# AN ENANTIOCONTROLLED ROUTE TO PROTOMYCINOLIDE IV AND ITS PRESUMED BIOGENETIC PRECURSORS USING (*S*)-*O*-BENZYLGLYCIDOL

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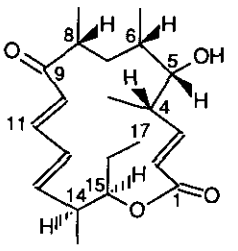
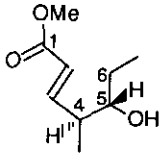
*Abstract* —— Starting with (*S*)-*O*-benzylglycidol (**9**) as only chiral building block, a formal synthesis of protomycinolide IV (**1**) and the first syntheses of its presumed biogenetic precursors methyl epimycinonate I (**2**), methyl mycinonate I (**3**), methyl mycinonate II (**4**), and decarboxymycinonic acid III (**5**), have been achieved *via* the eight-carbon unit (**8**) as a common intermediate.

## 1. INTRODUCTION

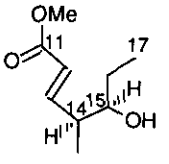
Protomycinolide IV (**1**) is a 16-membered macrolide produced by *Micromonospora griseorubida*.[1] Recently, four unsaturated carbonyl compounds, methyl epimycinonate I (**2**), methyl mycinonate I (**3**), methyl mycinonate II (**4**), and decarboxymycinonic acid III (**5**), presumed to be the biogenetic precursors of the macrolide (**1**), have been isolated from the same culture broth producing the macrolide[2] without determation of their configurations (**Figure 1**). We describe here the stereochemical determination of these presumed biogenetic intermediates (**2**)~(**5**) by enantiocontrolled synthesis and a formal synthesis of protomycinolide IV (**1**) *via* the common key intermediate (**8**) starting with a chiral building block (*S*)-*O*-benzylglycidol[3,4] (**9**).



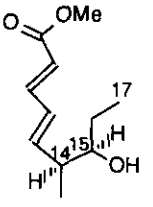
protomycinolide IV (1)



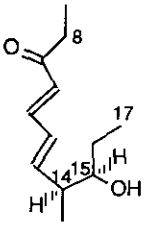
methyl epimycinonate I (2)



methyl mycinonate I (3)



methyl mycinonate II (4)



decarboxymycinonic acid III (5)

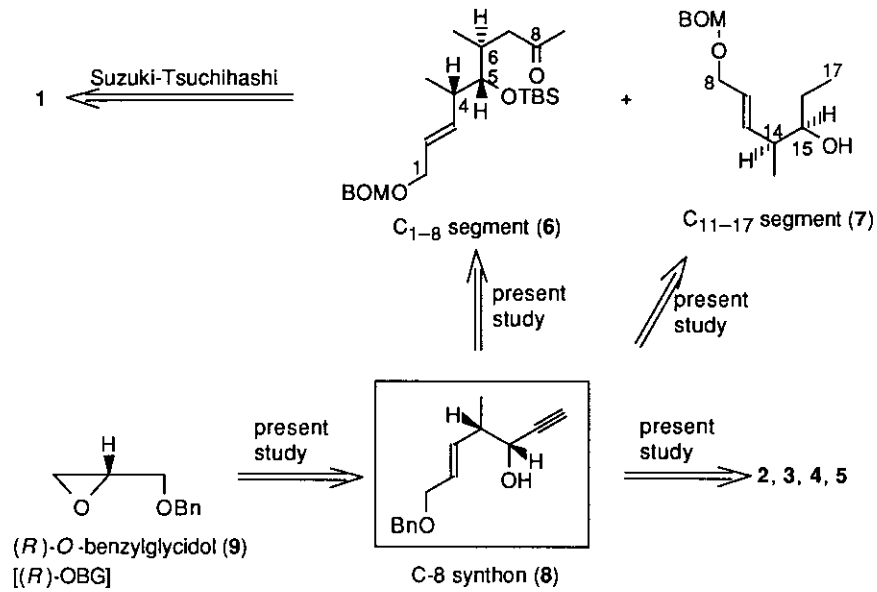
**Figure 1**

## 2. SYNTHETIC STRATEGY

Two total syntheses of protomycinolide IV (**1**), the first by Yamaguchi *et al.*,[5] and the second by Suzuki *et al.*,[6] have been reported to date.[7] In the present synthesis,[8] we intended to use the eight-carbon unit[7] (**8**) available from (*S*)-*O*-benzylglycidol (**9**) as the common building block for the further construction of the known $C_{1\text{-}8}$ (**6**) and $C_{11\text{-}17}$ (**7**) segments of protomycinolide IV (**1**) as well as the first construction of four presumed biogenetic precursors,[8] methyl epimycinonate I (**2**), methyl mycinonate I (**3**), methyl mycinonate II (**4**), and decarboxymycinonic acid III (**5**) (**Scheme 1**).

## 3. SYNTHESIS OF THE COMMON BUILDING BLOCK (8)

We have already reported the efficient synthesis[9] of the (*S*)-(*Z*)-olefinic alcohol (**12**) starting from (*S*)-*O*-benzylglycidol (**9**) *via* the rearrangement of the terminal acetylene (**10**) to the internal acetylene (**11**). In the present synthesis **12** was first transformed into the propargyl ether (**14**) in two steps in a good overall yield employing a modified Williamson conditions using a complex of potassium fluoride and neutral alumina as catalyst.[10] Treatment of **14** with *n*-butyllithium underwent a



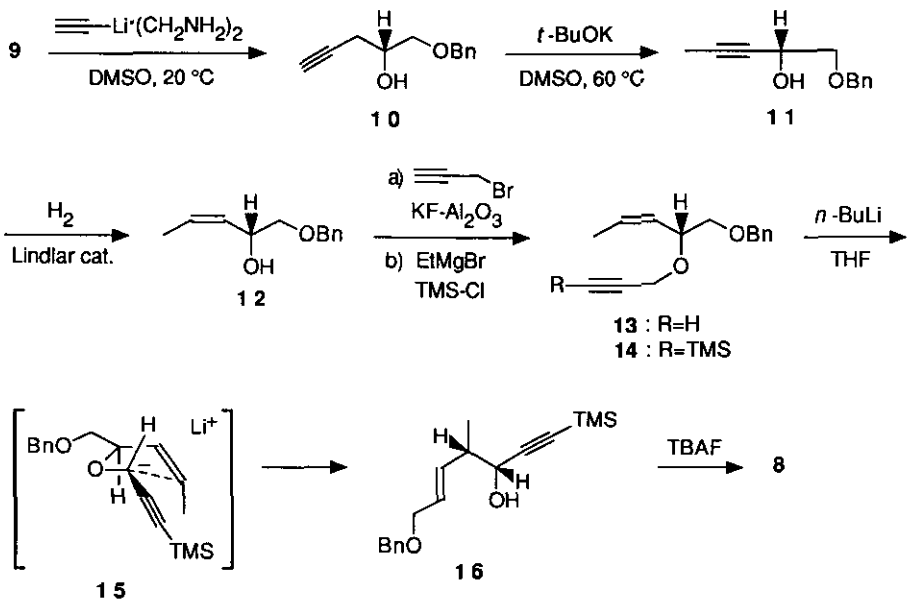

Bn=$C_6H_5CH_2$–; TBS=*tert* Bu(Me)$_2$Si–; BOM=$C_6H_5CH_2OCH_2$–

**Scheme 1**

facile diastereoselective [2,3]-Wittig rearrangement[11] to afford the *syn* product (**16**) exclusively in 73% yield presumably *via* the least hindered folded envelope transition state[11] (**15**). This was then treated with tetrabutylammonium fluoride to give the key common building block (**8**) in an excellent yield. Optical purity of **8** was determined to be ≥98% ee by $^1$H nmr (500 MHz) measurement of its MTPA esters (*R*- and *S*-) (**Scheme 2**).

4. SYNTHESES OF THE PRESUMED BIOGENETIC PRECURSORS[8]

(i) Synthesis of the '$C_{1-6}$' Precursor Methyl Epimycinonate I (**2**) ——— In order to discriminate the olefinic and the acetylenic bond, **8** was first treated with *N*-bromosuccinimide (NBS) in the presence of sodium hydrogen carbonate to give the bromo ether (**17**) as a mixture of diastereomers. Catalytic hydrogenation of the acetylenic bond of **17** followed by treating the resulting saturated product (**18**) with zinc powder in the presence of hydrochloric acid regenerated the olefinic bond to

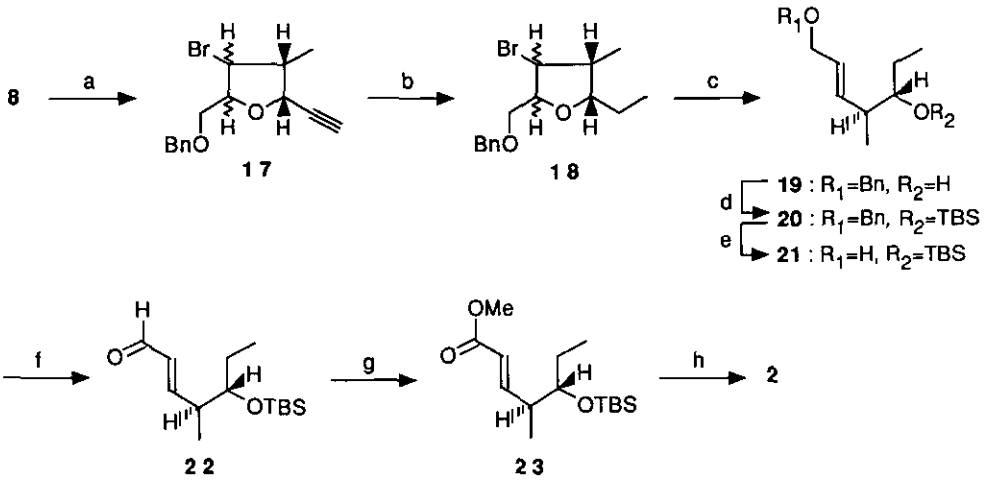



Bn=$C_6H_5CH_2$–; TMS=$(Me)_3Si$–; TBAF=$^nBu_4N^+F^-$

**Scheme 2**

give **19** in a satisfactory overall yield. Sequential protection of the secondary alcohol and debenzylation yielded the primary alcohol (**21**) which gave the unsaturated ester (**23**) *via* the aldehyde (**22**) by employing Corey's procedure.[12] Deprotection of **23** with hydrochloric acid afforded the secondary alcohol (**2**) whose physical and spectral data were identical with those of natural methyl epimycinonate I (**2**) corresponding to the $C_{1\text{-}6}$ moiety of protomycinolide IV (**1**) (**Scheme 3**).

(ii) Synthesis of the '$C_{11\text{-}17}$' Precursor Methyl Mycinonate I (**3**), the '$C_{9\text{-}17}$' Precursor Methyl Mycinonate II (**4**), and the '$C_{8\text{-}17}$' Precursor Decarboxymycinonic acid III (**5**) ——— On the other hand, the secondary hydroxy center of **8** was first inverted by employing the Mitsunobu reaction[13] to give the epimeric alcohol (**25**) having the $C_{14}$ and $C_{15}$ stereocenters *via* the benzoate (**24**). Employing exactly the same approach as that for the epimeric counterpart (**8**), **25** could be transformed into the α,β-unsaturated ester (**3**), *via* the aldehyde (**31**), whose physical and spectral data were identical with those of natural methyl mycinonate I (**3**) corresponding to the $C_{11\text{-}17}$




**Scheme 3**

*Reagents and conditions*: a, NBS, THF; b, $H_2$, $PtO_2$; c, Zn, MeOH; d, TBS-Cl, imidazole; e, Li, liq. $NH_3$; f, $MnO_2$; g, $MnO_2$, NaCN, MeOH; h, conc. HCl (cat.), MeOH.

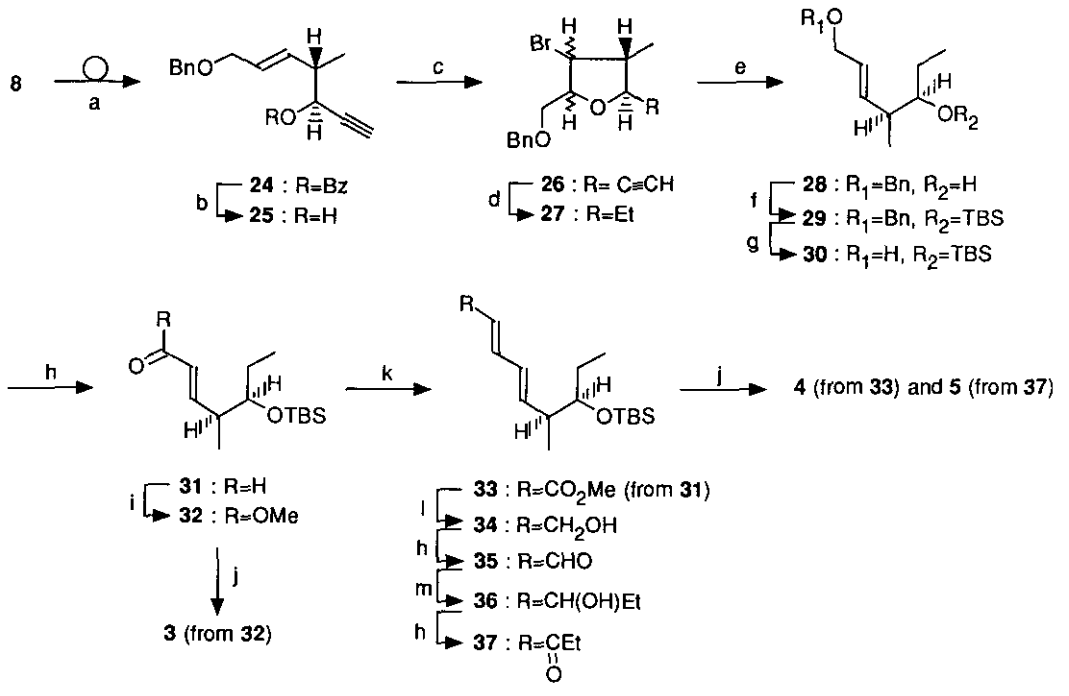
moiety of protomycinolide IV (**1**). The Horner-Emmons condensation of aldehyde (**31**) followed by deprotection of the resulting **33** afforded the diene (**4**) whose physical and spectral data were identical with those of natural methyl mycinonate II (**4**) corresponding to the $C_{9\text{-}17}$ moiety of protomycinolide IV (**1**).

The protected diene intermediate (**33**) was further transformed into the dienone (**5**), *via* the intermediates, (**34**), (**35**), (**36**), and (**37**), whose physical and spectral data were identical with those of natural decarboxymycinonic acid III (**5**) corresponding to the $C_{8\text{-}17}$ moiety of protomycinolide IV (**1**) (**Scheme 4**).

Since the biogenesis of protomycinolide IV (**1**) as well as other related natural macrolides has not been clarified,[14] the present stereochemical determination and synthesis of the presumed biogenetic intermediates (**2**) ~ (**5**) are noteworthy.

5. SYNTHESIS OF THE $C_{1\text{-}8}$ SEGMENT OF PROTOMYCINOLIDE IV[7]

To introduce the $C_6$-methyl group having the requisite stereochemistry **8** was first transformed into the butenolide (**42**). Thus, **8** was treated with butyllithium followed by carbon dioxide to give the acid (**38**) which on partial reduction followed




Bn=$C_6H_5CH_2$–; Bz=$C_6H_5CO$–; TBS=*tert* $Bu(Me)_2Si$–

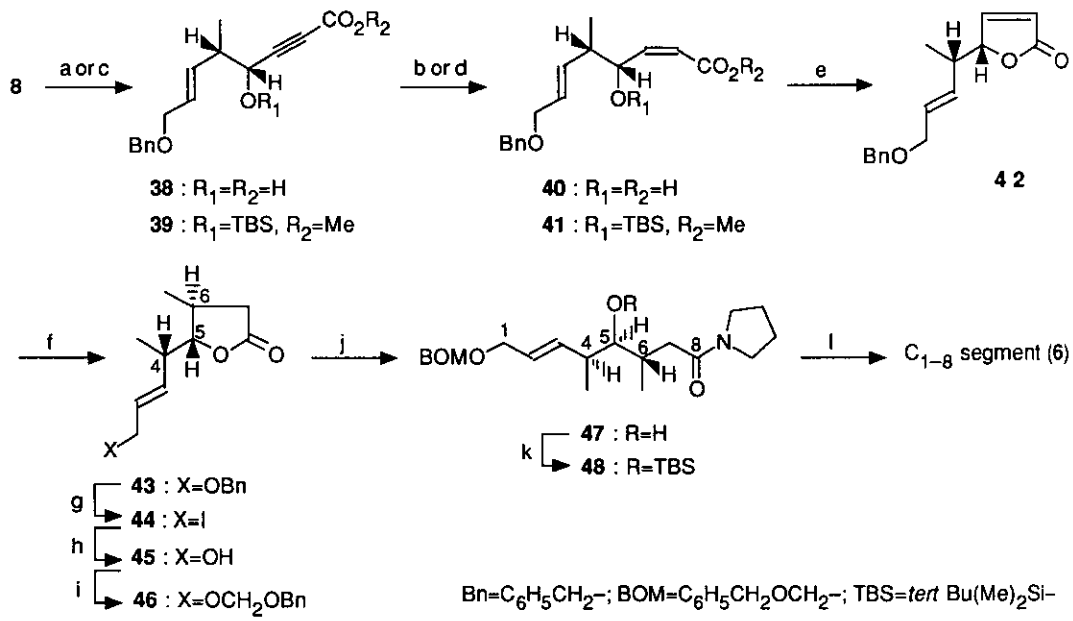
**Scheme 4**

*Reagents and conditions*: a, $PhCO_2H$, $Ph_3P$, *i*-$PrOCON{=}NCO_2$-*i*-Pr; b, $K_2CO_3$, MeOH; c, NBS, $NaHCO_3$, THF; d, $H_2$, $PtO_2$; e, Zn, AcOH (cat.), MeOH; f, TBS-Cl, imidazole; g, Li, liq. $NH_3$; h, $MnO_2$; i, $MnO_2$, NaCN, MeOH; j, conc. HCl (cat.), MeOH; k, $(i\text{-PrO})_2P(O)CH_2CO_2Me$, *tert*-BuOK; l, $(i\text{-Bu})_2AlH$; m, EtMgBr.

by thermal cyclization furnished the butenolide (**42**) in 40% overall yield *via* **38** and **40**. The same compound (**42**) was also obtained in 75% overall yield by treating the silyl ether (**39**) of **8** with methyl chloroformate in the presence of butyllithium followed by partial reduction and acid treatment.

As expected the reaction of the butenolide (**42**) with lithium dimethylcuprate occurred diastereoselectively from the less hindered face of the molecule to give the *trans*-5,6-product (**43**) in an excellent yield. Since debenzylation under Birch conditions was found to be difficult by contamination of overreduction products, **42** was first treated with trimethylsilyl iodide[15] to yield the allyl iodide (**44**) which was immediately exposed to aqueous sodium hydrogen carbonate to give rise to the

alcohol (**45**) in 68% overall yield. After protecting **45** by benzyloxymethyl (BOM) group,[16] the resulting ether (**46**) was exposed to the complex prepared from pyrrolidine and trimethylaluminum[17] to give the amide alcohol (**47**) whose secondary hydroxy group was protected by *tert*-butyldimethylsilyl (TBS) group. Finally, the amide (**48**) was reacted with methyllithium to afford the $C_{1-8}$ segment (**6**) of the Suzuki-Tsuchihashi synthesis[6,18] in 46% overall yield from **47** (**Scheme 5**).



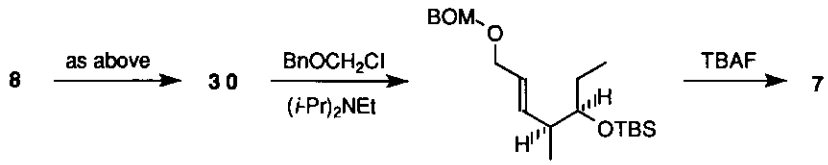

**Scheme 5**

*Reagents and conditions*: a, *n*-BuLi, then $CO_2$; b, $H_2$, Lindlar catalyst, then reflux, benzene (for **38** *via* **40**); c, (i) TBS-Cl, imidazole, (ii) *n*-BuLi, then $ClCO_2Me$; d, $H_2$, Lindlar catalyst; e, conc. HCl (cat.), MeOH (for **41**); f, $Me_2CuLi$; g, TMS-Cl, NaI; h, aq. $NaHCO_3$; i, BOM-Cl, $(i\text{-}Pr)_2NEt$; j, $Et_2AlN(CH_2)_4$; k, TBS-Cl, imidazole; l, MeLi.

## 6. SYNTHESIS OF THE $C_{11-17}$ SEGMENT OF PROTOMYCINOLIDE IV

Synthesis of the $C_{11-17}$ segment of protomycinolide IV (**1**) has virtually been accomplished in the synthesis of the $C_{11-17}$ biogenetic precursor (**3**). In order to connect **8** with the known Suzuki-Tsuchihashi intermediate[6] (**7**), the primary alcohol

(**30**) used in the synthesis of the $C_{11-17}$ precursor (**3**) was alkylated with benzyloxymethyl chloride followed by removal of the protecting group of the secondary hydroxy group of the bis-ether product (**49**) to give rise to **7**[6,18] in 75% overall yield (**Scheme 6**).




**49**

BOM=$C_6H_5CH_2OCH_2$-; TBS=*tert*-Bu(Me)$_2$Si-; TBAF=*n*-$Bu_4N^+F^-$

**Scheme 6**

## 7. CONCLUSION

In conclusion a formal total synthesis of protomycinolide IV (**1**) and the first enantiocontrolled syntheses of its presumed biogenetic precursors, methyl epimycinonate I (**2**), methyl mycinonate I (**3**), methyl mycinonate II (**4**), and decarboxymycinonic acid III (**5**), have been achieved starting from a single chiral building block (*S*)-*O*-benzylglycidol (**9**) *via* the eight-carbon unit (**8**) as a common intermediate.

## EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Ir spectra were measured with a JASCO-IR-700 spectrophotometer. $^1$H Nmr spectra were recorded on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Mass spectra were measured with a JEOL JMS-DX303 instrument. Reactions were carried out under argon.

*(R)*-(Z)-1-Benzyloxy-2-propargyloxy-3-pentene (**13**)

Method A: To a stirred mixture of (*R*)-(–)-alcohol (**12**) (1.0 g, 5.2 mmol), tetra-*n*-butylammonium hydrogen sulfate (88 mg), and 60% (w/v) aqueous NaOH (20 ml)

was added propargyl bromide (3.1 g, 26.0 mmol) at 0 °C and the stirring was continued for 26 h at room temperature. The mixture was diluted with water and ether and the organic layer was separated. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave an oil which was purified on a silica gel column (50 g) using $Et_2O$-hexane (1:50 v/v) as eluent to give the ether (**13**) (0.92g, 77%) as a colorless oil

Method B: A suspension of (*R*)-(−)-alcohol (**12**) (21.7 g, 112.8 mmol), propargyl bromide (53.7 g, 451.3 mmol), and KF-$Al_2O_3$ (2:3 w/w) (144.3 g) in acetonitrile (500 ml) was stirred at room temperature for 14 h. After filtration, the mixture was evaporated under reduced pressure to leave the residue which was purified on a silica gel column (1000 g) using $Et_2O$-hexane (1:15 v/v) as eluent to give the ether (**13**) (18.2 g, 70%) as a colorless oil; bp 130 °C/0.2 Torr (Kugelrohr); $[\alpha]_D^{25}$ −85.38° (*c* 1.04, $CHCl_3$). Ir (film) $\nu_{max}$: 2110 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 6.02-5.12 (m, 2H), 4.60 (s, 2H), 4.88-4.50 (m, 1H), 4.19 (t, *J*=2.5 Hz, 2H), 1.73 (dd, *J*=6.8, 1.7 Hz, 3H); ms (m/z): 189 ($M^+$-$CH_3CH$=CH-), 91 (100%). *Anal.* Calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88. Found: C 77.58, H 7.90.

(*R*)-(Z)-1-Benzyloxy-2-(3'-trimethylsilylpropargyloxy)-3-pentene (**14**) —— To a stirred solution of the ether (**13**) (10.0 g, 43.5 mmol) in THF (150 ml) was added EtMgBr (1.3 M in THF) (40 ml, 52 mmol) at 0 °C and after 3 h trimethylsilyl chloride (14.2 g, 130.4 mmol) was added at the same temperature and after 3 min an excess of saturated aqueous $NH_4Cl$ was added to the mixture. The mixture was extracted with ether and the extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave a residue which was purified on a silica gel column (250 g) using $Et_2O$-hexane (1:30 v/v) as eluent to give the silylated product (**14**) (12.2 g, 93%) as a colorless oil; bp 130 °C/0.2 Torr (Kugelrohr); $[\alpha]_D^{27}$ −80.74° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 2180 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.34 (s, 5H), 6.01-5.12 (m, 2H), 4.60 (s, 2H), 4.79-4.90 (m, 1H), 4.18 (d, *J*=2.9 Hz, 2H), 3.73-3.53 (m, 2H), 1.71 (dd, *J*=7.1, 1.4 Hz, 3H), 0.18 (br s, 9H); ms (m/z): 302

($M^+$), 91 (100%). Exact Mass Calcd for $C_{18}H_{26}O_2Si$: 302.1703. Found: 302.1711. *Anal.* Calcd for $C_{18}H_{26}O_2Si$: C 71.47, H 8.66. Found: C 71.44, H 8.72.

(3*R*,4*S*)-(*E*)-7-Benzyloxy-4-methyl-1-trimethylsilylhept-5-en-1-yn-3-ol (**16**) —— To a stirred solution of the ether (**14**) (100 mg, 0.33 mmol) in THF (2 ml) was added *n*-BuLi (1 M in hexane, 0.60 ml, 0.6 mmol) at –70 °C and the stirring was continued for 4 h. After addition of saturated aqueous $NH_4Cl$ (3 ml) at the same temperature, the mixture was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:7 v/v) as eluent to give the alcohol (**16**) (73.4 mg, 73%) as a colorless oil; $[\alpha]_D^{24}$ +18.91° (*c* 0.62, $CHCl_3$). Ir (film) $\nu_{max}$: 3400, 2170 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.82-5.67 (m, 2H), 4.52 (s, 2H), 4.24 (dd, *J*=7.4, 6.8 Hz, 1H), 4.08-3.94 (m, 2H), 2.67-2.28 (m, 1H), 1.86 (d, *J*=7.4 Hz, 1H, exchangeable with $D_2O$), 1.12 (d, *J*=6.8 Hz, 3H), 0.17 (br s, 9H); ms (m/z): 301 ($M^+$-1), 91 (100%). *Anal.* Calcd for $C_{18}H_{28}O_2Si$: C 71.47, H 8.66. Found: C 71.29, H 8.73.

(3*R*,4*S*)-(*E*)-7-Benzyloxy-4-methylhept-5-en-1-yn-3-ol (**8**) —— A mixture of the silylacetylene (**16**) (1.77 g, 5.86 mmol) and tetra-*n*-butylammonium fluoride (1 M in THF) (17.6 ml, 17.6 mmol) in THF (20 ml) was stirred at room temperature for 8 min. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column (30 g) using $Et_2O$-hexane (1:7 v/v) as eluent to give the acetylene (**8**) (1.29 g, 96%) as a colorless oil; bp 130 °C/0.2 Torr (Kugelrohr); $[\alpha]_D^{25}$ +18.15° (*c* 1.15, $CHCl_3$). Ir (film) $\nu_{max}$: 3500, 2100 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.30 (s, 5H), 5.82-5.68 (m, 2H), 4.15 (s, 2H), 4.26 (dd, *J*=5.1, 2.3 Hz, 1H), 4.08-3.92 (m, 2H), 2.45 (d, *J*=2.3 Hz, 1H), 2.70-2.30 (m, 1H), 2.10-1.82 (br s, 1H, exchangeable with $D_2O$), 1.12 (d, *J*=7.1 Hz, 3H); ms (m/z): 230 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{18}O_2$: 230.1307. Found: 230.1293.

(2*R*,3*S*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethynyl-3-methyltetrahydrofuran (**17**) —— To a stirred solution of the eneyne (**8**) (20 mg, 0.09 mmol) in THF (1 ml) was added *N*-bromosuccinimide (23 mg, 0.13 mmol) at room temperature. After

stirring at the same temperature for 3 h, the mixture was diluted with $Et_2O$ and the mixture was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (3 g) using $Et_2O$-hexane (1:15 v/v) as eluent to give the bromo ether (**46**) (21 mg, 78%) as a colorless oil. Ir (film) $\nu_{max}$: 2120 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.38 (s, 5H), 4.76 (dd, *J*=8.0, 2.3 Hz, 1H), 4.64 (s, 2H), 4.31-4.09 (m, 1H), 3.90 (d, *J*=9.1 Hz, 1H), 3.79-3.61 (m, 2H), 2.81-2.32 (m, 1H), 2.52 (d, *J*=2.3 Hz, 1H), 1.22 (d, *J*=7.1 Hz, 2H); ms (m/z): 310, 308 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{17}O_2Br$: 310.0392; 308.0411. Found: 310.0382; 308.0411.

(2*S*,3*S*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethyl-3-methyltetrahydrofuran (**18**) ——— A suspension of the bromoacetylene (**17**) (333.7 mg, 1.01 mmol) and $PtO_2$ (17 mg) in hexane (3 ml) was hydrogenated under atmospheric pressure of hydrogen at room temperature for 40 min. The suspension was filtered and evaporated under reduced pressure to leave an oil wich was purified on a silica gel column (3.0 g) to give the saturated product (**18**) as separable isomers (**18a**) and (**18b**) both as colorless oil.

**18a** (200.6 mg, 60%): Ir (film) $\nu_{max}$: 1090 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.60 (s, 2H), 4.28-3.45 (m, 5H), 2.48 (sext, *J*=6.9 Hz, 1H), 1.44 (q, *J*=7.1 Hz, 2H), 1.01 (d, *J*=7.1 Hz, 3H), 0.96 (t, *J*=7.1 Hz, 3H); ms (m/z): 316, 314 ($M^+$), 91 (100%).

**18b** (67.2 mg, 20%): Ir (film) $\nu_{max}$: 1090 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.60 (s, 2H), 4.28-3.45 (m, 5H), 2.48 (sext, *J*=6.9 Hz, 1H), 1.44 (q, *J*=7.1 Hz, 2H), 1.11-0.83 (m, 3H), 1.01 (d, *J*=7.1 Hz, 3H); ms (m/z): 316, 314 ($M^+$), 91 (100%).

(3*S*,4*S*)-(*E*)-7-Benzyloxy-4-methylhept-5-en-3-ol (**19**) ——— A suspension of the bromo ether (**18**) (155.4 mg, 0.50 mmol) and zinc dust (164 mg, 2.5 matom) in MeOH (5 ml) was refluxed for 3 h. After filtration, the filtrate was evaporated under reduced pressure. The residue was taken up into $Et_2O$ and was filtered using Celite pad. The filtrate was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (3 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the enol (**19**) (102.3

mg, 87%) as a colorless oil; $[\alpha]_D^{26}$ –24.55° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 2450 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.35 (s, 5H), 5.78-5.59 (m, 2H), 4.51 (s, 2H), 4.00 (d, *J*=4.3 Hz, 2H), 3.53-3.22 (m, 1H), 2.52-2.04 (s, 1H), 1.78-1.22 (m, 2H, 1H exchangeable with $D_2O$), 1.03 (d, *J*=7.1 Hz, 3H), 0.96 (t, *J*=8.0 Hz, 3H); ms (m/z): 234 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{22}O_2$ ($M^+$): 234.1619. Found: 234.1620.

(4*S*,5*S*)-(*E*)-1-Benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methyl-2-heptene (**20**) —— A mixture of the enol (**19**) (576.4 mg, 2.51 mmol), *tert*-butyldimethylsilyl chloride (755.4 mg, 5.01 mmol), and imidazole (767.7 mg, 11.3 mg) in DMF (5 ml) was stirred at room temperature for 11 h. The mixture was diluted with $Et_2O$ and was washed with saturated aqueous NaHCO3, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (30 g) using $Et_2O$-hexane (1:50 v/v) as eluent to give the silyl ether (**20**) (827 mg, 95%) as a colorless oil; $[\alpha]_D^{30}$ –25.05° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 1255, 1105, 780, 840, 700 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.90-5.38 (m, 2H), 4.50 (s, 2H), 3.99 (d, *J*=4.9 Hz, 2H), 3.46 (q, *J*=5.4 Hz, 1H), 2.34 (m, 1H), 1.62-1.24 (m, 2H), 0.97 (d, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.86 (t, *J*=7.8 Hz, 3H), 0.04 (s, 6H); ms (m/z): 319 ($M^+$-$C_2H_5$), 173 (100%). Exact Mass Calcd for $C_{19}H_{31}O_2Si$ ($M^+$-$C_2H_5$): 319.2093. Found: 319.2115.

(4*S*,5*S*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methyl-2-hepten-1-ol (**21**) —— To a stirred solution of the benzyl ether (**20**) (755.9 mg, 2.17 mmol) in THF (25 ml) and liquid $NH_3$ (25 ml) was added lithium (152 mg, 21.7 matom) portionwise. After having faded blue color, MeOH (5 ml) was added to the mixture and $NH_3$ was evaporated at atmospheric pressure. The residue was diluted with dichloromethane and the solution was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (20 g) using $Et_2O$ hexane (1:4 v/v) to give the primary alcohol (**21**) (543.7 mg, 97%) as a colorless oil; $[\alpha]_D^{25}$ –29.47° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 3125 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ 5.89-5.42 (m, 2H), 4.10 (br d, *J*=4.2 Hz, 2H), 3.46 (q, *J*=5.4 Hz, 1H), 2.32 (m, 1H), 1.62-1.20 (m, 3H, 1H exchangeable with $D_2O$), 0.97 (d, *J*=6.8 Hz, 3H), 0.89 (t, *J*=7.8 Hz, 3H), 0.03 (s,

6H); ms (m/z): 257 ($M^+$+1), 133 (100%). Exact Mass Calcd for $C_{14}H_{29}O_2Si$ ($M^+$-1): 257.1936. Found: 257.1942.

(4*S*,5*S*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methylhept-2-en-1-ol (**22**) —— A suspension of the enol (**21**) (107.8 mg, 0.42 mmol) and $MnO_2$ (1.08 g) in $CH_2Cl_2$ (3 ml) was stirred at room temperature for 4.5 h. After filtration using Celite pad, the filtrate was evaporated under reduced pressure and the residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the aldehyde (**22**) (83.7 mg, 78%) as a colorless oil; $[\alpha]_D^{29}$ –63.20° (*c* 1.0, $CHCl_3$). Ir (film) $\nu_{max}$: 1692 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 9.52 (d, *J*=7.8 Hz, 1H), 6.95 (dd, *J*=15.9, 6.6 Hz, 1H), 6.11 (ddd, *J*=15.9, 7.8, 1.5 Hz, 1H), 3.61 (td, *J*=6.6, 4.9 Hz, 1H), 2.62 (m, 1H), 1.66-1.21 (m, 2H), 1.07 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.88 (t, *J*=7.6 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ms (m/z): 256 ($M^+$), 73 (100%). Exact Mass Calcd for $C_{14}H_{28}O_2Si$: 256.1859. Found: 256.1882.

Methyl (4*S*,5*S*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methyl-2-heptenoate (**23**) —— A suspension of the aldehyde (**22**) (295.7 mg), $MnO_2$ (3.24 g) and NaCN (283.1 mg, 5.78 mmol) in MeOH (10 ml) containing acetic acid (0.10 ml, 1.73 mmol) was stirred at room temperature for 17 h. After filtration using Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (8 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the ester (**23**) (274 mg, 76%) as a colorless oil; $[\alpha]_D^{25}$ –42.46° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 1728, 1659 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.01 (dd, *J*=15.9, 7.6 Hz, 1H), 5.80 (dd, *J*=15.9, 1.5 Hz, 1H), 3.73 (s, 3H), 3.54 (q, *J*=5.4 Hz, 1H), 2.48 (m, 1H), 1.62-1.28 (m, 2H), 1.02 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.86 (t, *J*=7.8 Hz, 3H), 0.04 (s, 6H); ms (m/z): 285 ($M^+$-1), 73 (100%). Exact Mass Calcd for $C_{15}H_{29}O_3Si$ ($M^+$-1): 285.1886. Found: 185.1862.

Methyl (4*S*,5*S*)-(*E*)-5-Hydroxy-4-methyl-2-heptenoate (Methyl Epimycinonate I) (**2**) —— To a stirred solution of the silyl ether (**23**) (197.2 mg, 0.69 mmol) in MeOH (3 ml) was added 35% hydrochloric acid (3 drops) at room temperature and the stirring was continued for 12 h at the same temperature. After evaporation of the solvent

under reduced pressure, the residue taken up into $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the '$C_{1-6}$' precursor (**2**) (112.0 mg, 94%) as a colorless oil; $[\alpha]_D^{26}$ –43.78° (*c* 1.01, MeOH) [lit.,[2b] $[\alpha]_D^{25}$ –45.9° (*c* 1.01, MeOH)]. Ir (film) $\nu_{max}$: 3460, 1725, 1710, 1660 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 6.95 (dd, *J*=15.9, 7.9 Hz, 1H), 5.87 (dd, *J*=15.9, 1.2 Hz, 1H), 3.74 (s, 3H), 3.49 (ddd, *J*=9.1, 4.9, 3.7 Hz, 1H), 2.44 (sext, d, *J*=6.7, 1.2 Hz, 1H), 1.63-1.46 (m, 1H, exchangeable with $D_2O$), 1.56 (m, *J*=7.3, 3.7 Hz, 1H), 1.40 (hept, *J*=7.3 Hz, 1H), 1.09 (d, *J*=7.3 Hz, 3H); ms (m/z): 141 ($M^+$-OMe), 114 (100%). Exact Mass Calcd for $C_8H_{13}O_2$ ($M^+$-OMe): 141.0915. Found: 141.0925. The spectral data were identical with those of the natural origin[2] (**2**).

(3*S*,4*S*)-(*E*)-3-Benzyloxy-7-benzyloxy-4-methylhept-5-en-1-yne (**24**) —— To a stirred solution of the eneyne (**8**) (49.3 mg, 0.21 mmol) in THF (2 ml) was added benzoic acid (34.0 mg, 0.28 mmol), triphenylphosphine (84.0 mg, 0.32 mmol), and diisopropyl azodicarboxylate (64.9 mg, 0.32 mmol) at 0 °C and the mixture was stirred for 35 min at the same temperature. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column (15 g) using $Et_2O$-hexane (1:50 v/v ~ 1:15 v/v) as eluent to give the benzoate (**24**) (5.34 mg, 75%) as a colorless oil; bp 182 °C/0.04 Torr (Kugelrohr); $[\alpha]_D^{25}$ –31.74° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 3290, 2130, 1720 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 8.16-7.95 (m, 2H), 7.70-7.38 (m, 3H), 7.30 (s, 5H), 5.84-5.68 (m, 2H), 5.54 (dd, *J*=6.1, 2.2 Hz, 1H), 4.47 (s, 2H), 4.00 (m, 2H), 2.78 (m, 1H), 2.49 (d, *J*=2.2 Hz, 1H), 1.25 (d, *J*=6.8 Hz, 3H); ms (m/z): 334 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{22}H_{22}O_3$: 334.1568. Found: 334.1535. *Anal.* Calcd for $C_{22}H_{22}O_3$: C 79.01, H 6.63. Found: C 79.21, H 6.73.

(3*S*,4*S*)-(*E*)-7-Benzyloxy-4-methylhept-5-en-1-yn-3-ol (**25**) —— To a stirred solution of the benzoate (**24**) (2.78 g, 8.31 mmol) in MeOH (20 ml) was added $K_2CO_3$ (1.72 g, 12.5 mmol) at room temperature and the stirring was continued for 1 h at the same temperature. After evaporation of the solvent, the residue taken into $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and

evaporated under reduced pressure. The residue was purified on a silica gel column (80 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the alcohol (**25**) (1.86 g, 97%) as a colorless oil; bp 162 °C/0.3 Torr (Kugelrohr); $[\alpha]_D^{25}$ –15.38° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 3380, 3280, 2120 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.82-5.65 (m, 2H), 4.52 (s, 2H), 4.22 (dd, *J*=5.9, 2.2 Hz, 1H), 4.02 (m, 2H), 2.50 (m, 1H), 2.47 (d, *J*=2.2 Hz, 1H), 1.98 (br d, *J*=5.9 Hz, 1H, exchangeable with $D_2O$), 1.15 (d, *J*=6.8 Hz, 3H); ms (m/z): 230 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{18}O_2$: 230.1307. Found: 230.1338. *Anal.* Calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88. Found: C 78.22, H 8.03.

(2*S*,3*S*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethynyl-3-methyltetrahydrofuran (**26**) —— To a stirred suspension of the eneyne (**25**) (2.88 g, 12.5 mmol) and $NaHCO_3$ (10.5 g, 125 mmol) was added *N*-bromosuccinimide (2.67 g, 15 mmol) at room temperature and the stirring was continued for 1 h. The mixture was diluted with $Et_2O$ and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (150 g) using $Et_2O$-hexane (1:60~1:30 v/v) as eluent to give the bromo ether (**26**) (2.58 g, 66%) as a colorless oil. Ir (film) $\nu_{max}$: 3200, 2140 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.68 (d, *J*=12.2 Hz, 1H), 4.52 (d, *J*=12.2 Hz, 1H), 4.37-4.14 (m, 2H), 3.90 (d, *J*=9.8 Hz, 1H), 3.77-3.63 (m, 2H), 2.79-2.32 (m, 1H), 2.54 (d, *J*=2.2 Hz, 1H), 1.22 (d, *J*=6.6 Hz, 3H); ms (m/z): 310, 308 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{17}O_2Br$: 310.0391; 308.0411. Found: 310.0383; 308.0414.

(2*R*,3*S*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethyl-3-methyltetrahydrofuran (**27**) —— A suspension of the bromoacetylene (**26**) (2.62 g, 8.5 mmol) and $PtO_2$ (79 mg) in hexane (10 ml) was hydrogenated under atmospheric pressure of hydrogen at room temperature for 2.5 h. The suspension was filtered and the filtrate was evaporated under reduced pressure to leave an oil which was purified on a silica gel column (80 g) using $Et_2O$-hexane (1:60 v/v) as eluent to give the saturated product (**27**) (2.12 g, 80%) as a colorless oil. Ir (film) $\nu_{max}$: 1455, 1120, 1070, 740, 700 $cm^{-1}$: $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.69 (d, *J*=12.2 Hz, 1H), 4.54 (d, *J*=12.2 Hz, 1H), 4.12 (ddd, *J*=8.8, 3.9, 2.7 Hz, 1H), 3.86 (d, *J*=9.8 Hz, 1H), 3.73-3.40 (m, 3H), 2.33-1.23 (m, 3H), 1.11 (d,

*J*=6.6 Hz, 3H), 0.98 (t, *J*=7.6 Hz, 3H); ms (m/z): 314, 312 ($M^+$), 112 (100%). Exact Mass Calcd for $C_{15}H_{21}O_2Br$: 314.0704; 312.0725. Found: 314.0688; 312.0706.

(3*R*,4*S*)-(*E*)-7-Benzyloxy-4-methylhept-5-en-3-ol (**28**) —— A suspension of the bromo ether (**27**) (2.08 g, 6.64 mmol) and zinc dust (2.17 g, 33.2 matom) in MeOH (5 ml) containing 35% hydrochloric acid (3 drops) was refluxed for 10 h. After filtration, the filtrate was evaporated under reduced pressure. The residue taken up into $Et_2O$, after filtration using Celite pad, was washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (80 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the enol (**28**) (1.53 g, 99%) as a colorless oil; $[\alpha]_D^{23}$ −12.62° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 3450 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.78-5.59 (m, 2H), 4.51 (s, 2H), 4.08-3.92 (m, 2H), 3.33 (m, 1H), 2.25 (m, 1H), 1.73-1.18 (m, 3H, 1H exchangeable with $D_2O$), 1.04 (d, *J*=6.8 Hz, 3H), 0.95 (t, *J*=7.6 Hz, 3H); ms (m/z): 234 ($M^+$), 68 (100%). Exact Mass Calcd for $C_{15}H_{22}O_2$ ($M^+$): 234.1620. Found: 234.1606.

(4*S*,5*R*)-(*E*)-1-Benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methyl-2-heptene (**29**) —— A mixture of the enol (**28**) (1.23 g, 5.55 mmol), *tert*-butyldimethylsilyl chloride (1.67 g, 11.1 mmol), and imidazole (1.70 g, 24.97 mmol) in DMF (10 ml) was stirred at room temperature for 14 h. The mixture was diluted with $Et_2O$ and was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (80 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the silyl ether (**29**) (1.87 g, 97%) as a colorless oil; $[\alpha]_D^{23}$ −7.79° (*c* 1.03, $CHCl_3$). Ir (film) $\nu_{max}$: 1250, 1100, 835, 775, 735, 700 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.88-5.35 (m, 2H), 4.50 (s, 2H), 3.99 (d, *J*=4.6 Hz, 2H), 3.46 (td, *J*=6.1, 3.9 Hz, 1H), 2.32 (m, 1H), 1.52-1.20 (m, 2H), 1.00 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, *J*=7.6 Hz, 3H), 0.04 (s, 6H); ms (m/z): 319 ($M^+$-$C_2H_5$), 173 (100%). Exact Mass Calcd for $C_{19}H_{31}O_2Si$ ($M^+$-$C_2H_5$): 319.2093. Found: 319.2079.

(4*S*,5*R*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methyl-2-hepten-1-ol (**30**) —— To a stirred solution of the benzyl ether (**29**) (1.83 g, 5.27 mmol) in THF (50 ml) and liquid $NH_3$ (50 ml) was added lithium (738 mg, 106.3 matom) portionwise. After

having faded blue color, MeOH (10 ml) was added to the mixture and $NH_3$ was evaporated at atmospheric pressure. The residue was diluted with dichloromethane and the solution was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (50 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the primary alcohol (**30**) (1.20 g, 89%) as a colorless oil; $[\alpha]_D^{24}$ –7.03° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 3340 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 5.86-5.40 (m, 2H), 4.10 (br s, 2H), 3.45 (td, *J*=6.1, 4.2 Hz, 1H), 2.32 (m, 1H), 2.18-1.17 (m, 3H, 1H exchangeable with $D_2O$), 0.99 (d, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.84 (t, *J*=7.8 Hz, 3H), 0.04 (s, 6H); ms (m/z): 229 ($M^+$-$C_2H_5$), 133 (100%). Exact Mass Calcd for $C_{12}H_{25}O_2Si$ ($M^+$-$C_2H_5$): 229.1624. Found: 229.1633.

(4*S*,5*R*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methylhept-2-en-1-al (**31**) —— A suspension of the enol (**30**) (325.7 mg, 1.26 mmol) and $MnO_2$ (3.26 g) in $CH_2Cl_2$ (6 ml) was stirred at room temperature for 6 h. After filtration using Celite pad, the filtrate was evaporated under reduced pressure and the residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the aldehyde (**31**) (294.4 mg, 91%) as a colorless oil; $[\alpha]_D^{28}$ –10.05° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 1692, 1630 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 9.51 (d, *J*=7.8 Hz, 1H), 6.89 (dd, *J*=15.9, 7.8 Hz, 1H), 6.10 (ddd, *J*=15.9, 7.8, 1.0 Hz, 1H), 3.57 (td, *J*=6.1, 4.2 Hz, 1H), 2.61 (m, 1H), 1.68-1.19 (m, 2H), 1.10 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.86 (t, *J*=7.8 Hz, 3H), 0.06 (s, 6H); ms (m/z): 256 ($M^+$), 78 (100%). Exact Mass Calcd for $C_{14}H_{28}O_2Si$: 256.1858. Found: 256.1869.

Methyl (4*S*,5*R*)-(*E*)-5-*tert*-Butyldimethylsilyloxy-4-methyl-2-heptenoate (**32**) —— A suspension of the aldehyde (**31**) (198.7 mg), $MnO_2$ (2.0 g), and NaCN (190.2 mg, 3.88 mmol) in MeOH (3 ml) containing acetic acid (0.04 ml, 1.17 mmol) was stirred at room temperature for 2 h. After filtration using Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$, brine, dried over brine, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the ester (**32**) (185.5 mg, 73%) as a colorless oil; $[\alpha]_D^{28}$ –16.27° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 1730, 1655 $cm^{-1}$; $^1H$ nmr (CDCl3) δ: 6.98

(dd, *J*=15.9, 7.8 Hz, 1H), 5.80 (dd, *J*=15.9, 1.2 Hz, 1H), 3.73 (s, 3H), 3.53 (td, *J*=5.9, 4.6 Hz), 2.48 (m, 1H), 1.70-1.22 (m, 2H), 1.04 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (t, *J*=7.8 Hz, 3H), 0.04 (s, 6H); ms (m/z): 285 ($M^+$-1), 73 (100%). Exact Mass Calcd for $C_{15}H_{29}O_3Si$ ($M^+$-1): 285.1886. Found: 285.1849.

Methyl (4*S*,5*R*)-(*E*)-5-Hydroxy-4-methyl-2-heptanoate (Methyl Mycinonate I) (**3**) ——– To a stirred solution of the silyl ether (**32**) (137.4 mg, 0.48 mmol) in MeOH (2 ml) was added 35% hydrochloric acid (3 drops) at room temperature and the stirring was continued for 4 h at the same temperature. After evaporation of the solvent under reduced pressure, the residue taken up into $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the '$C_{11-17}$' precursor (**3**) (78.4 mg, 95%) as a colorless oil; $[\alpha]_D^{24}$ –8.10° (*c* 0.94, MeOH) [lit.,[2b] $[\alpha]_D$ –8.1° (*c* 0.94, MeOH)]. Ir (film) $\nu_{max}$: 3450, 1730, 1710, 1660 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 6.98 (dd, *J*=15.9, 8.6 Hz, 1H), 5.88 (dd, *J*=15.9, 1.2 Hz, 1H), 3.74 (s, 3H), 3.47 (quint, *J*=4.5 Hz, 1H), 2.43 (m, *J*=6.5, 1.2 Hz, 1H), 1.65-1.50 (m, 1H, exchangeable with $D_2O$), 1.55 (m, *J*=7.3, 4.3 Hz, 1H), 1.43 (hept, *J*=7.3 Hz, 1H), 1.11 (d, *J*=6.7 Hz, 3H), 0.97 (t, *J*=7.3 Hz, 3H); ms (m/z): 155 ($M^+$-OH), 114 (100%). Exact Mass Calcd for $C_9H_{15}O_2$ ($M^+$-OH): 155.1072. Found: 155.1055. Spectral data were identical with those of the natural origin[2] (**3**).

Methyl (6*S*,7*R*)-(2*E*,4*E*)-7-*tert*-Butyldimethylsilyloxy-6-methylnona-2,4-dienoate (**33**) ——– To a stirred solution of methyl diisopropylphosphonoacetate (1.35 ml, 5.81 mmol) in THF (6 ml) and potassium *tert*-butoxide (495.5 mg) was added the aldehyde (**31**) (697.4 mg, 3.16 mmol) in THF (2 ml) at –30 °C and the stirring was continued for 1 h at the same temperature. The mixture was treated with saturated aqueous $NaHCO_3$ (8 ml) and the mixture was extracted with $Et_2O$. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (25 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the ester (**33**) (551.1 mg, 79%) as a pale yellow oil; $[\alpha]_D^{26}$ –18.04° (*c* 1.02, CHCl3). Ir (film) $\nu_{max}$: 1727, 1645, 1620 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.45-7.12 (m,

1H), 6.65-6.24 (m, 2H), 5.79 (d, *J*=15.4 Hz, 1H), 3.74 (s, 3H), 3.49 (td, *J*=5.9, 3.9 Hz, 1H), 2.42 (m, 1H), 1.54-1.18 (m, 2H), 1.03 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, *J*=7.6 Hz, 3H), 0.04 (s, 6H); ms (m/z): 311 ($M^+$-1), 73 (100%). Exact Mass Calcd for $C_{17}H_{31}O_3Si$ ($M^+$-1): 311.2043. Found: 311.2019.

Methyl (6*S*,7*R*)-(2*E*,4*E*)-7-Hydroxy-6-methylnonan-2,4-dienoate (Methyl Mycinonate II) (**4**) —— To a stirred solution of the silyl ether (**33**) (25.8 mg, 0.08 mmol) in MeOH (2 ml) was added 35% hydrochloric acid (2 drops) at room temperature and the stirring was continued for 5 h at the same temperature. After evaporation of the solvent under reduced pressure, the residue taken up into $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the '$C_{11\text{-}17}$' precursor (**4**) (16.0 mg, 98%) as a colorless oil; $[\alpha]_D^{24}$ –14.03° (*c* 1.04, MeOH) [lit.,[2b] $[\alpha]_D^{25}$ –5.2° (*c* 1.00, MeOH)]. Ir (film) $\nu_{max}$: 3450, 1720, 1705, 1640, 1620, $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.28 (dd, *J*=15.3, 10.4 Hz, 1H), 6.23 (dd, *J*=15.3, 10.4 Hz, 1H), 6.11 (dd, *J*=15.3, 7.9 Hz, 1H), 5.83 (d, *J*=15.3 Hz, 1H), 3.74 (s, 3H), 3.42 (ddd, *J*=8.5, 4.9, 4.3 Hz, 1H), 2.37 (sext, *J*=7.3 Hz, 1H), 1.64-1.50 (m, 1H, exchangeable with $D_2O$), 1.55 (m, *J*=7.4, 4.3 Hz, 1H), 1.41 (m, *J*=7.3, 4.3 Hz, 1H), 1.41 (hept, *J*=7.3 Hz, 1H), 1.09 (d, *J*=6.7 Hz, 3H), 0.96 (t, *J*=7.3 Hz, 3H); ms (m/z): 199 ($M^+$-1), 140 (100%). Spectral data were identical with those of the natural origin[2] (**4**).

(6*S*,7*R*)-(2*E*,4*E*)-7-*tert*-Butyldimethylsilyloxy-6-methylnonan-2,4-dien-1-ol (**34**) —— To a stirred solution of the ester (**33**) (217.9 mg, 0.70 mmol) in THF (4 ml) was added diisobutylaluminum hydride (0.76 M in toluene) (4.6 ml, 3.50 mmol) at 0 °C and the stirring was continued for 30 min at the same temperature. The mixture was treated with 30% $NH_4OH$ and the mixture was diluted with $Et_2O$. The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:10 v/v) as eluent to give the primary alcohol (**34**) (194.6 mg, 98%) as a colorless oil; $[\alpha]_D^{28}$ –9.82° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 3330 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 6.42-5.50 (m, 4H), 4.30-4.06 (m, 2H), 3.45 (td, *J*=6.1, 4.2 Hz, 1H), 2.34 (m, 1H), 1.60-1.17 (m, 3H, 1H

exchangeable with $D_2O$), 0.99 (d, $J$=6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, $J$=7.8 Hz, 3H), 0.04 (s, 6H); ms (m/z): 283 ($M^+$-1), 73 (100%). Exact Mass Calcd for $C_{16}H_{31}O_2Si$ ($M^+$-1): 283.2093. Found: 283.2082.

(6*S*,7*R*)-(2*E*,4*E*)-7-*tert*-Butyldimethylsilyloxy-6-methylnona-2,4-dien-1-al (**35**) —— A suspension of the alcohol (**34**) (164.5 mg, 0.58 mmol) and $MnO_2$ (1.65 g) in $CH_2Cl_2$ (5 ml) was stirred at room temperature for 2 h. After filtration using Celite pad, the filtrate was evaporated under reduced pressure and the residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the aldehyde (**35**) (139.1 mg, 85%) as a colorless oil; $[\alpha]_D^{28}$ −14.73° (*c* 1.02, $CHCl_3$). Ir (film) $\nu_{max}$: 1690, 1640, 1600 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 9.55 (d, $J$=7.8 Hz, 1H), 7.23-6.94 (m, 1H), 6.38-6.20 (m, 2H), 6.08 (dd, $J$=15.1, 7.8 Hz, 1H), 3.52 (td, $J$=6.1, 4.2 Hz, 1H), 2.48 (m, 1H), 1.56-1.22 (m, 2H), 1.06 (d, $J$=6.8 Hz, 3H), 0.90 (s, 9H), 0.86 (t, $J$=7.6 Hz, 3H), 0.05 (s, 6H); ms (m/z): 281 ($M^+$+1), 73 (100%). Exact Mass Calcd for $C_{16}H_{29}O_2Si$ ($M^+$-1): 281.1937. Found: 281.1937.

(2*RS*,8*S*,9*R*)-(4*E*,6*E*)-9-*tert*-Butyldimethylsilyloxy-8-methylundeca-4,6-dien-3-ol (**36**) —— To a stirred solution of the aldehyde (**35**) (102.3 mg, 0.36 mmol) in THF (3 ml) was added ethylmagnesium bromide (2.27 M in THF) (0.32 ml, 0.73 mmol) at −30 °C. After 10 min saturated aqueous $NH_4Cl$ was added to the mixture with stirring. The mixture was extracted with $Et_2O$ and the extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:10 v/v) as eluent to give the secondary alcohol (**36**) (104.2 mg, 92%) as a colorless oil. Ir (film) $\nu_{max}$: 3340 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 6.37-5.93 (m, 4H), 4.05 (br q, $J$=6.7 Hz, 1H), 3.45 (td, $J$=6.1, 4.2 Hz, 1H), 2.53-2.11 (m, 1H), 1.78-1.21 (m, 5H, 1H exchangeable with $D_2O$), 1.08-0.72 (m, 9H), 0.89 (s, 9H), 0.04 (s, 6H); ms (m/z): 283 ($M^+$-$C_2H_5$), 173 (100%). Exact Mass Calcd for $C_{16}H_{31}O_2Si$ ($M^+$-$C_2H_5$): 283.2094. Found: 283.2097.

(8*S*,9*R*)-(4*E*,6*E*)-9-*tert*-Butyldimethylsilyloxy-8-methylundecan-4,6-dien-3-one (**37**) —— A suspension of the secondary alcohol (**36**) (256.2 mg, 0.82 mmol) and $MnO_2$ (2.56 g) in $CH_2Cl_2$ (10 ml) was stirred at room temperature for 2 h. The mixture,

after filtration using Celite pad, was evaporated under reduced pressure and the residue was purified on a silica gel column (10 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the ketone (**37**) (221.2 mg, 87%) as a colorless oil; $[\alpha]_D^{25}$ –18.57° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 1690, 1670, 1635, 1600 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.32-6.99 (m, 1H), 6.37-5.92 (m, 3H), 3.49 (td, *J*=6.1, 4.2 Hz, 1H), 2.66-2.18 (m, 1H), 2.58 (q, *J*=7.3 Hz, 2H), 1.54-0.68 (m, 11H), 0.89 (s, 9H), 0.04 (s, 6H); ms (m/z): 295 ($M^+$-$CH_3$), 73 (100%). Exact Mass Calcd for $C_{17}H_{31}O_2Si$ ($M^+$-$CH_3$): 295.2094. Found: 295.2095.

(8*S*,9*R*)-(4*E*,6*E*)-9-Hydroxy-8-methylundecan-4,6-dien-3-one (Decarboxymycinonic Acid III) (**5**) —— To a stirred solution of the silyl ether (**37**) (74.9 mg, 0.24 mmol) in MeOH (2 ml) was added 35% hydrochloric acid (3 drops) at room temperature and the stirring was continued for 3 h at the same temperature. After evaporation of the solvent under reduced pressure, the residue taken up into $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the '$C_{8-17}$' precursor (**5**) (43.3 mg, 91%) as a colorless oil; $[\alpha]_D^{27}$ –8.90° (*c* 0.78, MeOH) [lit.,[2b] $[\alpha]_D^{25}$ –6.3° (*c* 0.86, MeOH)]. Ir (film) $\nu_{max}$: 3450, 1685, 1660, 1630, 1595 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.15 (dd, *J*=15.9, 9.1 Hz, 1H), 6.24 (dd, *J*=15.3, 10.4 Hz, 1H), 6.15 (dd, *J*=15.3, 7.9 Hz, 1H), 6.12 (d, *J*=15.9 Hz, 1H), 3.43 (quint, *J*=4.3 Hz, 1H), 2.58 (q, *J*=7.3 Hz, 2H), 2.38 (sext, *J*=6.7 Hz, 1H), 1.66-1.50 (m, 1H, exchangeable with $D_2O$), 1.55 (m, d, J=7.3, 4.3 Hz, 1H), 1.42 (hept, *J*=7.3 Hz, 1H), 1.11 (t, *J*=7.3 Hz, 3H), 1.10 (d, *J*=6.7 Hz, 3H), 0.97 (t, *J*=7.3 Hz, 3H); ms (m/z): 197 ($M^+$+1), 109 (100%). Exact Mass Calcd for $C_{12}H_{21}O_2$ ($M^+$+1): 197.1542. Found: 197.1516. Spectral data were identical with those of the natural origin[2] (**5**).

(4*R*,5*S*)-(2*Z*,6*E*)-8-Benzyloxy-4-hydroxy-5-methyl-2,6-octadienoic Acid Lactone (**42**) from the Eneyne (**8**) —— To a stirred solution of the eneyne (**8**) (100 mg, 0.44 mmol) in THF (3 ml) was treated with *n*-butyllithium (1.57 M in hexane) (0.67 ml, 1.04 mmol) at –30 °C for 15 min, then $CO_2$ was introduced for 40 min at the same temperature. The mixture was treated with brine (5 ml) and the aqueous layer was

separated. After washing with $Et_2O$, the aqueous layer was made acidic by addition of 35% hydrochloric acid and was extracted with $Et_2O$. The extract was dried over $MgSO_4$ and evaporated under reduced pressure to give the crude acid (**38**) (96.2 mg) which was used for the next reaction without purification.

The crude acid (**38**) (96.2 mg) was hydrogenated in ethyl acetate (1 ml) under atmospheric pressure in the presence of Lindlar catalyst (5 mg) at room temperature for 16 h to give the crude (*Z*)-olefinic acid (**40**) (96.1 mg), after evaporation of the solvent under reduced pressure, which was used for the next reaction without purification.

A solution of the crude acid (**40**) (96.1 mg) in benzene (2 ml) was refluxed using a Dean-Stark apparatus for 16.5 h. The mixture was diluted with $Et_2O$ and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (4 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the butenolide (**42**) (45.1 mg, 40% overall from **8**) as a colorless oil; $[\alpha]_D^{26}$ –99.8° (*c* 1.01, $CHCl_3$). Ir (film) $\nu_{max}$: 1790, 1760 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.42 (dd, *J*=5.7, 1.4 Hz, 1H), 7.33 (s, 5H), 6.12 (dd, *J*=5.7, 2.0 Hz, 1H), 5.79-5.58 (m, 2H), 4.50 (s, 2H), 3.98 (d, *J*=4.9 Hz, 2H), 2.78-2.30 (m, 1H), 1.14 (d, *J*=7.1 Hz, 3H); ms (m/z): 259 ($M^+$+1), 91 (100%). *Anal.* Calcd for $C_{18}H_{18}O_3$: C 74.39, H 7.02. Found: C 74.31, H 7.22.

Methyl (4*R*,5*S*)-(*E*)-8-Benzyloxy-4-*tert*-butyldimethylsilyloxy-5-methyl-oct-6-en-2-ynoate (**41**) ——— A mixture of the eneyne (**8**) (2.10 g, 9.55 mmol) *tert*-butyldimethylsilyl chloride (2.67 g, 17.7 mmol), and imidazole (2.80 ml, 41.3 mmol) in DMF (30 ml) was stirred at room temperature for 12 h. The mixture was diluted with $Et_2O$ and was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (60 g) using $Et_2O$-hexane (1:30 v/v) as eluent to give the silyl ether of **8** (2.96 g, 93%); bp 190-200 °C/0.4 Torr (Kugelrohr); $[\alpha]_D^{24}$ +17.61° (*c* 0.99, $CHCl_3$). Ir (film) $\nu_{max}$: 3320 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.32 (s, 5H), 5.80-5.60 (m, 2H), 4.50 (s, 2H), 4.21 (dd, *J*=5.6, 2.2 Hz, 1H), 4.01 (d, *J*=4.6 Hz, 2H), 2.40 (m, 1H), 2.38 (d, *J*=2.2 Hz, 1H),

1.10 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ms (m/z): 344 ($M^+$), 75 (100%).

To a stirred solution of the above silyl ether (5.40 g, 15.7 mmol) in THF (100 ml) was treated with *n*-butyllithium (1.6 M in hexane) (12.5 ml, 20.0 mmol) at –78 °C for 30 min, then methyl chloroformate (1.80 ml, 23.6 mmol) was added at –50 °C and the mixture was stirred for 30 min. The mixture was treated with saturated aqueous $NH_4Cl$ (30 ml) and extracted with $Et_2O$. The extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (210 g) using $Et_2O$-hexane (1:20 v/v) as eluent to give the ester (**39**) (5.77 g, 92%) as a pale yellow oil; bp 175 °C/0.5 Torr (Kugelrohr); $[\alpha]_D^{25}$ +21.75° (*c* 1.00, $CHCl_3$). Ir (film) $\nu_{max}$: 2325, 1730 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.70 (m, 2H), 4.50 (s, 2H), 4.32 (d, *J*=5.6 Hz, 1H), 4.04 (m, 2H), 3.74 (s, 3H), 2.50 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ms (m/z): 402 ($M^+$), 91 (100%). *Anal.* Calcd for $C_{23}H_{34}O_4Si$: C 68.62, H 8.51. Found: C 68.43, H 8.47.

Methyl (4*R*,5*S*)-(2*Z*,6*E*)-8-Benzyloxy-4-*tert*-butyldimethylsilyloxy-5-methylocta-2,6-dienolate (**41**) —— A suspension of the acetylene (**39**) (5.70 g, 14.18 mmol) and Lindlar catalyst (219 mg) in benzene (200 ml) containing quinoline (0.8 ml) was hydrogenated under atmospheric pressure at room temperature for 12 h. After filtration using Celite pad, the filtrate was evaporated under reduced pressure and the residue was purified on a silica gel column (180 g) using $Et_2O$-hexane (1:20 v/v) as eluent to give the (Z)-olefin (**41**) (5.58 g, 97%) as a colorless oil; bp 175-185 °C/0.5 Torr (Kugelrohr); $[\alpha]_D^{25}$ –5.39° (*c* 1.04, $CHCl_3$). Ir (film) $\nu_{max}$: 1725 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.32 (s, 5H), 6.07 (dd, *J*=11.7, 8.3 Hz, 1H), 5.81-5.58 (m, 3H), 5.27 (dd, *J*=8.3, 5.6 Hz, 1H), 4.47 (s, 2H), 3.97 (d, *J*=4.9 Hz, 2H), 3.69 (s, 3H), 2.42 (m, 1H), 1.03 (d, *J*=6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H); ms (m/z): 404 ($M^+$), 229 (100%). *Anal.* Calcd for $C_{23}H_{36}O_4Si$: C 68.27, H 8.97. Found: C 68.07, H 9.08.

(4*R*,5*S*)-(2*Z*,6*E*)-8-Benzyloxy-4-hydroxy-5-methylocta-2,6-dienoic Acid Lactone (**42**) from the Silyl Ether (**41**) —— To a stirred solution of the silyl ether (**41**) (5.50 g, 13.6

mmol) in MeOH (140 ml) was added 35% hydrochloric acid (14 ml) at room temperature and the stirring was continued for 30 min at the same temperature. The mixture was diluted with $Et_2O$ and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (150 g) using $Et_2O$-hexane (1:2 v/v) as eluent to give the butenolide (**42**) (3.20 g, 90%), as a colorless oil, which was identical with the material described above.

(3*S*,4*S*,5*S*)-(*E*)-8-Benzyloxy-4-hydroxy-3,5-dimethyloct-6-enoic Acid Lactone (**43**) —— To a stirred suspension of CuI (100 mg, 0.52 mmol) in $Et_2O$ (1 ml) was added methyllithium (1.09 M in $Et_2O$) (0.96 ml, 1.05 mmol) at 0 °C. After 1.5 h at the same temperature, to this mixture was added the butenolide (**42**) (45.1 mg, 0.18 mmol) in $Et_2O$ (1 ml) at the same temperature. After 10 min, the mixture was diluted with $Et_2O$ and was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (3 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the δ-lactone (**43**) (31.1 mg, 65%) as a colorless oil; $[\alpha]_D^{24}$ –3.03° (*c* 1.32, $CHCl_3$). Ir (film) $\nu_{max}$: 1780 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.32 (s, 5H), 5.77-5.56 (m, 2H), 4.53 (s, 2H), 4.07-3.80 (m, 3H), 2.85-1.94 (m, 4H), 1.14 (d, *J*=5.8 Hz, 3H), 1.13 (d, *J*=6.5 Hz, 3H); ms (m/z): 274 ($M^+$), 91 (100%). Exact Mass Calcd for $C_{15}H_{18}O_2$ ($M^+$+1): 275.1648. Found: 275.1653. *Anal.* Calcd for $C_{15}H_{18}O_2$: C 74.42, H 8.08. Found: C 74.26, H 8.08.

(3*S*,4*S*,5*S*)-(*E*)-4-Hydroxy-8-iodo-3,5-dimethyloct-6-enoic Acid Lactone (**44**) —— To a stirred solution of the benzyloxylactone (**43**) (200 mg, 0.73 mmol) and NaI (543 mg, 3.6 mmol) in $CH_2Cl_2$-MeCN (2:21) (7 ml) was added trimethylsilyl chloride (0.46 ml, 3.6 mmol) at 0 °C and the stirring was continued for 4 h at room temperature. The mixture was treated with saturated aqueous $NaHCO_3$ (3 ml) and extracted with $Et_2O$. The extract was washed with 2% aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (10 g) using AcOEt:hexane (1:15 v/v) as eluent to give the iodide (**44**) (204 mg, 95%) as a pale yellow oil; $[\alpha]_D^{23}$ +2.15° (*c* 0.74, $CHCl_3$). Ir (film) $\nu_{max}$: 1770 $cm^{-1}$,

$^1$H nmr ($CDCl_3$) δ: 5.87 (dt, *J*=15.1, 7.1 Hz, 1H), 5.57 (dd, *J*=15.1, 7.1 Hz, 1H), 4.00-3.77 (m, 1H), 3.86 (d, *J*=7.1 Hz, 2H), 2.92-1.98 (m, 4H), 1.14 (d, *J*=6.6 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H); ms (m/z): 295 ($M^+$+1), 167 (100%). Exact Mass Calcd for $C_{10}H_{16}O_2I$ ($M^+$+H): 295.0195. Found: 295.0170.

(3*S*,4*S*,5*S*)-(*E*)-4,8-Dihydroxy-3,5-dimethyloct-6-enoic Acid Lactone (**45**) —— A solution of the iodide (**44**) (204 mg, 0.69 mmol) and $NaHCO_3$ (1.0 g, 13.8 mmol) in 50% aqueous THF (20 ml) was stirred at room temperature for 4 days. The mixture was extracted with AcOEt and the extract was washed with 2% aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:1 v/v) as eluent to give the primary alcohol (**45**) (92 mg, 72%) as a pale yellow oil; $[\alpha]_D^{30}$ +5.66° (*c* 0.99, $CHCl_3$). Ir (film) $\nu_{max}$: 3400, 1760 cm$^{-1}$; $^1$H nmr ($CDCl_3$) δ: 5.96-5.41 (m, 2H), 4.12 (d, *J*=4.2 Hz, 2H), 3.92 (t, *J*=5.9 Hz, 1H), 2.86-1.98 (m, 4H), 1.60 (br s, 1H, exchangeable with $D_2O$), 1.13 (d, *J*=5.9 Hz, 3H), 1.11 (d, *J*=6.6 Hz, 3H); ms (m/z): 185 ($M^+$+1), 99 (100%). Exact Mass Calcd for $C_{10}H_{16}O_3$ ($M^+$+H): 184.1090. Found: 184.1095.

(3*S*,4*S*,5*S*)-(*E*)-8-Benzyloxymethoxy-4-hydroxy-3,5-dimethyloct-6-enoic Acid Lactone (**46**) —— A mixture of the primary alcohol (**45**) (44.8 mg, 0.24 mmol), benzyloxymethyl chloride (0.07 ml, 0.49 mmol), and (*i*-Pr)$_2$NEt (0.17 ml, 0.98 mmol) in $CH_2Cl_2$ (1.5 ml) was stirred at room temperature for 12 h. The mixture was diluted with $Et_2O$ and washed with 5% hydrochloric acid, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation the solvent under reduced pressure, the residue was purified on a silica gel column (6 g) using $Et_2O$-hexane (1:2 v/v) as eluent to give the ether (**46**) (60.0 mg, 81%) as a colorless oil; $[\alpha]_D^{23}$ –2.46° (*c* 0.81, $CHCl_3$). Ir (film) $\nu_{max}$: 1780 cm$^{-1}$; $^1$H nmr ($CDCl_3$) δ: 7.34 (s, 5H), 5.77-5.56 (m, 2H), 4.77 (s, 2H), 4.61 (s, 2H), 4.18-4.02 (m, 2H), 3.92 (t, *J*=6.1 Hz, 1H), 2.84-1.95 (m, 4H), 1.10 (d, *J*=6.8 Hz, 6H); ms (m/z): 305 ($M^+$+1), 91 (100%). *Anal.* Calcd for $C_{18}H_{24}O_4$: C 71.02, H 7.95. Found: C 70.93, H 8.12.

*N*-[(3*S*,4*S*,5*S*)-(*E*)-8-Benzyloxymethoxy-4-hydroxy-3,5-dimethyloct-6-enoyl]-pyrrolidine (**47**) —— To a stirred solution of pyrrolidine (0.46 ml) in benzene (7.64

ml) was added $Et_3Al$ (19% solution in hexane, 5 mmol) (1.9 ml) dropwise at room temperature. This complex (1 ml, 0.5 mmol) was then added to a solution of the lactone (**46**) (34.5 mg, 0.11 mmol) in benzene (1 ml) at 5 °C with stirring. After stirring for 1 h at the same temperature, the mixture was treated with saturated aqueous $NH_4Cl$ (2 ml) and extracted with AcOEt. The extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated reduced pressure. The residue was purified on a silica gel column (5 g) using AcOEt-hexane (3:1 v/v) as eluent to give the amide alcohol (**47**) (41.1 mg, 97%) as a colorless oil; $[\alpha]_D^{29}$ +11.76° (*c* 0.88, $CHCl_3$). Ir (film) $\nu_{max}$: 3380, 1610 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.30 (s, 5H), 5.98-5.39 (m, 2H), 4.75 (s, 2H), 4.60 (s, 2H), 4.09 (d, *J*=5.1 Hz, 2H), 3.58-3.10 (m, 5H), 2.70-1.60 (m, 9H, exchangeable with $D_2O$), 1.07 (d, *J*=6.6 Hz, 3H), 0.98 (d, *J*=5.7 Hz, 3H); ms (m/z): 375 ($M^+$), 70 (100%). Exact Mass Calcd for $C_{22}H_{33}NO_4$: 375.2409. Found: 375.2408. *Anal.* Calcd for $C_{22}H_{23}NO_4$: C 70.35, H 8.86, N 3.73. Found: C 69.94, H 8.74, N 3.95.

*N*-[(3*S*,4*S*,5*S*)-(*E*)Benzyloxymethoxy-4-*tert*-butyldimethylsilyloxy-3,5-dimethyloct-6-enoyl]pyrrolidine (**48**) —— A mixture of the alcohol (**47**) (38.4 mg, 0.10 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.05 ml, 0.03 mmol) and 2,6-lutidine (0.05 ml, 0.41 mmol) was stirred at room temperature for 10 min and the mixture was treated with saturated aqueous $NaHCO_3$ (2 ml) and extracted with $Et_2O$. The extract was washed with 5% hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:3 v/v) as eluent to give the silyl ether (**48**) (34.0 mg, 68%) as a colorless oil accompanied by the lactone (**46**) (6.3 mg, 26%); $[\alpha]_D^{24}$ –21.25° (*c* 0.89, $CHCl_3$). Ir (film) $\nu_{max}$: 1640 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.34 (s, 5H), 5.93-5.34 (m, 2H), 4.76 (s, 2H), 4.61 (s, 2H), 4.07 (d, *J*=5.2 Hz, 2H), 3.58-3.23 (m, 5H), 2.60-1.65 (m, 8H), 1.10-0.85 (m, 6H), 0.92 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ms (m/z): 489 ($M^+$), 284 (100%). Exact Mass Calcd for $C_{28}H_{47}NO_4Si$: 489.3280. Found: 489.3274. *Anal.* Calcd for $C_{24}H_{47}NO_4Si$: C 68.67, H 9.68, N 2.86. Found: C 68.93, H 9.79, N 2.99.

(4*S*,5*S*,6*S*)-(*E*)-9-Benzyloxymethoxy-5-*tert*-butyldimethylsilyloxy-4,6-dimethylnon-7-enyl-2-one (The Suzuki-Tsuchihashi $C_{1\text{-}8}$ Segment) (**6**) ——— To a stirred solution of the amide (**48**) (32.1 mg, 0.07 mmol) in THF (1 ml) was added methyllithium (1.4 M in THF) (0.1 ml, 0.13 mmol) at –78 °C and the stirring was continued for 45 min. The mixture was treated with saturated aqueous $NH_4Cl$ (1 ml) and extracted with $Et_2O$. The extract was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using $Et_2O$-hexane (1:5 v/v) as eluent to give the ketone (**6**) as a colorless oil; $[\alpha]_D^{20}$ –8.79° (*c* 0.91, $CHCl_3$) [lit.,[2b] $[\alpha]_D^{32}$ –9.2° (*c* 1.1, $CHCl_3$)]. Ir (film) $\nu_{max}$: 1770 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.35-7.27 (m, 5H), 5.71 (dd, *J*=15.3, 7.6 Hz, 1H), 5.54 (dtd, *J*=15.3, 6.1, 1.2 Hz, 1H), 4.77 (s, 2H), 4.61 (s, 2H), 4.08 (d, *J*=6.1 Hz, 2H), 3.37 (dd, *J*=5.5, 3.7 Hz, 1H), 2.66 (dd, *J*=15.9, 2.4 Hz, 1H), 2.35 (sext, *J*=6.7 Hz, 1H), 2.20 (m, 1H), 2.15 (dd, *J*=15.9, 9.8 Hz, 1H), 2.09 (s, 3H), 1.01 (d, *J*=6.7 Hz, 3H), 0.91 (s, 9H), 0.89 (d, *J*=6.7 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ms (m/z): 349 ($M^+$-$C_5H_9O$), 229 (100%). Spectral data were virtually identical with those reported by Suzuki and Tsuchihashi.[6]

(3*R*,4*S*)-(*E*)-7-Benzyloxymethoxy-3-*tert*-butyldimethylsilyloxy-4-methyl-hept-5-ene (**49**) ——— A mixture of the alcohol (**30**) (152.3 mg, 0.59 mmol), benzyloxymethyl chloride (0.25 ml, 1.77 mmol), and ethyldiisopropylamine (0.51 ml, 2.95 mmol) in $CH_2Cl_2$ (3 ml) was stirred at room temperature for 11.5 h. The mixture diluted with ether was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (15 g) using $Et_2O$-hexane (1:100 v/v) as eluent to give the silyl ether (**49**) (223.1 mg, 100%) as a colorless oil; $[\alpha]_D^{29}$ –3.59° (*c* 1.00, $CHCl_3$). Ir (film) $\nu_{max}$: 1250, 1100, 855, 770, 695 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.34 (s, 5H), 5.88-5.33 (m, 2H), 4.77 (s, 2H), 4.62 (s, 2H), 4.08 (d, *J*=5.1 Hz, 2H), 3.45 (td, *J*=5.9, 4.2 Hz, 1H), 2.32 (m, 1H), 1.51-1.21 (m, 2H), 0.99 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, *J*=7.6 Hz, 3H), 0.03 (s, 6H); ms (m/z): 349 ($M^+$-$C_2H_5$), 173 (100%). Exact Mass Calcd for $C_{20}H_{23}O_2Si$ ($M^+$-$C_2H_5$): 349.2199. Found: 349.2220.

(3*R*,4*S*)-(*E*)-7-Benzyloxymethoxy-4-methylhept-5-en-1-ol (The Suzuki-Tsuchihashi $C_{11-17}$ Segment) (**7**) ——— A mixture of the bis-ether (**49**) (174.0 mg, 0.46 mmol) and tetra-*n*-butylammonium fluoride (1 M in THF) (1.84 ml, 1.84 mmol) in THF (3 ml) was stirred at room temperature for 19.5 h. The mixture diluted with $Et_2O$ was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (8 g) using $Et_2O$-hexane (1:4 v/v) as eluent to give the secondary alcohol (**7**) (92.2 mg, 80%) as a colorless oil; $[\alpha]_D^{30}$ –9.75° (*c* 1.30, $CHCl_3$) [lit.,[2b] $[\alpha]_D^{21}$ –9.6° (*c* 1.3, $CHCl_3$)]. Ir (film) $\nu_{max}$: 3470 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 7.35 (s, 5H), 5.71-5.61 (m, 2H), 4.78 (s, 2H), 4.62 (s, 2H), 4.10 (d, *J*=4.3 Hz, 2H), 3.33 (m, 1H), 2.25 (sext, *J*=6.5 Hz, 1H), 1.72-1.49 (m, 2H, 1H exchangeable with $D_2O$), 1.45-1.34 (m, 1H), 1.04 (d, *J*=7.3 Hz, 3H), 0.96 (t, *J*=7.3 Hz, 3H); ms (m/z): 265 ($M^+$), 68 (100%). Spectral data were identical with those reported.[6,18]

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