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PAPER

A [Pd]-mediated ω-alkynone cycloisomerization approach for the central tetrahydropyran unit and the synthesis of C(31)–C(48) fragment of aflastatin A†

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A concise assembly of the central tetrahydropyran unit of aflastatin A featuring a Pd-mediated alkynone cycloisomerization to provide a glycal and its subsequent stereoselective hydroboration to deliver the requisite stereochemistry at C(33) and C(34) centers is documented.

Introduction

Aflastatin A (**1**) was isolated by Sakuda and co-workers from the mycelia of *Streptomyces* sp. MRI 142.[1] Aflastatin A belongs to the class of polyol natural products and contains a tetramic acid derivative with a highly oxygenated long alkyl side chain, as well as a tetrahydropyran ring. Aflastatin A shows strong inhibitory activity against aflatoxin production without significantly affecting the growth of *Aspergillus parasiticus*.[2] Sakuda and co-workers proposed the relative and absolute structure of aflastatin A with the help of chemical degradation and extensive NMR studies.[3] The assigned absolute stereochemistry of the degradation product C(9)–C(27) polyol has been cross-checked by chemical synthesis and correlation studies by Evans *et al.*[4] The absolute stereochemistry of the tetrahydropyran ring moiety of aflastatin A was assigned based on the relative stereochemistry around the ring and the absolute configuration at C(33). Initially proposed configurations at the diol [C(8), C(9)] and pentaol [C(25)–C(29)] moieties have been recently cross-checked by partial chemical synthesis and NMR correlations in light of the remarks from Kishi's group.[5] The absolute configuration of aflastatin A has been revised as given in Fig. 1.[6] In the context of our current program pertaining to the total synthesis of complex polyol natural products[7] and Pd-mediated cycloisomerization on sugar building blocks,[8] aflastatin A has been selected as a particular target. As a first step towards its total synthesis, herein we describe our preliminary efforts culminating in a stereoselective approach for the synthesis of the C(31)–C(48) fragment of aflastatin A.[9]

Results and discussion

The retrosynthetic strategy for the C(31)–C(48) fragment is described in Fig. 1. The central issue of the synthesis of the C(31)–C(48) fragment is the construction of the key pyran ring with requisite stereochemistry. The intent was to explore a Pd-mediated ω-alkynone cycloisomerization[10] and subsequent regio- and stereoselective hydroboration[11] of the resulting *C*-glycal **3**. Though there exist two competitive pathways for the proposed cycloisomerization, considering our previous results, a preference for 6-*endo*-dig over the 5-*exo*-dig cyclization was foreseen.[8–10] The preceding hydroboration of the resulting *C*-glycal **3** can be expected from the end opposite to that of the 35-benzyloxy group, thus ensuring the requisite stereochemistry at C(33) and C(34).[11] For the synthesis of the key ω-ynone **4**, the addition of alkyne **5** to epoxide **6**[12] was identified as the principal coupling strategy. For the construction of the key alkyne **5**, D-ribose containing the requisite stereochemistry at C(2) and C(3) matching with that of C(35) and C(36), respectively, of aflastatin A (Fig. 1) was selected as a chiral precursor. The C(1) of a ribose derivative can be further extended to the alkyne C(33)–C(34) unit and C(4) to the carbonyl present at C(37). In order to introduce the hydroxyl group at C(39), a regioselective Wacker oxidation of an olefin **7** followed by 1,3-*syn* reduction was envisaged.[13]

In order to check the feasibility of alkynone cycloisomerization, a model study has been carried out with alkynol **12**. The synthesis of compound **12** started from the known alkyne **9**[14] (Scheme 1). The free hydroxyl group in compound **9** was protected as its TBS ether **10**. Treatment of compound **10** with *n*-BuLi followed by $BF_3{\cdot}Et_2O$ at −78 °C and addition of ethylene oxide **6** to the intermediate furnished compound **11** in 84% yield. The free hydroxyl group in compound **11** was benzylated with NaH and BnBr in DMF and then the TBS protecting group was removed with TBAF in THF to deliver the key alkynol **12**. The oxidation of the 2°-OH in **12** with IBX gave the ω-ynone which was subjected to cycloisomerization [$Pd(OAc)_2$ in MeOH] without purification to afford the dihydropyrans **13α** and **13β** (3 : 1) in 69% yield. The constitution of the dihydropyrans **13α** and **13β** was determined with the help of spectral and analytical data and the anomeric configuration was determined after the hydroboration. Whilst the major isomer was found to be stable, the minor isomer was hydrolysed slowly in $CDCl_3$ giving a

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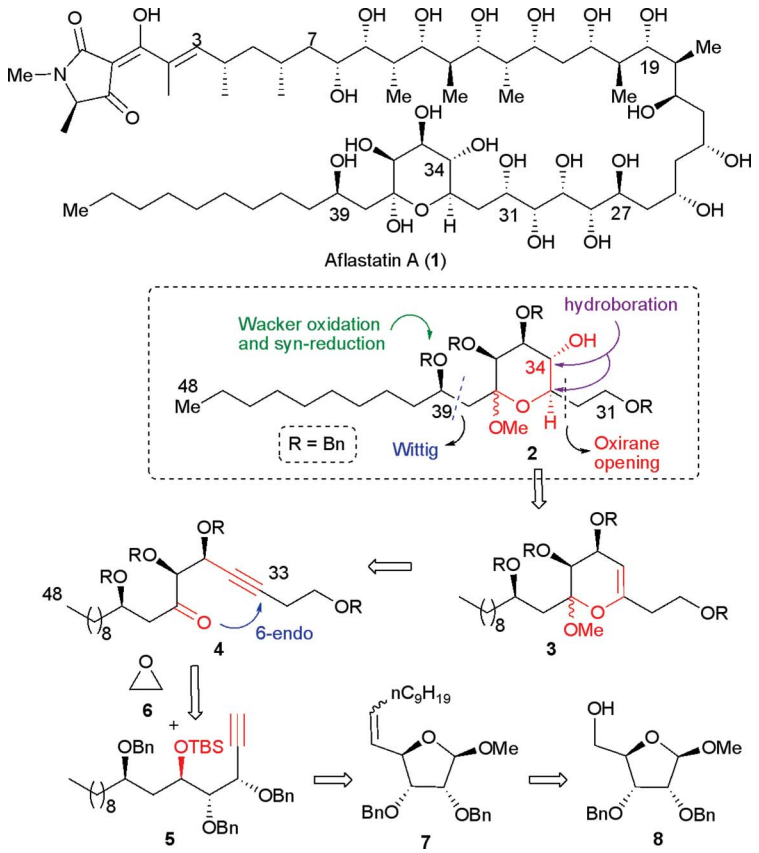


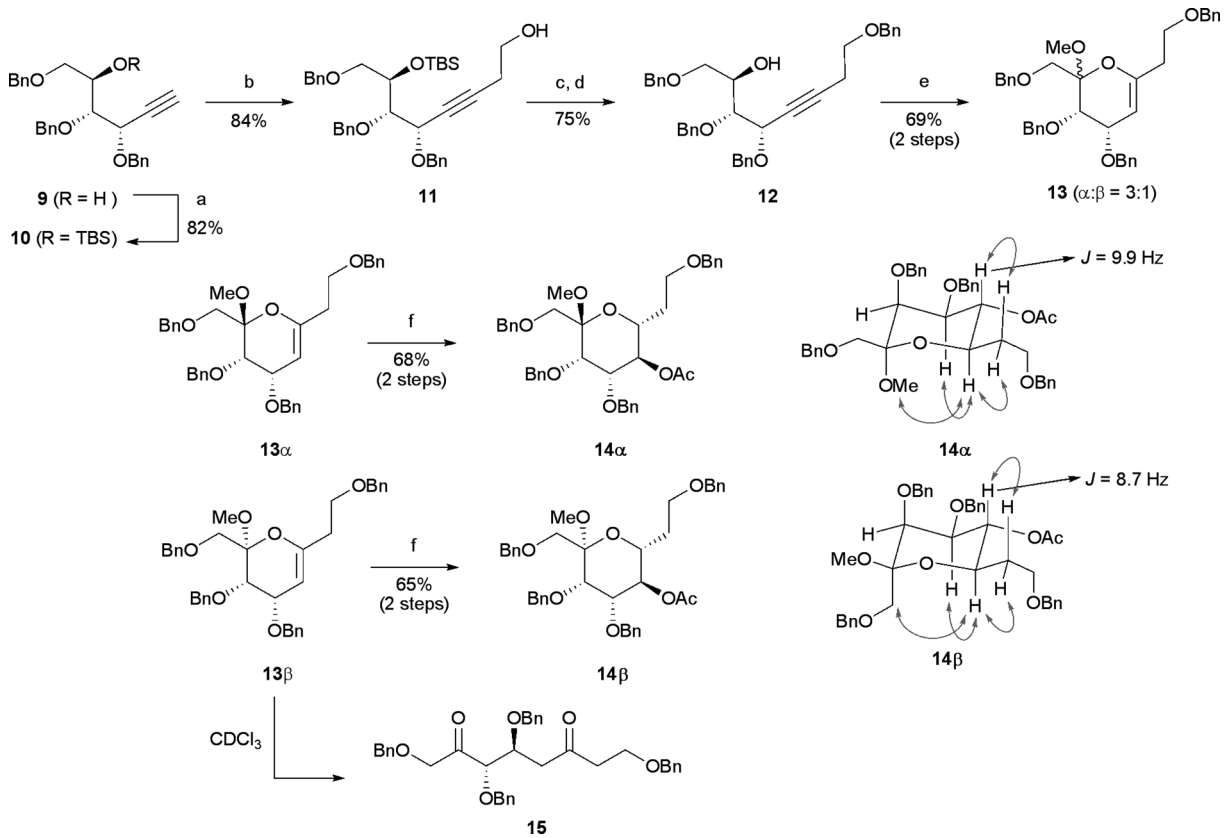
Fig. 1 Key [Pd]-mediated ω-ynone cycloisomerization for synthesis of the C(31)–C(48) fragment of aflastatin A (**1**).

1,5-diketone **15**. Hydroboration–oxidation of **13α** and **13β** was carried out separately with BH_3·DMS in THF at 0 °C followed by addition of NaOH–30% aq. H_2O_2 and the resulting alcohols were converted to the corresponding acetates **14α** and **14β** for structural characterization. In the ^{1}H NMR of **14α**, the C–H attached to acetate appeared down field at 5.24 ppm with diaxial coupling constants ($J \approx 10$ Hz) indicating a *trans*-orientation with respect to the adjacent methine hydrogens. The anomeric configuration of **14α** was determined as alpha with the help of nOe studies. The anomeric configuration of minor product **14β** was also determined in a similar fashion.

After the successful synthesis of the highly substituted tetrahydropyran ring [C(31)–C(38) fragment] of aflastatin A, next we proceeded further for the synthesis of the C(31)–C(48) fragment of aflastatin A. As a first step, the synthesis of the alkyne fragment **5** was undertaken (Scheme 2). The synthesis started with the oxidation of the primary hydroxyl group of known ribofuranoside derivative **8**[15] under Swern conditions and the subsequent Wittig reaction with the ylide generated from decyltriphenylphosphonium bromide and base (*n*-BuLi) to afford **7**(*Z*). In the ^{1}H NMR spectrum of **7**(*Z*), the two olefinic protons resonated down field at 5.35 (J = 10.8 Hz) and 5.69 ppm (J = 10.8 Hz) while in the ^{13}C NMR, the olefinic carbons appeared at 129.5 and 134.9 ppm respectively.

After screening several Pd-complexes and conditions, the regioselective oxidation of **7** could successfully be carried out employing $PdCl_2$ in dimethyl acetamide and water at 90 °C for 12 h under O_2 atmosphere. The ketone **16** was obtained in 76% yield and with complete regioselectivity.[13a] The resulting ketone after stereoselective reduction employing lithium iodide and LAH delivered alcohol **17**[13b] and the diastereomeric ratio was found to be 9 : 1. The major diastereomer **17** was separated and the stereochemistry of the newly generated asymmetric centre was fixed by converting it into the acetonide derivative **20** by a sequence of reactions: hydrolysis, Ohira–Bestmann homologation and acetonide protection.[16] In the ^{13}C NMR, the acetal carbon was seen to resonate at 98.5 ppm and the two methyl carbons at 19.6 and 30.1 ppm, characteristic of the acetonide of a 1,3-*syn* diol.[17] After determining the stereochemistry at C(39) in **17**, we proceeded further for the synthesis of the alkyne **5**. The protection of the free hydroxyl group in **17** as its benzyl ether **18** followed by hydrolysis and treatment of intermediate lactal with Ohira–Bestmann reagent afforded the alkyne **21**. The free hydroxy group in compound **21** was protected as its TBS ether to complete the synthesis of the key alkyne fragment **5**.

Next, the opening of ethylene oxide **6** with the alkyne **5** was carried out to secure the alcohol **22** in 87% yield. Benzylation of the free hydroxyl group in compound **22** gave **23**, which upon deprotection of the TBS ether gave the key alkynol **24**. Oxidation of the alkynol **24** (IBX/ethyl acetate) followed by Pd-mediated cycloisomerization of the resulting carbonyl compound gave **3α** (the anomeric configuration was fixed at a later stage) as the main product. Subsequently, the hydroboration of glycal **3α** followed by acetylation gave **2α** in 65% yield. The structure of compound **2α** was established with the help of the 2D NMR studies. In the ^{1}H NMR of **2α**, the C(34)–H appeared at 5.23 ppm as a broad



Scheme 1 *Reagents and conditions*: (a) TBSCl, Im., DMF, rt, 4 h; (b) *n*-BuLi, $BF_3{\cdot}Et_2O$, ethylene oxide, THF, –78 °C; (c) NaH, BnBr, DMF, 0 °C–rt, 2 h; (d) TBAF, THF, rt, 4 h; (e) i. IBX, EtOAc, reflux, 3 h; ii. $Pd(OAc)_2$, MeOH, rt, 2 h; (f) i. $BH_3{\cdot}DMS$, THF, 0 °C, 3 h, then H_2O_2 (30%), 3 N NaOH, rt, 8 h; ii. Ac_2O, Py, CH_2Cl_2, 3 h.

triplet with characteristic diaxial coupling constant $J = 9.8$ Hz. In the ^{13}C NMR, C(33) and C(37) appeared at 79.1 and 102.0 ppm, respectively. Further, in the NOESY spectrum of **2α**, a cross peak between the –OCH_3 group and C(33)–H suggested the assigned anomeric configuration.

In order to address whether the observed α-anomeric selectivity was apparent due to the hydrolysis of the corresponding β-anomer during the isolation (considering the hydrolysis of β-anomer **13β** noticed in the model studies) the crude cycloisomerization reaction mixture was subjected to the hydroboration–oxidation. This resulted in the isolation of the β-anomer **2β** as a minor compound (6 : 1 anomeric selectivity) indicating the ready hydrolysis of the corresponding glycal. The spectral data of **2β** are similar to those of **14β**. For example, in the ^1H NMR, the C(34)–H appeared at 5.26 ppm ($J = 9.2$ Hz) as a broad triplet and the C(33) and C(37) appeared at 77.3 and 100.8 ppm, respectively, in the ^{13}C NMR.

Conclusion

In conclusion, the synthesis of the C(31)–C(48) subunit of aflastatin A was documented. The 6-*endo*-dig ω-ynone cycloisomerization and hydroboration are the key reactions that addressed the central tetrahydropyran ring construction with the requisite stereochemistry at the C(33), C(34) centers. Further studies to extend this strategy in the direction of the total synthesis of aflastatin A are in progress.

Experimental part

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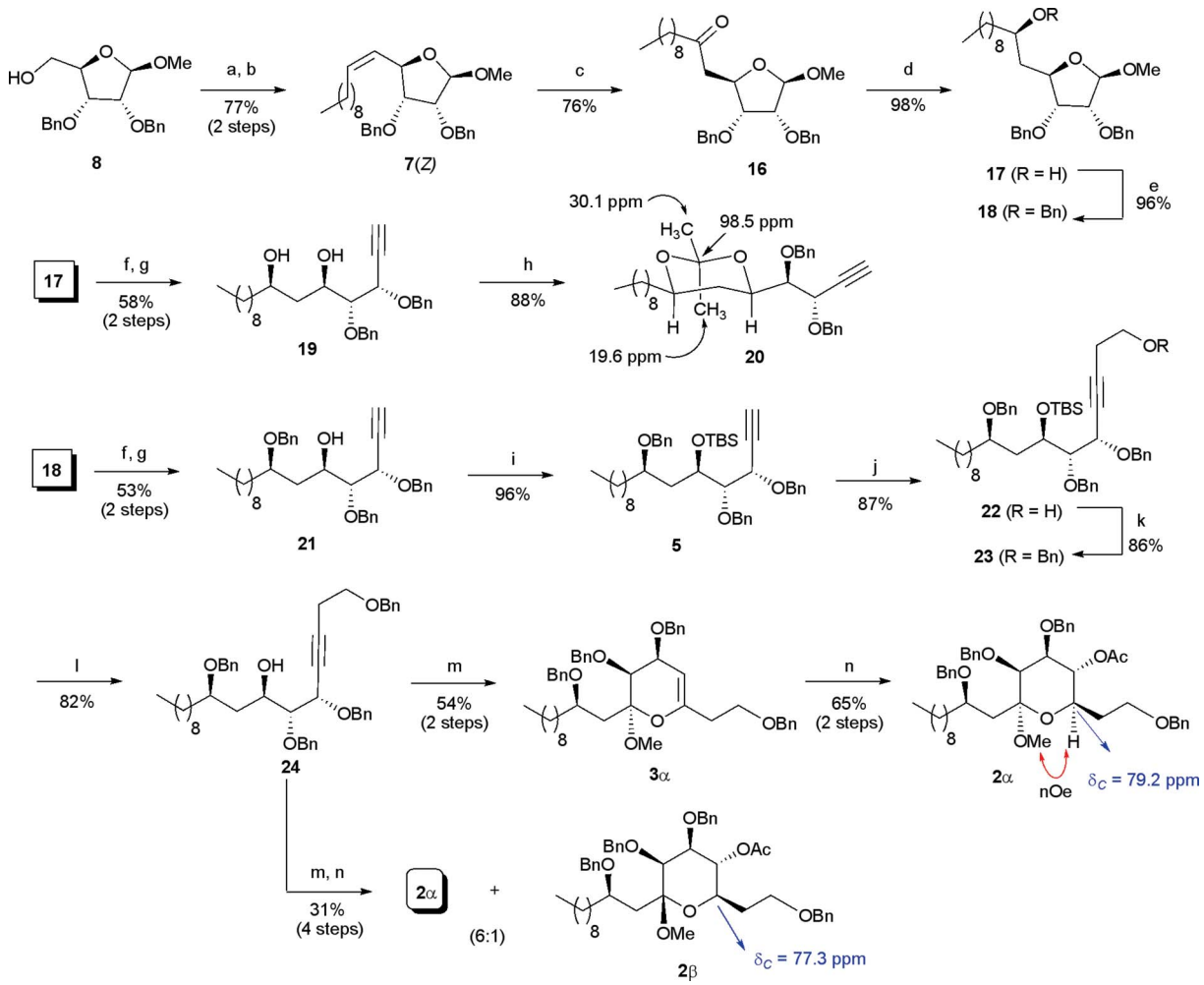
To a solution of alcohol **12** (100 mg, 0.18 mmol) in ethyl acetate (10 mL) was added IBX (76 mg, 0.26 mmol) at room temperature and the mixture was stirred at reflux temperature for 3 h. After the complete consumption of the starting material, the reaction mixture was cooled in an ice bath and filtered through a Celite bed, and the combined filtrate was evaporated under reduced pressure. The residual crude ketone (89 mg) was dissolved in anhydrous methanol (10 mL) and the solution was degassed by passing argon for 45 min. To this, $Pd(OAc)_2$ (4 mg, 16 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through a Celite bed and the filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (silica 230–400 mesh, 2 : 8 ethyl acetate/petroleum ether) to procure compound **13α** (60 mg, 52% yield) and **13β** (19 mg, 17% yield) as colorless oils.

Spectral data of compound 13α. $[\alpha]_D^{25}$ +19.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3015, 2928, 1454, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.38 (t, $J = 6.9$ Hz, 2H), 3.16 (s, 3H), 3.51 (d, $J = 10.3$ Hz, 1H), 3.55–3.60 (m, 2H), 3.70 (d, $J = 10.3$ Hz, 1H), 4.02 (dd, $J = 1.8, 4.1$ Hz, 1H), 4.34 (d, $J = 12.1$ Hz, 1H), 4.38–4.40 (m, 1H), 4.48 (bs, 2H), 4.51 (d, $J = 6.6$ Hz, 1H), 4.57 (bs, 2H), 4.62 (d, $J = 11.7$ Hz, 1H), 4.82 (bs, 1H), 4.93 (d, $J = 11.7$ Hz, 1H), 7.27–7.33 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.1 (t), 48.5



Scheme 2 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, NEt_3, DCM, −78 °C; (b) $C_{10}H_{21}{\cdot}PPh_3Br$, *n*-BuLi, THF, 0 °C–rt, 2 h; (c) $PdCl_2$, DMA, H_2O, O_2, 90 °C, 12 h; (d) LiI, LAH, Et_2O, −100 °C, 45 min; (e) NaH, BnBr, DMF, 0 °C–rt, 3 h; (f) H_2SO_4, dioxane : H_2O, reflux, 6 h; (g) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, rt, 7 h; (h) *p*-TSA, dimethoxy propane (DMP), 0 °C–rt, 2 h; (i) TBSOTf, NEt_3, DCM, −15 °C, 2 h; (j) *n*-BuLi, $BF_3{\cdot}Et_2O$, ethylene oxide, THF, −78 °C, 2.5 h; (k) NaH, BnBr, DMF, 0 °C–rt, 3 h; (l) TBAF, THF, rt, 2.5 h; (m) i. IBX, EtOAc, reflux, 3 h; ii. $Pd(OAc)_2$, MeOH, 2.5 h; (n) i. $BH_3{\cdot}DMS$, THF, 0 °C, 2 h, then 30% aq. H_2O_2, 3 N NaOH, rt, 6 h; ii. Ac_2O, Py, CH_2Cl_2, 3 h.

(q), 64.7 (t), 67.6 (t), 70.3 (d), 70.9 (t), 72.1 (d), 72.9 (t), 73.3 (t), 74.6 (t), 98.9 (d), 101.4 (s), 127.33 (d, 2C), 127.42 (d, 2C), 127.51 (d), 127.57 (d), 127.68 (d, 2C), 127.9 (d), 128.12 (d, 3C), 128.22 (d, 2C), 128.30 (d, 4C), 128.41 (d, 2C), 137.5 (s), 138.3 (s), 138.66 (s, 2C), 147.8 (s) ppm; MALDI-TOF: 603.19 (12% [M + Na]$^+$), 619.15 (100% [M + K]$^+$); Anal. Calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94; Found: C, 76.75; H, 6.81.

Spectral data of compound 13β. $[\alpha]_D^{25}$ +29.1 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3019, 2928, 1455, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (t, J = 6.8 Hz, 2H), 3.33 (s, 3H), 3.62 (t, J = 6.8 Hz, 2H), 3.69 (d, J = 8.9 Hz, 1H), 3.87–3.92 (m, 2H), 4.01 (d, J = 5.3 Hz, 1H), 4.48 (s, 2H), 4.52–4.55 (m, 2H), 4.56–4.61 (m, 3H), 4.70 (d, J = 11.9 Hz, 1H), 4.85 (d, J = 4.8 Hz, 1H), 7.24–7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.3 (t), 50.0 (q), 66.2 (d), 67.4 (t), 68.6 (t), 71.0 (t), 72.6 (t), 72.9 (t), 73.5 (t), 74.1 (d), 97.3 (d), 100.2 (s), 127.4 (d), 127.47 (d, 2C), 127.58 (d, 3C), 127.76 (d, 2C), 128.13 (d, 2C), 128.24 (d, 4C), 128.32 (d, 4C), 128.38 (d, 2C), 138.0 (s), 138.1 (s), 138.2 (s), 139.0 (s), 150.3 (s) ppm; MALDI-TOF: 603.10 (100% [M + Na]$^+$); Anal. Calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94; Found: C, 76.40; H, 6.99.

Characterization data of diketone 15

During the collection of the spectral data, compound **13β** (minor) in $CDCl_3$ was found to convert into diketone **15**. $[\alpha]_D^{25}$ −8.7 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3031, 2924, 1727, 1712, 1455, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.67 (t, J = 6.2 Hz, 2H), 2.74 (dd, J = 5.6, 17.5 Hz, 1H), 2.85 (dd, J = 7.1, 17.5 Hz, 1H), 3.69 (t, J = 6.2 Hz, 2H), 4.12 (d, J = 3.1 Hz, 1H), 4.31 (s, 2H), 4.39 (ddd, J = 3.1, 5.6, 7.1 Hz, 1H), 4.43–4.47 (m, 3H), 4.51–4.58 (m, 5H), 7.19–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.7 (t), 44.1 (t), 64.9 (t), 72.8 (t), 72.9 (t), 73.2 (t), 73.3 (t), 74.2 (t), 75.7 (d), 84.0 (d), 127.68 (d, 4C), 127.81 (d, 2C), 127.92 (d, 3C), 128.03 (d, 2C), 128.1 (d), 128.31 (d, 2C), 128.37 (d, 2C), 128.43 (d, 2C), 128.51 (d, 2C), 137.1 (s), 137.2 (s), 137.8 (s), 138.0 (s), 206.8 (s), 207.5 (s) ppm; MALDI-TOF: 589.17 (30% [M + Na]$^+$), 605.13 (100% [M + K]$^+$); HRMS: 589.2566 ([M + Na]$^+$) calculated, 589.2493 ([M + Na]$^+$)

observed; Anal. Calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.76; Found: C, 76.38; H, 6.89.

Synthesis of acetate 14α

To an ice-cooled solution of compound **13α** (44 mg, 0.076 mmol) in anhydrous THF (4 ml), was added neat BH_3·DMS (16.4 µL, 0.152 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C, treated with 3 N NaOH (0.5 mL) followed by 30% H_2O_2 (0.5 mL), and stirred at room temperature for 8 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (5 mL) and water (2 mL), the organic layer dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 1 mL anhydrous DCM. To this solution, acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The contents were stirred for 3 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (10 mL) three times. The residue was purified by column chromatography (silica 230–400 mesh, 15 : 85 ethyl acetate/petroleum ether) to procure compound **14α** (32 mg, 68% yield) as a colorless oil. $[\alpha]_D^{25}$ –2.4 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3019, 2929, 1739, 1371, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.66–1.72 (m, 1H), 1.80–1.87 (m, 1H), 1.97 (s, 3H), 3.12 (s, 3H), 3.42 (d, *J* = 10.1 Hz, 1H), 3.48–3.52 (m, 1H), 3.59 (dd, *J* = 4.9, 9.4 Hz, 1H), 3.63 (d, *J* = 10.1 Hz, 1H), 3.71 (dt, *J* = 2.4, 10.1, 1H), 3.98 (dd, *J* = 2.9, 9.8 Hz, 1H), 4.07 (d, *J* = 2.9 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.43 (s, 1H), 4.44 (s, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.53 (s, 1H), 4.56 (s, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 5.24 (bt, *J* = 9.9 Hz, 1H), 7.23–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.1 (q), 31.6 (t), 47.8 (q), 65.2 (t), 66.0 (t), 67.7 (d), 71.7 (t), 71.8 (d), 72.9 (t), 73.4 (t), 74.8 (d), 74.9 (t), 78.4 (d), 100.8 (s), 127.28 (d, 2C), 127.39 (d), 127.42 (d), 127.5 (d), 127.63 (d, 2C), 127.9 (d), 127.97 (d, 2C), 128.13 (d, 2C), 128.21 (d, 2C), 128.27 (d, 2C), 128.30 (d, 2C), 128.44 (d, 2C), 137.6 (s), 138.1 (s), 138.5 (s), 138.6 (s), 170.1 (s) ppm; MALDI-TOF: 663.23 (100% $[M + Na]^+$), 679.19 (87% $[M + K]^+$); HRMS: 663.2934 ($[M + Na]^+$) expected, 663.2907 ($[M + Na]^+$) observed.; Anal. Calcd for $C_{39}H_{44}O_8$: C, 73.10; H, 6.92; Found: C, 73.02; H, 6.98.

Synthesis of acetate 14β

To an ice-cooled solution of compound **13β** (19 mg, 0.033 mmol) in anhydrous THF (4 ml), was added neat BH_3·DMS (7.1 µL, 0.066 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C, treated with 3 N NaOH (0.3 mL) followed by 30% H_2O_2 (0.3 mL), and stirred at room temperature for 8 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (3 mL) and water (1 mL), the organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 0.5 mL anhydrous DCM. To this solution, acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The contents were stirred for 3 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (5 mL) four times. The residue was purified by column chromatography (silica 230–400 mesh, 15 : 85 ethyl acetate/petroleum ether) to procure compound **14β** (14 mg, 65% yield) as a colorless oil. $[\alpha]_D^{25}$ –15.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3019, 2927, 1738, 1452, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.84–1.94 (m, 2H), 1.97 (s, 3H), 3.28 (s, 3H), 3.46–3.52 (m, 3H), 3.56 (dd, *J* = 3.0, 9.1 Hz, 1H), 3.59 (dd, *J* = 4.9, 9.1 Hz, 1H), 3.62–3.66 (m, 1H), 4.10 (d, *J* = 3.0 Hz, 1H), 4.23 (d, *J* = 12.4 Hz, 1H), 4.37 (d, *J* = 4.1 Hz, 1H), 4.39 (d, *J* = 4.3 Hz, 1H), 4.46–4.52 (m, 3H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 5.21 (bt, *J* = 8.7 Hz, 1H), 7.16–7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (q), 32.8 (t), 49.4 (q), 65.8 (t), 66.8 (t), 70.7 (d), 71.1 (t), 71.9 (d), 72.9 (t), 73.4 (t), 74.2 (d), 74.9 (t), 76.6 (d), 100.3 (s), 127.3 (d), 127.53 (d, 2C), 127.60 (d, 2C), 127.69 (d, 2C), 127.75 (d, 2C), 127.9 (d), 128.01 (d, 2C), 128.23 (d, 4C), 128.34 (d, 2C), 128.52 (d, 2C), 137.6 (s), 138.1 (s), 138.4 (s), 138.8 (s), 170.0 (s) ppm; MALDI-TOF: 658.63 (100% $[M + NH_4^+]$), 663.48 (31% $[M + Na]^+$); HRMS: 679.2673 ($[M + K]^+$) calculated, 679.2650 ($[M + K]^+$) observed; Anal. Calcd for $C_{39}H_{44}O_8$: C, 73.10; H, 6.92; Found: C, 73.37; H, 6.66.

Pd(II)-Mediated cycloisomerization and synthesis of glycals 3

To a solution of alcohol **24** (40 mg, 58 µmol) in ethyl acetate (5 mL) was added IBX (32 mg, 116 µmol) at room temperature and the mixture was stirred at reflux temperature for 3 h. After the complete consumption of the starting material, the reaction mixture was cooled in and ice bath and filtered through a Celite bed. The filtrate was evaporated under reduced pressure. The residual crude ketone (38 mg, 55 µmol) was dissolved in anhydrous methanol (10 mL) and the solution was degassed by passing argon for 30 min. To this, $Pd(OAc)_2$ (4 mg, 17 µmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through a Celite bed and the filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (silica 230–400 mesh, 2 : 8 ethyl acetate/petroleum ether) to procure compound **3α** (22 mg, 54% yield) as colorless oils. $[\alpha]_D^{25}$ +29.4 (*c* 0.3, $CHCl_3$); IR (neat): $\tilde{\nu}$ 3018, 2925, 1454, 1215, 1095, 759, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.81 (t, *J* = 6.8 Hz, 3H), 1.19 (bs, 14H), 1.43–1.54 (m, 2H), 1.92 (dd, *J* = 4.7, 14.8 Hz, 1H), 2.29 (dd, *J* = 7.3, 14.8 Hz, 1H), 2.32 (t, *J* = 6.8 Hz, 2H), 3.23 (s, 3H), 3.47–3.50 (m, 1H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.71 (d, *J* = 5.2 Hz, 1H), 3.81 (t, *J* = 5.2 Hz, 1H), 4.26 (d, *J* = = 11.3 Hz, 1H), 4.30–4.36 (m, 2H), 4.40–4.43 (m, 2 H), 4.46–4.54 (m, 3H), 4.81 (d, *J* = 5.1 Hz, 1H), 7.18–7.28 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 24.7 (t), 29.3 (t), 29.6 (t), 29.7 (t), 29.9 (t), 31.9 (t), 34.3 (t), 34.4 (t), 35.6 (t), 49.3 (q), 66.0 (d), 67.5 (t), 70.7 (t), 70.9 (t), 72.0 (t), 72.9 (t), 75.7 (d), 77.0 (d), 97.2 (d), 100.2 (s), 127.35 (d, 2C), 127.5 (d), 127.65 (d, 3C), 127.77 (d, 2C), 128.08 (d, 4C), 128.09 (d, 2C), 128.26 (d, 2C), 128.32 (d, 2C), 128.44 (d, 2C), 138.1 (s), 138.2 (s), 138.8 (s), 139.1 (s), 149.9 (s) ppm; MALDI-TOF: 743.62 (100%, $[M + Na]^+$), 759.60 (33% $[M + K]^+$); Anal. Calcd for $C_{47}H_{60}O_6$: C, 78.30; H, 8.39; Found: C, 78.25; H, 8.45.

Synthesis of acetate 2α

To an ice-cooled solution of compound **3α** (18 mg, 0.025 mmol) in anhydrous THF (2 ml), was added neat BH_3·DMS (4.4 µL, 0.050 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C, treated with 3 N NaOH (0.2 mL) followed by 30% H_2O_2 (0.3 mL), and stirred at room

temperature for 6 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (5 mL) and water (2 mL), the organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 0.5 mL anhydrous DCM. To this solution, acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The contents were stirred for 3 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (3 × 5 mL). The residue was purified by column chromatography (silica 230–400 mesh, 15 : 85 ethyl acetate/petroleum ether) to procure compound **2α** (12 mg, 65% yield) as colorless oil. $[\alpha]_D^{25}$ +37.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3018, 2925, 1736, 1459, 1216, 1095, 767, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 6.8 Hz, 3H), 1.27–1.32 (m, 14H), 1.59–1.66 (m, 3H), 1.69–1.72 (m, 1H), 1.79–1.85 (m, 1H), 1.97 (s, 3H), 2.34 (dd, J = 10.1, 15.4 Hz, 1H), 3.11 (s, 3H), 3.50–3.54 (m, 1H), 3.56–3.59 (m, 3H), 3.60–3.63 (m, 1H), 3.64–3.68 (m, 1H), 3.92 (dd, J = 2.6, 9.8 Hz, 1H), 4.02 (d, J = 2.6 Hz, 1H), 4.31–4.41 (m, 3H), 4.44–4.47 (m, 2H), 4.50 (d, J = 12.4 Hz, 1H), 4.60 (d, J = 10.6 Hz, 1H), 4.62 (d, J = 10.6 Hz, 1H), 5.23 (bt, J = 9.8 Hz, 1H), 7.17–7.24 (m, 6H), 7.27–7.35 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.1 (q), 22.7 (t), 24.6 (t), 29.4 (t), 29.6 (t), 29.7 (t), 30.0 (t), 31.7 (t), 31.9 (t), 33.7 (t), 35.1 (t), 47.7 (q), 66.2 (t), 67.8 (d), 71.42 (t, 2C), 71.8 (d), 72.9 (t), 74.1 (t), 75.9 (d), 76.5 (d), 79.1 (d), 102.0 (s), 126.9 (d), 127.2 (d), 127.3 (d), 127.5 (d), 127.61 (d, 2C), 127.69 (d, 2C), 127.85 (d, 2C), 128.06 (d, 2C), 128.23 (d, 2C), 128.29 (d, 4C), 128.37 (d, 2C), 138.3 (s), 138.4 (s), 138.7 (s), 139.3 (s), 170.2 (s) ppm; MALDI-TOF: 803.66 (40% $[M + Na]^+$), 819.64 (100% $[M + K]^+$); HRMS: 803.4499 ($[M + Na]^+$) expected, 803.4424 ($[M + Na]^+$) observed; Anal. Calcd for $C_{49}H_{64}O_8$: C, 75.35; H, 8.26; Found: C, 75.39; H, 8.55.

Representative experiment for the sequence of oxidation–cyclization–hydroboration–acetylation to isolate the minor 2β-acetate

To a solution of alcohol **24** (100 mg, 0.14 mmol) in ethyl acetate (10 mL) was added IBX (81 mg, 0.28 mmol) at room temperature and the mixture was stirred at reflux temperature for 3 h. After the complete consumption of the starting material, the reaction mixture was cooled in an ice bath and filtered through a Celite bed. The filtrate was evaporated under reduced pressure. The residual crude ketone (96 mg) was dissolved in anhydrous methanol (15 mL) and the solution was degassed by passing argon for 30 min. To this, $Pd(OAc)_2$ (9 mg, 42 μmol) was added and the mixture stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through a Celite bed and the filtrate was concentrated under reduced pressure to procure crude compound **3** (64 mg). The resulting crude glycal mixture was used immediately for hydroboration–oxidation and acetylation without any purification.

To an ice-cooled solution of crude compound **3** (64 mg, 89 μmol) in anhydrous THF (3 ml), was added neat BH_3·DMS (8.8 μL, 178 μmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C, treated with 3 N NaOH (0.3 mL) followed by 30% H_2O_2 (0.4 mL), and stirred at room temperature for 6 h. Then, the THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (5 mL) and water (2 mL), the organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was dissolved in 0.5 mL anhydrous DCM. To this solution, acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The contents were stirred for 3 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; traces of solvent were removed by co-evaporation with toluene (3 × 5 mL). The residue was purified by column chromatography (silica 230–400 mesh, 15 : 85 ethyl acetate/petroleum ether) to procure compound **2α** (30 mg, 26.5% yield, 4 steps) and 2β (5 mg, 4.4% yield, 4 steps) as colorless oils.

Spectral data for 2β. $[\alpha]_D^{25}$ +17.2 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ 3021, 2928, 1742, 1452, 1221, 1088, 769, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 6.7 Hz, 3H), 1.27 (bs, 14H), 1.41–1.45 (m, 1H), 1.49–1.54 (m, 1H), 1.77 (dd, J = 4.5, 15.2 Hz, 1H), 1.81–1.94 (m, 3H), 2.00 (s, 3H), 3.35 (s, 3H), 3.38–3.43 (m, 1H), 3.51–3.55 (m, 1H), 3.56–3.64 (m, 3H), 3.76 (d, J = 3.1 Hz, 1H), 4.31 (d, J = 12.5 Hz, 1H), 4.38–4.43 (m, 3H), 4.45–4.49 (m, 2H), 4.72 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 5.26 (t, J = 9.2 Hz, 1H), 7.17–7.24 (m, 6H), 7.26–7.38 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.1 (q), 22.7 (t), 24.8 (t), 29.3 (t), 29.6 (t), 29.63 (t), 29.7 (t), 29.9 (t), 31.9 (t), 32.4 (t), 34.9 (t), 36.1 (t), 50.1 (q), 66.1 (t), 69.4 (d), 71.2 (t), 71.5 (t), 71.8 (d), 73.0 (t), 74.6 (t), 75.3 (d), 76.8 (d), 77.3 (d), 100.8 (s), 127.3 (d), 127.49 (d, 2C), 127.5 (d), 127.6 (d), 127.67 (d, 4C), 128.03 (d, 2C), 128.27 (d, 2C), 128.30 (d, 6C), 128.4 (d), 138.1 (s), 138.4 (s), 138.6 (s), 138.8 (s), 169.9 (s) ppm; MALDI-TOF: 803.64 (25% $[M + Na]^+$), 819.61 (100% $[M + K]^+$); HRMS: 803.4499 ($[M + Na]^+$) calculated, 803.4446 ($[M + Na]^+$) observed; Anal. Calcd for $C_{49}H_{64}O_8$: C, 75.35; H, 8.26; Found: C, 75.41; H, 8.45.

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