International Journal of Chemical Science
www.chemicaljournals.com
Online ISSN: 2523-2843
Received: 16-03-2026, Accepted: 16-04-2026, Published: 01-05-2026
Volume 10, Issue 2, 2026, Page No. 43-49

Towards total synthesis of Milbemycin-β3

P Vinod Kumar Goud[1*], I Vani[2], R Venkateshwarlu[3], P Venkateswara Rao[3]
[1] Tara Government College (A), Sangareddy, Telangana, India
[2] Government Degree College, Kalwakurthy, Telangana, India
[3] Osmania University, Hyderabad, Telangana, India
Corresponding Author: P Vinod Kumar Goud

Abstract
An efficient synthesis of (3R,5S,10S,11R)-5-(benzyloxy)-10-methyldodec-7-yne-1,3,11-triol was carried out in higher yields using retrosynthetic analysis of Milbemycin-β3. This compound in turn was prepared from commercially available L-aspartic acid and Geraniol. The compound (3R,5S,10S,11R)-5-(benzyloxy)-10-methyldodec-7-yne-1,3,11-triol can be used for the total synthesis of Milbemycin-β3.

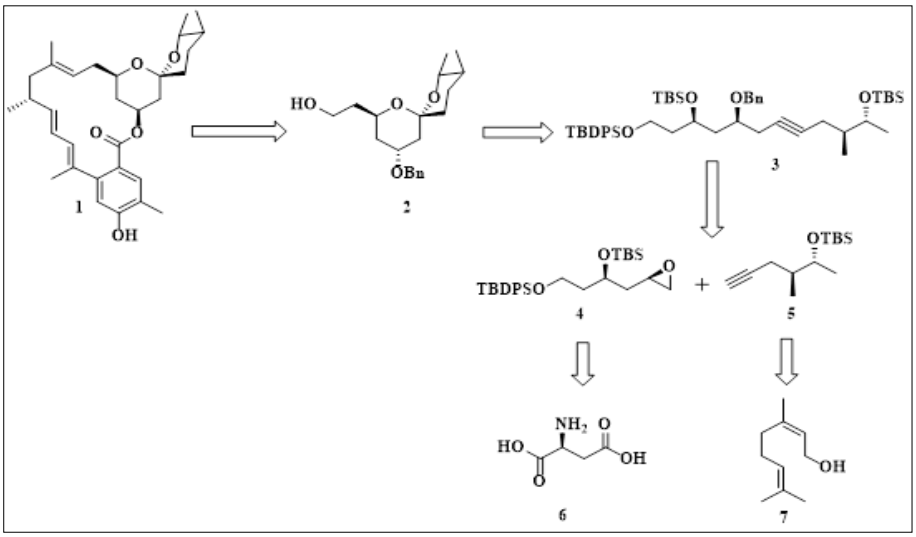
Keywords: Total synthesis, retrosynthesis, mibemycin- β3, geraniol etc

Introduction

Milbemycins are a class of structurally unique macrolides, whose first members (β_1- β_3) were reported by Mishima *et al* [1] in 1975 from *Streptomyces* B-41-146. Subsequently, an additional 17 members of this class were isolated and shown to possess significant antibiotic as well as remarkable insecticidal activity [2]. The subsequent screening of this antibiotic complex possessed remarkable pesticidal activity [3] against a host of agricultural pests, including aphids, laval forms of insects of the order Lepidopera, mit*es,* rice leaf beetles, and tent caterepillars, with little or no associated phytotoxicity. The key common features present in all the milbemycins are the 16-membered macrocyclic ring and the spiro ketal moiety. Milbemycin β_3, is the simplest member of the series. The combination of biological activity and structural novelty of these compounds has sparked a massive effort towards their total synthesis. The first synthesis of milbemycin β_3 was reported by Smith [4] in 1982. Since that time, numerous synthetic studies on the spiroketal [5] and hexahydrobenzofuran fragments [6] of these molecules have been reported.

Retrosynthetic Analysis of Milbemycin- B3 (1)

Retrosynthetic analysis of milbimycin-β3 (1) is depicted in Scheme 1. We envisioned that milbimycin-β3 (1) could be synthesized via spiro ketal 2 using mercuric triflate mediated cyclisation, which could be obtained from opening of epoxide 4 with triple bond 5 under the Yamaguchi–Hirao protocol [7]. The epoxide fragment 4 could be synthesized from commertially available L-aspartic acid diol 6. The alkyne fragment 5 could be synthesized comerially available geraniol 7.



Scheme 1: Retrosynthetic analysis milbemycin-β3

Present Work

Synthesis of Fragmet-4

Our synthesis commenced from the chiral epoxide (*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)oxirane 11 which was prepared from commercially available amino acid L-aspartic acid 6 in 85% yield over three steps following literature protocol [8]. The spectral data (see Experimental section) were in good agreement with that of reported values. Its ^{1}H NMR studies exhibited the resonance at the respective chemical shifts 3.04 (m, 1H), 2.71 (dd, J = 4.9, 4.3 Hz, 1H), 2.45 (dd, J = 5.0, 2.7 Hz, 1H) ppm indicates epoxide protons, which are commonly appears in this region and

which showed resonances at their corresponding chemical shift as a singlet for two benzylic protons and a two doublets for aromatic protons. The structure 11 was further confirmed by its HRMS which showed a moleculer ion peak at *m/z* 341.69 $[M + Na]^+$. The optical rotation of the compound 11 was found to be $[\alpha]_D^{25}$ +12.5 (*c* 1.0, $CHCl_3$) which was correlated with that of the earlier reported value.

Conversion of epoxide (11) into a homoallyl alcohol (*S*)-1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (12) through the copper iodide catalyzed addition of a vinyl Grignard reagent at −78 ºC to room temperature was achieved in 93% yield. The ^1H NMR spectrum of compound 12 revealed two methylene protons adjacent to the double bond at δ 2.24 (t, *J* = 6.3 Hz, 2H) ppm and characteristic terminal olefin protons at δ 5.88−5.78 (m, 1H), 5.13−5.06 (m, 2H) ppm. IR absorption showed characteristic band at 3439 cm^{-1} for hydroxyl functionality. A peak at *m/z* 259.1320 for $[M + Na]^+$ in ESI-MS spectrum finally confirmed the product formation.

Compound 12 was treated with di-*tert*-butyl carbonate [9] in the presence of Et_3N and catalytic amount (10 mole %) of DMAP to form (S)-tert-Butyl (1-((tert-butyldiphenylsilyl)oxy)hex-5-en-3-yl) carbonate (13) in 92% yield . ^1H NMR spectrum showed tertiary butyl group peak appeared at δ 1.04 ppm, corresponding oxygen attached tertiary carbon peak appeared in ^{13}C NMR spectrum at δ 80.9 ppm, IR absorption band at 3430 cm^{-1} disclosed the absence of hydroxyl functional group and ESI-MS showed $[M + Na]^+$ *m/z* 455.79 further proved the formation of product.

Boc protected compound 13 was converted to iodo-carbonate by using Bartlett-Smith iodo-carbonate cyclization reaction [10] protocol with *N*-iodo succinimide in CH_3CN at 0 ºC as a colorless liquid. This iodo-carbonate is unstable on long standing and it was immediately converted into (R)-4-((tert-Butyldiphenylsilyl)oxy)-1-((R)-oxiran-2-yl)butan-2-ol (14) by using K_2CO_3 in MeOH at rt with 85% yield . ^1H NMR spectrum showed epoxide proton peaks appeared at δ 3.12 (m, 1H), 2.78 (m, 1H), 2.51 (m, 1H) ppm and corresponding carbon peaks appeared at δ 49.8, 46.5 ppm in ^{13}C NMR spectrum. IR absorption showed a characteristic band at 3451 cm^{-1} for hydroxyl functionality. ESI-MS also showed $[M + Na]^+$ peak at *m/z* 377.7 confirmed the product formation.

The compound 14 was protected as its silyl ether using TBSCl and imidazole in CH_2Cl_2 at 0 ºC to afford epoxide fragment 4 in 93% yield. ^1H NMR spectrum compound 4 revealed the presence corresponding to TBS protected compound indicated the product formation. ^{13}C NMR spectrum showed the presence of resonance correspond to trimethylsilyl (TBS) group and terminal epoxide carbons, confirmed the product formation. The structure of compound 4 was further confirmed by its ESI-MS showed $[M + Na]^+$ *m/z* 485.9.

Synthesis of Fragment-5

Sharpless asymmetric epoxidation [11] of 7 with D-(-)-DET and TBHP proceeded smoothly to afford the ((2R,3S)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methanol (15) with 80% yield. ^1H NMR showed peaks at *δ* 2.97 ppm for oxirane and ^{13}C NMR showed peaks at *δ* 61.5 and 61.1 ppm, structure was further confirmed by its ESI-MS data which showed a moleculer ion peak at *m/z* 171.5 $[M + H]^+$.

Epoxide selectivly opened using sodium cyanoborohydide[12] in the presence of $BF_3.Et_2O$, smoothly to afford (2S,3S)-3,7-Dimethyloct-6-ene-1,2-diol (16) with 70% yield. ^1H NMR study revealed the absence of resonance peaks due to oxirane proton peaks whereas the presence of new peaks at *δ* 3.53-3.47 ppm was in support of this transformation. ^{13}C NMR spectrum also revealed the disappearance oxirane signals and showed new peaks at *δ* 61.5, 61.1 and 76.1, 64.4 ppm. The structure of compound 16 was further confirmed by ESI-MS which showed a moleculer ion peak at *m/z* 173.8 $[M + H]^+$.

1,2- Diol[6] 16 treated with *P*-Toulene sulphonyl chloride in the presence of triethyl amine afforded primary tosyl protected compound. This compound is treated with Lithium aluminium hydride [13] to get (2R,3S)-3,7-Dimethyloct-6-en-2-ol (18) which was confirmed by 1H NMR singnals at *δ* 3.67 (s, 1H) correspond to secondary alcohol group proton. In addition to this,^{13}C NMR showed resonance signals corresponding to hydroxyl attached carbon group at *δ* 71.9 ppm indicated the product formation.

Protection of alcohol 18 using TBSCl in presence of imidazole and CH_2Cl_2 afforded *tert*-Butyl(((2R,3S)-3,7-dimethyloct-6-en-2-yl)oxy)dimethylsilane (19) in 97% yield. The ^1H NMR spectrum showed two peaks at δ 0.89 (s, 9H) and 0.04 (s, 6H) ppm confirming the presence of TBS group. ESI-HRMS spectrum showed peak at *m/z* 293.73 $[M + Na]^+$ further confirmed the structure.

One-pot oxidative cleavage of the double bond in 19 using Jin's [14] protocol (OsO_4, $NaIO_4$ and 2,6-lutidine) in 1,4-dioxane at ambient temperature obtained the corresponding aldehyde. The formation of (4S,5R)-5-((tert-Butyldimethylsilyl)oxy)-4-methylhexanal (20) was confirmed by its ^1H NMR spectrum which showed a singlet at δ 9.76 (s, 1H) ppm and absence olefin peak at δ 5.42 ppm. The ^{13}C NMR spectrum which showed the peak at δ 202.9 and absence of peaks at δ 131.0, 124.9 ppm and appearance of molecular ion peak at *m/z* 245.48 $[M + Na]^+$ in ESI mass spectrum further confirmed the formation of product.

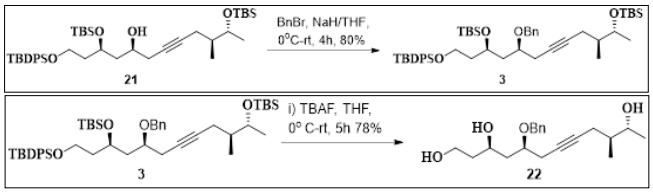
The compound 20 was transformed to compound[15] 5 using triphenylphosphine(TPP), brominr (Br_2) and triethyl amine in dichloromethane at -78º C, afforded *gem*-dibromide. *gem*-dibromide passing through column quickly and used compound next step. The compound immediately treated with *t*-BuOK furnishes triple bond compound 5 with 75% yield over two steps. The structure was further confirmed by appearance of triple bond at 2.60 (m, 1H) ppm, ^{13}C NMR also shows the peaks at 83.7 and 68.9 ppm respectivly. ESI-HRMS spectrum showed peak at *m/z* 244$[M + NH_4]^+$ further confirmed the structure.

Coupling of Two Fragments (4 & 5)

Having secured both the coupling partners epoxide 5 and alkyne 4, the stage was set to examine the opening of epoxide 5 with the alkyne 4 under the Yamaguchi–Hirao protocol[1] Accordingly, treatment of alkyne 4 with *n*-BuLi were added to epoxide 3 with $BF_3 \cdot Et_2O$ (in a separate round bottomed flask) to afford the homopropargyl alcohol 21 (85%). The product 21 formation was confirmed by ^1H NMR which showed characteristics peaks at required region . A peak at *m/z* 712 for $[M + H]^+$ in ESI-MS spectrum finally confirmed the product formation.

The hydroxyl functionality present in 21 was protected as its benzyl ether with benzyl bromide in presence of sodium

hydride and TBAI in THF at room temperature for 12h to achieve 3 in 90% yield. The TBS group in compound 3 was selectively removed by using TBAF in THF at room temperature for 6 h to afford compound (3R,5S,10S,11R)-5-(Benzyloxy)-10-methyldodec-7-yne-1,3,11-triol (22) in 70% yield. The product 22 formation was confirmed by ^{1}H NMR which showed absence of peak at δ 0.02 (d, *J* = 4.2 Hz, 12H) ppm and δ −4.2, −4.9 ppm in ^{13}C NMR spectrum, explains deprotection of TBS group. A peak at *m/z* 357for $[M + Na]^+$ in ESI-MS spectrum finally confirmed the product formation.



Scheme 2: Synthesis of triol 22

Experimental section

(*S*)-2-bromosuccinic acid (9)

A 1000 ml 2-necked round-bottomed flask was charged with (*S*)-L- (+)-aspartic acid **9** (18.8 g, 141 mmol) and KBr (72.5 g, 609 mmol). 300 ml of a 2.5 M aq. solution of H_2SO_4 were added in one portion and then the solution was cooled to –5 °C. A solution of sodium nitrite (16.8 g, 243 mmol) in 40 ml H_2O was added with careful temperature monitoring, such that the reaction temperature was maintained below 0 °C for the entire 90 min addition period. After completion of the addition of $NaNO_2$ the resulting dark brown reaction mixture was stirred for 2 h at –5 °C and then extracted with ethyl acetate (4 × 100 ml). The combined organic extracts were washed with 100 ml half sat. aq. NaCl, then dried over Na_2SO_4 and concentrated under reduced pressure to yield the desired product **9** as a white solid (24.6 g, 88%).

$[\alpha]_D^{25}$	: -32.0 (*c* 2.0, MeOH).
IR (KBr, neat)	: 3330, 2952, 2838, 2645, 2532, 1700, 1304, 1179, 1020, 922, 780 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	: δ 4.97 (br s, 2 H); 4.56 (dd, J = 8.6, 6.2, 1 H); 3.19 (dd, J = 17.2, 8.7, 1 H); 2.95 (dd, J = 17.2, 6.2, 1 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 173.20; 172.38; 40.78; 40.11ppm.

(*S*)-2-bromobutane-1,4-diol (10)

To a cooled (0 °C) solution of (*S*)-2-bromosuccinic acid (**9**) (23.9 g, 121 mmol) in 250 ml THF was added borane•THF (1 M in THF, 364 ml, 364 mmol) over a period of 1 h. After the addition, the cooling bath was removed and the light-yellow solution was stirred for 15 min, resulting in the formation of a thick, milky-white suspension. Stirring was continued at room temperature for 3 h, when the reaction mixture was cooled to 0 °C and the excess borane quenched by dropwise addition of 5 ml H_2O. K_2CO_3 (5.0 g) was then added to the reaction mixture and solids were removed by decantation. The solid residue was washed with Et_2O (3 × 40 ml) and the combined original supernatant and Et_2O washes were concentrated to an oily, yellow residue. This material was triturated with Et_2O (4 × 40 ml) and borate salts removed by filtration. The combined filtrates were dried over $NaSO_4$, filtered, and evaporated to a thick, yellow oil 10 (38.5 g), which was purified by flash chromatography over silica gel (ethyl acetate /hexane/MeOH 6:6:1) to give the desired product 10 as a white foam (18.3 g, 89%).

$[\alpha]_D^{25}$	: -40.1 (*c* 2.0, $CHCl_3$).
IR (KBr, neat)	: 3328, 2935, 2886, 2362, 1635, 1420, 1266, 1052, 909, 731 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	: δ 4.30 (dtd, J = 8.2, 5.4, 5.1, 1 H); 3.90–3.76 (m, 4 H); 3.47 (br s, 1 H); 3.03 (br s, 1 H); 2.21–2.04 (m, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 67.09; 60.02; 54.64; 37.84 ppm.

(*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)oxirane (11)

To a cooled (–5 °C) suspension of NaH (60% in mineral oil, 12.8 g, 319 mmol) in 140 ml THF was added a solution of (*S*)-2-bromobutane-1,4-diol (10) (18.0 g, 106 mmol) in 60 ml THF over 15 min. After 2 h of stirring at –5 °C, a solution of crude TBDPS-Cl (27.4 g, 136 mmol) in 100 ml THF was added in one portion and suspension was stirred for further 5 min at –5 °C. Then the reaction mixture was warmed to room temperature and the reaction was left to proceed for further 2 h. Sat. aq. NH_4Cl (100 ml) was then added carefully at 0 °C the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were washed successively with 100 ml H_2O and 100 ml sat. aq. NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 1:1) to give the desired product 11 as a colorless oil (14.1 g, 64%).

$[\alpha]_D^{20}$	: +11.0 (*c* 1.3, $CHCl_3$).
IR (KBr, neat)	: 2923, 2855, 2380, 1724, 1611, 1512, 1247, 1096, 1034, 822 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	: δ 7.20 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.63-3.55 (m, 2H), 3.04 (m, 1H), 2.71 (dd, *J* = 4.9, 4.3 Hz, 1H), 2.45 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.82 (m, 1H), 1.71 (m, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 159.1, 130.3, 129.2, 113.7, 72.7, 66.7, 55.2, 50.1, 47.1, 32.9 ppm.
ESI-HRMS	: *m/z* calc. for $C_{12}H_{16}O_3Na$ $[M + Na]^+$: 231.0628, found: 231.0631.

(*S*)-1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (12)

To a solution of chiral epoxide **11** (10.0 g, 48.01 mmol) in dry THF (150 mL), CuI (0.91 g, 4.80 mmol) was added and the mixture was stirred at 25 ºC for 30 min. It was cooled to −20 ºC and vinyl magnesium bromide (96.03 mL, 1M in THF, 96.03 mmol) was slowly added at the same temperature. It was allowed to stir for another 2 h at the same temperature. The reaction (monitored by TLC) was quenched with saturated aqueous NH_4Cl solution (100 mL) and diluted with ethyl acetate (100 mL). The two layers were separated and aqueous layer was washed with ethyl acetate (2 × 100 mL). The combined organic layer was washed with brine (2 × 200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product which was then purified by column

chromatography over silica gel (ethyl acetate/hexane = 1:9) to give the corresponding allylic alcohol 12 (10.55 g, 93%) as a colorless liquid.

$[\alpha]_D^{20}$	: −8.5 (*c* 0.35, $CHCl_3$).
IR (neat)	: *v* 3439, 2926, 2861, 1612, 1513, 1452, 1247, 1090, 1032 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	: δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.88-5.78 (m, 1H), 5.13-5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.71-3.58 (m, 2H), 2.90 (br s, 1H), 2.24 (t, *J* = 6.3 Hz, 2H), 1.78-1.72 (m, 2H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 159.2, 134.8, 129.9, 129.2, 117.4, 113.7, 72.8, 70.4, 68.5, 55.2, 41.8, 35.7 ppm.
HRMS (ESI)	: *m/z* calcd. for $C_{14}H_{20}O_3Na$ $[M + Na]^+$: 259.1305, found: 259.1320.

(S)-tert-Butyl (1-((tert-butyldiphenylsilyl)oxy)hex-5-en-3-yl) carbonate (13):

To a stirred solution of alcohol **12** (4 g, 0.011 mol) in anhydrous CH_2Cl_2 (40 mL), di-*tert*-butyl dicarbonate [$(Boc)_2O$; 5.18 mL, 0.022 mol], followed by Et_3N (4.74 mL, 0.033 mol) and DMAP (0.13 g, 0.0011 mol) were added at room temperature. After stirring for 6 h, the reaction was quenched with 5% aqueous $KHSO_4$ solution (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/hexane = 1:19) to give the Boc-protected compound 13 (4.71 g, 92%) as a colorless liquid.

$[\alpha]_D^{20}$	−19.2 (*c* 0.40, $CHCl_3$).
IR (neat)	*v* 2950, 2534, 1766, 1583, 1258, 1151, 1006, 954, 776 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.67-7.63 (m, 4H), 7.42-7.36 (m, 6H), 5.78 (m, 1H), 5.11-5.00 (m, 2H), 4.96 (m, 1H), 3.79-3.65 (m, 2H), 2.41-2.34 (m, 2H), 1.87-1.81 (m, 2H), 1.47 (d, *J* = 4.42 Hz, 2H), 1.04 (s, 9H) ppm. 6777777
^{13}C NMR (125 MHz, $CDCl_3$)	δ 153.1, 135.4, 133.4, 129.5, 127.5, 117.8, 81.5, 80.9, 73.5, 60.0, 38.8, 36.2, 27.8, 27.7, 26.7, 19.1 ppm.
ESI-MS	455.79 $[M + H]^+$

(R)-4-((tert-Butyldiphenylsilyl)oxy)-1-((R)-oxiran-2-yl)butan-2-ol (14)

To a stirred solution of carbonate 13 (3.5 g, 0.007 mol) in acetonitrile (80 mL), was added *N*-iodosuccinimide (5.19 g, 0.023 mol) at −40 ºC. The resulting mixture was warmed up and stirred at 0 ºC for 4 h. After completion of the reaction (monitored by TLC), it was quenched with aqueous $Na_2S_2O_3$ solution (20 mL), followed by of saturated aqueous $NaHCO_3$ solution (20 mL). Acetonitrile was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was quickly purified by flash column chromatography over silica gel (ethyl acetate/hexane = 2:3) to furnish the desired iodo-carbonate derivative 16 (3.59 g, 89%) as a colorless liquid, which was not very stable and used immediately. To a solution of iodocarbonate 16 (3.5 g, 0.006 mol) in MeOH (50 mL), K_2CO_3 (2.76 g, 0.02 mol) was added and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), MeOH was evaporated under reduced pressure. The residue was diluted with H_2O (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which on purification by column chromatography over silica gel (ethyl acetate/hexane = 3:7) afforded the desired epoxy alcohol 14 (2.10 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$	-118.9 (c 0.1, $CHCl_3$)
IR (neat)	*v* 3367, 2255, 1710, 1544, 1485, 1257, 1182, 1007, 854, 774, 652 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.70-7.65 (m, 4H), 7.47-7.37 (m, 6H), 4.11 (m, 1H), 3.95-3.81 (m, 2H), 3.48 (s, 1H), 3.12 (m, 1H), 2.78 (m, 1H), 2.51 (m, 1H), 1.85-1.67 (m, 4H), 1.06 (s, 9H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	*δ* 135.4, 132.8, 129.8, 127.7, 69.7, 63.2, 49.8, 46.5, 39.8, 38.2, 26.7, 18.9 ppm.
ESI-MS	377.79 $[M+Na]^+$

(R)-2,2,3,3,10,10-Hexamethyl-5-(((R)-oxiran-2-yl)methyl)-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (4)

To a stirred solution of alcohol 1**7** (2.5 g, 0.006 mol) in CH_2Cl_2 (25 mL) under nitrogen atmosphere at room temperature, was added TBSCl (1.51 g, 0.01 mol), imidazole (1.37 g, 0.02 mol). The reaction mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the reaction was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography over silica gel (ethyl acetate/hexane = 1:9) to give 4 (3.04 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$	-118.9 (c 0.1, $CHCl_3$)
IR (neat)	*v* 2755, 1768, 1564, 1522, 1445, 1257, 1112, 1007, 1001, 894, 754, 682 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$)	δ 7.69-7.61 (m, 4H), 7.43-7.35 (m, 6H), 4.12 (m, 1H), 3.76-3.66 (m, 2H), 3.02 (m, 1H), 2.41 (m, 1H), 1.69-1.62 (m, 2H), 1.05 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	*δ* 135.5, 133.8, 129.5, 127.6, 71.6, 70.0, 67.3, 60.6, 49.3, 46.6, 43.3, 40.6, 40.1, 39.8, 26.8, 25.7, 19.1, 17.9, -4.69, -4.60 ppm.
ESI-MS	485.92 $[M+H]^+$

((2R,3S)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methanol (15)

To a freshly flame dried double necked round bottom flask equipped with activated 4 Å molecular sieves (~3.0 g) and dry CH_2Cl_2 (60 mL) at –20 ºC were added $Ti(O^iPr)_4$ (0.95 mL, 3.23 mmol), (–)-diisopropyl tartrate (0.74 mL, 4.31 mmol) and the mixture was stirred for 30 min. To this reaction mixture was added allylic alcohol **1** (10 g, 10.79 mmol) in an interval of 30 min. and TBHP (4.98 mL, 32.37 mmol, 6.5 M solution in toluene) were added and stirring was continued till completion of the reaction. The reaction mixture was warmed to 0 ºC and filtered through Celite pad. The filtrate was quenched with water (40 mL), 15% aqueous

NaOH solution (10 mL) and stirred vigorously for 3 h. The biphasic solution was separated and aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexane = 2:8) to afford the pure epoxide 15 (10.26 g, 93%) as a colorless liquid.

$[\alpha]_D^{25}$	-4.57 (c 0.7, $CHCl_3$)
IR (neat)	*v* 3462, 2875, 1590, 1452, 1330, 1150, 1032, 861 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 5.09 (m, 1H), 3.81 (m, 1H), 3.66 (m, 1H), 2.97 (m, 1H), 2.35 (m, 1H), 2.16-2.00 (m, 2H), 1.62 (s, 3H), 1.34 (s, 3H), 1.26 (s, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 132.4, 123.2, 64.2, 61.5, 61.1, 33.0, 25.5, 24.1, 22.1, 17.5 ppm.
ESI-MS	171.5 [M + H]$^+$

(2S,3S)-3,7-Dimethyloct-6-ene-1,2-diol (16)

To a solution of epooxide 15 (3 g, 7.76 mmol) in anhydrousTHF (25 mL) was added $BF_3.OEt_2$ (2.84 g, 23.28 mmol) followed by Sodium cyano borohydride (4.59 mL, 15.52 mmol). After 8 h saturated aqueous HCl (10 mL) was added followed by water (20 mL) and the layers were separated. The aqueous layer was extracted with Ethyl acetate (4 x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The compound Purified by using column chromatography on silica gel (ethyl acetate/hexane = 5:5) gave diol 16 (8.09 g, 80%) as acolourless viscous oil.

$[\alpha]_D^{25}$	+0.93 (c 4.3, $CHCl_3$)
IR (neat)	*v* 3470, 2965, 1620, 1552, 1230, 1102, 1007 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 5.09 (m, 1H), 3.67 (m, 1H), 3.53-3.47 (m, 2H), 3.38 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.25 (m, 1H), 1.17 (m, 1H), 0.89 (d, *J* = 6.74 Hz, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 131.4, 124.3, 76.1, 64.4, 35.6, 32.4, 25.6, 25.3, 17.5, 15.0 ppm.
HRMS (ESI)	173.8 [M + H]$^+$

(2R,3S)-3,7-Dimethyloct-6-en-2-ol (18)

To a stirredsolution of diol **16** (7.5 g, 80.15 mmol) in CH_2Cl_2 (210 mL) at 0 °C, Et_3N (14.0 mL, 100.19 mmol) followed by *n*-Bu_2SnO (0.50 g, 2.00 mmol) and *p*-TsCl (15.28 g, 80.15 mmol) were added. The reactionmixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed with water (2 × 5 mL), brine (2 × 5 mL) anddried (Na_2SO_4). Solvent was evaporated to give 17, which was used as such for the next step without characterization.

To a stirred suspension of $LiAlH_4$ (2.92 g, 76.92 mmol) in THF (50 mL) at 0 °C, a solution of 17 (12.79 g, 76.92 mmol) in THF (100 mL) was added dropwise under nitrogen atmosphere andstirred at room temperature for 3 h, coled to 0 °C and treated withsaturated Na_2SO_4 solution (10 mL) and filtered. Aqueous layer was extracted ethyl acetate (50 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, ethyl acetate/hexane = 1:4) furnished 18 (4.40 g, 72%) as a colourless liquid

$[\alpha]_D^{25}$	-13.71 (c 0.7, $CHCl_3$)
IR (neat)	*v* 3490, 2960, 1750, 1632, 1530, 1202, 1117, 1056, 828, 759 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 5.10 (m, 1H), 3.67 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.56-1.43 (m, 3H), 1.12 (d, *J* = 6.40 Hz, 3H), 0.88 (d, *J* = 6.86 Hz, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 131.4, 124.3, 76.1, 35.6, 32.4, 25.6, 25.3, 17.5, 15.0 ppm

***tert*-Butyl(((2R,3S)-3,7-dimethyloct-6-en-2-yl)oxy)dimethylsilane (19)**

To a stirred solution of above secondary alcohol 18 (4 g, 4.94 mmol) in dry CH_2Cl_2 (40 mL) were added imidazole (0.50 g, 7.42 mmol), *tert*-butyldimethylsilyl chloride (0.82 g, 5.87 mmol), and a catalytic amount of DMAP at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and the resulting solution was washed with water (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:4) to afford silyl ether 19 (6.50 g, 94%).

$[\alpha]_D^{25}$	+ 9.0.00 (*c* 0.8, $CHCl_3$)
IR (neat)	*v* 2850, 1497, 1197, 1092, 1045, 850, 709
^1H NMR (300 MHz, $CDCl_3$)	δ 5.10 (m, 1H), 3.67 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.53-1.35 (m, 2H), 1.09 (m, 1H), 1.03 (d, *J* = 6.23 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 6.72 Hz, 3H), 0.04 (d, *J* = 2.69 Hz, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 131.0, 124.9, 71.9, 39.8, 32.7, 25.9, 25.7, 19.2, 17.6, 14.3, -4.3, -4.8 ppm.
HRMS (ESI)	293.73 [M+Na]$^+$

(4S,5R)-5-((tert-Butyldimethylsilyl)oxy)-4-methylhexanal (20)

To a solution of alkene **19** (6 g, 29.37 mmol) in 1,4-dioxane/water (3:1; 100 mL), 2,6-lutidine (6.28 g, 58.74 mmol), OsO_4 (0.14 g, 0.58 mmol) followed by $NaIO_4$ (25.12 g, 117.48 mmol) were sequentially added at room temperature and the thick mixture was stirred for 3 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was quickly washed with 1N HCl (2 × 50 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:4) to afford silyl ether 20 (3.90 g, 72%).

$[\alpha]_D^{25}$	-8.00 (*c* 1.2, $CHCl_3$)
IR (neat)	*v* 3310, 2710, 2210, 1617, 1580, 1107, 1002, 892, 711 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 9.76 (t, *J* = 1.83 Hz, 1H), 3.65 (m, 1H), 2.48 (m, 1H), 2.37 (m, 1H), 1.80 (m, 1H), 1.48-1.31 (m, 2H), 1.07 (d, *J* = 6.23 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J* = 6.60 Hz, 3H), 0.03 (d, *J* = 4.40 Hz, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 202.9, 71.8, 42.0, 39.9, 31.9, 27.1, 25.8, 24.3, 20.0, 18.0, 14.8, 14.6, -4.3, -4.8 ppm.
HRMS (ESI)	245.48 [M+Na]$^+$

***tert*-Butyldimethyl(((2R,3S)-3-methylhex-5-yn-2-yl)oxy)silane (5)**

To a stirred solution of triphenyl phosphite (1.1 mL, 4.2 mmol, 1.5 equiv) in dry CH_2Cl_2 (30 mL) at -78 ºC was added Br_2 (0.19 mL, 3.6 mmol, 1.3 equiv) dropwise. Then freshly distilled triethylamine (1.2 mL, 8.4 mmol, 3.0 equiv) and a solution of above aldehyde (3 g, 2.8 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) were added successively at the same temperature and stirred for 1 h. The reaction was warmed to rt and solvent was evaporated in vacuo. The resulting crude upon purification by flash column chromatography on silica gel afforded *gem*-dibromide. To a solution of *gem*-dibromide (18) (0.7 g, 2.20mmol, 1.0 equiv) in dry hexane (20 mL) were added *t*-BuOK (0.75 g, 6.60 mmol, 3.0 equiv) and 18-crown-6 (0.03 g, 0.11 mmol, 0.05 equiv) successively and the mixture was refluxed for 8 h under argon. The reaction mixture was quenched with cold water (20 mL) and Et_2O (50 mL) was added at room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 X 25 mL). The combined organic extracts were washed with water (2 X 50 mL), brine (1 X 50 mL), dried over anhydrous Na_2SO_4 and distilled at 50 ºC under atmospheric pressure to give crude product which was purified by flash column chromatography on silica gel (solvent gradient: 1% Et_2O/ pentane) to afford alkyne (1.94 g, 94%) as a colourless liquid.

$[\alpha]_D^{25}$	+1.50 (*c* 0.8, $CHCl_3$)
IR (neat)	ν 3301, 2552, 1552, 1257, 1082, 834, 754 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 3.70 (m, 1H), 2.29 (m, 1H), 2.12 (m, 1H), 1.93 (d, J = 2.9 Hz, 1H), 1.67 (m, 1H), 1.10 (d, J = 6.11 Hz, 3H), 0.98 (d, J = 6.84 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 83.7, 71.0, 68.9, 40.0, 33.8, 25.8, 21.6, 20.6, 19.4, 18.0, 15.0, -4.2, -4.8 ppm.
HRMS (ESI)	244 $[M+NH_4]^+$

(7R,9S,14S,15R)-7-((tert-Butyldimethylsilyl)oxy)-2,2,14,15,17,17,18,18-octamethyl-3,3-diphenyl-4,16-dioxa-3,17-disilanonadec-11-yn-9-ol (21)

To A flame-dried round bottom flask was charged with alkyne 5 (0.7 g, 17.60 mmol) in anhydrous THF (40 mL) and cooled to −78 °C. To this solution, *n*-BuLi (2.5M in hexanes, 7.04 mL, 17.60 mmol) was added drop-wise via syringe, warmed slowly to 0 ºC. During this period, the reaction mixture turned to dark red in color. After 30 min, epoxide 4 (1g, 8.80 mmol) in dry THF (40 mL) was slowly added followed by $BF_3.OEt_2$ (2.17 mL, 17.60 mmol) at −78 °C and stirred for an additional 1 h. After completion (monitored by TLC), the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL), diluted with ethyl acetate (100 mL) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (ethyl acetate/hexane = 1:9) provided the desired secondary alcohol 21 (1.24 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$	+1.50 (*c* 0.8, $CHCl_3$)
IR (neat)	ν 3385, 2890, 2652, 1652, 1458, 1192, 854, 764 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 7.68-7.63 (m, 4H), 7.46-7.34 (m, 6H), 4.12 (m, 1H), 3.82 (m, 1H), 3.75-3.67 (m, 2H), 3.04 (m, 1H), 2.33-2.20 (m, 2H), 2.07 (m, 1H), 1.89-1.68 (s, 3H), 1.58 (s, 3H), 1.09-1.02 (m, 12H), 0.93 (d, J = 6.84 Hz, 3H), 0.89-0.83 (m, 18H), 0.09 (s, 3H), 07-0.01(m, 9H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 83.7, 71.0, 68.9, 40.0, 33.8, 25.8, 21.6, 20.6, 19.4, 18.0, 15.0, -4.2, -4.8 ppm.
HRMS (ESI)	712 $[M+H]^+$

(3R,5S,10S,11R)-5-(Benzyloxy)-10-methyldodec-7-yne-1,3,11-triol (22)

To a solution of 3 (0.8 g, 1.20 mmol) in THF (10 mL) at 0 °C was added TBAF (1.0 M solution in THF, 4.81 mL, 4.81 mmol) dropwise. The resulting brown solution was stirred at room temperature for 4 h. The solvent was removed in vacuo, and the crude residue was purified by flash column chromatography on silicagel (ethyl acetate/hexane = 3:7) to afford triol 22 (0.26 g, 78%) as a yellow liquid.

$[\alpha]_D^{25}$	-4.00 (c 0.10, $CHCl_3$)
IR (neat)	*v* 3478, 3371, 2965, 1780, 1564, 1532, 1425, 1227, 1122, 1129, 858, 754, 651 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	δ 7.39-7.29 (m, 5H), 4.73 (d, J = 11.29 Hz, 1H), 4.48 (d, J = 11.29 Hz, 1H), 4.09 (m, 1H), 3.86-3.76 (m, 4H), 2.59-2.51 (m, 2H), 2.48-2.41 (m, 2H), 1.92-1.81 (m, 2H), 1.77-1.60 (m, 2H), 1.25 (m, 1H), 1.17 (d, J = 6.40 Hz, 3H), 0.97 (d, J = 7.32 Hz, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	δ 137.4, 128.5, 127.8, 81.2, 78.1, 71.0, 61.0, 41.1, 39.7, 38.5, 23.8, 22.3, 20.4, 15.7 ppm.
ESI-MS	357 $[M+Na]^+$.

References

1. Mishima H, Kurabayashi M, Tamura C, Sato S, Kuwano H, Saito A. Milbemycins. Tetrahedron Letters, 1975, 711–714.
2. Mishima H, Junya I, Muramatsu S, Ono M. Journal of Antibiotics,1983:36:980. Ono M, Mishima H, Takiguchi Y, Terao M. Journal of Antibiotics,1983:36:991.
3. Takiguchi Y, Mishima H, Okuda M, Terao M, Aoki A, Fukuda R. Journal of Antibiotics,1980:33:1120.
4. Smith AB III, Schow SR, Bloom JD, Thompson AS, Winzenberg KN. Journal of the American Chemical Society,1982:104:4015. Schow SR, Bloom JD, Thompson AS, Winzenberg KN, Smith AB III. Journal of the American Chemical Society,1986:108:2662.
5. (a) Hanessian S, Ugolini A, Therien M. Journal of Organic Chemistry,1983:48:4427. (b) Baker R, Swain CJ, Head JC. Journal of the Chemical Society, Chemical Communications,1985:309. (c) Kocienski P, Street SDA. Journal of the Chemical Society, Chemical Communications,1984:571. (d) Godoy J, Ley SV, Lygo B. Journal of the Chemical Society, Chemical Communications,1984:1381. (e) Culshaw D, Grice P, Ley SV, Strange GA. Tetrahedron Letters,1986:26:5837.

6. (a) Prashad M, Fraser-Reid B. Journal of Organic Chemistry,1986:50:1564. (b) Crimmins MT, Lever JG. Tetrahedron Letters,1986:27:291. Crimmins MT, Hollis WG Jr, Lever JG. Tetrahedron Letters,1987:28:3647. (c) Jung ME, Street LJ. Journal of the American Chemical Society,1984:106:8327. (d) Kozikowski AP, Maloney-Husa KE. Tetrahedron Letters,1986:26:5759. (e) Ireland RE, Obrecht DM. Helvetica Chimica Acta,1986:69:1273. (f) Hanessian S, Beaulieu P, Dube D. Tetrahedron Letters,1986:27:5071. (g) Barrett AGM, Capps N. Tetrahedron Letters,1986:27:5571. (h) Ardisson J, Ferezou JP, Julia M, Pancrazi A. Tetrahedron Letters,1987:28:2001.
7. Yamaguchi M, Hirao I. Tetrahedron Letters,1983:24:391.
8. (a) Glaus F, Altmann K-H. Angewandte Chemie International Edition,2012:51:3405. (b) Wullschleger CW, Gertsch J, Altmann K-H. Organic Letters,2010:12:1120. (c) Volkmann RA, Kelbaugh PR, Nason DM, Jasys VJ. Journal of Organic Chemistry,1992:57:4352. (d) Frick JA, Klassen JB, Bathe A, Abramson JM, Rapoport H. Synthesis,1992:621.
9. Moreau X, Bazan-Tejeda B, Campagne J-M. Journal of the American Chemical Society,2005:127:7288.
10. (a) Bartlett PA, Meadows JD, Brown EG, Morimoto A, Jernstedt KK. Journal of Organic Chemistry,1982:47:4013. (b) Duan JJ-W, Smith AB III. Journal of Organic Chemistry,1993:58:3703. (c) Taylor RE, Jin M. Organic Letters,2003:5:4959.
11. Martin VS, Woodard SS, Katsuki T, Yamada Y, Ikeda M, Sharpless KB. Journal of the American Chemical Society,1981:103:6237–6240.
12. Yadav VK, Agrawal D. Total syntheses of (+)-7-epi-goniofufurone, (+)-goniopypyrone and (+)-goniofufurone from a common precursor. Chemical Communications,2007:48:5232–5234.
13. Martinelli MJ, Nayyar NK, Moher ED, Dhokte UP, Pawlak JM, Vaidyanathan R. Dibutyltin oxide catalyzed selective sulfonylation of α-chelatable primary alcohols. Organic Letters,1999:1:447–450.
14. Yu W, Mei Y, Kang Y, Hua Z, Jin Z. Improved procedure for the oxidative cleavage of olefins by OsO4–NaIO4. Organic Letters,2004:6(19):3217–3219.
15. Lu H-H, Martinez MD, Shenvi RA. An eight-step gram-scale synthesis of (−)-jiadifenolide. Nature Chemistry,2015:7(7):604–607.