Lewis Acid Promoted Reactions of 11-Methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one and Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one with Ethyl Diazoacetate

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The reaction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**1**) with ethyl diazoacetate (EDA, 1 equiv) in the presence of $F_3B{\cdot}OEt_2$, when performed at −78 °C → −40 °C, afforded three products: diethyl 3,6-dioxopentacyclo[6.5.0.0^{4,12}.0^{5,10}.0^{9,13}]tridecane-2,7-dicarboxylate (**2**, 6.4%), ethyl 2,6-dioxopentacyclo[5.5.0.0^{4,11}.0^{5,9}.0^{8,12}]dodecane-3-carboxylate (**5**, 7.4%), and a novel heterocyclic compound, **7** (31%), whose structure was established by X-ray structural analysis. Further reaction of **5** with excess EDA in the presence of $F_3B{\cdot}OEt_2$ at +10 °C → 25 °C produced diethyl 2,6-dioxopentacyclo[6.5.0.0^{4,12}.0^{5,10}.0^{9,13}]tridecane-2,6-dicarboxylate (**8**, 35%) along with recovered **5** (23%). The corresponding low-temperature (−78 °C → −40 °C) ring homologation of 11-methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**3**) gave two products, **9** and **10**. Decarboxylation of the mixture of **9** and **10** yielded a mixture of **11** and **12** (product ratio ca. 15:1). Ozonolysis of this mixture followed by reductive workup afforded two isomeric cage diketones, **13** and **16**, in 5.4% and 90% yield, respectively. Finally, low-temperature (−78 °C) ring homologation of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**4**) with EDA (1 equiv)–$F_3B{\cdot}OEt_2$ gave ethyl 3-oxopentacyclo[5.5.0.0^{4,11}.0^{5,9}.0^{8,12}]dodecane-2-carboxylate (**17**, ca. 90%) along with two unidentified products. Decarboxylation of this product mixture afforded a single cage ketone, **18**, in 94% yield. Reduction of **18** with $NaBH_4$–$CeCl_3$ gave the corresponding cage alcohol, **19** (87%), whose structure was established via X-ray crystallographic analysis of its corresponding 3,5-dinitrobenzoate derivative, **20**.

Introduction and Experimental Results

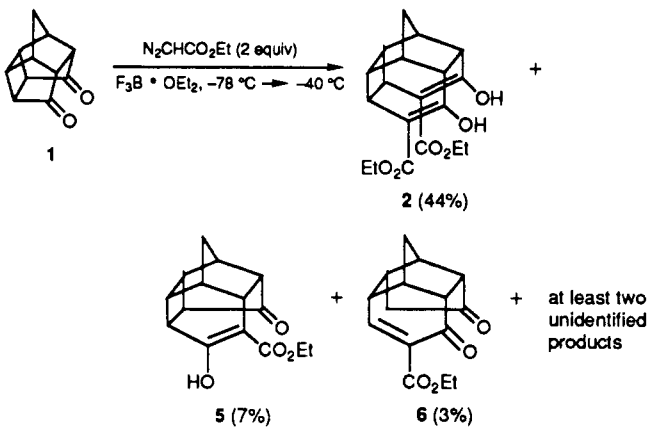
Recently, we reported the results of a study of Lewis acid promoted ring homologation of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (PCUD-8,11-dione, **1**) with ethyl diazoacetate (EDA).[2] A single bishomologation product, **2** (Scheme I), was obtained from the reaction of **1** with EDA (2 equiv) at −78 °C to −40 °C in the presence of boron trifluoride etherate. In a subsequent study, it was found that the corresponding reaction of **1** with EDA (1 equiv) at 0 °C to +25 °C afforded a complex mixture of at least five products, three of which were fully characterized, i.e., **2**, **5**, and **6**.[3] We now report the results of studies of low-temperature reactions of **1** with 1 and with 2 equiv of EDA in the presence of $F_3B{\cdot}OEt_2$.

In addition, we were interested in determining whether the second ketone carbonyl functionality in **1** [i.e., the C=O group at C(11)] influences the regioselectivity of ring monohomologation at the C(8) carbonyl group in the PCUD-8-one system. Accordingly, the corresponding low-temperature reactions of the title compounds, 11-methylene-PCUD-8-one and PCUD-8-one (**3** and **4**, respectively), with EDA–$F_3B{\cdot}OEt_2$ also were studied.

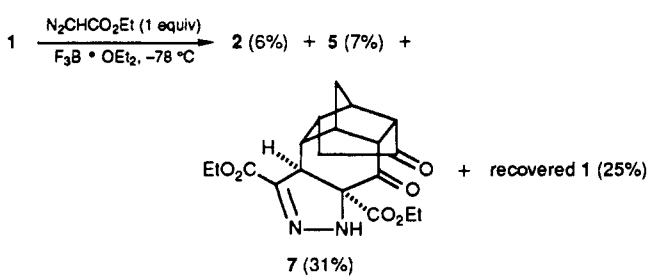
In view of the complexity of boron trifluoride promoted reactions of **1** with EDA,[3] we began by reinvestigating the low-temperature reaction of **1** with EDA (2 equiv) in the presence of $F_3B{\cdot}OEt_2$. Previously,[2] we reported the isolation of **2** in 21% yield from this reaction. We now find that at least *five* products are formed, three of which have been fully characterized (i.e., **2**,[2] **5**,[3] and **6**,[3] Scheme I).

Next, the reaction of **1** with EDA (1 equiv) and $F_3B{\cdot}OEt_2$ at −78 °C to −40 °C was investigated. The following products of this reaction have been isolated and characterized: **2** (6%),[2] **5** (7%),[3] and a novel heterocyclic compound, **7** (31%, Scheme II). The structure of **7** was established unequivocally via single-crystal X-ray structural analysis.

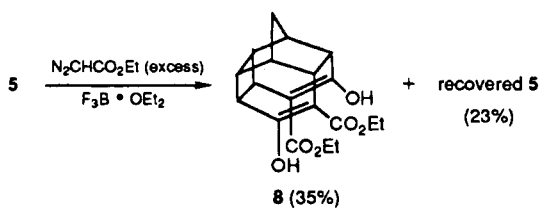
Scheme I



Scheme II



Scheme III



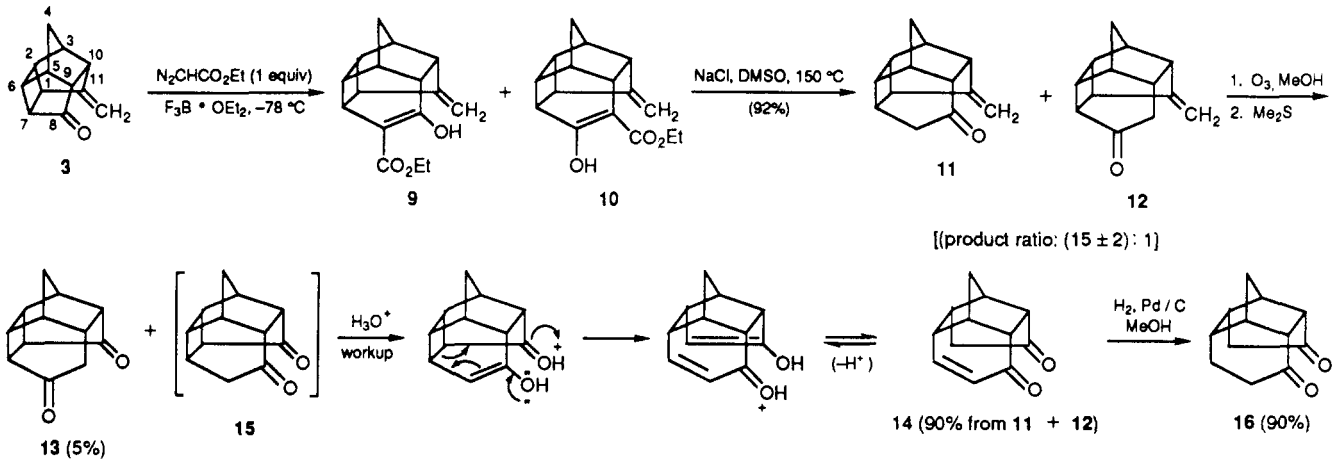
(1) (a) Robert A. Welch Postdoctoral Fellow, 1987. (b) Robert A. Welch Postdoctoral Fellow, 1987–1989. (c) Robert A. Welch Predoctoral Fellow, 1988–1989.

(2) Marchand, A. P.; Arney, B. E., Jr.; Gilardi, R.; Flippen-Anderson, J. L. *J. Org. Chem.* **1987**, *52*, 3455.

(3) Marchand, A. P.; Annapurna, P.; Reddy, S. P.; Watson, W. H.; Nagl, A. *J. Org. Chem.* **1989**, *54*, 187.

0022-3263/90/1955-3493$02.50/0

Scheme IV

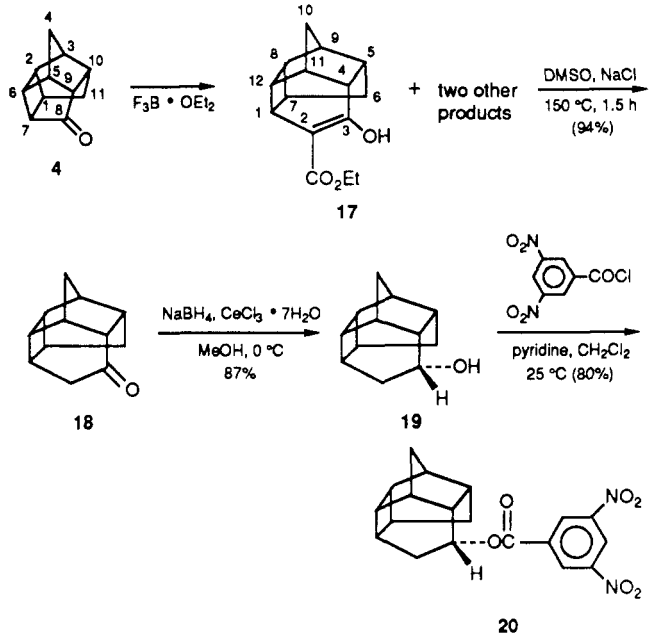


In addition, we have examined ring homologation of **5**[3] with EDA (2 equiv) in the presence of $F_3B{\cdot}OEt_2$ at +10 °C to +25 °C. Interestingly, the major product of this reaction was found to be **8** (35% yield, Scheme III). Compound **8** was identified readily by analysis of its proton and carbon-13 NMR spectra. Advantage was taken of the fact that **8** is isomeric with **2**, but **8** lacks a plane of symmetry.

The corresponding low-temperature (−78 °C to −40 °C) ring monohomologation reaction when applied to **3**[4] afforded an intractable mixture of two products, **9** and **10** (Scheme IV). The mixture of **9** and **10** was decarboxylated by using the procedure described by Krapcho and coworkers,[5] thereby affording a mixture of two cage enones, **11** and **12**. The product ratio **11**:**12** was determined to be (15 ± 2):1 via careful integration of resonances that appeared in the lowfield region (i.e., δ 100–215) of the gated-decoupled carbon-13 NMR spectrum of the product mixture. Ozonolysis of a mixture of **11** and **12**, followed by reductive workup, afforded **13** and **14** in yields of 5.4% and 90%, respectively. The results of an earlier study[3] suggest that **14** may be formed from intermediate cage diketone **15**, which is unstable to the reaction conditions and suffers acid promoted retro-Michael reaction. Compound **14** is unstable and difficult to handle; its structure was assigned via catalytic hydrogenation to **16**, a known compound.[5]

Finally, the corresponding low-temperature (−78 °C) ring monohomologation of **4**[4,7] was studied. The reaction product was purified initially via column chromatography; the eluate was further purified via fractional recrystallization first from 95% aqueous ethanol and then from methanol. The ^{13}C NMR spectrum of the product thereby obtained, mp 52.0–53.5 °C, contained 45 resonances, which corresponds to a mixture of three monohomologation products. Based upon analysis of the ^{13}C NMR spectrum of the product mixture, structure **17** (Scheme V) was assigned to the predominant reaction product (ca. 90%). The presence of quaternary carbon resonances at δ 96.57, 171.20, and 177.44 is consistent with the suggested enolic

Scheme V



structure for **17**. Interestingly, a single cage ketone, **18**, was isolated upon decarboxylation[5] of the product mixture. This result suggests that this mixture contains isomeric components (i.e., the enol form of **17** depicted in Scheme V along with two keto forms that contain exo and endo CO_2Et groups, respectively). In support of this conclusion, satisfactory elemental microanalysis corresponding to $C_{15}H_{18}O_3$ was obtained for this mixture (see the Experimental Section).

Further evidence to support the suggested structure **17** was garnered by subsequent reduction of its decarboxylation product, **18**, with $NaBH_4$–$CeCl_3$ (Scheme V).[8] Reduction of the carbonyl moiety in **18** occurred stereospecifically from the exo face of the C=O group, thereby affording the corresponding endo alcohol, **19**, in 87% yield. Compound **19** then was converted into the corresponding 3,5-dinitrobenzoate derivative, **20**.[9] The structure of **20** was established unequivocally via single-crystal X-ray structural analysis.

(4) Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1983**, *48*, 5392.
(5) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. (b) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1974**, 1091.
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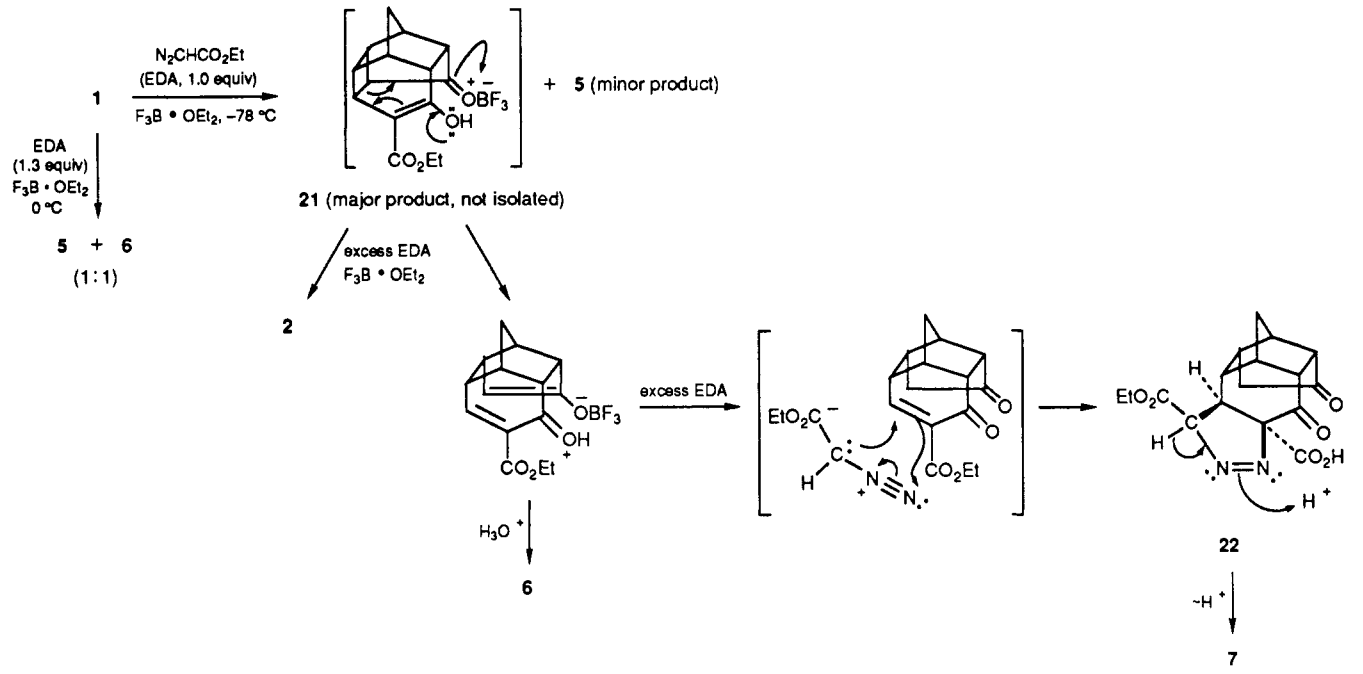
Scheme VI



Discussion

Taken together with past results from our laboratory,[2,3,6] a comprehensible pattern of behavior emerges from the present study of boron trifluoride promoted ring homologations of **1** with EDA. The key to understanding the course of the low-temperature reaction of **1** with EDA–$F_3B{\cdot}OEt_2$ is the realization that ring homologation occurs *regioselectively*, thereby affording both of the two possible ring monohomologation products, **5** and **21** (Scheme VI). The major product of this reaction, **21**, cannot be isolated. However, if excess EDA is present, **21** is trapped to provide the symmetric bishomologation product, **2**. In the absence of excess EDA, the presumed intermediate, **21**, undergoes retro-Michael reaction to afford **6**.[3] In the present study, it was demonstrated that **6** can react further with excess EDA at low temperature to afford **7**. This can occur via regiospecific intermolecular [3 + 2] cycloaddition of EDA to **6** followed by a facile prototropic shift that converts intermediate **22** into the corresponding Δ^2-pyrazoline, **7** (Scheme VI).[10]

Compound **5** appears to react very sluggishly with excess EDA–$F_3B{\cdot}OEt_2$ at low temperature to afford the unsymmetrical bishomologation product, **8**. Formation of **8** becomes relatively significant only when this reaction is performed at higher temperatures (i.e., 10–25 °C).

Low-temperature ring monohomologation of **3** with EDA (1 equiv)–$F_3B{\cdot}OEt_2$ appears also to proceed in highly regioselective fashion. Interestingly, migratory aptitudes in both the reaction of **1** and of **3** with EDA–$F_3B{\cdot}OEt_2$ appear to be comparable. In each substrate, the C(7)–C(8) σ-bond migrates preferentially to afford the major homologation product (i.e., **21** and **9**, respectively).

Finally, low-temperature ring homologation of **4** appears to proceed regiospecifically, again with preferential concomitant migration of the C(7)–C(8) σ-bond, to afford **17** in excellent yield along with two isomeric minor products. Since this compound does not contain a carbonyl functionality at C(6), there is no opportunity for retro-Michael reaction. Accordingly, **17** is stable to both the reaction and workup conditions.

The fact that each of these ring monohomologations proceeds with preferential migration of the C(7)–C(8) bond merits comment. Liu and co-workers[11] have observed that the major product obtained via $F_3B{\cdot}OEt_2$-promoted ring monohomologation of cycloalkanones proceeds with preferential migration of the less substituted α-carbon terminus. They considered this result to reflect the fact that transition states for competing 1,2-carbon–carbon bond migrations vary in their relative sensitivities to steric environment. In emphasizing the importance of an antiperiplanar relationship between the migrating carbon–carbon σ-bond and the leaving group, Mock and Hartman[12] suggested that regioselectivity of bond migration in reactions of this type is subject to conformational control, although they noted that this effect may be mitigated somewhat by other contributing steric factors.

Our results in systems **1**, **3**, and **4**, presented herein, collectively suggest that the sterically preferred transition state is achieved when the leaving group (N_2^+) is situated antiperiplanar to the C(7)–C(8) bond in the substrate.[3] However, detailed understanding of the relative importance of various steric factors on the regioselectivity of ring monohomologations in substituted PCUD-8-ones necessarily awaits the application of a higher level of theoretical analysis.

Experimental Section

Melting points are uncorrected. High-resolution mass spectra were obtained by personnel at the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, NE.

Low-Temperature BF_3-Promoted Reaction of 1 with EDA (2 equiv). A suspension of **1**[13] (2.00 g, 11.5 mmol) in anhydrous

(10) See: Regitz, M.; Heydt, H. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 398–451.

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ether (65 mL) was cooled externally to −78 °C. Boron trifluoride etherate (5.6 mL, 46 mmol) was added slowly with stirring during 10 min. After all of the Lewis acid catalyst had been added, EDA (2.4 mL, 23 mmol) was added dropwise at such a rate that a slow, steady stream of nitrogen was evolved during the addition. The reaction mixture was stirred for 1 h after the addition of EDA had been completed. The temperature of the reaction was allowed to increase to −40 °C, and stirring was continued at this temperature for an additional 1 h. The reaction was quenched via addition of saturated aqueous sodium bicarbonate solution (40 mL). The reaction mixture then was poured into a separatory funnel that contained water (200 mL). The layers were separated, and the ether layer was washed sequentially with 10% aqueous sodium bicarbonate solution (2 × 65 mL) and water (2 × 65 mL). The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue, a yellow oil (4.5 g), was purified via column chromatography on silica gel. Elution with 8% ethyl acetate–hexane mixed solvent afforded **2** (1.76 g, 44%), mp 113–114 °C (lit. mp 108.5–109 °C,[2] mp 113–114 °C[3]). The infrared, proton NMR, and carbon-13 NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra of authentic **2**.[2]

Further elution of the chromatography column with 10% ethyl acetate–hexane mixed solvent gave **5** (0.20 g, 7%) as a colorless oil, which resisted attempts at crystallization (lit.[3] mp 95–97 °C). The infrared, proton NMR, and carbon-13 NMR spectra of this material matched closely the corresponding spectra of authentic **5**.[3]

Further gradient elution with 20–40% ethyl acetate–hexane mixed solvent afforded at least two unidentified products (0.4 g). Finally, gradient elution with 45–50% ethyl acetate–hexane mixed solvent gave **6**, mp 125.5–126.5 °C (lit.[3] mp 126.5–127 °C). The infrared, proton NMR, and carbon-13 NMR spectra of this material matched closely the corresponding spectra of authentic **6**.[3]

Low-Temperature BF_3-Promoted Reaction of 1 with EDA (1 equiv). A suspension of **1** (1.04 g, 6.0 mmol) in anhydrous ether (35 mL) was cooled externally to −78 °C. Boron trifluoride etherate (0.74 mL, 6.0 mmol) was added dropwise with stirring. After all of the Lewis acid catalyst had been added, EDA (0.63 mL, 6.0 mmol) was added dropwise. The reaction mixture was stirred for 4 h after the addition of EDA had been completed. The reaction was quenched via addition of saturated aqueous sodium bicarbonate solution (25 mL). The ether layer was separated, and the aqueous layer was extracted with methylene chloride (60 mL). The combined organic layers were washed successively with water (50 mL) and brine (15 mL). The organic layer was dried (anhydrous sodium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue, a yellow oil (1.51 g), was purified by column chromatography on silica gel. Elution with 8% ethyl acetate–hexane mixed solvent afforded **2** (0.13 g, 6%). Further elution of the chromatography column with 10% ethyl acetate–hexane mixed solvent gave **5** (0.115 g, 7%).

Further elution with 30% ethyl acetate–hexane mixed solvent afforded unreacted starting material (**1**, 0.26 g, 25%). Finally, elution with 40% ethyl acetate–hexane mixed solvent gave **7** (0.70 g, 31%). Pure **7** was obtained via recrystallization from ethyl acetate–hexane mixed solvent as a colorless microcrystalline solid: mp 174–175 °C; IR (KBr) 3325 (br, s), 1740 (br, s), 1685 cm^{-1} (br, s); ^1H NMR ($CDCl_3$) δ 1.15–1.50 (m, 6 H), 1.75 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.85 (*AB*, J_{AB} = 10.5 Hz, 1 H), 2.18–3.10 (m, 8 H), 3.92 (s, 1 H), 4.12–4.45 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.29 (q), 13.66 (q), 36.50 (t), 37.66 (d), 37.95 (d), 38.39 (t), 38.48 (d), 46.50 (d), 48.75 (d), 49.83 (d), 55.67 (d), 61.24 (t), 62.55 (t), 74.93 (s), 145.53 (s), 160.58 (s), 169.31 (s), 200.2 (s), 215.65 (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 300 (50.0), 273 (88.5), 227 (100.0), 199 (20.5), 143 (10.2). Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.96; H, 5.92. Found: C, 60.67; H, 5.79. Independent verification of the structure suggested for **7** was obtained via single-crystal X-ray structural analysis (vide infra).

Reaction of 5 with Excess EDA–F_3B·OEt_2. A solution of **5** (710 mg, 2.73 mmol) in anhydrous ether (40 mL) was cooled externally to 10 °C. Boron trifluoride etherate (773 mg, 5.46 mmol) was then added slowly with stirring during 5 min. After all of the F_3B·OEt_2 had been added, EDA (620 mg, 5.46 mmol) was added dropwise. After the addition of EDA had been completed, the reaction mixture was allowed to warm slowly to room temperature and then stirred for 48 h. The reaction mixture was cooled externally to 0 °C, and the reaction was quenched via addition of saturated aqueous sodium bicarbonate solution (15 mL). The ether layer was separated, and the aqueous layer was extracted with methylene chloride (25 mL). The combined organic layers were dried (anhydrous sodium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel. Elution of the chromatography column with 10% ethyl acetate–hexane mixed solvent afforded **8** (330 mg, 35%) as a colorless microcrystalline solid: mp 82–84 °C; IR (film) 2980 (s), 2940 (m), 1635 (s), 1610 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.10–1.35 (m, 6 H), 1.40 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.60 (*AB*, J_{AB} = 10.8 Hz, 1 H), 2.10 (m, 1 H), 2.25 (m, 1 H), 2.60–2.84 (m, 3 H), 3.20–3.40 (m, 2 H), 3.85 (m, 1 H), 4.00–4.25 (m, 4 H), 11.90 (s, 1 H), 12.08 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.23 (q), 14.29 (q), 32.97 (d), 35.18 (d), 36.54 (d), 37.36 (t), 38.51 (d), 39.28 (d), 40.58 (d), 40.81 (d), 46.37 (d), 60.11 (t), 60.23 (t), 96.71 (s), 98.78 (s), 171.06 (s), 171.61 (s), 174.43 (s), 178.14 (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 228 (45.8), 200 (44.3), 180 (43.5), 178 (100.0), 117 (33.3); mass calcd for $C_{19}H_{22}O_6$ M_r 346.1417, found (high-resolution mass spectrometry) M_r 346.1416.

Reaction of 3 with EDA–F_3B·OEt_2. A solution of **3**[4] (1.03 g, 6.00 mmol) in anhydrous ether (40 mL) was cooled externally to −78 °C. Boron trifluoride etherate (850 mg, 6.00 mmol) then was added slowly with stirring during 5 min. After all of the F_3B·OEt_2 had been added, EDA (680 mg, 6.00 mmol) was added dropwise such that nitrogen was evolved at a slow, steady rate. The reaction mixture was stirred at −78 °C for 4 h after the addition of EDA had been completed. The reaction was quenched via addition of saturated aqueous sodium bicarbonate solution (20 mL). The ether layer was separated and then washed sequentially with water (15 mL) and brine (10 mL). The organic layer was dried (anhydrous sodium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residual yellow oil was purified via column chromatography on silica gel. Elution of the chromatography column with 1% ethyl acetate–hexane mixed solvent afforded an intractable mixture of **9** and **10** (product ratio 15:1, 1.1 g). This material was used as obtained in the next step without further purification. Continued elution of the chromatography column afforded unreacted **3** (175 mg, 17%).

Decarboxylation of the Mixture of 9 and 10. The procedure of Krapcho and co-workers[5] was utilized. Thus, a mixture of **9** and **10** (1.70 g, 6.60 mmol), sodium chloride (800 mg, 13.7 mmol), DMSO (8 mL), and water (7 drops) was heated at 150 °C under argon for 2 h. The reaction mixture then was poured into ice–water (100 mL), and the resulting mixture was extracted with methylene chloride (2 × 40 mL). The combined organic layers were washed sequentially with water (4 × 30 mL) and brine (20 mL), dried (anhydrous sodium sulfate), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel (6% ethyl acetate–hexane mixed solvent as eluent) to afford an intractable mixture of **11** and **12** (1.13 g, 92%). This material was used in the next step as obtained without further purification: IR (KBr) 1720 (s), 1625 (s), 1600 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.40 (*AB*, J_{AB} = 10.3 Hz, 1 H), 1.50 (*AB*, J_{AB} = 10.3 Hz, 1 H), 1.85–3.05 (m, 10 H), 4.50–4.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.31 (d), 35.01 (d), 35.69 (d), 37.16 (t), 37.46 (d), 38.01 (t), 38.30 (t), 38.77 (t), 38.92 (d), 39.63 (d), 44.06 (d), 44.29 (d), 45.18 (d), 45.94 (d), 46.95 (d), 48.58 (d), 49.44 (d), 49.66 (d), 57.80 (d), 107.20 (t), 107.77 (t), 152.53 (s), 153.65 (s), 211.93 (s), 213.90 (s); mass spectrum (70 eV), *m/e* (relative intensity) 186 (molecular ion, 47.9), 171 (10.0) 115 (33.2), 108 (49.5), 91 (87.1).

Ozonolysis of the Mixture of 11 and 12. A solution of the mixture of **11** and **12** (1.10 g, 5.91 mmol) in anhydrous methanol (60 mL) was cooled externally to −78 °C. A stream of ozone and oxygen was passed through the cold reaction mixture, during which time a transient blue color appeared. Ozonolysis was continued until the blue color persisted. Argon then was bubbled through the cold reaction mixture to purge excess ozone. The reaction was quenched via addition of dimethyl sulfide (2 mL). The cold bath was replaced by an external ice–water bath, and the quenched reaction mixture was allowed to warm to 0 °C. The reaction mixture was stirred at 0 °C for 1 h, the ice–water bath then was

removed, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was purified via column chromatography on silica gel (28% ethyl acetate–hexane mixed solvent as eluent). The first chromatography fractions afforded pure **13** (60 mg, 5.4%) as a colorless microcrystalline solid: mp 233–234 °C (lit.[6] mp 233–234 °C). The infrared, proton NMR, and carbon-13 NMR spectra of this material were identical in all respects with the corresponding spectra of authentic **13**.[6]

Further elution of the chromatography column with 45% ethyl acetate–hexane mixed solvent gave **14** (1.00 g, 90%) as a colorless microcrystalline solid: mp 183–186 °C (lit.[6] mp 183–186 °C). Compound **14** was characterized via catalytic hydrogenation, which afforded **16**. The infrared, proton NMR, and carbon-13 NMR spectra of the material thereby obtained were identical in all respects with the corresponding spectra of authentic **16**.[6]

Low-Temperature Reaction of 4 with EDA (1 equiv)-$F_3B{\cdot}OEt_2$. A solution of **4** (2.14 g, 13.4 mmol) in anhydrous ether (200 mL) was cooled externally to −78 °C. Boron trifluoride etherate (2.13 g, 15.0 mmol) then was added slowly with stirring during 5 min. After all of the $F_3B{\cdot}OEt_2$ had been added, EDA (1.71 g, 15.0 mmol) was added dropwise. After the addition of EDA had been completed, the reaction mixture was stirred at −78 °C for 2 h. The temperature of the reaction mixture was increased to −40 °C, and stirring was continued at this temperature for 2 h. The temperature then was increased to −20 °C, and stirring was continued for 1 h. Finally, the temperature of the reaction mixture was increased to 0 °C, and stirring was continued for 1 h. The reaction then was quenched via gradual addition of saturated aqueous sodium bicarbonate solution (40 mL). The ether layer was separated and washed with water (50 mL). The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel. Elution of the chromatography column with hexane afforded a pale yellow oil (3.06 g) that solidified upon cooling. Recrystallization of this material, first from 95% aqueous ethanol and then from methanol, afforded a colorless microcrystalline solid: mp 52.0–53.5 °C; IR (KBr) 1615 (vs), 1415 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.15–3.10 (m, 14 H), 3.45 (m, 1 H), 4.10 (m, 2 H), 11.95 (s, 1 H); ^{13}C NMR ($CDCl_3$; the chemical shifts of the 15 carbon atoms that correspond to the major product, **17**, are italicized) δ 14.02 (q), 14.12 (q), *14.25* (q), *29.07* (d), *30.64* (t), 31.04 (t), 32.47 (d), 32.95 (d), 34.91 (d), *35.30* (t), 35.69 (d), 38.18 (d), *38.37* (d), 38.57 (t), 38.67 (t), 39.10 (d), 39.53 (d), *39.62* (d), *40.50* (d), 40.70 (d), *41.06* (d), 43.34 (d), *43.78* (d), 44.12 (d), 44.26 (d), 44.36 (d), *47.53* (d), 47.75 (d), 47.90 (d), *48.26* (d), 54.67 (d), 54.81 (d), 55.52 (d), 55.57 (d), *59.90* (t), 60.77 (t), 61.14 (t), *96.57* (s), 169.23 (s), 169.67 (s), *171.20* (s), *177.44* (s), 209.03 (s), 209.06 (s), 209.65 (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 174 (7.8), 145 (1.7), 108 (100.0), 95 (42.2), 91 (15.7), 79 (32.2), 67 (23.6). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.37; H, 7.28.

Decarboxylation of 17.[5] A mixture of **17** (1.15 g, 4.67 mmol), sodium chloride (200 mg, 3.4 mmol), DMSO (2 mL), and water (300 mg) was heated at 150 °C for 1.5 h and then was allowed to cool to room temperature. The reaction mixture then was diluted with water (20 mL), and the resulting mixture was extracted with methylene chloride (3 × 30 mL). The combined organic layers were washed with water (3 × 20 mL), dried (anhydrous magnesium sulfate), and filtered, and the filtrate was concentrated in vacuo. The residue, a colorless solid, was sublimed at 100 °C (2.0 Torr), thereby affording pure **18** (766 mg, 94%) as a colorless microcrystalline solid: mp 220–221 °C; IR (KBr) 2980 (s), 2900 (m), 1715 (s), 1465 (m), 1405 (m), 1350 (m), 1235 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.37–1.59 (m, 4 H), 2.01–2.06 (m, 2 H), 2.30 (br s, 1 H), 2.40–2.60 (m, 4 H), 2.70–2.88 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 29.01 (d), 30.62 (t), 35.54 (d), 38.46 (t), 38.56 (t), 38.90 (d), 39.53 (d), 42.93 (d), 44.45 (d), 47.16 (d), 56.00 (d), 215.96 (s); mass spectrum (70 eV), *m/e* (relative intensity) 174 (molecular ion, 13.0), 108 (100.0), 95 (43.5), 91 (24.9). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.04; H, 8.01.

Pentacyclo[5.5.0.$0^{4,11}$.$0^{5,9}$.$0^{8,12}$]dodecan-*endo*-3-ol.[8] A solution of **18** (200 mg, 1.15 mmol) and cerium(III) chloride heptahydrate (895 mg, 2.4 mmol) in methanol (6 mL) was cooled externally to 0 °C. To the cooled, stirred reaction mixture was added sodium borohydride (90 mg, 2.4 mmol) in small portions in such a way that the temperature of the reaction mixture did not rise significantly above 0 °C. The reaction mixture was stirred for 15 min after all of the reducing agent had been added. The reaction then was quenched via addition of water (10 mL), and the resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with water (2 × 5 mL), dried (anhydrous magnesium sulfate), and filtered, and the filtrate was concentrated in vacuo. The residue, a colorless solid, was purified via column chromatography on silica gel by using a 5–10% ethyl acetate–hexane gradient elution scheme. Pure **19** (175 mg, 87%) was thereby obtained as a colorless microcrystalline solid: mp 225–226 °C; IR (KBr) 3330 (vs), 2970 (s), 2900 (m), 1465 (m), 1445 (m), 1315 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.25–1.45 (m, 3 H), 1.50–1.70 (m, 2 H), 1.85–2.00 (m, 3 H), 2.05–2.15 (m, 1 H), 2.25–2.45 (m, 3 H), 2.55–2.70 (m, 3 H), 4.05–4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.56 (d), 30.75 (t), 31.68 (t), 35.40 (d), 38.13 (t), 39.08 (d), 39.80 (d), 41.41 (d), 44.75 (d), 46.87 (d), 49.88 (d), 68.66 (d); mass spectrum (70 eV), *m/e* (relative intensity) 176 (molecular ion, 10.8), 158 (10.3), 143 (11.6), 130 (15.3), 129 (23.8), 92 (100.0). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.52; h, 9.34.

The corresponding 3,5-dinitrobenzoate derivative, **20**, was prepared by reacting a solution of **19** (100 mg, 0.57 mmol) in dry methylene chloride (25 mL) with 3,5-dinitrobenzoyl chloride in the presence of pyridine (0.5 g, excess) overnight at ambient temperature.[9] The material thereby obtained was purified via column chromatography on silica gel (10% ethyl acetate–hexane mixed solvent as eluent). Pure **20** (170 mg, 80%) was obtained as a pale green microcrystalline solid: mp 167–168 °C; IR (KBr) 3120 (m), 2980 (s), 2900 (m), 1715 (s), 1625 (m), 1540 (m), 1470 (m), 1350 (s), 1290 (s) 1185 (m), 1085 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.34–1.70 (m, 4 H), 2.02–2.22 (m, 3 H), 2.36–2.56 (m, 4 H), 2.62–2.82 (m, 3 H), 5.40–5.60 (m, 1 H), 9.05–9.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 28.72 (t), 29.91 (d), 30.83 (t), 35.33 (d), 38.21 (t), 38.54 (d), 39.66 (d), 41.69 (d), 43.70 (d), 44.61 (d), 49.78 (d), 75.34 (d), 122.12 (d), 129.28 (d), 134.72 (s), 148.64 (s), 162.12 (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 92 (100), 79 (59.3), 66 (60.5), 39 (61.6). Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90. Found: C, 61.80; H, 4.95. Independent verification of the structure suggested for **20** was obtained via single-crystal X-ray structural analysis (vide infra).

Single-Crystal X-ray Structural Analyses of 7 and 20. All X-ray data were collected on a Nicolet R3m/μ update of a $P2_1$ diffractometer; data were collected by using Mo Kα monochromated radiation (λ = 0.71073 Å. All computer programs were supplied by Nicolet for a Desktop 30 Microeclipse and Nova 4/C configuration. Atomic scattering factors and anomolous dispersion corrections were taken from the *International Tables for X-ray Crystallography*.[14]

Crystal Data for 7. The space group is *C*2/*c* with a = 23.198 (3) Å, b = 8.943 (1) Å, c = 21.983 (2) Å, β = 219.26 (1)°, Z = 8, D(calcd) = 1.408 g cm^{-3}, and μ = 0.99 cm^{-1}. An empirical absorption correction was applied. The structure was solved by direct methods and refined by a block-cascade least-squares procedure with the ethyl side-chain hydrogen atoms allowed to ride at fixed distances on the attached carbon atoms with a refined isotropic thermal parameter. All other hydrogen atom positions were refined. A total of 2116 independent reflections were collected that had intensities greater than $3\sigma(I)$. Refinement for 309 parameters led to a final R of 0.0584 with S = 1.466, $(\Delta/\sigma)_{max}$ = 0.019 with the largest residual peaks in the final difference map of −0.27 and +0.30 e $Å^{-3}$.

Crystal Data for 20. The space group is triclinic, P1, with a = 6.661 (1) Å, b = 10.469 (3) Å, c = 12.006 (3) Å, α = 88.13 (2)°, β = 81.08 (2)°, γ = 88.63 (2)°, Z = 4, D(calcd) = 1.488 g cm^{-3}, and μ = 1.05 cm^{-1}. An empirical absorption correction was applied. The structure was refined by using a block-cascade least-squares technique; hydrogen atoms were refined with isotropic thermal parameters. A total of 2607 independent reflections were collected that had intensities greater than $3\sigma(I)$. Refinement for 317 parameters led to a final R of 0.0585 with S = 1.595, $(\Delta/\sigma)_{max}$ = 0.015

(14) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV. (Present distributor, D. Reidel: Dordrecht).

with the largest residual peaks in the final difference map of −0.22 and +0.22 e Å^{-3}.

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Supplementary Material Available: Structure drawings of **7** and **20**, tables of atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atoms coordinates and isotropic displacement parameters for **7** and **20**, and a discussion of features of the X-ray structures of **7** and **20** (13 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of (±)-Debromoaplysin, (±)-Aplysin, (±)-Debromoaplysinol, (±)-Aplysinol, and (±)-Isoaplysin

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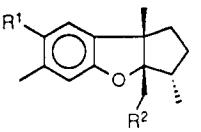
Stereocontrolled synthesis in racemic form of the title marine sesquiterpenes is described. Alkylation of styrenol **6** with α-bromopropanoic acid furnished acid **7**. Similar alkylation with α-bromo-β-methoxypropanoic acid provided acid **8**. Intramolecular cycloaddition of the ketene generated from the acid chloride of **7** afforded cyclobutanone **9** whereas **8** led to a mixture of **10** and **11**, but following a modified condition **10** could be obtained exclusively. Regioselective ring expansion of **9** and **10** to cyclopentanones **13** and **15** followed by addition of methylmagnesium iodide and dehydration provided olefins **16** and **17**. Hydrogenation of these using Pd–C catalyst lacked selectivity, but PtO_2 showed selectivity, affording (±)-**2** and **19**, respectively. Controlled bromination of **2** furnished (±)-aplysin (**1**), and **19** yielded **21**. Demethylation of **19** afforded (±)-debromoaplysinol (**3**). Similarly **21** furnished (±)-aplysinol (**4**). Bromination of **3** resulted in (±)-isoaplysin (**5**).

The red alga *Laurencia* and the sea hare *Aplysia* species provide a rich haul of halogenated sesquiterpenes.[1] Aplysin (**1**)[2] belongs to the first class of halogenated sesquiterpenes isolated from marine sources. The presumptive precursor of **1**, debromoaplysin (**2**)[2] and the related debromoaplysinol (**3**),[3] aplysinol (**4**),[2,4] and isoaplysin (**5**)[5] have also been isolated from these sources. These sesquiterpenes represent a new structural type, and some of them also display antifeedant properties which help protect the host mollusks from raptorial advances. The co-occurrence of the unhalogenated forms suggests the possibility of these functioning as antioxidants to scavenge reactive halogens. Commensurate with the novel structure and associated properties of these compounds have also been synthetic efforts. These efforts have spanned several years,[6] resulting in the synthesis of **1** and **2**. Recently we disclosed[7] a short and stereocontrolled synthesis of **1** and **2**. We now provide details of this and the first synthesis of **3**, **4**, and **5** in racemic form with full stereocontrol.

We envisaged development of the tricarbocyclic framework through a one-carbon ring enlargement of appropriately substituted dihydrocyclobutabenzofuranones, readily accessible from intramolecular cycloaddition of a



1: R^1 = Br; R^2 = H
2: R^1 = R^2 = H
3: R^1 = H; R^2 = OH
4: R^1 = Br; R^2 = OH
5: R^1 = H; R^2 = Br

phenoxy ketene onto an *ortho-situated* styrene. Indeed in recent years such an intramolecular ketene–alkene cycloaddition[8] has emerged as an important and versatile method for synthesis of polycyclic compounds. Further with a simple modification in the substrate at the initial stage, a single starting material should serve the synthetic requirements for all of the targeted natural products. Successful application of this methodology has led to the synthesis of **1**–**5** in good overall yields as shown below.

The starting material chosen was the styrenol **6**.[9] This already incorporates two of the methyl groups present in **1**–**5**, and introduction of the bromine atom into the aromatic ring as necessary for **1** and **4** can be effected at the last stage of the synthesis as already established.[6b] The styrenol **6** was alkylated in the presence of sodium hydride with α-bromopropanoic acid and furnished the phenoxypropanoic acid **7** in 63% yield (Scheme I). This acid, as its sodium salt, was reacted with oxalyl chloride to provide an acid chloride[10] which on treatment with Et_3N in benzene at reflux resulted in generation of the ketene and concomitant intramolecular cycloaddition[11] to afford the

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