Helenanolides: Stereocontrolled Total Synthesis of *dl*-Bigelovin, *dl*-Mexicanin I, and *dl*-Linifolin A

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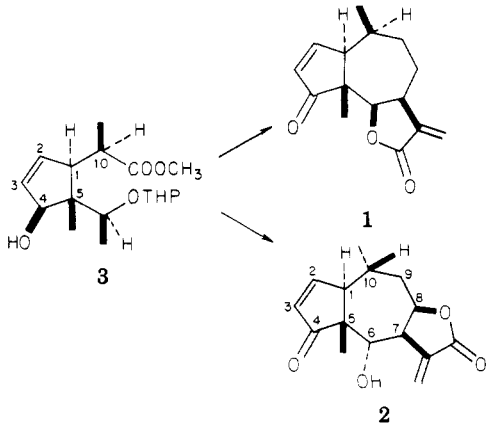
Stereocontrolled total syntheses of the sesquiterpene lactones *dl*-bigelovin (**11**), *dl*-mexicanin I (**12**), and *dl*-linifolin A (**13**) are described. The syntheses start with the hydroazulenone **4** and proceed via the key epoxy alcohol **9**. Elaboration of **9** into the tricyclic γ-lactone **14** *dl*-bigelovin. α-methylenation. Subsequent oxidation at C(4) completes the synthesis of *dl*-bigelovin. Epoxide opening of **9** with dilithioacetate provides access to tricyclic lactone **23** which gives way to **24** via reduction of ketone **25**. Cleavage of the benzyl ether in **24** followed by α-methylenation and oxidation generates *dl*-mexicanin I. Acetylation of **12** affords *dl*-linifolin A.

Our early efforts in the pseudoguaianolide area[1] were focused on the development of a general synthetic route to the ambrosanolides[2] (cf. ambrosin **1**) and the helenanolides[3] (cf. helenalin **2**) from a common synthetic intermediate. The successful realization of this plan, which culminated in the first total synthesis of *dl*-ambrosin[2a,4] and *dl*-helenalin,[3a,5] was completed in 1978 and employed as a key cornerstone cyclopentenol **3**. Central to our strategy for the transformation of **3** into *dl*-helenalin was hydroazulenone **4**,[6] which permitted facile elaboration of the three contiguous chiral centers at C(6), C(7), and C(8) via a series of remarkable stereospecific operations. It was indeed surprising and was unanticipated to find that epoxidation of hydrozulenone **4** by employing *tert*-butyl hydroperoxide–Triton B and subsequent reduction of the C(8) carbonyl generated exclusively epoxy alcohol **5**. Treatment of **5** with lithium lithioacetate and subsequent cleavage of the benzyl ether furnished tricyclic lactone **6** which was converted into *dl*-helenalin, thereby confirming the stereochemical assignments at C(6), C(7), and C(8).[5] While it was not surprising that the hindered *tert*-butyl hydroperoxide anion approached the enone system of hydroazulenone **4** from the side opposite the bulky C(5) methyl group, the exclusive delivery of hydride from the α face was. However, examination of a Dreiding model of intermediate epoxy enone **7**, after the fact, clearly reveals, in view of torsinal strain imposed on the system by the presence of the trans-fused cyclopentene ring, that approach of hydride can only occur from the α face of the



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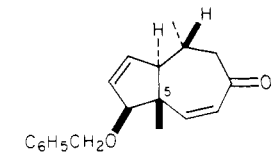

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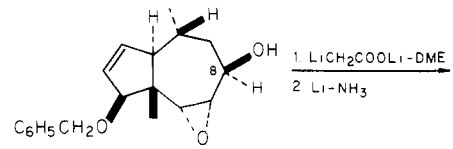

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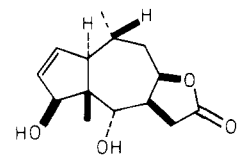

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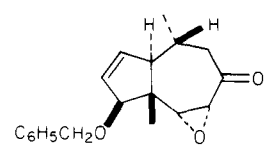

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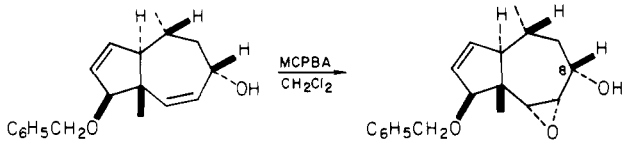
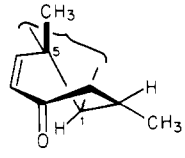
molecule due to the fact that β attack would be severely hindered by the C(5) methyl group and the C(10) proton.[7]

It was during the course of the present investigation that we examined the reduction of hydroazulenone **4** with lithium aluminum hydride. Quite unexpectedly, reduction of **4** gave rise to a single crystalline alcohol, **8**, in excellent



8 **9**

yield. Identical results were obtained with sodium borohydride, diisobutylaluminum hydride, and lithium tri-*tert*-butoxyaluminum hydride. Subsequent epoxidation of **8** with *m*-chloroperbenzoic acid provided exclusively epoxy alcohol **9**. The lack of epoxidation at the C(2)–C(3) carbon–carbon double bond is not unexpected in view of the Henbest principle.[8] The above structural assignments were readily confirmed by two key observations: (1) Collins oxidations of **5** and **9** both led in high yield to the formation of epoxy ketone **7**, suggesting that both **5** and **9** were isomeric at C(8); (2) epoxide **5** was converted into *dl*-helenalin, which unambiguously established the configuration at C(6) and C(8) in both **5** and **9**. Dreiding models clearly revealed once again (cf. twist–boat conformation **10**) that access to the ketone function by hydride from the α face is severely hindered due to the C(1) proton.[7]



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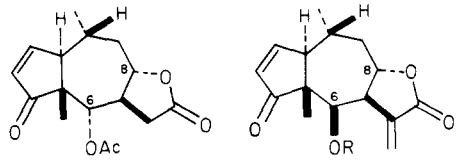
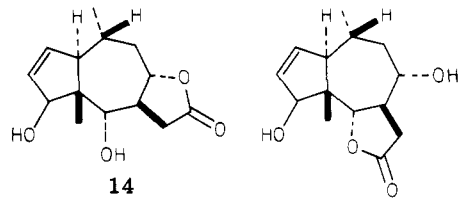
The efficient preparation of alcohol **9** from hydroazulenone **4** led us to explore the possibility of employing **9** as a common intermediate in helenanolide total synthesis. We detail below the transformation of **9** into *dl*-bigelovin (**11**), *dl*-mexicanin I (**12**), and *dl*-linifolin A (**13**).[9]



11 **12**, R = H
13, R = Ac

Note that the basic carbon skeleton of helenalin, bigelovin, mexicanin I, and linifolin A are all isomeric, differing only in the configuration about C(6) and C(8) on the seven-membered ring.

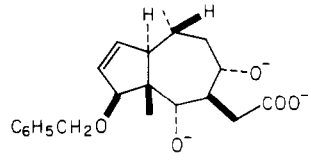
***dl*-Bigelovin.** Application of the methodology developed during our helenalin study[3a,5] to the construction of *dl*-bigelovin[10] from epoxy alcohol **9** proceeded in a facile and efficient manner despite the potential for problems. Of primary concern to us was the thermodynamic relationship between tricyclic γ-lactones **14** and **15**, both potential candidates arising from the treatment of epoxide



14 **15**

9 with lithium lithioacetate,[11] and subsequent cleavage of the benzyl ether. Despite the fact that the pseudoguaianolide literature did not shed any light on this important question, we forged ahead.

Elaboration of the γ-butyrolactone ring and cleavage of the benzyl ether were achieved by treatment of epoxide **9** with excess Creger dianion (lithium lithioacetate) in dimethoxyethane[12] followed by direct addition of the resultant intermediate trianion **16** to a solution of lithium



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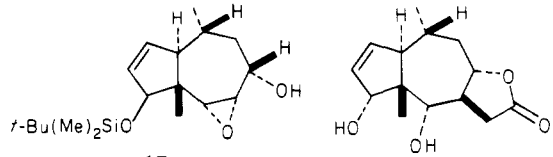
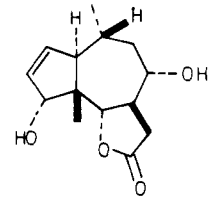
in liquid ammonia. Workup led, much to our surprise, to a single crystalline tricyclic γ-lactone in 85% yield as evidenced by IR (1770 cm^{-1}) and ^1H NMR analysis. The question of lactone orientation, C(8) normal vs. C(6) allo, was readily answered by ^1H NMR which revealed the C(8) proton as a doublet of doublets of doublets (ddd) centered at δ 4.46 with J values of 11.8, 10.0, and 3.2 Hz. The C(6) proton appeared at δ 3.67 as a doublet (J = 8.7 Hz). The above ^1H NMR data are only consistent with structure **14**.

We were indeed fortunate to have obtained a single tricyclic lactone, since after the completion of our work, Vandewalle and co-workers reported[13] that treatment of epoxide **17** with lithium lithioacetate followed by cleavage of the silyl ether resulted in a 2:1 ratio of bicyclic lactones **18** and **19**, respectively.



17 **18**



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Completion of the synthesis of *dl*-bigelovin required introduction of an α-methylene unit into the γ-lactone ring and oxidation of the C(4) hydroxyl. α-Methylenation was performed on the bistetrahydropyranylated lactone **20**. Hydroxymethylation,[14] mesylation, and β elimination as

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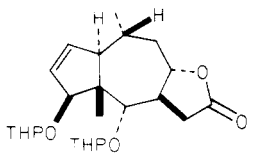

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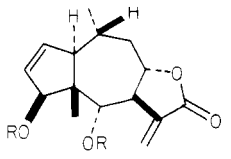
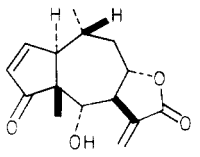


21

described previously[15] led in 61% overall yield to **21** (R = THP). Hydrolysis (60% acetic acid, 45 °C, 1.5 h) of the protecting groups gave rise to crystalline diol **21** (R = H), mp 152–153 °C. Bigelovin, like helenalin, is very unstable under both acidic and basic conditions.[10] Furthermore, the instability of bigelovin to acid and base has precluded the isolation of deacetylbigelovin (**22**).[10] Oxidation of **21**



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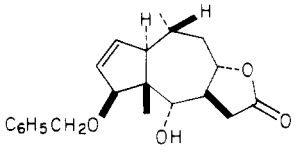
(R = H) with manganese dioxide in methylene chloride–benzene (2:1) afforded (77%) pure tricyclic enone **22**, mp 186–187 °C, after chromatography on SilicAR CC-7. Acetylation of **22** was carried out at room temperature in pyridine with acetic anhydride in the presence of 4-(dimethylamino)pyridine.[16] An 81% isolated yield of racemic bigelovin (**11**), mp 195.5–197.5 °C) was obtained after chromatography on SilicAR CC-7 whose spectral properties were identical with those reported in the literature for the natural material. The total synthesis of *dl*-bigelovin confirms the structural assignment put forth some years ago by Professor Werner Herz.

***dl*-Mexicanin I and *dl*-Linifolin A.** In view of the availability of epoxy alcohol **9** by a stereocontrolled process, it seemed only reasonable to consider **9** as an intermediate along the pathway to mexicanin I (**12**).[17] Our experience in the bigelovin synthesis (vide supra) led us to examine the condensation of epoxy alcohol **9** with lithium lithioacetate in hopes of obtaining directly, tricyclic lactone **23**.



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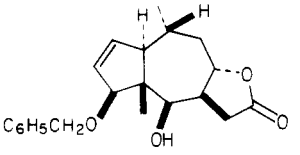
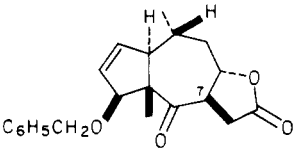


24

Treatment of epoxide **9** with the dianion of acetic acid in dimethoxyethane at 55 °C followed by a workup with 10% hydrochloric acid gave rise exclusively to tricyclic lactone **23**, mp 141–143 °C.

An inversion of configuration at C(6) in compound **23** would give way to the carbon framework (cf. **24**) of both mexicanin I (**12**) and linifolin A (**13**) having all chiral centers in the proper configuration. At first glance this approach would appear to warrant merit. Some years ago Herz and co-workers[18] examined, in an attempt to deduce the stereochemical relationships between tetrahydrohelenalin, dihydromexicanin C, and tetrahydrobigelovin, the interconversion of pseudoguaianolides by inversion of the configuration of C(6) by direct displacement. Unfortunately the vast majority of systems studied led to elimination rather than displacement. Our own attempts to invert the configuration at C(6) in **23** by displacement of the corresponding mesylate with a variety of nucleophiles were unsuccessful.

An indirect way to achieve the desired transformation (cf. **23** → **24**) would be to oxidize **23** to ketone **25** followed



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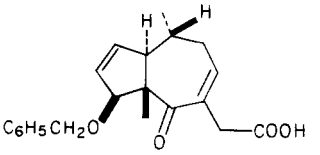
by reduction to **24**. It was anticipated that reduction of **25** would be influenced by the presence of the bulky C(5) angular methyl group. Hence, hydride attack should occur from the α face. This approach is only viable if irreversible β elimination[19] of the C(8) oxygen (cf. **25** → **26**) and/or



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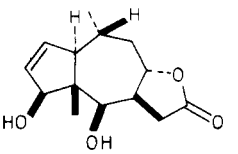
epimerization at C(7) can be avoided. In light of the above considerations, execution of the desired transformation would require careful experimentation. Toward this end, tricyclic ketone **24**, obtained by oxidation (Jones reagent) at −10 °C, was immediately reduced with sodium borohydride, giving rise exclusively to tricyclic alcohol **24** in 70% overall yield. The epimeric alcohol **23** could not be detected. Analysis of the ^{1}H NMR spectrum of **24** revealed the C(6) methine proton as a doublet of doublets centered at δ 4.09 with coupling constants of 5.0 and 2.7 Hz, respectively. Upon addition of D_2O, the doublet of doublets collapsed to a doublet with J = 5.0 Hz.

With all the stereochemistry of mexicanin I embodied in hydroazulenol **24**, we turned our attention to completing our initially stated goal, the total synthesis of mexicanin I (**12**) and linifolin A (**13**).[20] Our first attempts to transform **24** into **12** proceeded along lines established in our helenalin synthesis, since standard conditions for cleaving of the benzyl ether are not compatible with the existing functionality. Thus, hydrolysis of lactone **24** with potassium hydroxide in dimethoxyethane followed by direct treatment of the resultant dianion **24** with lithium in liquid ammonia gave rise upon acidic workup to a single crystalline tricyclic diol: mp 169–171 °C; 70% yield. Examination of the ^{1}H NMR spectrum (Me_2SO-d_6, 220 MHz) immediately established that the debenzylation product was not the desired tricyclic trans lactone **27**. The



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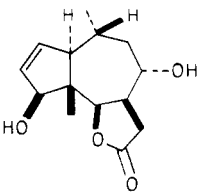

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presence of a one-proton multiplet at δ 3.80 and a one-

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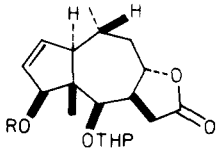
proton doulet at δ 4.70 with a coupling constant of 7.5 Hz suggested the presence of a C(6)–C(7) cis-fused γ-lactone. *Indeed*, the product of the above reaction was the cis-fused tricyclic lactone **28**. After the fact, this result is in keeping with our observation in the helenalin synthesis where one observes complete preference for formation of a C(7)–C(8) cis-fused lactone over the C(6)–C(7) trans-fused lactone.

In view of the above oversight, it became clear that maintainence of the C(7)–C(8) trans-fused tricyclic lactone unit would necessitate prior protection of the C(6) hydroxyl. Thus, the tetrahydropyranyl ether of alcohol **24** was subjected to sequential treatment with 1.2 equiv of potassium hydroxide, lithium in liquid ammonia, and 1 N hydrochloric acid (pH 5) The resultant sensitive diol acid was treated with dicyclohexylcarbodiimide in methylene chloride to effect lactonization, thus avoiding complications due to any inadvertent loss of the C(6) tetrahydropyranyl ether. Tricyclic alcohol **29** (R = H) was obtained in 75% overall yield.

Tetrahydropyranylation of **29** (R = H) gave the diadduct **29** (R = THP) which was subjected to α-methylenation.[14]



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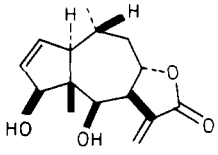

30

The three-step sequence [(1) hydroxymethylation, (2) mesylation, and (3) β elimination] was carried out in 54% overall yield. Removal of the protecting groups with 60% aqueous acetic acid at 45 °C afforded (88%) crystalline α-methylene lactone **30**, mp 144–145 °C. Analysis of the ^{1}H NMR spectrum revealed that the C(7)–C(8) trans-fused γ-lactone fragment was still intact. Oxidation of **30** by using manganese dioxide in methylene chloride–benzene (2:1) produced (78%) pure crystalline *dl*-mexicanin I (**12**, mp 246–248 °C) whose spectral properties were identical with the reported data for the natural product. The transformation of *dl*-mexicanin I into *dl*-linifolin A (**13**) was achieved in 86% yield by using acetic anhydride in pyridine containing a catalytic amount of 4-(dimethylamino)pyridine. The crystalline *dl*-linifolin A (**13**, mp 182.0–182.5 °C) obtained was identical in all respects with an authentic sample of linifolin A by comparison of spectral properties (IR, NMR, and mass spectrometry) and thin-layer mobility in several solvent systems. The total synthesis of mexicanin I and linifolin A confirms the structural assignments made for these two closely related pseudoguaianolides.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian T-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Ether, tetrahydrofuran, dimethoxyethane, and dioxane were distilled under argon from sodium metal with benzophenone ketyl as an indicator. Dimethylformamide, hexamethylphosphoramide, dimethyl sulfoxide, pyridine, and benzene were distilled from calcium hydride. Methylene chloride was passed through a column of alumina prior to use.

(1α,3aβ,4β,8aα)-3a,4,5,8a-Tetrahydro-4,8a-dimethyl-1-(phenylmethoxy)-6(1*H*)-azulenol (8). To a suspension of 81 mg (2.12 mmol) of lithium aluminum hydride in 5 mL of dry tetrahydrofuran at 0 °C was added a solution of 300 mg (1.06 mmol) of enone **4** in 5 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred at 0 °C for 30 min, after which time it was quenched with reagent grade ether. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, leaving 304 mg (quantitative) of crystalline allyl alcohol **8**: mp 62–64 °C; homogeneous by TLC analysis, R_f 0.39 (hexanes–ether, 1:1); IR ($CHCl_3$) 3600, 3550–3250, 3060, 3000, 2920, 2870, 1600, 1500, 1455, 1350, 1155, 1130, 1075, 1040, 1030, 910 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H), 5.6–6.0 (m, 4 H), 4.64 (m, 2 H), 4.35 (br s, 1 H), 1.8–2.4 (m, 4 H), 1.6 (br s, 2 H), 1.06 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.18; H, 8.47.

(1aα,2β,4β,4aβ,7α,7aα,7bα)-1a,2,3,4,4a,7,7a,7b-Octahydro-4,7a-dimethyl-7-(phenylmethoxy)azuleno[4,5-*b*]oxiren-2-ol (9). To a solution of 304 mg (1.06 mmol) of allyl alcohol **8** in 25 mL of dry methylene chloride was added 217 mg (1.06 mmol) of 85% *m*-chloroperbenzoic acid. The reaction mixture was stirred at room temperature for 17 h. The reaction was quenched by the addition of solid sodium bicarbonate and the solvent removed in vacuo. The oily residue obtained was diluted with ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration and evaporation gave 275 mg of a residue which was directly chromatographed on 15 g of silica gel. Elution with 1:1 hexanes–ether provided 206 mg (65%) of crystalline epoxy alcohol **9**: mp 98–100 °C; R_f 0.42 (hexanes–ether, 1:2); IR ($CHCl_3$) 3600, 3550–3200, 3060, 2980, 2870, 1500, 1460, 1385, 1355, 1300, 1160, 1110, 1080, 1045, 1020, 975, 940, 920 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.3–7.4 (m, 5 H), 5.7–5.8 (m, 2 H), 4.66 (AB q, 2 H, $\Delta\nu_{AB}$ = 20.5 Hz, J = 11.9 Hz), 4.57 (m, 1 H), 4.14 (dd, 1 H, J = 10.7, 3.5 Hz), 3.33–3.21 (m, 2 H), 2.34 (dd, 1 H, J = 10.3, 1.6 Hz), 1.4–2.2 (m, 4 H), 1.01 (d, 3 H, J = 6.1 Hz), 0.94 (s, 3 H). Recrystallization from hexanes–ether provided analytically pure **9**, mp 99–100 °C. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.70; H, 8.05.

(3aα,4α,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4,5-dihydroxy-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (14). To a solution of 1.86 mL (24.4 mmol) of freshly distilled diisopropylamine in 9 mL of dry dimethoxyethane under nitrogen at −42 °C (dry ice/3-pentanone) was added 8.16 mL (24.4 mmol) of a 1.50 M solution of *n*-butyllithium in hexane over a 10-min period. The solution was stirred at −42 °C for 10 min, followed by the addition of 360 μL (6.2 mmol) of scrupulously dried acetic acid (the acetic acid was first distilled from potassium permanganate and subsequently from boron triacetate). The above suspension was heated to 43 °C with stirring for 90 min. A solution of 127 mg (0.42 mmol) of epoxy alcohol **9** in 7 mL of dry dimethoxyethane was added to the reaction mixture. The reaction mixture was stirred at 55 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with 5 mL of dimethoxyethane. The reaction mixture was transferred via a cannula into a solution of 80 mL of ammonia containing 80 mg (11.4 mmol) of lithium metal. After the mixture was stirred for 1 min, the reaction was quenched by the addition of solid ammonium chloride. The ammonia was removed under reduced pressure, and 5 mL of water was added. The resulting solution was acidified with 10% hydrochloric acid to pH 3 and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. The residue obtained upon evaporation of the solvent was dissolved in 75 mL of benzene and evaporated. This process was repeated two times. TLC analysis indicated lactonization to be complete. The residue (200 mg) obtained was purified on 20 g of silica gel. Elution with ethyl acetate provided 93 mg (85% yield) of crystalline diol **14**: mp 185–187 °C: R_f 0.78 (acetone); IR ($CHCl_3$) 3610, 3600–3200, 3030, 3010, 2960, 1770, 1470, 1420, 1380, 1365, 1345, 1270, 1210, 1165, 1060, 1020, 985 cm^{-1}; NMR [250 MHz, $(CD_3)_2CO$] δ 5.7 (m, 1 H), 5.6 (m, 1 H), 5.34 (br s, 1 H), 4.46 (ddd, 1 H, J = 11.8, 10.0, 3.2 Hz), 3.67 (d, 1 H, J = 8.7 Hz), 2.87 (br s, 2 H), 2.37 (dt, 1 H, J = 10.8, 4.2 Hz), 1.88 (m, 1 H), 1.30 (AB q, 1 H, $\Delta\nu_{AB}$ = 21.4 Hz, J = 12.1 Hz), 1.11 (d, 3 H, J = 7.5 Hz), 1.02 (s, 3 H). Recrys-

tallization from chloroform–ether–hexanes provided analytically pure lactone diol **14**, mp 186–188 °C. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; 4, 7.99. Found: C, 66.51; H, 7.80.

(3aα,4α,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[5,6-*b*]furan-2(3*H*)-one (20). A solution of 93 mg (0.36 mmol) of lactone diol **14** in 20 mL of dry methylene chloride containing 5 mg of *p*-toluenesulfonic acid was cooled to 0 °C and treated with 200 μL (0.5 mmol) of dihydropyran. After 1 h at 0 °C and 1 h at room temperature, the reaction was quenched with solid sodium bicarbonate, diluted with 50 mL of ether, and washed with 5 mL of brine. The organic phase was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to afford 127 mg of residue. Chromatography on 10 g of silica gel (elution with hexanes–ether, 1:2) gave 115 mg (76%) of bis-tetrahydropyranylated lactone **20**: (IR ($CHCl_3$) 3070, 3000, 2940, 2850, 1765, 1465, 1450, 1440, 1380, 1360, 1350, 1340, 1315, 1280, 1270, 1195, 1150, 1120, 1070, 1030, 1015, 980, 970 cm^{-1}) which was used directly in the next reaction.

(3aα,4α,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4,5-dihydroxy-3-methylene-4a,8-dimethylazuleno[6,5-*b*]-furan-2(3*H*)-one (21, R = H). To a solution of diisopropylamine (74 μL, 0.5 mmol) in 1.5 mL dry tetrahydrofuran cooled to −78 °C was added 324 μL (0.5 mmol) of *n*-butyllithium in hexane. After 15 min, a solution of 140 mg (0.33 mmol) of bis(tetrahydropyranyl) ether **20** in 1 mL of dry tetrahydrofuran was added dropwise over a period of 30 min. After 30 min at −78 °C, the reaction mixture was warmed to −25 °C, and formaldehyde, generated from 300 mg of paraformaldehyde at 150 °C, was passed into the reaction mixture with the aid of a stream of dry nitrogen. After complete depolymerization, the reaction mixture was stirred for an additional 30 min at −25 °C. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was diluted with 30 mL of ether and 30 mL of ethyl acetate and directly dried over anhydrous magnesium sulfate. Evaporation under reduced pressure provided 145 mg of a residue which was purified on 10 g of silica gel. Elution with ether gave 105 mg (70%) of hydroxymethylated lactone [IR ($CHCl_3$) 3620, 3600–3200 cm^{-1}] which was used directly in the next reaction.

A solution of the above hydroxymethylated lactone (105 mg, 0.23 mmol) in 2 mL of pyridine containing 40 μL (0.46 mmol) of methanesulfonyl chloride was allowed to stir at 0 °C for 1 h and at room temperature for 1 h. The reaction mixture was quenched with 3 mL of water and repeatedly extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Concentration in vacuo left 105 mg of essentially pure mesylate [NMR δ (CCl_4) 6.0–5.7 (m, 2 H), 3.0 (s, 3 H); IR ($CHCl_3$) 3000, 2950, 2850, 1765, 1470, 1460, 1445, 1365, 1320, 1300, 1280, 1200, 1175, 1155, 1130, 1075, 1035, 1020, 975, 945, 910 cm^{-1}] which was used directly in the next reaction.

The above mesylate (110 mg, 0.23 mmol) was dissolved in 3 mL of dry benzene to which 50 μL of 1,5-diazabicyclo[5.4.0]undec-5-ene was added. After 1 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on 10 g of silica gel. Elution with hexanes–ether (1:2) gave 66 mg of α-methylene lactone **21** (R = THP): 61% yield (from **20**); IR ($CHCl_3$) 3080, 3000, 2950, 2870, 2850, 1765, 1755, 1660, 1465, 1450, 1440, 1380, 1355, 1290, 1275, 1260, 1180, 1170, 1120, 1075, 1030, 1020, 1010, 980, 905 cm^{-1}.

A solution of 30 mg (0.060 mmol) α-methylene lactone **21** (R = THP) in 1 mL of glacial acetic acid/water (60:40, v/v) was stirred at 45 °C for 90 min. Removal of the solvent under reduced pressure (<0.1 mm) gave an oily residue which was directly chromatographed on 5 g of SilicAR CC-7. Elution with ether gave 15 mg (82%) of crystalline α-methylene lactone **21** (R = H): mp 152–153 °C; R_f 0.12 (ether); IR ($CHCl_3$) 3600, 3550–3100, 3000, 2980, 2930, 1760, 1660, 1465, 1455, 1400, 1375, 1355, 1330, 1270, 1160, 1120, 1100, 1050, 1010, 980, 950, 920, 910 cm^{-1}; NMR δ (250 MHz) ($CDCl_3$) 6.25 (d, 1 H, J = 3.0 Hz), 6.10 (d, 1 H, J = 3.0 Hz), 5.78 (m, 1 H), 5.69 (m, 1 H), 5.32 (m, 1 H), 4.44 (ddd, 1 H, J = 12.3, 9.7, 2.6 Hz), 3.91 (dd, 1 H, J = 9.4, 4.7 Hz), 2.90 (m, 1 H), 2.52 (m, 1 H), 2.4 (m, 1 H), 2.37 (d, 1 H, J = 4.7 Hz), 1.88 (m, 2 H), 1.78 (d, 1 H, J = 9 Hz), 1.40 (q, 1 H, J = 12.3 Hz), 1.12 (d, 3 H, J = 6.3 Hz), 1.02 (s, 3 H). Recrystallization from acetone–hexanes provided analytically pure **21** (R = H), mp 152–153 °C. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.36; H, 7.68.

(3aα,4α,4aβ,7aα,8α,9aβ)-3,3a,4,4a,6,8,9,9a-Octahydro-4-hydroxy-4a,8-dimethyl-3-methyleneazuleno[6,5-*b*]furan-2,5-dione (22). A suspension of 120 mg of freshly prepared manganese dioxide and 13 mg (0.049 mmol) of α-methylene lactone **21** (R = H) in a solution of 2 mL of dry methylene chloride and 3 mL of benzene was stirred at room temperature for 30 min. The mixture was diluted with 20 mL of ether and filtered. The oxide cake was washed with ether (5 × 5 mL). The combined filtrate and washings were evaporated to dryness, and the residue was chromatographed on neutral silica gel (SilicAR CC-7, Aldrich). Elution with ether yielded 10 mg (77%) of crystalline **22**: mp 185–187 °C; R_f 0.48, ether; IR ($CHCl_3$) 3570, 3060, 3020, 2975, 2940, 1765, 1698, 1660, 1580, 1455, 1445, 1400, 1385, 1370, 1355, 1338, 1265, 1220, 1160, 1140, 1120, 1100, 1070, 1050, 1025, 1000, 982, 970, 960, 945, 935 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.77 (dd, 1 H, J = 6.4, 1.5 Hz), 6.24 (d, 1 H, J = 3.3 Hz), 6.14 (dd, 1 H, J = 6.0, 2.9 Hz), 6.02 (d, 1 H, J = 3.3 Hz), 4.53 (ddd, 1 H, J = 11.2, 10.5, 2.9 Hz), 4.15 (dd, 1 H, J = 8.6, 2.1 Hz), 3.08–2.86 (m, 3 H), 2.52 (ddd, 1 H, J = 12.5, 4.0, 3.4 Hz), 2.04 (m, 1 H), 1.52 (m, 1 H), 1.28 (d, 3 H, J = 6.2 Hz), 1.19 (s, 3 H). Recrystallization from acetone–hexanes provided analytically pure **22**: mp 186–187 °C; high-resolution mass spectrum; m/e 262.12090 (calcd for $C_{15}H_{18}O_4$ m/e 262.12051).

***dl*-Bigelovin (11).** A solution of 5.5 mg (0.021 mmol) of lactone **22**, 0.5 mg of 4-(dimethylamino)pyridine, 0.5 mL of pyridine, and 0.1 mL of acetic anhydride was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. The oily residue was chromatographed directly on neutral silica gel (SilicAR CC-7). Elution with ether provided 6.5 mg (81%) of crystalline *dl*-bigelovin: mp 194–196 °C; R_f 0.57 (ether); IR ($CHCl_3$) 3020, 2960, 2935, 1765, 1730, 1710, 1665, 1585, 1460, 1410, 1390, 1375, 1350, 1340, 1285, 1275, 1240, 1160, 1140, 1130, 1100, 1070, 1045, 1025, 1000, 980, 960, 940 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.71 (dd, 1 H, J = 6.1, 1.8 Hz), 6.23 (d, 1 H, J = 3.5 Hz), 6.11 (dd, 1 H, J = 6.1, 3.0 Hz), 5.92 (d, 1 H, J = 3.5 Hz), 5.61 (d, 1 H, J = 7.4 Hz), 4.61 (ddd, 1 H, J = 12.1, 11.4, 3.1 Hz), 3.0–3.1 (m, 2 H), 2.58 (dt, 1 H, J = 13.2, 3.8 Hz), 1.9–2.1 (m, 4 H), 1.97 (s, 3 H), 1.54 (m, 1 H), 1.29 (d, 3 H, J = 7.2 Hz), 1.21 (s, 3 H). Recrystallization from acetone–hexanes gave analytically pure *dl*-bigelovin, mp 195.5–197 °C. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.81; H, 6.58.

(3aα,4α,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4-hydroxy-4a,8-dimethyl-5-(phenylmethoxy)azuleno[6,5-*b*]-furan-2(3*H*)-one (23). To a solution of 620 μL (8.2 mmol) of freshly dried diisopropylamine in 3 mL of dry dimethoxyethane under nitrogen at −42 °C (dry ice/3-pentanone) was added 2.72 mL (4.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane over a 10-min period. The solution was stirred at −42 °C for 10 min, followed by addition of 120 μL (2.06 mmol) of scrupulously dried acetic acid in 1 mL of dimethoxyethane. The suspension was heated to 43 °C with stirring and maintained at that temperature for 90 min. A solution of 42 mg (0.14 mmol) of epoxy alcohol **9** in 1 mL of dimethoxyethane was added to the reaction mixture. The reaction mixture was stirred at 55 °C for 8 h. After the mixture was cooled to 0 °C, 4 mL of water was added, and the resulting solution was extracted with two 20-mL portions of ether. The combined ether extracts were washed with 10 mL of a 2% sodium hydroxide solution. The combined aqueous phases were acidified to pH 3 with 10% aqueous hydrochloric acid and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 50 mL of benzene and evaporated to dryness. This process was repeated until lactonization was complete. The crude product was purified on 10 g of silica gel. Elution with hexanes–ether (1:3) gave 40 mg (82%) of pure crystalline lactone **23**: mp 141–143 °C; R_f 0.70, ether; IR ($CHCl_3$) 3580, 3070, 3030, 3010, 2980, 2940, 2870, 1770, 1500, 1470, 1455, 1420, 1380, 1365, 1355, 1265, 1200, 1170, 1110, 1065, 1045, 1030, 1010, 990, 940, 910 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.80 (m, 2 H), 4.92 (m, 1 H), 4.57 (AB q, 2 H, $\Delta\nu_{AB}$ = 51 Hz, J = 12.2 Hz), 4.50 (m, 1 H), 3.56 (d, 1 H, J = 8.7 Hz), 2.84 (m, 1 H), 2.4–2.5 (m, 2 H), 1.84 (m, 1 H), 1.08 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H); high-resolution mass spectrum, m/e 342.18044 (calcd for $C_{21}H_{26}O_4$ m/e 342.18311).

(3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4-hydroxy-4a,8-dimethyl-5-(phenylmethoxy)azuleno[6,5-*b*]-furan-2(3*H*)-one (24). A solution of 198 mg (0.59 mmol) of hydroxy lactone **23** in 15 mL of reagent grade acetone cooled to −10 °C was treated with standard Jones reagent dropwise until the red color persisted. After 20 min at −10 °C, the mixture was quenched with 2-propanol. The acetone was evaporated under vacuum at 5–10 °C. The resulting residue was diluted with 15 mL of chloroform and washed with brine. The aqueous phase was extracted three times with chloroform. The combined chloroform extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure (ca. 5–10 °C), leaving 200 mg of ketone **25** (R_f 0.88, ether) which was used immediately in the next reaction.

To a solution of 198 mg (0.58 mmol) of the above ketone **25** dissolved in 10 mL of absolute ethanol (cooled to 0 °C) was added portionwise 40 mg (1.04 mmol) of sodium borohydride. The mixture was stirred at 0 °C for 15 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride, and the solvent was removed under reduced pressure. The residue was taken up in 30 mL of chloroform and 2 mL of brine. The aqueous phase was extracted twice with 10-mL portions of chloroform. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo, and 157 mg of crude product was obtained. Chromatography on 10 g of silica gel (elution with ether) provided 138 mg (70% overall yield from **23**) of pure **24** as an amorphous solid: R_f 0.69 ether; IR ($CHCl_3$) 3650–3200, 3075, 3030, 3010, 2960, 2940, 2880, 2860, 2825, 1780, 1610, 1500, 1470, 1460, 1425, 1400, 1355, 1335, 1315, 1290, 1200, 1160, 1130, 1095, 1075, 1000, 970, 915, 880 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.83 (s, 2 H), 4.62 (AB q, 2 H, $\Delta\nu_{AB}$ = 40 Hz, J = 11.7 Hz), 4.38 (m, 1 H), 4.09 (dd, 1 H, J = 5.0, 2.7 Hz), 3.04 (dd, 1 H, J = 16.0, 12.3 Hz), 2.2–2.6 (m, 5 H), 2.40 (dd, 1 H, J = 12.3, 8.7 Hz), 1.97 (d, 1 H, OH, J = 2.7 Hz), 1.26 (m, 1 H), 1.09 (d, 3 H, J = 6.5 Hz), 1.03 (s, 3 H). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.46; H, 7.60.

(3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-8-hydroxy-4a,8-dimethyl-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-azuleno[6,5-*b*]furan-2(3*H*)-one (29, R = H). A solution of 130 mg (0.38 mmol) of hydroxy lactone **24** in 4 mL of dry methylene chloride containing 1 mg of *p*-toluenesulfonic acid was cooled to 0 °C and treated with 50 μL (0.62 mmol) of dihydropyran. After 30 min at 0 °C, the reaction was quenched with solid sodium bicarbonate and the mixture placed directly onto a column of 10 g of silica gel. Elution with 2:3 hexane–ether gave 141 mg (87%) of the corresponding tetrahydropyranyl ether which was homogeneous by TLC analysis [R_f 0.26 (hexane–ether, 2:3); IR ($CHCl_3$) 3080, 3010, 2950, 2870, 2850, 1780, 1500, 1470, 1455, 1440, 1420, 1360, 1200, 1160, 1130, 1080, 1040, 1020, 1000, 910 cm^{-1}] and used directly in the next reaction.

To 3 mL of freshly distilled dimethoxyethane containing 28 mg (0.4 mmol) of finely powdered potassium hydroxide was added 135 mg (0.32 mmol) of the above THP ether in 3 mL of dimethoxyethane. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with 3 mL of dimethoxyethane and by use of nitrogen pressure was transferred via a cannula into a solution of 80 mg (11.4 mmol) of lithium metal dissolved in 50 mL of freshly distilled anhydrous ammonia. After the mixture was stirred for 1 min, the reaction was quenched with solid ammonium chloride. The ammonia was removed under reduced pressure and 10 mL of water added. The reaction mixture was neutralized and acidified to pH 5 with 10% aqueous hydrochloric acid (Congo red) and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and filtered. Evaporation provided (3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-3,6-dihydroxy-3a,8-dimethyl-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5-azuleneacetic acid which was dissolved in 8 mL of dry methylene chloride and treated with 70 mg (0.35 mmol) of dicyclohexylcarbodiimide. After 25 min at room temperature, the reaction mixture was concentrated under reduced pressure and placed directly on a column of 15 g of silica gel. Elution with ether afforded (88%) **29** (R = H) as a mixture of two diastereomers. Upper isomer: 43 mg; R_f 0.61 (ether); IR ($CHCl_3$) 3620, 3600–3200, 3010, 2950, 2860, 1780, 1660, 1475, 1460, 1205, 1185, 1160, 1130, 1020, 1000 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.86–4.84 (m, 1 H), 4.73–4.61 (m, 2 H), 4.18 (d, 1 H, J = 5.17 Hz), 3.90–3.83 (m, 1 H), 3.52–3.43 (m, 1 H), 3.23 (dd, 1 H, J= 17.5, 12.15 Hz), 2.80–2.64 (m, 1 H), 2.47–2.30 (m, 3 H), 2.11 (d, 1 H, OH, J = 8.3 Hz), 1.09 (d, 3 H, J = 6.5 Hz), 0.92 (s, 3 H). Lower isomer: 52 mg; R_f 0.46; IR ($CHCl_3$) 3600–3200, 3020, 2970, 2870, 1780, 1760, 1660, 1360, 1285, 1210, 1190, 1160, 1140, 1080, 1040, 1025, 1000, 920 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.76 (br s, 1 H), 4.30 (d, 1 H, J = 2.62 Hz), 4.10 (d, 1 H, J = 7.38 Hz), 1.09 (d, 3 H, J = 6.3 Hz), 1.00 (s, 3 H).

(3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4,5-dihydroxy-3-methylene-4a,8-dimethylazuleno[6,5-*b*]-furan-2(3*H*)-one (30). A solution of 129 mg (0.38 mmol) of hydroxy lactone **29** (R = H) in 4.5 mL of dry methylene chloride containing 4 mg of *p*-toluenesulfonic acid was cooled to 0 °C and was treated with 60 μL (0.15 mmol) of dihydropyran. The reaction mixture was stirred at room temperature for 3 h and quenched with solid sodium bicarbonate. Chromatography on 5 g of silica gel (elution with hexanes–ether, 2:3) afforded (79%) 126 mg of bis(tetrahydropyranyl) ether **29** (R = THP) which was used directly in the next reaction.

To a solution of diisopropylamine (62 μL, 0.42 mmol) in 1.2 mL of dry tetrahydrofuran cooled to −78 °C was added 272 μL (0.42 mmol) of *n*-butyllithium in hexane. After 15 min, a solution of 116 mg (0.27 mmol) of tricyclic lactone **29** (R = THP) in 0.6 mL of dry tetrahydrofuran was added dropwise over a period of 30 min. After 30 min at −78 °C, the reaction mixture was warmed to −25 °C, and formaldehyde, generated from 300 mg of paraformaldehyde at 150 °C, was passed into the reaction mixture with the aid of a stream of dry nitrogen. After complete depolymerization, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was diluted with 30 mL of ethyl acetate and 5 mL of brine. The aqueous phase was extracted twice with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo afforded 115 mg of crude product which was purified on 10 g of SilicAR CC-7. Elution with ether gave 80 mg (66% yield) of hydroxymethylated lactone [IR ($CHCl_3$) 3650–3200, 1755 cm^{-1}] which was used directly in the next reaction.

A solution of the above hydroxymethylated lactone (80 mg, 0.177 mmol) in 1.5 mL of pyridine containing 30 μL (0.34 mmol) of methanesulfonyl chloride was allowed to stir at 0 °C for 1 h and at room temperature for 30 min. The reaction mixture was quenched by the addition of 3 mL of water. The product was isolated by extraction with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, leaving 87 mg of essentially pure mesylate [IR ($CHCl_3$) 3030, 2950, 2850, 1775, 1365, 1180, 1160, 1130, 1080, 1040, 1020, 1000, 980, 960, 910 cm^{-1}] which was used directly in the next reaction.

The above mesylate (87 mg, 0.177 mmol) was dissolved in 1.5 mL of dry benzene to which was added 30 μL of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 30 min at room temperature, the reaction was concentrated in vacuo, and the residue was chromatographed on 10 g of silica gel. Elution with hexane–ether (1:3) gave 64 mg (83% yield over two steps) of (3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-octahydro-4a,8-dimethyl-3-methylene-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]-azuleno[6,5-*b*]furan-2(3*H*)-one: IR ($CHCl_3$) 1760, 1670 cm^{-1}.

A solution of 23 mg (0.053 mmol) of 3aα,4aβ,4aβ,5β,7aα,8α,9aβ)-3a,4,4a,5,7a,8,9,9a-octahydro-4a,8-dimethyl-3-methylene-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[6,5-*b*]furan-2(3*H*)-one in 1 mL of glacial acetic acid/water (60:40 v/v) was stirred at 45 °C for 90 min. Removal of the solvent under reduced pressure (<0.1 mm) gave an oily residue which was directly chromatographed on 5 g of SilicAR CC-7. Elution with acetone gave 10 mg (86%) of crystalline α-methylene lactone **30**: mp 143–144 °C; R_f 0.83 (acetone); IR ($CHCl_3$) 3650, 3500–3200, 2950, 2850, 1760, 1160, 1120, 1010, 980 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 6.40 (d, 1 H, J = 3.5 Hz), 5.85 (m, 1 H), 5.70 (m, 1 H), 5.60 (d, 1 H, J = 3.5 Hz), 4.7–4.8 (m, 2 H), 4.54 (dd, 1 H, J_{OH} = 4.3 Hz, J = 3.2 Hz), 3.1–3.2 (m, 1 H), 2.4–2.5 (m, 2 H), 1.9–2.1 (m, 3 H), 1.33 (m, 1 H), 1.13 (d, 3 H, J = 6.5 Hz), 1.03 (s, 3 H). Recrystallization from acetone–hexane provided analytically pure **30**: mp 144–145 °C; high-resolution mass spectrum, m/e 264.1335

(calcd for $C_{15}H_{20}O_4$ m/e 264.1361).

Mexicanin I (12). A suspension of freshly prepared manganese dioxide (90 mg) and 9 mg (0.0378 mmol) of α-methylene lactone **30** in a solution of 2 mL of dry methylene chloride and 3 mL of benzene was stirred at room temperature for 30 min. The mixture was diluted with 20 mL of ether and filtered. The oxide cake was washed with ether (5 × 5 mL). The combined filtrate and washings were evaporated to dryness, and the residue was chromatographed on neutral silica gel (SilicAR CC-7). Elution with ether yielded 7 mg (78%) of crystalline mexicanin I: mp 244–247 °C; R_f 0.39 (ether); IR (KBr pellet) 3500, 2970, 2910, 2880, 2850, 1750, 1690, 1580, 1460, 1440, 1405, 1340, 1310, 1280, 1240, 1160, 1140, 1130, 1070, 1050, 1030, 1010, 985, 945, 890 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.66 (dd, 1 H, J = 6.1, 1.8 Hz), 6.41 (d, 1 H, J = 3.5 Hz), 6.16 (dd, 1 H, J = 6.1, 2.7 Hz), 5.67 (d, 1 H, J = 3.5 Hz), 4.81 (m, 1 H), 4.54 (dd, 1 H, J = 5.2, 2.7 Hz), 3.11 (m, 1 H), 2.68 (m, 1 H), 2.57 (m, 1 H), 2.42 (d, 1 H, J = 2.7 Hz), 2.22 (m, 1 H), 1.39 (m, 1 H), 1.25 (d, 3 H, J = 6.5 Hz), 1.24 (s, 3 H). Recrystallization from acetone–hexane provided analytically pure mexicanin I, mp 246–248 °C. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.50; H, 6.90.

Linifolin A (13). A solution of 5 mg (0.019 mmol) of mexicanin I, 0.5 mg of 4-(dimethylamino)pyridine, 0.5 mL of pyridine, and 0.1 mL of acetic anhydride was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure, leaving an oily residue which was chromatographed (ether elution) directly on neutral silica gel (SilicAR CC-7), providing 5 mg (86% yield) of crystalline linifolin A: mp 181–182 °C; R_f 0.42 (ether); IR ($CHCl_3$) 3020, 2950, 2870, 2850, 1765, 1755, 1710, 1585, 1460, 1400, 1380, 1320, 1290, 1250, 1160, 1150, 1130, 1060, 1015, 1000, 960, 930 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.59 (dd, 1 H, J = 6.0, 1.80 Hz), 6.29 (d, 1 H, J = 3.5 Hz), 6.12 (dd, 1 H, J = 6.0, 3.0 Hz), 5.96 (d, 1 H, J = 4.7 Hz), 5.70 (d, 1 H, J = 3.5 Hz), 4.81 (ddd, 1 H, J = 11.6, 9.2, 2.9 Hz), 3.26 (m, 1 H), 2.78 (dt, 1 H, J = 10.4, 2.2 Hz), 2.58 (ddd, 1 H, J = 13.3, 4.5, 2.9 Hz), 2.23 (m, 1 H), 2.08 (s, 3 H), 1.42 (m, 1 H), 1.26 (d, 3 H, J = 6.5 Hz), 1.23 (s, 3 H). Recrystallization from acetone–hexanes gave pure linifolin A, mp 182–182.5 °C. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.88; H, 6.60.

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Methods for the Stereoselective Cis Cyanohydroxylation and Carboxyhydroxylation of Olefins

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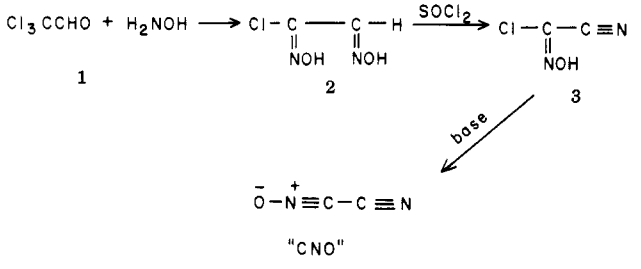
Two valuable reagents for the cis-specific vicinal cyanohydroxylation and carboxyhydroxylation of olefins are described. The cyanohydroxylation process is based on the decarboxylative ring opening of 3-carboxyisoxazolines prepared by the [3 + 2] cycloaddition reaction of carbethoxyformonitrile oxide with various alkenes. Fragmentation of the isoxazolines prepared from *cis*- and *trans*-2-butene has been found to occur without any crossover in stereochemistry. The carboxyhydroxylation process begins with the dipolar cycloaddition reaction of the nitrile oxide derived from the tetrahydropyranyl ether derivative of 2-nitroethanol. Deprotection, hydrogenation, and oxidative cleavage of the derived dihydroxy ketone yield the stereochemically pure β-hydroxy carboxylic acid.

In pursuit of new strategies for the stereospecific vicinal functionalization of alkenes, we have been inspired to investigate two old, yet relatively unappreciated reagents, carbethoxyformonitrile oxide (CEFNO)[1] and cyanogen *N*-oxide (CNO).[2] Since available literature evidence indicates that these reagents can be used to effect the vicinal cyanohydroxylation of olefins through decarboxylative ring opening,[3] such reactive dipoles might ideally serve to assemble useful part structures for natural product synthesis. Eventually one would want to be able to develop chiral variants of these or related products so that they could be used to prepare β-hydroxy nitriles in optically pure form. Additionally, one could hope to achieve the diastereoselective assembly of part structures through the cycloaddition of the achiral dipoles to optically pure alkenes.

Thus, in order to eventually probe the chiral-selective assembly of small molecules through dipolar cycloaddition

Scheme I



reactions, we first established the scope of reactivity of CEFNO and CNO with a variety of variously substituted olefins and then ascertained the level of stereoselectivity associated with the decarboxylative ring-opening process. Additionally, one other dipole, that prepared from the tetrahydropyranyl derivative of 2-nitroethanol,[4] has been used as a reagent for bringing about the cis carboxyhydroxylation of olefins. In this ancillary study, the nitrogen–oxygen bond of the isoxazoline is first cleaved by hydrogenation, and then the dihydroxy ketone which is

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