Tetrahedron 64 (2008) 5162–5167

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of clavosolide A

Tushar Kanti Chakraborty *, Vakiti Ramkrishna Reddy, Praveen Kumar Gajula

Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 4 February 2008
Received in revised form 12 March 2008
Accepted 13 March 2008
Available online 15 March 2008

Keywords:
Clavosolides
Clavosolide A
Epoxide opening
2-Methyl-1,3-diol
Diolide

ABSTRACT

For the total synthesis of (−)-clavosolide A described herein, a Schmidt glycosidation reaction was used to attach the sugar moiety at an early stage in the synthesis to the 4-hydroxy group of the substituted tetrahydropyran unit of the molecule, which itself was built following a Ti(III)-mediated method developed by us earlier, and at the end, it was the Yamaguchi reaction that was successfully employed for the cyclodimerization of the two halves of the molecule leading to its total synthesis.

1. Introduction

There are many instances where the structures of the natural products, isolated from various sources, were first wrongly assigned, but corrected later on by chemical synthesis.[1] Clavosolides A–D (**1**–**4**), isolated from extracts of the marine sponge *Myriastra clavosa* collected in Philippines,[2] are some of the recent examples. Crude extracts of *Myriastra clavosa* displayed promising cytotoxic and antiproliferative effects in antitumor screens. However, thorough evaluation of the cytotoxic properties of the clavosolides was not possible due to the limited natural abundance of these compounds. The symmetric structure of the 16-membered core diolide ring in these molecules, with highly substituted tetrahydropyran units, disubstituted cyclopropyl rings, and permethylated xylose moieties, attracted the attention of many synthetic chemists leading to their successful syntheses.[3–9] Syntheses of the originally assigned structure of clavosolide A[3a,b] revealed that it was actually an isomer of the natural product and Willis et al.[3b] proposed a revised structure **5** for the molecule based on NMR and molecular modeling. Subsequently, a total synthesis of the revised structure for clavosolide A was accomplished by Lee et al.[4] Unfortunately, an error, which was subsequently corrected by them,[5] in the sign of the optical rotation led them mistakenly to conclude that the compound synthesized by them was the antipode of the natural product. This error was revealed by Willis et al.,[6] as well as by Smith and Simov,[7] who had synthesized the revised structure and established that this was indeed the naturally occurring (−)-clavosolide A (**5**). Subsequently, we also reported the total synthesis of the revised structure of (−)-clavosolide A.[8] Recently, the total synthesis of (−)-clavosolide B was also accomplished by Lee et al.[9] (Fig. 1).

One unsatisfactory aspect, in all the reported syntheses of clavosolide A,[3–8] was the forcible wastage of the invaluable aglycon in the glycosidation step that resulted in the formation of unwanted isomers along with the requisite target. To rectify this problem of

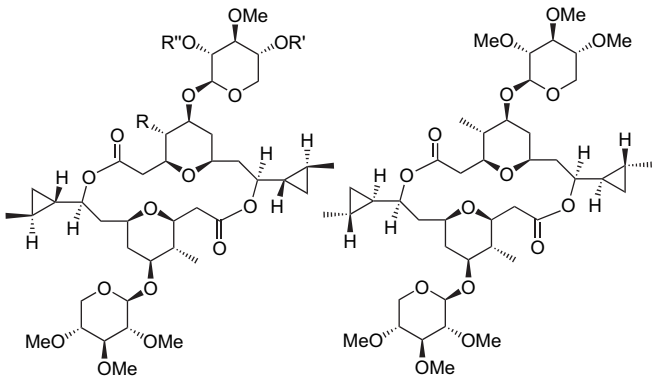


Figure 1. Structures of clavosolides.

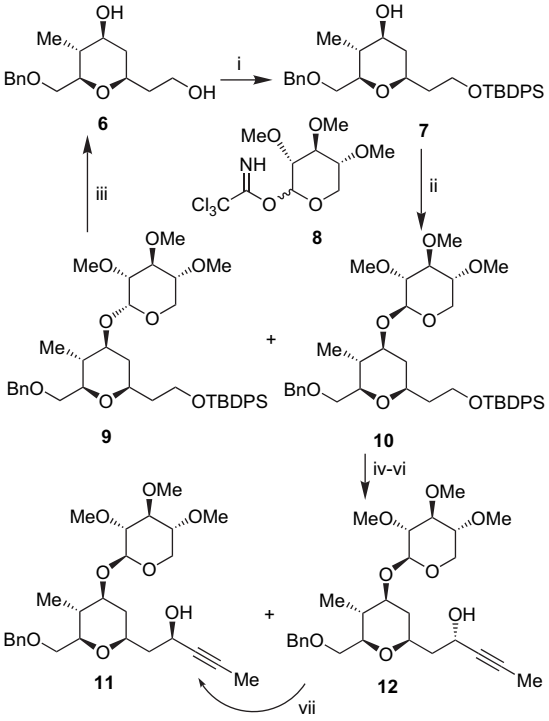
* Corresponding author. Tel.: +91 40 2719 3154; fax: +91 40 2719 3275/3108.
E-mail address: chakraborty@iict.res.in (T.K. Chakraborty).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.039

loosing the priceless material at the final step, we decided to carry out the glycosidation at an early stage[10] and use *O*-glycoside as the protecting group during the entire synthesis. The detail account of this modified approach to (−)-clavosolide A is described in this paper.

2. Results and discussions

Our synthesis started with the tetrahydropyranyl compound **6** (Scheme 1), which was synthesized earlier by us[3a] applying a methodology developed for the synthesis of highly substituted tetrahydropyrans by a Ti(III)-mediated opening of trisubstituted epoxy alcohols.[11]



Scheme 1. Synthesis of compound **11**. Reagents and conditions: (i) TBDPSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, 4 h, 85%; (ii) **8**, TMSOTf, 4 Å MS, CH_2Cl_2, rt, 2 h, 84%; (iii) HF-Py (60–70%), rt, 6 h, 89%; (iv) TBAF, THF, 0 °C to rt, 3 h, 95%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 96%; (vi) LDA, propyne, THF, −78 °C, 0.5 h, then the aldehyde, 1 h, 90%; (vii) (a) DEAD, Ph_3P, *p*-nitrobenzoic acid, 1 h; (b) K_2CO_3, MeOH, rt, 30 min, 92% in two steps.

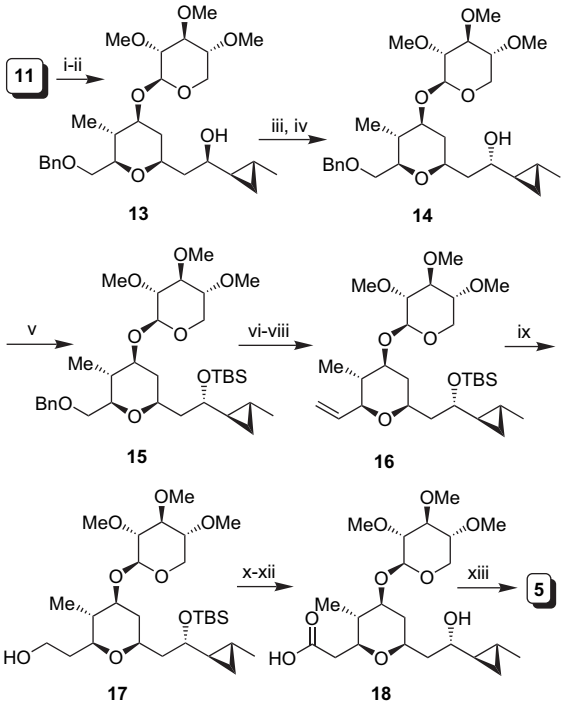
The primary hydroxyl group of **6** was selectively protected as *tert*-butyldiphenylsilyl ether in the presence of the secondary hydroxyl group, using 1.1 equiv of TBDPSCl, 1.5 equiv of TEA, and 0.1 equiv of DMAP in CH_2Cl_2 at 0 °C to room temperature for 4 h, to give the desired compound **7** in 85% yield. Schmidt glycosidation[12] of **7** with 2,3,4-tri-*O*-methyl-D-xylopyranosyl trichloroacetimidate **8**[3a] using TMSOTf in the presence of 4 Å MS in CH_2Cl_2 furnished, as expected, a mixture (~1:1) of two products, which could be separated easily to give the unwanted α-product **9** along with the desired β-product **10**. The unwanted α-product **9** was subjected to deglycosidation using HF-py,[13] to recover the material as tetrahydropyran **6**, which was recycled to afford more quantities of the desired β-product **10**. Desilylation of **10** gave an alcohol that was oxidized to the corresponding aldehyde and treated with Li-propynilide, generated from propyne and LDA, to furnish a mixture of propargylic alcohols **11** and **12** in 90% overall yield and in 1:2 ratio. The isomers could be separated easily by standard silica gel column chromatography. The stereochemistries of the isomers were assigned based on methods described earlier.[3a]

We needed the 9*R*-stereoisomer **11** to give the requisite (*R*,*R*)-cyclopropane ring, since the cyclopropanation reaction is predominantly *syn*-selective.[14] It was envisaged that inversion of the C9–OH would re-establish the *S*-configuration in the product. In order to generate more of the requisite propargylic alcohol **11**, the major isomer **12** was subjected to Mitsunobu inversion[15] followed by benzoate deprotection under basic conditions to provide **11** in 92% overall yield from **12**.

The remaining steps of the synthesis are shown in Scheme 2. Red-Al reduction of **11** gave an *E*-allylic alcohol, in 80% yield, which under modified Simmons–Smith cyclopropanation conditions[16] furnished the expected *syn*-product **13** as the major isomer (de >96%) in 91% yield. The stereochemistry of the major product was assigned based on earlier reports.[14] It now remained to invert the C9-stereocentre. However, Mitsunobu reaction failed to provide the inverted product. Therefore, an oxidation–reduction sequence was contemplated as there are many methods known for diastereoselective hydride reduction of cyclopropyl ketones.[17]

Oxidation of **13** with Dess–Martin periodinane (DMP)[18] provided the 9-keto intermediate, which was subjected to hydride reduction using lithium aluminum hydride (LAH) in THF at 0 °C to give the required 9*S*-isomer **14** as the major product in 5:1 ratio. The minor isomer could be separated easily by silica gel column chromatography to give **14** in 54% overall yield after two steps.

Silylation of **14** gave the intermediate **15** in 89% yield. Debenzylation of **15** was followed by DMP oxidation to give an aldehyde, which was subjected to olefination to furnish **16** in 67% yield in two steps from the alcohol. Hydroboration of **16** gave, exclusively, the primary alcohol **17**, in 91% yield, which was oxidized to the corresponding acid in two steps and 87% overall yield from **17**. Acid-catalyzed desilylation of the resulting acid furnished the hy-



Scheme 2. Synthesis of clavosolide A (**5**). Reagents and conditions: (i) Red-Al, Et_2O, 0 °C, 4 h, 80%; (ii) CH_2I_2, Et_2Zn, CH_2Cl_2, −20 °C to 0 °C, 5 h, 91%; (iii) DMP, CH_2Cl_2, 0 °C to rt, 30 min, 85%; (iv) LAH, THF, −78 °C, 20 min, 63%; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 4 h, 89%; (vi) H_2, Pd–C, EtOAc, 1 h, 91%; (vii) DMP, CH_2Cl_2, 0 °C to rt, 20 min; (viii) $Ph_3P{=}CH_2$, Et_2O, 0 °C, 10 min, 67% in two steps; (ix) $(chex)_2BH$, THF, 0 °C, 1 h, then 30% H_2O_2, NaOH, 2 h, 91%; (x) DMP, CH_2Cl_2, 0 °C to rt, 20 min; (xi) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, rt, *t*-BuOH, 1 h, 87% in two steps; (xii) CSA, MeOH-CH_2Cl_2 (1:1), 0 °C to rt, 1 h, 85%; (xiii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h; the mixed anhydride was then added to DMAP, toluene, 10^{-3} M, 80 °C, 5 h, then 12 h at rt, 71%.

droxy-acid **18**, in 85% yield, which was subjected to cyclodimerization reaction under Yamaguchi conditions.[19] Following an inverse-addition protocol, the mixed anhydride from **18**, dissolved in toluene, was slowly added using a syringe pump over ca. 5 h to a solution of DMAP in toluene (final concentration 10^{-3} M) at 80 °C followed by stirring at room temperature for 12 h to furnish the desired diolide **5** in 71% yield. The ^{1}H and ^{13}C NMR spectra and optical rotation, $[\alpha]_D$ −42.4 (*c* 0.125, $CHCl_3$), of our synthetic product **5** matched with those reported for the natural clavosolide A (literature: $[\alpha]_D$ −48.5 (*c* 1, $CHCl_3$)).[2a]

In summary, we achieved the total synthesis of clavosolide A by carrying out the glycosidation reaction in the early part of the synthesis and used the *O*-glycosylated product in the remaining steps. The overall yield calculated from the desilylated product from **10** to the final product was 8.6% as compared to 1.93% from the corresponding C4-OTBDPS protected intermediate reported in our earlier synthesis.[8]

3. Experimental section

3.1. General experimental procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid–heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4)–heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under electron impact ionization (EI), liquid secondary ion mass spectrometric (LSIMS) technique, electron spray ionization (ESI), and MALDI techniques. Optical rotations were measured with a digital polarimeter. NMR spectra were recorded on 500, 300, and 200 MHz spectrometers at 30 °C with 2–10 mM solutions in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on 150, 100, 75, and 50 MHz spectrometers with complete proton decoupling.

3.1.1. Synthesis of **7**

To a stirred solution of **6** (2.0 g, 7.14 mmol) in CH_2Cl_2 (20 mL), Et_3N (1.48 mL, 10.71 mmol) and TBDPSCl (2.01 mL, 7.85 mmol) were added sequentially at 0 °C under nitrogen atmosphere. Next, a catalytic amount of DMAP (87 mg, 0.71 mmol) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 3 h. It was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (2×10 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 20–22% EtOAc in petroleum ether eluant) afforded pure compound **7** (3.14 g, 85%) as colorless liquid. R_f=0.52 (SiO_2, 40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +1.2 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3430, 3068, 2927, 2856, 1725, 1620, 1457, 1428, 1384, 1109, 822, 738, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67–7.24 (m, 15H, aromatic protons), 4.53 (ABq, *J*=12.6 Hz, 2H, OC*H*$_2$Ph), 3.91–3.47 (m, 5H, O–C*H*$_2$– and O–C*H*–), 3.33 (m, 1H, O–C*H*–), 3.07 (m, 1H, O–C*H*–), 1.96–1.62 (m, 2H, C*H*), 1.50 (m, 1H, C*H*), 1.36–1.18 (m, 2H, C*H*), 1.04 (s, 9H, *tert*-butyl protons), 0.94 (d, *J*=6.0 Hz, 3H, Me protons); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 133.8, 135.4, 129.5, 128.2, 127.7, 127.5, 127.4, 80.7, 73.7, 73.3, 72.3, 70.6, 60.2, 40.9, 40.1, 38.7, 26.8, 19.2, 12.6; HRMS (ESIMS) calcd for $C_{32}H_{42}O_4NaSi$ $[M+Na]^+$: 541.2750, found: 541.2738.

3.1.2. Synthesis of **10**

A solution of the aglycon **7** (3.0 g, 5.79 mmol) and trichloroacetimidate **8** (1.90 g, 5.79 mmol) in CH_2Cl_2 (15 mL) was stirred with 4 Å MS (75 mg) for 15 min at room temperature and then treated with TMSOTf (5.79 mL, 0.0579 mmol, 0.01 M solution CH_2Cl_2) at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was quenched with Et_3N (2 drops), washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 18–26% EtOAc in petroleum ether eluant) eluted first the desired β-product **10** (1.72 g, 43%) along with unwanted α-product **9** (1.64 g, 41%) as colorless oils.

Analytical data for **10**: R_f=0.55 (SiO_2, 40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −6.18 (*c* 1.7, $CHCl_3$); IR (neat): ν_{max} 3016, 1471, 1426, 1364, 1213, 1161, 1089, 984, 927, 750, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.25 (m, 15H, aromatic protons), 4.55 (ABq, *J*=12.3 Hz, 2H, OC*H*$_2$Ph), 4.31 (d, *J*=7.4 Hz, 1H, anomeric proton), 3.96 (dd, *J*=11.5, 5.1 Hz, 1H, OC*H*–), 3.87 (m, 1H, OC*H*–), 3.77 (m, 1H, OC*H*–), 3.63 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.59–3.53 (m, 3H, OC*H*$_2$–, OC*H*–), 3.48 (s, 3H, OMe), 3.33–3.23 (m, 2H, OC*H*–), 3.15–3.09 (m, 3H, OC*H*–), 3.01 (m, 1H, OC*H*–), 2.11 (dd, *J*=11.9, 4.3 Hz, 1H, C*H*), 1.86 (m, 1H, C*H*), 1.80–1.86 (m, 2H, C*H*), 1.46 (q, *J*=11.5 Hz, 1H, C*H*), 1.05 (s, 9H, *tert*-butyl protons), 0.99 (d, *J*=6.4 Hz, 3H, Me protons); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 135.5, 134.0, 134.0, 129.5, 129.5, 128.2, 127.7, 127.6, 127.5, 127.4, 105.4, 85.6, 83.9, 83.7, 81.1, 79.4, 73.4, 72.3, 70.8, 63.2, 60.7, 60.7, 60.3, 58.7, 40.2, 38.8, 38.7, 26.9, 19.2, 12.6; MS (ESIMS) *m*/*z* (%): 715 (96) $[M+Na]^+$; HRMS (ESIMS) calcd for $C_{40}H_{56}O_8NaSi$ $[M+Na]^+$: 715.3642, found: 715.3631.

Analytical data for compound **9**: R_f=0.52 (SiO_2, 40% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +28.0 (*c* 0.43, $CHCl_3$); IR (neat): ν_{max} 2929, 2856, 1739, 1464, 1429, 1369, 1161, 1101, 1037, 822, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.29 (m, 15H, aromatic protons), 5.07 (d, *J*=3.7 Hz, anomeric proton), 4.55 (ABq, *J*=12.1 Hz, 2H, OC*H*$_2$Ph), 3.93–3.79 and 3.76–3.67 (m, 3H, OC*H*), 3.64 (s, 3H, OMe), 3.63–3.55 and 3.53–3.37 (m, 3H, OC*H*), 3.50 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.33–3.22 and 3.21–3.10 (m, 6H, OC*H*$_2$– and OC*H*–), 2.07 (m, 1H, C*H*), 1.96–1.69 (m, 3H, C*H*), 1.25 (q, *J*=11.6 Hz, 1H, C*H*), 1.04 (s, 9H, *tert*-butyl protons), 0.95 (d, *J*=6.8 Hz, 3H, Me protons); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 135.5, 135.5, 134.0, 129.5, 128.2, 127.7, 127.6, 127.4, 98.7, 83.2, 82.3, 82.2, 81.1, 80.0, 73.4, 72.2, 71.0, 60.5, 60.3, 59.8, 59.0, 58.8, 39.8, 38.8, 26.9, 19.2, 12.6; HRMS (ESIMS) calcd for $C_{40}H_{56}O_8NaSi$ $[M+Na]^+$: 715.3642, found: 715.3650.

3.1.3. Synthesis of **6** from **9**

A polypropylene reaction vial was charged with compound **9** (158 mg, 0.23 mmol) and HF-py (4 mL, 60–70%), and the mixture was stirred at 25 °C for 6 h. The mixture was diluted with 10 mL of MeOH and concentrated under a stream of nitrogen. The residue was washed with 15 mL of EtOAc followed by decanting the solvent and this was repeated three times. The crude product was further purified by column chromatography (SiO_2, 55–60% EtOAc in petroleum ether eluant) to afford pure diol **6** (58 mg, 89%) as colorless liquid. R_f=0.4 (SiO_2, 80% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +3.42 (*c* 1.43, $CHCl_3$); IR (neat): ν_{max} 3348, 3016, 1421, 1368, 1213, 1082, 1045, 1028, 876, 748, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H, aromatic protons), 4.55 (ABq, *J*=11.9 Hz, 2H, OC*H*$_2$Ph), 3.81 (t, *J*=6.0 Hz, 2H, OC*H*$_2$), 3.64 (dd, *J*=10.6, 2.3 Hz, 1H, OC*H*), 3.63 (m, 1H, OC*H*), 3.51 (dd, *J*=10.6, 6.0 Hz, 1H, OC*H*), 3.36 (dt, *J*=10.6, 4.5 Hz, 1H, OC*H*), 3.23 (ddd, *J*=10.6, 6.0, 2.3 Hz, 1H, OC*H*), 3.02 (br s, 1H, O*H*), 2.16 (br s, 1H, O*H*), 1.94 (ddd, *J*=12.1, 4.5, 2.3 Hz, 1H, C*H*), 1.84 (m, 1H, C*H*), 1.76–1.66 (m, 1H, C*H*), 1.50–1.37 (m, 2H, C*H*), 0.95 (d, *J*=6.8 Hz, 3H, Me protons); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 138.0, 128.3, 127.7, 127.6, 80.5, 75.7, 73.4, 73.1, 71.0, 61.1, 40.9, 40.2, 37.6, 12.6; HRMS (ESIMS) calcd for $C_{16}H_{24}O_4Na$ $[M+Na]^+$: 303.1572, found: 303.1565.

3.1.4. Synthesis of **11**

To a stirred solution of **10** (1.70 g, 2.45 mmol) in dry THF (7 mL), TBAF (1 M in THF, 2.7 mL, 2.7 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. It was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with EtOAc (2×10 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 35–40% EtOAc in petroleum ether eluant) afforded pure primary alcohol (1.05 g, 95%) as colorless oil, which was used directly in the next step.

To a solution of oxalyl chloride (0.29 mL, 3.37 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C, DMSO (0.51 mL, 7.2 mmol) was added slowly in dropwise manner, with stirring under nitrogen atmosphere. After 15 min stirring, the alcohol prepared above (1.0 mg, 2.25 mmol) dissolved in dry CH_2Cl_2 (10 mL) was added to the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (1.56 mL, 11.25 mmol) was added and stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with $CHCl_3$ (2×10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The aldehyde, thus obtained, was directly used after flash chromatography (955 mg, 96%) for the next reaction without further characterization.

Under nitrogen atmosphere, a solution of *n*-butyl lithium in hexane (1.6 M solution, 2.4 mL, 3.83 mmol) was added to a solution of DIPA (0.56 mL, 4.01 mmol) in THF (5 mL) at 0 °C and the mixture was stirred for 15 min. It was then added to a solution of propyne (0.27 mL, 4.77 mmol) in THF (5 mL) at −78 °C and the mixture was stirred for 1 h. Then, a solution of the aldehyde (955 mg, 1.91 mmol), prepared above, in dry THF (6 mL) was added to the reaction mixture. After stirring for 1 h at −78 °C, the reaction mixture was quenched by adding saturated aqueous NH_4Cl solution (10 mL), extracted with EtOAc (2×10 mL), washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–35% EtOAc in petroleum ether eluant) first eluted compound **11** (329 mg, 31%) followed by compound **12** (627 mg, 59%) as colorless oils.

Data for **11**: R_f=0.42 (silica gel, 50% EtOAc in petroleum ether). $[\alpha]_D^{25}$ −51.0 (*c* 2.55, $CHCl_3$). IR (neat): ν_{max} 3444, 3017, 1420, 1213, 1161, 1089, 928, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H, aromatic protons), 4.55 (ABq, *J*=12.1 Hz, 2H, OC*H*$_2$Ph), 4.59 (m, 1H, propargylic C*H*OH), 4.30 (d, *J*=7.6 Hz, 1H, anomeric proton), 3.96 (dd, *J*=11.3, 5.3 Hz, 1H, OC*H*), 3.87 (dt, *J*=11.3, 2.3 Hz, 2H, OC*H*), 3.65–3.58 (m, 1H, OC*H*), 3.60 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.52–3.42 (m, 1H, OC*H*), 3.46 (s, 3H, OMe), 3.30–3.22 (m, 2H, OC*H*), 3.13–3.05 (m, 2H, OC*H*), 2.95 (m, 1H, OC*H*), 2.06–1.96 (m, 2H, C*H*), 1.83 (d, *J*=2.3 Hz, 3H, propargylic Me), 1.75 (ddd, *J*=14.4, 6.0, 2.3 Hz, 1H, C*H*), 1.61 (m, 1H, C*H*), 1.39 (m, 1H, C*H*), 0.94 (d, *J*=6.0 Hz, 3H, Me protons); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.2, 127.5, 127.4, 100.4, 85.1, 83.2, 80.6, 80.4, 80.1, 79.2, 78.2, 73.2, 73.0, 70.7, 63.1, 60.4, 60.4, 60.4, 58.5, 42.2, 37.6, 36.5, 12.7, 3.4; HRMS (ESI) calcd for $C_{27}H_{40}O_8Na$ $[M+Na]^+$, 515.2620; found, 515.2624.

3.1.5. Synthesis of **11** from **12**

To a stirred solution of **12** (610 mg, 1.239 mmol) in dry THF (8 mL), PPh_3 (1.138 g, 4.34 mmol), *p*-nitrobenzoic acid (869 mg, 5.2 mmol), and DEAD (0.683 mL, 4.34 mmol) were added sequentially at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and stirred for 1 h. It was then concentrated in vacuo. Purification by column chromatography (SiO_2, 15–16% EtOAc in petroleum ether eluant) afforded the benzoate ester (762 mg, 96%) as a clear oil, which was directly used for the next reaction without further characterization.

To the above prepared ester (762 mg, 1.188 mmol) in dry MeOH (4 mL), dry K_2CO_3 (180 mg, 1.306 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to come reach temperature and stirred for 30 min. Aqueous NH_4Cl solution (5 mL) was added to it and extracted with EtOAc (2×5 mL), washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 18–20% EtOAc in petroleum ether eluant) afforded pure propargylic alcohol **11** (561 mg, 96%) as colorless liquid.

3.1.6. Synthesis of **13**

To a stirred solution of **11** (829 mg, 1.684 mmol) in dry ether (5 mL), Red-Al (1.92 mL, 6.736 mmol, 3.5 M solution in toluene) was added slowly in dropwise manner at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 4 h. It was re-cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with ether (2×5 mL), washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–35% EtOAc in petroleum ether eluant) afforded pure *E*-allylic alcohol intermediate (666 mg, 80%) as colorless liquid.

To a stirred solution of the *E*-allylic alcohol (665 mg, 1.346 mmol) in dry CH_2Cl_2 (4 mL), Et_2Zn (6.73 ml, 6.73 mmol) and CH_2I_2 (1.085 mL, 13.46 mmol) were added slowly in dropwise manner at −20 °C. The reaction mixture was warmed to 0 °C and stirred for 5 h. It was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with EtOAc (2×5 mL), washed with 10% aqueous $NaHCO_3$ (5 mL), water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–35% EtOAc in petroleum ether eluant) afforded pure compound **13** (622 mg, 91%) as colorless liquid. R_f=0.48 (SiO_2, 50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −36.0 (*c* 2.69, $CHCl_3$); IR (neat): ν_{max} 3446, 3017, 1519, 1420, 1213, 1046, 927, 750, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.27–7.19 (m, 5H, aromatic protons), 4.49 (ABq, *J*=11.8 Hz, 2H, OC*H*$_2$Ph), 4.31 (d, *J*=7.4 Hz, 1H, anomeric proton), 3.98 (dd, *J*=11.0, 5.1 Hz, 1H, OC*H*), 3.72 (m, 1H, OC*H*), 3.64–3.40 (m, 3H, OC*H*), 3.55 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.35–3.17 (m, 3H, OC*H*), 3.13–2.91 (m, 3H, OC*H*), 2.52 (br s, 1H, O*H*), 2.04 (ddd, *J*=12.5, 4.4, 1.5 Hz, 1H, C*H*), 1.88 (m, 1H, C*H*), 1.80 (m, 1H, C*H*), 1.56 (m, 1H, C*H*), 1.40 (m, 1H, C*H*), 0.95 (d, *J*=5.1 Hz, 3H, CHMe), 0.90 (d, *J*=6.6 Hz, 3H, CHMe), 0.52 (m, 3H, cyclopropane C*H*), 0.22 (m, 1H, cyclopropane C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.3, 127.6, 127.5, 100.5, 85.2, 83.3, 81.0, 79.4, 78.6, 73.4, 73.1, 72.2, 70.9, 63.2, 60.6, 60.6, 58.6, 42.2, 37.7, 36.8, 26.1, 18.4, 12.9, 11.2, 10.0; MS (ESIMS) *m*/*z* (%): 531 (100) $[M+Na]^+$; HRMS (ESIMS) calcd for $C_{28}H_{44}O_8Na$ $[M+Na]^+$: 531.2933, found: 531.2947.

3.1.7. Synthesis of **14**

To a stirred solution of **13** (620 mg, 1.22 mmol) in CH_2Cl_2 (4 mL), Dess–Martin periodinane (DMP) (621 mg, 1.464 mmol) was added at 0 °C and the reaction mixture was allowed to reach room temperature and stirred for 20 min under nitrogen atmosphere. Saturated $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (2 mL) were then added, and the biphasic mixture was stirred for 15 min and extracted with EtOAc. The organic phase was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 15–18% EtOAc in petroleum ether eluant) afforded pure ketone (525 mg, 85%) as colorless liquid, which was used in the next step without further characterization.

To a stirred solution of the ketone (525 mg, 1.037 mmol) in dry THF (5 mL), LAH (79 mg, 2.074 mmol) was added at −78 °C. After being stirred for 30 min at the same temperature, it was quenched with saturated aqueous Na_2SO_4 (5 mL) at 0 °C and stirred for another 15 min. Precipitated solid was filtered through a short pad

of Celite and the filter cake was washed with ether (2×5 mL). The filtrate and the washings were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 28–30% EtOAc in petroleum ether eluant) afforded compound **14** (332 mg, 63%) as colorless oil. R_f=0.50 (SiO_2, 50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −34.5 (*c* 1.53, $CHCl_3$); IR (neat): ν_{max} 3440, 3017, 1522, 1423, 1213, 1045, 928, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H, aromatic protons), 4.55 (ABq, *J*=12.8 Hz, 2H, OCH_2Ph), 4.29 (d, *J*=6.8 Hz, 1H, anomeric proton), 3.96 (dd, *J*=11.1, 5.1 Hz, 1H, OC*H*), 3.70–3.57 (m, 2H, OC*H*), 3.60 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.50–3.37 (m, 3H, OC*H*), 3.46 (s, 3H, OMe), 3.30–3.16 (m, 2H, OC*H*), 3.15–3.04 (m, 2H, OC*H*), 2.96 (m, 1H, OC*H*), 2.06 (m, 1H, C_3–*H*), 1.82 (m, 1H, C*H*), 1.72 (m, 1H, C*H*), 1.58 (m, 1H, C*H*), 1.35 (m, 1H, C*H*), 1.06 (d, *J*=5.3 Hz, 3H, CHMe), 0.93 (d, *J*=6.0 Hz, 3H, CHMe), 0.78 (m, 1H, cyclopropane C*H*), 0.61 (m, 1H, cyclopropane C*H*), 0.30 (m, 1H, cyclopropane C*H*), 0.18 (m, 1H, cyclopropane C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 128.3, 127.7, 127.6, 100.5, 85.5, 85.2, 83.3, 80.9, 79.3, 78.3, 76.3, 76.0, 73.5, 71.0, 63.2, 60.6, 58.7, 42.3, 37.8, 37.1, 26.1, 18.7, 12.8, 11.1, 10.1; MS (ESIMS) *m*/*z* (%): 531 (100) $[M+Na]^+$; HRMS (ESIMS) calcd for $C_{28}H_{44}O_8Na$ $[M+Na]^+$: 531.2933, found: 531.2925.

3.1.8. Synthesis of **15**

To a stirred solution of **14** (330 mg, 0.649 mmol) in CH_2Cl_2 (3 mL), 2,6-lutidine (0.226 mL, 1.948 mmol) and TBSOTf (0.223 mL, 0.97 mmol) were added sequentially at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h. It was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (2×5 mL). The organic extracts were combined, washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 18–20% EtOAc in petroleum ether eluant) gave pure compound **15** (360 mg, 89%) as clear oil. R_f=0.51 (SiO_2, 35% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −29.8 (*c* 2.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H, aromatic protons), 4.58 (ABq, *J*=12.1 Hz, 2H, OCH_2Ph), 4.31 (d, *J*=7.6 Hz, 1H, anomeric proton), 3.97 (dd, *J*=11.3, 4.5 Hz, 1H, OC*H*), 3.67–3.50 (m, 3H, OC*H*), 3.61 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.42 (dt, *J*=10.6, 4.5 Hz, 1H, OC*H*), 3.31–3.19 (m, 2H, OC*H*), 3.15–3.03 (m, 3H, OC*H*), 2.98–2.93 (m, 1H, OC*H*), 2.09 (m, 1H, C*H*), 1.95 (m, 1H, C*H*), 1.67–1.58 (m, 2H, C*H*), 1.23 (m, 1H, C*H*), 1.02 (d, *J*=6.0 Hz, 3H, CHMe), 0.94 (d, *J*=6.8 Hz, 3H, CHMe), 0.88 (s, 9H, *tert*-butyl protons), 0.67–0.53 (m, 2H, cyclopropane C*H*), 0.30 (m, 1H, cyclopropane C*H*), 0.18 (m, 1H, cyclopropane C*H*), 0.06 (s, 3H, SiMe), 0.03 (s, 3H, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 128.2, 127.6, 127.4, 100.3, 85.2, 83.3, 81.2, 79.4, 78.6, 73.4, 73.4, 72.7, 71.1, 63.2, 60.6, 60.6, 58.7, 44.5, 37.8, 36.6, 26.0, 25.9, 18.6, 18.1, 13.0, 11.3, 10.6, −4.1, −4.5.

3.1.9. Synthesis of **16**

To a solution of the silyl ether **15** (350 mg, 0.56 mmol) in EtOAc (3 mL), 10% Pd–C (78 mg) was added and the mixture was hydrogenated using a H_2-filled balloon for 1 h. It was then filtered through a short pad of Celite and the filter cake was washed with EtOAc (2×5 mL). The filtrate and washings were combined and concentrated in vacuo. Purification by column chromatography (SiO_2, 28–30% EtOAc in petroleum ether eluant) furnished the debenzylated intermediate (272 mg, 91%) as colorless oil, which was used directly in the next step.

The debenzylated product (272 mg, 0.511 mmol) in CH_2Cl_2 (3 mL) was oxidized with Dess–Martin periodinane (DMP, 325 mg, 0.766 mmol) under nitrogen atmosphere at 0 °C, then allowed to reach room temperature and stirred for 30 min. Saturated $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (2 mL) were then added, and the biphasic mixture was stirred for 15 min and extracted with EtOAc (2×5 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The aldehyde thus obtained was directly used after flash chromatography for the next reaction without further characterization.

Sodamide (160 mg, 4.088 mmol) was added to a suspension of methyltriphenylphosphonium iodide (620 mg, 1.533 mmol) in dry ether (10 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred for 6 h. The resulting methylenetriphenylphosphorane was added to a solution of the aldehyde, prepared above and dissolved in ether (5 mL), at 0 °C. After 10 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL). The layers were separated. The aqueous layer was extracted with ether (2×5 mL), washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (SiO_2, 15–18% EtOAc in petroleum ether eluant) afforded pure compound **16** (181 mg, 67% in two steps) as colorless liquid. R_f=0.45 (silica gel, 25% EtOAc in petroleum ether). $[\alpha]_D^{25}$ −35.8 (*c* 0.83, $CHCl_3$). IR (neat): ν_{max} 3017, 2924, 1213, 1090, 928, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (ddd, *J*=17.4, 10.6, 6.8 Hz, 1H, olefinic proton), 5.25 (d, *J*=17.4 Hz, 1H, olefinic proton), 5.17 (d, *J*=10.6 Hz, 1H, olefinic proton), 4.32 (d, *J*=7.6 Hz, 1H, anomeric proton), 3.98 (dd, *J*=11.3, 4.5 Hz, OC*H*), 3.61 (s, 3H, OMe), 3.58 (m, 1H, OC*H*), 3.55 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.45–3.35 (m, 2H, OC*H*), 3.32–3.18 (m, 2H, OC*H*), 3.14–3.04 (m, 2H, OC*H*), 2.96 (dd, *J*=9.1, 7.6 Hz, 1H, C3–*H*), 2.11 (m, H, C*H*), 1.94 (m, 1H, C*H*), 1.68–1.58 (m, 2H, C*H*), 1.40 (m, 1H, C*H*), 1.03 (d, *J*=5.3 Hz, 3H, CHME), 0.94 (d, *J*=6.0 Hz, 3H, CHME), 0.88 (s, 9H, *tert*-butyl protons), 0.64 (m, 1H, cyclopropane C*H*), 0.57 (m, 1H, cyclopropane C*H*), 0.31 (m, 1H, cyclopropane C*H*), 0.18 (m, 1H, cyclopropane C*H*), 0.06 (s, 3H, SiMe), 0.03 (s, 3H, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 117.0, 100.2, 85.3, 83.4, 82.9, 79.4, 78.5, 73.4, 72.5, 63.3, 60.6, 60.5, 58.7, 44.5, 41.3, 36.8, 26.1, 25.9, 18.7, 18.1, 13.3, 11.4, 10.6, −4.0, −4.5. HRMS (ESI) calcd for $C_{28}H_{52}O_7NaSi$ $[M+Na]^+$, 551.3380; found, 551.3394.

3.1.10. Synthesis of **17**

(*c*Hex)$_2$BH (2.076 mmol) was freshly prepared from cyclohexene (0.436 mL, 4.15 mmol) and BH_3·DMS (0.19 mL, 2.076 mmol) in dry THF (2 mL) at room temperature. To the above prepared (*c*hex)$_2$BH solution, olefinic compound **16** (180 mg, 0.34 mmol) in THF (5 mL) was added at 0 °C under nitrogen atmosphere. After being stirred for 4 h at the same temperature, dry MeOH (0.168 mL, 4.152 mmol), NaOH (3 N aqueous solution, 1.038 mL, 3.114 mmol), and H_2O_2 (30%, w/v, 0.823 mL, 7.266 mmol) were added sequentially. Then, the reaction mixture was slowly warmed to 55 °C and stirred at that temperature for 1 h, during which time the turbid solution became clear. It was cooled to room temperature and extracted with EtOAc (2×10 mL). The combined organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–33% EtOAc in petroleum ether eluant) afforded compound **17** (168 mg, 91%) as colorless liquid. R_f=0.52 (SiO_2, 60% EtOAc in petroleum ether); $[\alpha]_D^{25}$ −33.2 (*c* 0.25, $CHCl_3$); IR (neat): ν_{max} 3480, 1462, 1213, 1089, 1213, 1089, 928, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.31 (d, *J*=7.2 Hz, 1H, anomeric proton), 3.98 (dd, *J*=11.3, 5.3 Hz, 1H, OC*H*), 3.82–3.72 (m, 2H, OC*H*), 3.65–3.51 (m, 2H, OC*H*), 3.61 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.40 (dd, *J*=11.3, 4.5 Hz, 1H, OC*H*), 3.32–3.18 (m, 2H, OC*H*), 3.16–3.02 (m, 2H, OC*H*), 2.96 (m, 1H, OC*H*), 2.12 (br s, 1H, O*H*), 2.09–1.82 (m, 2H, C*H*), 1.78–1.54 (m, 2H, C*H*), 1.46 (m, 1H, C*H*), 1.30 (m, 1H, C*H*), 1.03 (d, *J*=5.6 Hz, 3H, CHME), 0.97 (d, *J*=6.0 Hz, 3H, CHME), 0.89 (s, 9H, *tert*-butyl protons), 0.66 (m, 1H, cyclopropane C*H*), 0.58 (m, 1H, cyclopropane C*H*), 0.33 (m, 1H, cyclopropane C*H*), 0.22 (m, 1H, cyclopropane C*H*), 0.06 (s, 3H, SiMe), 0.02 (s, 3H, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 100.3, 85.2, 83.3, 82.2, 79.4, 78.0, 73.5, 72.9, 63.3, 61.5, 60.7, 60.7, 58.8, 44.7, 41.3, 36.8, 34.7, 26.0, 25.9, 18.6, 18.1, 13.1, 11.5, 10.8, −4.1, −4.6; HRMS (ESIMS) calcd for $C_{28}H_{54}O_8NaSi$ $[M+Na]^+$: 569.3485, found: 569.3498.

*3.1.11. Synthesis of **18***

Compound **17** (165 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was oxidized with Dess–Martin periodinane (DMP, 189 mg, 0.45 mmol) under the same conditions followed for the synthesis of **16**. The resulting aldehyde was directly used after flash chromatography in the next reaction.

To a stirred solution of the aldehyde in *t*-BuOH/2-methyl-2-butene (2:1, 3 mL) at room temperature, $NaClO_2$ (67.83 mg, 0.75 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (117 mg, 0.75 mmol), dissolved in minimum amount of water, were added. After being stirred for 1 h, the solvent was removed in rotary evaporator and the residue was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 60–65% EtOAc in petroleum ether eluant) afforded the acid (123 mg, 87% in two steps) as colorless liquid, which was used directly in the next step.

To a stirred solution of the acid (120 mg, 0.215 mmol) in dry CH_2Cl_2/MeOH (2:1, 3 ml), CSA (25 mg, 0.107 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 h. Then, it was quenched with water (3 mL), extracted with EtOAc (2×5 mL), washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 90–95% EtOAc in petroleum ether eluant) furnished compound **18** (81 mg, 85%) as colorless liquid. R_f=0.35 (silica gel, EtOAc). $[\alpha]_D^{25}$ −23.1 (*c* 0.23, $CHCl_3$). IR (neat): ν_{max} 3448, 2924, 2853, 2361, 1631, 1459, 1380, 1093, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.28 (d, *J*=7.4 Hz, 1H, anomeric proton), 3.97 (dd, *J*=11.7, 5.0 Hz, 1H, OC*H*), 3.68–3.37 (m, 1H, OC*H*), 3.60 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.51–3.38 (m, 2H, OC*H*), 3.47 (s, 3H, OMe), 3.26 (ddd, *J*=5.2, 8.6, 9.4 Hz, 1H, OC*H*), 3.17 (dd, *J*=2.4, 8.9 Hz, 1H, OC*H*), 3.14–3.03 (m, 2H, OC*H*), 3.01 (br s, 1H, O*H*), 2.94 (dd, *J*=7.3, 9.0 Hz, 1H, OC*H*), 2.69 (dd, *J*=2.6, 15.2 Hz, 1H, C*H*), 2.40 (dd, *J*=4.8, 12.8 Hz, 1H, C*H*CO–), 2.05 (dd, *J*=4.8, 12.8 Hz, 1H, C*H*CO–), 1.89–1.55 (m, 2H, C*H*), 1.47–1.16 (m, 2H, C*H*), 1.01 (d, *J*=5.9 Hz, 3H, CHMe), 0.98 (d, *J*=6.5 Hz, 3H, CHMe), 0.76 (m, 1H, cyclopropane C*H*), 0.58 (m, 1H, cyclopropane C*H*), 0.24 (m, 1H, cyclopropane C*H*), 0.17 (m, 1H, cyclopropane C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 100.5, 85.2, 83.3, 79.3, 78.3, 77.0, 76.9, 63.3, 60.6, 60.6, 58.7, 52.3, 41.8, 41.1, 38.5, 37.2, 25.8, 25.2, 22.7, 18.5, 13.0, 11.7, 10.2; HRMS (ESI) calcd for $C_{22}H_{38}O_9NaSi$ $[M+Na]^+$, 469.2413; found, 469.2409.

*3.1.12. Synthesis of clavosolide A (**5**)*

2,4,6-Trichlorobenzoyl chloride (0.17 mL, 1.1 mmol) was added to a stirred solution of the seco acid **18** (50 mg, 0.11 mmol) and triethyl amine (0.3 mL, 2.2 mmol) in dry THF (3 mL) at room temperature under nitrogen atmosphere. After being stirred for 3 h, the TEA·HCl salt was filtered off and the filtrate was diluted with dry toluene (5 mL). This solution was then added slowly to a stirred solution of DMAP (134 mg, 1.1 mmol) in dry toluene (110 mL) at 90 °C through a syringe pump over 5 h. Then it was cooled to room temperature and stirred for further 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with EtOAc (2×5 mL), washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 55–60% EtOAc in petroleum ether eluant) afforded clavosolide A (**5**) (34 mg, 71%). R_f=0.55 (silica gel, 70% EtOAc in petroleum ether). $[\alpha]_D^{25}$ −42.4 (*c* 0.13, $CHCl_3$); IR (neat): ν_{max} 3016, 1728, 1213, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, proton numbering as in Ref. 2a): δ 4.42 (dt, *J*=9.0, 1.0 Hz, 2H, –C*H*OCO–), 4.26 (d, *J*=7.5 Hz, 2H, anomeric proton), 3.95 (dd, *J*=11.5, 5.0 Hz, 2H, C19–*H*), 3.61 (s, 6H, OMe), 3.57 (s, 6H, OMe), 3.48–3.43 (m, 4H, OC*H*), 3.46 (s, 6H, OMe), 3.27–3.21 (m, 4H, OC*H*), 3.09 (t, *J*=8.0 Hz, 2H, C17–*H*), 3.08 (dd, *J*=11.5, 8.0 Hz, 2H, C19–*H*′), 2.95 (t, *J*=8.0 Hz, 2H, C16–*H*), 2.54 (dd, *J*=17.0, 3.5 Hz, 2H, C2–*H*), 2.41 (dd, *J*=17.0, 6.5 Hz, 2H, C2–*H*′), 2.04 (dd, *J*=11.5, 5.0 Hz, 2H, C6–*H*), 1.88 (dt, *J*=15.7, 9.0 Hz, 2H, C8–*H*), 1.67 (ddd, *J*=15.7, 2.4, 1.0 Hz, 2H, C6–*H*′), 1.37 (q, *J*=11.5 Hz, 2H, C6–*H*′), 1.37 (m, 2H, C4–*H*), 0.96 (two d, *J*=6.5 Hz, 12H, methyls), 0.83 (m, 2H, C11–*H*), 0.72 (tt, *J*=9.0, 5.0 Hz, 2H, C10–*H*), 0.33 (dt, *J*=8.0, 5.0 Hz, 2H, C13–*H*), 0.22 (dt, *J*=8.0, 5.0 Hz, 2H, C13–*H*′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 105.5, 85.5, 83.8, 83.2, 79.3, 77.2, 77.0, 74.8, 63.2, 60.8, 60.8, 58.8, 42.5, 41.2, 40.7, 39.2, 24.7, 18.5, 12.6, 12.0, 10.9. HRMS (ESI) calcd for $C_{44}H_{72}O_{16}Na$ $[M+Na]^+$, 879.4718; found, 879.4687.

Acknowledgements

The authors wish to thank DST, New Delhi for a Ramanna Fellowship (SR/S1/RFOC-06/2006; T.K.C.), CSIR (V.R.R) and UGC (P.K.G), New Delhi for research fellowships.

References and notes

1. Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.
2. (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386–388; (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303–1306.
3. For total syntheses of the first reported structure of clavosolide A see: (a) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett.* **2006**, *47*, 2099–2102; (b) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097–5099; For synthesis of the monomeric unit see: (c) Yakambram, P.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 3781–3783.
4. Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D.-H. *Org. Lett.* **2006**, *8*, 661–664.
5. Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D.-H. *Org. Lett.* **2006**, *8*, 3411.
6. Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319–3322.
7. Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318.
8. Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett.* **2006**, *47*, 7435–7438.
9. Son, J. B.; Hwang, M.-H.; Lee, W.; Lee, D.-H. *Org. Lett.* **2007**, *9*, 3897–3900.
10. A similar approach was adopted by Lee et al. in their recently reported synthesis of clavosolide B (Ref. 9).
11. Chakraborty, T. K.; Reddy, V. R.; Reddy, T. J. *Tetrahedron* **2003**, *59*, 8613–8622.
12. Schimdt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
13. Wanner, J.; Tang, D.; McComas, C. C.; Crowley, B. M.; Jiang, W.; Moss, J.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1169–1173.
14. (a) Charette, A. B.; Label, H. *J. Org. Chem.* **1995**, *60*, 2966–2967; (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
15. (a) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772; (b) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753; (c) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.
16. (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324; (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.
17. (a) Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511–3521; (b) Yokomatsu, T.; Yamagishi, T.; Suemune, K.; Abe, H.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Tetrahedron Lett.* **2000**, *56*, 7099–7108; (c) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamasihita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915–923; (d) Ono, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 221–224.
18. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
19. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.