Synthetic Studies of Carolacton: Enantioselective Total Synthesis of C1–C8 and C9–C19 Fragments of the Molecule

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Received: 16.06.2013; Accepted after revision: 12.07.2013

Abstract: This paper describes synthetic studies towards carolacton, a highly potent antibiotic against dental caries and endocarditis related bacterium *Streptococcus mutans*. The synthesis of the 12-membered lactone with a diversely functionalized keto acid side chain was accomplished by utilizing a blend of chiral pool and aldol strategies. Carbon chain C1–C8 was derived by utilizing Paterson aldol methodology and a Corey–Fuchs reaction. The C9–C19 chain was prepared by means of iterative Evans asymmetric alkylations and an *E*-selective cross-metathesis reaction.

Key words: *Streptococcus mutans*, carolacton, antibiotic, Paterson aldol reaction, cross metathesis

Streptococcus mutans biofilms on various body tissues, medical devices, and implants[1,2] are a matter of serious concern due to their strong resistance to available antibiotics. These biofilms cause dental caries, periodontal decay, and are found to be highly resistant[3,4] compared to when they are present in their natural habitat. Therefore, the development of efficient antibiotics to eradicate these biofilms formed via bacterial aggregation is an active area of research. Recently Müller et al. isolated[5a] carolacton (Figure 1) from the extracts of the *Sorangium cellulosum* strain and this has the ability to destroy these biofilms[5b] at considerably low concentrations. Structural assignment based on NMR showed that it is a 12-membered macrolide with a highly functionalized keto acid side chain. Further development of carolacton skeleton based motifs are highly promising towards the elimination of *Streptococcus mutans* biofilms and related complications. We have undertaken the total synthesis of carolacton because of its interesting biological functions and complex architecture. Our approach is highly diversified so that, as it can be utilized for the synthesis of various carolacton analogues and subsequent biological evaluations. While this work was still ongoing, the first total synthesis of carolacton was reported by Kirschning et al.[6a] A synthetic study towards the total synthesis of carolacton appeared in the literature during preparation of this manuscript.[6b] In this paper we report our efforts towards synthetic studies of carolacton.

Structural analysis of carolacton (**1**) revealed that macrolactonization of the seco acid **2** followed by protecting group deprotection and functional group manipulations would provide the target molecule. The seco acid **2** could

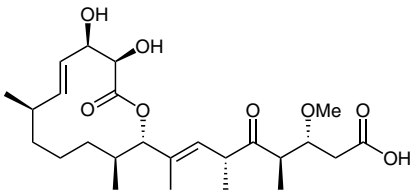
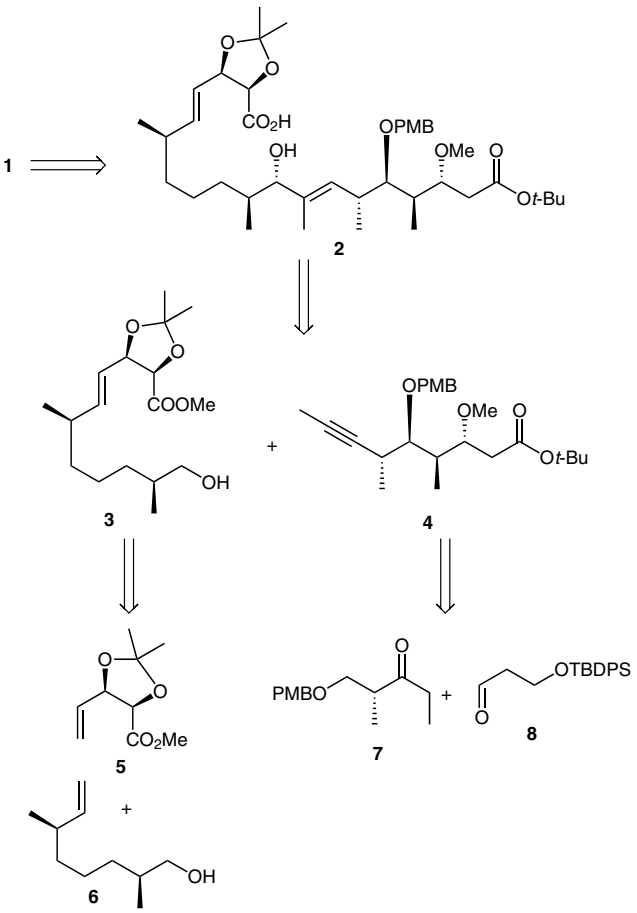


Figure 1 Structure of carolacton

be obtained from olefinic alcohol **3** and the *tert*-butyl ester **4** by utilizing the Nozaki–Hiyama–Kishi reaction (similar to the Kirschning approach). The olefinic fragment **3** with *E*-configuration could be obtained from the two olefinic fragments **5** and **6** by means of a cross-metathesis reaction. The other fragment **4** could be obtained via Paterson aldol reaction between **7** and **8** followed by functional group interconversion (Scheme 1).

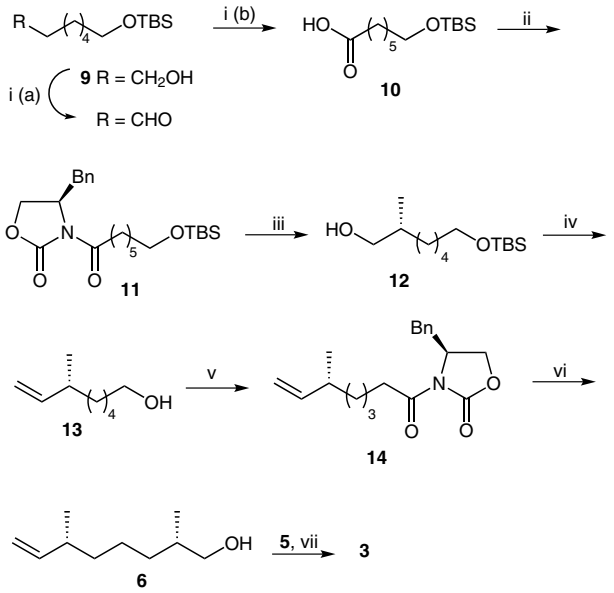


Scheme 1 Retrosynthetic analysis of carolacton

SYNTHESIS 2013, 45, 2745–2751
Advanced online publication: 15.08.2013
DOI: 10.1055/s-0033-1339500; Art ID: SS-2013-T0411-OP

Thus our synthesis commenced from the known compound **9**[7] (Scheme 2), which on two-step oxidation[8] afforded the known acid **10**;[9] coupling of the acid with (*R*)-4-benzyloxazolidin-2-one provided compound **11**.[10] Methylation[11] of **11** with iodomethane in the presence of sodium hexamethyldisilazanide in tetrahydrofuran at –78 °C followed by chiral auxiliary removal provided the known primary alcohol **12**.[12] Oxidation of the alcohol **12** under Swern conditions provided an aldehyde, which on one-carbon homologation with methylenetriphenylphosphorane followed by tetrabutylammonium fluoride mediated TBS deprotection furnished known compound **13**.[13] The alcohol **13** was oxidized to an acid by a two-step oxidation protocol and then coupled with the chiral auxiliary to give **14**, which on methylation with iodomethane followed by removal of chiral auxiliary furnished alcohol **6**. The crucial cross-metathesis reaction[14] between **6** and the known compound **5**[15] was achieved with Grubbs second-generation catalyst (Grubbs II) to afford the alcohol **3** with the required *E*-configured olefinic moiety in 73% yield.

The synthesis of alkyne compound **4** started with the addition of the enolate generated from the known ketone **7**[16] under Paterson conditions[17] to the aldehyde **8** and gave β-hydroxy keto compound **15** (96%, dr > 99:1). Hydroxy-directed keto reduction by using the Evans protocol[18] provided the 1,3-*anti*-diol compound **16**, which on oxidative rearrangement with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone followed by O-methylation with iodomethane and sodium hydride in tetrahydrofuran provided globally protected compound **17**. Opening of the 4-methoxybenzylidene ring with diisobutylaluminum hydride afforded primary alcohol **18**, which on oxidation[19] followed by Corey–Fuchs[20] reaction and methylation of the terminal alkyne with iodomethane afforded compound **19**. TBDPS deprotection of **19** furnished primary alcohol **20**, which on two-step oxidation followed by esterification of the resultant acid with *tert*-butyl trichloroacetimidate[21] provided known ester compound **4** (Scheme 3).



Scheme 2 Synthesis of fragment **3**: *Reagents and conditions*: (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C, 2 h; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methylbut-2-ene, 0 °C to r.t., 1 h, 80% over 2 steps; (ii) PivCl, Et_3N, THF, –20 °C, 1 h, then LiCl, (*R*)-4-benzyloxazolidin-2-one, –20 °C, 1 h, 0 °C, 2 h, 85%; (iii) (a) MeI, NaHMDS, THF, –78 °C, 3 h; (b) $LiBH_4$, Et_2O, H_2O, 0 °C, 30 min, 81% over 2 steps; (iv) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C, 2 h; (b) $Ph_3P^+MeI^-$, NaHMDS, THF, –78 °C to r.t., 2 h; (c) TBAF, THF, 0 °C to r.t., 1 h, 86% over 3 steps; (v) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C, 2 h; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methylbut-2-ene, 0 °C to r.t., 1 h; (c) PivCl, Et_3N, THF, –20 °C, 1 h, then LiCl, (*S*)-4-benzyloxazolidin-2-one, –20 °C, 1 h, 0 °C, 2 h, 81% over 3 steps; (vi) (a) MeI, NaHMDS, THF, –78 °C, 4 h; (b) $LiBH_4$, Et_2O, H_2O, 0 °C, 30 min, 80% over 2 steps; (vii) Grubbs II (10 mol%), CH_2Cl_2, reflux, 7 h, 73%.

In conclusion we have achieved the enantioselective total synthesis of C1–C8 and C9–C19 fragments of carolacton. The strategy developed here is highly flexible and convergent. The key features of the synthesis include a cross-metathesis reaction, Evans asymmetric alkylation, and Paterson aldol reaction.

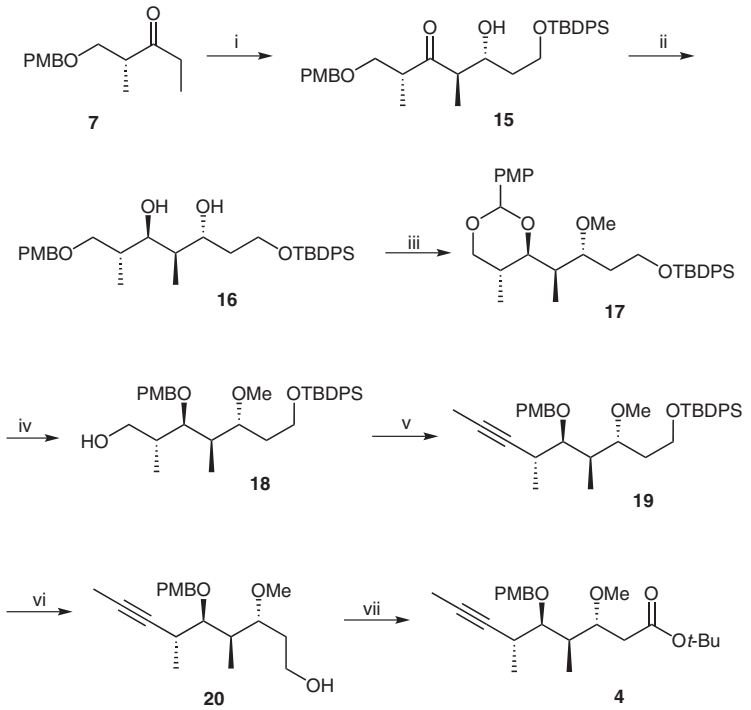
^1H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz (Avance), Varian Unity 500 MHz (Innova) and 700 MHz spectrometers at r.t. in $CDCl_3$ solvent by using TMS as internal standard. FTIR spectra were recorded on an Alpha (Bruker) infrared spectrophotometer. Horiba Sepa 300 polarimeter was used to record the optical rotations. All the reactions were carried out under inert atmosphere in flame dried glass apparatus. Freshly distilled anhyd solvents were used to carry out the reactions. All the chemicals from Aldrich were used as received. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns.

7-(*tert*-Butyldimethylsiloxy)heptanal; Typical Procedure for the Swern Oxidation

To a cooled soln of $(COCl)_2$ (1.57 mL, 18.25 mmol) in anhyd CH_2Cl_2 (30 mL) at –78 °C was added anhyd DMSO (2.76 mL, 38.95 mmol) slowly under a N_2 atmosphere. After 15 min, alcohol **9** (3 g, 12.17 mmol) in anhyd CH_2Cl_2 (10 mL) was added by cannula. The mixture was stirred for 30 min at –78 °C, then Et_3N (8.46 mL, 60.86 mmol) was added, and the mixture was stirred at this temperature for 45 min. The mixture was quenched with sat. aq NH_4Cl soln (20 mL) and extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a plug of silica gel and used in the next step without characterization.

7-(*tert*-Butyldimethylsiloxy)heptanoic Acid (10); Typical Procedure for the Pinnick Oxidation

To a soln of 7-(*tert*-butyldimethylsiloxy)heptanal in *t*-BuOH (40 mL) at 0 °C 2-methylbut-2-ene (12.1 mL) was added; this was followed, after 5 min, by the addition of $NaClO_2$ (4.38 g, 48.69 mmol) and NaH_2PO_4 (7.59 g, 48.69 mmol) dissolved in the minimum amount of H_2O. The resulting mixture was stirred at r.t. for 1 h. The mixture pH was adjusted to 2 with 1 M HCl and extracted with EtOAc (2 × 60 mL). The combined organic layers were washed sequentially with sat. aq $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), concentrated in vacuo, and purified by column chromato-



Scheme 3 Synthesis of fragment **4**: *Reagents and conditions*: (i) Cy_2BCl, Et_3N, Et_2O, –78 °C to 0 °C, 2.5 h, then **8**, –78 °C to r.t., 12 h, 96%, dr > 99:1; (ii) $Me_4NHB(OAc)_3$, AcOH–acetone (1:1), –20 °C, 24 h, 81%; (iii) (a) DDQ, 4 Å MS, CH_2Cl_2, –10 °C to 0 °C, 1 h; (b) MeI, NaH, DMAP, THF, 0 °C to r.t., 3 h, 78% over 2 steps; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 74%; (v) (a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 1 h; (b) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 1 h; (c) BuLi, MeI, THF, –78 °C to r.t., 3 h, 70% over 3 steps; (vi) TBAF, THF, 0 °C to r.t., 1 h, 90%; (vii) (a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 1 h; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methylbut-2-ene, 0 °C to r.t., 1 h; (c) *tert*-butyl trichloroacetimidate, CSA, CH_2Cl_2, 0 °C to r.t., 24 h, 60% over 3 steps.

graphy to provide **10** (2.53 g, 80%) as a colorless oil; R_f = 0.3 (30% EtOAc–petroleum ether).

IR (neat): 2934, 1708, 1462, 1097, 833 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 3.59 (t, *J* = 7.3 Hz, 2 H), 2.32 (t, *J* = 7.3 Hz, 2 H), 1.67–1.58 (m, 2 H), 1.54–1.46 (m, 2 H), 1.37–1.30 (m, 14 H), 0.87 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 63.0, 33.9, 32.4, 28.7, 25.8, 25.3, 24.5, 18.1, -5.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{28}O_3SiNa$: 283.1705; found: 283.1700.

(*R*)-4-Benzyl-3-[7-(*tert*-butyldimethylsiloxy)heptanoyl]oxazolidin-2-one (11); Typical Procedure

To a stirred soln of acid **10** (2.5 g, 9.6 mmol) in anhyd THF (30 mL) at –20 °C was added Et_3N (3.33 mL, 24.0 mmol) followed by PivCl (1.18 mL, 9.6 mmol). The mixture was stirred for 1 h at –20 °C, and then LiCl (0.61 g, 14.4 mmol) followed by (*R*)-4-benzyloxazolidin-2-one (1.7 g, 9.6 mmol) were added and stirring was continued for 1 h at –20 °C and then 2 h at 0 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL) and extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a residue that was purified by column chromatography to yield **11** (3.42 g, 85%) as a colorless oil; R_f = 0.35 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –35.3 (*c* 4, $CHCl_3$).

IR (neat): 2935, 2860, 1782, 1383, 1096 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 7.36–7.30 (m, 2 H), 7.27 (m, 1 H), 7.22–7.19 (m, 2 H), 4.67 (m, 1 H), 4.22–4.13 (m, 2 H), 3.61 (t, *J* = 7.0 Hz, 2 H), 3.29 (dd, *J* = 13.0, 3.0 Hz, 1 H), 3.01–2.85 (m, 2 H), 2.77 (dd, *J* = 14.0, 10.0 Hz, 1 H), 1.75–1.66 (m, 2 H), 1.58–1.49 (m, 2 H), 1.44–1.35 (m, 4 H), 0.90 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 153.3, 135.2, 129.3, 128.8, 127.2, 66.0, 63.0, 55.0, 37.7, 35.3, 32.5, 28.8, 25.8, 25.5, 24.1, 18.2, –5.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{37}NO_4SiNa$: 442.2389; found: 442.2375.

(*R*)-4-Benzyl-3-[(*R*)-7-(*tert*-butyldimethylsiloxy)-2-methylheptanoyl]oxazolidin-2-one; Typical Procedure

To a soln of **11** (3 g, 7.15 mmol) in anhyd THF (20 mL) at –78 °C, 1 M NaHMDS (107 mL, 10.7 mmol) was added slowly with stirring under a N_2 atmosphere. The mixture was stirred at –78 °C for 30 min, MeI (1.34 mL, 21.4 mmol) was added, and it was stirred for an additional 3 h at –78 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL), warmed to r.t., and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography to afford the methylated product as a colorless oil.

(*R*)-7-(*tert*-Butyldimethylsiloxy)-2-methylheptan-1-ol (12); Typical Procedure

To an ice-cooled soln of methylated compound (2.5 g, 5.7 mmol) in Et_2O (18 mL), containing 1 drop of H_2O, was added $LiBH_4$ (0.37 g, 17.3 mmol) portionwise. The mixture was stirred at r.t. for 30 min. The reaction was quenched by slow dropwise addition of sat. aq NH_4Cl (10 mL) at 0 °C. The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to afford **12** (1.21 g, 81%) as a colorless oil; R_f = 0.4 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ +6.7 (*c* 5, $CHCl_3$).

IR (neat): 3347, 2930, 2860, 1464, 1098, 834 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 3.60–3.55 (m, 2 H), 3.45 (m, 1 H), 3.37 (m, 1 H), 2.02 (br s, 1 H), 1.58 (m, 1 H), 1.53–1.46 (m, 2 H), 1.41–1.34 (m, 2 H), 1.33–1.25 (m, 3 H), 1.08 (m, 1 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.0, 63.1, 35.5, 33.0, 32.6, 26.6, 26.0, 25.8, 18.2, 16.4, -5.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{32}O_2SiNa$: 283.2099; found: 283.2102.

(*R*)-6-Methyloct-7-en-1-ol (13)

Compound **12** (1 g, 3.84 mmol) was subjected to Swern oxidation following the typical procedure for 7-(*tert*-butyldimethylsiloxy)heptanal to yield (*R*)-7-(*tert*-butyldimethylsiloxy)-2-methylheptanal, which was used directly in the next step without characterization.

To a suspension of methyltriphenylphosphonium iodide (3.41 g, 8.44 mmol) in anhyd THF (8 mL) at 0 °C was added 1 M NaHMDS (7.68 mL, 7.68 mmol) slowly. The mixture was stirred at this temperature for 30 min, then it was cooled to –78 °C, and (*R*)-7-(*tert*-butyldimethylsiloxy)-2-methylheptanal dissolved in THF (4 mL) was added slowly. The mixture was allowed to reach r.t. over a period of 2 h. H_2O (10 mL) was added to the mixture, and it was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed sequentially with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography yielded (*R*)-8-(*tert*-butyldimethylsiloxy)-3-methylocta-1,8-diene as a clear oil.

To a stirred soln of (*R*)-8-(*tert*-butyldimethylsiloxy)-3-methylocta-1,8-diene in anhyd THF (9 mL), 1 M TBAF (2.7 mL, 2.7 mmol) was added at 0 °C and the mixture was allowed to reach r.t. After 1 h the reaction was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed sequentially with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatographic purification of the residue provided alcohol **13** (0.368 g, 86%) as a liquid; R_f = 0.3 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –15.79 (*c* 1, $CHCl_3$).

IR (neat): 3327, 2926, 1642, 1054, 910 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 5.69 (m, 1 H), 5.0–4.87 (m, 2 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 2.11 (m, 1 H), 1.63–1.51 (m, 2 H), 1.38–1.24 (m, 6 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 112.2, 62.9, 37.6, 36.5, 32.7, 26.9, 25.7, 20.1.

MS (EI): *m*/*z* = 142 (M^+).

(*S*)-4-Benzyl-3-[(*R*)-6-methyloct-7-enoyl]oxazolidin-2-one (14)

Compound **13** (0.35 g, 2.46 mmol) was subjected to the Swern oxidation following the typical procedure for 7-(*tert*-butyldimethylsiloxy)heptanal followed by Pinnick oxidation following the typical procedure for **10** to provide the acid as a clear oil.

The above acid was treated with (*S*)-4-benzyloxazolidin-2-one according to the typical procedure for **11** to yield **14** (0.43 g, 81%) as a colorless oil; R_f = 0.3 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ +41.0 (*c* 1.2, $CHCl_3$).

IR (neat): 2924, 2859, 1780, 1699, 1205 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 7.38–7.26 (m, 3 H), 7.24–7.18 (m, 2 H), 5.69 (m, 1 H), 5.01–4.88 (m, 2 H), 4.68 (m, 1 H), 4.24–4.13 (m, 2 H), 3.29 (dd, *J* = 13.6, 3.0 Hz, 1 H), 3.04–2.83 (m, 2 H), 2.77 (dd, *J* = 13.6, 9.8 Hz, 1 H), 2.14 (m, 1 H), 1.77–1.63 (m, 2 H), 1.23 (s, 4 H), 0.99 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 153.4, 144.5, 135.2, 129.3, 128.8, 127.2, 112.4, 66.0, 55.0, 37.8, 37.6, 36.2, 35.4, 26.9, 26.7, 24.2, 20.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NO_3Na$: 338.1732; found: 338.1730.

(2*S*,6*R*)-2,6-Dimethyloct-7-en-1-ol (6)

Compound **14** (0. 5 g, 1.6 mmol) was subjected to Evans methylation according to the typical procedure for (*R*)-4-benzyl-3-[(*R*)-7-(*tert*-butyldimethylsiloxy)-2-methylheptanoyl]oxazolidin-2-one to provide the methylated product as clear oil.

The methylated compound was treated with $LiBH_4$ according to the typical procedure for **12** to yield **6** (0.11 g, 80%) as a colorless oil; R_f = 0.4 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –29.6 (*c* 0.5, $CHCl_3$).

IR (neat): 3316, 2923, 1696, 1519, 1207 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 5.68 (m, 1 H), 4.98–4.86 (m, 2 H), 3.49 (m, 1 H), 3.41 (m, 1 H), 2.11 (m, 1 H), 1.66 (m, 1 H), 1.42–1.31 (m, 2 H), 1.31–1.23 (m, 3 H), 1.10 (m, 1 H), 0.97 (d, *J* = 6.2 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 112.2, 62.9, 37.6, 36.5, 32.7, 26.9, 25.7, 20.1.

MS (EI): *m*/*z* = 156 (M^+).

Methyl (4*R*,5*R*)-5-[(3*R*,7*S*,*E*)-8-Hydroxy-3,7-dimethyloct-1-enyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate (3)

To a degassed soln of **5** (0.089 g, 0.48 mmol) and **6** (0.05 g, 0.32 mmol) in anhyd CH_2Cl_2 (2 mL) was added Grubbs II catalyst (5 mg, 10 mol%) at r.t. under a N_2 atmosphere. The resulting pale purple color soln was heated to reflux (40 °C) for 7 h. After complete consumption of the starting material, the solvent was removed under vacuo. The resulting crude residue was purified by column chromatography to afford **3** (0.73 g, 73%) as a clear oil; R_f = 0.2 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –54.87 (*c* 0.8, CH_2Cl_2).

IR (neat): 3563, 2925, 1647, 1516, 1204 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 5.74 (dd, *J* = 15.0, 8.0 Hz, 1 H), 5.27 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.76 (t, *J* = 8.0 Hz, 1 H), 4.63 (d, *J* = 7.0 Hz, 1 H), 3.70 (s, 3 H), 3.47 (m, 1 H), 3.41 (m, 1 H), 2.15 (m, 1 H), 1.82 (br s, 1 H), 1.62 (s, 3 H), 1.59 (m, 1 H), 1.39 (s, 3 H), 1.37–1.22 (m, 5 H), 1.12–1.07 (m, 1 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 142.8, 122.1, 110.9, 78.9, 77.8, 68.1, 51.7, 36.7, 36.2, 35.6, 33.1, 26.9, 25.5, 24.5, 20.1, 16.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{30}O_5Na$: 337.1990; found: 337.1984.

(2*R*,4*R*,5*R*)-7-(*tert*-Butyldiphenylsiloxy)-5-hydroxy-1-(4-methoxybenzyloxy)-2,4-dimethylheptan-3-one (15)

To a cooled soln of Cy_2BCl (19 mL, 19 mmol) in anhyd Et_2O (30 mL) at –78 °C were added sequentially dropwise Et_3N (3.17 mL, 22.8 mmol) and ketone **7** (3 g, 12.7 mmol) in Et_2O (10 mL). The milky mixture was stirred at 0 °C for 2.5 h. The soln was again cooled to –78 °C before slow addition of 3-(*tert*-butyldiphenylsiloxy)propanal (**8**, 5.98 g, 19 mmol) and the resulting soln was stirred for 2 h at this temperature. Then the mixture was kept at –25 °C for overnight and after that it was stirred at 0 °C for 30 min. The reaction was quenched successively with MeOH (38 mL), pH 7 buffer (38 mL), and 30% H_2O_2 (38 mL), and it was stirred for 30 min at r.t. The organic layer was extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to provide the β-hydroxy ketone **15** (6.68 g, 96%) as a colorless oil; R_f = 0.3 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –6.14 (*c* 1.4, $CHCl_3$).

IR (neat): 3463, 2936, 1704, 1513, 1097 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 7.72–7.65 (m, 4 H), 7.47–7.35 (m, 6 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.38 (d, *J* = 12.0 Hz, 1 H), 4.02 (m, 1 H), 3.92–3.80 (m, 2 H), 3.79 (s, 3 H), 3.64 (t, *J* = 8.5 Hz, 1 H), 3.42 (m, 1 H), 3.07 (m, 1 H), 2.78 (m, 1 H), 1.82–1.57 (m, 2 H), 1.09–1.03 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.3, 159.1, 135.5, 133.28, 133.22, 129.9, 129.7, 129.1, 127.6, 113.7, 72.9, 72.2, 72.0, 62.1, 55.2, 51.9, 45.8, 36.0, 26.8, 19.0, 13.5, 12.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{44}O_5SiNa$: 571.2855; found: 571.2865.

(2*R*,3*R*,4*R*,5*R*)-7-(*tert*-Butyldiphenylsiloxy)-1-(4-methoxybenzyloxy)-2,4-dimethylheptane-3,5-diol (16)

Compound **15** (6 g, 10.9 mmol) was taken up in AcOH–acetone (1:1, 34 mL) and the soln was cooled to –20 °C. Then $Me_4NHB(OAc)_3$ (7.19 g, 27.3 mmol) was added very quickly to the mixture and it was stirred at this temperature for 24 h. After completion of the reaction it was quenched with sat. sodium potassium tartrate soln (25 mL) and the mixture was stirred at r.t. for 3 h. The organic layer was extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), and dried (Na_2SO_4). The organic soln was concentrated in vacuo and purified by column chromatography provided **16** (4.87 g, 81%) as a colorless oil; R_f = 0.25 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –10.19 (*c* 2, $CHCl_3$).

IR (neat): 3451, 2930, 1612, 1079 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 7.71–7.64 (m, 4 H), 7.47–7.34 (m, 6 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 4.48 (d, *J* = 11.3 Hz, 1 H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.03 (br s, 1 H), 3.94–3.84 (m, 4 H), 3.83–3.77 (m, 1 H), 3.79 (s, 3 H), 3.54 (d, *J* = 6.7 Hz, 2 H), 2.03–1.81 (m, 2 H), 1.72 (m, 1 H), 1.58 (m, 1 H), 1.05 (s, 9 H), 0.97 (d, *J* = 7.5 Hz, 3 H), 0.76 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 135.4, 133.2, 133.1, 129.9, 129.6, 129.2, 127.6, 113.7, 75.7, 75.2, 74.8, 73.0, 63.3, 55.2, 39.0, 37.1, 35.9, 26.7, 19.0, 13.1, 9.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{46}O_5SiNa$: 573.3012; found: 573.3007.

***tert*-Butyl{(3*R*,4*R*)-3-methoxy-4-[(4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]pentyloxy}diphenylsilane (17)**

To a soln of **16** (4 g, 7.26 mmol) and 4Å molecular sieves (5.2 g, 1.3 equiv with respect to weight) in anhyd CH_2Cl_2 (22 mL), DDQ (1.64 g, 7.26 mmol) was added at –10 °C and the mixture was kept at this temperature for 60 min and then warmed slowly to 0 °C over a period of 1 h. After complete consumption of the starting material the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to provide the rearranged compound as a colorless liquid.

To a stirred ice cooled soln of the rearranged compound in anhyd THF (14 mL) was added NaH (0.45 g, 11.4 mmol). After 15 min, MeI (0.85 mL, 13.7 mmol) and DMAP (0.055 g, 0.46 mmol) were added to the mixture at 0 °C. The mixture was stirred for 12 h at r.t., and then the reaction was quenched with sat. aq NH_4Cl (10 mL) at 0 °C and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to provide **17** (2.1 g, 78%) as a clear oil; R_f = 0.55 (10% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –21.15 (*c* 2.5, $CHCl_3$).

IR (neat): 2940, 1615, 1246, 1080 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 7.74–7.62 (m, 4 H), 7.48–7.32 (m, 8 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 5.48 (s, 1 H), 4.13 (dd, *J* = 11.3, 4.5 Hz, 1 H), 3.90–3.72 (m, 3 H), 3.80 (s, 3 H), 3.60–3.46 (m, 2 H), 3.33 (s, 3 H), 2.14–1.92 (m, 2 H), 1.86 (m, 1 H), 1.62 (m, 1 H), 1.06 (s, 9 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.74 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 135.9, 135.5, 133.8, 131.5, 129.4, 127.5, 127.1, 113.4, 100.5, 81.9, 78.8, 73.2, 60.3, 58.3, 55.2, 37.7, 34.7, 30.3, 26.7, 19.1, 11.9, 9.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{46}O_5SiNa$: 585.3009.2099; found: 585.3004.

(2*R*,3*R*,4*R*,5*R*)-7-(*tert*-Butyldiphenylsiloxy)-5-methoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptan-1-ol (18)

To a soln of **17** (2 g, 3.55 mmol) in anhyd CH_2Cl_2 (11 mL) at –78 °C, a 1 M DIBAL-H (10.6 mL, 10.6 mmol) was added dropwise and the mixture was stirred at this temperature for 2 h. The reaction was then quenched by slow addition of few drops of anhyd MeOH followed by sat. aq sodium potassium tartrate soln (10 mL). The mixture was stirred (~2 h) until two clear layers separated. The aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic extracts were washed sequentially with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography of the residue provided alcohol **18** (1.48 g, 74%) as a colorless liquid; R_f = 0.3 (20% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ +2.35 (*c* 0.85, $CHCl_3$).

IR (neat): 3445, 2938, 1513, 1094 cm^{-1}.

^1H NMR (300 MHz, $CDC1_3$): δ = 7.70–7.64 (m, 4 H), 7.45–7.34 (m, 6 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 4.55 (dd, *J* = 10.5, 2.2 Hz, 2 H), 3.82–3.75 (m, 2 H), 3.79 (s, 3 H), 3.71–3.59 (m, 2 H), 3.56 (dd, *J* = 6.7, 3.7 Hz, 1 H), 3.39 (m, 1 H), 3.25 (s, 3 H), 2.82 (br s, 1 H), 1.98–1.86 (m, 2 H), 1.81 (m, 1 H), 1.69 (m, 1 H), 1.05 (s, 9 H), 0.92 (d, *J* = 7.5 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 135.5, 133.6, 130.5, 129.5, 129.2, 127.5, 113.7, 83.9, 78.9, 74.6, 66.1, 60.0, 55.9, 55.1, 38.3, 37.7, 32.7, 26.7, 19.1, 14.7, 10.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{48}O_5SiNa$: 587.3168; found: 587.3150.

(2*R*,3*R*,4*R*,5*R*)-7-(*tert*-Butyldiphenylsiloxy)-5-methoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptanal; Typical Procedure for the Dess–Martin Periodinane Oxidation

To a soln of **18** (1 g, 1.77 mmol) in anhyd CH_2Cl_2 (6 mL) were added $NaHCO_3$ (0.59 g, 7.08 mmol) and Dess–Martin periodinane (DMP) (1.5 g, 3.54 mmol) sequentially at 0 °C. The mixture was stirred at r.t. for 1 h and then quenched with sat. aq $NaHCO_3$ soln (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2 × 10 mL), and the combine organic extracts were washed sequentially with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a short bed of silica gel and used directly in the next step without characterization.

***tert*-Butyl[(3*R*,4*R*,5*R*,6*R*)-3-methoxy-5-(4-methoxybenzyloxy)-4,6-dimethylnon-7-ynyloxy}diphenylsilane (19)**

To an ice cooled soln of Ph_3P (1.99 g, 7.08 mmol) in CH_2Cl_2 (6 mL) was added CBr_4 (1.17 g, 3.54 mmol). The resulting mixture was stirred at r.t. for 30 min. The mixture was again cooled to 0 °C and (2*R*,3*R*,4*R*,5*R*)-7-(*tert*-butyldiphenylsiloxy)-5-methoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptanal was added by cannula to the mixture. The mixture was stirred at r.t. for ~30 min. Then the mixture was diluted with petroleum ether and passed through a plug of silica gel and used directly in the next step.

To a soln of the above compound in anhyd THF (6 mL) cooled to –78 °C, was added 1.6 M BuLi (2.76 mL, 4.4 mmol); the resulting soln was stirred for 2 h at –78 °C. MeI (1 mL, 7.08 mmol) was added to the mixture at –78 °C and it was stirred for ~2–3 h at r.t. The resulting soln was quenched with sat. aq NH_4Cl (4 mL) and extracted

with EtOAc (2 × 10 mL). The combined organic extracts were washed sequentially with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to afford **19** (0.709 g, 70%) as a clear oil; R_f = 0.4 (10% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ +1.20 (*c* 3, $CHCl_3$).

IR (neat): 2934, 2866, 2360, 1513, 1094 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 7.75–7.66 (m, 4 H), 7.46–7.36 (m, 6 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.53 (d, *J* = 11.0 Hz, 1 H), 3.86–3.76 (m, 2 H), 3.80 (s, 3 H), 3.52 (m, 1 H), 3.34 (t, *J* = 6.0 Hz, 1 H), 3.29 (s, 3 H), 2.75 (m, 1 H), 2.19 (m, 1 H), 1.79 (d, *J* = 2.0 Hz, 3 H), 1.73 (m, 1 H), 1.64 (m, 1 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 1.09 (s, 9 H), 0.92 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 135.4, 134.7, 133.8, 131.0, 129.5, 129.2, 127.5, 113.5, 82.6, 81.1, 78.3, 74.0, 60.3, 56.2, 55.2, 37.4, 32.8, 29.6, 26.7, 19.1, 17.8, 9.7, 3.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{48}O_4SiNa$: 595.3219; found: 595.3210.

(3*R*,4*R*,5*R*,6*R*)-3-Methoxy-5-(4-methoxybenzyloxy)-4,6-dimethylnon-7-yn-1-ol (20)

To a stirred soln of **19** (0.5 g, 0.88 mmol) in anhyd THF (3 mL), 1 M TBAF (0.88 mL, 0.88 mmol) was added at 0 °C and the mixture was allowed to reach r.t. After 1 h the mixture was quenched by addition of sat. aq NH_4Cl (2 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed sequentially with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography purification of the residue provided **20** (0.26 g, 90%) as a colorless oil; R_f = 0.3 (30% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –2.54 (*c* 2, $CHCl_3$).

IR (neat): 3397, 2924, 2359, 1512, 1040 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 7.28 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 4.71 (d, *J* = 11.0 Hz, 1 H), 4.45 (d, *J* = 11.0 Hz, 1 H), 3.79 (s, 3 H), 3.79–3.71 (m, 2 H), 3.49 (m, 1 H), 3.35 (s, 3 H), 3.32 (t, *J* = 5.5 Hz, 1 H), 2.86 (br s, 1 H), 2.73 (m, 1 H), 2.24 (m, 1 H), 1.78 (d, *J* = 2.7 Hz, 3 H), 1.73–1.68 (m, 2 H), 1.19 (d, *J* = 7.3 Hz, 3 H), 0.92 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 130.7, 129.2, 113.5, 82.0, 82.0, 81.1, 73.6, 61.0, 56.1, 55.1, 51.6, 36.6, 31.0, 29.2, 17.3, 9.6, 3.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{30}O_4Na$: 357.2041; found: 357.2038.

***tert*-Butyl (3*R*,4*R*,5*R*,6*R*)-3-methoxy-5-(4-methoxybenzyloxy)-4,6-dimethylnon-7-ynoate (4)**

Compound **20** (0.1 g, 0.3 mmol) was subjected to Dess–Martin periodinane oxidation following the typical procedure for (2*R*,3*R*,4*R*,5*R*)-7-(*tert*-butyldiphenylsiloxy)-5-methoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptanal and then Pinnick oxidation following the typical procedure for **10** to afford the acid as a colorless oil.

To an ice-cooled soln of the acid in anhyd CH_2Cl_2 (2 mL) was added *tert*-butyl trichloroacetimidate (0.062 g, 0.28 mmol) in CH_2Cl_2 (2 mL). After 5 min CSA (3 mg, 0.01 mmol) was added. The resulting mixture was stirred at r.t. for ~24 h. After complete consumption of the starting material, the mixture was quenched with sat. aq $NaHCO_3$ (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed sequentially with H_2O (1 mL) and brine (1 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography to yield **4** (0.029 g, 60%) as a clear oil; R_f = 0.5 (10% EtOAc–petroleum ether).

$[\alpha]_D^{24}$ –7.22 (*c* 0.1, CH_2Cl_2).

IR (neat): 2925, 1714, 1512, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDC1_3$): δ = 7.29 (d, *J* = 8.0 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 4.76 (d, *J* = 11.0 Hz, 1 H), 4.46 (d, *J* = 11.0 Hz, 1 H), 3.80 (s, 3 H), 3.68 (m, 1 H), 3.42 (dd, *J* = 7.0, 4.0 Hz, 1 H), 3.34 (s, 3 H), 2.74 (m, 1 H), 2.43 (dd, *J* = 15.0, 4.0 Hz, 1 H), 2.34 (dd, *J* = 15.0, 7.0 Hz, 1 H), 2.12 (m, 1 H), 1.79 (d, *J* = 2.0 Hz, 3 H), 1.46 (s, 9 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4, 159.0, 131.0, 129.3, 113.6, 81.9, 81.5, 80.3, 79.7, 77.2, 73.7, 56.8, 55.2, 37.9, 37.6, 29.6, 28.0, 17.5, 9.5, 3.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{36}O_5Na$: 427.2460; found: 427.2458.

Acknowledgement

Author (K.S.R.) is thankful to CSIR, New Delhi, India, for a research fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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