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Registry No. 1, 69705-23-3; 2, 23029-25-6; 7a, 70415-60-0; 8, 23057-33-2; 10, 27041-32-3.

William T. Brown, W. M. Jones*
Department of Chemistry, University of Florida
Gainesville, Florida 32601
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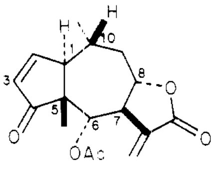
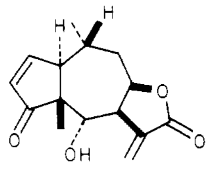
Helenanolides: Total Synthesis of *dl*-Bigelovin

Summary: A total synthesis of *dl*-bigelovin (1) is recorded which features as a key step a remarkable stereospecific reduction of hydroazulenone 3.

Sir: The helenanolides, which are characterized by the presence of a C(10) α-oriented methyl group and six chiral centers about a flexible hydroazulene ring system [e.g., bigelovin (1),[1] helenalin (2)[2]], belong to the pseudoguaianolide family of sesquiterpene lactones. Despite the fact that the relative and absolute configuration of numerous helenanolides have been known for many years, success at total synthesis has only been recorded on one previous occasion (cf. helenalin[3]). We wish to communicate herein the total synthesis of *dl*-bigelovin (1) which maintains complete stereochemical control during elaboration of the chirality at C(6), C(7), and C(8) on the hydroazulene ring system.

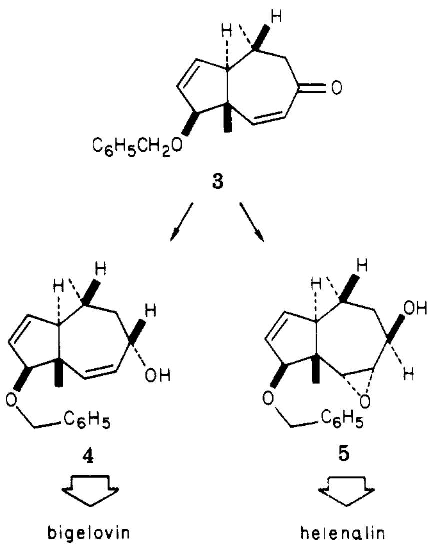


1

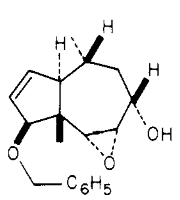


2

The key hydroazulenone intermediate 3, available through total synthesis,[3] upon reduction[4] with lithium aluminum hydride in tetrahydrofuran at 0 °C gave rise *exclusively in quantitative yield* to the crystalline allylic alcohol 4, mp 62–64 °C.[5] We were unable to find any evidence of hydride attack on the α-face of the carbonyl, which would have given rise to the corresponding C(8) isomeric allylic alcohol. This remarkable stereospecific reduction was unanticipated in view of our earlier efforts in the helenalin series. For example, we had previously established unambiguously that expoxidation (*t*-BuOOH, Triton B, THF) of enone 3 followed by reduction ($NaBH_4$, EtOH, 0 °C) afforded *exclusively* alcohol 5, mp 90–91 °C.[3]



With the configuration at C(8) assured, we proceeded with introduction of the remaining two chiral centers. Epoxidation of 4 employing *m*-chloroperbenzoic acid in methylene chloride provided in 65% yield the pure crystalline *syn*-epoxy alcohol 6, mp 99–100 °C. Elaboration of the γ-butyrolactone ring and cleavage of the benzyl ether were achieved by treatment of epoxide 6 with excess dilithioacetate[6] in dimethoxyethane (55 °C, 17 h) followed by direct addition of the intermediate trianion to a solution of lithium in liquid ammonia. Workup with 10% hydrochloric acid generated, as the sole product, tricyclic lactone 7: mp 186.0–188.5 °C; IR (KBr) 3475, 3350, 1765 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.46 (ddd, 1 H, J = 3.2, 10.0, 11.8 Hz, H-8), 3.67 (d, 1 H, J = 8.7 Hz, H-6). The tetrahydropyranylated derivative of 7, prepared in 76% yield [dihydropyran, *p*-toluenesulfonic acid, methylene chloride, 0 °C, 1 h], was subjected to α-methylenation (61% overall yield) using the α-hydroxymethylation procedure:[7] (1) LDA, THF, HCHO, −20 °C; (2) MsCl, Py; (3) DBU, PhH. Cleavage of the tetrahydropyranyl ethers with 60% acetic acid (45 °C, 1.5 h) gave (82%) crystalline diol 8 (mp 152–153 °C; IR ($CHCl_3$) 3600, 3425, 1760 cm^{-1}), which upon oxidation with manganese dioxide in methylene chloride–benzene (2:1) (25 °C, 30 min) afforded a 77% yield of pure tricyclic enone 9: mp 186–187 °C; IR ($CHCl_3$) 3555, 1764, 1700 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 = 6.4, 2.8 Hz), 6.02 (d, 1 H, J = 3.3 Hz)]. Acetylation (Ac_2O, Py, DMAP,[8] 25 °C, 3 h) of tricyclic alcohol 9 provided an 81% yield of pure crystalline *dl*-bigelovin (1), mp 195.5–197.5 °C, whose spectral properties



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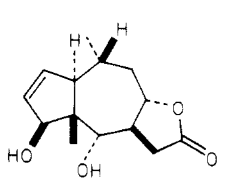

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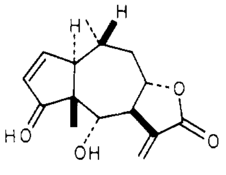

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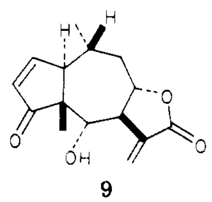

9

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[5] Professor Vandewalle (Ghent) has informed us of a similar observation using a related enone.

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were identical with those of the natural product.[9,10] The total synthesis of bigelovin confirms the structural assignment of the natural material put forth some years ago by Professor Herz.[1b]

Acknowledgments. This investigation was supported by a Public Health Service Research Grant (CA 13689-07) from the National Cancer Institute, the National Institutes of Health NMR Facility for Biomedical Studies (RR-00292), and, in part, by G. D. Searle and Co.

Registry No. 1, 70981-13-4; **3**, 68241-54-3; **4**, 70913-22-3; **6**, 70981-14-5; **7**, 70913-23-4; **8**, 70913-24-5; **9**, 70981-15-6.

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(9) *dl*-Bigelovin: IR ($CHCl_3$) 1758, 1730, 1707, 1662, 1585, 1241 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 7.72 (dd, 1 H, J = 1.8, 6.1 Hz, H-2), 6.23 (d, 1 H, J = 3.5 Hz, exocyclic methylene), 6.11 (dd, 1 H, J = 3.0, 6.1 Hz, H-3), 5.93 (d, 1 H, J = 3.5 Hz, exocyclic methylene), 5.62 (d, 1 H, J = 7.6 Hz, H-6), 4.61 (ddd, 1 H, J = 3.0, 10.9, 12.2 Hz, H-8), 3.14–3.00 (m, 2 H), 2.58 (dt, 1 H), 2.15–1.90 (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).

(10) We are indebted to Professors Werner Herz and T. J. Mabry for spectra of natural bigelovin.

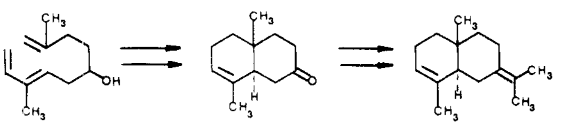
Paul A. Grieco,* Yasufumi Ohfune, George Majetich
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received May 7, 1979

An Intramolecular Diels-Alder Approach to Diterpenes

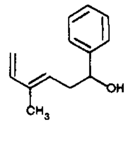
Summary: The synthesis of three dienes **4a**, **4b**, and **4c**, suitably constituted for intramolecular Diels–Alder cyclization to tricyclic compounds **6a**, **6b**, and **6c**, is described. The newly formed rings are mainly cis fused. The method results in the addition of two fused six-membered rings to *o*-vinylbenzaldehyde derivatives in a two-step bis annelation sequence.

Sir: The Diels–Alder reaction is one of the most useful reactions in organic synthesis. Although the intramolecular Diels–Alder reaction[1] has been used in several terpene syntheses before,[2] the only *general* application of the reaction to polycyclic terpenes centers on reactions of the *o*-quinodimethane type.[3] We have recently reported[4] a synthesis of the Eudesmane sesquiterpene (±)-selenadiene via the scheme shown in eq 1. We now report preliminary studies in the extension of this methodology to the synthesis of tricyclic compounds related to diterpenes.

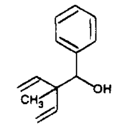


(1)

The requisite dienes for our Diels-Alder strategy are readily available via the addition of 3-methylpentadienyllithium (3-MPL)[5] to an aldehyde. For example, benzaldehyde reacts with 3-MPL to give 51% **1** and 36% **2**. As reported earlier,[6] the undesired branched isomer **2** can be isomerized to **1** by KH/THF/0 °C.



1



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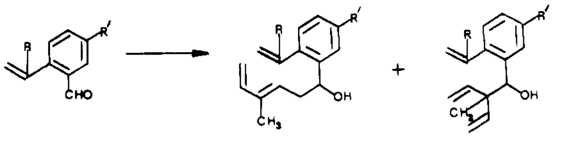
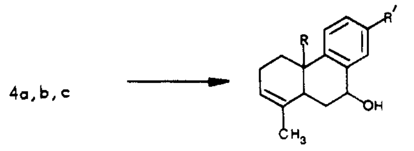
Substituted dienes **4a** and **4b** were prepared as follows. *o*-Vinylbenzaldehyde **3a**[7] reacts with 3-MPL (THF, 0 °C) to give 48% of **4a**[8] and 22% of **5a**. In contrast to the bicyclic series,[4] compound **4a** cyclizes readily. Pure **4a** reacts to give **6a** cleanly at 100 °C ($T_{1/2}$ = 2 h, 72% yield).



3a, R=H , R'=H
3b, $R=CH_3, R'=H$
3c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$

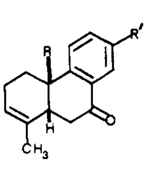
4a, R=H , R'=H
4b, $R=CH_3, R'=H$
4c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$

5a, R=H , R'=H
5b, $R=CH_3, R'=H$
5c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$

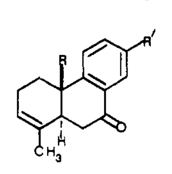


6a, R=H , R'=H
6b, $R=CH_3, R'=H$
6c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$

Compound **3b**[9] reacts with 3-MPL to produce a 50% yield of **4b** and 11% of **5b**. As expected, the presence of an incipient angular methyl slows the Diels–Alder reaction markedly. Compound **4b** does not undergo cyclization below 140 °C, where it begins to decompose. However, the trimethylsilyl ether of **4b** undergoes intramolecular Diels–Alder reaction (180 °C, 24 h) giving the expected **6b** (silyl ether) which was hydrolyzed (KF/CH_3OH) and oxidized (Jones) to **7b**/**8b**. The overall yield of tricyclic



7a, R=H , R'=H
7b, $R=CH_3, R'=H$
7c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$



8a, R=H , R'=H
8b, $R=CH_3, R'=H$
8c, $R=CH_3, R'=\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_3$

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