1,1′-Bis(2-quinolyl)ferrocene (5a). The procedure described above for **3a** was followed using 0.27 g (1 mmol) of 1,1′-diacetylferrocene[15] (**4a**) and 0.29 g (2.4 mmol) of 2-aminobenzaldehyde (**2a**) to give 0.335 g (75%) of **5a** after chromatography on alumina (50 g) eluting with 1:1 hexane/EtOAc: mp 209–210 °C (lit.[12] mp 209–211 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, H_8, 2 H, $J_{7,8}$ = 78.5 Hz), 7.58 (m, H_6, 2 H), 7.40 (d, H_5, 2 H, $J_{5,6}$ = 4.0 Hz), 7.38 (H_6, 2 H), 7.19 (d, H_4, 2 H, $J_{3,4}$ = 8.6 Hz), 6.98 (d, H_3, 2 H), 5.05 (t, H_α, 4 H), 4.43 (t, H_β, 4 H), 1.68 (s, H_2O); ^{13}C NMR (75 MHz, $CDCl_3$) 157.2, 148.0, 134.9, 129.0, 128.6, 127.4, 126.3, 125.0, 119.1, 85.6, 71.2, 69.0 ppm; IR (KBr) 3106, 1618, 1530, 1452, 1331, 1119, 935, 841, 792 cm^{-1}.

1,1′-Bis[2-(1,8-naphthyridyl)]ferrocene (5b). The procedure described above for **3a** was followed using 0.32 g (1.2 mmol) of 1,1′-diacetylferrocene[15] (**4a**) and 0.32 g (2.6 mmol) of 2-aminonicotinaldehyde (**2b**) to give 0.4 g (75%) of **5b** after chromatography on alumina (35 g) eluting with 1:19 MeOH/CH_2Cl_2: mp >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (dd, 2 H, H_7, $J_{6,7}$ = 4.2 Hz), 7.60 (dd, 2 H, H_5, $J_{5,6}$ = 8.0 Hz), 7.29 (dd, 2 H, H_6), 7.12 (d, 2 H, H_4, $J_{3,4}$ = 8.5 Hz), 7.06 (d, 2 H, H_3), 5.26 (t, 4 H, H_α), 4.51 (t, 4 H, H_β), 1.64 (s, H_2O); ^{13}C NMR[14] (75 MHz, $CDCl_3$), 152.8, 136.5, 135.4, 120.3 (2 carbons), 84.5, 71.9, 69.4 ppm; IR (KBr) 1606, 1552, 1513, 1448, 1301, 1157, 1108, 845, 816, 778 cm^{-1}. Anal. Calcd for $C_{26}H_{18}FeN_4 \cdot {}^1/_3H_2O$: C, 69.66; H, 4.16; N, 12.50. Found: C, 69.28; H, 3.76; N, 12.25.

1,1′-Bis[2-(8-methoxyquinolyl)]ferrocene (5c). A solution of 0.216 g (0.8 mmol) of 1,1′-diacetylferrocene[15] (**4a**) and 0.30 g (2 mmol) of 3-methoxy-2-aminobenzaldehyde (**2c**) in 15 mL of absolute EtOH was refluxed for 15 min. Then, 6 drops of 15% methanolic KOH was added and the solution was refluxed for 24 h. The solvent was evaporated and the crude product was recrystallized from a mixture of 1:1 hexane/$CHCl_3$ to provide 0.22 g (62%) of **5c**: mp 200–201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, 2 H, H_6, $J_{5,6}$ = 8.0, $J_{6,7}$ = 7.5 Hz), 7.23 (d, 2 H, H_4, $J_{3,4}$ = 8.5 Hz), 7.11 (d, 2 H, H_3), 7.04 (d, 2 H, H_5), 6.98 (d, 2 H, H_7), 5.05 (t, 4 H, H_α), 4.38 (t, 4 H, H_β), 4.06 (s, 6 H, OCH_3), 1.74 (s, H_2O); ^{13}C NMR (75 MHz, $CDCl_3$) 156.6, 155.0, 140.0, 134.9, 127.6, 125.1, 119.8, 119.6, 108.3, 86.0, 71.1, 69.3, 56.3 (OCH_3) ppm; IR (KBr) 1612, 1568, 1524, 1494, 1467, 1435, 1340, 1269, 1120, 1109, 842, 768 cm^{-1}. Anal. Calcd for $C_{30}H_{24}FeN_2O_2 \cdot {}^1/_4H_2O$: C, 71.37; H, 4.86; N, 5.55. Found: C, 71.40; H, 4.82; N, 5.60.

1,1′-Bis[2-(3-methylquinolyl)]ferrocene (5d). The procedure described above for **3a** was followed using 0.26 g (0.9 mmol) of 1,1′-dipropionylferrocene[15] (**4b**) and 0.24 g (2 mmol) of 2-aminobenzaldehyde (**2a**) to give, after evaporation of the solvent, 0.110 g (26%) of **5d**: mp 263–264 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, H_8, $J_{7,8}$ = 8.4 Hz), 7.58 (dd, H_7, $J_{6,7}$ = 7.2 Hz), 7.41 (dd, H_6, $J_{5,6}$ = 8.0 Hz), 7.30 (d, H_5), 6.47 (s, H_4), 5.29 (t, 4 H, H_α), 4.46 (t, 4 H, H_β), 2.30 (6 H, CH_3), 1.67 (s, H_2O); ^{13}C NMR (75 MHz, $CDCl_3$) 156.3, 146.3, 136.0, 128.6, 128.4, 128.0, 126.4, 125.0, 86.4, 71.0, 70.5, 21.4 ppm; IR (KBr) 1660, 1605, 1590, 1485, 1405, 1270, 895, 745 cm^{-1}. Anal. Calcd for $C_{30}H_{24}FeN_2 \cdot {}^1/_2H_2O$: C, 75.48; H, 5.28; N, 5.87. Found: C, 75.83; H, 5.24; N, 5.86.

1,1′-Bis[2-(3-methyl-1,8-naphthyridyl)]ferrocene (5e). The procedure described above for **3a** was followed using 150 mg (0.5 mmol) of 1,1′-dipropionylferrocene[15] (**4b**) and 183 mg (1.5 mmol) of 2-aminonicotinaldehyde (**2b**) to give 95 mg (40%) of **5e** after chromatography on alumina eluting with 1% MeOH/EtOAc: mp 220–223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, H_7, $J_{6,7}$ = 4.2 Hz) 7.64 (d, H_5, $J_{5,6}$ = 8.0 Hz), 7.33 (dd, H_6), 6.59 (s, H_4), 5.47 (s, 4 H, H_α), 4.42 (s, 4 H, H_β), 2.39 (s, 6 H, CH_3), 1.61 (s, H_2O); IR (KBr) 1608, 1600, 1555, 1490, 1445, 1100, 903 cm^{-1}. The ^{13}C NMR of **5e** was not reported because of its poor solubility in common NMR solvents. Anal. Calcd for $C_{28}H_{22}FeN_4 \cdot {}^1/_4H_2O$: C, 70.83; H, 4.74; N, 11.80. Found: C, 70.71; H, 4.80; N, 11.69.

1,1′-Bis[2-(8-methoxy-3-methylquinolyl)]ferrocene (5f). A solution of 0.125 g (0.42 mmol) of 1,1′-dipropionylferrocene[15] (**4b**) and 0.150 g (1 mmol) of 3-methoxy-2-aminobenzaldehyde (**2c**) in 15 mL of absolute EtOH was refluxed for 15 min. Then, 6 drops of 15% methanolic KOH was added and the solution was refluxed for 48 h. The solution was cooled and the precipitate formed was filtered and chromatographed on alumina eluting with 2:1 hexane/$CHCl_3$ to provide 0.052 g (24%) of **5f**: mp 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, H_6, $J_{5,6}$ or $J_{6,7}$ = 8.1 Hz, $J_{5,6}$ or $J_{6,7}$ = 7.5 Hz), 6.95 (d, H_5 or H_7), 6.95 (d, H_5 or H_7), 6.60 (s, H_4), 5.31 (t, 4 H, H_α), 4.41 (t, 4 H, H_β), 4.08 (s, 6 H, OCH_3), 2.33 (s, 6 H, CH_3), 1.63 (s, H_2O); ^{13}C NMR (75 MHz, $CDCl_3$) 155.5, 155.2, 138.5, 136.0, 129.4, 127.8, 125.1, 118.8, 107.2, 86.9, 71.1, 70.6, 56.2, 21.2 ppm; IR (CH_2Cl_2) 3680, 3050, 2970, 2290, 1600, 1555, 1420, 1270, 1250, 1110, 890, 760 cm^{-1}. Anal. Calcd for $C_{32}H_{28}FeN_2O_2$: C, 72.74; H, 5.34; N, 5.30. Found: C, 72.50; H, 5.32; N, 5.30.

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Supplementary Material Available: Experimental details for the X-ray determination including data collection and processing parameters, atomic coordinates, bond lengths and angles, and proton and carbon NMR spectra of compounds **3a–f** and **5a–f** (18 pages). Ordering information is given on any current masthead page.

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Synthesis of Macrocyclic Dilactones by Cyclization of Sulfonium Salts

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An efficient method for the formation of macrocyclic dilactones via cyclization of (ω-carboxyalkyl)diphenylsulfonium salts **3** containing an ester linkage under mild conditions is described. These sulfonium salts **3** were cyclized in the presence of cesium carbonate under high-dilution conditions to give 11- to 16-membered dilactones **4** in good yields. The cyclization of sulfonium salt **22** was successfully carried out for the synthesis of 11-membered dilactonic pyrrolizidine alkaloid, 13,13-dimethyl-1,2-didehydrocrotalanine **23**.

Much attention has been focused in recent years on the synthesis of macrolides, particularly dilactones, from the viewpoint of their bioactivities, ability to complex with metal cations, and usefulness as perfumes.[1] The growing

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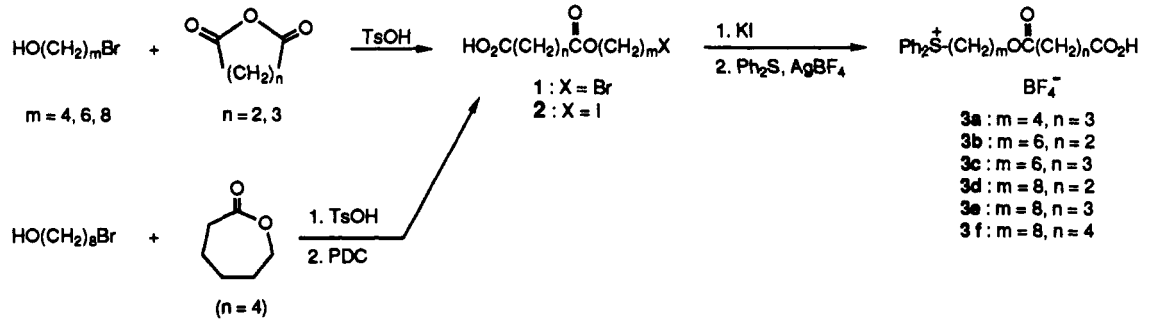
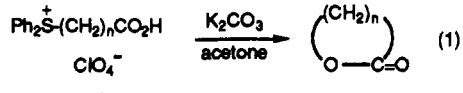
Scheme I



need for macrocyclic compounds has stimulated research efforts for their efficient preparation,[2] and many preparative methods of macrocyclic compounds have been developed.[3] However, there is only a limited number of methods for the preparation of macrocyclic dilactones. Macrocyclic dilactones have been prepared by treatment of cesium dicarboxylates with dihalides,[4] by catalytic esterification of dicarboxylic acids and diols using lipase,[5] and by condensation or depolymerization.[6] These synthetic methods provided mixtures of dilactones and tetralactones and required harsh conditions such as high temperature and pressure.

Macrocyclic dilactone pyrrolizidine alkaloids have attracted much interest due to their potent hepatotoxic and antitumor activities.[7] Successful syntheses of these macrocyclic pyrrolizidine alkaloids bearing 11-membered dilactonic skeleton such as (+)-dicrotaline have been reported by Robins using Corey lactonization,[8] by Meinwald on crobarbatine acetate,[9] and by Vedejs utilizing fluoride-induced cyclization of mesylate.[10]

In our previous work,[11] we reported that cyclization of (ω-carboxyalkyl)diphenylsulfonium salts gave macrocyclic lactones in high yields under weakly basic conditions (eq 1). It is presumed that intramolecularly electrostatic



(1)

Table I. Yields of Dilactones and Tetralactones from Sulfonium Salts 3

sulfonium salt	ring size of 4	yield[a] (%) 4	5	Ph_2S
3a	11	42	trace	90
3b	12	68	2	92
3c	13	75	1	99
3d	14	73	3	92
3e	15	74	6	96
3f	16	71	12	92

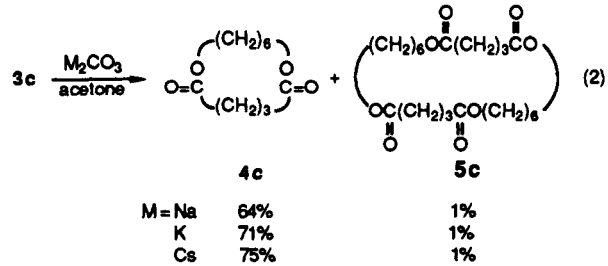
[a] Isolated yield.

interaction between the carboxylate ion and the sulfonium cation of (ω-carboxyalkyl)diphenylsulfonium salt plays an important role in this lactonization reaction.[11c,12] In this paper we describe an efficient method for the formation of macrocyclic dilactones by cyclization of sulfonium salts and a further application of this methodology in the preparation of 13,13-dimethyl-1,2-didehydrocrotalanine, analogous to naturally occurring dilactone (+)-dicrotaline.

Results and Discussion

(ω-Carboxyalkyl)diphenylsulfonium salts **3** containing an ester linkage were prepared as shown in Scheme I. Succinic and glutaric anhydrides were treated with the corresponding ω-bromo alcohols in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford dicarboxylic acid mono(ω-bromoalkyl) esters **1a–e**. Bromide **1f** ($n = 4$) was prepared by treatment of 6-hexanolide with 8-bromo-1-octanol, followed by PDC oxidation. After conversion of bromide **1** into iodide **2**, diphenylsulfonium salts **3** were obtained from an excess of diphenyl sulfide, **2**, and silver tetrafluoroborate.

The cyclization using sulfonium salt **3c** in acetone was carried out under high-dilution conditions in the presence of M_2CO_3, and the results are presented in eq 2. The use of cesium carbonate as a base in this reaction system gave the best result (**4c**, 75%).[13]



(2)

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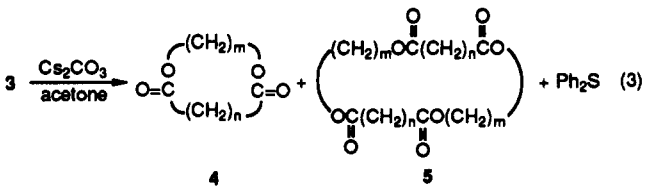
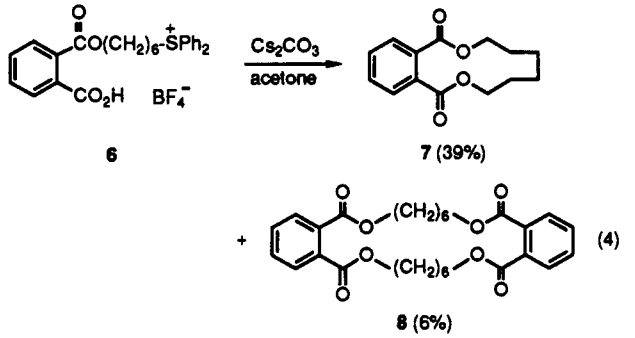
The cyclization of diphenylsulfonium salts **3a–f** was performed under Cs_2CO_3/acetone/high-dilution conditions (eq 3), and the results are summarized in Table I. 11- to



4 5

16-membered dilactones **4a–f** were obtained in moderate to good yields, together with a small amount of tetralactones **5**, without formation of oligomers. The inclusion of an aromatic ring moiety in macrocyclic dilactones greatly increases ability to complex with metal cations.[14] However, the yields of these compounds were low (2.6–15.5%).[6b,14f] The cyclization of sulfonium salt **6**, prepared from phthalic anhydride as a starting material, gave 12-membered dilactone **7** containing a benzene moiety in moderate yield (eq 4). These dilactonization reactions



6 7 (39%) 8 (6%)

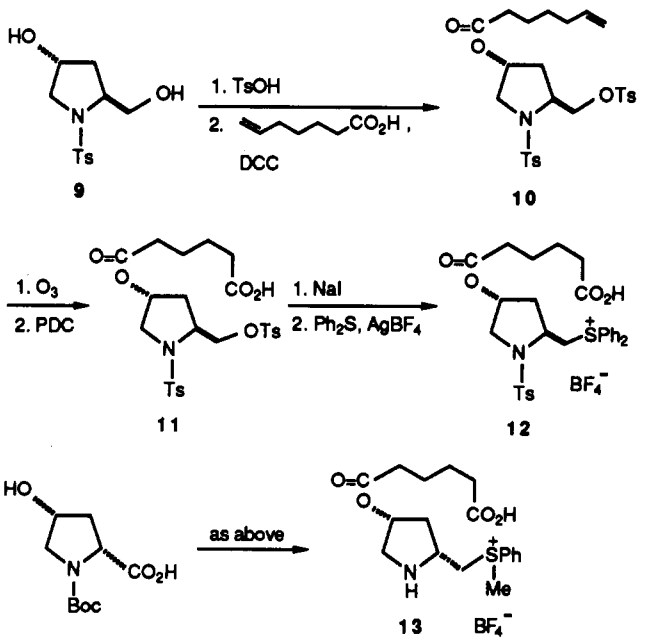
gave better results, in comparison with previous methods.[4–6,14f]

Although diphenyl sulfide was obtained quantitatively in this cyclization, the yields of dilactone and tetralactone were 42–83%. β-Elimination reaction might occur as the side reaction of this cyclization.[15] However, we could not detect β-elimination products from the reaction mixture.

In order to investigate the relationship between the configuration of sulfonium salts and their cyclization reaction, sulfonium salts *trans*-**12** and *cis*-**13** derived from 4-hydroxy-L- and -D-proline, respectively, were prepared (Scheme II), and the cyclization reactions were performed (Scheme III). The primary hydroxyl group of diol **9**, prepared from 4-hydroxy-L-proline according to the literature,[16] was selectively tosylated, and the tosylate was condensed with 6-heptenoic acid using DCC. The resulting ester **10** was treated with ozone, followed by PDC oxidation, to give carboxylic acid **11**, which was converted to the iodide. This iodide obtained was subjected to the reaction with diphenyl sulfide in the presence of silver tetrafluoroborate to give *trans*-sulfonium salt **12**. The amino group of *cis*-4-hydroxy-D-proline was protected as an *N*-Boc group and then allowed similar reactions as above to afford *cis*-sulfonium salt **13**.

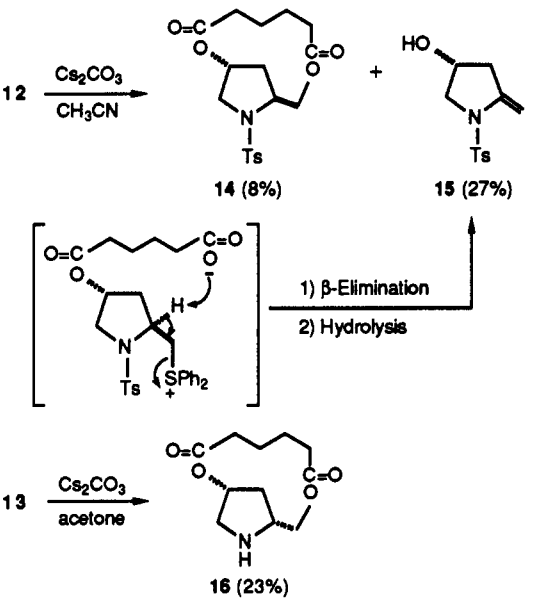
Inspection of molecular models of *trans*-**12** and *cis*-**13** suggested that *trans*-**12** would be more difficult to cyclize

Scheme II



9 10 11 12 13

Scheme III



14 (8%) 15 (27%) 16 (23%)

than *cis*-**13**. As shown in Scheme III, *trans*-**12** cyclized to give a small amount of dilactone **14** (8%), and alcohol **15** was obtained in 27% yield by β-elimination reaction, followed by hydrolysis of the ester group. On the other hand, the reaction of *cis*-**13** gave dilactone **16** in 23% yield without formation of the corresponding β-elimination product. These findings suggest that carboxylate anion attacks β-hydrogen intramolecularly, and β-elimination reaction takes place predominantly when the cyclization reaction of sulfonium salts is difficult. As mentioned above (Table I), β-elimination reaction might occur together with dilactonization, and diphenyl sulfide was obtained quantitatively.

In view of these encouraging results, we decided to examine the effectiveness of the method for the synthesis of 13,13-dimethyl-1,2-didehydrocrotalanine **23**,[8a] a naturally occurring macrocyclic dilactone (Scheme IV). According to the literature,[10] acyl phosphate **18** was obtained by the reaction of 3,3-dimethylglutaric anhydride with

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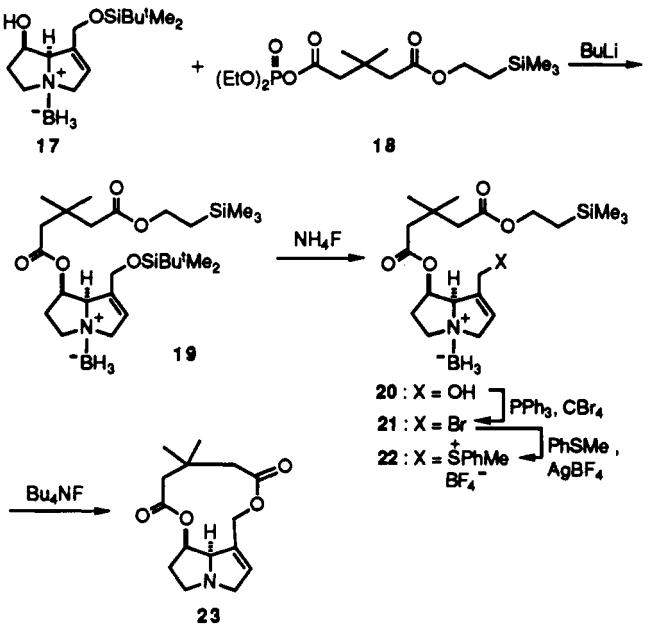
Scheme IV



(2-trimethylsilyl)ethanol, followed by treatment with diethyl chlorophosphate. The resulting **18** was coupled[10] with retronecine–borane complex **17**,[17] prepared from retronecine *tert*-butyldimethylsilyl ether[18] and borane–THF. Diester **19** was deprotected with ammonium fluoride to give alcohol **20**,[18b] which was converted to bromide **21** by use of PPh_3/CBr_4. Methylphenylsulfonium salt **22** was prepared from bromide **21** and thioanisole in the presence of silver tetrafluoroborate. Previously, we found that alkylation of 2-(methoxycarbonyl)-1-indanone with allylmethylphenylsulfonium salt gave an allylated product without competing methylation.[12a] Therefore, it was expected that the carboxylate ion of sulfonium salt **22** would selectively attack the allylic carbon atom. In the synthesis of **23**, the carboxylate anion was generated by fluoride-initiated deprotection of the trimethylsilylethyl ester, rather than by metal carbonate deprotonation of the free acid in order to compare with previous reports.[10] When the reaction of **22** with tetrabutylammonium fluoride was carried out in CH_3CN at rt, the deprotected product, 13,13-dimethyl-1,2-didehydrocrotalanine **23** was obtained in good yield (70%) as the sole product. The spectral data of **23** obtained are identical with those of the literature.[8a] The yield of this cyclization was better than that of Robins's method[8] and was comparable to that reported by Vedejs.[10]

In conclusion, the cyclization of (ω-carboxyalkyl)-sulfonium salts containing an ester linkage under mild conditions gave macrocyclic dilactones in moderate to good yields. This cyclization methodology is applicable to the synthesis of 13,13-dimethyl-1,2-didehydrocrotalanine, a (+)-dicrotaline analog containing an 11-membered dilactonic skeleton.

Experimental Section

^1H NMR spectra were recorded at 60 or 400 MHz, and ^{13}C NMR spectra were recorded at 22.5 or 100 MHz. Mass spectra were determined at 70 eV. Optical rotations were measured in a 1.0- or 0.5-dm cell. Melting points were determined in open capillary tubes and are uncorrected.

Dry solvents were purified as follows. Acetone was dried over molecular sieves (4A); acetonitrile, benzene, CH_2Cl_2, and DMF were distilled from CaH_2; THF was freshly distilled from sodium benzophenone ketyl before use.

ω-Iodocarboxylic Acids Containing an Ester Group 2. A mixture of succinic or glutaric anhydride (10 mmol) and the corresponding ω-bromo alcohols (11 mmol) in benzene (30 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid was refluxed overnight. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography (hexane–ether (1:1)) to give **1** (70–74%). The resulting bromide **1** was treated with KI (3 equiv in refluxing acetone) to give iodide **2** quantitatively.

ω-Iodocarboxylic acids 2a: oil; ^1H NMR ($CDCl_3$) δ 1.50–2.20 (m, 6 H), 2.27–2.67 (m, 4 H), 3.07–3.39 (m, 2 H), 3.97–4.32 (m, 2 H), 10.7 (br s, 1 H); IR (neat) 2400–3600, 1728, 1703 cm^{-1}; MS *m/z* 314 (M^+), 187, 169.

2b: mp 41–43 °C; ^1H NMR ($CDCl_3$) δ 1.18–2.15 (m, 8 H), 2.64 (s, 4 H), 3.18 (t, *J* = 6.9 Hz, 2 H), 3.96–4.27 (m, 2 H), 11.0 (br s, 1 H); IR (neat) 2700–3650, 1727, 1702 cm^{-1}; MS *m/z* 329 (M^+ + 1), 311, 211; HRMS calcd for $C_{10}H_{18}O_4I$ (M^+ + 1) 329.0250, found 329.0309.

2c: mp 29–31 °C; ^1H NMR ($CDCl_3$) δ 1.13–2.21 (m, 10 H), 2.27–2.67 (m, 4 H), 3.18 (t, *J* = 6.6 Hz, 2 H), 3.93–4.24 (m, 2 H), 10.9 (br s, 1 H); IR (neat) 2800–3650, 1710 cm^{-1}; MS *m/z* 343 (M^+ + 1), 325, 211; HRMS calcd for $C_{11}H_{19}O_4I$ 342.0328, found 342.0404.

2d: oil; ^1H NMR ($CDCl_3$) δ 1.05–2.13 (m, 12 H), 2.63 (s, 4 H), 3.17 (t, *J* = 6.7 Hz, 2 H), 3.93–4.24 (m, 2 H), 10.1 (br s, 1 H); IR (neat) 2400–3700, 1732, 1713 cm^{-1}; MS *m/z* 357 (M^+ + 1), 339, 239; HRMS calcd for $C_{12}H_{21}O_4I$ 356.0485, found 356.0504.

2e: mp 47–49 °C; ^1H NMR ($CDCl_3$) δ 1.05–2.20 (m, 14 H), 2.25–2.67 (m, 4 H), 3.18 (t, *J* = 6.5 Hz, 2 H), 3.94–4.27 (m, 2 H), 10.9 (br s, 1 H); IR (KBr) 2500–3400, 1724, 1690 cm^{-1}; MS *m/z* 370 (M^+), 353, 324; HRMS calcd for $C_{13}H_{23}O_4I$ 370.0641, found 370.0726.

2f: oil; ^1H NMR ($CDCl_3$) δ 1.01–2.07 (m, 16 H), 2.13–2.67 (m, 4 H), 3.17 (t, *J* = 6.8 Hz, 2 H), 3.85–4.23 (m, 2 H), 10.8 (br s, 1 H); IR (neat) 2400–3600, 1730, 1705 cm^{-1}; MS *m/z* 384 (M^+), 367, 338; HRMS calcd for $C_{14}H_{25}O_4I$ 384.0798, found 384.0883.

Sulfonium Salts 3. To a mixture of **2** (3.4 mmol) and $AgBF_4$ (0.87 g, 4.4 mmol), cooled in an ice bath, was added diphenyl sulfide (6.35 g, 34 mmol) dropwise. After being stirred for 3 days at rt, the reaction mixture was passed through a silica gel short column and eluted with acetone. After removal of solvent, the residue was washed with ether to give **3** (80–94%).

Sulfonium salts 3a: oil; ^1H NMR (acetone-d_6) δ 1.50–2.07 (m, 6 H), 2.18–2.62 (m, 4 H), 3.90–4.63 (m, 4 H), 7.56–7.88 (m, 6 H), 7.97–8.30 (m, 4 H), 9.17 (br s, 1 H); IR (neat) 2700–3600, 1726, 1061 cm^{-1}.

3b: oil; ^1H NMR (acetone-d_6) δ 1.18–1.93 (m, 8 H), 2.58 (s, 4 H), 3.77–4.57 (m, 4 H), 7.46–7.89 (m, 6 H), 7.98–8.35 (m, 4 H), 9.17 (br s, 1 H); IR (neat) 2700–3700, 1715, 1055 cm^{-1}.

3c: oil; ^1H NMR (acetone-d_6) δ 1.17–2.02 (m, 10 H), 2.17–2.58 (m, 4 H), 3.80–4.50 (m, 4 H), 7.54–7.87 (m, 6 H), 7.96–8.36 (m, 4 H), 9.17 (br s, 1 H); IR (neat) 2800–3660, 1719, 1056 cm^{-1}.

3d: oil; ^1H NMR (acetone-d_6) δ 1.16–1.98 (m, 12 H), 2.59 (s, 4 H), 3.87–4.67 (m, 4 H), 7.47–7.87 (m, 6 H), 7.97–8.33 (m, 4 H), 9.17 (br s, 1 H); IR (neat) 2700–3700, 1726, 1063 cm^{-1}.

3e: oil; ^1H NMR (acetone-d_6) δ 1.15–2.20 (m, 14 H), 2.23–2.70 (m, 4 H), 3.82–4.57 (m, 4 H), 7.57–7.90 (m, 6 H), 8.00–8.30 (m, 4 H), 9.56 (br s, 1 H); IR (neat) 2700–3700, 1724, 1056 cm^{-1}.

3f: oil; ^1H NMR (acetone-d_6) δ 1.17–1.97 (m, 16 H), 2.15–2.57 (m, 4 H), 3.73–4.57 (m, 4 H), 7.57–7.88 (m, 6 H), 7.97–8.33 (m, 4 H), 8.92 (br s, 1 H); IR (neat) 2700–3600, 1727, 1075 cm^{-1}.

Sulfonium Salt 6. 6-Iodohexyl phthalic acid monoester was prepared from phthalic anhydride and 6-bromohexanol, followed by conversion of the bromide into the iodide with KI. Reaction of the iodide and phenyl sulfide in the presence of $AgBF_4$ gave **6**: oil; ^1H NMR (acetone-d_6) δ 1.27–2.01 (m, 8 H), 4.03–4.53 (m, 4 H), 7.42–7.87 (m, 10 H), 7.95–8.22 (m, 4 H), 9.56 (br s, 1 H); IR (neat) 2700–3700, 1715, 1070 cm^{-1}.

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General Procedure for Cyclizations. To a stirred suspension of Cs_2CO_3 (1.97 g, 6 mmol) in refluxing acetone (100 mL) was added sulfonium salt **3c** (0.98 g, 2 mmol) in acetone (100 mL) over 1.5 days. After refluxing for additional 12 h, the reaction mixture was passed through a silica gel short column. The solvent was removed, and the residue was chromatographed on silica gel (hexane–ether (3:1)) to give pure product **4c** (0.32 g, 75%).

Dilactones 4a: 0.16 g (42%); oil; ^1H NMR ($CDCl_3$) δ 1.60–2.26 (m, 6 H), 2.30–2.68 (m, 4 H), 3.83–4.40 (m, 4 H); IR (neat) 1731 cm^{-1}; MS m/z 187 ($M^+ + 1$), 158, 128; HRMS calcd for $C_9H_{15}O_4$ ($M^+ + 1$) 187.0970, found 187.0922.

4b: 0.27 g (68%); oil; ^1H NMR ($CDCl_3$) δ 1.19–1.97 (m, 8 H), 2.59 (s, 4 H), 3.93–4.37 (m, 4 H); IR (neat) 1732 cm^{-1}; MS m/z 201 ($M^+ + 1$), 172. 154; HRMS calcd for $C_{10}H_{17}O_4$ ($M^+ + 1$) 201.1127, found 201.1088.

4c: 0.32 g (75%); oil; ^1H NMR ($CDCl_3$) δ 1.19–2.22 (m, 10 H), 2.28–2.65 (m, 4 H), 3.87–4.47 (m, 4 H); IR (neat) 1733 cm^{-1}; MS m/z 215 ($M^+ + 1$), 186, 156; HRMS calcd for $C_{11}H_{19}O_4$ ($M^+ + 1$) 215.1284, found 215.1297.

4d: 0.34 g (73%); mp 67–68 °C; ^1H NMR ($CDCl_3$) δ 1.23–2.00 (m, 12 H), 2.63 (s, 4 H), 3.97–4.40 (m, 4 H); IR (KBr) 1725 cm^{-1}; MS m/z 229 ($M^+ + 1$), 200, 157; HRMS calcd for $C_{12}H_{21}O_4$ ($M^+ + 1$) 229.1440, found 229.1448.

4e: 0.34 g (74%); mp 27–28 °C; ^1H NMR ($CDCl_3$) δ 1.19–2.23 (m, 14 H), 2.30–2.67 (m, 4 H), 3.97–4.37 (m, 4 H); IR (neat) 1730 cm^{-1}; MS m/z 243 ($M^+ + 1$), 214, 186; HRMS calcd for $C_{13}H_{23}O_4$ ($M^+ + 1$) 243.1597, found 243.1503.

4f: 0.34 g (71%); oil; ^1H NMR ($CDCl_3$) δ 1.11–2.00 (m, 16 H), 2.23–2.63 (m, 4 H), 3.96–4.40 (m, 4 H); IR (neat) 1731 cm^{-1}; MS m/z 256 (M^+), 228, 129; HRMS calcd for $C_{14}H_{25}O_4$ ($M^+ + 1$) 257.1753, found 257.1737.

7: 0.16 g (39%); mp 63–64 °C (lit.[14f] 63.7–64.5 °C); ^1H NMR ($CDCl_3$) δ 1.33–2.10 (m, 8 H), 4.10–4.63 (m, 4 H), 7.33–7.87 (m, 4 H); IR (neat) 1724 cm^{-1}; MS m/z 248 (M^+), 204, 149; HRMS calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049, found 248.1064.

The following tetralactones **5b–f** and **8** were characterized by MS data.

Tetralactones **5b**: MS m/z 401 ($M^+ + 1$), 301, 201.

5c: MS m/z 429 ($M^+ + 1$), 400, 315.

5d: MS m/z 456 (M^+), 441, 429.

5e: MS m/z 484 (M^+), 440, 426.

5f: MS m/z 514 ($M^+ + 2$), 500, 480.

8: MS m/z 497 ($M^+ + 1$), 366, 352.

Preparation of Ester 10. To a solution of *p*-toluenesulfonyl chloride (5.35 g, 28 mmol) in pyridine (11 mL) at −20 °C was added **9**[16] (6.91 g, 25 mmol). After being stirred for 2 h, the mixture was quenched by addition of cooled 2 N HCl (120 mL) and extracted three times with AcOEt (300 mL). The combined extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the O-monotosylated product (9.80 g, 90%): oil; ^1H NMR (acetone-d_6) δ 1.53–2.21 (m, 2 H), 2.35 (s, 3 H), 2.41 (s, 3 H), 2.98–4.57 (m, 7 H), 7.17–7.93 (m, 8 H); IR (neat) 3520, 1360, 1340, 1168, 1150 cm^{-1}; MS m/z 426 ($M^+ + 1$), 407, 394; $[\alpha]^{25}_D$ −81.2° (*c* 2.82, EtOH). To a CH_2Cl_2 (6 mL) solution of the preceding tosylate (1.72 g, 4 mmol), 6-heptenoic acid (0.52 g, 4 mmol), and a catalytic amount of DMAP was added DCC (1.04 g, 5 mmol) at 0 °C. The mixture was stirred for 5 min at 0 °C and then overnight at rt. The resulting precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel chromatography (hexane–AcOEt (3:1)) to give ester **10** (1.39 g, 64%): oil; ^1H NMR ($CDCl_3$) δ 1.20–1.78 (m, 6 H), 1.87–2.27 (m, 4 H), 2.43 (s, 6 H), 3.42–3.60 (m, 2 H), 3.70–4.60 (m, 3 H), 4.73–4.91 (m, 1 H), 4.93–5.18 (m, 2 H), 5.42–6.03 (m, 1 H), 7.14–7.93 (m, 8 H); IR (neat) 1732, 1641, 1346, 1160, 979, 913 cm^{-1}; MS m/z 536 ($M^+ + 1$), 467, 426; HRMS calcd for $C_{26}H_{33}O_7NS_2$ 535.1699, found 535.1681; $[\alpha]^{25}_D$ −70.1° (*c* 2.93, $CHCl_3$).

Preparation of Carboxylic Acid 11. A solution of **10** (0.54 g, 1 mmol) in CH_2Cl_2 (15 mL) was treated with a stream of ozone at −78 °C until blue color persisted. The excess ozone was purged from the solution with a stream of nitrogen, and methyl sulfide (4.4 mL) was added dropwise. The reaction mixture was allowed to warm slowly to rt and stirred for 1 day. The mixture was diluted with CH_2Cl_2 (50 mL) and washed three times with brine (10 mL). The combined brine layers were extracted with CH_2Cl_2 (50 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on silica gel (hexane–AcOEt (1:1)) to provide the aldehyde (0.39 g, 72%): oil; ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 6 H), 1.95–2.22 (m, 2 H), 2.26–2.57 (m, 8 H), 3.35–3.63 (m, 2 H), 3.66–4.57 (m, 3 H), 4.83–5.15 (m, 1 H), 7.10–7.92 (m, 8 H), 9.63 (s, 1 H); IR (neat) 2724, 1729, 1354, 1157 cm^{-1}; MS m/z 538 ($M^+ + 1$), 509, 494; HRMS calcd for $C_{25}H_{31}O_8NS_2$ 537.1491, found 537.1554; $[\alpha]^{25}_D$ −63.6° (*c* 3.21, $CHCl_3$). A mixture of the preceding aldehyde (0.39 g, 0.7 mmol) and PDC (0.55 g, 1.4 mmol) in DMF (1.1 mL) under nitrogen was stirred for 6 h at rt. The reaction mixture was quenched with water (30 mL) and extracted 10 times with ether (50 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel (hexane–AcOEt (1:1)) afforded carboxylic acid **11** (0.32 g, 77%): oil; ^1H NMR ($CDCl_3$) δ 1.30–1.87 (m, 6 H), 1.91–2.63 (m, 10 H), 3.37–3.59 (m, 2 H), 3.63–4.60 (m, 3 H), 4.83–5.13 (m, 1 H), 7.10–7.90 (m, 8 H), 9.83 (br s, 1 H); IR (neat) 2300–3700, 1733, 1707, 1348, 1159 cm^{-1}; MS m/z 555 ($M^+ + 2$), 382, 368; HRMS calcd for $C_{25}H_{32}O_9NS_2$ ($M^+ + 1$) 554.1519, found 554.1549; $[\alpha]^{23}_D$ −63.1° (*c* 3.38, $CHCl_3$).

Preparation of Sulfonium Salt 12. An acetone (8 mL) solution of **11** (1.12 g, 2 mmol) and NaI (0.92 g, 6 mmol) was refluxed for 3 h. The reaction mixture was diluted with ether, and the precipitate was removed by filtration. Concentration of the filtrate afforded the iodide (1.00 g, 97%) as a colorless solid: mp 76–78 °C; ^1H NMR ($CDCl_3$) δ 1.17–1.83 (m, 6 H), 1.88–2.60 (m, 7 H), 3.39–4.57 (m, 5 H), 4.87–5.17 (m, 1 H), 7.13–7.45 (m, 2 H), 7.52–7.90 (m, 2 H), 10.4 (br s, 1 H); IR (KBr) 2500–3600, 1741, 1698, 1344, 1159 cm^{-1}; MS m/z 511 ($M^+ + 2$), 492, 451; HRMS calcd for $C_{18}H_{24}O_6NSI$ 509.0369, found 509.0382; $[\alpha]^{24}_D$ −72.2° (*c* 4.46, $CHCl_3$). Sulfonium salt **12** (0.50 g, 41%) was prepared from the preceding iodide (0.96 g, 1.9 mmol), diphenyl sulfide (7.06 g, 38 mmol), and $AgBF_4$ (0.44 g, 2 mmol): oil; ^1H NMR (acetone-d_6) δ 1.32–1.78 (m, 6 H), 2.14–2.57 (m, 7 H), 2.76–3.97 (m, 3 H), 4.85–5.50 (m, 3 H), 7.20–7.90 (m, 10 H), 8.02–8.37 (m, 5 H); IR ($CHCl_3$) 2800–3700, 1733, 1708, 1351, 1163 cm^{-1}; $[\alpha]^{25}_D$ −6.96° (*c* 2.34, $CHCl_3$).

Cyclization of Sulfonium Salt 12. This reaction was carried out by use of **12** (0.24 g, 0.36 mmol), Cs_2CO_3 (0.86 g, 2.7 mmol), and CH_3CN (100 mL) in a similar manner as described in general procedure to give dilactone **14** (11 mg, 8%) and alcohol **15** (25 mg, 27%). **14**: oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47–1.72 (m, 6 H), 2.27–2.40 (m, 4 H), 2.43 (s, 3 H), 3.57 (d, J = 4.1 Hz, 2 H), 3.81–4.13 (m, 1 H), 4.32–4.50 (m, 2 H), 4.87–5.14 (m, 1 H), 7.32, 7.72 (ABq, J = 8.2 Hz, 4 H); IR ($CHCl_3$) 1724, 1348, 1162 cm^{-1}; MS m/z 381 (M^+), 297, 253; HRMS calcd for $C_{18}H_{23}O_6SN$ 381.1246, found 381.1197; $[\alpha]^{23}_D$ +6.03° (*c* 0.25, $CHCl_3$). **15**: mp 111–113 °C; ^1H NMR ($CDCl_3$) δ 2.07 (br s, 1 H), 2.39 (s, 3 H), 3.05–3.30 (m, 2 H), 3.51 (d, J = 7.5 Hz, 2 H), 3.97–4.05 (m, 1 H), 5.76 (s, 2 H), 7.25, 7.62 (ABq, J = 8.2 Hz, 4 H); IR ($CHCl_3$) 3200–3600, 3015, 1656, 1350, 1165, 905 cm^{-1}; MS m/z 253 (M^+), 236, 184; HRMS calcd for $C_{12}H_{15}O_3SN$ 253.0773, found 253.0795; $[\alpha]^{27}_D$ −99.3° (*c* 1.04, $CHCl_3$).

***N*-Boc-*cis*-4-hydroxy-D-proline.** To a mixture of *cis*-4-hydroxy-D-proline (0.92 g, 7 mmol), Et_3N (1.46 mL), water (7 mL), MeOH (10.5 mL), and dioxane (3.5 mL) was added BOC–ON (1.73 g, 7 mmol), and the mixture was stirred for 3 h at rt. After removal of solvent, the residue was added to water (10 mL) and washed three times with benzene (14 mL). The solution was acidified with 5% citric acid and extracted three times with AcOEt (100 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Recrystallization from acetone–AcOEt afforded the pure product (1.39 g, 85%) as colorless crystals: mp 140–141 °C; ^1H NMR (acetone-d_6) δ 1.40 (s, 9 H), 2.09–2.48 (m, 2 H), 3.40–3.63 (m, 2 H), 4.13–4.51 (m, 2 H), 6.67 (br s, 2 H); IR (KBr) 2300–3700, 1665–1736 cm^{-1}; MS m/z 232 ($M^+ + 1$), 186, 158; HRMS calcd for $C_{10}H_{18}O_5N$ ($M^+ + 1$) 232.1185, found 232.1192; $[\alpha]^{22}_D$ +47.1° (*c* 2.29, EtOH).

***N*-Boc-*cis*-4-hydroxy-D-proline Methyl Ester.** To a MeOH (25 mL) solution of the preceding N-protected material (3.70 g, 16 mmol) was added an ether solution of CH_2N_2 until yellow color persisted. After removal of the solvent, the residue was purified by silica gel chromatography (hexane–AcOEt (1:2)) to give the methyl ester (3.93 g, 70%) as colorless crystals: mp 78–79 °C; ^1H NMR ($CDCl_3$) δ 1.42 (m, 9 H), 2.07–2.64 (m, 2 H), 3.37–3.67 (m, 3 H), 3.73 (s, 3 H), 4.13–4.53 (m, 2 H); IR (KBr) 3475, 1727,

1675 cm^{-1}; MS m/z 245 (M$^+$), 172, 158; HRMS calcd for $C_{11}H_{19}O_5N$ 245.1263, found 245.1285; $[\alpha]^{25}_D$ +63.8° (c 2.21, EtOH).

N-Boc-*cis*-4-hydroxy-D-prolininol. A suspension of the methyl ester (2.88 g, 12 mmol) and $LiBH_4$ (1.26 g, 58 mmol) in THF (45 mL) was stirred for 7 h at 0 °C and then overnight at rt. The reaction mixture, cooled in an ice bath, was quenched with water (30 mL) and neutralized with 0.5 N HCl. The solution was extracted three times with AcOEt (200 mL). The extracts were washed with 2 N NaOH, 0.5 N HCl, and water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from ether–hexane to yield the pure product (1.88 g, 74%) as colorless crystals: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.87–2.67 (m, 2 H), 3.30–3.53 (m, 2 H), 3.56–4.43 (m, 4 H), 4.75 (br s, 2 H); IR (KBr) 3443, 1683, 1653 cm^{-1}; MS m/z 217 (M$^+$), 186, 162; HRMS calcd for $C_{10}H_{19}O_4N$ 217.1314, found 217.1312; $[\alpha]^{23}_D$ +42.6° (c 2.43, EtOH).

N-Boc-3(S)-hydroxy-5(S)-[(tosyloxy)methyl]pyrrolidine: mp 116–117 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.98–2.20 (m, 2 H), 2.28 (br s, 1 H), 2.42 (s, 3 H), 3.30–3.53 (m, 2 H), 3.84–4.53 (m, 4 H), 7.28, 7.72 (ABq, J = 8.0 Hz, 4 H); IR (KBr) 3456, 1670, 1361, 1176 cm^{-1}; MS m/z 371 (M$^+$), 345, 327; HRMS calcd for $C_{17}H_{26}O_6NS$ (M$^+$ + 1) 372.1481, found 372.1482; $[\alpha]^{25}_D$ +17.7° (c 2.16, $CHCl_3$).

N-Boc-3(S)-(6-heptenoyloxy)-5(S)-[(tosyloxy)methyl]-pyrrolidine: oil; ^{1}H NMR ($CDCl_3$) δ 1.17–1.77 (m, 13 H), 1.90–2.34 (m, 6 H), 2.43 (s, 3 H), 3.37–3.65 (m, 2 H), 3.90–4.32 (m, 3 H), 4.80–4.90 (m, 1 H), 4.93–5.37 (m, 2 H), 5.45–6.07 (m, 1 H), 7.29, 7.73 (ABq, J = 8.5 Hz, 4 H); IR (neat) 1734, 1692, 1639, 1364, 1175 cm^{-1}; MS m/z 481 (M$^+$), 426, 381; HRMS calcd for $C_{24}H_{35}O_7NS$ 481.2134, found 481.2146; $[\alpha]^{23}_D$ +11.9° (c 2.60, $CHCl_3$).

N-Boc-3(S)-[(5-formylpentanoyl)oxy]-5(S)-[(tosyloxy)-methyl]pyrrolidine: oil; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 1.52–1.84 (m, 4 H), 2.07–2.66 (m, 6 H), 2.44 (s, 3 H), 3.37–3.67 (m, 2 H), 3.90–4.31 (m, 3 H), 5.10–5.42 (m, 1 H), 7.30, 7.72 (ABq, J = 8.0 Hz, 4 H), 9.69 (s, 1 H); IR (neat) 1731, 1691, 1366, 1176 cm^{-1}; MS (CI, i-C_4H_{10}) m/z 526 (M$^+$ + $C_3H_7^+$), 426, 441; $[\alpha]^{26}_D$ +5.11° (c 2.17, $CHCl_3$).

N-Boc-3(S)-[(5-carboxypentanoyl)oxy]-5(S)-[(tosyloxy)methyl]pyrrolidine: oil; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.51–1.84 (m, 4 H), 2.08–2.40 (m, 6 H), 2.43 (2, 3 H), 3.35–3.70 (m, 2 H), 3.89–4.33 (m, 3 H), 5.05–5.43 (m, 1 H), 7.30, 7.71 (ABq, J = 8.0 Hz, 4 H), 9.22 (br s, 1 H); IR (neat) 2450–3700, 1733, 1694, 1368, 1175 cm^{-1}; MS (CI, i-C_4H_{10}) m/z 542 (M$^+$ + $C_3H_7^+$), 397, 310; HRMS calcd for $C_{23}H_{34}O_9NS$ (M$^+$ + 1) 500.1954, found 500.1952; $[\alpha]^{25}_D$ +8.89° (c 2.13, $CHCl_3$).

N-Boc-3(S)-[(5-carboxypentanoyl)oxy]-5(S)-(iodomethyl)pyrrolidine: mp 97–99 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.57–1.88 (m, 4 H), 2.15–2.65 (m, 6 H), 3.17–3.70 (m, 4 H), 3.83–4.33 (m, 1 H), 5.08–5.39 (m, 1 H), 9.38 (br s, 1 H); IR (KBr) 3229, 1733, 1669 cm^{-1}; MS m/z 456 (M$^+$ + 1), 382, 354; HRMS calcd for $C_{16}H_{27}O_6NI$ (M$^+$ + 1) 456.0883, found 456.0821; $[\alpha]^{26}_D$ +23.0° (c 2.10, $CHCl_3$).

Sulfonium Salt 13. Sulfonium salt **13** (0.20 g, 65%) was prepared from the preceding iodide (0.26 g, 0.6 mmol), thioanisole (0.15 g, 1.2 mmol), and $AgBF_4$ (0.17 g, 0.8 mmol) in CH_3CN (2 mL): oil; ^{1}H NMR (acetone-d_6) δ 1.47–1.78 (m, 4 H), 2.17–2.59 (m, 7 H), 2.77 (s, 3 H), 3.20–3.73 (m, 4 H), 3.93–4.47 (m, 1 H), 5.00–5.77 (m, 1 H), 7.13–7.88 (m, 5 H), 8.07 (br s, 1 H); IR (neat) 2700–3700, 1720, 1055 cm^{-1}; $[\alpha]^{26}_D$ +14.3° (c 14.5, acetone).

Cyclization of Sulfonium Salt 13. This reaction was carried out by use of **13** (0.19 g, 0.35 mmol), Cs_2CO_3 (0.34 g, 1 mmol), and acetone (50 mL) as described in the general procedure to give the dilactone **16** (18 mg, 23%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–1.94 (m, 4 H), 2.29–2.45 (m, 7 H), 3.46–3.59 (m, 2 H), 4.27 (br s, 2 H), 4.69 (br s, 1 H), 5.35 (br s, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 23.7, 29.7, 34.0, 34.2, 53.1, 57.3, 63.7, 75.2, 172.0, 173.3; IR ($CHCl_3$) 1725 cm^{-1}; MS m/z 227 (M$^+$ + 1), 209, 169; HRMS calcd for $C_{11}H_{17}O_4N$ (M$^+$ + 1) 227.1157, found 227.1137; $[\alpha]^{28}_D$ −9.78° (c 2.42, $CHCl_3$).

3,3-Dimethylglutaric Acid Mono[2-(trimethylsilyl)ethyl] Ester. A mixture of 3,3-dimethylglutaric anhydride (1.42 g, 10 mmol), 2-(trimethylsilyl)ethanol (1.43 g, 13 mmol), and a catalytic amount of p-toluenesulfonic acid was refluxed for 1 day. After concentration in vacuo, the residue was chromatographed on silica gel to give the desired product (2.31 g, 89%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.97 (t, J = 8.55 Hz, 2 H), 0.99 (s, 6 H), 2.39 (s, 2 H), 2.45 (s, 2 H), 4.14 (t, J = 8.55 Hz, 2 H), 10.5 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.57, 17.4, 27.7, 32.5, 45.0, 45.2, 62.5, 172.3, 177.7; IR (neat) 2400–3600, 1724, 1704 cm^{-1}; MS m/z 262 (M$^+$ + 2), 245, 227.

Esterification of 17 with 18.[10] To a THF (11 mL) solution of the preceding carboxylic acid (0.62 g, 2.4 mmol) and Et_3N (0.33 mL) under nitrogen was added diethyl chlorophosphate (0.34 mL, 2.4 mmol) at 0 °C, and the mixture was stirred for 1 h at rt. The resulting precipitate was removed by filtration and concentrated in vacuo to afford acyl phosphate **18**. To a THF (11 mL) solution of retronecine silyl ether **17**[18] (0.33 g, 1.2 mmol) and a catalytic amount of DMAP under nitrogen was added a hexane solution (1.1 mL) of n-BuLi (1.7 mmol) at 0 °C. After the reaction mixture stirred for 10 min, a THF (6 mL) solution of **18** was added, and then the mixture was stirred for 1.5 h at rt. The solvent was removed in vacuo, and column chromatography of the residue on alumina (hexane–ether (1:1)) afforded retronecine monoester **19** (0.19 g, 31%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 15 H), 0.87 (s, 9 H), 0.92–0.96 (m, 2 H), 1.05 (s, 3 H), 1.06 (s, 3 H), 1.97–2.02 (m, 1 H), 2.31–2.44 (m, 5 H), 3.02 (td, J = 5.70 and 11.4 Hz, 1 H), 3.52–3.56 (m, 1 H), 3.68–3.72 (m, 1 H), 4.08–4.14 (m, 5 H), 4.32 (br s, 1 H), 5.40–5.42 (m, 1 H), 5.53 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.53, −5.50, −1.58, 17.4, 18.2, 25.8, 27.6, 32.5, 33.3, 44.9, 45.1, 59.9, 62.2, 62.6, 71.9, 73.5, 84.2, 119.7, 137.1, 170.5, 171.7; IR (neat) 3500, 2362, 1727 cm^{-1}; MS m/z 524 (M$^+$ − 1), 496, 468; $[\alpha]^{26}_D$ −14.7° (c 1.48, $CHCl_3$).

Desilylation of 19. This reaction was carried out according to the literature.[18b] Purification of column chromatography on silica gel (hexane–ether (1:2)) gave the desired alcohol **20** (34 mg, 34%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.95 (t, J = 8.55 Hz, 2 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 2.02 (dd, J = 5.37 and 13.7 Hz, 1 H), 2.30–2.42 (m, 1 H), 2.32, 2.45 (ABq, J = 14.2 Hz, 2 H), 2.37, 2.43 (ABq, J = 15.6 Hz, 2 H), 3.02–3.08 (m, 1 H), 3.58 (t, J = 9.03 Hz, 1 H), 3.70–3.74 (m, 1 H), 4.09–4.19 (m, 6 H), 4.35 (br s, 1 H), 5.49 (br s, 1 H), 5.60 (s, 1 H); IR (neat) 3500, 2362, 1727 cm^{-1}; MS m/z 410 (M$^+$ − 1), 369, 309; $[\alpha]^{22}_D$ +7.14° (c 3.33, $CHCl_3$).

Bromination of Allylic Alcohol 20. To a solution of alcohol **20** (30 mg, 0.07 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (0.10 g, 0.38 mmol) and CBr_4 (0.15 g, 0.45 mmol) rapidly at −15 °C under nitrogen. After being stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ and brine (13 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The oily residue was purified by chromatography on silica gel (hexane–ether (1:1)) to give bromide **21** (32 mg, 91%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.96 (t, J = 8.55 Hz, 2 H), 1.07 (s, 6 H), 2.05 (dd, J = 5.38 and 13.7 Hz, 1 H), 2.36 (s, 2 H), 2.41 (d, J = 3.91 Hz, 2 H), 2.44–2.49 (m, 1 H), 3.08 (td, J = 5.70, 11.4 Hz, 1 H), 3.60 (t, J = 9.04 Hz, 1 H), 3.70–3.77 (m, 1 H), 3.89–4.21 (m, 3 H), 4.17 (t, J = 13.9 Hz, 2 H), 4.46 (d, 21.5 Hz, 1 H), 5.50 (br s, 1 H), 5.78 (d, J = 9.28 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.57, 17.4, 27.8, 32.4, 33.3, 39.6, 44.6, 44.9, 62.4, 62.8, 71.7, 73.3, 84.3, 125.2, 133.0, 170.6, 171.8; IR (neat) 2354, 1734 cm^{-1}; MS m/z 461 (M$^+$ − 14, Br = 81), 446, 415; HRMS calcd for $C_{20}H_{37}O_4NBSiBr$ (Br = 81) 475.1748, found 475.1831; $[\alpha]^{23}_D$ −14.4° (c 1.37, $CHCl_3$).

Sulfonium Salt 22. Sulfonium salt **22** (17 mg, 56%) was prepared from **21** (24 mg, 0.05 mmol), thioanisole (72 mg, 0.58 mmol), and $AgBF_4$ (33 mg, 0.15 mmol) as described above: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.94 (t, J = 8.06 Hz, 2 H), 1.02 (d, J = 5.37 Hz, 3 H), 1.08 (d, J = 2.44 Hz, 3 H), 2.20–2.26 (m, 1 H), 2.37 (d, J = 6.35 Hz, 2 H), 2.43 (s, 2 H), 2.77 (s, 1 H), 3.30 (d, J = 32.7 Hz, 3 H), 3.40–3.42 (m, 1 H), 3.74 (t, J = 8.79 Hz, 1 H), 4.01–4.21 (m, 3 H), 4.12 (t, J = 8.55 Hz, 2 H), 4.35 (d, J = 17.1 Hz, 1 H), 4.47 (br s, 1 H), 5.54 (br s, 1 H), 5.95 (s, 1 H), 7.63–7.76 (m, 3 H), 7.97–8.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.51, 17.4, 27.8, 32.6, 38.7, 39.3, 44.2, 44.8, 60.3, 62.5, 69.4, 72.1, 81.8, 118.9, 126.3, 131.1, 131.3, 132.6, 151.3, 171.2, 171.9; IR (CH_2Cl_2) 2356, 1736, 1636, 1076 cm^{-1}; $[\alpha]^{22}_D$ −147° (c 0.87, $CHCl_3$).

Cyclization of Sulfonium Salt 22.[10] To a CH_3CN (1 mL) solution of tetrabutylammonium fluoride (0.1 mmol) was added a CH_3CN (10 mL) solution of **22** (17 mg, 0.03 mmol) at rt over 4 h, and the mixture was stirred overnight. Concentration in vacuo and purification by silica gel column chromatography ($CHCl_3$–

MeOH (30:1)) afforded **23**[8a] (5.3 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.28 (s, 3 H), 2.03–2.20 (m, 2 H), 2.08, 2.40 (ABq, J = 12.9 Hz, 2 H), 2.17, 2.26 (ABq, J = 15.4 Hz, 2 H), 2.61–2.68 (m, 1 H), 3.44–3.51 (m, 2 H), 4.02 (d, J = 16.6 Hz, 1 H), 4.10, 5.34 (ABq, J = 12.5 Hz, 2 H), 4.47 (br s, 1 H), 5.16 (br s, 1 H), 5.91 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 29.9, 34.1, 34.9, 43.7, 44.2, 53.7, 59.8, 61.6, 74.5, 77.2, 130.1, 132.8, 170.9, 171.2; IR (CH_2Cl_2) 1733, 1675 cm^{-1}; MS m/z 279 (M^+), 234, 218; HRMS calcd for $C_{15}H_{21}O_4N$ 279.1471, found 279.1494; $[\alpha]^{24}_D$ +42.4° (c 0.17, $CHCl_3$) (lit.[8a] $[\alpha]^{22}_D$ +42.4° ($CHCl_3$)).

Supplementary Material Available: ^{1}H NMR spectra for compounds **2a–f, 3a–f, 4a–f, 6, 7, 10–16,** and **19–23** and ^{13}C NMR spectra for compounds **16, 19,** and **21–23** (50 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Total Syntheses of (−)-Acetomycin and Its Three Stereoisomers at C-4 and C-5

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The total synthesis of the antitumor and antimicrobial agent (−)-acetomycin (**1**) from the previously reported tetrahydrofuran **10**, a derivative of D-glucose is described. Reactions which altered only the side chains of **10** gave the substituted tetrahydrofuran **20**, which was then converted into the acyclic alcohol **38** and oxidized to the corresponding carboxylic acid **39**. Ozonolysis of the vinyl group of **39** gave an aldehyde, spontaneous cyclization of which afforded a 5:1 mixture of the diastereomeric γ-hydroxy γ-lactone **40**. Treatment of the mixture with acetic anhydride in pyridine gave predominantly (>45:1) the α-acetate **41**. On the other hand, treatment of compounds **40** with methanesulfonyl chloride/triethylamine in benzene, followed by treatment of the mixture of mesylates so formed with silver acetate and tetrabutylammonium acetate, resulted in the formation of a 1.3:1 mixture of **41** and the β-acetate **42**. Removal of the MOM protecting group of **41** and **42** and pyridinium chlorochromate (PCC) oxidation of the products gave (+)-5-*epi*-acetomycin (**2**) and **1**, respectively. In a similar manner, (−)-4-*epi*-acetomycin (**3**) and (+)-4,5-di-*epi*-acetomycin (**4**) were synthesized from the substituted tetrahydrofuran **11**. The results of preliminary studies of the in vitro inhibitory effects of compounds **2–4** on the growth of several tumor cells are also presented.

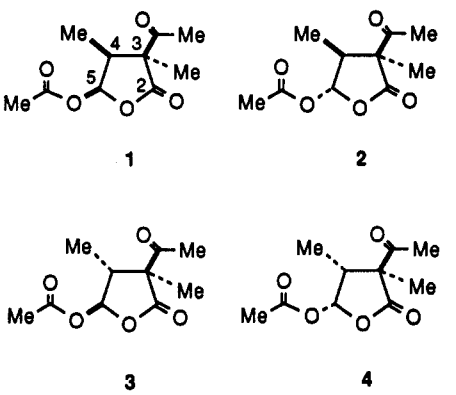
Introduction

In 1958, Prelog, Keller-Schierlein, and their co-workers isolated acetomycin from cultures of *Streptomyces ramulosus* (ETH 17653).[1] This antibiotic displayed broad but weak antimicrobial activity toward both Gram-positive and Gram-negative bacteria. Spectroscopic (UV, IR) analysis of acetomycin and its degradation products showed the structure to be 4-acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic acid γ-lactone.[2,3] However, the configurations about its three asymmetric carbons were not established. Feeding experiments demonstrated that acetomycin is biosynthesized from acetate, L-methionine, and D-glucose.[4]

In 1985, Zeeck and co-workers[5] determined the absolute and relative configurations of the bromo acetate of one of the two diastereomeric alcohols formed by the $NaBH_3CN$ reduction of the keto carbonyl group of acetomycin. Recently, an X-ray crystallographic analysis of acetomycin itself confirmed the absolute configuration.[6]

Acetomycin also inhibits the growth, in vitro, of such tumor cells as those of HCT-human colon adenocarsinoma and L1210 murine leukemia.[7] However, no inhibitory activity is observed in vivo. It has been suggested[8] that, in the latter case, acetomycin is inactivated by enzymatic hydrolysis of the acetoxy group. Reduction of the keto carbonyl group of acetomycin and acetylation of the resulting diastereomeric alcohols yields products which display no antimicrobial activity.[5]

Chart I



The novel structure and potential pharmacological importance of this antibiotic prompted us to carried out total syntheses of acetomycin and three of its stereoisomers. We describe here, in detail, the total syntheses of (−)-1; its (+)-5-epimer, (+)-5-*epi*-acetomycin (**2**);[9,10] and two other

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