

2), 109765-90-4; **5b**, 82111-61-3; **5c**, 109765-91-5; **6a**, 109765-93-7; **6b**, 109765-95-9; **6c**, 58588-90-2; **7a**, 109765-94-8; **7c**, 109765-96-0; **8c**, 109765-97-1; **9**, 109765-98-2; **10**, 109765-99-3; **11**, 109766-00-9; **12**, 109766-01-0; PrCHO, 123-72-8; MeCHO, 75-07-0; CH₂O, 50-00-0.

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Stereoselective Construction of Functionalized *cis*-1,2-Dialkylcyclohexanecarboxylates: A Novel Synthesis of (±)-Geijerone and γ -Elemene

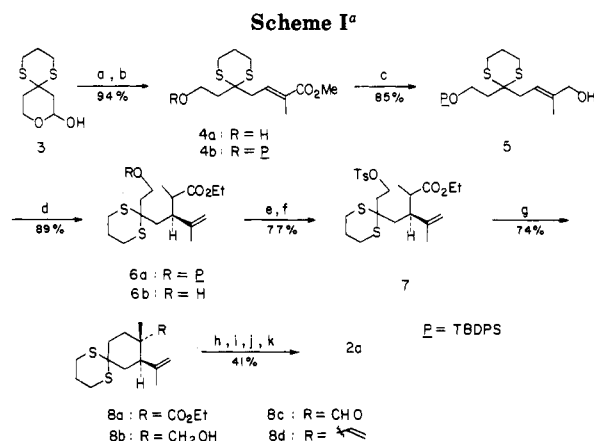
Summary: General applicability of our intramolecular ester enolate alkylation method to the stereoselective construction of functionalized *cis*-1,2-dialkylcyclohexanecarboxylates is illustrated in the context of a novel synthesis of (±)-geijerone and a formal synthesis of γ -elemene.

Sir: Functionalized *cis*-1,2-dialkylcyclohexanecarboxylates **1** are very important and frequently encountered structural features in the synthesis of natural products.¹ We recently reported a novel approach based upon intramolecular ester enolate alkylation in an unfunctionalized model system.²



In this communication we describe a novel synthesis of (±)-geijerone³ (**2a**) and a formal synthesis of γ -elemene⁴ (**2b**), a member of elemanoid sesquiterpenes, in order to demonstrate that our intramolecular alkylation strategy should be applicable to the synthesis of a variety of functionalized *cis*-1,2-dialkylcyclohexanecarboxylates as summarized in Scheme I.

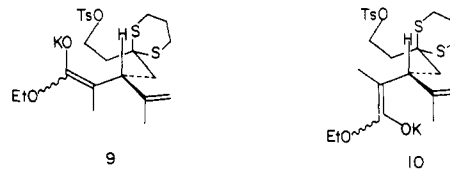
Condensation of lactol⁵ **3** with methyl (triphenylphosphoranylidene)propionate followed by protection of the hydroxyl group with *tert*-butylchlorodiphenylsilane⁶ afforded ester **4b** in 94% yield. Reduction of unsaturated ester **4b** with LAH in THF gave the corresponding allylic alcohol **5**, which was subjected to Johnson's ortho ester Claisen rearrangement⁷ to produce ester **6a** as a 1:1 mix-



(a) Ph₃C(CH₃)CO₂Me, CH₂Cl₂, reflux, 4 h; (b) TBDPS-Cl, imidazole, DMF, room temperature, 13 h; (c) LAH, THF, 0 °C, 2 h; (d) CH₃CH₂C(OEt)₃, phenol, 165 °C, 15 h; (e) (*n*-Bu)₄NF, THF, room temperature, 2 h; (f) TsCl, DMAP, CH₂Cl₂, 0 °C, 3 h; (g) KHMDS, THF, -78 to 0 °C, 3 h; (h) DIBAL, toluene, -20 °C, 15 min; (i) DCC, pyridinium trifluoroacetate, DMSO-PhH (1:3), room temperature, 2 h; (j) Ph₃PCH₃I, *n*-BuLi, Et₂O, reflux, 1 h; (k) excess CH₃I, CH₃CN-H₂O (9:1), room temperature, 24 h.

ture of stereoisomers in 78% yield for two steps. Deprotection of the silyl group with fluoride and tosylation yielded key intramolecular alkylation substrate **7** in 77% overall yield.

Treatment of ester **7** with KHMDS⁸ in THF at -78 °C followed by warming to 0 °C for 3 h produced the desired cyclohexanecarboxylate **8a** with greater than 96% stereoselectivity⁹ in 74% yield, probably through eclipsed transition state **9** rather than bisected **10**.¹⁰



Reduction with DIBAL, Moffatt oxidation, Wittig reaction, and hydrolysis of thioketal group proceeded uneventfully to give (±)-geijerone with spectral data fully consistent with those reported.¹¹ Since (±)-geijerone was converted to γ -elemene by Yoshikoshi, the present synthesis also constitutes a formal synthesis of the sesquiterpene.⁴

In summary synthesis of (±)-geijerone was achieved in a stereoselective manner in 11 steps and 16.6% overall yield from lactol **3**, suggesting a broad potential of our intramolecular ester enolate alkylation method. Work is in progress to apply this methodology to more elaborate systems.

(1) For an extremely elegant use of intramolecular alkylation to six-membered rings, see: Stork, G. *Heterocycles Special Issue* 1987, 25.

(2) Ahn, S. H.; Kim, D.; Chun, M. W.; Chung, W. *Tetrahedron Lett.* 1986, 27, 943.

(3) Isolation and structure of geijerone: (a) Thomas, A. F. *Helv. Chim. Acta* 1972, 55, 815. (b) Thomas, A. F. *Ibid.* 1972, 55, 2429. Synthesis of (±)-geijerone: Kato, M.; Kurihara, H.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* 1979, 2470.

(4) Isolation and structure of γ -elemene: (a) Gough, J. H.; Sutherland, M. D. *Aust. J. Chem.* 1964, 17, 1270. (b) Bernardi, R.; Cardani, C.; Ghiringhelli, D.; Selva, A. *Chim. Ind. (Milan)* 1970, 52, 581. (c) Ganter, C.; Keller-Wojtkiewicz, F. B. *Helv. Chim. Acta* 1971, 54, 183. Synthesis of γ -elemene: ref 3b.

(5) Lactol **3** was prepared by a conventional four-step sequence from diethyl acetone-1,3-dicarboxylate (1,3-propanedithiol, BF₃·Et₂O; 1.1 equiv of KOH, EtOH; ClCO₂CH₃, TEA, NaBH₄; DIBAL, toluene).

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(8) The more highly aggregated and less reactive lithium enolate, generated by LDA, gave much less satisfactory yield (18%) of the cyclized product under similar condition with a slightly better stereoselectivity (97%).

(9) Capillary GC analysis (0.2 mm i.d. × 50 m long CBP-1 column, 260 °C) revealed the presence of less than 4% of a minor isomer.

(10) Compound **8a**: IR (film) ν 1730, 1640 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 1.12 (s, 3 H), 1.23 (t, *J* = 7 Hz, 3 H), 1.63 (s, 3 H), 1.45-3.14 (m, 13 H), 4.09 (q, *J* = 7 Hz, 2 H), 4.68 (br s, 1 H), 4.83 (m, 1 H); ¹³C NMR (CDCl₃, 20.15 MHz) δ 14.24, 15.17, 23.20, 26.02, 26.14, 26.44, 30.03, 33.18, 38.29, 43.86, 46.59, 49.98, 60.55, 113.47, 145.66, 177.51; HRMS calcd for C₁₆H₂₆O₂S₂ 314.1374, found 314.1375.

(11) We thank Professor Yoshikoshi (Tohoku University) for kindly providing us with reference spectra of racemic geijerone.

Acknowledgment. This research was supported by a grant from the Korea Science and Engineering Foundation. We are very grateful to Professor Steven M. Weinreb (PSU) for HRMS data. Thanks are also due to Dr. Ho Koon Park (KAIST) for a generous gift of diethyl acetone-1,3-dicarboxylate and Mr. Kyeong Ho Kim for measurement of spectroscopic data. Special thanks are extended to Dr. Kurt Loening of Chemical Abstracts Service for advice in naming the compounds contained in this manuscript.

Registry No. 2a, 62075-35-8; 3, 110144-06-4; (*E*)-4a, 110144-07-5; (*Z*)-4a, 110144-16-6; (*E*)-4b, 110144-08-6; (*Z*)-4b, 110144-17-7; 5, 110144-09-7; 6a (isomer 1), 110144-10-0; 6a (isomer 2), 110144-18-8; 6b (isomer 1), 110173-81-4; 6b (isomer 2), 110144-19-9; 7 (isomer 1), 110144-11-1; 7 (isomer 2), 110144-20-2; 8a, 110144-12-2; 8b, 110144-13-3; 8c, 110144-14-4; 8d, 110144-15-5; diethyl acetone-1,3-dicarboxylate, 105-50-0; methyl 2-(triphenylphosphoranylidene)propionate, 2605-68-7; methyltriphenylphosphonium iodide, 2065-66-9; γ -elemene, 29873-99-2.

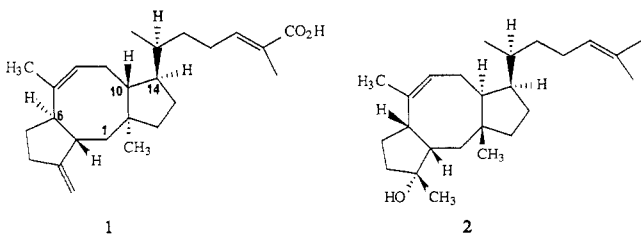
Supplementary Material Available: Experimental procedure for reactions described in Scheme I (7 pages). Ordering information is given on any current masthead page.

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A Synthetic Entry into the Ophiobolane Ring System

Summary: A stereocontrolled construction of the angularly fused 5-8-5 ring system characteristic of the ophiobolin and ceroplastol sesterterpenes is reported. The synthesis is based on the elaboration of a *cis*-hydroazulene intermediate into the dicyclopenta[*a,d*]cyclooctane system with control of relative stereochemistry at several critical centers.

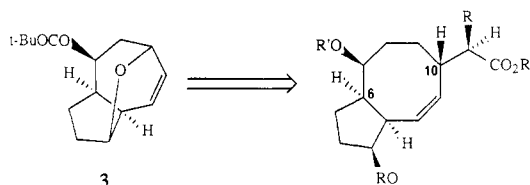
Sir: The dicyclopenta[*a,d*]cyclooctane ring system is the characteristic structural feature of the ophiobolane class of sesterterpenes. These natural products possess intriguing structural arrays and typically exhibit a wide range of biological activity. Representative examples of these substances are ceroplasteric acid (1)¹ and ophiobolin F (2).²



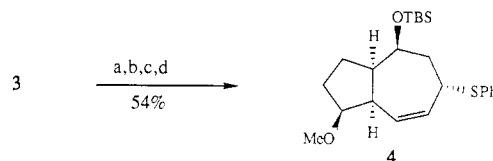
A growing number of additional members of this class of compounds have been isolated as well.³ Several interesting approaches to the preparation of the ophiobolane system

have been reported in the last few years,⁴ but no total synthesis has, as yet, been forthcoming.

Our strategic plan centered on the efficient assembly of the 5-8-5 carbon skeleton with concomitant control of the relative stereochemistries at the three critical positions C₆, C₁₀, and C₁₄ as found in ceroplasteric acid (1). It was envisaged that the highly functionalized and readily available *cis*-hydroazulene 3⁵ would serve admirably as a building block from which to elaborate the elements of the C-ring via a silyl enolate Claisen protocol.⁶ Subsequent one-carbon ring expansion to the eight-membered ring would provide a precursor to the requisite 5-8-5 carbon backbone.



Treatment of 3 with thiophenol/BF₃·Et₂O at room temperature,^{5c,7} followed by protecting group manipulation gave allylic sulfide 4 in 54% overall yield. Formation of



(a) BF₃·Et₂O/PhSH, room temperature; (b) NaH, MeI; (c) LiAlH₄, Et₂O; (d) TBDMSCl, imidazole

the corresponding sulfoxide with *m*-CPBA at -78 °C followed by a thermally induced [2,3]-sigmatropic rearrangement⁸ in the presence of trimethyl phosphite provided the allylically transposed alcohol 5 in 71% yield.

At this point, a study was initiated to ascertain the stereochemical course of the enolate-Claisen reaction in our system. The correct configuration at C₁₀ (ophiobolane numbering) is assured by virtue of the chirality transfer from the carbon-oxygen bond to the carbon-carbon bond inherent in this process. However, the stereochemistry at C₁₄ (ophiobolane numbering) is a consequence of the ester enolate geometry and the transition state of the reaction.⁶ Acylation of 5 with propionic anhydride/DMAP/Et₃N and treatment with LDA followed by *tert*-butyldimethylsilyl chloride (TBDMSCl) at -78 °C gave the requisite silyl ketene acetal⁹ (Scheme I). Heating this material in re-

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(7) An easily separated mixture of sulfide 4 and its allylically transposed isomer were isolated from this reaction in a 9:1 ratio, respectively.

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