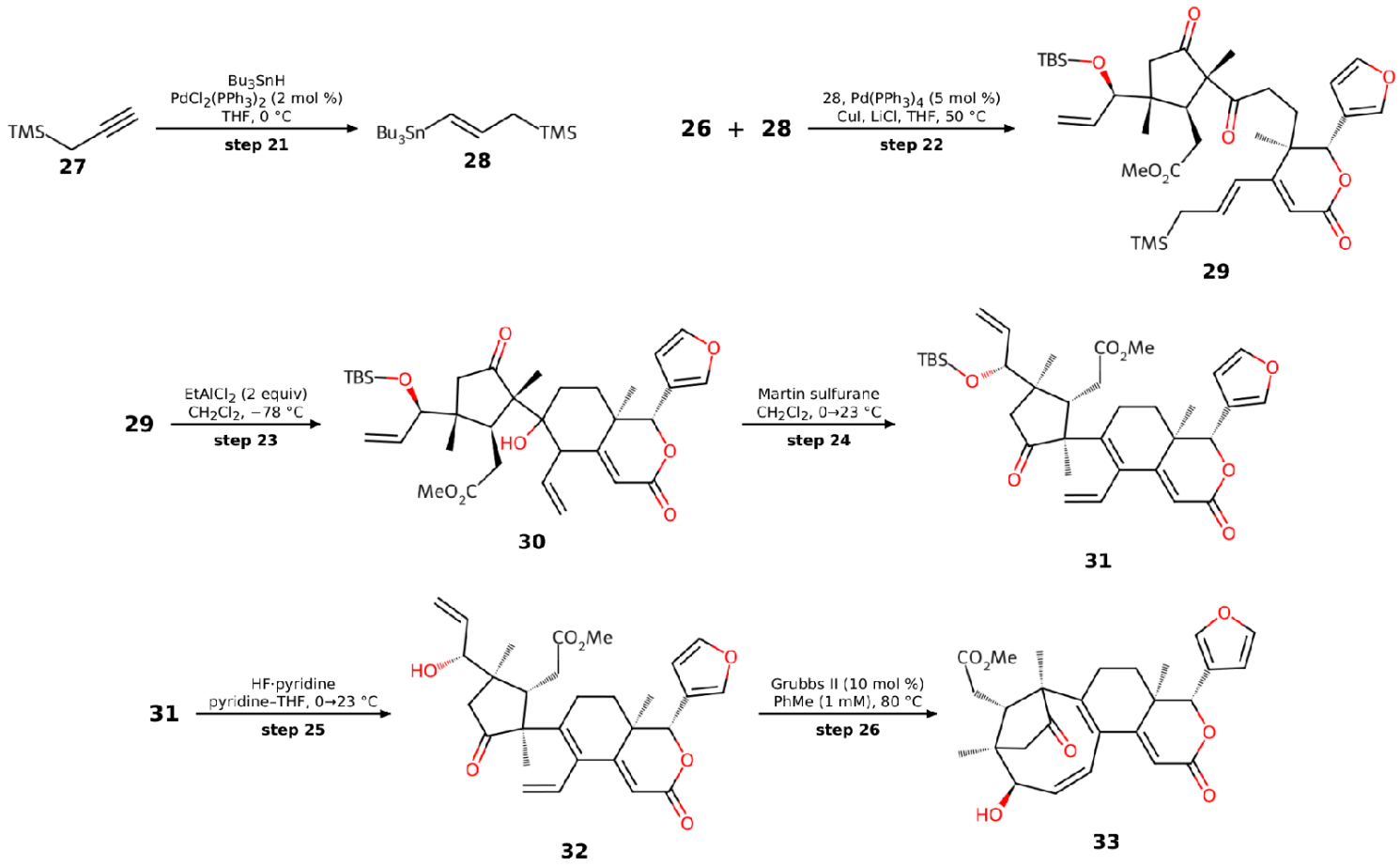
Proposed total synthesis of methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate (34), $C_{29}H_{32}O_8$

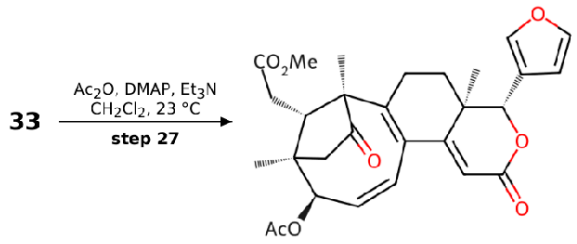
Assumption: the name carries no descriptor for C11; the hashed C11–OAc bond of the drawing is read as 11R (the 11S epimer is obtained by using (+)-N-methylephedrine in step 14).

Reaction scheme (compound numbers under the structures, step numbers under the arrows; TBS = t-BuMe_2Si, Tf = CF_3SO_2, TMS = Me_3Si, Bn = benzyl, DMP = Dess–Martin periodinane)

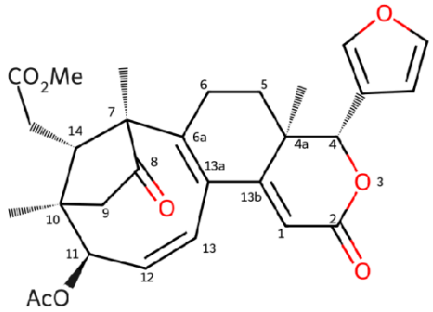



16
IBX, DMSO, 70 °C
step 12
17
O3, CH2Cl2–MeOH, −78 °C
(Sudan III); Me2S
step 13
18
13, Zn(OTf)2, Et3N
(−)-N-methylephedrine
toluene, 23 °C
step 14
TMS
OH
19
19
K2CO3, MeOH, 23 °C
step 15
OH
20
H2, Lindlar cat.
quinoline, EtOAc
step 16
OH
21
TBSOTf, 2,6-lutidine
CH2Cl2, −78→0 °C
step 17
TBS
22
22 +
TBS
23
23, TBSNTf2 (5 mol %)
CH2Cl2, −78 °C
step 18
TBS
CO2Me
TBS
24
24 + 11
11, BF3·OEt2
CH2Cl2, −78 °C
step 19
TBS
CO2Me
OH
TfO
25
DMP, NaHCO3
CH2Cl2, 23 °C
step 20
TBS
CO2Me
TfO
26


TMS
27
Bu3SnH
PdCl2(PPh3)2 (2 mol %)
THF, 0 °C
step 21
Bu3Sn
TMS
28
26 + 28
28, Pd(PPh3)4 (5 mol %)
CuI, LiCl, THF, 50 °C
step 22
TBS
MeO2C
TMS
29
29
EtAlCl2 (2 equiv)
CH2Cl2, −78 °C
step 23
HO
30
Martin sulfurane
CH2Cl2, 0→23 °C
step 24
CO2Me
31
31
HF·pyridine
pyridine–THF, 0→23 °C
step 25
32
Grubbs II (10 mol %)
PhMe (1 mM), 80 °C
step 26
33



34



Target 34 with the ring locants of the systematic name (4R, 4aR, 7S, 10R, 11R, 14S; 12Z). Flat projection: the wedge/hash pattern differs from the perspective drawing of the question but encodes the same descriptors.

Retrosynthetic overview

1. 34 ⇐ 33 (acetylation) ⇐ 32: the eight-membered ring is closed last by RCM at C12=C13 (Z enforced by the ring).

2. Ring C (tetrasubstituted C6a=C13a) ⇐ intramolecular Hosomi–Sakurai of dienyl allylsilane 29 onto the C6a ketone of a β-diketone, then dehydration; the allylsilane comes from a Stille coupling on lactone enol triflate 26.

3. C6a–C7 bond and quaternary C7 ⇐ Mukaiyama aldol of silyl enol ether 24 with aldehyde 11; C14 ⇐ Mukaiyama–Michael on cyclopentenone 22 (trans,trans three-component pattern).

4. Cyclopentenone 22 (C10, C11) ⇐ 3-methylcyclopentenone: Cu-catalysed asymmetric conjugate addition, methylation/dehydrogenation, ozonolysis, Carreira alkynylation, Lindlar reduction.

5. Furyl lactone aldehyde 11 (C4, C4a) ⇐ Evans aldol, Fráter–Seebach allylation, acetate Dieckmann, triflation, hydroboration. Ring order: lactone and cyclopentanone (separately) → ring C → eight-membered ring.

Forward route, step by step

Step 1

Reactants: **1** (R)-4-benzyl-3-propionyloxazolidin-2-one (commercial); **2** furan-3-carbaldehyde (commercial)
Product: **3** (R)-4-benzyl-3-[(2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoyl]oxazolidin-2-one (Evans syn aldol)
Conditions: Bu_2BOTf, i-Pr_2NEt, CH_2Cl_2, −78 → 0 °C; then 2, −78 → 0 °C; pH 7 buffer, H_2O_2/MeOH
Why: Z-boron enolate reacts through a Zimmerman–Traxler chair: Evans syn aldol; the (R)-auxiliary fixes the furyl carbinol (future C4, R).

Step 2

Reactants: **3** (R)-4-benzyl-3-[(2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoyl]oxazolidin-2-one (Evans syn aldol)
Product: **4** methyl (2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoate
Conditions: MeOMgBr, MeOH–CH_2Cl_2, 0 °C (auxiliary recovered)
Why: Mild transesterification at the exocyclic imide carbonyl removes the auxiliary without retro-aldol or epimerisation.

Step 3

Reactants: **4** methyl (2R,3R)-3-(furan-3-yl)-3-hydroxy-2-methylpropanoate; **5** allyl bromide (commercial)
Product: **6** methyl (S)-2-[(S)-furan-3-yl(hydroxy)methyl]-2-methylpent-4-enoate
Conditions: LDA (2.2 equiv), THF, −78 → −20 °C; then 5, HMPA, −78 → 0 °C
Why: Fráter–Seebach alkylation: the Li-chelated alkoxide–enolate is allylated on the face anti to the furyl group, which sets the quaternary centre (future C4a) with methyl and furyl syn, as in the target.

Step 4

Reactants: **6** methyl (S)-2-[(S)-furan-3-yl(hydroxy)methyl]-2-methylpent-4-enoate
Product: **7** methyl (S)-2-[(S)-acetoxy(furan-3-yl)methyl]-2-methylpent-4-enoate
Conditions: Ac_2O, DMAP, pyridine, CH_2Cl_2, 23 °C
Why: Acetylation installs the two carbons that become C2/C1 of the lactone and blocks retro-aldol.

Step 5

Reactants: **7** methyl (S)-2-[(S)-acetoxy(furan-3-yl)methyl]-2-methylpent-4-enoate
Product: **8** (5S,6S)-5-allyl-6-(furan-3-yl)-4-hydroxy-5-methyl-5,6-dihydro-2H-pyran-2-one (enol form of the β-keto-δ-lactone; 5-Me and 6-furyl cis)
Conditions: LiHMDS (3 equiv), THF, −78 → 0 °C; then 1 M HCl
Why: Intramolecular Claisen (Dieckmann) of the acetate enolate onto the methyl ester closes the δ-lactone; the quaternary carbon has no α-H, so no elimination or epimerisation can occur.

Step 6
Reactants: 8 (5S,6S)-5-allyl-6-(furan-3-yl)-4-hydroxy-5-methyl-5,6-dihydro-2H-pyran-2-one (enol form of the β-keto-δ-lactone; 5-Me and 6-furyl cis)
Product: 9 (2S,3S)-3-allyl-2-(furan-3-yl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Conditions: Tf_2O, Et_3N, CH_2Cl_2, −78 °C
Why: The β-keto lactone can enolise in one direction only, so O-triflation gives a single enol triflate (handle for the later Stille coupling).

Step 7
Reactants: 9 (2S,3S)-3-allyl-2-(furan-3-yl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Product: 10 (2S,3S)-2-(furan-3-yl)-3-(3-hydroxypropyl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Conditions: 9-BBN, THF, 0 → 23 °C; then $NaBO_3·4H_2O$, H_2O
Why: 9-BBN hydroborates only the terminal alkene (the enoate C=C is trisubstituted and electron-poor); perborate work-up spares triflate and lactone.

Step 8
Reactants: 10 (2S,3S)-2-(furan-3-yl)-3-(3-hydroxypropyl)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Product: 11 (2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-3-(3-oxopropyl)-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C
Why: Neutral oxidation of the primary alcohol to the aldehyde needed for the fragment union.

Step 9
Reactants: 12 3-methylcyclopent-2-en-1-one (commercial); **13** ethynyltrimethylsilane (commercial)
Product: 14 (S)-3-methyl-3-[1-(trimethylsilyl)vinyl]cyclopentan-1-one
Conditions: 13, DIBAL-H, hexanes, 55 °C [gives i-Bu_2Al–$C(SiMe_3)=CH_2$]; then 12, $CuCl_2·2H_2O$ (5 mol %), chiral sulfonate-NHC–Ag complex (2.5 mol %), THF, 22 °C
Why: NHC–Cu-catalysed conjugate addition of the silyl-substituted vinylalane to the β-methyl enone (Hoveyda) creates the quaternary stereocentre (future C10) under catalyst control.

Step 10
Reactants: 14 (S)-3-methyl-3-[1-(trimethylsilyl)vinyl]cyclopentan-1-one
Product: 15 (S)-3-methyl-3-vinylcyclopentan-1-one
Conditions: CF_3CO_2H, CH_2Cl_2, 0 → 22 °C
Why: Protodesilylation of the α-silyl vinyl group unmasks the vinyl group; the ketone is untouched.

Step 11
Reactants: 15 (S)-3-methyl-3-vinylcyclopentan-1-one
Product: 16 (4S)-2,4-dimethyl-4-vinylcyclopentan-1-one (C2 epimers, inconsequential)
Conditions: LDA, THF, −78 °C; then MeI, −78 → 0 °C
Why: Kinetic deprotonation occurs at the unhindered α-CH2 remote from the quaternary carbon; the new methine is removed in step 12.

Step 12
Reactants: 16 (4S)-2,4-dimethyl-4-vinylcyclopentan-1-one (C2 epimers, inconsequential)
Product: 17 (S)-2,4-dimethyl-4-vinylcyclopent-2-en-1-one
Conditions: IBX, DMSO, 70 °C
Why: Dehydrogenation can only occur toward the methyl-bearing side because the other β-carbon is quaternary, so a single enone forms.

Step 13
Reactants: 17 (S)-2,4-dimethyl-4-vinylcyclopent-2-en-1-one
Product: 18 (R)-1,3-dimethyl-4-oxocyclopent-2-ene-1-carbaldehyde
Conditions: O_3, CH_2Cl_2–MeOH, −78 °C (Sudan III end-point); then Me_2S
Why: The electron-rich monosubstituted vinyl group is ozonised much faster than the electron-poor enone C=C; the aldehyde has no α-H.

Step 14

Reactants: 18 (R)-1,3-dimethyl-4-oxocyclopent-2-ene-1-carbaldehyde; **13** ethynyltrimethylsilane (commercial)
Product: 19 (R)-4-[(S)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl]-2,4-dimethylcyclopent-2-en-1-one
Conditions: 13, $Zn(OTf)_2$, (−)-N-methylephedrine, Et_3N, toluene, 23 °C
Why: Carreira alkynylation is chemoselective for the aldehyde (zinc acetylides ignore the enone) and reagent-controlled; it sets the carbinol centre (future C11).

Step 15

Reactants: 19 (R)-4-[(S)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl]-2,4-dimethylcyclopent-2-en-1-one
Product: 20 (R)-4-[(R)-1-hydroxyprop-2-yn-1-yl]-2,4-dimethylcyclopent-2-en-1-one
Conditions: K_2CO_3, MeOH, 23 °C
Why: Selective C-desilylation of the alkynylsilane.

Step 16

Reactants: 20 (R)-4-[(R)-1-hydroxyprop-2-yn-1-yl]-2,4-dimethylcyclopent-2-en-1-one
Product: 21 (R)-4-[(R)-1-hydroxyallyl]-2,4-dimethylcyclopent-2-en-1-one
Conditions: H_2 (1 atm), Lindlar catalyst, quinoline, EtOAc, 23 °C
Why: Semi-hydrogenation of the terminal alkyne stops at the alkene; the conjugated enone is not reduced.

Step 17

Reactants: 21 (R)-4-[(R)-1-hydroxyallyl]-2,4-dimethylcyclopent-2-en-1-one
Product: 22 (R)-4-[(R)-1-(tert-butyldimethylsilyloxy)allyl]-2,4-dimethylcyclopent-2-en-1-one
Conditions: TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 → 0 °C
Why: Silyl protection of the hindered allylic alcohol for the Lewis-acid steps.

Step 18

Reactants: 22 (R)-4-[(R)-1-(tert-butyldimethylsilyloxy)allyl]-2,4-dimethylcyclopent-2-en-1-one; **23** tert-butyl[(1-methoxyvinyl)oxy]dimethylsilane (ketene silyl acetal of methyl acetate; commercial)
Product: 24 methyl 2-[(1S,5R)-3-(TBSO)-5-[(R)-1-(TBSO)allyl]-2,5-dimethylcyclopent-2-en-1-yl]acetate (TBS enol ether; CH_2CO_2Me cis to the ring methyl, trans to the CH(OTBS)vinyl group)
Conditions: 23 (1.5 equiv), $TBSNTf_2$ (5 mol %, from $HNTf_2$), CH_2Cl_2, −78 °C
Why: Mukaiyama–Michael addition takes place anti to the bulky CH(OTBS)CH=CH_2 group and sets the CH_2CO_2Me-bearing centre (future C14); silyl transfer gives the enol ether regiospecifically at the future C7.

Step 19

Reactants: 24 methyl 2-[(1S,5R)-3-(TBSO)-5-[(R)-1-(TBSO)allyl]-2,5-dimethylcyclopent-2-en-1-yl]acetate (TBS enol ether; CH_2CO_2Me cis to the ring methyl, trans to the CH(OTBS)vinyl group); **11** (2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-3-(3-oxopropyl)-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate
Product: 25 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{1-hydroxy-3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-(triflyloxy)-3,6-dihydro-2H-pyran-3-yl]propyl}-2,5-dimethyl-3-oxocyclopentyl]acetate (carbinol epimers, inconsequential)
Conditions: 11, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C
Why: Mukaiyama aldol: the aldehyde approaches the tetrasubstituted enol ether trans to the adjacent CH_2CO_2Me group (prostaglandin-type trans,trans pattern), creating the quaternary centre (future C7); the new carbinol centre is destroyed in step 20.

Step 20

Reactants: 25 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{1-hydroxy-3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-(triflyloxy)-3,6-dihydro-2H-pyran-3-yl]propyl}-2,5-dimethyl-3-oxocyclopentyl]acetate (carbinol epimers, inconsequential)
Product: 26 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-(triflyloxy)-3,6-dihydro-2H-pyran-3-yl]propanoyl}-2,5-dimethyl-3-oxocyclopentyl]acetate (non-enolisable β-diketone)
Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23 °C
Why: Neutral oxidation gives the non-enolisable β-diketone and avoids the retro-aldol that a base would trigger.

Step 21

Reactants: 27 trimethyl(prop-2-yn-1-yl)silane (propargyltrimethylsilane; commercial)

Product: 28 (E)-tributyl[3-(trimethylsilyl)prop-1-en-1-yl]stannane

Conditions: Bu_3SnH, $PdCl_2(PPh_3)_2$ (2 mol %), THF, 0 °C

Why: syn-Hydrostannation places tin on the terminal carbon and gives the E-alkenylstannane.

Step 22

Reactants: 26 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{3-[(2S,3S)-2-(furan-3-yl)-3-methyl-6-oxo-4-(triflyloxy)-3,6-dihydro-2H-pyran-3-yl]propanoyl}-2,5-dimethyl-3-oxocyclopentyl]acetate (non-enolisable β-diketone); **28** (E)-tributyl[3-(trimethylsilyl)prop-1-en-1-yl]stannane

Product: 29 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{3-[(2R,3R)-2-(furan-3-yl)-3-methyl-6-oxo-4-[(E)-3-(trimethylsilyl)prop-1-en-1-yl]-3,6-dihydro-2H-pyran-3-yl]propanoyl}-2,5-dimethyl-3-oxocyclopentyl]acetate

Conditions: 28, $Pd(PPh_3)_4$ (5 mol %), CuI, LiCl, THF, 50 °C

Why: Stille coupling of the electron-poor enol triflate; the neutral conditions tolerate the β-diketone (no retro-Claisen).

Step 23

Reactants: 29 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-{3-[(2R,3R)-2-(furan-3-yl)-3-methyl-6-oxo-4-[(E)-3-(trimethylsilyl)prop-1-en-1-yl]-3,6-dihydro-2H-pyran-3-yl]propanoyl}-2,5-dimethyl-3-oxocyclopentyl]acetate

Product: 30 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-[(1R,8aR)-1-(furan-3-yl)-6-hydroxy-8a-methyl-3-oxo-5-vinyl-3,5,6,7,8,8a-hexahydro-1H-isochromen-6-yl]-2,5-dimethyl-3-oxocyclopentyl]acetate (C5/C6 diastereomers of the isochromenone, both removed in step 24)

Conditions: $EtAlCl_2$ (2 equiv), CH_2Cl_2, −78 °C

Why: Intramolecular Hosomi–Sakurai: the chelation-activated side-chain ketone is attacked by the γ-carbon of the allylsilane through a six-membered transition state, closing ring C and releasing the terminal vinyl group; C–C formation is irreversible and no basic alkoxide (retro-aldol) is formed.

Step 24

Reactants: 30 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-[(1R,8aR)-1-(furan-3-yl)-6-hydroxy-8a-methyl-3-oxo-5-vinyl-3,5,6,7,8,8a-hexahydro-1H-isochromen-6-yl]-2,5-dimethyl-3-oxocyclopentyl]acetate (C5/C6 diastereomers of the isochromenone, both removed in step 24)

Product: 31 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-[(1R,8aR)-1-(furan-3-yl)-8a-methyl-3-oxo-5-vinyl-3,7,8,8a-tetrahydro-1H-isochromen-6-yl]-2,5-dimethyl-3-oxocyclopentyl]acetate (cross-conjugated trienoate)

Conditions: Martin sulfurane, CH_2Cl_2, 0 → 23 °C

Why: Neutral dehydration of the tertiary alcohol; loss of the doubly allylic H gives the tetrasubstituted alkene conjugated with the lactone enoate.

Step 25

Reactants: 31 methyl 2-[(1S,2S,5R)-5-[(R)-1-(TBSO)allyl]-2-[(1R,8aR)-1-(furan-3-yl)-8a-methyl-3-oxo-5-vinyl-3,7,8,8a-tetrahydro-1H-isochromen-6-yl]-2,5-dimethyl-3-oxocyclopentyl]acetate (cross-conjugated trienoate)

Product: 32 methyl 2-[(1S,2S,5R)-2-[(1R,8aR)-1-(furan-3-yl)-8a-methyl-3-oxo-5-vinyl-3,7,8,8a-tetrahydro-1H-isochromen-6-yl]-5-[(R)-1-hydroxyallyl]-2,5-dimethyl-3-oxocyclopentyl]acetate

Conditions: HF·pyridine, pyridine–THF, 0 → 23 °C

Why: Buffered fluoride removes the TBS group without touching the lactone, the furan or the ketone; the free allylic alcohol also accelerates RCM.

Step 26

Reactants: 32 methyl 2-[(1S,2S,5R)-2-[(1R,8aR)-1-(furan-3-yl)-8a-methyl-3-oxo-5-vinyl-3,7,8,8a-tetrahydro-1H-isochromen-6-yl]-5-[(R)-1-hydroxyallyl]-2,5-dimethyl-3-oxocyclopentyl]acetate

Product: 33 methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate

Conditions: Grubbs II catalyst (10 mol %), toluene (1 mM), 80 °C

Why: The two side chains are cis-1,3 on the cyclopentanone and therefore pre-organised; only the two monosubstituted alkenes can react, and the eight-membered ring accommodates only the Z-alkene.

Step 27

Reactants: 33 methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate

Product: 34 target: methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate

Conditions: Ac_2O, DMAP, Et_3N, CH_2Cl_2, 23 °C

Why: Acetylation of the hindered allylic alcohol completes the target with all six stereocentres and the Z-alkene in place.

Result of the self-check

Changed after checking: (i) the planned C-5 allylation of the β-keto-δ-lactone dianion (it would ring-open by β-elimination of the carboxylate) was replaced by Fráter–Seebach allylation plus acetate Dieckmann closure (steps 3–5); (ii) a base-mediated vinylogous aldol closure of ring C (the aldolate would fragment by retro-aldol at C6a–C7) was replaced by the allylsilane/Sakurai closure and neutral dehydration (steps 21–24); (iii) a late oxidation/CBS sequence at C11 (not chemoselective versus the C8 ketone) was replaced by an early reagent-controlled alkynylation (step 14). Molecular formulae of all 34 compounds, the atom balance of all 27 steps, the CIP descriptors of every stereocentre and the wedge/hash bonds of every drawn structure were verified with RDKit; compound 34 is $C_{29}H_{32}O_8$ (4R,4aR,7S,10R,11R,14S,Z).

Summary

Total step count: 27 (8 for aldehyde 11, 10 for enol ether 24, 1 for stannane 28, 8 from the union to 34).

Longest linear sequence: 18 steps (12 → 24 → 34: steps 9–20 and 22–27).

Most likely to fail, with fallback:

(a) Step 26, RCM to the eight-membered ring (diene terminus, hindered allylic carbinol next to a quaternary carbon). Fallback: relay RCM – use allyl propargyl ether instead of 13 in step 14, so that Lindlar reduction gives the (Z)-CH=CH–$CH_2OCH_2CH=CH_2$ relay arm; the catalyst then loads at the unhindered allyl ether, expels 2,5-dihydrofuran and delivers the carbene at C12 for ring closure onto the diene terminus.

(b) Step 23, Sakurai closure onto the hindered β-diketone with an electron-poor dienylsilane. Fallback: In-mediated Barbier cyclisation (THF–H_2O, neutral) of the corresponding dienylic bromide, made by Stille coupling with (E)-$Bu_3SnCH=CHCH_2OTES$, TES removal and CBr_4/PPh_3.

(c) Steps 18/19, Mukaiyama–Michael/aldol on the hindered α-methyl enone next to a quaternary carbon (rate, facial selectivity). Fallback: Cs_2CO_3-mediated dimethyl malonate addition and Krapcho decarboxylation, regeneration of the more substituted TBS enol ether (TBSOTf, Et_3N), then aldol through the zinc enolate at −78 °C.

Compound list (formula, molecular weight and isomeric SMILES used for the drawings and checks)

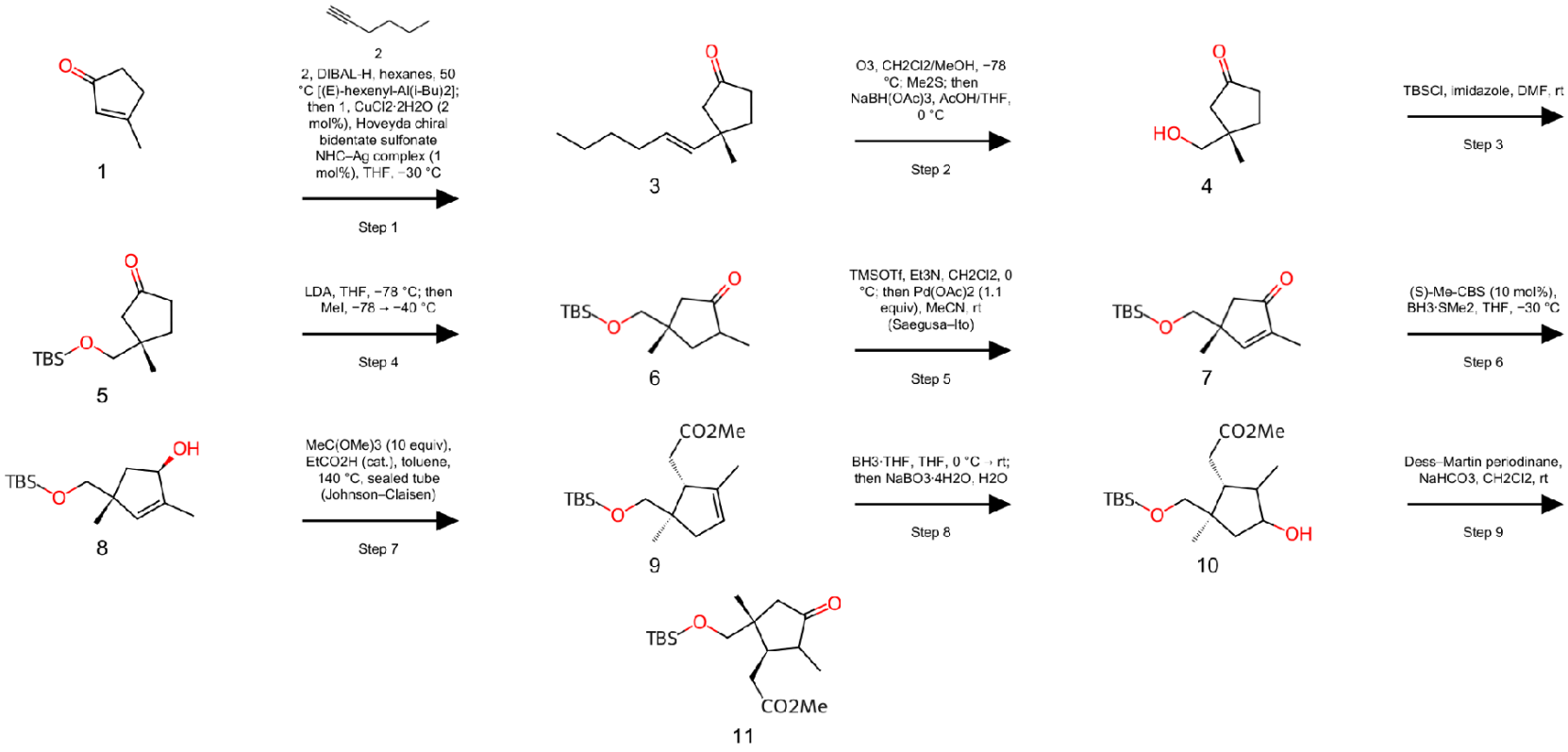
No.	Formula	MW	SMILES
1	$C_{13}H_{15}NO_3$	233.27	CCC(=O)N1C(=O)OC[C@H]1Cc1ccccc1
2	$C_5H_4O_2$	96.08	O=Cc1ccoc1
3	$C_{18}H_{19}NO_5$	329.35	C[C@@H](C(=O)N1C(=O)OC[C@H]1Cc1ccccc1)[C@@H](O)c1ccoc1
4	$C_9H_{12}O_4$	184.19	COC(=O)[C@H](C)[C@@H](O)c1ccoc1
5	C_3H_5Br	120.98	C=CCBr
6	$C_{12}H_{16}O_4$	224.26	C=CC[C@](C)(C(=O)OC)[C@@H](O)c1ccoc1
7	$C_{14}H_{18}O_5$	266.29	C=CC[C@](C)(C(=O)OC)[C@@H](OC(C)=O)c1ccoc1
8	$C_{13}H_{14}O_4$	234.25	C=CC[C@]1(C)C(O)=CC(=O)O[C@H]1c1ccoc1
9	$C_{14}H_{13}F_3O_6S$	366.31	C=CC[C@]1(C)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]1c1ccoc1
10	$C_{14}H_{15}F_3O_7S$	384.33	C[C@@]1(CCCO)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]1c1ccoc1
11	$C_{14}H_{13}F_3O_7S$	382.31	C[C@@]1(CCC=O)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]1c1ccoc1
12	C_6H_8O	96.13	CC1=CC(=O)CC1
13	$C_5H_{10}Si$	98.22	C#C[Si](C)(C)C
14	$C_{11}H_{20}OSi$	196.37	C=C([C@@]1(C)CCC(=O)C1)[Si](C)(C)C
15	$C_8H_{12}O$	124.18	C=C[C@@]1(C)CCC(=O)C1
16	$C_9H_{14}O$	138.21	C=C[C@]1(C)CC(=O)C(C)C1
17	$C_9H_{12}O$	136.19	C=C[C@@]1(C)C=C(C)C(=O)C1
18	$C_8H_{10}O_2$	138.17	CC1=C[C@](C)(C=O)CC1=O
19	$C_{13}H_{20}O_2Si$	236.39	CC1=C[C@](C)([C@H](O)C#C[Si](C)(C)C)CC1=O
20	$C_{10}H_{12}O_2$	164.20	C#C[C@@H](O)[C@@]1(C)C=C(C)C(=O)C1
21	$C_{10}H_{14}O_2$	166.22	C=C[C@@H](O)[C@@]1(C)C=C(C)C(=O)C1
22	$C_{16}H_{28}O_2Si$	280.48	C=C[C@@H](O[Si](C)(C)C(C)(C)C)[C@@]1(C)C=C(C)C(=O)C1
23	$C_9H_{20}O_2Si$	188.34	C=C(OC)O[Si](C)(C)C(C)(C)C
24	$C_{25}H_{48}O_4Si_2$	468.83	C=C[C@@H](O[Si](C)(C)C(C)(C)C)[C@]1(C)CC(O[Si](C)(C)C(C)(C)C)=C(C)[C@H]1CC(=O)OC
25	$C_{33}H_{47}F_3O_{11}SSi$	736.88	C=C[C@@H](O[Si](C)(C)C(C)(C)C)[C@]1(C)CC(=O)[C@](C)(C(O)CC[C@]2(C)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]2c2ccoc2)[C@H]1CC(=O)OC
26	$C_{33}H_{45}F_3O_{11}SSi$	734.86	C=C[C@@H](O[Si](C)(C)C(C)(C)C)[C@]1(C)CC(=O)[C@](C)(C(=O)CC[C@]2(C)C(OS(=O)(=O)C(F)(F)F)=CC(=O)O[C@H]2c2ccoc2)[C@H]1CC(=O)OC
27	$C_6H_{12}Si$	112.25	C#CC[Si](C)(C)C
28	$C_{18}H_{40}SiSn$	403.32	CCCC[Sn](CCCC)(CCCC)/C=C/C[Si](C)(C)C
29	$C_{38}H_{58}O_8Si_2$	699.05	C=C[C@@H](O[Si](C)(C)C(C)(C)C)[C@]1(C)CC(=O)[C@](C)(C(=O)CC[C@]2(C)C(/C=C/C[Si](C)(C)C)=CC(=O)O[C@H]2c2ccoc2)[C@H]1CC(=O)OC
30	$C_{35}H_{50}O_8Si$	626.86	C=CC1C2=CC(=O)O[C@@H](c3ccoc3)[C@]2(C)CCC1(O)[C@@]1(C)C(=O)C[C@@](C)([C@@H](C=C)O[Si](C)(C)C(C)(C)C)[C@@H]1CC(=O)OC
31	$C_{35}H_{48}O_7Si$	608.85	C=CC1=C([C@@]2(C)C(=O)C[C@@](C)([C@@H](C=C)O[Si](C)(C)C(C)(C)C)[C@@H]2CC(=O)OC)CC[C@]2(C)C1=CC(=O)O[C@H]2c1ccoc1
32	$C_{29}H_{34}O_7$	494.58	C=CC1=C([C@@]2(C)C(=O)C[C@@](C)([C@H](O)C=C)[C@@H]2CC(=O)OC)CC[C@]2(C)C1=CC(=O)O[C@H]2c1ccoc1
33	$C_{27}H_{30}O_7$	466.53	COC(=O)C[C@@H]1[C@]2(C)C(=O)C[C@@]1(C)[C@H](O)/C=C\C1=C2CC[C@]2(C)C1=CC(=O)O[C@H]2c1ccoc1
34	$C_{29}H_{32}O_8$	508.57	COC(=O)C[C@@H]1[C@]2(C)C(=O)C[C@@]1(C)[C@H](OC(C)=O)/C=C\C1=C2CC[C@]2(C)C1=CC(=O)O[C@H]2c1ccoc1

Mythos 5.1's route to triconnarin D

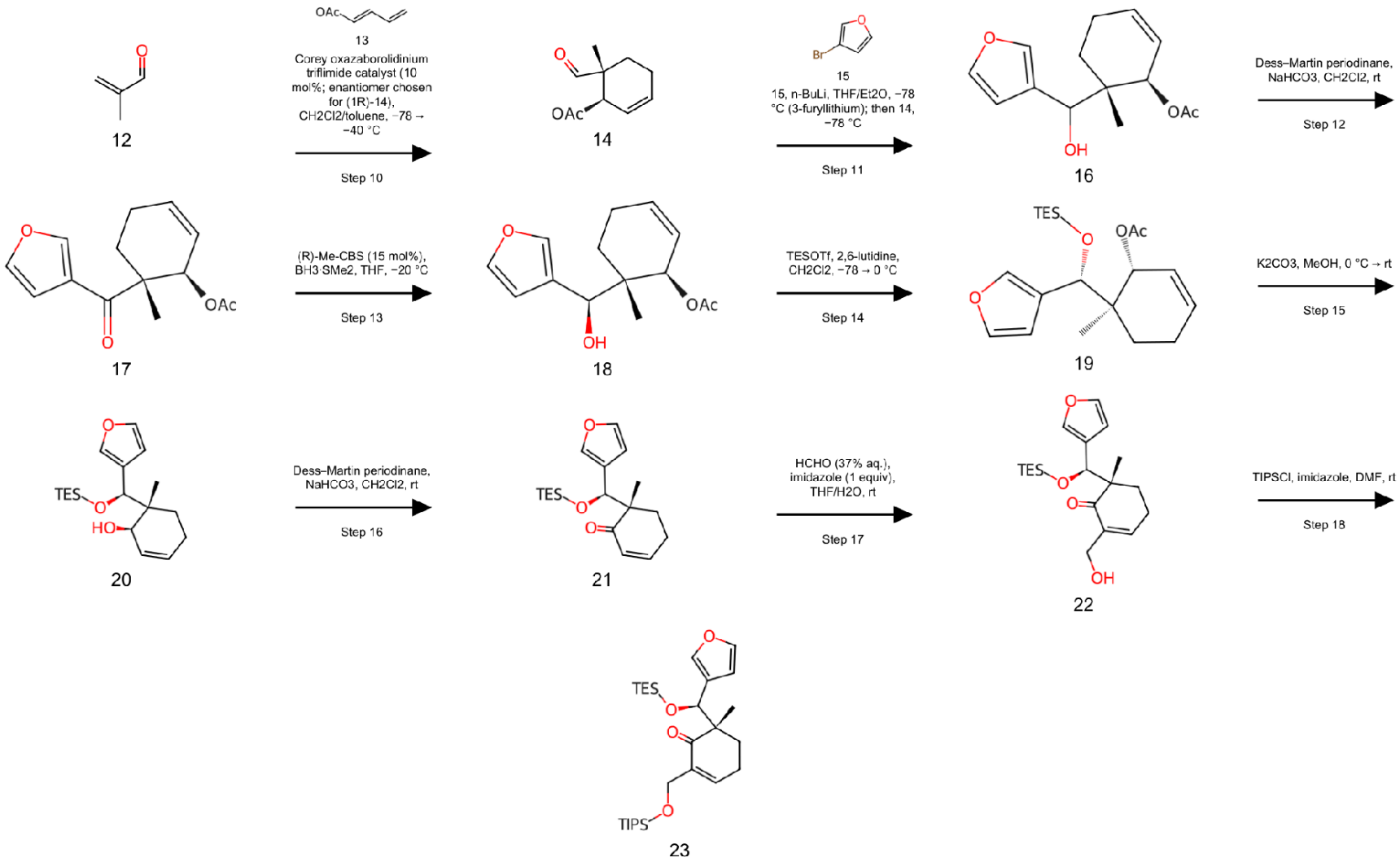
Proposed total synthesis of methyl 2-((4R,4aR,7S,10R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate (36, $C_{29}H_{32}O_8$)

Reaction scheme. Every numbered compound is drawn with its stereochemistry; conditions are written above each arrow; reagents drawn as structures above an arrow are the second reactant of that step. Compound numbering follows the order of first appearance. Abbreviations: TBS = tert-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

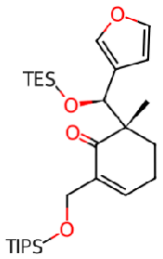
Fragment F1: the cyclopentanone (compounds 1–11)



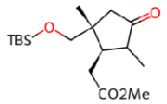
Fragment F2: ring B (compounds 12–23)



Fragment union, ring A and the nine-membered ring (compounds 23–36)



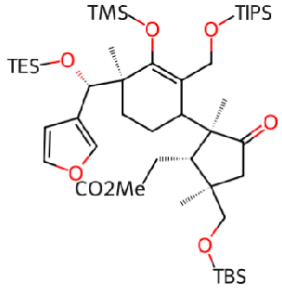
23



11

11: TMSOTf, Et3N, CH2Cl2, 0 °C (thermodynamic, tetrasubstituted TMS enol ether); then 23, Me3SiNTf2 (5 mol%), CH2Cl2, −78 °C (Mukaiyama–Michael)

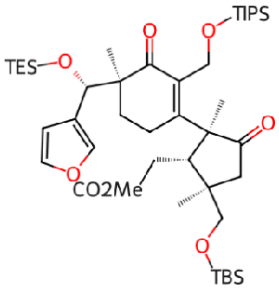
Step 19



24

Pd(OAc)2 (1.1 equiv), MeCN, rt (Saegusa–Ito)

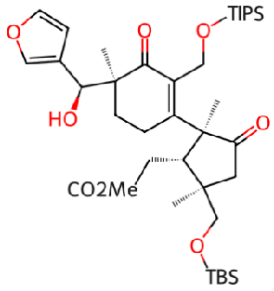
Step 20



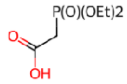
25

PPTS (cat.), MeOH/CH2Cl2, 0 °C

Step 21



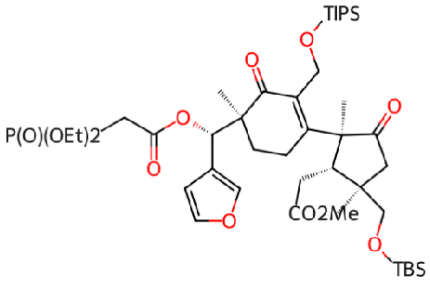
26



27

27, 2,4,6-trichlorobenzoyl chloride, Et3N, THF; then 26, DMAP, toluene, rt (Yamaguchi esterification)

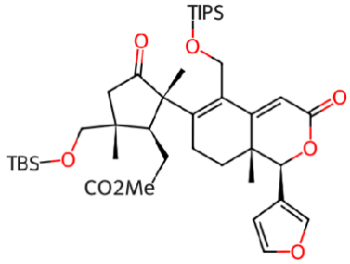
Step 22



28

NaH (1.5 equiv), THF, 0 °C → 65 °C (intramolecular HWE)

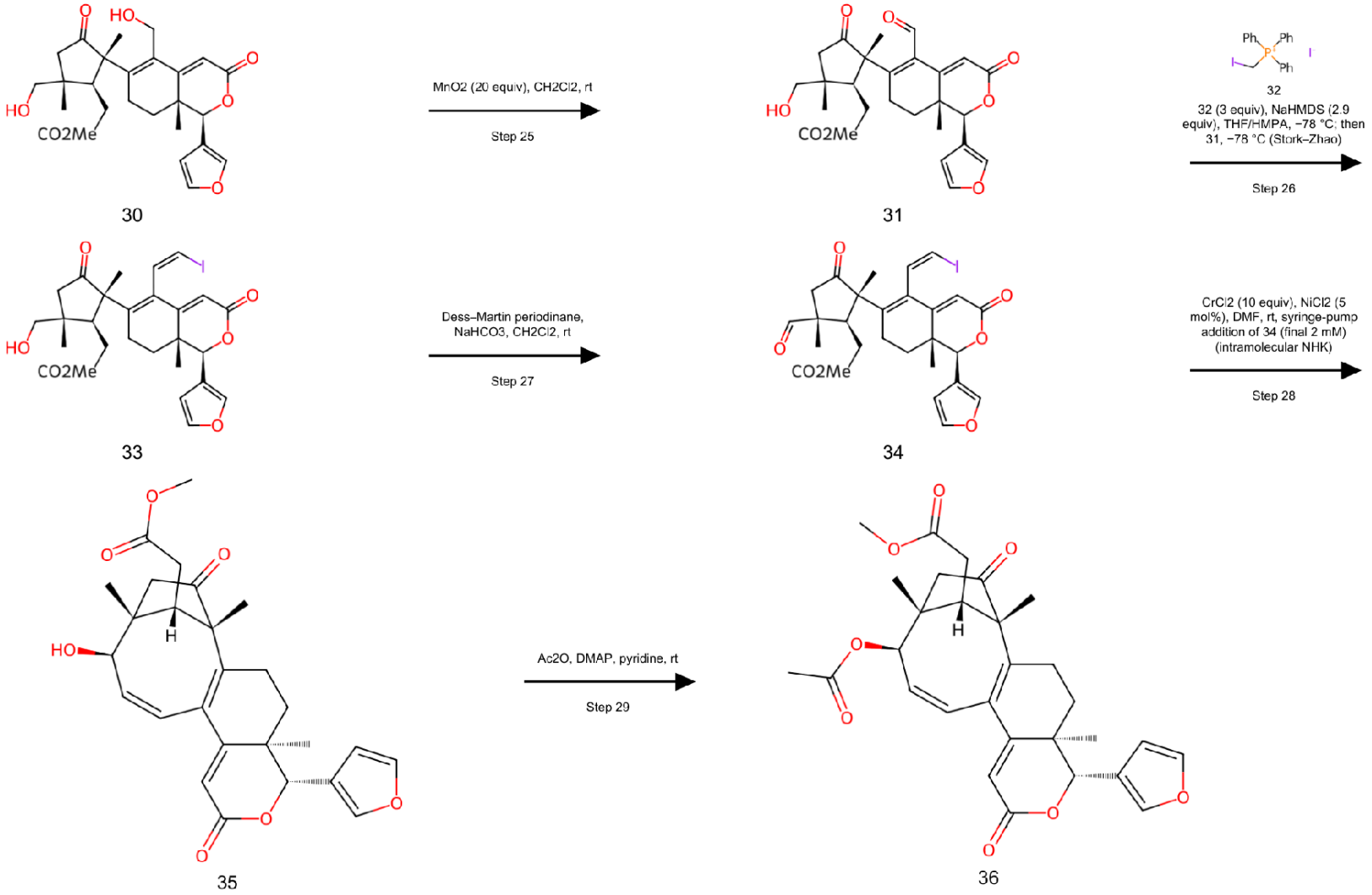
Step 23



29

TBAF (4 equiv), THF, rt

Step 24


30
MnO2 (20 equiv), CH2Cl2, rt
Step 25
31
32
32 (3 equiv), NaHMDS (2.9 equiv), THF/HMPA, −78 °C; then 31, −78 °C (Stork–Zhao)
Step 26
33
Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Step 27
34
CrCl2 (10 equiv), NiCl2 (5 mol%), DMF, rt, syringe-pump addition of 34 (final 2 mM) (intramolecular NHK)
Step 28
35
Ac2O, DMAP, pyridine, rt
Step 29
36

Retrosynthetic overview

• Disconnect the C11 acetate and the nine-membered ring last: the C11–C12 bond (with the Z-alkene) comes from an intramolecular Nozaki–Hiyama–Kishi (NHK) addition of a (Z)-dienyl iodide to a neopentyl aldehyde (34 → 35).
• Ring A (the furyl α,β-unsaturated δ-lactone) is closed by an intramolecular Horner–Wadsworth–Emmons (HWE) of a C4 phosphonoacetate onto the ring-B enone ketone (28 → 29); the C13a=C6a bond comes from a Saegusa dehydrogenation (24 → 25).
• The C6a–C7 bond (quaternary C7) joins the two fragments by a Mukaiyama–Michael addition of the cyclopentanone enol silane 11 to the cyclohexenone 23 (step 19).
• Ring B with the C4a quaternary centre comes from an oxazaborolidinium-catalysed Diels–Alder of methacrolein with 1-acetoxybutadiene; C4 is set by CBS reduction of a 3-furyl ketone.
• The cyclopentanone (C7, C10, C14) comes from 3-methylcyclopentenone: C10 by Cu–NHC asymmetric conjugate addition, C14 by CBS reduction/Johnson–Claisen chirality transfer. Ring order: cyclopentanone and ring B separately, then C6a–C7, then ring A, then the nine-membered ring.

Target check and assumption

The structure planned for was rebuilt from the name and compared with the drawing: a 6-membered α,β-unsaturated δ-lactone (ring A) bearing the furan-3-yl group at C4 and a quaternary methyl at C4a, fused to a cyclohexadiene (ring B, C6a=C13a endocyclic; C13b=C1 and C13=C12 exocyclic), fused to a nine-membered ring bridged by C14 (C7–C14–C10) that contains the C8 ketone and the (Z)-C12=C13 alkene; substituents: C7-Me, C10-Me, C11-OAc, C14-CH_2CO_2Me. RDKit gives $C_{29}H_{32}O_8$ and (4R,4aR,7S,10R,14S,Z) for the drawn compound 36, and the relative configuration is: furan cis to the C4a methyl; C7-Me, C10-Me and the C14 acetate chain all on one face of the cyclopentanone, with C6a and C11 on the other face.
Assumption: the given name carries no descriptor for C11 (the OAc carbon) and the drawing shows no wedge there, so the (11R) epimer is targeted; the (11S) epimer is available by DMP oxidation of 35 and NaBH4/CeCl3 reduction.

Numbered compounds

1: 3-methylcyclopent-2-en-1-one [C6H8O]
2: hex-1-yne [C6H10]
3: (3S)-3-[(1E)-hex-1-en-1-yl]-3-methylcyclopentan-1-one [C12H20O]
4: (3S)-3-(hydroxymethyl)-3-methylcyclopentan-1-one [C7H12O2]
5: (3S)-3-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methylcyclopentan-1-one [C13H26O2Si]
6: (4S)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopentan-1-one (mixture of C2 epimers) [C14H28O2Si]
7: (4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopent-2-en-1-one [C14H26O2Si]
8: (1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopent-2-en-1-ol (OH cis to the C4-methyl) [C14H28O2Si]
9: methyl 2-[(1R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,5-dimethylcyclopent-2-en-1-yl]acetate (CH2CO2Me cis to the C5-methyl) [C17H32O3Si]
10: methyl 2-[(1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-3-hydroxy-2,4-dimethylcyclopentyl]acetate (mixture at C2 and C3) [C17H34O4Si]
11: methyl 2-[(1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethyl-3-oxocyclopentyl]acetate (C2 epimers; cyclopentanone fragment) [C17H32O4Si]
12: 2-methylprop-2-enal (methacrolein) [C4H6O]
13: (1E)-buta-1,3-dien-1-yl acetate [C6H8O2]
14: (1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-ene-1-carbaldehyde (CHO trans to OAc) [C10H14O3]
15: 3-bromofuran [C4H3BrO]
16: [(1S,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanol (mixture of carbinol epimers) [C14H18O4]
17: [(1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanone [C14H16O4]
18: (R)-[(1S,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanol [C14H18O4]
19: (1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-yl acetate [C20H32O4Si]
20: (1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-ol [C18H30O3Si]

21: (6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-one [C18H28O3Si]
22: (6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-2-(hydroxymethyl)-6-methylcyclohex-2-en-1-one [C19H30O4Si]
23: (6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methyl-2-{[(triisopropylsilyl)oxy]methyl}cyclohex-2-en-1-one (ring-B fragment) [C28H50O4Si2]
24: Mukaiyama–Michael adduct drawn as the ring-B TMS enol ether: the cyclopentanone of 11 joined through its new quaternary C7 (Me, C8=O, C14) to C6a of the cyclohexene of 23 (C6a–H epimeric); ring B carries the C13b–OTMS enol ether (C13a=C13b), C13a–CH2OTIPS, C4a–Me and the C4 (furan-3-yl)(OTES)methyl group; C10–CH2OTBS, C14–CH2CO2Me; (4S,4aS,7S,10R,14S) in target numbering [C48H90O8Si4]
25: Saegusa product: as 24 but ring B is the cyclohexenone C13b(=O)–C13a(CH2OTIPS)=C6a(C7), a tetrasubstituted enone; C8 ketone unchanged; (4S,4aS,7S,10R,14S) [C45H80O8Si3]
26: as 25 with the C4 hydroxyl free (TES removed); (4S,4aS,7S,10R,14S) [C39H66O8Si2]
27: 2-(diethoxyphosphoryl)acetic acid [C6H13O5P]
28: phosphonoacetate of 26: C4–O–C(=O)CH2P(O)(OEt)2; (4S,4aS,7S,10R,14S) [C45H77O12PSi2]
29: tricyclic dienoate lactone (rings A and B closed): (4R,4aR,7S,10R,14S)-4-(furan-3-yl)-4a,7,10-trimethyl-13a-(TIPSO-methyl)-10-(TBSO-methyl)... i.e. the target's isochromenone/cyclohexadiene/cyclopentanone core with C1=C13b and C13a=C6a, C13a–CH2OTIPS, C10–CH2OTBS, C8 ketone, C14–CH2CO2Me [C41H66O8Si2]
30: diol: 29 with both silyl groups removed (allylic C13–OH, neopentyl C11–OH); (4R,4aR,7S,10R,14S) [C26H32O8]
31: dienal: 30 with the allylic C13 alcohol oxidized to C13a–CHO; C11–CH2OH intact [C26H30O8]
32: (iodomethyl)triphenylphosphonium iodide [C19H17I2P]
33: (Z)-vinyl iodide: 31 with C13a–CH=CH–I (Z); C11–CH2OH intact; (4R,4aR,7S,10R,14S) [C27H31IO7]
34: aldehyde: 33 with C11 as CHO (the NHK substrate) [C27H29IO7]
35: NHK product: the 7,10-methanocyclonona[f]isochromene skeleton of the target with C11–OH, (Z)-C12=C13; methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-4-(furan-3-yl)-11-hydroxy-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate [C27H30O7]
36: target: methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]isochromen-14-yl)acetate (C29H32O8) [C29H32O8]

Forward route, step by step

Step 1
Reactants: 1 (3-methylcyclopent-2-en-1-one); 2 (hex-1-yne)
Product: 3 ((3S)-3-[(1E)-hex-1-en-1-yl]-3-methylcyclopentan-1-one)
Conditions: 2, DIBAL-H, hexanes, 50 °C [(E)-hexenyl-Al(i-Bu)2]; then 1, CuCl2·2H2O (2 mol%), Hoveyda chiral bidentate sulfonate NHC–Ag complex (1 mol%), THF, −30 °C
Why: Cu–NHC-catalysed enantioselective conjugate addition of the alkenylaluminium to the β-methyl enone builds the all-carbon quaternary centre that becomes C10 (catalyst enantiomer chosen for (3S)-3).

Step 2
Reactants: 3 ((3S)-3-[(1E)-hex-1-en-1-yl]-3-methylcyclopentan-1-one)
Product: 4 ((3S)-3-(hydroxymethyl)-3-methylcyclopentan-1-one)
Conditions: O3, CH2Cl2/MeOH, −78 °C; Me2S; then NaBH(OAc)3, AcOH/THF, 0 °C
Why: Ozonolysis excises the butyl chain to a neopentyl aldehyde, which NaBH(OAc)3 reduces chemoselectively in the presence of the cyclopentanone.

Step 3
Reactants: 4 ((3S)-3-(hydroxymethyl)-3-methylcyclopentan-1-one)
Product: 5 ((3S)-3-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methylcyclopentan-1-one)
Conditions: TBSCl, imidazole, DMF, rt
Why: Standard silylation of the primary neopentyl alcohol; the ketone is untouched.

Step 4
Reactants: 5 ((3S)-3-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methylcyclopentan-1-one)
Product: 6 ((4S)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopentan-1-one (mixture of C2 epimers))
Conditions: LDA, THF, −78 °C; then MeI, −78 → −40 °C
Why: Kinetic deprotonation of a 3,3-disubstituted cyclopentanone occurs at the α-CH2 remote from the quaternary carbon, so methylation goes to C7 (epimers, later erased).

Step 5
Reactants: 6 (see list)
Product: 7 ((4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopent-2-en-1-one)
Conditions: TMSOTf, Et3N, CH2Cl2, 0 °C; then Pd(OAc)2 (1.1 equiv), MeCN, rt (Saegusa–Ito)
Why: Dehydrogenation is regiospecific for the C7=C14 enone: only the tetrasubstituted enol silane has a β-hydrogen (C14–H), since C10 carries no H.

Step 6
Reactants: 7 ((4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopent-2-en-1-one)
Product: 8 ((1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethylcyclopent-2-en-1-ol (OH cis to the C4-methyl))
Conditions: (S)-Me-CBS (10 mol%), BH3·SMe2, THF, −30 °C
Why: Catalyst-controlled 1,2-reduction of the enone places the C8 hydroxyl on the same face as the C10 methyl, overriding the weak 1,3-bias of the remote quaternary centre.

Step 7
Reactants: 8 (see list)
Product: 9 (methyl 2-[(1R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,5-dimethylcyclopent-2-en-1-yl]acetate (CH2CO2Me cis to the C5-methyl))
Conditions: MeC(OMe)3 (10 equiv), EtCO2H (cat.), toluene, 140 °C, sealed tube (Johnson–Claisen)
Why: The [3,3] shift is suprafacial, so the C8 carbinol chirality is transferred to C14: the CH2CO2Me arrives cis to the C10 methyl (as in the target) and the alkene moves to C7=C8.

Step 8
Reactants: 9 (see list)
Product: 10 (methyl 2-[(1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-3-hydroxy-2,4-dimethylcyclopentyl]acetate (mixture at C2 and C3))
Conditions: BH3·THF, THF, 0 °C → rt; then NaBO3·4H2O, H2O
Why: Anti-Markovnikov hydroboration of the trisubstituted alkene puts oxygen on the less substituted carbon C8; C7/C8 configurations are inconsequential.

Step 9
Reactants: 10 (see list)
Product: 11 (methyl 2-[(1R,4R)-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2,4-dimethyl-3-oxocyclopentyl]acetate (C2 epimers; cyclopentanone fragment))
Conditions: Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Why: Oxidation gives the cyclopentanone fragment 11 (C7 epimers, which is irrelevant because C7 is enolised in step 19); the ester and silyl ether survive.

Step 10
Reactants: 12 (2-methylprop-2-enal); 13 ((1E)-buta-1,3-dien-1-yl acetate)
Product: 14 ((1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-ene-1-carbaldehyde (CHO trans to OAc))
Conditions: Corey oxazaborolidinium triflimide catalyst (10 mol%; enantiomer chosen for (1R)-14), CH2Cl2/toluene, −78 → −40 °C
Why: Oxazaborolidinium-catalysed Diels–Alder of the α-methyl enal: 1-acyloxy dienes give the 'ortho' regiochemistry, and the catalyst controls the face of the dienophile α-carbon, creating the C4a quaternary centre (the C13b centre is erased later).

Step 11
Reactants: 14 ((1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-ene-1-carbaldehyde); 15 (3-bromofuran)
Product: 16 ([(1S,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanol (mixture of carbinol epimers))
Conditions: 15, n-BuLi, THF/Et2O, −78 °C (3-furyllithium); then 14, −78 °C
Why: 3-Furyllithium adds to the aldehyde (the acetate is inert at −78 °C); the carbinol stereochemistry does not matter because it is oxidised next.

Step 12
Reactants: 16 (see list)
Product: 17 ([(1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanone)
Conditions: Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Why: Oxidation to the 3-acylfuran removes the poorly controlled carbinol centre.

Step 13
Reactants: 17 ([(1R,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanone)
Product: 18 ((R)-[(1S,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanol)
Conditions: (R)-Me-CBS (15 mol%), BH3·SMe2, THF, −20 °C
Why: Reagent-controlled CBS reduction of the tert-alkyl 3-furyl ketone (quaternary carbon = large group, furyl = small) sets C4 (R), which puts the furan cis to the C4a methyl in the later lactone.

Step 14
Reactants: 18 ((R)-[(1S,2R)-2-(acetyloxy)-1-methylcyclohex-3-en-1-yl](furan-3-yl)methanol)
Product: 19 ((1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-yl acetate)
Conditions: TESOTf, 2,6-lutidine, CH2Cl2, −78 → 0 °C
Why: TES protection of the hindered secondary carbinol; TES is chosen because it can be removed later with mild acid while TBS/TIPS ethers survive.

Step 15
Reactants: 19 ((1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-yl acetate)
Product: 20 ((1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-ol)
Conditions: K2CO3, MeOH, 0 °C → rt
Why: Methanolysis of the secondary acetate; the TES ether and furan are stable to mild carbonate.

Step 16
Reactants: 20 ((1R,6R)-6-[(R)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-ol)
Product: 21 ((6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-one)
Conditions: Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Why: Oxidation of the allylic alcohol gives the cyclohexenone directly (C13b=O conjugated with C13a=C6a), the Michael acceptor.

Step 17
Reactants: 21 ((6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methylcyclohex-2-en-1-one)
Product: 22 ((6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-2-(hydroxymethyl)-6-methylcyclohex-2-en-1-one)
Conditions: HCHO (37% aq.), imidazole (1 equiv), THF/H2O, rt
Why: Morita–Baylis–Hillman with formaldehyde installs C13 as a hydroxymethyl at the enone α-carbon; the β-carbon (C6a) is an unsubstituted CH so the MBH manifold is open.

Step 18
Reactants: 22 (see list)
Product: 23 ((6S)-6-[(S)-(furan-3-yl)(triethylsilyloxy)methyl]-6-methyl-2-{[(triisopropylsilyl)oxy]methyl}cyclohex-2-en-1-one (ring-B fragment))
Conditions: TIPSCl, imidazole, DMF, rt
Why: TIPS protection of the allylic alcohol gives the ring-B fragment 23; TIPS is robust to the mild acid used later to remove TES.

Step 19
Reactants: 11 (see list); 23 (see list)
Product: 24 (Mukaiyama–Michael adduct drawn as the ring-B TMS enol ether: the cyclopentanone of 11 joined through its new quaternary C7 (Me, C8=O, C14) to C6a of the cycl…)
Conditions: 11: TMSOTf, Et3N, CH2Cl2, 0 °C (thermodynamic, tetrasubstituted TMS enol ether); then 23, Me3SiNTf2 (5 mol%), CH2Cl2, −78 °C (Mukaiyama–Michael)
Why: The enone approaches the tetrasubstituted enol silane anti to the vicinal C14–CH2CO2Me, creating quaternary C7 with C6a trans to the acetate chain (as in the target); silyl transfer gives the ring-B enol ether directly, so no free enolate can β-eliminate the OTIPS group.

Step 20
Reactants: 24 (see list)
Product: 25 (Saegusa product: as 24 but ring B is the cyclohexenone C13b(=O)–C13a(CH2OTIPS)=C6a(C7), a tetrasubstituted enone; C8 ketone unchanged; (4S,4aS,7S,10R,14S))
Conditions: Pd(OAc)2 (1.1 equiv), MeCN, rt (Saegusa–Ito)
Why: Dehydrogenation of the isolated enol silane through β-hydride elimination of C6a–H regenerates the enone with the tetrasubstituted C13a=C6a bond; the non-silylated C8 ketone is untouched.

Step 21
Reactants: 25 (see list)
Product: 26 (as 25 with the C4 hydroxyl free (TES removed); (4S,4aS,7S,10R,14S))
Conditions: PPTS (cat.), MeOH/CH2Cl2, 0 °C
Why: Mild acid cleaves the TES ether selectively; the primary TBS and TIPS ethers, furan and ketones survive.

Step 22
Reactants: 26 (as 25 with the C4 hydroxyl free); 27 (2-(diethoxyphosphoryl)acetic acid)
Product: 28 (phosphonoacetate of 26: C4–O–C(=O)CH2P(O)(OEt)2; (4S,4aS,7S,10R,14S))
Conditions: 27, 2,4,6-trichlorobenzoyl chloride, Et3N, THF; then 26, DMAP, toluene, rt (Yamaguchi esterification)
Why: The mixed anhydride acylates the hindered secondary alcohol to give the phosphonoacetate tethered to the C13b ketone.

Step 23
Reactants: 28 (phosphonoacetate of 26: C4–O–C(=O)CH2P(O)(OEt)2;)
Product: 29 (tricyclic dienoate lactone (rings A and B closed): (4R,4aR,7S,10R,14S)-4-(furan-3-yl)-4a,7,10-trimethyl-13a-(TIPSO-methyl)-10-(TBSO-methyl)... i.e. the targe…)
Conditions: NaH (1.5 equiv), THF, 0 °C → 65 °C (intramolecular HWE)
Why: The phosphonate carbanion closes the six-membered α,β-unsaturated δ-lactone onto the C13b enone ketone (which has no enolisable α-H); the ring fixes the C1=C13b geometry and gives the C1=C13b–C13a=C6a dienoate.

Step 24
Reactants: 29 (see list)
Product: 30 (diol: 29 with both silyl groups removed (allylic C13–OH, neopentyl C11–OH); (4R,4aR,7S,10R,14S))
Conditions: TBAF (4 equiv), THF, rt

Why: Both silyl ethers (primary TBS and TIPS) are removed; lactone, methyl ester and furan tolerate fluoride.

Step 25
Reactants: 30 (see list)
Product: 31 (dienal: 30 with the allylic C13 alcohol oxidized to C13a–CHO; C11–CH2OH intact)
Conditions: MnO2 (20 equiv), CH2Cl2, rt
Why: Manganese dioxide oxidises only the allylic C13 alcohol to the dienal; the neopentyl C11–CH2OH is untouched.

Step 26
Reactants: 31 (dienal: 30 with the allylic C13 alcohol oxidized to C13a–CHO; C11–CH2OH intact); 32 ((iodomethyl)triphenylphosphonium iodide)
Product: 33 ((Z)-vinyl iodide: 31 with C13a–CH=CH–I (Z); C11–CH2OH intact; (4R,4aR,7S,10R,14S))
Conditions: 32 (3 equiv), NaHMDS (2.9 equiv), THF/HMPA, −78 °C; then 31, −78 °C (Stork–Zhao)
Why: Iodomethylenation of the enal with the non-stabilised iodo-ylide is Z-selective, giving the (Z)-iodo-diene; the free primary alcohol is tolerated by using excess ylide.

Step 27
Reactants: 33 ((Z)-vinyl iodide: 31 with C13a–CH=CH–I)
Product: 34 (aldehyde: 33 with C11 as CHO (the NHK substrate))
Conditions: Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Why: Oxidation of the neopentyl alcohol to the C11 aldehyde; the vinyl iodide, lactone and furan are stable.

Step 28
Reactants: 34 (aldehyde: 33 with C11 as CHO)
Product: 35 (NHK product: the 7,10-methanocyclonona[f]isochromene skeleton of the target with C11–OH, (Z)-C12=C13; methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-4-(furan-3-yl)-11-h…)
Conditions: CrCl2 (10 equiv), NiCl2 (5 mol%), DMF, rt, syringe-pump addition of 34 (final 2 mM) (intramolecular NHK)
Why: The vinylchromium adds to the neopentyl aldehyde with retention of the Z-geometry, closing the nine-membered ring; the cis-1,3 disposition of the C6a and C11 chains on the cyclopentanone preorganises the closure, and the (11R) carbinol is assumed (C11 is undefined in the target; the epimer is reachable by DMP oxidation and NaBH4/CeCl3 reduction).

Step 29
Reactants: 35 (see list)
Product: 36 (target: methyl 2-((4R,4aR,7S,10R,11R,14S,Z)-11-acetoxy-4-(furan-3-yl)-4a,7,10-trimethyl-2,8-dioxo-2,4,4a,5,6,7,8,9,10,11-decahydro-7,10-methanocyclonona[f]is…)
Conditions: Ac2O, DMAP, pyridine, rt
Why: Acetylation of the secondary allylic alcohol completes the target; no stereocentre is touched.

What I changed after checking: a Felkin–Anh model predicted that direct 3-furyllithium addition to aldehyde 14 gives the wrong C4 epimer, so C4 is now set by oxidation/(R)-CBS reduction (steps 12–13); the C14 acetate chain, originally planned by a conjugate addition whose facial bias (Me vs CH2OTBS on C10) is too weak, is now installed by CBS reduction/Johnson–Claisen chirality transfer (steps 6–7); and the fragment union uses a Mukaiyama–Michael instead of a lithium enolate so that the ring-B α-(silyloxymethyl) enolate cannot β-eliminate.

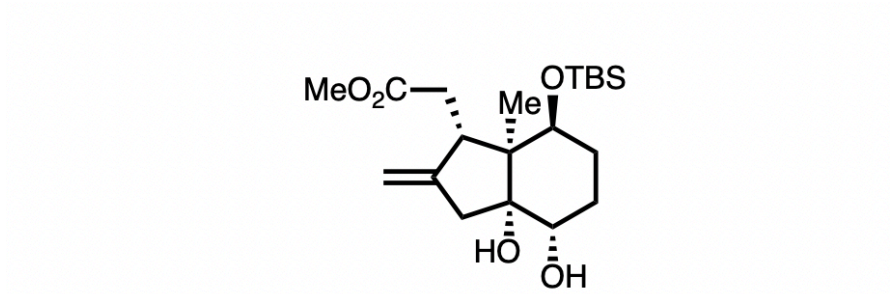
Summary

Total step count: 29 steps (fragment F1: 9 steps, 1→11; fragment F2: 9 steps, 12→23; union and completion: 11 steps, 19–29). Longest linear sequence: 20 steps (either fragment, 9 steps, plus the 11 steps from the fragment union to 36).
Three steps most likely to fail, each with a fallback:
• Step 28 (intramolecular NHK closing the nine-membered ring). Fallback: ring-closing metathesis instead — methylenate dienal 31 (Ph3P=CH2), add vinylmagnesium bromide to aldehyde 34, then Hoveyda–Grubbs II in refluxing toluene at 1 mM; or SmI2-mediated Barbier cyclisation of the same vinyl iodide/aldehyde pair.
• Step 19 (Mukaiyama–Michael creating the quaternary C7 next to a tertiary centre). Fallback: generate the lithium enolate from the TMS enol ether with MeLi, add 23 with HMPA at −78 °C and trap with TMSCl in situ; or run the silyl enol ether/enone reaction under high pressure (10 kbar) or in 5 M LiClO4/Et2O.

• Step 23 (intramolecular HWE onto the hindered, conjugated C13b ketone). Fallback: intramolecular Reformatsky (C4 bromoacetate, SmI2) followed by MsCl/DBU dehydration; or a Peterson variant (C4 trimethylsilylacetate, LDA).

Bicyclic intermediate (Newhouse laboratory)

The intermediate is a hydrindane with five contiguous stereocenters. The Newhouse group is actively pursuing a synthesis of this intermediate within the context of the natural product.



methyl 2-((1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-3a,4-dihydroxy-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl)acetate
Chemical Formula: $C_{20}H_{36}O_5Si$

The drawing as Professor Newhouse sent it and as the models received it.

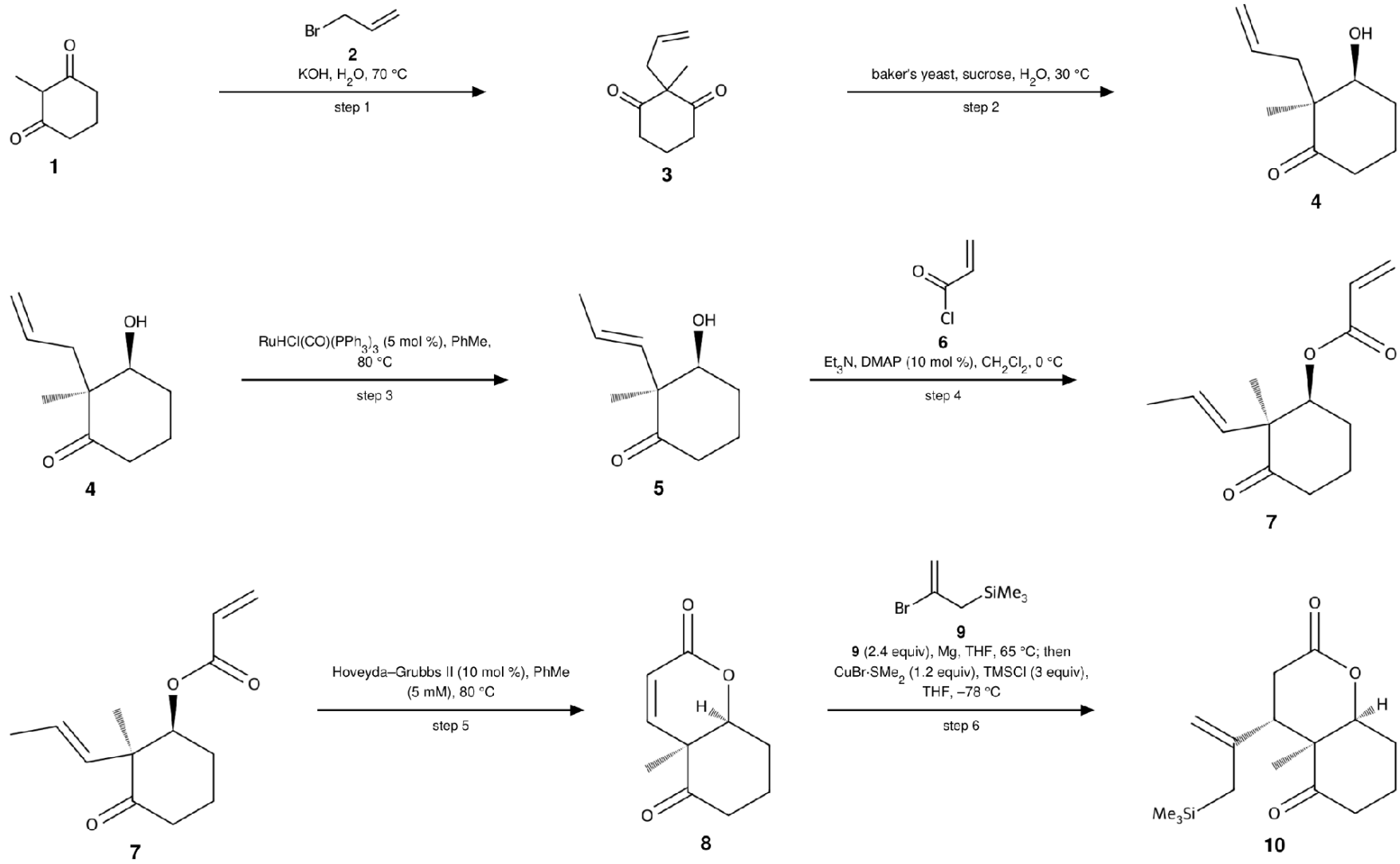
Route document	Steps
Opus 5.5's route to the bicyclic intermediate	10
Mythos 5.2's route to the bicyclic intermediate	14
Mythos 5.1's route to the bicyclic intermediate	15

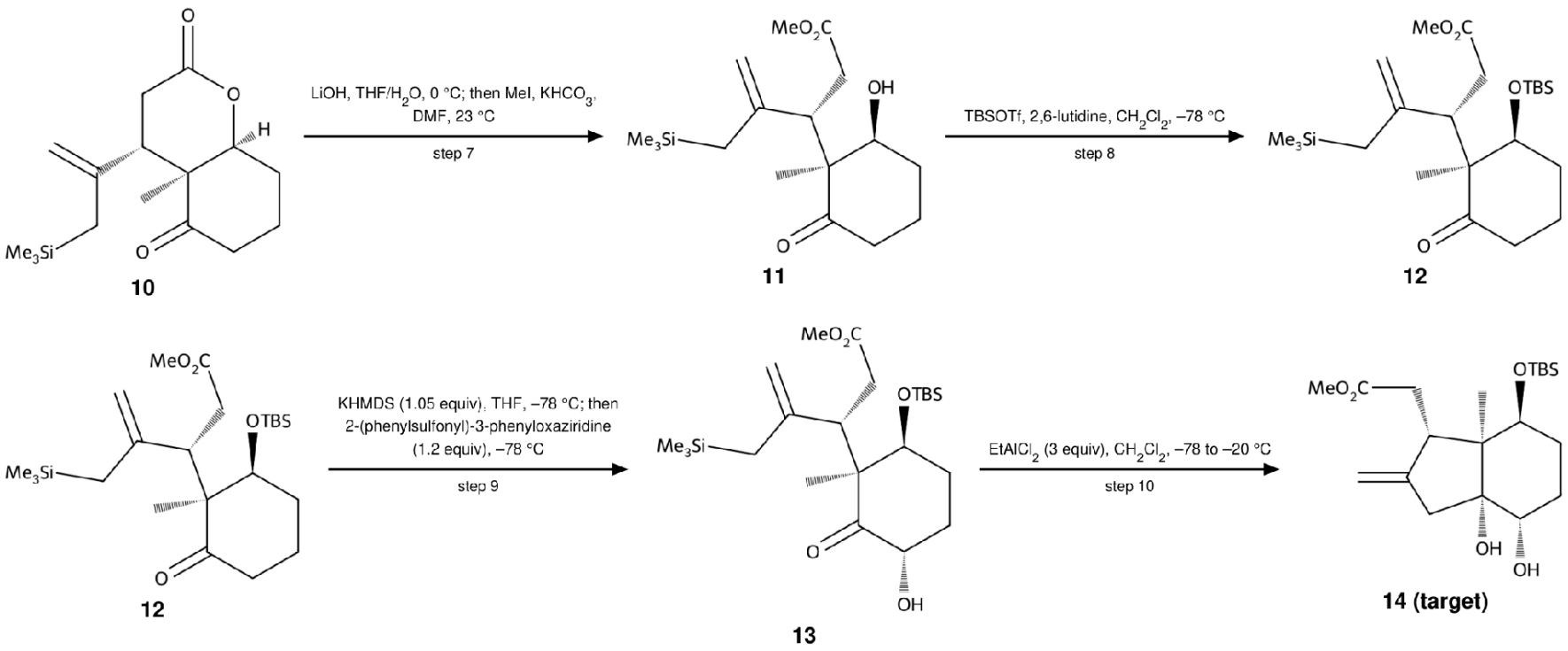
Note on Mythos 5.1. Mythos 5.1 read two hashed bonds in the drawing as wedges and stated the resulting configuration in its one-line assumption. It wrote its route to that diastereomer, with both ring-fusion centers inverted. The document is shown as the model wrote it.

Opus 5.5's route to the bicyclic intermediate

Reaction scheme

Target **14**: methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1*H*-inden-1-yl]acetate, $C_{20}H_{36}O_5Si$





Abbreviations: TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; DMAP = 4-(dimethylamino)pyridine; KHMDS = potassium hexamethyldisilazide; Tf = trifluoromethanesulfonyl; Hoveyda–Grubbs II = second-generation Hoveyda–Grubbs Ru metathesis catalyst; Boc = *tert*-butoxycarbonyl; TES = triethylsilyl; PPTS = pyridinium *p*-toluenesulfonate.

Proposed asymmetric total synthesis of the target hydrindane 14

Target **14**: methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1*H*-inden-1-yl]acetate, $C_{20}H_{36}O_5Si$

Retrosynthetic overview

1. Last ring: the cyclopentane (C3–C3a bond) closes by an intramolecular Hosomi–Sakurai addition of the allylsilane in **13** to the C3a ketone, which creates the exo-methylene and the cis-fused 3a-OH together.

2. C4–OH: α-hydroxylation of ketone **12** (Davis oxaziridine), on the face away from the axial C1 side chain.

3. C1–C2 bond: cuprate 1,4-addition of $CH_2{=}C(CH_2SiMe_3)^-$ to the cis-fused unsaturated δ-lactone **8**, which is then opened to the methyl ester and the 7-OTBS ether (**10** → **12**).

4. Lactone **8**: acrylate ring-closing metathesis onto the (*E*)-propenyl group of **5**, made by alkene isomerisation of Brooks' allyl ketone **4**.

5. C7/C7a: baker's-yeast desymmetrisation of 2-allyl-2-methylcyclohexane-1,3-dione **3** (from **1** + **2**). Ring order: cyclohexane (present in **1**) → temporary δ-lactone (step 5, opened in step 7) → cyclopentane (step 10).

Notes

Assumption: baker's-yeast reduction of **3** gives the reported (2*S*,3*S*)-hydroxy ketone (Brooks' ketone), in which the OH is cis to the allyl group; this is exactly the C7/C7a configuration the target needs.

Compound numbers are given to the substrates, the carbon building blocks and all intermediates; common reagents are listed only in the conditions. Atom numbers C1–C9 refer to the target (C8/C9 = CH_2CO_2Me).

Route (forward direction)

Step 1

Reactants: **1**, 2-methylcyclohexane-1,3-dione; **2**, allyl bromide (3-bromoprop-1-ene)

Product: **3**, 2-allyl-2-methylcyclohexane-1,3-dione ($C_{10}H_{14}O_2$)

Conditions: KOH, H_2O, 70 °C

Why: The acidic C2–H of the dione is removed in water and the stabilised enolate is C-allylated by the soft allylic bromide, giving a quaternary but still prochiral carbon (no stereocentre yet).

Step 2

Reactants: **3**

Product: **4**, (2*S*,3*S*)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (Brooks' ketone; OH cis to allyl, trans to CH_3; $C_{10}H_{16}O_2$)

Conditions: baker's yeast, sucrose, H_2O, 30 °C

Why: The yeast reductase reduces only one of the two enantiotopic carbonyls, from one face, so one operation sets both future C7 (*S*, carbinol) and C7a (*S*, quaternary), with the OH cis to the allyl group and trans to CH_3.

Step 3

Reactants: **4**

Product: **5**, (2*S*,3*S*)-3-hydroxy-2-methyl-2-[(*E*)-prop-1-en-1-yl]cyclohexan-1-one ($C_{10}H_{16}O_2$)

Conditions: $RuHCl(CO)(PPh_3)_3$ (5 mol %), PhMe, 80 °C

Why: Ru–H addition/β-hydride elimination moves the terminal alkene into the more stable (*E*)-disubstituted position; it cannot migrate further because C7a carries no H, so no stereocentre is affected.

Step 4

Reactants: **5**; **6**, acryloyl chloride (prop-2-enoyl chloride)

Product: **7**, (1*S*,2*S*)-2-methyl-3-oxo-2-[(*E*)-prop-1-en-1-yl]cyclohexyl prop-2-enoate ($C_{13}H_{18}O_3$)

Conditions: Et_3N, DMAP (10 mol %), CH_2Cl_2, 0 °C

Why: DMAP-catalysed acylation of the hindered secondary alcohol forms the acrylate without breaking the C7–O bond, so C7 keeps its configuration.

Step 5

Reactants: 7

Product: 8, (4a*S*,8a*S*)-4a-methyl-4a,7,8,8a-tetrahydro-2*H*-chromene-2,5(6*H*)-dione, the cis-fused bicyclic α,β-unsaturated δ-lactone (angular CH_3 and H-8a cis; $C_{10}H_{12}O_3$)

Conditions: Hoveyda–Grubbs II (10 mol %), PhMe (5 mM), 80 °C

Why: Ring-closing metathesis joins the acrylate CH to the propenyl CH with loss of propene; because the ester oxygen and the propenyl group are cis on the ring, only the cis-fused six-membered lactone can form.

Step 6

Reactants: 8; **9**, (2-bromoallyl)trimethylsilane [(2-bromoprop-2-en-1-yl)trimethylsilane]

Product: 10, (4*R*,4a*S*,8a*S*)-4a-methyl-4-[3-(trimethylsilyl)prop-1-en-2-yl]-3,4,4a,7,8,8a-hexahydro-2*H*-chromene-2,5(6*H*)-dione (new C4 substituent cis to the angular CH_3; $C_{16}H_{26}O_3Si$)

Conditions: 9 (2.4 equiv), Mg, THF, 65 °C; then $CuBr{\cdot}SMe_2$ (1.2 equiv), TMSCl (3 equiv), THF, –78 °C

Why: The cuprate adds 1,4 to the lactone β-carbon (target C1) from the convex face, syn to the angular CH_3, because the fused cyclohexanone blocks the other face (a force-field conformer check finds that face far more crowded); this gives the target's C1 configuration (4*R* here, 1*S* in **14**), and the ketone is untouched at –78 °C.

Step 7

Reactants: 10

Product: 11, methyl (3*R*)-3-[(1*S*,2*S*)-2-hydroxy-1-methyl-6-oxocyclohexyl]-4-methylidene-5-(trimethylsilyl)pentanoate ($C_{17}H_{30}O_4Si$)

Conditions: LiOH, THF/H_2O, 0 °C; then MeI, $KHCO_3$, DMF, 23 °C

Why: Hydroxide opens the lactone irreversibly to the carboxylate, which is methylated without acidification so the δ-hydroxy ester cannot re-close; no bond to a stereocentre is broken (C1 is β to the carbonyl and cannot epimerise).

Step 8

Reactants: 11

Product: 12, methyl (3*R*)-3-[(1*S*,2*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-methyl-6-oxocyclohexyl]-4-methylidene-5-(trimethylsilyl)pentanoate ($C_{23}H_{44}O_4Si_2$)

Conditions: TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C

Why: TBSOTf silylates the hindered secondary alcohol quickly at –78 °C, before the ketone can form a silyl enol ether, and 2,6-lutidine scavenges the TfOH that would otherwise protodesilylate the allylsilane.

Step 9

Reactants: 12

Product: 13, methyl (3*R*)-3-[(1*S*,3*S*,6*S*)-6-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-1-methyl-2-oxocyclohexyl]-4-methylidene-5-(trimethylsilyl)pentanoate (3-OH cis to 1-CH_3; $C_{23}H_{44}O_5Si_2$)

Conditions: KHMDS (1.05 equiv), THF, –78 °C; then 2-(phenylsulfonyl)-3-phenyloxaziridine (1.2 equiv), –78 °C

Why: The ketone can enolise only toward C4 (C7a is quaternary) and is more acidic than the ester; in the favoured half-chair the C1 side chain is pseudo-axial on the β face, so the oxaziridine attacks C4 from the α (CH_3) face to give the 4α-OH (4*S*), cis to CH_3.

Step 10

Reactants: 13

Product: 14, target: methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1*H*-inden-1-yl]acetate, $C_{20}H_{36}O_5Si$

Conditions: $EtAlCl_2$ (3 equiv), CH_2Cl_2, –78 to –20 °C

Why: $EtAlCl_2$ turns the 4-OH into an aluminium alkoxide (releasing ethane rather than HCl) that chelates and activates the C3a ketone; the allylsilane, held on the β face by the axial C1 tether, then adds 5-exo to close the cis-fused cyclopentane, which sets C3a (*R*; OH α, cis to CH_3 and 4-OH) and forms the exo-methylene as $SiMe_3$ is lost.

Changed after checking: I moved the C4 hydroxylation ahead of the ring closure, because hydride opening of a directed epoxide after cyclisation clashed with the methyl ester and risked lactonising the 3a-alkoxide; I also replaced a reversible K_2CO_3/MeOH lactone opening with LiOH then MeI, and swapped $TiCl_4$ for $EtAlCl_2$ so the free 4-OH cannot release HCl onto the allylsilane.

Summary

Total steps: 10 (all linear). Longest linear sequence: 10 steps from **1** (the Grignard reagent from **9** is made in situ within step 6).

Stereocentres: C7 and C7a are set in step 2, C1 in step 6, C4 in step 9 and C3a in step 10. C7a and C3a are fully substituted, and C1 and C7 are never next to a carbonyl, so none of them can epimerise later. C4 sits next to the ketone only between steps 9 and 10, and no base is used after step 9.

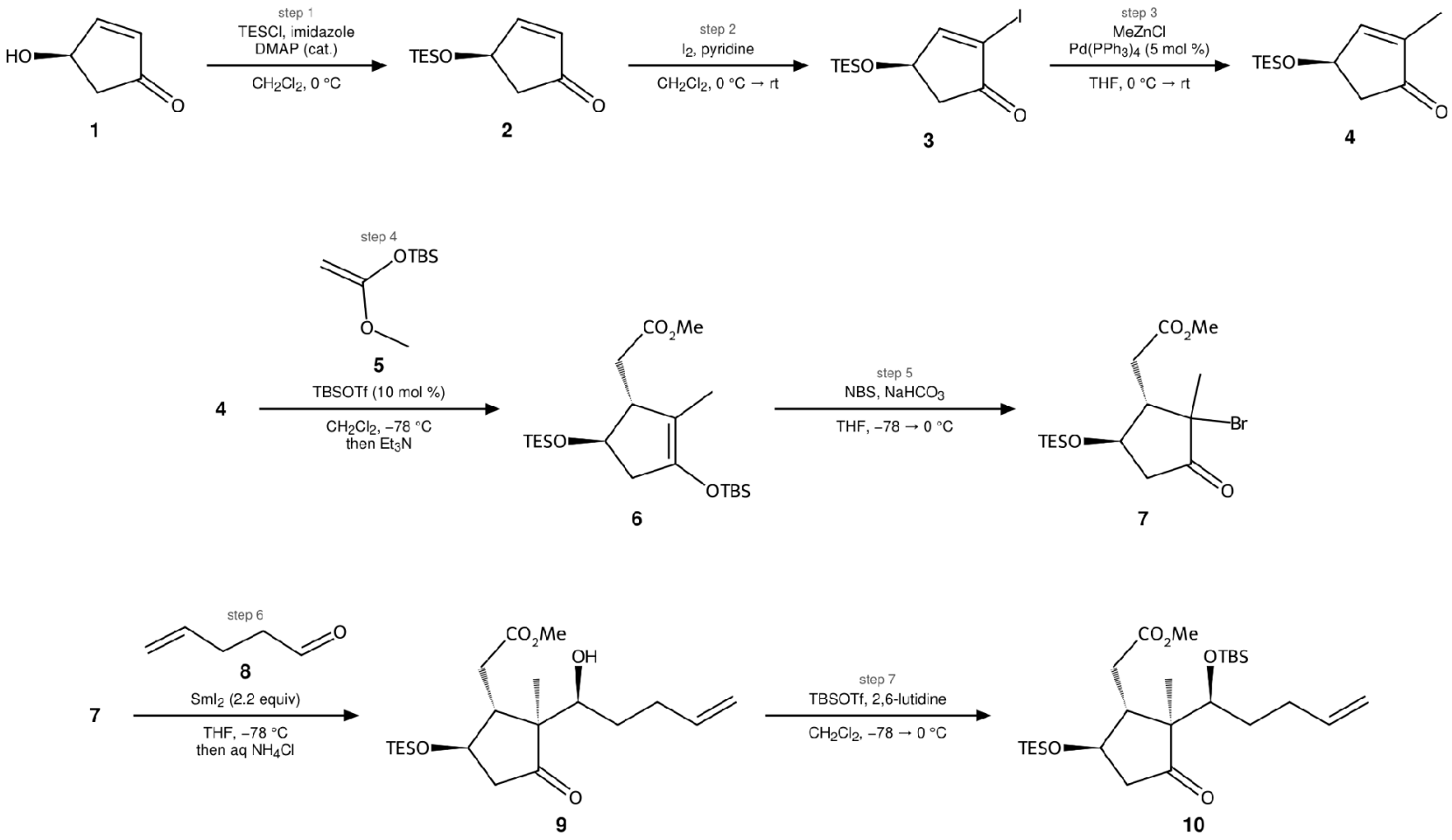
Three steps most likely to fail, each with a fallback:

1. **Step 9 (face selectivity at C4 and competing ester enolisation)**. Fallback: if the 4β-alcohol forms, install C4 after the ring closure by tethered delivery instead: dehydrogenate **12** to the enone, run the $EtAlCl_2$ cyclisation (1,2-addition), then Boc_2O/DMAP, I_2 iodocarbonate cyclisation (forces the 3a,4-cis diol), Bu_3SnH and K_2CO_3/MeOH.
2. **Step 10 (Sakurai ring closure onto a ketone next to a quaternary carbon)**. Fallback: protect the 4-OH as its TES ether (TESOTf, 2,6-lutidine), cyclise with $TiCl_4$/2,6-di-*tert*-butylpyridine at –78 °C, then remove the TES group with PPTS in MeOH.
3. **Step 6 (1,4-addition at a β-carbon flanked by a quaternary centre)**. Fallback: use Rh-catalysed 1,4-addition of CH_2=C(Bpin)CH_2SiMe_3 ($[Rh(cod)OH]_2$, dioxane/H_2O, 60 °C), or add isopropenyl cuprate instead and close the ring in step 10 by a Me_2AlCl type-II carbonyl-ene reaction.

Abbreviations: TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; DMAP = 4-(dimethylamino)pyridine; KHMDS = potassium hexamethyldisilazide; Tf = trifluoromethanesulfonyl; Hoveyda–Grubbs II = second-generation Hoveyda–Grubbs Ru metathesis catalyst; Boc = *tert*-butoxycarbonyl; TES = triethylsilyl; PPTS = pyridinium *p*-toluenesulfonate.

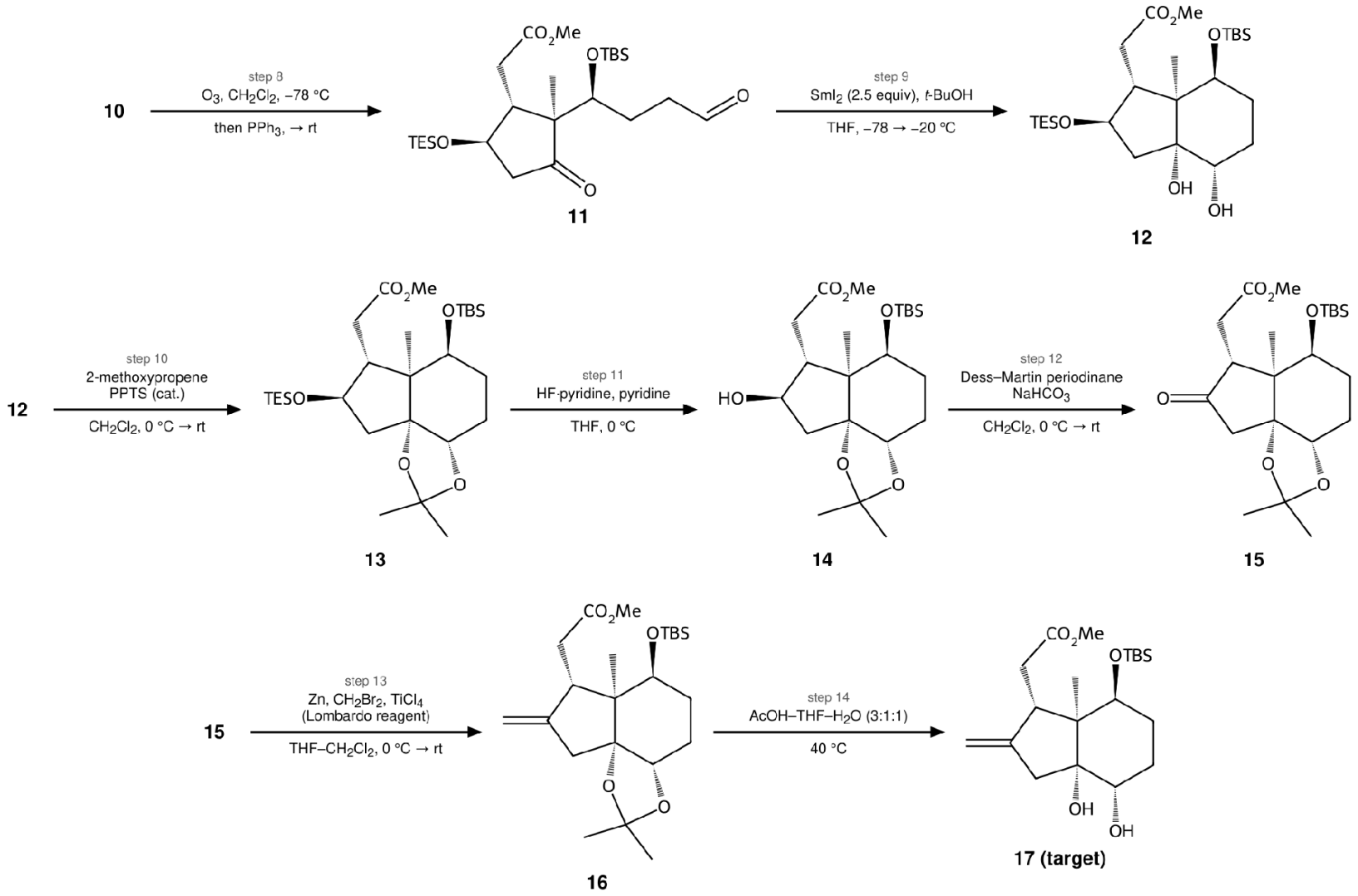
Mythos 5.2's route to the bicyclic intermediate

Scheme (part 1 of 2). Forward route from (*R*)-4-hydroxycyclopent-2-en-1-one (**1**) to the target **17** (14 steps, fully linear). Compound numbers are given under the structures; conditions are written over/under the arrows; building blocks **5** and **8** are drawn over the arrows of the steps in which they react.



TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; NBS = *N*-bromosuccinimide; PPTS = pyridinium *p*-toluenesulfonate; DMAP = 4-(dimethylamino)pyridine. Wedged and hashed bonds show absolute configuration; the plain bonds at the brominated carbon of **7** denote a mixture of epimers.

Scheme (part 2 of 2). Forward route from (*R*)-4-hydroxycyclopent-2-en-1-one (**1**) to the target **17** (14 steps, fully linear). Compound numbers are given under the structures; conditions are written over/under the arrows; building blocks **5** and **8** are drawn over the arrows of the steps in which they react.



TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; NBS = *N*-bromosuccinimide; PPTS = pyridinium *p*-toluenesulfonate; DMAP = 4-(dimethylamino)pyridine. Wedged and hashed bonds show absolute configuration; the plain bonds at the brominated carbon of **7** denote a mixture of epimers.

Proposed total synthesis of methyl 2-((1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-3a,4-dihydroxy-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl)acetate (17), $C_{20}H_{36}O_5Si$

Assumption: catalogue compounds (*R*)-4-hydroxycyclopent-2-en-1-one (**1**, ≥98% ee), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (**5**) and pent-4-enal (**8**) count as commercial (backup source of **2**: commercial (1*R*,4*S*)-*cis*-4-acetoxycyclopent-2-en-1-ol via TESCl; K_2CO_3/MeOH; PDC); the printed name and the wedges/hashes of the drawing were checked against each other and agree, so the target is unambiguous.

1. Retrosynthetic overview

1. **17** ⇒ acetonide **16** ⇒ C2 ketone **15**: the exocyclic methylene is a masked C2 carbonyl, i.e. the oxidised form of the C2–OTES 'relay' stereocentre (functional-group changes only).
2. Six-membered ring (formed last): C3a–C4 bond by SmI_2 ketyl (pinacol) cyclisation of keto-aldehyde **11** → *cis*-fused hydrindane with the *cis*-3a,4-diol (**12**).
3. C7a–C7 bond (quaternary centre + C7 carbinol): chelation-controlled Reformatsky-type aldol of the C7a samarium enolate (from bromoketone **7**) with pent-4-enal (**8**); ozonolysis later reveals the C4 aldehyde.
4. C1–CH_2CO_2Me bond: Mukaiyama–Michael addition of ketene silyl acetal **5** to enone **4**, *anti* to the 4-silyloxy group.
5. Five-membered ring is bought, not made: every stereocentre is relayed from the single stereocentre of (*R*)-4-hydroxycyclopent-2-enone (**1**). Ring order: cyclopentane (from **1**) → cyclohexane (step 9).

2. Numbered compounds

1 (*R*)-4-hydroxycyclopent-2-en-1-one — commercial starting material. $C_5H_6O_2$, M = 98.1

2 (*R*)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one — TES ether of 1. $C_{11}H_{20}O_2Si$, M = 212.4

3 (*R*)-2-iodo-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one — α-iodoenone. $C_{11}H_{19}IO_2Si$, M = 338.3

4 (*R*)-2-methyl-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one — α-methyl enone. $C_{12}H_{22}O_2Si$, M = 226.4

5 1-[(*tert*-butyldimethylsilyl)oxy]-1-methoxyethene, CH_2=C(OMe)OTBS — commercial ketene silyl acetal of methyl acetate. $C_9H_{20}O_2Si$, M = 188.3

6 methyl 2-[(1*R*,5*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-5-[(triethylsilyl)oxy]cyclopent-2-en-1-yl]acetate — TBS enol ether; CH_2CO_2Me *trans* to OTES. $C_{21}H_{42}O_4Si_2$, M = 414.7

7 methyl 2-[(1*S*,5*R*)-2-bromo-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate — tertiary α-bromoketone, both C2 epimers (centre re-planarised in step 6); C1 label is *S* only because Br raises the CIP priority of C2. $C_{15}H_{27}BrO_4Si$, M = 379.4

8 pent-4-enal — commercial. C_5H_8O, M = 84.1

9 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-hydroxypent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate — aldol; ring methyl *cis* to CH_2CO_2Me, carbinol chain *cis* to OTES. $C_{20}H_{36}O_5Si$, M = 384.6

10 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]pent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate — TBS ether of 9. $C_{26}H_{50}O_5Si_2$, M = 498.9

11 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-4-oxobutyl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate — keto-aldehyde. $C_{25}H_{48}O_6Si_2$, M = 500.8

12 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate — *cis*-hydrindane *cis*-diol; 3a-OH, 4-OH, 7a-Me and side chain on one face, 2-OTES and 7-OTBS on the other. $C_{25}H_{50}O_6Si_2$, M = 502.8

13 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate — 3a,4-acetonide of 12. $C_{28}H_{54}O_6Si_2$, M = 542.9

14 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-3a,4-(isopropylidenedioxy)-7a-methyloctahydro-1*H*-inden-1-yl]acetate — C2 alcohol. $C_{22}H_{40}O_5Si$, M = 428.6

15 methyl 2-[(1*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-oxooctahydro-1*H*-inden-1-yl]acetate — C2 ketone. $C_{22}H_{38}O_6Si$, M = 426.6

16 methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl]acetate — acetonide of the target. $C_{23}H_{40}O_5Si$, M = 424.6

17 methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl]acetate — TARGET. $C_{20}H_{36}O_5Si$, M = 384.6

3. Route, step by step (forward direction)

Step 1

Reactants: **1** (*R*)-4-hydroxycyclopent-2-en-1-one

Product: **2** (*R*)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one

Conditions: TESCl, imidazole, DMAP (cat.), CH_2Cl_2, 0 °C

Why: Routine O-silylation under buffered conditions that do not provoke β-elimination; TES (not TBS) is chosen so that this oxygen can later be unmasked selectively beside the C7–OTBS ether that must remain in the target.

Step 2

Reactants: **2** (*R*)-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one

Product: **3** (*R*)-2-iodo-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one

Conditions: I_2, pyridine–CH_2Cl_2 (1:1), 0 °C → rt

Why: Johnson α-iodination of the enone (conjugate addition of pyridine, iodination of the enolate, loss of pyridine); the C4 stereocentre is not involved.

Step 3

Reactants: **3** (*R*)-2-iodo-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one

Product: **4** (*R*)-2-methyl-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one

Conditions: MeZnCl, $Pd(PPh_3)_4$ (5 mol %), THF, 0 °C → rt

Why: Negishi coupling of an α-iodoenone runs at or below room temperature under essentially neutral conditions, so the base-sensitive β-silyloxy enone neither eliminates nor racemises.

Step 4

Reactants: **4** (*R*)-2-methyl-4-[(triethylsilyl)oxy]cyclopent-2-en-1-one; **5** 1-[(*tert*-butyldimethylsilyl)oxy]-1-methoxyethene, CH_2=C(OMe)OTBS

Product: **6** methyl 2-[(1*R*,5*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-5-[(triethylsilyl)oxy]cyclopent-2-en-1-yl]acetate

Conditions: **5** (1.5 equiv), TBSOTf (10 mol %), CH_2Cl_2, –78 °C; Et_3N quench

Why: Silyl-triflate-catalysed Mukaiyama–Michael addition takes place on the enone face *anti* to the adjacent OTES group (the selectivity exploited in prostaglandin three-component couplings), which sets C1 with CH_2CO_2Me *trans* to OTES; silyl transfer traps the C7a enolate regiospecifically as its TBS enol ether.

Step 5

Reactants: **6** methyl 2-[(1*R*,5*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-5-[(triethylsilyl)oxy]cyclopent-2-en-1-yl]acetate

Product: **7** methyl 2-[(1*S*,5*R*)-2-bromo-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Conditions: NBS, $NaHCO_3$, THF, –78 → 0 °C

Why: The electron-rich tetrasubstituted silyl enol ether is brominated regiospecifically at C7a; the configuration of this tertiary bromide is irrelevant because the centre becomes an enolate again in step 6, and silyl ethers and ester are inert to NBS.

Step 6

Reactants: **7** methyl 2-[(1*S*,5*R*)-2-bromo-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate; **8** pent-4-enal

Product: **9** methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-hydroxypent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Conditions: SmI_2 (2.2 equiv), THF, –78 °C, **7** + **8** (1.1 equiv) added together; sat. aq NH_4Cl at –78 °C

Why: Two-electron reduction of the C–Br bond gives the regiodefined Sm(III) enolate, which adds to the aldehyde through a chelated chair (Zimmerman–Traxler) transition state on the ring face *anti* to the C1 side chain: this fixes the quaternary C7a (methyl *cis* to CH_2CO_2Me) and, with the alkyl chain equatorial, the (*S*)-carbinol C7 (conformer analysis: only the 7*S* isomer fits the chelated chair); the medium is non-basic, so ester, β-silyloxy ketone and the retro-aldol-prone product survive.

Step 7

Reactants: 9 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-hydroxypent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Product: 10 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]pent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Conditions: TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 → 0 °C

Why: The reactive silyl triflate silylates the hindered neopentylic secondary alcohol at low temperature without retro-aldol; this TBS ether is the one retained in the target.

Step 8

Reactants: 10 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]pent-4-en-1-yl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Product: 11 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-4-oxobutyl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Conditions: O_3, CH_2Cl_2, –78 °C; then PPh_3, –78 °C → rt

Why: The terminal alkene is the only ozone-reactive group, so the C4 aldehyde is unveiled without touching ketone, ester or silyl ethers.

Step 9

Reactants: 11 methyl 2-[(1*R*,2*S*,5*R*)-2-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-4-oxobutyl]-2-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopentyl]acetate

Product: 12 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate

Conditions: SmI_2 (2.5 equiv), *t*-BuOH (2 equiv), THF, –78 → –20 °C

Why: The aldehyde ketyl adds to the ring ketone and closes the six-membered ring; the three-carbon tether hangs from the β-face of C7a, so *cis* ring fusion is strongly favoured (C3a–OH *cis* to the angular methyl), and the Sm(III)-bridged transition state delivers the *cis*-1,2-diol (C4–OH on the same face); silyl ethers and ester are inert to SmI_2 at low temperature.

Step 10

Reactants: 12 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate

Product: 13 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate

Conditions: 2-methoxypropene, PPTS (cat.), CH_2Cl_2, 0 °C → rt

Why: The *cis*-1,2-diol closes to a five-membered isopropylidene acetal under acid mild enough to spare the TES ether; masking the tertiary C3a–OH prevents retro-aldol/β-elimination once C2 becomes a ketone.

Step 11

Reactants: 13 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl]acetate

Product: 14 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-3a,4-(isopropylidenedioxy)-7a-methyloctahydro-1*H*-inden-1-yl]acetate

Conditions: HF·pyridine, pyridine, THF, 0 °C

Why: Buffered HF·pyridine cleaves the unhindered secondary TES ether orders of magnitude faster than the neopentylic secondary TBS ether; acetonide and ester are untouched.

Step 12

Reactants: 14 methyl 2-[(1*R*,2*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-3a,4-(isopropylidenedioxy)-7a-methyloctahydro-1*H*-inden-1-yl]acetate

Product: 15 methyl 2-[(1*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-oxooctahydro-1*H*-inden-1-yl]acetate

Conditions: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C → rt

Why: Buffered DMP oxidises the only free hydroxyl under near-neutral conditions, so the epimerisable C1 centre and the β-alkoxy ketone (C3a–O) are not disturbed.

Step 13

Reactants: 15 methyl 2-[(1*R*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-oxooctahydro-1*H*-inden-1-yl]acetate

Product: 16 methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl]acetate

Conditions: Zn, CH_2Br_2, $TiCl_4$ (Lombardo reagent), THF–CH_2Cl_2, 0 °C → rt

Why: The non-basic *gem*-dimetallic reagent methylenates ketones in the presence of esters without enolisation, so there is no C1 epimerisation or E1cB opening of the acetonide (the C1 descriptor changes from *R* to *S* only because C2 drops in CIP priority).

Step 14

Reactants: 16 methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-(isopropylidenedioxy)-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl]acetate

Product: 17 methyl 2-[(1*S*,3a*R*,4*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methyleneoctahydro-1*H*-inden-1-yl]acetate

Conditions: AcOH–THF–H_2O (3:1:1), 40 °C

Why: Mild aqueous acid hydrolyses the isopropylidene acetal while the hindered secondary TBS ether, the methyl ester and the 1,1-disubstituted alkene survive, releasing the 3a,4-diol of the target.

Changed after checking: the C2–O protecting group was switched from TBS to TES (it has to come off before the C7–OTBS); the originally planned open-transition-state Mukaiyama aldol of **6** was replaced by bromination/SmI_2-Reformatsky aldol (steps 5–6) because conformer analysis showed that only the chelated chair leads to the required 7*S* carbinol; and Wittig methylenation was replaced by the non-basic Lombardo reagent.

4. Closing summary

Total step count: 14 (building blocks **5** and **8** are purchased). Longest linear sequence: 14 steps from **1** (the route is fully linear).

Three steps most likely to fail, each with one fallback:

1. **Step 6 (Reformatsky-type aldol that creates the quaternary centre).** Risk: simple protonation of the hindered Sm enolate (debrominated ketone), aldehyde pinacol or Sm-promoted aldol–Tishchenko reduction, or modest C7 selectivity. **Fallback:** Wessjohann-type $CrCl_2$/LiI (THF, rt) Reformatsky aldol of **7** with **8**: non-basic, no retro-aldol or Tishchenko pathway, same closed transition state.
2. **Step 9 (SmI_2 ketyl/pinacol ring closure).** Risk: over-reduction of the aldehyde to the primary alcohol, a low *cis*/*trans* diol ratio, or lactonisation of the Sm alkoxide onto the ester. **Fallback:** low-valent titanium pinacol coupling ($TiCl_3(DME)_{1.5}$, Zn–Cu, DME, rt, stopped at the diol), which also favours *cis*-diols in six-ring closures.
3. **Step 4 (Mukaiyama–Michael addition to a hindered α-methyl-γ-silyloxy enone).** Risk: sluggish addition, competing 1,2-addition, or Lewis-acid loss of the OTES group. **Fallback:** the neutral HgI_2-catalysed (or 5 M $LiClO_4$–Et_2O) silyl-transfer Michael addition of **5**, documented for 4-silyloxycyclopentenones.

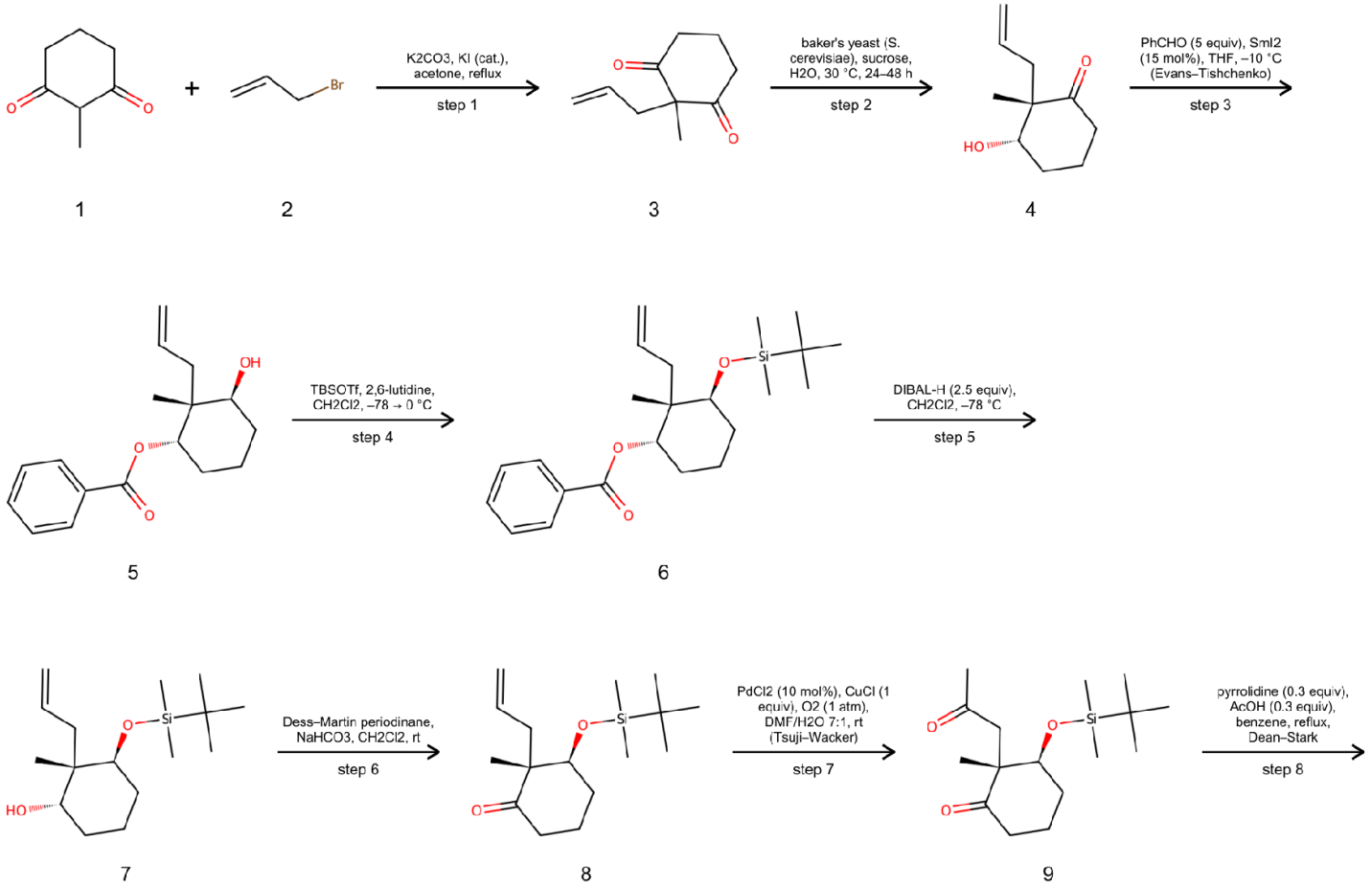
Where each stereocentre of the target is set: C1 in step 4 (addition *anti* to OTES); C7a and C7 in step 6 (aldol *anti* to the C1 side chain, chelated chair); C3a and C4 in step 9 (*cis* ring fusion, *cis*-diol). The C2 stereocentre inherited from **1** is a relay only and is deliberately destroyed in step 12. C1 is the only epimerisable centre, and only while C2 is a ketone (**15**), which is handled exclusively under buffered, non-basic conditions; the C7a/C7 aldol unit is secured against retro-aldol by silylation in step 7.

Verification performed with RDKit: (i) the stereoisomer named (1*S*,3a*R*,4*S*,7*S*,7a*S*) was embedded in 3D and has side chain, 7a-Me, 3a-OH and 4-OH on one face and 7-OTBS on the other, exactly as drawn in the question; (ii) molecular formulae of all 17 compounds and the mass balance of every step were confirmed (e.g. **9** and **17** are isomers, $C_{20}H_{36}O_5Si$); (iii) CIP descriptors in the names were computed, not assigned by hand; (iv) the pre-cyclisation intermediates **9**–**11** were generated from **12** by formal bond cleavage so that the carried-through stereocentres cannot be mis-transcribed; (v) every drawing in the scheme was tested by re-perceiving its stereochemistry from the 2D coordinates and wedges alone and comparing it with the intended structure.

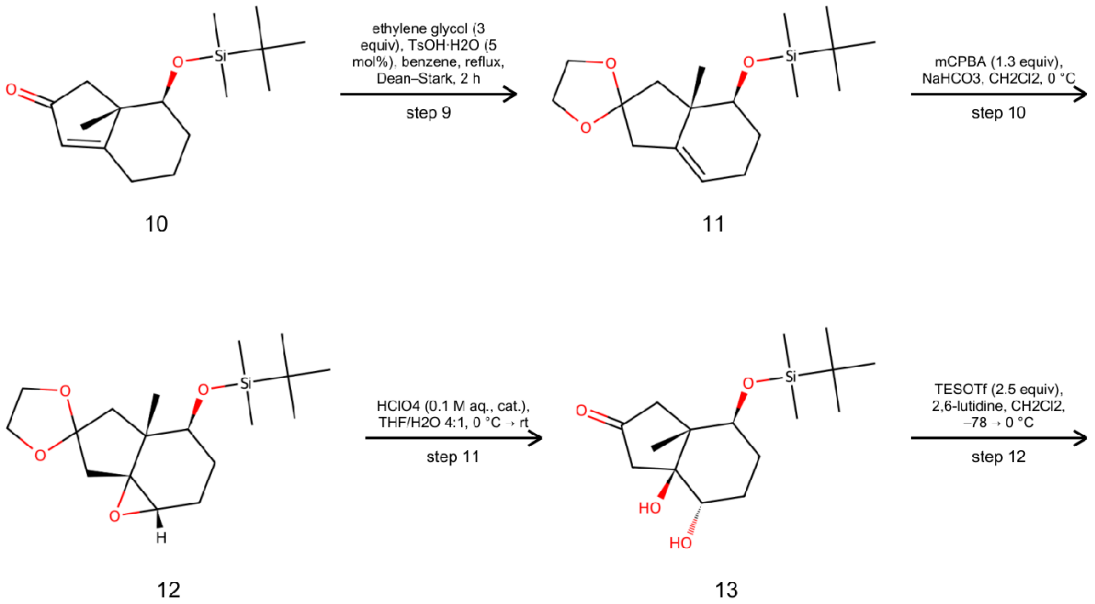
Mythos 5.1's route to the bicyclic intermediate

(written for a diastereomer of the target)

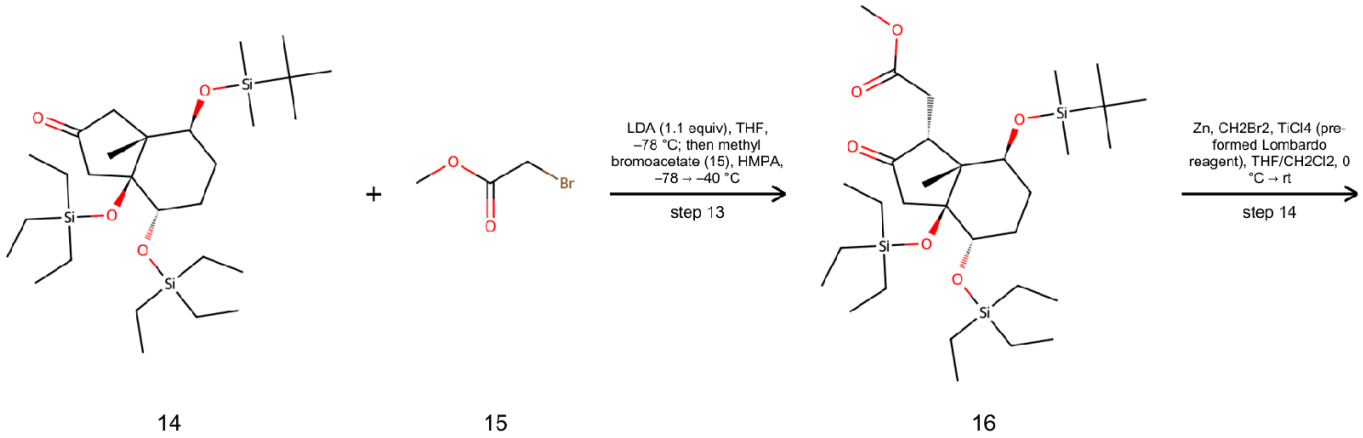
Scheme. Forward synthesis of 18 (compound numbers under structures; conditions over arrows)



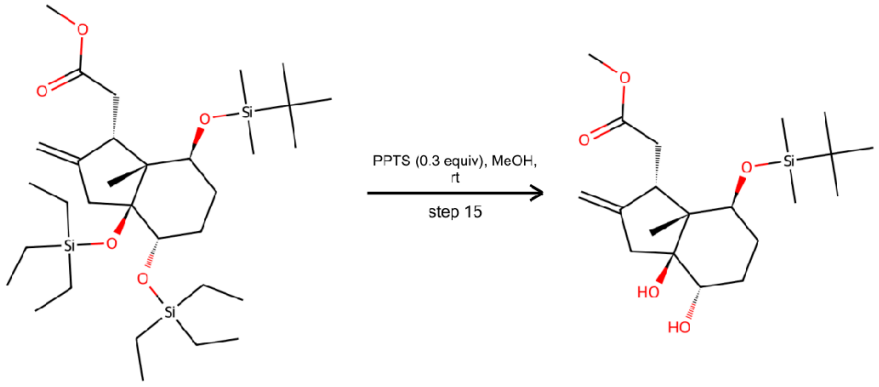
Scheme. Forward synthesis of 18 (compound numbers under structures; conditions over arrows) (continued)



Scheme. Forward synthesis of 18 (compound numbers under structures; conditions over arrows) (continued)



14 15 16



17 18

Proposed total synthesis of methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1H-inden-1-yl]acetate (18)

Assumption. Stereochemical assumption: the wedges and dashes of the drawing are taken as authoritative (Me on C7a, OTBS on C7 and the 3a-OH on one face; the 4-OH and the CH2CO2Me chain on the other face), which corresponds to (1S,3aS,4S,7S,7aR). The caption's 3aR,7aS descriptors would describe a different diastereomer and are not followed.

Retrosynthetic overview

1. 18 ⇐ 17 ⇐ 16 ⇐ 14 + 15: the exocyclic methylene is installed last (non-basic Lombardo methylenation) after a kinetic C1-alkylation of the doubly TES-protected keto-diol anti to the angular methyl; both TES groups are removed in the final step.
2. 14 ⇐ 13 ⇐ 12 ⇐ 11 ⇐ 10: the trans-3a,4-diol comes from epoxidation of the Δ3a,4-alkene anti to the angular methyl and trans-diaxial hydrolytic opening; the alkene is created from hydrindenone 10 by deconjugative ketalisation.
3. 10 ⇐ 9 ⇐ 8: the five-membered ring is closed by intramolecular aldol condensation of a 1,4-diketone obtained by Wacker oxidation of the allyl ketone 8.
4. 8 ⇐ 5 ⇐ 4 ⇐ 3 ⇐ 1 + 2: the quaternary C7a and the C7 oxygen come from baker's-yeast desymmetrisation of 2-allyl-2-methylcyclohexane-1,3-dione; an Evans–Tishchenko-based swap of the ketone and carbinol positions puts the C7 oxygen syn to the methyl and selects the drawn enantiomer.
5. Ring order: the six-membered ring is the commercial dione (never constructed); the five-membered ring is closed at step 8; no further ring is formed.

Numbered compounds

1: 2-methylcyclohexane-1,3-dione (commercial) — C7H10O2, MW 126.2
2: allyl bromide (commercial) — C3H5Br, MW 121.0
3: 2-allyl-2-methylcyclohexane-1,3-dione — C10H14O2, MW 166.2
4: (2S,3S)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (OH anti to Me, syn to allyl) — C10H16O2, MW 168.2
5: (1S,2R,3S)-3-hydroxy-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate (trans-1,3-diol monobenzoate; free OH syn to Me) — C17H22O3, MW 274.4
6: (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate — C23H36O3Si, MW 388.6
7: (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-ol — C16H32O2Si, MW 284.5
8: (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-one (OTBS syn to Me) — C16H30O2Si, MW 282.5
9: (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(2-oxopropyl)cyclohexan-1-one — C16H30O3Si, MW 298.5
10: (7S,7aS)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one (enone, C3=C3a; OTBS syn to Me) — C16H28O2Si, MW 280.5
11: (7'S,7'aS)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-1',3',5',6',7',7'a-hexahydrospiro[1,3-dioxolane-2,2'-indene] (ethylene ketal; alkene moved to C3a=C4) — C18H32O3Si, MW 324.5
12: (3'aR,4'S,7'S,7'aR)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-3'a,4'-epoxyhexahydrospiro[1,3-dioxolane-2,2'-indene] (the 3a,4-epoxide of 11; oxirane anti to the angular Me) — C18H32O4Si, MW 340.5
13: (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methylhexahydro-1H-inden-2(3H)-one (keto-diol; 3a-OH syn to Me, 4-OH anti) — C16H30O4Si, MW 314.5
14: (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-3a,4-bis[(triethylsilyl)oxy]hexahydro-1H-inden-2(3H)-one — C28H58O4Si3, MW 543.0
15: methyl bromoacetate (commercial) — C3H5BrO2, MW 153.0
16: methyl 2-[(1R,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-oxo-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate (CH2CO2Me anti to Me) — C31H62O6Si3, MW 615.1
17: methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-methylidene-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate — C32H64O5Si3, MW 613.1
18: methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1H-inden-1-yl]acetate (target) — C20H36O5Si, MW 384.6

Forward route

Step 1
Reactants: 1 2-methylcyclohexane-1,3-dione (commercial); 2 allyl bromide (commercial)
Product: 3 2-allyl-2-methylcyclohexane-1,3-dione
Conditions: K2CO3, KI (cat.), acetone, reflux
Why: The stabilised C2-enolate of the dione is C-allylated by allyl bromide; the product is achiral (both carbonyls equivalent).

Step 2
Reactants: 3 2-allyl-2-methylcyclohexane-1,3-dione
Product: 4 (2S,3S)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (OH anti to Me, syn to allyl)
Conditions: baker's yeast (S. cerevisiae), sucrose, H2O, 30 °C, 24–48 h
Why: Enzymatic desymmetrisation reduces one enantiotopic carbonyl with hydride delivered from the methyl face, giving the (2S,3S)-hydroxy ketone (OH anti to Me, syn to allyl) in high ee; this sets the absolute configuration of the quaternary centre that becomes C7a.

Step 3
Reactants: 4 (2S,3S)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (OH anti to Me, syn to allyl)
Product: 5 (1S,2R,3S)-3-hydroxy-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate (trans-1,3-diol monobenzoate; free OH syn to Me)
Conditions: PhCHO (5 equiv), SmI2 (15 mol%), THF, −10 °C (Evans–Tishchenko)
Why: The samarium hemiacetal formed on the C3-OH delivers hydride intramolecularly to the C1 ketone through a six-membered transition state, giving the 1,3-anti (trans) diol monobenzoate: the new carbinol (future C7) is created on the methyl face (S) while the ester sits on the original oxygen, so the two oxygens are differentiated by mechanism rather than by sterics.

Step 4
Reactants: 5 (1S,2R,3S)-3-hydroxy-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate (trans-1,3-diol monobenzoate; free OH syn to Me)
Product: 6 (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate
Conditions: TBSOTf, 2,6-lutidine, CH2Cl2, −78 → 0 °C
Why: Silylation of the only free hydroxyl installs the C7 TBS ether that is carried unchanged to the target.

Step 5
Reactants: 6 (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexyl benzoate
Product: 7 (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-ol
Conditions: DIBAL-H (2.5 equiv), CH2Cl2, −78 °C
Why: Reductive removal of the benzoate frees the carbinol that will become C3a; the silyl ether and terminal alkene survive.

Step 6
Reactants: 7 (1S,2S,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-ol
Product: 8 (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-one (OTBS syn to Me)
Conditions: Dess–Martin periodinane, NaHCO3, CH2Cl2, rt
Why: Oxidation to the ketone completes the swap of oxidation states: the ketone is now on the carbon that becomes C3a and the TBS-oxy carbon (C7) is syn to the methyl, i.e. the (2R,3S) series required by the drawn enantiomer.

Step 7
Reactants: 8 (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(prop-2-en-1-yl)cyclohexan-1-one (OTBS syn to Me)
Product: 9 (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(2-oxopropyl)cyclohexan-1-one
Conditions: PdCl2 (10 mol%), CuCl (1 equiv), O2 (1 atm), DMF/H2O 7:1, rt (Tsuji–Wacker)
Why: Markovnikov Wacker oxidation converts the terminal alkene into the methyl ketone, giving the 1,4-diketone needed to close the five-membered ring; ketone and silyl ether are untouched.

Step 8
Reactants: 9 (2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-(2-oxopropyl)cyclohexan-1-one
Product: 10 (7S,7aS)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one (enone, C3=C3a; OTBS syn to Me)
Conditions: pyrrolidine (0.3 equiv), AcOH (0.3 equiv), benzene, reflux, Dean–Stark
Why: The enamine of the less hindered methyl ketone attacks the ring ketone (intramolecular aldol) and the ketol dehydrates to the conjugated hydrindenone; the ring fusion carbon C3a is sp2, so no new stereocentre is formed and C7/C7a are untouched.

Step 9
Reactants: 10 (7S,7aS)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one (enone, C3=C3a; OTBS syn to Me)
Product: 11 (7'S,7'aS)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-1',3',5',6',7',7'a-hexahydrospiro[1,3-dioxolane-2,2'-indene] (ethylene ketal; alkene moved to C3a=C4)
Conditions: ethylene glycol (3 equiv), TsOH·H2O (5 mol%), benzene, reflux, Dean–Stark, 2 h
Why: Ketalisation of the enone goes through the dienol ether and re-protonates at C3, moving the alkene out of conjugation to C3a=C4 (the Δ4→Δ5 migration seen for 3-keto-steroid ketals); C1 is still CH2, so no stereocentre can epimerise under the acidic conditions.

Step 10
Reactants: 11 (7'S,7'aS)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-1',3',5',6',7',7'a-hexahydrospiro[1,3-dioxolane-2,2'-indene] (ethylene ketal; alkene moved to C3a=C4)
Product: 12 (3'aR,4'S,7'S,7'aR)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-3'a,4'-epoxyhexahydrospiro[1,3-dioxolane-2,2'-indene] (the 3a,4-epoxide of 11; oxirane anti to the angular Me)
Conditions: mCPBA (1.3 equiv), NaHCO3, CH2Cl2, 0 °C
Why: The trisubstituted alkene is epoxidised on the face opposite the axial angular methyl and the C7-OTBS (both on the top face), giving the α-oxirane (oxygen anti to Me).

Step 11
Reactants: 12 (3'aR,4'S,7'S,7'aR)-7'-[(tert-butyldimethylsilyl)oxy]-7'a-methyl-3'a,4'-epoxyhexahydrospiro[1,3-dioxolane-2,2'-indene] (the 3a,4-epoxide of 11; oxirane anti to the angular Me)
Product: 13 (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methylhexahydro-1H-inden-2(3H)-one (keto-diol; 3a-OH syn to Me, 4-OH anti)
Conditions: HClO4 (0.1 M aq., cat.), THF/H2O 4:1, 0 °C → rt
Why: Acid opens the epoxide at the tertiary carbon with anti (trans-diaxial) delivery of water: the new C3a-OH is syn to the methyl and the retained C4-O is anti to it, exactly the target relationship; the dioxolane is hydrolysed in the same pot to return the ketone.

Step 12
Reactants: 13 (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methylhexahydro-1H-inden-2(3H)-one (keto-diol; 3a-OH syn to Me, 4-OH anti)
Product: 14 (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-3a,4-bis[(triethylsilyl)oxy]hexahydro-1H-inden-2(3H)-one
Conditions: TESOTf (2.5 equiv), 2,6-lutidine, CH2Cl2, –78 → 0 °C
Why: Both the secondary and the tertiary hydroxyl are converted into TES ethers (removable later in the presence of the hindered secondary TBS); at low temperature the ketone is not converted to its silyl enol ether, and the β-silyloxy ketone can no longer retro-aldolise under the basic conditions of the next step.

Step 13
Reactants: 14 (3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-3a,4-bis[(triethylsilyl)oxy]hexahydro-1H-inden-2(3H)-one; 15 methyl bromoacetate (commercial)
Product: 16 methyl 2-[(1R,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-oxo-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate (CH2CO2Me anti to Me)
Conditions: LDA (1.1 equiv), THF, –78 °C; then methyl bromoacetate (15), HMPA, –78 → –40 °C
Why: Kinetic deprotonation occurs at C1 (the C3 methylene is buried between the C3a-OTES and C4-OTES groups), and the electrophile approaches the planar enolate from the face opposite the angular methyl, the C7-OTBS and the C3a-OTES, placing the CH2CO2Me group anti to the methyl (this is the configuration that is 1S in the target; it is labelled 1R in 16 only because the ketone changes the CIP priorities); the ester is introduced only after every equilibrating step, so this kinetic configuration is never scrambled.

Step 14
Reactants: 16 methyl 2-[(1R,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-oxo-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate (CH2CO2Me anti to Me)
Product: 17 methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-methylidene-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate
Conditions: Zn, CH2Br2, TiCl4 (pre-formed Lombardo reagent), THF/CH2Cl2, 0 °C → rt
Why: The non-basic titanium/zinc methylenating reagent converts the hindered, enolisable ketone into the exocyclic methylene without epimerising C1 and without touching the methyl ester or the silyl ethers.

Step 15
Reactants: 17 methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-7a-methyl-2-methylidene-3a,4-bis[(triethylsilyl)oxy]octahydro-1H-inden-1-yl]acetate
Product: 18 methyl 2-[(1S,3aS,4S,7S,7aR)-7-[(tert-butyldimethylsilyl)oxy]-3a,4-dihydroxy-7a-methyl-2-methylideneoctahydro-1H-inden-1-yl]acetate (target)
Conditions: PPTS (0.3 equiv), MeOH, rt
Why: Mild acidic methanolysis removes both TES ethers (tertiary and secondary) while the hindered secondary TBS ether at C7, next to the quaternary centre, survives, delivering the target.

What changed after checking: (i) CIP analysis of the yeast product showed its hydroxyl is anti to the methyl, so an Evans–Tishchenko oxidation-state swap (steps 3–6) was inserted to reach the drawn enantiomer with the C7 oxygen syn to Me; (ii) force-field energies indicated that the C1 side chain is thermodynamically preferred syn to the methyl, so the alkylation was moved after every acidic or equilibrating step (steps 9–12) and the ketone is methylenated with a non-basic reagent; (iii) one stereo tag in epoxide 12 was corrected after a 3D face analysis so that the oxirane is anti to the methyl.

Closing summary

Total step count: 15 steps (14 if 2-allyl-2-methylcyclohexane-1,3-dione, 3, is purchased).

Longest linear sequence: 15 steps; the route is fully linear (allyl bromide and methyl bromoacetate enter as reagents).

Three steps most likely to fail, each with one fallback:

• Step 3 (Evans–Tishchenko reduction of a cyclic β-hydroxy ketone flanked by a quaternary centre; slow or incomplete). Fallback: Me4NBH(OAc)3 in AcOH/MeCN gives the same trans-1,3-diol; mono-silylate with TBSCl/imidazole, separate the two regioisomeric mono-TBS ethers and carry the one with OTBS syn to Me forward to DMP.

• Step 9 (deconjugative ketalisation: incomplete C3=C3a → C3a=C4 migration, or loss of the TBS ether under TsOH). Fallback: form the extended TMS dienol ether (TMSOTf, Et3N), protonate kinetically (AcOH, –78 °C) to the β,γ-enone and ketalise under Noyori conditions (TMSOTf cat., 1,2-bis(trimethylsilyloxy)ethane, –78 °C); or replace TsOH by PPTS with longer reaction time.
• Step 13 (regioselectivity of enolate formation, C1 versus C3, and possible β-elimination of the C3a-OTES from the C3 enolate). Fallback: trap the LDA enolates with TMSCl, separate the two silyl enol ether regioisomers, regenerate the C1 lithium enolate with MeLi (Stork–Hudrlik) and alkylate; the enone formed by β-elimination is separable and recyclable through steps 9–12.