trimethylsilyl chloride (.22 mL, 1.73 mmol) were added. After 20 min CH_2Cl_2 (30 mL) was added, the solution was washed with 1 M aqueous Na_2HPO_4/KH_2PO_4 (20 mL), the aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phase was dried, filtered, and evaporated to give the crude silyl enol ethers (436 mg, 90% yield). These ethers and $Pd(OAc)_2$ (367 mg) in CH_3CN (16 mL) were stirred for 42 h, during which time a Pd mirror formed. Filtration through silica (EtOAc/hexane, 33/67) followed by MPLC (EtOAc/hexane, 1/4) gave pure **27d** (72 mg, 19% recovery), a 1/4 mixture of **27d** and **28d** (46 mg, 12% recovery), and after distillation Boc-anatoxin (**32b**, 154 mg, 41% yield): bp 110 °C (0.10 torr); TLC (EtOAc/hexane, 25/75) R_f 0.22; IR 1691, 1667, 1400 cm^{-1}; ^1H NMR δ 1.36, 1.43 (9 H, s), 1.60–1.80 (3 H, m), 2.00–2.55 (5 H, m), 2.28 (3 H, s), 4.25–4.45 (1 H, m), 5.15–5.25 (1 H, m), 6.82 (1 H, t, J = 5.9 Hz); (1*S*)-**32b**; $[\alpha]^{24}_D$ +51.9° (*c* 0.795, CH_2Cl_2); (1*R*)-**32b**, $[\alpha]^{24}_D$ −47.2° (*c* 0.839, CH_2Cl_2); ^{13}C NMR δ 23.9, 25.2, 28.2, 28.5, 30.1, 31.2, 32.3, 52.8, 55.5, 79.0, 142.0, 150.1, 152.9, 197.5. Anal. ($C_{15}H_{23}NO_3$) C, H, N.

2-Acetyl-9-azabicyclo[4.2.1]-2-nonene [(1*S*)-2 and (1*R*)-1]. A solution of Boc-anatoxin (**32b**, 39 mg, 0.147 mmol) and trifluoroacetic acid (0.39 mL) in CH_2Cl_2 (5 mL) was stirred for 1 h, the solution was poured into cold saturated aqueous $NaHCO_3$ (10 mL); then $CHCl_3$ (20 mL) and 1 M aqueous K_2CO_3 (20 mL) were added. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The organic phases were dried and filtered. This solution could be evaporated to give the free base. Alternatively a 1.2 M ethanolic HCl solution (1.5 mL) was added; the solution was stirred briefly, evaporated, and dried (25 °C, 0.10 torr, 15 h) to give anatoxin-*a* hydrochloride as a glass (29 mg, 97% yield). Anatoxin (free base): TLC ($MeOH/CHCl_3$, 10/90) R_f 0.05 (streaking); ^1H NMR δ 1.50–2.25 (7 H, m), 2.28 (3 H, s), 2.40–2.55 (2 H, m), 3.70–3.83 (1 H, m), 4.65 (1 H, d, J = 8.5 Hz), 6.88 (1 H, ddd, J = 1.2, 4.8, 7.0 Hz). Anatoxin hydrochloride: TLC ($MeOH/CHCl_3$, 10/90) R_f 0.05–0.12; UV (absolute EtOH) λ_{max} 226 nm, ϵ 10 700 (lit.[4c] UV (95% EtOH) λ_{max} 226 nm, ϵ 8500); ^1H NMR δ 1.75–2.00 (3 H, m), 2.20–2.75 (5 H, m), 2.32 (3 H, s), 4.27–4.40 (1 H, m), 5.15–5.25 (1 H, m), 7.12 (1 H, dd, J = 3.7, 7.7 Hz), 9.30–9.50 (1 H, s), 9.85–1 0.05 (1 H, s); ^{13}C NMR δ 23.6, 25.2, 27.5, 27.8, 30.3, 52.1, 58.3, 143.8, 145.4, 196.4; (1*S*)-2, $[\alpha]^{23}_D$ −46.3 (*c* 0.574, absolute EtOH); (1*R*-**1**, $[\alpha]^{24}_D$ +43.2 (*c* 0.676, absolute EtOH) [lit.[4c] $[\alpha]^{24}_D$ +36° (*c* 0.85, EtOH)].

2-Acetyl-9-azabicyclo[4.2.1]nonane [(1*S*)-27b,28b and (1*R*)-27b,28b] Hydrochloride. Boc-dihydroanatoxin (**27d/28d**, 148 mg) was converted to a 3/1 mixture of β- and α-dihydroanatoxin hydrochlorides (106 mg, 94% yield) by use of the procedure described for Boc-anatoxin. The amorphous solid was recrystallized from CH_2Cl_2/EtOAc to give pure β-dihydroanatoxin (**28b**) hydrochloride: mp 170–172 °C; TLC ($MeOH/CHCl_3$, 10/90) R_f 0.10–0.20 (streaking); ^1H NMR δ 1.50–2.40 (10 H, m), 2.17 (3 H, s), 2.62 (1 H, dd), 4.20–4.35 (1 H, m), 4.60–4.75 (1 H, m), 9.00–9.20 (1 H, s), 10.00–10.20 (1 H, s); ^{13}C NMR δ 21.5, 26.7, 27.1, 27.7, 30.9, 31.1, 55.4, 55.8, 58.1, 207.7. α-Dihydroanatoxin (**27b**) hydrochloride: TLC ($MeOH/CHCl_3$, 1/9, R_f 0.23–0.27); ^1H NMR δ 2.20 (s), 3.35–3.50 (m); ^{13}C NMR δ 21.5, 24.3, 24.6, 28.9, 31.2, 31.4, 52.7, 56.5, 57.6, 207.4.

2-Acetyl-9-(methoxy(trifluoromethyl)phenylacetyl)-9-azabicyclo-[4.2.1]-2-nonene [(1*S*)-32c and (1*R*)-32c]. A solution of anatoxin (from Boc-anatoxin, 45 mg, 0.17 mmol) and *N*-methylmorpholine (0.04 mL) was added to a solution of (−)-MTPA chloride[38] (75 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 1.5 h, CH_2Cl_2 (25 mL) was added, the solution was washed with 0.5 M aqueous H_3PO_4 (20 mL), the aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phase was dried, filtered, and evaporated to an oil. The diastereomeric ratio was determined by ^1H NMR and HPLC of this material. Column chromatography (EtOAc/hexane, 1/2) gives the pure amide **32c** (51 mg, 79% yield). Amide **32c** from (+)-anatoxin: TLC (EtOAc/hexane, 1/2) R_f 0.21; HPLC (CH_3CN/H_2O, 45/55, Ultrasphere (ODS 5 RP, 1.5 mL/min) t_R 18.6 min, 6.5% minor diastereomer; ^1H NMR δ 1.20–2.60 (8 H, m), 2.26, 2.35 (3 H, s), 3.60–3.70 (3 H, m), 4.70–4.90 (1 H, m) 4.93–5.04 (1 H, m), 6.70–6.78 (m) and 6.84 (t, J = 5.4 Hz) total 1 H, 7.35–7.60 (5 H, m). Anal. ($C_{20}H_{22}F_3NO_3$) C, H, N. Amide **32c** from (−)-anatoxin: TLC (EtOAc/hexane, 1/2) R_f 0.21; HPLC (as above) t_R 15.1 min, 2% minor diastereomer; ^1H NMR δ 1.50–2.55 (8 H, m), 1.77 (3 H, s), 3.70 (3 H, q, J = 2.4 Hz), 4.70–4.85 (1 H, m), 5.47 (1 H, d), 6.27 (1 H, t, J = 5.5 Hz), 7.20–7.60 (5 H, m). Anal. ($C_{20}H_{22}F_3NO_3$) C, H, N.

Stereocontrolled Total Synthesis of (−)-Picrotoxinin and (+)-Coriamyrtin via a Common Isotwistane Intermediate

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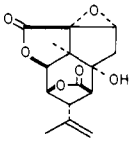
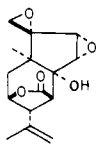
Abstract: Stereocontrolled total synthesis of (−)-picrotoxinin (**1**) and (+)-coriamyrtin (**2**), toxic sesquiterpenoids of plant origin, is described, utilizing isotwistane compounds as common and key intermediates.

Picrotoxin, the poisonous principle isolated first in 1811 from the plant *Menispermum cocculus*,[1] is a molecular compound composed of toxic picrotoxinin (**1**) and nontoxic picrotin. It took about 150 years for the complex structure of **1** to be elucidated.[2] Picrotoxinin (**1**) has been known not only as one of the most toxic compounds of plant origin but also as the substance indispensable to the neuropharmacological studies.[3] Coriamyrtin (**2**), the toxin isolated initially in 1864 from the European *Coriaria* species[4a] and later from the same species native in Japan,[4b] belongs to the picrotoxane group, and the unique structure **2** was established in 1964.[5] The biological properties of **2** are known to be similar to those of **1**.[6] Total synthesis of (−)-**1**[7] and (−)-picrotin[8] by Corey and Pearce was reported in 1979 and in 1980, respectively, and that of racemic **2**[9] by Inubushi et al. in 1982.



1



2

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(2) (a) Conroy, H. *J. Am. Chem. Soc.* **1951**, *73*, 1889; **1952**, *74*, 491, 3046; **1957**, *79*, 1726, 5550. (b) Craven, B. M. *Tetrahedron Lett.* **1960**, *No. 19*, 21.
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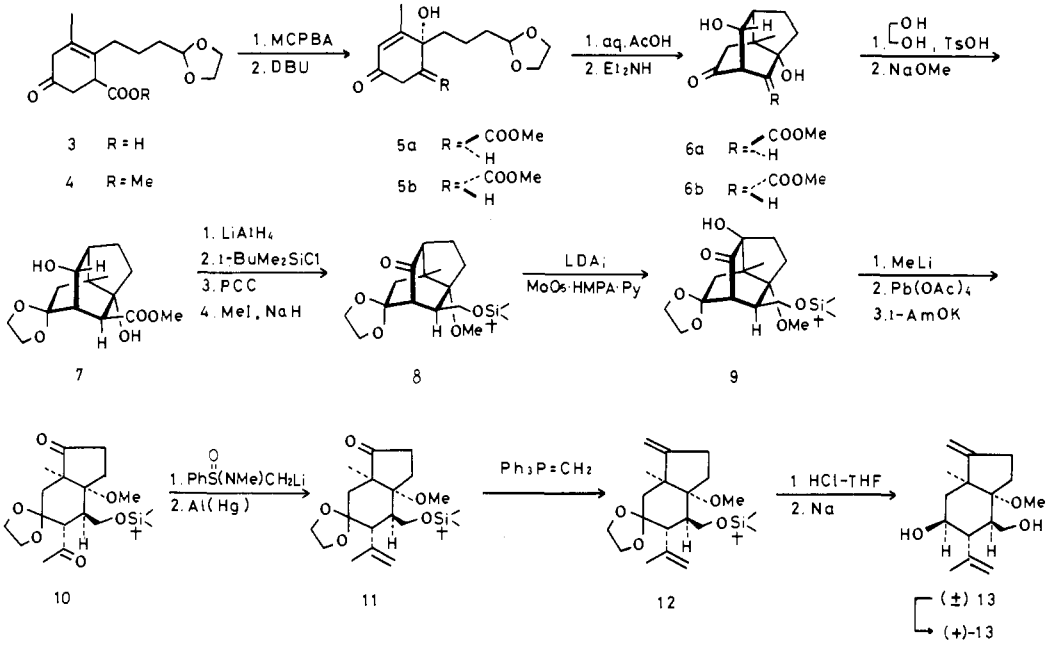
Scheme I



Described herein is the stereocontrolled total synthesis of (−)-**1** and (+)-**2** via a common isotwistane intermediate, using a novel bridgehead hydroxylation of the bicyclo[3.2.1]octan-2-one part included in the isotwistane skeleton as one of the key steps.

A carboxylic acid **3**[10] was esterified (CH_2N_2) and the ester **4** was converted by epoxidation with MCPBA in CH_2Cl_2 and subsequent treatment with DBU in benzene into a separable 3:1 mixture of diastereomeric conjugated enones, **5a** and **5b** (78%). Deacetalization of the mixture of **5a** and **5b** followed by double cyclization with diethylamine in aqueous MeOH provided a separable 6:5 mixture of epimeric keto esters having the isotwistane skeleton, **6a** and **6b** (98% from **5**). The NMR spectral data of **6a** and **6b** suggested the indicated stereochemical assignments. Separation of **6a** and **6b** was not necessary, since the mixture of **6a** and **6b** could be led to a single compound **7** possessing the desired stereochemistry as to the ester group (51%) by acetalization and subsequent treatment with NaOMe in MeOH. The ester **7** was transformed into ketone **8** in 56% overall yield in four steps: (1) reduction ($LiAlH_4$); (2) *tert*-butyldimethylsilylation;[11] (3) oxidation (buffered PCC);[12] and (4) methylation (MeI–NaH, DMF). The bridgehead enolate of **8** was reacted with MoO_5·Py·HMPA[13] to give an α-hydroxy ketone **9** (87%).[14] It is worthy of note that success of the bridgehead hydroxylation in **8** is due to the conformational factor: the cyclohexanone ring in the bicyclo[3.2.1]octan-2-one moiety in **8** is locked in the boat form (see i in footnote 15), making generation of the bridgehead enolate favorable.[15] Reaction of **9** with methyllithium in ether gave a 16:1 mixture of diastereomeric 1,2-diols, oxidative cleavage of which with lead tetraacetate in benzene followed by base-catalyzed epimerization[16] (*t*-AmOK, *t*-AmOH–benzene) provided diketone **10** (61%).[17] Although simultaneous methylenation of both keto groups in **10** in a single step was examined, the desired diolefin **12** was obtained in quite low yield. Methylenation of the methyl ketone group in **10** was effected by the Johnson method[18] to give keto olefin **11** (67%), the Wittig reaction of which under the Conia conditions[19] provided **12** (87%). Conversion of **12** into diol **13** was executed in 89% yield by the following two-step sequence: (1) simultaneous deacetalization and desilylation under the acidic conditions and (2) stereospecific reduction of the keto group by sodium (EtOH, wet Et_2O).[20] It should be noted that reduction of the keto group in the deacetalization compound of **12** with a variety of complex metal hydrides [$LiAlH_4$, $LiAlH(t\text{-}BuO)_3$, DIBAL, L-Selectride (Aldrich) etc.] yielded exclusively a diastereomer of **13** regarding the secondary hydroxyl group. Optical resolution of **13** was conducted by the following sequence: (1) conversion of **13** [(+)-$PhCCF_3(OMe)COCl$] into diastereomeric bis-MTPA esters followed by chromatographic separation and (2) reduction of the ester ($LiAlH_4$) to give (+)-**13** [29% from (±)-**13**].

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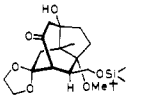
(14) Without protection of the *tert*-hydroxyl group in 7 as methyl ether, the bridgehead hydroxylation proceeded in very poor yield.
(15) In contrast to **8**, no bridgehead hydroxylation occurred in the conformationally flexible bicyclo[3.2.1]octan-2-one (ii) under conditions **8** → **9**. Nickon et al. reported that the bridgehead deuteration took place more readily in the boat-form locked bicyclo[3.2.1]octan-2-one than in the corresponding, conformationally flexible one: Nickon, A.; Covey, D. F.; Huang, F.-c.; Kuo, Y.-N. *J. Am. Chem. Soc.* **1975**, *97*, 904.

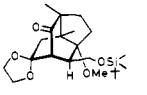
i ii

(16) Epimerization employing sodium methoxide (MeOH, 25 °C) was examined, resulting in the preferential formation of the intramolecular aldol product (iii) and its desilylated derivative.



iii

(17) The approach for effecting the C–C bond cleavage of the isotwistane skeleton by a method other than that described (**8** → **9** → **10**) was also investigated: bridgehead methylation of **8** (LDA; MeI, THF, −78 °C) afforded a ketone (iv), Baeyer–Villiger oxidation of which was attempted under various conditions only to recover iv.



iv

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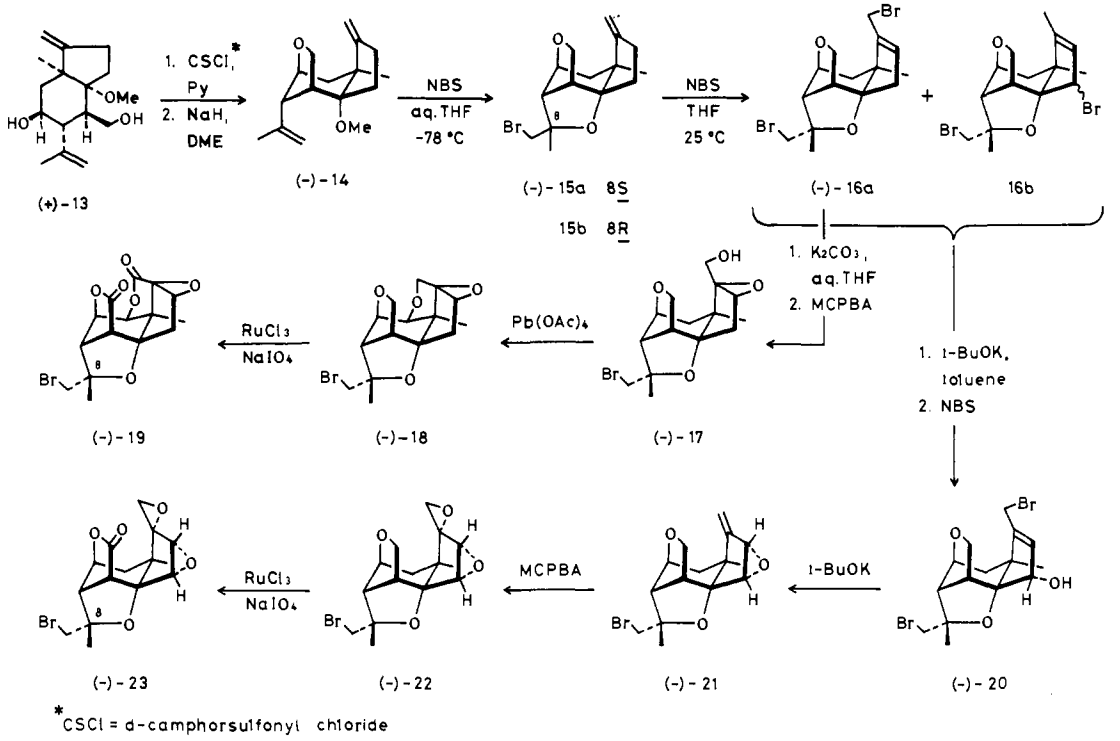
(20) In the second step of the conversion, **12** → **13**, immediate neutralization of bases produced during reduction by ion-exchange resin IRC-50 was vital, since a trace amount of such bases catalyzed isomerization of the isopropenyl to the isopropylidene group.

Scheme II



Conversion of (+)-**13** into cyclic ether (-)-**14** was carried out in 65% yield by selective sulfonylation[21] of the primary hydroxyl group with *d*-camphorsulfonyl chloride in pyridine and subsequent intramolecular S_N2 displacement with NaH in DME. When (-)-**14** was subjected to the action of *N*-bromosuccinimide (NBS) in aqueous THF at −78 °C, formation of the bromo ether with concomitant cleavage of the methyl ether grouping occurred, providing a mixture of two epimeric bromo ethers (-)-**15a** (37%) and **15b**[22] (28%), from which (-)-**15a** was separated. Further treatment of (-)-**15a** with NBS in THF at 25 °C gave a separable mixture of dibromides (-)-**16a** (40%) and **16b** (two epimers, 31%). Transformation of (-)-**16a** into epoxide (-)-**17** was achieved in 67% overall yield in two steps: (1) hydrolysis (K_2CO_3, aqueous THF) to the allylic alcohol and (2) epoxidation (MCPBA). Oxidative cyclization of (-)-**17** was effected with lead tetraacetate in benzene at reflux to give an epoxy cyclic ether (-)-**18** in 41% yield. Ruthenium tetraoxide (RuO_4) oxidation[23] of (-)-**18** at 50 °C under the buffered conditions gave bromo dilactone (-)-**19** (36%), which was identical with (-)-β-bromopicrotoxinin[2b,24] obtained from natural **1**. Reduction of (-)-**19** with zinc powder yielded synthetic (-)-picrotoxinin (**1**) in 99% yield, identity of which with natural **1**[24] was secured by spectral (IR, ^1H NMR, MS, $[\alpha]_D$) and chromatographic comparison.

The mixture of dibromides (-)-**16a** and **16b**, without separation, was dehydrobrominated with *t*-BuOK in toluene at reflux to give a conjugated diene, which was then treated with NBS in aqueous THF affording allylic alcohol (-)-**20** as a sole product in 43% overall yield. Action of *t*-BuOK on (-)-**20** in toluene at 70 °C provided allylic epoxide (-)-**21** (82%), which on oxidation with MCPBA in CH_2Cl_2 yielded diepoxide (-)-**22** (54%). The RuO_4 oxidation of (-)-**22** under the buffered conditions afforded in 58% yield diepoxy lactone (-)-**23**, identical with (-)-α-bromocoriamyrtin[25] derived from natural **2**. Reduction of (-)-**23** with zinc powder provided synthetic (+)-coriamyrtin (**2**) in 99% yield and proved to be identical with natural **2**[4b] by spectral (IR, ^1H NMR, MS, $[\alpha]_D$) and chromatographic comparison.

Experimental Section[26]

Conjugated Enones 5a and 5b. Treatment of **3**[10] with ethereal CH_2N_2 gave **4** as an oil quantitatively. Epoxidation of **4** (520 mg, 1.84 mmol) with MCPBA (432 mg, 2.50 mmol) in CH_2Cl_2 (14 mL) at −20 °C for 3 h gave an oily product, which was treated with DBU (0.44 mL, 2.95 mmol) in benzene (22 mL) at room temperature to afford an oily mixture. Column chromatography on silica gel (1:1 hexane–EtOAc) gave 429 mg (78%) of a 3:1 mixture of **5a** and **5b**. Separation of the mixture by preparative TLC (3:1 $CHCl_3$–ether, developed twice) gave **5a** and **5b** as a colorless oil, respectively. **5a**: IR 3500, 1740, 1715, 1670, 1630 cm^{-1}; ^1H NMR δ 2.07 (d, J = 1.5 Hz, 3 H), 2.60–3.00 (m, 2 H), 3.23 (dd, J = 12.0, 7.0 Hz, 1 H), 3.80 (s, 3 H), 3.80–4.00 (m, 4 H), 4.02 (s, 1 H, OH), 4.83 (br t, J = 4.5 Hz, 1 H), 5.84 (m, 1 H); m/e calcd for $C_{15}H_{22}O_6$ (M^+) 298.1410, found 298.1427. **5b**: IR 3470, 1740, 1710, 1670, 1620 cm^{-1}; ^1H NMR δ 2.03 (d, J = 1.5 Hz, 3 H), 2.64 (dd, J = 17.5, 5.5 Hz, 1 H), 2.98 (ddd, J = 17.5, 3.5, 1.0 Hz, 1 H), 3.23 (dd, J = 5.5, 3.5 Hz, 1 H), 3.72 (s, 3 H), 3.80–4.00 (m, 4 H), 4.63 (s, 1 H, OH), 4.87 (br t, J = 4.5 Hz, 1 H), 5.79 (m, 1 H); m/e calcd for $C_{15}H_{22}O_6$ (M^+) 298.1410, found 298.1413.

Keto Esters 6a and 6b. A solution of a mixture of **5a** and **5b** (626 mg, 2.10 mmol) in AcOH (33 mL) and H_2O (11 mL) was stirred for 4 h at 45 °C. Normal workup gave a crude oily product (560 mg), which was dissolved in MeOH (57 mL) and H_2O (2.8 mL). To the stirred solution was added Et_2NH (2.8 mL, 27.1 mmol), and the mixture was stirred for 13 h at room temperature. Normal workup afforded a 6:5 mixture of two diastereomers **6a** and **6b** almost quantitatively. Recrystallization from EtOH provided 107 mg (20%) of **6a**: the residue obtained on evaporation of the mother liquor was separated by preparative TLC (1:1 benzene–acetone) to give an additional 176 mg (33%) of **6a** for a total yield of 283 mg (53%) and 240 mg (45%) of **6b**, respectively. **6a**: mp

(21) When TsCl or MsCl was employed, selective monosulfonylation at the primary hydroxyl group of (+)-**13** could not be achieved.

(22) The isomer **15b** was also conveniently converted into (-)-**1** and (+)-**2** via α-bromopicrotoxinin (the C-8 epimer of (-)-**19**) and β-bromocoriamyrtin (the C-8 epimer of (-)-**23**), respectively, in comparable yields by employing the same sequence of reactions as in the case of (-)-**15a**.

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(26) IR spectra were obtained with a JASCO Model IRS spectrophotometer in $CHCl_3$ solution unless otherwise noted. ^1H NMR spectra were measured at 90 MHz on a JEOL FX-90QE spectrometer in $CDCl_3$ unless otherwise indicated. Mass spectra were recorded on a Hitachi RMU-6C spectrometer and on a JEOL JMS-DX300 instrument. Optical rotations were measured with a JASCO DIP-4 polarimeter. Fuji-Davison silica gel BW-80 was employed for column chromatography. Merck precoated silica gel 60F254 plates were used for thin-layer chromatography (TLC) and Merck silica gel PF254 for preparative thin-layer chromatography. Melting points are not corrected.

195 °C dec; IR (KBr) 3430, 1726 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.99 (s, 3 H), 2.16 (d, J = 19.1 Hz, 1 H), 2.40 (d, J = 19.1 Hz, 1 H), 2.62 (br d, J = 5.0 Hz, 1 H), 2.83 (br s, 1 H), 3.71 (s, 3 H), 4.20 (d, J = 5.0 Hz, 1 H); m/e calcd for $C_{13}H_{18}O_5$ (M^+) 254.1149, found 254.1172. **6b**: amorphous solid; IR (KBr) 3440, 1733 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.96 (s, 3 H), 2.06 (d, J = 19.5 Hz, 1 H), 2.49 (d, J = 19.5 Hz, 1 H), 2.52 (d d, J = 5.0, 2.5 Hz, 1 H), 2.95 (d, J = 2.5 Hz, 1 H), 3.42 (d, J = 5.0 Hz, 1 H), 3.63 (s, 3 H); mass spectrum m/e (relative intensity) 254 (M^+, 64), 239 (11), 236 (37), 222 (22), 207 (22), 204 (46), 121 (100).

Ester 7. Acetalization of the mixture of **6a** and **6b** (355 mg, 1.40 mmol) with ethylene glycol and p-toluenesulfonic acid in benzene at reflux under a Dean-Stark trap gave a crude oily mixture of acetals (415 mg), which was dissolved in a 0.45 M solution of NaOMe in MeOH (1.50 mL) and the solution stirred for 6 h at room temperature. Amberlite IRC-50 (acid form, 640 mg) was added, and the mixture was passed through a column of Amberlite IRC-50 (640 mg) with MeOH. The combined organic solutions were concentrated to give a viscous oily product. Purification by column chromatography on silica gel (1:1 benzene–ether) gave 212 mg (51%) of **7** as colorless crystals: mp 149.5–150.5 °C (hexane); IR 3480, 1740 cm^{-1}; ^{1}H NMR δ 0.90 (s, 3 H), 1.80 (d, J = 16.2 Hz, 1 H), 2.14 (d, J = 16.2 Hz, 1 H), 2.24 (d, J = 3.5 Hz, 1 H), 2.38 (br s, 1 H, OH), 3.06 (br s, 1 H), 3.74 (s, 3 H), 3.60–4.10 (m, 5 H), 4.34 (d, J = 11.0 Hz, 1 H, OH); m/e calcd for $C_{15}H_{22}O_6$ (M^+) 298.1410, found 298.1439.

Ketone 8. Reduction of **7** (71.0 mg, 0.24 mmol) with $LiAlH_4$ in THF at 0 °C gave an oily triol, the primary hydroxyl group of which was silylated by the procedure of Corey et al.[11] to afford a crude product: purification by column chromatography on silica gel (ether) provided 55.0 mg (60%) of the dihydroxy acetal, mp 123.5–125 °C (ether); IR 3500 cm^{-1}; ^{1}H NMR δ 0.08 (s, 6 H), 0.81 (s, 9 H), 1.74 (d, J = 15.5 Hz, 1H), 2.15 (d, J = 15.5 Hz, 1 H), 3.40 (br d, J = 10.9 Hz, 1 H), 3.60 (d d, J = 10.0, 3.0 Hz, 1 H), 3.70 (d d, J = 10.0, 5.4 Hz, 1 H), 3.80–4.10 (m, 4 H), 4.38 (d, J = 10.9 Hz, 1 H, OH). Subsequently oxidation of the dihydroxy acetal (70.5 mg, 0.18 mmol) was made by buffered PCC,[12] and the resulting crude product was purified by preparative TLC (1:1 benzene–EtOAc) to give 70.1 mg (100%) of the keto acetal as an amorphous solid: IR 3560, 1722 cm^{-1}; ^{1}H NMR δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.00 (s, 3 H), 1.72 (d, J = 15.0 Hz, 1 H), 2.37 (d, J = 15.0 Hz, 1 H), 2.44 (br s, 1 H), 3.40 (d d, J = 10.0, 4.7 Hz, 1 H), 3.60 (d d, J = 10.0, 1.5 Hz, 1 H), 3.70–4.10 (m, 4 H). Finally the tertiary hydroxyl group of the keto acetal (73.6 mg, 0.19 Hz, was methylated with MeI and NaH in DMF at room temperature, and the crude product was purified by preparative TLC (1:1 hexane-ether) to provide 71.8 mg (94%: 56% overal from **7**) of **8**: mp 90–91 °C (hexane); IR 1723 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6 H), 0.88 (s, 9 H), 0.93 (s, 3 H), 1.70 (d, J = 15.0 Hz, 1 H), 2.30 (d, J = 15.0 Hz, 1 H), 2.44 (br s, 1 H), 3.36 (s, 3 H), 3.40 (d d, J = 10.0, 7.0 Hz, 1 H), 3.70 (d d, J = 10.0, 6.0 Hz, 1 H), 3.80–4.10 (m, 4 H); m/e calcd for $C_{21}H_{36}O_5Si$ (M^+) 396.2322, found 396.2340.

α-Hydroxy Ketone 9. A 0.2 M solution of lithium diisopropylamide in THF (1.8 mL, 0.36 mmol) was slowly added to a solution of **8** (33.0 mg, 0.083 mmol) in THF (0.8 mL) at −78 °C with stirring under nitrogen. To the solution was added a molybdenum peroxide reagent[13] (MoO_5·Py·HMPA) (186 mg, 0.428 mmol) at −78 °C. The mixture was allowed to warm to −50 °C and stirred for 1.5 h at −50 °C; a saturated NH_4Cl solution (0.3 mL) was added, and the mixture was warmed to room temperature, diluted with H_2O (1.2 mL), and extracted with ether (4 × 30 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (1:3 hexane–ether) to give 30.0 mg (87%) of crystalline **9**: mp 98–99 °C (hexane); IR 3560, 1733 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6 H), 0.88 (s, 9 H), 0.99 (s, 3 H), 1.78 (d, J = 16.0 Hz, 1 H), 2.12 (d, J = 16.0 Hz, 1 H), 2.44 (t, J = 5.4 Hz, 1 H), 2.48 (br s, 1 H), 2.84 (br s, 1 H, OH), 3.34 (s, 3 H), 3.58 (dd, J = 11.0, 5.4 Hz, 1 H), 3.74 (d d, J = 11.0, 5.4 Hz, 1 H), 3.80–4.10 (m, 4 H); m/e calcd for $C_{21}H_{36}O_6Si$ (M^+) 412.2271, found 412.2276.

Diketone 10. Methyllithium in ether (1.5 mL of 1.45 M, 2.2 mmol) was added to a solution of **9** (44.0 mg, 0.107 mmol) in ether (2.4 mL) at 0 °C under nitrogen. The mixture was stirred for 2 h at room temperature. Normal workup and purification by preparative TLC (1:5 hexane–ether) gave 31.0 mg (68%) of a major diastereomer and 1.9 mg (4%) of a minor one. Properties of the major diastereomer are as follows: mp 80–81 °C (EtOH); IR 3380 cm^{-1}; ^{1}H NMR δ 0.07 (s, 6 H), 0.89 (s, 3 H), 0.90 (s, 9 H), 1.29 (s, 3 H), 1.80 (d, J = 10.0 Hz, 1 H), 1.90 (d, J = 10.0 Hz, 1 H), 2.10 (d, J = 1.5 Hz, 1 H), 2.74 (m, 1 H), 3.30 (s, 3 H), 3.60 (t, J = 10.5 Hz, 1 H), 3.85 (d d, J = 10.5, 7.2 Hz, 1 H), 3.80–4.10 (m, 4 H), 4.24 (s, 1 H, OH), 5.98 (s, 1 H, OH). A mixture of the major diastereomer (24.9 mg, 0.058 mmol) and $Pb(OAc)_4$ (76.8 mg, 0.17 mmol) in benzene (2.5 mL) was stirred for 1 h at room temperature. Normal workup and purification by preparative TLC (2:3 hexane-ether) provided 23.8 mg (96%) of an oxidized product: mp 87–89 °C (hexane); IR 1737, 1718 cm^{-1}; ^{1}H NMR δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.91 (s, 9 H), 1.15 (s, 3 H), 2.28 (s, 3 H), 3.13 (s, 3 H), 3.80–4.00 (m, 4 H). Oxidation of the minor diastereomer with $Pb(OAc)_4$ also afforded the oxidized product described above (95%). To a solution of the oxidized product (13.7 mg, 0.032 mmol) in t-AmOH (0.5 mL) was added t-AmOK in benzene (0.025 mL of 0.68 M, 0.017 mmol). The mixture was stirred for 2 h at room temperature. After normal workup, the crude product was purified by preparative TLC (4:1 $CHCl_3$–EtOAc) to give 12.1 mg (88%) of **10**: mp 153.5–154 °C (hexane); IR 1738, 1716 cm^{-1}; ^{1}H NMR δ 0.01 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 1.20 (s, 3 H), 1.40 (d, J = 14.4 Hz, 1 H), 1.50 (d, J = 14.4 Hz, 1 H), 2.28 (s, 3 H), 2.64 (d d d, J = 11.0, 4.5, 2.0 Hz, 1 H), 3.18 (s, 3 H), 3.42 (d, J = 11.0 Hz, 1 H), 3.50 (d d, J = 10.0, 4.5 Hz, 1 H), 3.70–4.10 (m, 5 H); m/e calcd for $C_{22}H_{38}O_6Si$ (M^+) 426.2427, found 426.2413.

Keto Olefin 11. Olefination of **10** was carried out by the procedure of Johnson.[18] Addition of (*N*-methylphenylsulfonimidoyl)methyllithium (generated by reaction of *N*,*S*-dimethyl-*S*-phenylsulfoximine and butyllithium in THF) to **10** (29.0 mg, 0.068 mmol) was effected in THF at 0 °C to afford a crude β-hydroxysulfoximine as an oil, which, without purification, underwent reductive elimination on treatment with Al–Hg in THF–AcOH–H_2O at room temperature to give crude **11**. Purification by preparative TLC (1:1 hexane–ether) provided 19.3 mg (67%) of **11**: mp 125.5–126 °C (MeOH); IR 3080, 1735, 1630 cm^{-1}; ^{1}H NMR δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.90 (s, 9 H), 1.22 (s, 3 H), 1.43 (br s, 2 H), 1.83 (br s, 3 H), 2.80 (br d, J = 10.5 Hz, 1 H), 3.21 (s, 3 H), 3.65 (d d, J = 10.0, 3.5 Hz, 1 H), 3.70–4.10 (m, 5 H), 4.88 (m, 1 H), 5.02 (m, 1 H); m/e calcd for $C_{23}H_{40}O_5Si$ (M^+) 424.2634, found 424.2649.

Diolefin 12. By the procedure of Conia,[19] **11** (9.2 mg, 0.022 mmol) was reacted at reflux with an ylide generated from methyltriphenylphosphonium bromide and t-AmOK in benzene. Purification by preparative TLC (7:1 hexane–ether) gave 8.0 mg (87%) of **12** as colorless crystals: mp 111–112 °C (MeOH); IR 3080, 1645 cm^{-1}; ^{1}H NMR δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.90 (s, 9 H), 1.26 (s, 3 H), 1.35 (d, J = 14.0 Hz, 1 H), 1.50 (d, J = 14.0 Hz, 1 H), 1.84 (br s, 3 H), 3.30 (s, 3 H), 3.50–4.05 (m, 6 H), 4.75 (m, 2 H), 4.88 (m, 1 H), 4.99 (m, 1 H); m/e calcd for $C_{24}H_{42}O_4Si$ (M^+) 422.2841, found 422.2836.

Diol 13. A solution of **12** (19.9 mg, 0.047 mmol) in 10% HCl (1 mL) and THF (1 mL) was stirred for 3.5 h at room temperature. Normal workup and purification by preparative TLC (4:1 $CHCl_3$–EtOAc) gave 11.8 mg (95%) of a hydroxy ketone: mp 100–101 °C (hexane); IR 3460, 1715, 1648 cm^{-1}; ^{1}H NMR δ 1.15 (s, 3 H), 1.79 (br s, 3 H), 3.36 (s, 3 H), 3.69 (m, 2 H), 4.77 (m, 1 H), 4.86 (m, 2 H), 5.03 (m, 1 H). To a solution of the hydroxy ketone (5.2 mg, 0.020 mmol) in ether saturated with H_2O (2.5 mL) and EtOH (0.13 mL) were added Na (30.0 mg, 1.30 mmol) and Amberlite IRC-50 (acid form, 1 g) at 0 °C. The mixture was stirred for 30 min at 0 °C, diluted with MeOH (4 mL), and stirred for 10 min at room temperature. The mixture was passed through a column of Amberlite IRC-50 (1.5 g) with MeOH. The combined organic solutions were concentrated to give crude crystals. Purification by preparative TLC (1:1 hexane–EtOAc) afforded 4.9 mg (94%) of **13**: mp 105.5–106 °C; IR 3440, 3080, 1649 cm^{-1}; ^{1}H NMR δ 1.23 (s, 3 H), 1.76 (br s, 3 H), 2.60 (m, 1 H), 3.28 (s, 3 H), 3.40–3.80 (m, 3 H), 4.70–4.90 (m, 2 H), 4.85 (m, 1 H), 5.00 (m, 1 H); m/e calcd for $C_{16}H_{26}O_3$ (M^+) 266.1875, found 266.1872.

Optical Resolution of Diol 13. A solution of **13** (6.5 mg, 0.024 mmol), (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[27] (MTPA Cl; 30.0 mg, 0.120 mmol), and 4-(dimethylamino)pyridine (33 mg, 0.27 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 3 h at room temperature. Normal workup and purification by preparative TLC (2:1 hexane–ether) afforded 6.3 mg (37%) of the less polar diastereomer [R_f 0.53 (2:1 hexane–ether)] of bis-MTPA esters and 6.2 mg (36%) of the more polar one [R_f 0.47 (2:1 hexane–ether)] as a viscous oil, respectively. The less polar diastereomer (7.2 mg, 0.010 mmol) was reduced with $LiAlH_4$ in THF at room temperature. Purification by preparative TLC (1:1 hexane–EtOAc) gave 2.1 mg (77%) of (+)-**13**: mp 84–86 °C (hexane); $[\alpha]^{23}_D$ +26° (c 0.61, $CHCl_3$); m/e calcd for $C_{16}H_{26}O_3$ (M^+) 266.1875, found 266.1872.

(−)-Cyclic Ether 14. Treatment of (+)-**13** (6.6 mg, 0.025 mmol) with d-camphorsulfonyl chloride (18.8 mg, 0.075 mmol) in pyridine (0.6 mL) at room temperature for 3 h afforded an oily mixture, which was purified by preparative TLC (1:1 hexane–EtOAc) to give 4.8 mg (83% based on reacted (+)-**13**) of a monosulfonate as a solid and 3.4 mg (52% recovery) of unreacted (+)-**13**. Properties of the monosulfonate are as follows: IR 3560, 1749 cm^{-1}; ^{1}H NMR δ 0.89 (s, 3 H), 1.14 (s, 3 H), 1.18 (s, 3 H), 1.76 (br s, 3 H), 2.91 (d, J = 15.0 Hz, 1 H), 3.28 (s, 3 H), 3.56 (d, J = 15.0 Hz, 1 H), 3.66 (d t, J = 4.5, 10.0 Hz, 1 H), 4.15 (d d, J = 3.0, 10.0 Hz, 1 H), 4.56 (d d, J = 2.5, 10.0 Hz, 1 H), 4.81 (m, 2 H), 5.02 (m, 1 H), 5.11 (m, 1 H). The monosulfonate (6.2 mg, 0.013 mmol) was

(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

treated with NaH in DME at reflux for 6 h. Normal workup and purification by preparative TLC (4:1 hexane–EtOAc) provided 2.5 mg (78%) of **14**: mp 83.5–85 °C (pentane); $[\alpha]^{22}_D$ −2.5° (*c* 0.32, $CHCl_3$); IR 3080, 1640 cm^{-1}; ^1H NMR δ 0.93 (s, 3 H), 1.90 (br s, 3 H), 2.55 (m, 1 H), 2.75 (m, 1 H), 3.26 (s, 3 H), 3.65–3.70 (m, 2 H), 4.35 (dt, *J* = 2.0, 5.0 Hz, 1 H), 4.68 (m, 1 H), 4.79 (dd, *J* = 3.0, 2.8 Hz, 1 H), 4.83 (m, 1 H), 4.93 (dd, *J* = 3.0, 2.8 Hz, 1 H); *m/e* calcd for $C_{16}H_{24}O_2$ (M^+) 248.1770, found 248.1767.

Diastereomeric Bromo Ethers (−)-15a and 15b. Treatment of (−)-**14** (17.0 mg, 0.068 mmol) with NBS (12.6 mg, 0.068 mmol) in THF (4.8 mL) and H_2O (0.4 mL) at −78 °C for 2.5 h gave a crude product. Separation and purification by repeating preparative TLC (3:1 hexane–ether) twice gave 7.9 mg (37%) of (−)-**15a** and 6.0 mg (28%) of **15b**. (−)-**15a**: mp 52–53 °C (hexane); $[\alpha]^{24}_D$ −25.8° (*c* 0.40, $CHCl_3$); IR 3080, 1650 cm^{-1}; ^1H NMR δ 0.99 (s, 3 H), 1.55 (s, 3 H), 3.43 (d, *J* = 10.0 Hz, 1 H), 3.70 (d, *J* = 10.0 Hz, 1 H), 3.77 (d d, *J* = 9.0, 6.0 Hz, 1 H), 4.00 (d, *J* = 9.0 Hz, 1 H), 4.45 (m, 1 H), 4.81 (t, *J* = 2.0 Hz, 1 H), 4.99 (t, *J* = 2.0 Hz, 1 H); *m/e* calcd for $C_{15}H_{21}O_2{}^{79}Br$ (M^+) 312.0719, found 312.0726. **15b**: amorphous solid; ^1H NMR δ 0.98 (s, 3 H), 1.56 (s, 3 H), 3.35 (br s, 2 H), 3.73 (d d, *J* = 9.0, 6.0 Hz, 1 H), 4.01 (d, *J* = 9.0 Hz, 1 H), 4.18 (m, 1 H), 4.78 (m, 1 H), 4.94 (m, 1 H).

Dibromides (−)-16a and 16b. The bromo ether (−)-**15a** (4.6 mg, 0.015 mmol) was treated with NBS (3.1 mg, 0.017 mmol) in THF (0.36 mL) at room temperature for 1 h. Normal workup afforded an oily residue. Separation and purification by preparative TLC (4:1 hexane–EtOAc) provided 2.3 mg (40%) of (−)-**16a** and 1.8 mg (31%) of **16b** as a solid, respectively. (−)-**16a**: $[\alpha]^{27}_D$ −134° (*c* 0.73, $CHCl_3$); IR 1037, 1019 cm^{-1}; ^1H NMR δ 1.22 (s, 3 H), 1.56 (s, 3 H), 1.60 (d d, *J* = 16.0, 3.5 Hz, 1 H), 2.19 (d d, *J* = 16.5, 3.5 Hz, 1 H), 2.25 (br d, *J* = 16.0 Hz, 1 H), 2.55 (t, *J* = 5.0 Hz, 1 H), 2.67 (t, *J* = 5.0 Hz, 1 H), 2.78 (d d, *J* = 16.5, 2.0 Hz, 1 H), 3.48 (d, *J* = 10.0 Hz, 1 H), 3.71 (br d, *J* = 10.0 Hz, 1 H), 3.78 (d d, *J* = 9.0, 5.0 Hz, 1 H), 3.99 (br d, *J* = 9.0 Hz, 1 H), 4.01 (m, 2 H), 4.45 (m, 1 H), 5.76 (m, 1 H); *m/e* calcd for $C_{15}H_{20}O_2{}^{79}Br_2$ (M^+) 389.9824, found 389.9860. **16b**: IR 1040, 1018 cm^{-1}; ^1H NMR δ 1.03 and 1.19 (s each, total 3 H), 1.26 and 1.34 (s each, total 3 H), 1.55 (s, 3 H), 3.42 (d, *J* = 11.0 Hz, 1H), 3.64 (d, *J* = 11.0 Hz, 1 H), 3.60–4.00 (m, 2 H), 4.45 (m, 1 H), 5.53 and 6.07 (m each, total 1 H); MS *m/e* (relative intensity) 394 (M^+ + 4, 15), 392 (M^+ + 2, 30), 390 (M^+, 16), 379 (1), 377 (2), 375 (1), 313 (95), 311 (100).

(−)-**Epoxide 17.** A solution of (−)-**16a** (8.7 mg, 0.022 mmol) in THF (0.8 mL) and 0.25 M aqueous K_2CO_3 (0.4 mL) was stirred for 26 h at 55 °C. Normal workup and purification by preparative TLC (1:4 $CHCl_3$–EtOAc) gave 5.6 mg (77%) of an allylic alcohol as an amorphous solid: IR 3450, 1030, 1024 cm^{-1}; ^1H NMR δ 1.14 (s, 3 H), 1.58 (s, 3 H), 1.90–2.40 (m, 2 H), 2.40–2.95 (m, 3 H), 3.48 (d, *J* = 11.0 Hz, 1 H), 3.72 (d, *J* = 11.0 Hz, 1 H), 3.76 (dd, *J* = 9.0, 5.0 Hz, 1 H), 4.12 (br d, *J* = 9.0 Hz, 1 H), 4.18 (br s, 2 H), 4.45 (m, 1 H), 5.56 (m, 1 H). The allylic alcohol (8.7 mg, 0.026 mmol) was oxidized with MCPBA (14.0 mg, 0.081 mmol) in CH_2Cl_2 (0.52 mL) for 14 h at room temperature. Normal workup and purification by preparative TLC (1:4 $CHCl_3$–EtOAc) provided 7.9 mg (87%) of (−)-**17** as an amorphous solid: $[\alpha]^{26}_D$ −101° (*c* 0.68, $CHCl_3$); IR 3460 cm^{-1}; ^1H NMR δ 1.04 (s, 3 H), 1.53 (s, 3 H), 1.79 (d d, *J* = 4.1, 14.0, Hz, 1 H), 2.05 (br d, *J* = 14.0 Hz, 1 H), 2.22 (br d, *J* = 16.3 Hz, 1 H), 2.57 (t, *J* = 4.9 Hz, 1 H), 2.75 (t, *J* = 4.9 Hz, 1 H), 3.40 (d, *J* = 11.0 Hz, 1 H), 3.53 (br d, *J* = 4.1 Hz, 1 H), 3.65 (br d, *J* = 11.0 Hz, 1 H), 3.85 (dd, *J* = 4.9, 10.0, Hz, 1 H), 4.09 (br d, *J* = 10.0 Hz, 1 H), 3.90–4.10 (m, 2 H), 4.47 (m, 1 H); *m/e* calcd for $C_{15}H_{21}O_4{}^{79}Br$ (M^+) 344.0617, found 344.0636.

(−)-**Epoxy Cyclic Ether 18.** A mixture of (−)-**17** (5.8 mg, 0.017 mmol) and $Pb(OAc)_4$ (8.0 mg, 0.018 mmol) in benzene (0.5 mL) was stirred at reflux for 1 h. After cooling, the mixture was diluted with ether and filtered through a short Florisil column with EtOAc. The combined organic solutions were concentrated to give an oily residue. Purification by preparative TLC (1:4 $CHCl_3$–EtOAc) yielded 2.4 mg (41%) of (−)-**18** as a solid: $[\alpha]^{28}_D$ −89° (*c* 0.33, $CHCl_3$); IR 1057, 1005 cm^{-1}; ^1H NMR δ 1.19 (s, 3 H), 1.53 (s, 3 H), 2.01 (d d, *J* = 14.5, 3.5 Hz, 1 H), 2.24 (d d, *J* = 14.5, 1.5 Hz, 1 H), 2.60–3.00 (m, 2 H), 3.42 (br s, 2 H), 3.59 (d d, *J* = 3.5, 1.5 Hz, 1 H), 3.90–4.10 (m, 2 H), 4.11 (br s, 2 H), 4.28 (d, *J* = 11.0 Hz, 1 H), 4.40–4.60 (m, 1 H); *m/e* calcd for $C_{15}H_{19}O_4{}^{79}Br$ (M^+) 342.0461, found 342.0490.

(−)-**Bromo Dilactone 19 [(−)-β-Bromopicrotoxinin].** A modified Sharpless[23] procedure was employed. A mixture of (−)-**18** (4.6 mg, 0.014 mmol), $NaIO_4$ (64.0 mg, 0.299 mmol), and $RuCl_3{\cdot}H_2O$ (1.8 mg, 0.008 mmol) in CCl_4 (0.2 mL), MeCN (0.2 mL), and phosphate buffer (0.05 M, pH 6.9; 0.3 mL) was stirred at 50 °C for 40 h. During the reaction, $RuCl_3{\cdot}H_2O$ (8.0 mg, 0.036 mmol) was occasionally added in portions. Then H_2O (1 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic solutions were washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated to give an oily residue. Purification by preparative TLC (1:4 $CHCl_3$–EtOAc) provided 1.8 mg (36%) of (−)-**19** as colorless crystals: mp 256 °C dec; $[\alpha]^{28}_D$ −132° (*c* 0.27, $CHCl_3$). The IR, ^1H NMR, and mass spectra and the TLC behaviors of (−)-**19** proved identical with those of (−)-β-bromopicrotoxinin[24] prepared from natural picrotoxinin.

(−)-**Picrotoxinin (1).** By the modified method of Horrmann,[24] (−)-**19** (2.8 mg, 0.008 mmol) was treated with Zn powder and NH_4Cl in EtOH at reflux for 1 h. Normal workup and purification by preparative TLC (1:1 benzene–EtOAc) gave 2.2 mg (99%) of (−)-**1** as colorless crystals: mp 201–202 °C (H_2O); $[\alpha]^{27}_D$ −6.7° (*c* 1.03, $CHCl_3$). The natural sample gave mp 200–202 °C and $[\alpha]^{27}_D$ −6.7° (*c* 1.03, $CHCl_3$). The IR, ^1H NMR, and mass spectra and the TLC behaviors (several solvent systems) of synthetic (−)-**1** proved identical in all respects with those of natural picrotoxinin.

(−)-**Allylic Alcohol 20.** To a solution of the mixture (−)-**16a** and **16b** (10.0 mg, 0.026 mmol) in toluene (2.0 mL) was added *t*-BuOK (60.0 mg, 0.535 mmol) under argon. The mixture was stirred at 110 °C overnight. After cooling, Amberlite IRC-50 (acid form, 1.4 g) was added and the mixture passed through a column of Amberlite IRC-50 (1.4 g). The column was washed with toluene. The combined organic solutions were concentrated to give 7.4 mg (93%) of crystalline conjugated diene: mp 69–71 °C (pentane); IR 1638 cm^{-1}; ^1H NMR δ 1.16 (s, 3 H), 1.58 (s, 3 H), 1.77 (d d, *J* = 16.0, 5.0 Hz, 1 H), 2.43 (br d, *J* = 16.0 Hz, 1 H), 2.61 (t, *J* = 5.0 Hz, 1 H), 2.85 (m, 1 H), 3.52 (d, *J* = 10.0 Hz, 1 H), 3.62 (d, *J* = 8.0 Hz, 1 H), 3.75 (d, *J* = 10.0 Hz, 1 H), 3.76 (d, *J* = 8.0 Hz, 1 H), 4.45 (br t, *J* = 5.0 Hz, 1 H), 4.79 (br s, 1 H), 4.88 (s, 1 H), 5.90 (d d, *J* = 6.0, 1.0 Hz, 1 H), 6.29 (d, *J* = 6.0 Hz, 1 H). The mixture of the conjugated diene (10.5 mg, 0.034 mmol) and NBS (17.8 mg, 0.098 mmol) in THF (1.0 mL) and H_2O (0.1 mL) was stirred at room temperature for 1.5 h. Normal workup and purification by preparative TLC (1:1 benzene–EtOAc) provided 6.4 mg (46%: 43% overall from **16a** and **16b**) of (−)-**20** as a colorless viscous oil: $[\alpha]^{23}_D$ −45.3° (*c* 1.10, $CHCl_3$); IR 3600, 3440, 1052, 1020 cm^{-1}; ^1H NMR δ 1.41 (s, 3 H), 1.59 (d d, *J* = 17.0, 4.0 Hz, 1 H), 1.60 (br s, 3 H), 2.28 (d d, *J* = 17.0, 2.0 Hz, 1 H), 2.67 (m, 2 H), 3.51 (d, *J* = 10.0 Hz, 1 H), 3.70 (d, *J* = 8.0 Hz, 1 H), 3.71 (d, *J* = 10.0 Hz, 1 H), 3.80 (br d, *J* = 8.0 Hz, 1 H), 4.04 (br s, 2 H), 4.22 (d, *J* = 3.0 Hz, 1 H), 4.45 (m, 1 H), 5.98 (m, 1 H); *m/e* calcd for $C_{14}H_{17}O_3{}^{79}Br_2$ ($M^+ - CH_3$) 390.9539, found 390.9575.

(−)-**Allylic Epoxide 21.** A mixture of (−)-**20** (14.0 mg, 0.034 mmol) and *t*-BuOK (28.0 mg, 0.25 mmol) in toluene (1.4 mL) was stirred at 70 °C for 1 h. The workup as described for the preparation of (−)-**20** and purification by preparative TLC (4:1 benzene–EtOAc) afforded 9.2 mg (82%) of (−)-**21** as colorless crystals: mp 134–135 °C (hexane); $[\alpha]^{23}_D$ −154° (*c* 0.77, $CHCl_3$); IR 1660, 1035 cm^{-1}; ^1H NMR δ 1.21 (s, 3 H), 1.59 (d d, *J* = 16.0, 4.5 Hz, 1 H), 1.60 (s, 3 H), 2.30 (d d, *J* = 16.0, 2.0 Hz, 1 H), 2.60 (t, *J* = 5.0 Hz, 1 H), 2.93 (d d d, *J* = 6.0, 5.0, 2.0 Hz, 1 H), 3.46 (d, *J* = 10.0 Hz, 1 H), 3.49 (d, *J* = 3.0 Hz, 1 H), 3.66 (d d, *J* = 9.0, 6.0 Hz, 1 H), 3.70 (d, *J* = 10.0 Hz, 1 H), 3.74 (d, *J* = 3.0 Hz, 1 H), 3.84 (d d, *J* = 9.0, 2.0 Hz, 1 H), 4.39 (d d d, *J* = 5.0, 4.5, 2.0 Hz, 1 H), 5.22 (s, 1 H), 5.32 (s, 1 H); *m/e* calcd for $C_{15}H_{19}O_3{}^{79}Br$ (M^+) 326.0512, found 326.0490.

(−)-**Diepoxide 22.** The allylic epoxide (−)-**21** (4.0 mg, 0.012 mmol) was oxidized with MCPBA (11.0 mg, 0.062 mmol) in CH_2Cl_2 (2.4 mL) for 39 h at room temperature. Normal workup and purification by preparative TLC (2:1 benzene–EtOAc) afforded 2.3 mg (54%) of (−)-**22** as colorless crystals: mp 126–127 °C (hexane); $[\alpha]^{22}_D$ −89.3° (*c* 0.14, $CHCl_3$); IR 1055, 1040, 1020 cm^{-1}; ^1H NMR δ 1.27 (s, 3 H), 1.62 (s, 3 H), 2.64 (d d, *J* = 4.9, 5.1 Hz, 1 H), 2.92 (d, *J* = 4.2 Hz, 1 H), 2.92 (m, 1 H), 3.17 (d, *J* = 4.2 Hz, 1 H), 3.27 (d, *J* = 3.1 Hz, 1 H), 3.46 (d, *J* = 10.1 Hz, 1 H), 3.50 (d, *J* = 3.1 Hz, 1 H), 3.68 (d, *J* = 10.1 Hz, 1 H), 3.83–3.87 (m, 2 H), 4.41 (m, 1 H); *m/e* calcd for $C_{15}H_{19}O_4{}^{79}Br$ (M^+) 342.0461, found 342.0444.

(−)-**Diepoxy Lactone 23 [(−)-α-Bromocoriamyrtin].** A mixture of (−)-**22** (2.0 mg, 0.006 mmol), $NaIO_4$ (20 mg, 0.094 mmol), and $RuCl_3{\cdot}H_2O$ (14.1 mg, 0.063 mmol) in CCl_4 (0.86 mL), MeCN (0.86 mL), and phosphate buffer (0.05 M, pH 6.9; 1.33 mL) was stirred for 39 h at room temperature. During the reaction, $RuCl_3{\cdot}H_2O$ (21.0 mg, 0.093 mmol) and $NaIO_4$ (30 mg, 0.14 mmol) were occasionally added in portions, respectively. The workup as described for the preparation of (−)-**19** and purification by preparative TLC (2:1 benzene–EtOAc) gave 1.2 mg (58%) of (−)-**23** as colorless crystals, mp 219–221 °C (EtOH); $[\alpha]^{26}_D$ −132° (*c* 1.10, $CHCl_3$). The IR, ^1H NMR, and mass spectra and the TLC behaviors of (−)-**23** proved identical with those of (−)-α-bromocoriamyrtin[25] prepared from natural coriamyrtin.

(+)-**Coriamyrtin 2.** As described for the conversion of (−)-**19** to (−)-**1**, (−)-**23** (4.0 mg, 0.011 mmol) was converted to (+)-**2**. Purification by preparative TLC (3:1 $CHCl_3$–EtOAc) provided 3.1 mg (99%) of (+)-**2** as colorless crystals, mp 228–231 °C (EtOH); $[\alpha]^{25}_D$ +55° (*c* 0.20, EtOH). The natural sample gave mp 227–231 °C and $[\alpha]^{25}_D$ +55° (*c* 0.20, EtOH). The IR, ^1H NMR, and mass spectra and the TLC behaviors (several solvent systems) of synthetic **2** proved identical in all

respects with those of natural coriamyrtin.

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Registry No. (-)-**1**, 17617-45-7; (+)-**2**, 2571-86-0; (±)-**3**, 90742-33-9; (±)-**4**, 90122-93-3; (±)-**5a**, 90122-94-4; (±)-**5b**, 90122-95-5; (±)-**6a**, 90821-12-8; (±)-**6b**, 90821-13-9; (±)-**7**, 90821-14-0; (±)-**8**, 90123-00-5; (±)-**9**, 90123-01-6; (±)-**10**, 90192-36-2; (±)-**11**, 90742-34-0; (±)-**12**, 90123-03-8; (±)-**13**, 90123-05-0; (+)-**13**, 90192-37-3; (-)-**14**, 90123-06-1; (-)-**15a**, 90123-07-2; **15b**, 90192-38-4; (-)-**16a**, 90123-08-3; **16b** (isomer 1), 90821-87-7; **16b** (isomer 2), 90821-15-1; (-)-**17**, 90742-35-1; (-)-**18**, 90123-10-7; (-)-**19**, 20744-71-2; (-)-**20**, 90123-12-9; (-)-**21**, 90123-13-0; (-)-**22**, 90123-14-1; (±)-**23**, 90192-39-5; (±)-ii, 61242-43-1; (±)-iii, 90742-36-2.

Synthesis of a Dodecaribonucleotide, GUAUCAAUAAAUG, by Use of "Fully" Protected Ribonucleotide Building Blocks

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Abstract: The fully protected ribonucleotide monomer units (**17**, **19**, **26**, and **32**) have been synthesized in excellent overall yields from unprotected ribonucleosides. Several carbamoyl groups were tested for protection of the guanosine base moiety. Finally, the diphenylcarbamoyl group was chosen and O^6-(diphenylcarbamoyl)-N^2-propionylguanosine was readily prepared in high yield and converted to the guanosine units **12** and **17**. The uridine unit **19** was prepared by the acylation of the previous unit **18** with anisoyl chloride in the presence of i-Pr_2EtN. In the case of the adenosine and cytidine units (**26** and **32**), the regioselective 2'-O-tetrahydropyranylation was involved in their syntheses. These "perfectly" protected monomer units have successfully been utilized in the synthesis of GUAUCAAUAAAUG, a modified 5'-terminal structure, of brome mosic virus (BMV) mRNA no. 4 filament. The dodecamer chain was elongated by fragment condensation from the 3'-5' direction. The yields of the oligomer blocks have proved to be dramatically high because no side reactions occurred during the condensation reactions. Indeed, the final coupling to give the target 12-mer was achieved in 91% yield. The deprotection of the fully protected in the usual manner gave GUAUCAAUAAAUG in ca. 30% yield.

Current progress in molecular biology is due partly to the continuous development in the chemical synthesis of oligonucleotides.[1] In a recent study, we have faced the serious side reactions resulting from the reactive amide functions of nucleoside base residues. Similar observations have been reported in a number of laboratories.[2] This problem is more serious in the synthesis of oligoribonucleotides than that of oligodeoxyribonucleotides, because the condensation reaction requires longer periods of time owing to the steric effect of 2'-hydroxyl protecting groups. Several protecting groups have recently been proposed to overcome the inevitable side reactions.[3-6] In previous papers,[7,8] we have demonstrated the utility of the complete protection for the guanine[7a-c] and uracil[8] residues.

In this paper, we report a new strategy of introducing the protecting groups to the amide functions of the guanine and uracil residues and its application to the synthesis of GUAUCAAUAAAUG, a modified 5'-terminal dodecaribonucleotide sequence of BMV mRNA filament,[9] no. 4, which has C in place of U at the fifth position from the 5'-terminus and is expected to bind more tightly to 18S rRNA than the original sequence (Figure 1).

Results and Discussion

We have recently described a general method for the synthesis of oligoribonucleotides by use of *S,S*-diphenyl *N*-(4-methoxytrityl)-2'-*O*-(tetrahydropyranyl)-5'-*O*-(4,4'-dimethoxytrityl)-ribonucleoside-3'-phosphorodithioates as the key intermediates.[10] Although a nonaribonucleotide, GpUpApUpUpApApUpAp, was successfully obtained by this method, we have encountered base modifications on the guanosine and uridine residues throughout

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