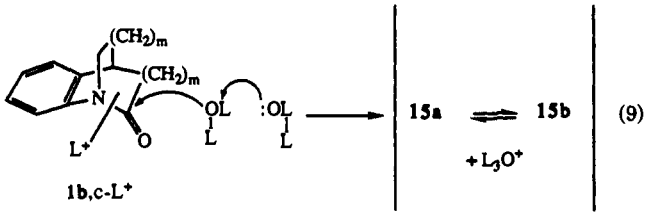
This isotope effect is consistent with the process shown in eq 9, wherein L_2O acts as a general base in delivering a second L_2O to the protonated amide to yield **15a,b**.[37]



(9)

Conclusions

(1) Progressive distortion of the anilides **3b** → **1d** → **1b,c** leads to a lengthening of the N—C(O) bond with only a small shortening of the C=O bond and a rehybridization of the N from sp^2 to sp^3 that accompanies rotation around the C—N bond. The insensitivity of the C=O bond length to the distortion is at first surprising but appears normal when compared with the lengths of C=O bonds in two series of RC(O)X derivatives where group X varies markedly in its ability to donate or withdraw electrons.

(2) Progressive distortion of the anilides leads to marked acceleration of the acid- and base-promoted hydrolyses. The respective domains are first order in $[H_3O^+]$ and $[OH^-]$, but there is a progressive increase in the kinetic pK_a of the protonated amide with distortion that arises from a shift from O to N protonation. The activation parameters indicate that the bulk of the rate increase in base that accompanies distortion results from a reduction in $\Delta H^{\ddagger}$ (13.2 kcal/mol (**1d**) to 7.58 kcal/mol (**1a**)) with an increase in the $\Delta S^{\ddagger}$ (-29.2 eu (**1d**) to -22.0 eu (**1a**)). In H_3O^+, analysis of the activation parameters is less straightforward since they pertain to a ratio of a kinetic and an equilibrium term (k_1/K_a').

(3) Solvent kinetic isotope data establish that both acetate and solvent act as general bases to deliver L_2O to the protonated forms of **1b** and **1c**.

Acknowledgment. We gratefully acknowledge the financial support of the University of Alberta and the Natural Sciences and Engineering Research Council of Canada. In addition, were are grateful to Dr. X. Huang for obtaining crystals of **1d** suitable for X-ray crystallographic study. Finally, we are indebted to Professor K. B. Wiberg for a preliminary draft of a manuscript.[14b]

Supplementary Material Available: Synthetic procedure for **3b**, tables of atomic coordinates and isotropic parameters of **1d** and **3b**, data collection techniques and structure solution and refinement details, tables of interatomic bond lengths and angles and torsional angles, tables of hydrogen atom coordinates and root-mean-square amplitudes, and figures giving labeling schemes for molecules A and B and the packing motif of A and B (19 pages); listing of structure factor amplitudes (19 pages). Ordering information is given on any current masthead page.

(37) The KIE can also be evaluated by the fractionation factor analyses.[38] Thus, for the acetate-promoted delivery of L_2O, if the ground state in the plateau region consists of **1b,c** + LOAc + L_2O and the transition state is as given in eq 8, the KIE is determined by a single proton in flight having a fractionation factor of 0.65-0.7 (KIE = k_{OAc}^{H}/k_{OAc}^{D} = 1.54-1.42). For water-promoted delivery of L_2O, if the ground state consists of **1b,c** + L_3O^+ + L_2O, the KIE = $(k_1/K_a')^{H_2O}/(k_1/K_a')^{D_2O}$ = 0.66 is determined by a single proton in flight (0.5) and the fractionation factor for L_3O^+ (0.69[3]). That the fractionation factors for a proton in flight from acetate + L_2O, and L_2O: + L_2O are slightly different is attributable to an earlier TS for the acetate promoted reaction.

(38) (a) Schowen, R. L. In *Isotope Effects on Enzyme Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, MD, 1977. (b) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275.

Terpenoids to Terpenoids: Enantioselective Construction of 5,6-, 5,7-, and 5,8-Fused Bicyclic Systems. Application to the Total Synthesis of Isodaucane Sesquiterpenes and Dolastane Diterpenes

Goverdhan Mehta,* Nacharaju Krishnamurthy, and Srinivas Rao Karra

Contribution from the School of Chemistry, University of Hyderabad, Hyderabad 500 134, India.
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Abstract: The prevalence of a C_{12} common core (**10**) in C_{15}–C_{30} terpenoids has been recognized. Construction of two "chirons" ((-)-**11** and (-)-**12a,b**), corresponding to **10**, from abundantly available (*R*)-(+)-limonene has been achieved through diastereoselective [3s.3s] sigmatropic processes **16** → **11** and **19** → **12**, respectively. Chirons **11** and **12** have been successfully annulated to bicyclic hydrindanones **21**, **23**, and **30**, hydrazulenoids **31**–**33**, and 5,8-fused system **42** through methodologies that are short and practical. Thus, these enantiomerically pure bicyclics are available as advanced building blocks for higher terpene synthesis. One of the hydrazulenoids ((-)-**31**) has been elaborated to isodaucane sesquiterpenes (+)-aphanamol I (**2**) and (+)-2-oxoisodauc-5-en-12-al (**46**) through a novel restructuring protocol (**31** → **50**). The stereo- and enantioselective synthesis reported here has established the absolute stereochemistry of isodaucane sesquiterpenes. The hydrazulenoid (-)-**31** has also been deployed for the first enantioselective synthesis of oxygenated dolastane diterpenes (+)-isoamijiol (**63**) and (+)-dolasta-1(15),7,9-trien-14-ol (**64**). The key step in this venture was the stereoselective annulation of a six-membered ring through radical-induced alkyne–carbonyl cyclization (**67** → **68**).

The overwhelming accent on carbohydrates as "chirons" for natural products synthesis, during the past decade, has somewhat marginalized the importance of abundantly available terpenes as building blocks for chiral synthesis.[1,2] This has come about despite the fact that many terpenes are cheap, readily accessible, and endowed with only one or two chiral centers with modest func-

(1) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergammon Press: Oxford, 1983.

(2) For leading examples of the use of terpenes in chiral synthesis, see: (a) Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253. (b) Money, T. Studies in Natural Products Chemistry. *Stereoselective Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. IV, Part C, p 625. (c) Thomas, A. F.; Bessiere, Y. *Nat. Prod. Rep.* **1989**, *6*, 291. (d) Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.

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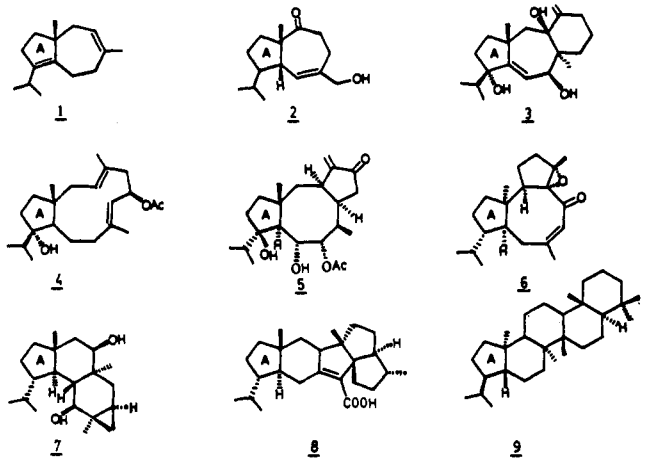
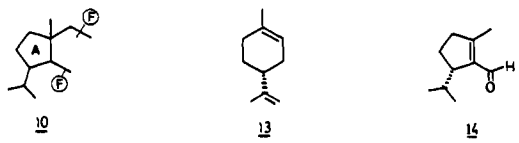
Chart I



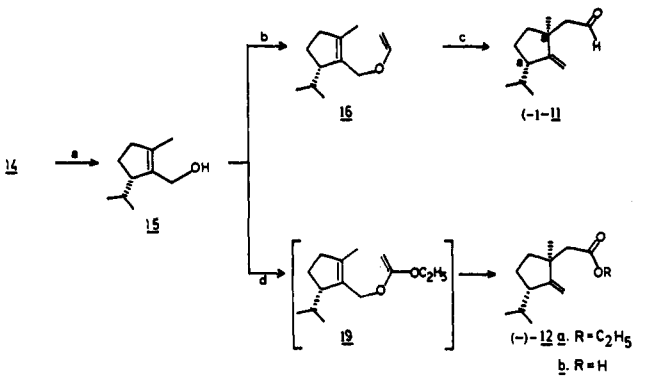
tionalization and thus do not require recourse to wasteful maneuvers to dispense with the excess functionality. More importantly, terpenes can be readily restructured into cyclic and acyclic fragments that can be directly incorporated into the carbocyclic frameworks of complex target structures. Diverse terpenoids from C_{10} to C_{30}, by virtue of their common biogenesis, invariably embody common carbocyclic structural moieties. Therefore, an operationally versatile strategy emerges in which such structural moieties extracted from a single, lower terpene chiron, e.g., a C_{10} monoterpene, can be evolved into a vast array of complex higher terpenes. Exploration of this strategy and pursuit of the "terpenoids to terpenoids" theme for chiral synthesis are the objectives of the present study.

In Chart I are displayed a few representative examples of C_{15} sesquiterpenes (daucene (**1**),[3] aphanamol I (**2**)[4]), C_{20} diterpenes (dolatriol (**3**),[5] 6-acetoxy-12-hydroxydolabella-3,7-diene (**4**),[6] fusicoplagin D (**5**),[7] 7,8-epoxy-4-basmen-6-one (**6**),[8] 2,8-dihydroxyverrucosane (**7**)),[9] a C_{25} sesterterpene (retigeranic acid (**8**)),[10] and a C_{30} triterpene (hopane (**9**)),[11] all of which share a common structural core (**10**) (ring A). These are among over



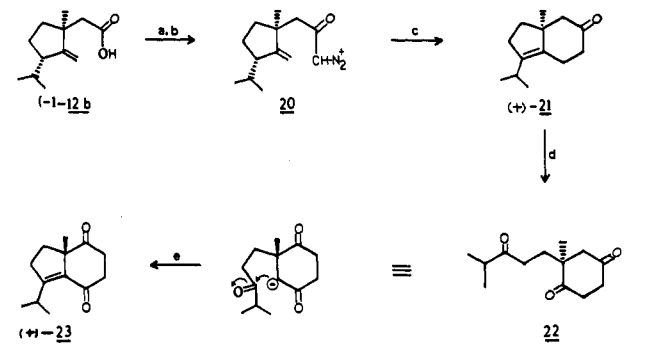
two dozen skeletal types and several hundred natural terpenes embellished with different stereochemical and functionalization patterns, which embody this cyclopentane fragment. We reasoned that a chiral bifunctional derivative (**10**), with well-defined stereochemistry, could serve as a versatile chiron for the synthesis of diverse terpenes displayed in Chart I and many others. The two functionalized side arms in **10** could be so created as to be amenable to the annulation of 6-, 7-, or 8-membered rings and

Scheme I[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 0.5 h, quantitative; (b) $CH_2{=}CHOCH_2CH_3$, $Hg(OAc)_2$, 30 °C, 20 h, 80%; (c) sealed tube, 200 °C, 1 h, 90%; (d) $CH_3C(OC_2H_5)_3$, $Hg(OAc)_2$, C_2H_5COOH, sealed tube, 200 °C, 6 h, 80%.

Scheme II[a]



[a] Reagents and conditions: (a) $(COCl)_2$–Py, 30 °C, 2 h; (b) CH_2N_2, ether, 5 °C, 12 h, 66% from **12b**; (c) BF_3 etherate, CH_2Cl_2, 0 °C, 3 min, 76%; (d) $RuCl_3$–$NaIO_4$, CH_3CN–CCl_4–H_2O, 30 °C, 1 h, 90%; (e) KOH, MeOH, Δ, 1 h, 36%.

construction of the rest of the carbocyclic framework. For this purpose, unsaturated aldehyde **11** and unsaturated ester **12a** of firmly secured stereochemistry appeared to be eminently serviceable.[12,13] To gain ready access to the chirons **11** and **12**, cheap and abundantly available (*R*)-(+)-limonene (**13**) was chosen as the chiral resource, particularly as it can be efficiently restructured into cyclopentene aldehyde **14**.[12,14]

Construction of the C_{12} Chirons (−)-11 and (−)-12. Enantiomerically pure aldehyde **11** and ester **12** were obtained from **14** as shown in Scheme I, by employing a diastereoselective [3s.3s]-shift (Claisen rearrangement) as the pivotal operation to set up the key quaternary carbon center. Chemoselective 1,2-reduction of the α,β-unsaturated enal **14** with $NaBH_4$–$CeCl_3$ reagent[15] furnished the allylic alcohol **15** in quantitative yield, which was transformed to the ethyl vinyl ether **16** on Hg^{2+}-catalyzed transetherification. Thermal activation of **16**, following the common Claisen rearrangement regimen, led to the exclusive formation of unsaturated aldehyde (−)-**11** in 90% yield.[13] Structure of **11** rests secured on its spectral data, particularly the methyl singlet at δ 1.09 and the quaternary sp^3 carbon signal at

(3) Glasby, J. S. *Encyclopedia of the Terpenoids*; John Wiley & Sons: New York, 1982.
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(7) Hashimoto, T.; Tari, M.; Tairo, Z.; Asakawa, Y. *Tetrahedron Lett.* **1985**, 6473.
(8) Wahlberg, I.; Eklund, A. M.; Nishida, T.; Enzell, C. R.; Berg, J. E. *Tetrahedron Lett.* **1983**, 843.
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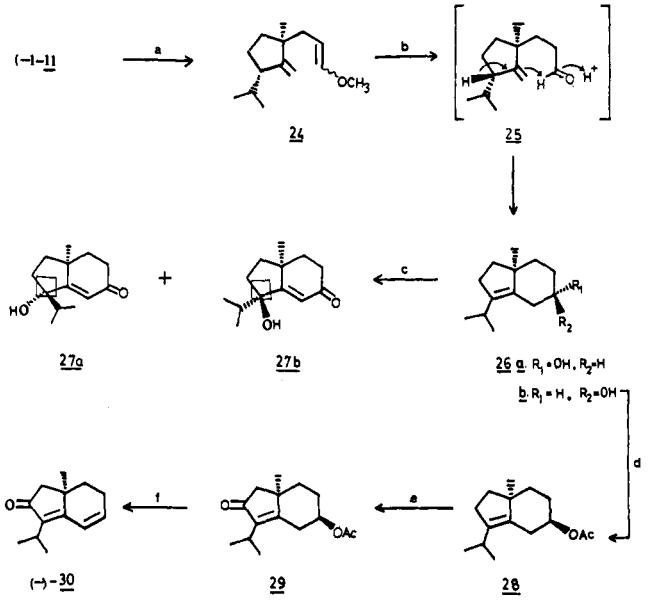
(13) Since the publication of our preliminary report,[12a] **11** has found use in diterpene synthesis related to **6**. Kang, H. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.
(14) (a) Yamasaki, M. *J. Chem. Soc., Chem. Commun.* **1972**, 606. (b) Lange, G. L.; Neidert, E. E.; Orrom, W. S.; Wallace, D. J. *Can. J. Chem.* **1978**, *56*, 1628. (c) Van Tamalen, E. E.; Milne, G. M.; Suffness, M. F.; Chauvin, M. C. R.; Anderson, R. J.; Achini, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 7202.
(15) Luche, J. *J. Am. Chem. Soc.* **1979**, *100*, 2226.

Scheme III[a]



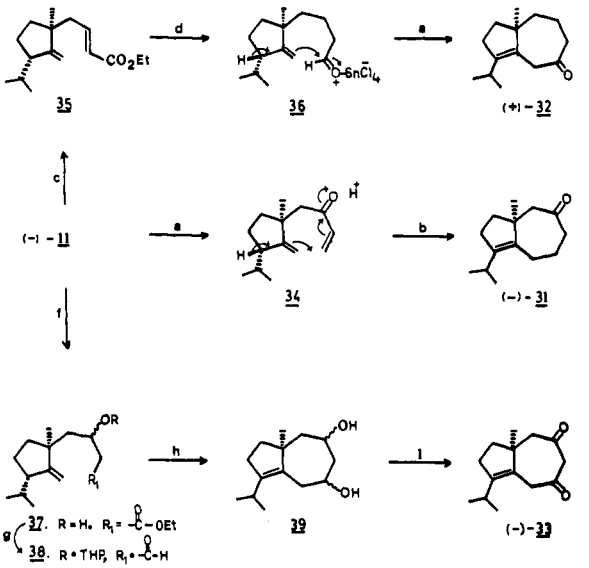
[a] Reagents and conditions: (a) $Ph_3P^+CH_2OCH_3Cl^-Na^+$ $C_5H_{11}O^-$, ether, 30 °C, 30 min, 90%; (b) 35% $HClO_4$–ether, 0–30 °C, 3 h, 73%; (c) PCC, molecular sieves (4 Å), CH_2Cl_2, 1 h, 45%; (d) $(CH_3CO)_2O$–Py, 30 °C, 12 h, 95%; (e) CrO_3–3,5-dimethylpyrazole, 30 °C, 30 h, 73%; (f) KOH, MeOH, 30 °C, 3 h, 75%.

δ 44.0. The diastereofacial selectivity in the Claisen rearrangement **16** → **11**, with the reaction exclusively taking place on the face opposite to the isopropyl group, was a desirable outcome and can be rationalized in terms of preference for the Claisen transition state **17** over **18**. On subjecting **15** to ortho ester Claisen rearrangement,[16] unsaturated ester (−)-**12a** was also obtained as a single diastereomer. After short access to enantiomerically pure **11** and **12a** from **14** through intramolecular chirality transfer was acquired, attention was turned toward the annulation processes.

5,6-Fused Bicyclic Systems. Several hydrindanones with variation in degree and location of functionalization and of relevance to higher terpene syntheses were conveniently assembled from **11** and **12**. Acid **12b** from **12a** was converted to the acid chloride and then to the diazo ketone **20**. Brief exposure of **20** to BF_3 etherate or trifluoroacetic acid led to a smooth cyclization,[17] and the bicyclic enone **21** was obtained quite cleanly. Enone **21** was further restructured via catalytic ruthenium oxidation[18] to trione **22** followed by base-catalyzed aldol cyclization–dehydration to **23** (Scheme II). The enedione **23** not only has amplified and redistributed functionality but also belongs to an enantiomeric series with respect to the precursor enone **21**. Thus, hydrindanones of both enantiomeric series are available from the same chiron **12**.

In an alternative route to the 5,6-fused system, aldehyde **11** was subjected to Wittig olefination with the ylide derived from (methoxymethyl)triphenylphosphonium chloride to give **24** (*E*/*Z* mixture). Mild acid hydrolysis of **24** furnished the homologated C_{13} aldehyde **25**, which concomitantly cyclized to a readily separable mixture (1:3) of homoallylic alcohols **26a** and **26b** (Scheme III). ^1H and ^{13}C NMR spectral data enabled distinction between the epimeric pair. PCC oxidation of either **26a** or **26b** led to an oxidative rearrangement and furnished a mixture of γ-hydroxy α,β-unsaturated enones **27a,b** bearing a characteristic hydroxyisopropyl functionality present in many terpenes (see Chart I). The acetate **28** from **26b** on allylic oxidation with CrO_3–3,5-dimethylpyrazole complex[11][19] furnished acetoxy enone **29**. On exposure to base, **29** underwent hydrolysis and elimination to the dienone **30** (Scheme III).

Scheme IV[a]



[a] Reagents and conditions: (a) (i) CH_2=CHBr, Mg, THF, 30 °C, 30 min, 75%; (ii) PCC, CH_2Cl_2, molecular sieves (4 Å), 30 °C, 1 h, 65%; (b) catalytic $HClO_4$–$(CH_3CO)_2O$, EtOAc, 30 °C, 25 min 65%; (c) $(EtO)_2P^+OCH_2COOEtBr^-$, NaH, THF, 30 °C, 1 h, 70%; (d) (i) Li–NH_3(liq), THF, 50%; (ii) PCC, CH_2Cl_2, 30 °C, 2 h, 50%; (e) (i) $SnCl_4$, CH_2Cl_2, 25 °C, 65%; (ii) PCC, CH_2Cl_2, molecular sieves (4 Å), 75%; (f) Zn, $BrCH_2COOEt$, dioxane, 30 °C, 1 h, 72%; (g) (i) dihydropyran, PPTS, CH_2Cl_2, 30 °C, 6 h, quantitative; (ii) Dibal-H, CH_2Cl_2, −78 °C, 30 min, 65%; (h) $SnCl_4$, CH_2Cl_2, 25 °C, 1 h, 20%; (i) PCC, CH_2Cl_2, molecular sieves (4 Å), 30 min, 60%.

5,7-Fused Bicyclic Systems. We recognized hydrazulenones **31**, **32**, and **33** as conveniently utilizable advanced precursors for further elaboration to sesqui- and diterpenes. Consequently, synthetic protocols for their construction from the chiron **11** were developed and are summarized in Scheme IV. The 5,7-fused bicyclic hydrazulenone **31** was assembled in three convenient steps from **11** via the α,β-unsaturated enone **34**. Acid-catalyzed enone–olefin cyclization in **34** was the pivotal step and proceeded smoothly to furnish (−)-**31**.[20] Absence of olefinic proton resonance in the proton NMR spectrum and the presence of three sp^2 carbon signals at δ 213.0, 141.9, and 138.7 were in full consonance with its structure (Scheme IV). The regioisomeric hydrazulenone **32** was approached from **11** with an intramolecular Lewis acid catalyzed ene reaction (Prins reaction) serving as the key step. Homologation of **11** through Wadsworth–Emmon modification of Wittig reaction using triethyl phosphonoacetate furnished the α,β-unsaturated ester **35**. Li–NH_3(liq) reduction on **35** led to a primary alcohol, which on PDC oxidation[21] gave the labile aldehyde **36**. Exposure of unsaturated aldehyde **36** to $SnCl_4$ resulted in the contemplated cyclization to a bicyclic alcohol, which was further oxidized to yield the desired hydrazulenone (+)-**32** in decent yield. Once again, **32** exhibited three sp^2 carbon resonances at δ 211.0, 145.7, and 131.4 in full agreement with its formulation. For the third and the more oxygenated hydrazulenone **33**, **11** was

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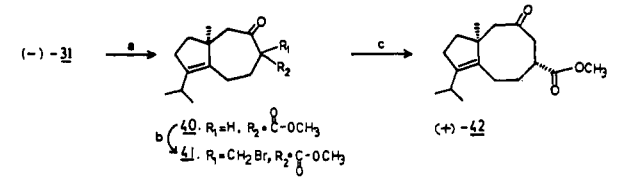
(17) (a) Erman, W. F.; Stone, L. C. *J. Am. Chem. Soc.* **1971**, *93*, 2821. (b) Mander, L. N.; Turner, J. V.; Coombe, B. G. *Aust. J. Chem.* **1974**, *27*, 1985 and earlier paper from this group. (c) Ghatak, U. R.; Sanyal, B. *J. Chem. Soc., Chem. Commun.* **1974**, 876. (d) Smith, A. B., III; Toder, B. H.; Branca, S. J.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *163*, 1990.
(18) Carlson, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(19) Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499.
(20) During the course of the present work, synthesis of racemic **31** was reported following an entirely different approach. Pattenden, G.; Robertson, G. M. *Tetrahedron Lett.* **1986**, 399. Begley, M. J.; Pattenden, G.; Robertson, G. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1085.
(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

Scheme V[a]

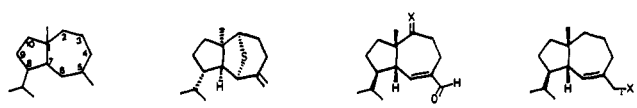


[a] Reagents and conditions: (a) $(CH_3O)_2C{=}O$, NaH, Δ, 6 h, 78%; (b) K_2CO_3–CH_2Br_2, $(CH_3)_2CO$, Δ, 16 h, 81%; (c) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, 16 h, 50%.

subjected to Reformatsky reaction with ethyl bromoacetate to furnish the homologated β-hydroxy ester **37**. The reactive β-hydroxy functionality in **37** was protected as a tetrahydropyranyl ether to avoid proclivity toward elimination, and the ester functionality was reduced with Dibal-H to furnish **38**. The labile aldehyde **38** was subjected to intramolecular ene cyclization with $SnCl_4$, which also led to deprotection of the THP group, and **39** was obtained as a mixture of diastereomers. PCC oxidation[22] of **39** delivered the hydrazulene-1,3-dione (−)-**33** (Scheme IV). The ^{13}C NMR spectrum of **33** exhibited signals at δ 203.0, 202.8, 148.8, and 130.0 due to two carbonyl groups and the tetrasubstituted olefin.

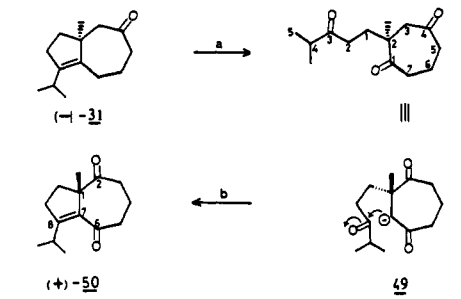
5,8-Fused Bicyclic System. For the construction of this ring system, one carbon ring expansion of hydrazulenone (−)-**31** appeared to be an advantageous approach. After unsuccessful efforts with more conventional protocols for this purpose, we were able to effect ring expansion employing Dowd methodology.[23] Regioselective enolate generated from (−)-**31** with NaH was quenched with dimethyl carbonate to furnish a diastereomeric mixture of α-ketoesters **40** (Scheme V). Further reaction with methylenedibromide in the presence of a base led to **41**. Reaction of **41** with tri-*n*-butylstannane led to a radical-induced ring expansion, and cyclooctanone ester (+)-**42** was realized. A 17-line ^{13}C NMR spectrum with diagnostic resonances at δ 210.9, 175.5, 144.6, and 135.9 secured the structure of **42**, which has the complete carbocyclic content corresponding to two of the rings of 5,8,5-fused diterpenes, e.g., **5** and **6**.

Total Synthesis of Isodaucane Sesquiterpenes (+)-Aphanamol I (2) and (+)-2-Oxoisodauc-5-en-12-al (46). Sesquiterpenes based on the hydrazulene-type isodaucane skeleton **43** are still of rare occurrence and have been discovered in nature only recently. The members of this family include (−)-mintsulfide (**44**) from pep-



permint oil,[24] (+)-aphanamol I (**2**) and II (**45**) from the Meliaceous plant *Aphanamixis grandifolia*,[4] 2-oxoisodauc-5-en-12-al (**46**) from *Chromolgen laevigata* (Lam),[25] isonitrile **47**, and isothiocyanate **48** from the marine sponge *Acanthella acuta*.[26] Total synthesis of isodaucane sesquiterpenes has not been accomplished so far, and with the exception of **44** their absolute configuration remains unknown.[27] Our synthetic interest in isodaucane ses-

Scheme VI[a]



[a] Reagents and conditions: (a) RuO_2–$NaIO_4$, CH_3CN–CCl_4–H_2O, 30 °C, 1 h, quantitative; (b) 5% KOH–CH_3OH, Δ, 30 min, 60%.

quiterpenes was aroused by the striking structural resemblance between them and the hydrazulenone (−)-**31**, which marked it out as an advanced precursor for their synthesis. We selected natural products **2** and **46** as our targets and hoped that their attainment from (−)-**31** would also elucidate their absolute configuration.[12b]

Elaboration of (−)-**31** to isodaucane sesquiterpenoids in general, and **2** and **46** in particular, required formulation of a strategy to effect three main manipulations. First and foremost was the question of generation and control of stereochemistry at C_1, C_7, and C_8 stereogenic centers. The cis ring junction and cis relationship between the C_1-methyl group and the C_8-isopropyl group represent a thermodynamically less stable stereochemical arrangement. This stereochemical pattern is obviously not accessible from (−)-**31** by simple hydrogenation. Moreover, the considerably hindered tetrasubstituted double bond in (−)-**31** was completely resistant to hydrogenation even at moderate pressures. Therefore, some new tactic had to be devised to secure correct C_1, C_7, and C_8 stereochemistry. Secondly, completion of the isodaucane carbon skeleton required installation of the 15th carbon atom at the remote C_5 in **31** at the desired oxidation level. Lastly, **2** and **46** carry oxygen functionalization across the seven-membered ring, and therefore considerable amplification and relocation of functionality in (−)-**31** was required.

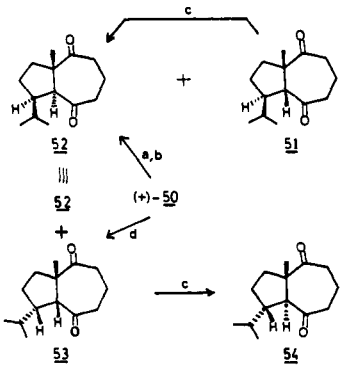
It was possible to devise a synthetic stratagem that provided a simple and satisfactory solution to all the three strategic requirements mentioned above. The tetrasubstituted double bond in (−)-**31** was cleaved by employing the Sharpless catalytic ruthenium oxidation procedure[18] to furnish the trione **49** in quantitative yield. The trione **49** was readily induced to undergo intramolecular aldol cyclization–elimination in the presence of base to give the bicyclic enedione (+)-**50** in 60% yield (Scheme VI). The enedione formulation **50** was fully consonant with the spectral data, particularly the ^{13}C NMR that exhibited four characteristic sp^2 carbon resonances at δ 213.7, 199.8, 167.3, and 136.8. Thus, in two steps, (−)-**31** was restructured to (+)-**50** with amplification and relocation of the functionalities at the desired position and the α,β-unsaturated enone moiety present now was more amenable to reductive maneuvers for generating the requisite stereochemistry. Interestingly, the restructured (+)-**50** now belongs to an enantiomeric series with respect to (−)-**31**.

Reduction of the enone moiety in (+)-**50** with Li–NH_3(liq) and PCC oxidation of the resulting product led to the saturated diones **51** and **52** in a 9:1 ratio. While the ^1H and ^{13}C NMR spectra of **51** and **52** were fully supportive of their gross structures, they were not incisive enough for making firm stereochemical assignments. However, firm stereochemical assignments could be made on the basis of the following observations. It was observed that the major isomer **51** on exposure to base completely equilibrated to the more stable trans ring junction isomer **52**.[28] Predominant formation of *cis*-**51** during $LiNH_3$(liq) reduction, though not entirely predictable, is in keeping with the recent observations on the metal ammonia reduction of several hydr-

(22) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(23) Dowd, P.; Choi, S-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493, 6548. Dowd, P.; Choi, S-C. *Tetrahedron* **1989**, *45*, 77.
(24) Yoshida, T.; Muraki, S.; Takahashi, K.; Kato, T.; Kabuto, C.; Suzuki, T.; Vyehara, T.; Ohnuma, T. *J. Chem. Soc., Chem. Commun.* **1979**, 512.
(25) Misra, L. N.; Jakupovic, J.; Bohlmann, F.; Schmeda-Hirschmann, G. *Tetrahedron* **1985**, *41*, 5353.
(26) Mayol, L.; Piccialli, V.; Sica, D. *Tetrahedron* **1987**, *43*, 5381.
(27) Formation of isodaucane-type skeleton during the acid-catalyzed cyclization of humulene and epoxygermacrene D has been observed earlier: Naya, Y.; Hirose, Y. *Chem. Lett.* **1973**, 133. Baines, D.; Forrester, J.; Parker, W. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1598. Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1979**, 4291. For the formation of (±)-aphanamol II, see: Shizuri, Y.; Yamaguchi, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, 57.

(28) Molecular mechanics calculations using the MM_2 program also indicated that trans-fused hydrazulenediones are more stable than the cis isomers. SE values for diones **51**–**54** are 20.94, 18.42, 20.58, and 18.72 kcal/mol, respectively.

Scheme VII[a]

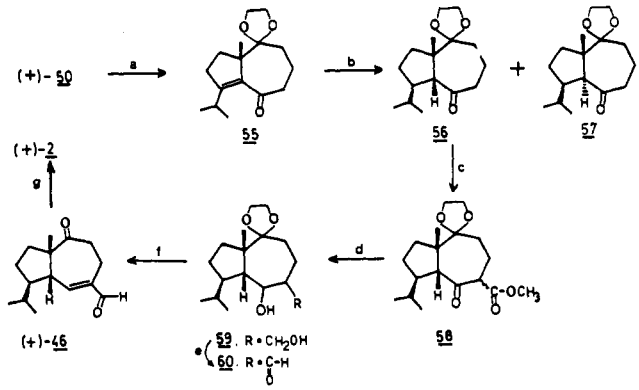


[a] Reagents and conditions: (a) Li-NH_3(liq), THF-MeOH; (b) PCC, CH_2Cl_2, molecular sieves (4 Å), 70%; (c) 5% KOH-CH_3OH, 24 h, 30 ° C, quantitative; (d) H_2, Pd/C, EtOAc, 20 psi, 1 h, 90%.

indanones, which mainly furnish cis-fused products.[29] In the reduction of enone (+)-**50**, two successive kinetic protonations result in the observed stereochemistry of **51**. Catalytic hydrogenation of (+)-**50** over Pd/C catalyst proceeded smoothly and produced separable isomers **52** and **53** in a 5:4 ratio. The marginally more abundant isomer **52** was found to be identical with the minor trans-fused product from the Li-NH_3(liq) reduction. With the propensity for cis addition of hydrogen to the double bond in mind, the two isomers obtained from **50** could be assigned as **52** and **53** having trans and cis ring junction stereochemistry, respectively. The cis-fused isomer **53** on exposure to base epimerized completely into a new stereoisomer (**54**) having a trans ring junction. In this manner, it was possible to gain access to all the four possible stereoisomers **51–54**, representing various stereochemical patterns present in nature, and their stereochemistry rests secured on an internally consistent correlation. Any other fixation of stereochemistry for **51–54** is not consistent with the observations summarized in Scheme VII.

After it was established that the requisite stereochemistry of isodaucane sesquiterpenes at C_1, C_7, and C_8 can be generated through metal–ammonia reduction of enedione (+)-**50**, our synthetic task was reduced to functional group adjustment and the introduction of a C_5-substituent. Reverting to (+)-**50**, the saturated carbonyl was chemoselectively protected to give monoacetal **55**. Li-NH_3(liq) reduction on **55** and PCC oxidation furnished a 7.5:1 mixture of saturated ketoacetals *cis*-**56** and *trans*-**57**, respectively. The *cis*-**56** could be deprotected and correlated with **51**. Kinetically controlled deprotonation of **56** with LiHMDS and quenching with methyl chloroformate furnished the α-ketoester **58** as a mixture of C_5 diastereomers. There was some ^1H NMR indication that the enol ester form of **58** was also present. Reduction of **58** with LAH led to diol **59** but in only 40% yield. However, $NaBH_4$ surprisingly proved superior for this reduction, and **59** could be obtained in 62% yield. Chemoselective Swern oxidation in **59** gave the hydroxy aldehyde **60** (Scheme VIII). Brief exposure of **60** to *p*-toluenesulfonic acid resulted in dehydration as well as deacetalization and furnished (+)-2-oxoisodauc-5-en-12-al (**46**), $[\alpha]_D$ 33°.[31] The IR and ^1H NMR values of **46** were found identical with those reported in literature.[25,31] Lastly, chemoselective reduction of (+)-**46** with $NaBH_4$–$CeCl_3$[15] combination gave (+)-aphanamol I (**2**), $[\alpha]_D$ 10°, whose identity was established by direct spectral (IR, ^1H NMR) comparison with the natural product.[4,32] Since aphanamol II (**45**) has been correlated with aphanamol I (**2**), our synthesis of the latter es-

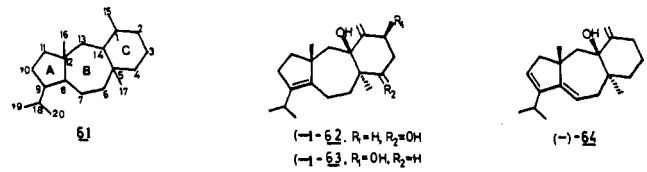
Scheme VIII[a]



[a] Reagents and conditions: (a) $(CH_2OH)_2$, *p*-TSA, C_6H_6, Δ, 92%; (b) Li-NH_3(liq), THF-MeOH, PCC, CH_2Cl_2, molecular sieves (4 Å), 72%; (c) *n*-BuLi-$(CH_3)_3SiNHSi(CH_3)_3$, THF, $ClCO_2CH_3$, −78 °C, 86%; (d) $NaBH_4$, MeOH, 0 °C, 62%; (e) $(COCl_2)_2$-DMSO, CH_2Cl_2, Et_3N, −60 °C, 70%; (f) *p*-TSA, C_6H_6, Δ, 37%; (g) $NaBH_4$–$CeCl_3$, $6H_2O$, MeOH, −5 °C, quantitative.

tablished the absolute configuration of both the natural products.

Total Synthesis of Dolastane Diterpenes (+)-Isoamijiol (63) and (+)-Dolasta-1(15),7,9-trien-14-ol (64). The dolastane diterpenes embodying a 5,7,6-fused tricarbocyclic framework (**61**) have frequently surfaced from marine sources, particularly seaweeds, ever since their first discovery in nature in 1976. Presently,



about 40 natural products based on skeleton **61**, with varying degrees of unsaturation and oxygen functionalization and biological activity, are known. Some dolastane prototypes are doubly unsaturated dolatriol (**3**),[5] (−)-amijiol (**62**),[33] (−)-isoamijiol (**63**),[33] and triply unsaturated (−)-dolasta-1(15),7,9-trien-14-ol (**64**).[34] This group of diterpenes attracted our attention on account of the skeletal resemblance between them and the hydrazulenone (−)-**31**, and we selected isoamijiol (**63**) and dolastatrienol (**64**) as the target structures.[20,35] We recognized that since **31** already represents the AB ring portion of dolastanes, the main task in its elaboration to dolastane prototypes would be stereoselective annulation of a six-membered ring (C) and generation of the crucial functionality in the form of a bridgehead allylic hydroxyl group. For this purpose, we opted for a radical cyclization based annulation strategy that has gained currency in recent years for generating the bridgehead α-hydroxy methylene moiety.[12a,36]

Deprotonation of (−)-**31** with LiHMDS in the presence of HMPA and quenching the enolate with triisopropylsilyl (TIPS) protected 5-iodo-1-pentyne gave **65** as a single stereoisomer in 80% yield.[37] To introduce the second quaternary methyl group, the

(29) (a) Sakurai, K.; Kitahara, T.; Mori, K. *Tetrahedron* **1990**, *46*, 761. (b) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, 149.

(30) Ōmura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(31) Specific rotation of the natural product has not been reported.[25] Copies of the spectra for comparison purposes could not be obtained from the researchers.[25]

(32) We thank Professor M. Nishizawa for the comparison spectra of aphanamol I (**2**).

(33) Ochi, M.; Watanabe, M.; Miura, M.; Taniguchi, M.; Tokoroyama, T. *Chem. Lett.* **1980**, 1229.

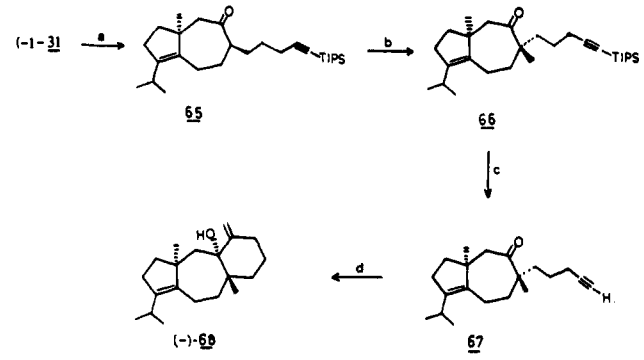
(34) Crews, P.; Klein, T. E.; Hogue, E. R.; Myers, B. L. *J. Org. Chem.* **1982**, *47*, 811.

(35) For synthetic studies on dolastane diterpenes, see: (a) ref 20. (b) Paquette, L. A.; Lin, H. S.; Belmont, D. T.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 4807. (c) Piers, E.; Frissen, R. W. *J. Org. Chem.* **1986**, *51*, 3405. (d) Piers, E.; Frissen, R. W. *J. Chem. Soc., Chem. Commun.* **1988**, 125. (e) Majetich, G.; Song, J. S.; Ringold, C.; Nemeth, G. A. *Tetrahedron Lett.* **1990**, 2239.

(36) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N.; Radhakrishnan, T. V.; Sohoni, S. V.; Thaker, V. B. *J. Org. Chem.* **1981**, *46*, 2622. (c) Pattenden, G.; Robertson, G. M. *Tetrahedron* **1985**, *41*, 4001.

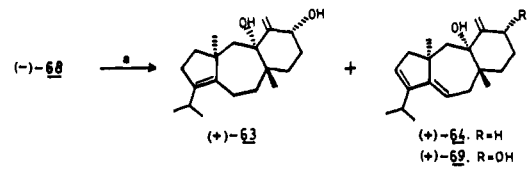
(37) The reaction sequence employed by us is similar to that employed by Pattenden.[20]

Scheme IX[a]



[a] Reagents and conditions: (a) *n*-BuLi–$(CH_3)_3SiNHSi(CH_3)_3$, HMPA, THF, $I(CH_2)_3C{\equiv}CSi[CH(CH_3)_2]_3$, −10 °C, 1 h, 80%; (b) NaH, DME, MeI, 30 °C, 24 h, 65%; (c) *n*-$Bu_4N^+F^-$, THF, 30 °C, 5 min, quantitative; (d) $C_{10}H_8$ Na, THF, 30 °C, 40%.

Scheme X[a]



[a] Reagents and conditions: (a) SeO_2, *t*-BuOOH, CH_2Cl_2, −4 to 0 °C, 60%.

thermodynamic enolate generated from **65** with NaH was quenched with methyl iodide to furnish **66**. The stereoselective placement of the methyl center was a consequence of the topological bias engendered by the preexisting C_1 quaternary methyl group in the bicyclic hydrazulenone framework. The towering presence of the TIPS protective group in **66** was now dispensed with tetra-*n*-butylammonium fluoride reagent. The resulting bicyclic ketoalkyne **67** was subjected to the key radical-induced alkyne–carbonyl cyclization.[36] In the event, titration of **67** with the dark green sodium naphthalenide solution furnished **68** and heralded the completion of the dolastane framework (Scheme IX). The trans selectivity of the newly appended ring in **68** follows from the remarkable similarity of the quaternary methyl resonances (δ 1.34 and 0.78) in it with the dolastane natural products (e.g., δ 1.34 and 0.77 in **63**).[33,34]

The final step in the synthesis of (+)-isoamijiol (**63**) was the introduction of the allylic hydroxyl group, and this was sought to be achieved through the Sharpless catalytic SeO_2 oxidation.[38] While the reaction was sensitive and yielded a mixture of products, the overall outcome was fortuitous. After careful and repeated chromatography, (+)-isoamijiol (**63**), $[\alpha]_D$ 45°, (+)-dolasta-1-(15),7,9-trien-14-ol (**64**),[39] $[\alpha]_D$ 200°, and (+)-dolasta-1-(15),7,9-trien-2,14-diol (**69**) were isolated in a ratio of ~2:3:1 (Scheme X). While natural products (+)-**63** and (+)-**64** were identified through spectral comparison with authentic samples,[40] the structure of **69** is tentatively assigned on the basis of spectral similarity with **64**. Thus, the first enantioselective synthesis of dolastane diterpenes was successfully accomplished.

Summary

In short, we have outlined practical and enantioselective approaches to several bicyclic hydrindanones and hydrazulenones from restructured (*R*)-(+)-limonene via a key C_{12} chiron. The 5,6-, 5,7-, and 5,8-fused bicyclic systems available in enantiomerically pure form are potentially serviceable for the synthesis of diverse higher terpenes.[13] As a demonstration of their utility, we have described the first enantioselective syntheses of isodaucane sesquiterpenes and dolastane diterpenes. Many synthetic efforts along the theme delineated here are currently underway and will be reported in due course.

Experimental Section

Melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected. Bulb-to-bulb distillations were carried out with use of oil baths for all liquid samples, and boiling points refer to the oil bath temperatures. Infrared spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometers. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin films between NaCl plates. ^1H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were recorded on a JEOL FX-100 spectrometer. Samples were made in chloroform-*d* solvent, and chemical shifts are reported in scale by using tetramethylsilane (Me_4Si) as the internal standard. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quadruplet, and multiplet, respectively. Optical rotations were measured on an AUTOPOL II polarimeter in chloroform solutions. Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyser. All reactions were monitored by TLC with use of appropriate solvent systems for development. Moisture-sensitive reactions were carried out by using standard syringe–septum techniques. Petroleum ether refers to the fraction boiling between 60 and 80 °C. Dichloromethane was distilled over P_2O_5. Benzene was distilled over sodium and stored over pressed sodium wire. Ether and THF were dried by distilling them from sodium benzophenone ketyl. All solvent extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure on a Buchi-E1 rotary evaporator. Yields reported are isolated yields of material judged homogenous by TLC and NMR spectroscopy.

(+)-3(*S*)-Isopropyl-1-methyl-2-(hydroxymethyl)cyclopent-1-ene (15). The aldehyde **14** (10.0 g, 65.8 mmol) obtained[14a,b] from (*R*)-(+)-limonene (**13**) was dissolved in dry methanol (100 mL), and $CeCl_3{\cdot}7H_2O$ (2.5 g) was added. The reaction mixture was cooled to 0 °C, and sodium borohydride (2.65 g, 70.0 mmol) was added in small portions. After stirring for 0.5 h, methanol was removed and the residue was diluted with water (50 mL) and extracted with ether (150 mL × 3). The ethereal extract was washed with dilute HCl and saturated $NaHCO_3$ and dried. Distillation furnished the allylic alcohol **15**: (9.6 g, 96%);[14c] bp 75 °C, (1.3 Torr); $[\alpha]_D$ 43° (*c* 1.0, $CHCl_3$); IR (neat) 3400, 2950, 1460, 1380, 1000 cm^{-1}; ^1H NMR δ 4.0 (2 H, m, $-CH_2OH$), 3.0–1.6 (7 H, m), 1.65 (3 H, br s, $-C{=}CH_3$), 0.9 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.65 (3 H, d, J = 7 Hz, $-CHCH_3$).

(−)-3(*S*)-Isopropyl-1-methyl-2-[(vinyloxy)methyl]cyclopent-1-ene (16). To a mixture of allylic alcohol **15** (9.5 g, 61.6 mmol) and freshly distilled ethyl vinyl ether (300 mL) was added mercuric acetate (1.0 g), and the reaction mixture was stirred at ~30 °C for 20 h. The excess ethyl vinyl ether was recovered by distillation, and the residue was filtered through a basic alumina (50 g) column by using petroleum ether to yield the pure vinyl ether **16**: 8.9 g, 80%; bp 100 °C (0.5 Torr); $[\alpha]_D$ −53° (*c* 1.0, $CHCl_3$); IR (neat) 3050, 2950, 1630, 1600, 1460, 1190, 800 cm^{-1}; ^1H NMR δ 6.6–6.2 (1 H, m, $-OCH{=}CH_2$), 4.4–3.8 (4 H, m, $-CH_2OCH{=}CH_2$), 3.0–1.8 (6 H, series of m), 1.7 (3 H, br s, $-C{=}CCH_3$), 0.9 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.7 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 151.8, 138.0, 132.7, 86.3, 63.1, 53.1, 38.0, 28.7, 21.9, 21.4, 16.0, 15.1. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.01; H, 11.15.

(−)-(2*S*,5*S*)-5-Isopropyl-2-methyl-2-(2-oxoethyl)methylenecyclopentane (11). Vinyl ether **16** (5.0 g, 27.8 mmol) was sealed in a Corning glass tube under N_2 and heated at 200 °C for 1 h. After cooling to ~30 °C, the crude product was charged on a silica gel (50 g) column. Elution with 5% ethyl acetate–petroleum ether furnished the aldehyde **11**: 4.5 g, 90%; bp 100 °C (0.5 Torr); $[\alpha]_D$ −70 °C (*c* 1.0, $CHCl_3$); IR (neat) 3050, 2950, 2750, 1720, 1640, 890 cm^{-1}; ^1H NMR δ 9.7 (1 H, t, J = 4 Hz, $O{=}CH$), 4.89 (1 H, d, J = 4 Hz, $-C{=}CH_2$), 4.85 (1 H, d, J = 4 Hz, $-C{=}CH_2$), 2.44 (2 H, m, $-CH_2CHO$), 2.25–1.3 (6 H, m), 1.09 (3 H, s, $-CCH_3$), 0.97 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.79 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 202.9, 161.0, 104.9, 54.4, 50.7, 44.4, 37.3, 28.8, 27.6, 23.0, 21.7, 16.4. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.14.

(−)-(2*S*,5*S*)-5-Isopropyl-2-methyl-2-(carbethoxymethyl)methylenecyclopentane (12a). A mixture of allylic alcohol **15** (5 g, 32.5 mmol), triethyl orthoacetate (25 mL), propionic acid (500 mg), and mercuric acetate (750 mg) was sealed under N_2 in a Corning glass tube and heated at 200 °C for 6 h. After cooling to ~30 °C, the crude product was charged on a silica gel (100 g) column. Elution with 3% ethyl acetate–petroleum ether furnished the compound **12a**: 5.5 g, 80%; $[\alpha]_D$ −53.7° (*c* 5.1, $CHCl_3$); IR (neat) 2975, 1755, 880 cm^{-1}; ^1H NMR δ 4.88–4.72 (m, 2 H), 4.10 (q, $J_1 = J_2$ = 7 Hz, 2 H), 2.6–1.44 (m, 8 H), 1.24 (t, J

(38) Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
(39) The optical rotation of the natural product has not been reported.[34]
(40) We thank Professors G. Pattenden, E. Piers, and M. Ochi for their kind help in making available the comparison spectra.

= 7 Hz, 3 H), 1.08 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H), 0.78 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 171.9, 161.9, 103.4, 59.6, 50.5, 45.9, 44.4, 37.1, 28.7, 26.8, 22.9, 21.6, 16.2, 14.1. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.71.

(+)-7-Isopropyl-1(*S*)-methylbicyclo[4.3.0]non-6(7)-en-3-one (21). A mixture of ester **12a** (1 g, 4.5 mmol) in 15 mL of MeOH with 10 mL of 5% (w/v) NaOH(aq) was refluxed for 2 h under N_2. The reaction mixture was cooled, diluted with water, and acidified with HCl (dil). Extraction with ethyl acetate (50 mL × 3), washing, and drying gave the crude acid **12b** (950 mg), which was directly used for the acid chloride preparation employing oxalyl chloride (1.2 mL, 3 equiv) and pyridine (0.5 mL, 1 equiv) in dichloromethane (50 mL). Filtration through a Celite pad gave the crude acid chloride: 680 mg; IR (neat) 3060, 1800, 890 cm^{-1}.

The above acid chloride was dissolved in ether (10 mL), and ethereal diazomethane was added (0–5 °C) until a yellow color persisted. The contents were left overnight at 5 °C and concentrated. The residue was filtered through a silica gel (15 g) column to furnish diazo ketone **20**: 450 mg, 66%; IR (neat) 3075, 2110, 1640, 1355, 885 cm^{-1}. To a solution of **20** (300 mg, 1.36 mmol) in dichloromethane (150 mL) was added 1.2 equiv of BF_3·Et_2O under N_2 at 0 °C. The reaction mixture was quenched after 3 min with $NaHCO_3$(aq) solution, washed and, dried. The crude product was charged on a silica gel (15 g) column and eluted with 10% ethyl acetate–petroleum ether to furnish the bicyclic enone **21**: 200 mg, 76%; $[\alpha]_D$ 19.2° (c 2.5, $CHCl_3$); IR (neat) 2955, 1710 cm^{-1}; ^{1}H NMR δ 2.78–1.34 (11 H, m), 0.94 (d, J = 7 Hz, 3 H), 0.88 (s, 3 H), 0.87 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 211.7, 140.4, 134.4, 56.0, 50.9, 41.1, 38.9, 29.1, 26.6, 24.4, 21.5, 21.3, 21.1. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.42; H, 10.47.

2(*S*)-Methyl-2-(4-methyl-3-oxopentyl)cyclohexane-1,4-dione (22). The bicyclic enone **21** (175 mg, 0.91 mmol) was dissolved in a mixture of (1:1:1) carbon tetrachloride, acetonitrile, and water (15 mL), and ruthenium trichloride (5 mg) followed by sodium metaperiodate (295 mg, 1.4 mmol) was added.[18] After stirring for 1 h, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a Celite pad. The organic phase was washed and dried. The crude product was passed through a silica gel (10 g) column in 30% ethyl acetate–petroleum ether to furnish trione **22**: 180 mg, 90%; mp 66 °C; IR (KBr) 2990, 1720, 1010 cm^{-1}; ^{1}H NMR δ 2.68–1.4 (11 H, m), 0.96 (s, 3 H), 0.92 (d, J = 7 Hz, 6 H); ^{13}C NMR δ 213.4, 211.9, 208.1, 50.2, 46.4, 40.6, 36.2, 36.1, 34.3, 31.5, 23.8, 17.9 (2 C). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.91; H, 8.99. Found: C, 69.76; H, 8.91.

(+)-7-Isopropyl-1(*S*)-methylbicyclo[4.3.0]non-6(7)-ene-2,5-dione (23). A mixture of triketone **22** (100 mg, 0.45 mmol) and 5% methanolic KOH (5 mL) was refluxed for 1 h. Methanol was removed, and the residue was diluted with water (10 mL). Extraction with ether (25 mL × 3), washing, and drying gave a crude product, which was filtered through a small silica gel (10 g) column. Elution with 15% ethyl acetate–petroleum ether furnished the compound **23**: 35 mg, 36%; $[\alpha]_D$ 234.2° (c 1.4, $CHCl_3$); IR (neat) 2975, 1720, 1680, 1610 cm^{-1}; ^{1}H NMR δ 3.88–3.56 (1 H, m), 2.88–1.70 (8 H, m), 1.30 (3 H, s), 1.06 (d, J = 7 Hz, 3 H), 1.0 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 213.9, 197.4, 168.2, 133.5, 59.2, 37.6, 35.8, 33.3, 29.2, 27.6, 24.3, 20.9, 20.6. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.56; H, 8.85.

(-)-(1*S*,4*S*)-7-Isopropyl-1-methylbicyclo[4.3.0]non-6(7)-en-4-ol (26a) and (-)-(1*S*,4*R*)-7-Isopropyl-1-methylbicyclo[4.3.0]non-6(7)-en-4-ol (26b). To a suspension of (methoxymethyl)triphenylphosphonium chloride (5.65 g, 16.5 mmol) in 25 mL of ether, freshly sublimed sodium t-amyl oxide (910 mg, 8.25 mmol) in 5 mL of ether was added. The resulting dark red reaction mixture was stirred for 15 min at 30 °C, and aldehyde **11** (1 g, 5.5 mmol) in 5 mL of ether was introduced. The reactants were stirred for 30 min and then quenched with water and extracted with ether (50 mL × 4). The crude product was filtered through a basic alumina column to afford E/Z-enol ethers **24**: 1.0 g, 90%; IR (neat) 3080, 3040, 1660, 880 cm^{-1}; ^{1}H NMR δ 6.24 (br d, J = 12 Hz, 1 H), 5.93 (d, J = 6 Hz, 1 H), 4.76 (4 H, m), 4.44–4.22 (2 H, m) 3.56 (3 H, m), 3.50 (3 H, s), 2.56–1.0 (12 H, m), 1.02–0.76 (complex doublets and singlets, 18 H). To a solution of enol ethers **24** (500 mg, 2.4 mmol) in 25 mL of ether, 35% perchloric acid (2 mL) was added at 0 °C. The reaction mixture was allowed to warm to ~30 °C and stirred for 3 h. The reaction was quenched with $NaHCO_3$(satd) solution, and the ethereal layer was washed and dried. Removal of the solvent afforded diastereomeric alcohols **26a** and **26b** (340 mg, 73%) in a 1:3 ratio. Chromatographic separation gave pure **26a** and **26b**. Data for **26a**: $[\alpha]_D$ - 6.4° (c 5.0, $CHCl_3$); ^{1}H NMR δ 3.60–3.16 (1 H, m), 2.80–1.04 (12 H, m), 1.00 (3 H, s), 0.96 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 139.5, 136.0, 71.9, 46.1, 38.8, 38.6, 33.1, 32.5, 28.8, 26.4, 22.6, 21.8, 21.1. Anal. Calcd for $C_{13}H_{22}O$: C, 80.71; H, 11.61. Found: C, 80.43; H, 11.54. Data for **26b**: mp 60 °C; $[\alpha]_D$ -7.0° (c 5.0, $CHCl_3$); IR (KBr) 3295, 2920, 1460, 1020, 985 cm^{-1}; ^{1}H NMR δ 4.04 (br s, 1 H), 2.84–1.40 (12 H, m), 1.03 (d, J = 7 Hz, 3 H), 1.04 (3 H, s), 0.97 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 142.6, 133.4, 67.0, 46.6, 39.2, 35.0, 31.0, 29.4, 28.0, 26.2, 22.2, 22.0, 21.1. Anal. Calcd for $C_{13}H_{22}O$: C, 80.71; H, 11.61. Found: C, 80.74; H, 11.64.

Oxidation of (-)-(1*S*,4*R*)-7-Isopropyl-1-methylbicyclo[4.3.0]non-6-(7)-en-4-ol (26b). To a suspension of pyridinium chlorochromate (361 mg, 1.0 mmol) molecular sieves (4 Å), in dichloromethane (5 mL) was added the alcohol **26b** (100 mg, 0.5 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred for 1 h at ~30 °C. Passage through a Florisil pad gave a product, which was charged on a silica gel (5 g) column. Elution with 50% ethyl acetate–petroleum ether afforded the enones **27a** and **27b**: 48 mg, 45%; IR (neat) 3350, 2980, 1650 cm^{-1}; ^{1}H NMR δ 5.98 (1 H, s), 5.96 (1 H, s), 2.6–1.48 (18 H, m), 1.36 (3 H, s), 1.20 (3 H, s), 1.08–0.96 (series of doublets, 12 H); ^{13}C NMR δ 201.3, 177.4, 174.4, 123.0, 122.7, 95.8, 94.9, 43.0, 42.8, 38.5, 37.0, 36.3, 33.9 (2 C), 30.6, 29.4, 29.1, 28.2, 23.5, 23.2, 18.3, 17.7, 17.8, 16.8, 16.3; HRMS (M^+) for $C_{13}H_{20}O_2$, calcd 208.1463; found 208.1466.

(+)-(1*R*,4*R*)-4-Acetoxy-7-isopropyl-1-methylbicyclo[4.3.0]non-6-(7)-en-8-one (29). 3,5-Dimethylpyrazole (562 mg, 5.85 mmol) was added to a suspension of chromium trioxide (584 mg, 5.84 mmol) in dichloromethane (15 mL) to give a deep red solution. To this, the acetate **28** (230 mg, 0.97 mmol) prepared from alcohol **26b** by the acetic anhydride–pyridine method in dichloromethane (2 mL) was added. The reaction mixture was stirred for 30 h at 30 °C. The reaction mixture was diluted with ether (30 mL × 4) and filtered through a small Celite pad. The residue was purified on a silica gel (10 g) column. Elution with 40% ethyl acetate–petroleum ether mixture gave **29**: 175 mg, 73%; mp 55 °C; $[\alpha]_D$ 86.8° (c 2.2, $CHCl_3$); IR (KBr) 2965, 1730, 1690, 1640, 1240 cm^{-1}; ^{1}H NMR δ 5.24 (1 H, m), 3.00–1.60 (9 H, m), 2.00 (3 H, s), 1.06 (3 H, s), 0.96 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 207.1, 173.2, 170.4, 144.3, 70.4, 51.6, 40.2, 34.8, 29.3, 26.0, 24.3, 24.1, 20.8, 21.1, 20.5. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.73.

(-)-7-Isopropyl-1(*R*)-methylbicyclo[4.3.0]nona-4(5),6(7)-dien-8-one (30). To a solution of **29** (24 mg, 0.096 mmol) in methanol (2 mL) was added a few drops of 20% methanolic KOH, and the mixture was stirred for 3 h at 30 °C. The reaction mixture was diluted with water and extracted with ethyl acetate (20 mL × 2). The oily residue was chromatographed on a silica gel (1 g) column to furnish **30**: 15 mg, 75%; $[\alpha]_D$ -274.2° (c 0.75, $CHCl_3$); IR (neat) 2940, 1685, 1625, 1100, 730 cm^{-1}; ^{1}H NMR δ 6.60 (br d, J = 8 Hz, 1 H), 6.28–6.00 (1 H, m), 2.96–1.32 (7 H, m), 1.06 (d, J = 7 Hz, 6 H) 0.95 (3 H, s); ^{13}C NMR δ 202.9, 168.8, 139.7, 137.2, 121.5, 51.4, 37.9, 33.7, 25.4, 24.2, 24.1, 21.1, 20.5. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.20; H, 9.56.

(-)-(2*S*,5*S*)-5-Isopropyl-2-methyl-2-(2-oxo-3-butenyl)methylenecyclopentane (34). To an ice-cooled solution of vinylmagnesium bromide (30 mmol), aldehyde **11** (5.0 g, 27.8 mmol) in THF (10 mL) was slowly added. The reaction mixture was warmed to ~30 °C, stirred for 1 h, and then quenched with ice–water. The resulting aqueous layer was extracted with ether (100 mL × 3). The combined ethereal extract was washed, dried, and concentrated to an oil, which was chromatographed on a silica gel (50 g) column. Elution with 10% ethyl acetate–petroleum ether furnished the allylic alcohol: 4.3 g, 75%; bp 120 °C (0.1 Torr); IR (neat) 3400, 3050, 2950, 1640, 1000, 910, 890 cm^{-1}; ^{1}H NMR δ 6.0–5.6 (2 H, m, -C*H*=CH$_2$), 5.3–4.7 (8 H, m, C=C*H*$_2$), 4.4–4.0 (2 H, m, -C*H*=CH$_2$), 2.6–1.3 (16 H, series of m), 1.06 and 1.01 (6 H, s, -CC*H*$_3$), 0.98 (6 H, d, J = 7 Hz, -CHC*H*$_3$), 0.77 and 0.75 (6 H, d, J = 7 Hz, -CHC*H*$_3$). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.58. The above allylic alcohol (4.0 g, 22.5 mmol) in dichloromethane (10 mL) was oxidized with pyridinium chlorochromate (6.5 g, 30 mmol), molecular sieves (4 Å) (5 g), in dichloromethane (50 mL). The reaction mixture was stirred for 1 h, diluted with ether (50 mL), and filtered through a Florisil (10 g) column. Removal of the solvent and elution with 5% ethyl acetate–petroleum ether from a silica gel (40 g) column furnished the pure enone **34**: 2.6 g, 65%; bp 120 °C (0.1 Torr); $[\alpha]_D$ - 62.2° (c 2.0, $CHCl_3$); IR (neat) 3050, 2950, 1680, 1610, 1400, 890 cm^{-1}; ^{1}H NMR δ 6.5–6.0 (2 H, m, -CH=C*H*$_2$, 5.7 (1 H, dd, J_1 = 9 Hz, J_2 = 3 Hz, -C*H*=CH$_2$), 4.78 (1 H, d, J = 4 Hz, -C=C*H*$_2$), 4.72 (1 H, d, J = 4 Hz, -C=C*H*$_2$), 2.7–1.2 (8 H, series of m), 1.08 (3 H, s, -CC*H*$_3$), 0.97 (3 H, d, J = 7 Hz, -CHC*H*$_3$), 0.77 (3 H, d, J = 7 Hz, -CHC*H*$_3$); ^{13}C NMR δ 188.6, 162.5, 137.7, 127.4, 104.8, 50.8, 50.5, 37.1, 28.6, 27.2, 23.0, 21.7, 21.2, 16.3. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.72; H, 10.73.

(-)-8-Isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7(8)-en-3-one (31). To a solution of enone **34** (2.5 g, 12.1 mmol) in dry ethyl acetate (50 mL) were added acetic anhydride (2 mL) and 70% perchloric acid (0.2 mL). The reactants were stirred at ~30 °C for 25 min and then quenched with saturated $NaHCO_3$ solution. The organic phase was washed, dried, and concentrated to give an oil, which was chromatographed on a silica gel (25 g) column. Elution with 10% ethyl acetate–petroleum ether fur-

nished the cyclized ketone **31**: 1.6 g, 65%; bp 120 °C (0.1 Torr); $[\alpha]_D$ −13° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 1695, 1460 cm^{-1}; ^1H NMR δ 2.8–1.5 (13 H, series of m), 1.0 (3 H, s, $-CCH_3$), 0.97 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.94 (3 H, d, *J* = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 213.0, 141.9, 138.7, 54.8, 47.59, 43.7, 38.0, 27.2, 26.5, 24.7, 24.1, 23.8, 21.3, 20.9. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.91; H, 10.91.

(−)-(2*S*,5*S*)-5-Isopropyl-1-methyl(3-carbethoxy-2-propenyl)-methylenecyclopentane (35). Sodium hydride (400 mg, 8.0 mmol) was placed in a round-bottom flask, and THF (5 mL) was introduced followed by triethyl phosphonoacetate (1.24 g, 10 mmol) in THF (5 mL). After stirring for 20 min at ~30 °C, aldehyde **11** (1.0 g, 5.2 mmol) in THF (5 mL) was added at 5–10 °C and stirring was continued for 1 h. The reaction mixture was quenched with water (25 mL) and extracted with ether (100 mL × 3). The combined ethereal extract was washed and dried, and the crude product was charged on a silica gel (15 g) column. Elution with 10% ethyl acetate–petroleum ether furnished the unsaturated ester **35**: 900 mg, 70%; bp 160 °C (1 Torr); $[\alpha]_D$ −35° (*c* 0.2, $CHCl_3$); IR (neat) 3050, 1725, 1650, 1460, 1270, 1180, 1040, 890 cm^{-1}; ^1H NMR δ 6.9 (1 H, dt, J_1 = 14 Hz, J_2 = 7 Hz, $-CH{=}CHCO_2C_2H_5$), 5.8 (1 H, br d, *J* = 14 Hz, $-CH{=}CHCO_2C_2H_5$), 4.8 (2 H, m, $-C{=}CH_2$), 4.15 (2 H, q, *J* = 8 Hz, $-OCH_2CH_3$), 2.5–1.3 (8 H, series of m), 1.25 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 1.0 (3 H, s, $-CCH_3$), 0.95 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.8 (3 H, d, *J* = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 166.7, 161.5, 146.7, 123.3, 104.3, 60.0, 50.9, 45.9, 44.6, 37.0, 29.0, 27.3, 23.1, 21.8, 16.6, 14.3. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.95; H, 10.42.

(−)-(2*R*,5*S*)-5-Isopropyl-2-methyl-2-(4-oxobutyl)methylenecyclopentane (36). Into a two-necked round-bottom flask was placed freshly distilled NH_3 (liq) (50 mL), and sodium metal (90 mg, 4.0 mmol) was added. The resulting blue solution was stirred for 15 min, and the ester **35** (500 mg, 2.0 mmol) in ether (5 mL) was added. After stirring for 1 h, the reaction mixture was quenched with NH_4Cl. The residue was dissolved in water (25 mL) and extracted with ether (50 mL × 3). The combined ethereal extract was washed and dried, and the crude product was charged on a silica gel (10 g) column. Elution with 15% ethyl acetate–petroleum ether furnished the primary alcohol: 180 mg, 50%; bp 150 °C (0.1 Torr); $[\alpha]_D$ −18.6° (*c* 0.7, $CHCl_3$); IR (neat) 3300, 3050, 2950, 1450, 1040, 890 cm^{-1}; ^1H NMR δ 4.75 (2 H, m, $-C{=}CH_2$), 3.6 (2 H, t, *J* = 6 Hz, $-CH_2OH$), 2.6–1.2 (12 H, series of m), 1.02 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.98 (3 H, s, $-CCH_3$), 0.75 (3 H, d, *J* = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 162.8, 103.1, 62.9, 51.3, 45.9, 41.8, 36.9, 33.6, 28.9, 27.3, 23.2, 22.0, 21.0, 16.6. Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 80.11; H, 12.48. The above alcohol (200 mg, 0.95 mmol) was oxidized with pyridinium dichromate (430 mg, 2.0 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at ~30 °C, diluted with ether (50 mL), and passed through a small Florisil pad (3 g). The crude product was charged on a silica gel (10 g) column. Elution with 10% ethyl acetate–petroleum ether furnished the labile aldehyde **36**: 100 mg, 50%; bp 145 °C (0.1 Torr); IR (neat) 3050, 2950, 2740, 1715 cm^{-1}; ^1H NMR δ 9.75 (1 H, br s, $O{=}CH$), 4.78 (2 H, m, $-C{=}CH_2$), 2.5–2.2 (4 H, m), 1.8–1.2 (8 H, series of m), 1.05–0.75 (9 H, series of s and d). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.79; H, 11.71.

(+)-8-Isopropyl-1(*R*)-methylbicyclo[5.3.0]dec-7(8)-en-5-one (32). To a solution of aldehyde **36** (100 mg, 0.5 mmol) in dichloromethane (10 mL) was added stannic chloride (0.1 mL) under N_2 at 0 °C. The reaction mixture was stirred for 30 min at 30 °C and quenched with $NaHCO_3$ solution. Extraction with dichloromethane (50 mL × 3), washing, and drying gave a crude product, which was chromatographed on a silica gel (10 g) column. Elution with 5% acetate–petroleum ether furnished the bicyclic alcohol: 65 mg, 65%; bp 150 °C (0.06 Torr); $[\alpha]_D$ 24° (*c* 0.8, $CHCl_3$); IR (neat) 3450, 2950, 1450, 1040 cm^{-1}; ^1H NMR δ 3.9 (1 H, m, $-CHOH$), 3.2–1.2 (13 H, series of m), 1.05 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.88 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.85 (3 H, s, $-CCH_3$); ^{13}C NMR δ 140.3, 137.0, 66.7, 50.0, 40.5, 39.7, 36.7, 30.9, 27.1, 27.0, 25.3, 21.6, 17.5. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.32; H, 11.64. To a suspension of pyridinium chlorochromate (65 mg, 0.3 mmol), molecular sieves (4 Å) (1 g), in dichloromethane (10 mL) was added the above alcohol (40 mg, 0.2 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was warmed to 30 °C, stirred for 1 h, diluted with ether (20 mL), and filtered through a small Florisil (5 g) pad. Removal of solvent gave an oily liquid, which was charged on a silica gel (10 g) column. Elution with 5% acetate–petroleum ether furnished the ketone **32**: 30 mg, 75%; bp 140 °C (0.1 Torr); $[\alpha]_D$ 60° (*c* 0.4, $CHCl_3$); IR (neat) 2950, 1700, 1450 cm^{-1}; ^1H NMR δ 3.24 (1 H, d, *J* = 16 Hz), 2.9 (1 H, br d, *J* = 16 Hz), 2.8–2.1 (5 H, m), 1.8–1.4 (6 H, m), 1.01 (3 H, s, $-CCH_3$), 0.98 (3 H, d, *J* = 7 Hz, $-CHCH_3$), 0.96 (3 H, d, *J* = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 211.0, 145.7, 131.4, 49.2, 43.9, 40.6, 38.5, 27.4, 27.0, 23.5, 20.8, 20.5. Anal. Calcd for $C_{14}H_{22}O_2$: C, 81.50; H, 10.75. Found: C, 81.41; H, 10.76.

(5*S*,2*S*)-5-Isopropyl-2-methyl-2-(3-carbethoxy-2-hydroxypropyl)-methylenecyclopentane (37). To a mixture of zinc (1.0 g, 15 mmol), iodine (100 mg), and ethyl bromoacetate (1.8 mL, 16 mmol) in dry dioxane (10 mL) was added aldehyde **11** (2.0 g, 11.11 mmol) in dry dioxane (10 mL). The reaction mixture was stirred at 30 °C for 1 h. The reaction was quenched with water and extracted with dichloromethane (100 mL × 3). The crude product was filtered through a silica gel (20 g) column. Elution with 20% ethyl acetate–petroleum ether furnished the hydroxy ester **37** (2.15 g, 72%) as a mixture of diastereomers: bp 140 °C (0.1 Torr); IR (neat) 3500, 3050, 2950, 1720, 1640, 1180, 1030, 890 cm^{-1}; ^1H NMR δ 5.0–4.8 (4 H, m, $-C{=}CH_2$), 4.15 (6 H, q, *J* = 7 Hz, OCH_2CH_3 and $-CHOH$), 3.1–2.9 (2 H, m), 2.6–1.3 (20 H, series of m), 1.3 (6 H, t, *J* = 7 Hz, OCH_2CH_3), 1.08 and 1.04 (6 H, s, $-CCH_3$), 1.0 (6 H, d, *J* = 7 Hz, $-CHCH_3$), 0.8 (6 H, d, *J* = 7 Hz, $-CHCH_3$). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.91; H, 10.75.

(5*S*,2*S*)-5-Isopropyl-2-methyl-2-[3-oxo-2-(tetrahydropyranyl)-propyl]methylenecyclopentane (38). A mixture of hydroxy ester **37** (2.0 g, 7.7 mmol), 3,4-dihydro-2*H*-pyran (2 mL, excess), and a catalytic amount of PPTS in dichloromethane (15 mL) was stirred for 6 h at ~30 °C. The reaction was quenched with water and extracted with dichloromethane (25 mL × 3). The combined organic extract was washed, dried, and concentrated to a crude product in quantitative yield: IR (neat) 3050, 2950, 1725, 1640, 1160, 1010, 880 cm^{-1}; ^1H NMR δ 4.9–4.5 (6 H, m), 4.2–3.3 (10 H, m), 3.0–1.2 (32 H, series of m), 1.2 (6 H, t, *J* = 7 Hz, $-OCH_2CH_3$), 1.0 and 0.98 (6 H, s, $-CCH_3$), 0.95 (6 H, d, *J* = 7 Hz, $-CHCH_3$), 0.85 (6 H, d, *J* = 7 Hz, $-CHCH_3$). The above THP-protected ester (1.0 g, 2.84 mmol) in 20 mL of dichloromethane was cooled to −78 °C, and DIBAL-H (3.0 mmol) was added. After stirring for 30 min, the reaction was quenched with methanol followed by water. The product was extracted with dichloromethane (50 mL × 3) to give an oil (1.5 g), which was filtered through a small silica gel (15 g) column. Elution with 15% ethyl acetate–petroleum ether furnished the labile aldehyde **38**: 570 mg, 65%; IR (neat) 3050, 2950, 2740, 1720, 1120, 1070, 1020, 810 cm^{-1}; ^1H NMR δ 9.77 (2 H, m, $O{=}CH$), 5.0–1.3 (44 H, series of m), 1.2–0.7 (18 H, series of s and d). Satisfactory analysis could not be obtained for this.

8-Isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7(8)-ene-3,5-diol (39). To a solution of the labile aldehyde **38** (1.0 g, 3.25 mmol) in dichloromethane (20 mL) was added stannic chloride (0.2 mL) at 0 °C. The reaction mixture was stirred for 1 h and then quenched with $NaHCO_3$ solution. The organic phase was washed, dried, and concentrated. The crude product (1.0 g) was chromatographed on a silica gel (20 g) column. Elution with ethyl acetate afforded the cyclized diol **39**: 145 mg, 20%; bp 170 °C (0.03 Torr); IR (neat) 3450, 2950, 1060 cm^{-1}; ^1H NMR δ 4.2–3.8 (2 H, m, $-CHOH$), 3.2–1.4 (11 H, series of m), 1.1–0.75 (9 H, series of s and m). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.63; H, 10.88.

(−)-8-Isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7(8)-ene-3,5-dione (33). The diol **39** (100 mg, 0.48 mmol) was oxidized with pyridinium chlorochromate (430 mg, 2.0 mmol) in the presence of molecular sieves (4 Å) (1 g) in dichloromethane at 0 °C. After 30 min, the reaction mixture was filtered through a small Florisil (5 g) column. The oily residue was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate–petroleum ether furnished the pure dione **33**: 60 mg, 60%; bp 150 °C (0.01 Torr); $[\alpha]_D$ −34.2° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 1700 cm^{-1}; ^1H NMR δ 3.60 (2 H, dd, J_{gem} = 15 Hz), 3.20 (2 H, dd, J_{gem} = 16 Hz), 2.8–1.6 (7 H, m), 1.1 (3 H, s, $-CCH_3$), 0.98 (6 H, d, *J* = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 203.0, 202.8, 148.8, 130.0, 59.2, 55.3, 49.1, 40.4, 36.7, 27.7, 27.1, 24.4, 21.0, 20.8. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.48; H, 9.42.

4-Carbomethoxy-8-isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7-en-3-one (40). To a suspension of sodium hydride (240 mg, 5.0 mmol) in dry dimethyl carbonate (10 mL) was added enone **31** (11.0 g, 4.85 mmol) in dry dimethyl carbonate (5 mL), and the contents were stirred at 30 °C for 6 h. The reaction mixture was diluted with ether (100 mL), washed with water, dried, and chromatographed on a silica gel (15 g) column. Elution with 5% EtOAc–hexane furnished the ketoester **40**: 1.0 g, 78%; bp 160 °C (0.1 Torr); IR (neat) 2950, 1730, 1700, 1640, 1440, 1240, 1020 cm^{-1}; ^1H NMR δ 3.78 (s, $-OCH_3$), 3.7 (s, $-OCH_3$), 2.8–2.5 (series of m), 1.05–0.85 (series of s and d). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.97; H, 9.35.

(+)-(1*S*,5*R*)-9-Isopropyl-1-methyl-5-carbomethoxybicyclo[6.3.0]undec-8(9)-en-3-one (42). A mixture of ketoester **40** (100 mg, 0.4 mmol), dry acetone (10 mL), and potassium carbonate (225 mg, 1.6 mmol) was refluxed for 1 h. Methylene bromide (210 mg, 1.2 mmol) was added and the mixture refluxed for 12 h. Acetone was removed, and the residue was diluted with water (15 mL) and extracted with ether (25 mL × 3). The ethereal extract was washed, dried, and chromatographed on a silica gel

(5 g) column to furnish the ester **41** 110 mg, 81% as a diastereomeric mixture: IR (neat): 2975, 1735, 1705, 1160 cm^{-1}; ^1H NMR δ 4.24–3.30 (4 H, m), 3.78 (3 H, s), 3.72 (3 H, s), 2.92–1.12 (22 H, m), 1.04–0.88 (series of s and d, 18 H). Anal. Calcd for $C_{17}H_{25}O_3Br$: C, 57.14; H, 7.05. Found: C, 56.92; H, 7.01. A solution of ester **41** (100 mg, 0.28 mmol), tri-*n*-butyltin hydride (85 mg, 0.29 mmol), and AIBN (20 mg) in 350 mL of dry benzene was refluxed for 16 h. The reaction mixture was washed with 10% potassium fluoride solution. The crude product was purified on a silica gel (10 g) column to give **42**: 40 mg, 50%; $[\alpha]_D$ 41.5° (*c* 1.3, $CHCl_3$); IR (neat) 2940, 1745, 1705, 1450 cm^{-1}; ^1H NMR δ 3.68 (3 H, s), 3.08–1.44 (14 H, m), 1.04 (3 H, s), 1.03 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 210.9, 175.5, 144.6, 135.9, 52.4, 52.1, 51.5, 47.4, 38.8 (2 C), 31.1, 27.2, 27.0, 25.3, 21.3, 20.9 (2 C). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found C, 73.45; H, 9.45.

(+)-2(*S*)-Methyl-2-(4-methyl-3-oxopentyl)cycloheptane-1,4-dione (49). A solution of ketone **31** (1.0 g, 4.85 mmol) in a (1:1:1) mixture of carbon tetrachloride–acetonitrile–water (each 5 mL) was oxidized with ruthenium dioxide (20 mg) and sodium metaperiodate (1.28 g, 6.0 mmol). After 1 h, the reaction was diluted with dichloromethane (50 mL) and filtered through a Celite pad. The filtrate was washed and dried, and the crude product was filtered through a small silica gel (5 g) column with 10% ethyl acetate–petroleum ether to furnish the triketone **49**: 1.0 g, quantitative; bp 160 °C (0.16 Torr); $[\alpha]_D$ 84.2° (*c* 3.0, $CHCl_3$); IR (neat) 2950, 1700, 1310, 1170, 920 cm^{-1}; ^1H NMR δ 3.1–2.2 (8 H, m), 2.1–1.5 (5 H, m), 1.12 (3 H, s, $-CCH_3$), 1.08 (6 H, d, J = 7 Hz, $-CH(CH_3)_2$); ^{13}C NMR δ 213.4, 213.2, 209.6, 50.0, 47.3, 43.5, 40.4, 39.6, 34.2, 32.5, 21.4, 20.6, 17.7 (2 C). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.87; H, 9.35.

(+)-8-Isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7-ene-2,6-dione (50). A mixture of triketone **49** (1.0 g, 4.5 mmol) and 5% methanolic KOH (25 mL) was refluxed for 1 h. Methanol was removed, and the residue was diluted with water (10 mL) and extracted with ether (100 mL × 3). The combined ethereal extract was washed and dried, and the crude oily product was charged on a silica gel (10 g) column. Elution with 15% ethyl acetate–petroleum ether furnished the enedione **50**: 600 mg, 60%; bp 155 °C (0.1 Torr); $[\alpha]_D$ 177.1 (*c* 2.0, $CHCl_3$); IR (neat) 2950, 1700, 1670, 1590, 930, 860 cm^{-1}; ^1H NMR δ 3.62 (1 H, m), 3.1–1.45 (10 H, series of m), 1.35 (3 H, s, $-CCH_3$), 1.06 (3 H, d, J = 7 Hz, $-CHCH_3$), 1.04 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 213.7, 199.8, 167.3, 136.8, 61.3, 41.4, 37.2, 35.0, 29.7, 27.7, 20.9, 20.7, 20.5 (2 C). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.31. Found: C, 76.51; H, 9.32.

Li–NH_3 Reduction of (+)-50. (+)-(1*S*,7*R*,8*R*)-8-Isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione (51) and (−)-(1*S*,7*S*,8*R*)-8-Isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione (52). To the blue solution obtained from NH_3(liq) (50 mL) and lithium metal (115 mg, 5 mmol) was added enedione **50** (200 mg, 0.90 mmol) in THF (5 mL). After stirring for 10 min, the reaction mixture was quenched with methanol (1 mL). The reaction mixture was diluted with water (25 mL) and extracted with ether (50 mL × 3). The combined ethereal extract was washed and dried to an oil which was used directly for the next step. To a suspension of pyridinium chlorochromate (220 mg, 1.0 mmol), molecular sieves (4 Å) (1 g), in dichloromethane (5 mL) was added the above diol (160 mg) in dichloromethane (5 mL) at 0 °C. After 1 h, the reaction mixture was filtered through a Florisil (3 g) column. Removal of the solvent gave an oily liquid, which was charged on a silica gel (2 g) column, and elution with 10% ethyl acetate–petroleum ether furnished the *cis*-dione **51**: 125 mg, 63%; bp 148 °C (0.1 Torr), $[\alpha]_D$ 26.2° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 1700 cm^{-1}; ^1H NMR δ 3.5 (1 H, d, J = 9 Hz), 2.8–1.2 (12 H, series of m), 1.0 (3 H, s, $-CCH_3$), 0.85 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.74 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 212.9, 210.5, 56.5, 51.7, 51.3, 45.1, 40.8, 35.8, 29.7, 28.1, 23.7, 23.0, 21.6, 21.5. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.11; H, 9.91. Further elution of the column with 15% ethyl acetate–petroleum ether furnished the *trans*-dione **52**: 15 mg, 7%; bp 145 °C (0.1 Torr); $[\alpha]_D$ −15° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 1700 cm^{-1}; ^1H NMR δ 3.0–1.2 (13 H, series of m), 1.4 (3 H, s, $-CCH_3$), 0.89 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.79 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 213.3, 211.1, 63.0, 59.2, 47.9, 42.6, 39.9, 34.8, 33.5, 27.5, 25.5, 21.5, 20.4, 20.2. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.33; H, 9.99.

Equilibration of (+)-51. Sodium (5 mg, 0.2 mmol) was dissolved in dry methanol under N_2, and the *cis*-dione **51** (25 mg, 0.11 mmol) in dry methanol (2 mL) was added. After stirring for 12 h, methanol was removed and the residue was worked up in the usual manner. The crude product was filtered through a small silica gel column with 5% ethyl acetate–petroleum ether to furnish the *trans*-dione **52** (25 mg, quantitative) identical in all respects with the sample obtained earlier.

Catalytic Hydrogenation of (+)-50. (−)-(1*S*,7*S*,8*R*)-8-Isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione (52) and (−)-(1*S*,7*R*,8*S*)-8-Isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione (53). A solution of the enedione **50** (500 mg, 22.5 mmol) in dry ethyl acetate (30 mL) was hydrogenated (25 psi of pressure) over 10% Pd/C (100 mg) for 1 h. The catalyst was filtered off, and the solvent was removed to furnish the saturated dione mixture, which was chromatographed on a silica gel (25 g) column. Elution with 10% ethyl acetate–petroleum ether furnished the *trans*-dione **52** (250 mg, 50%), which was found identical with the minor product obtained in the NH_3 (liq) reduction of **50**. Further elution with 12% ethyl acetate–petroleum ether furnished the *cis*-dione **53**: 200 mg, 40%; bp 145 °C (1 Torr); $[\alpha]_D$ −55° (*c* 1.0, $CHCl_3$); IR (neat) 2950 1700 cm^{-1}; ^1H NMR δ 3.25–1.2 (13 H, series of m), 1.35 (3 H, s, $-CCH_3$), 0.88 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.78 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 214.5, 212.0, 59.4, 58.7, 49.8, 45.4, 40.1, 31.7, 29.0, 28.0, 26.4, 23.8, 22.7, 21.8. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.49; H, 9.91.

Equilibration of 53. (−)-(1*S*,7*S*,8*S*)-8-Isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione (54). Sodium (5 mg, 0.2 mmol) was dissolved in dry methanol (2 mL), and the *cis*-dione **53** (25 mg, 0.11 mmol) was added in dry methanol (2 mL) under N_2. The contents were stirred at ~30 °C for 12 h. Usual workup gave an oily product, which was filtered through a silica gel column with 5% ethyl acetate–petroleum ether to furnish the *trans*-dione **54**: 25 mg, quantitative; bp 150 °C (0.1 Torr); $[\alpha]_D$ −43° (*c*, 1.0, $CHCl_3$); IR (neat) 2955, 1690, 1370, 1180 cm^{-1}; ^1H NMR δ 3.0–2.4 (5 H, m), 2.1–1.2 (8 H, m), 0.98 (3 H, s, $-CCH_3$), 0.78 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.70 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 213.5, 210.3, 58.1, 57.3, 44.1, 43.4, 41.2, 35.6, 32.2, 24.3, 21.0, 20.7, 20.2, 19.7. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.92; H, 9.95.

(+)-8-Isopropyl-1(*S*)-methylbicyclo[5.3.0]dec-7-ene-2,6-dione 2-Ethylene Ketal (55). A mixture of enedione **50** (100 mg, 0.45 mmol), ethylene glycol (0.2 mL), and a catalytic amount of PTS (25 mg) in benzene (15 mL) was refluxed for 15 h. The reaction mixture was diluted with benzene (25 mL), washed with aqueous $NaHCO_3$, and dried. Elution with 10% ethyl acetate–petroleum ether from a silica gel column (5 g) furnished the ene acetal **55**: 110 mg, 92%; mp 83–84 °C; $[\alpha]_D$ 84.26° (*c* 1.0, $CHCl_3$); IR (KBr) 1670, 1615, 1340, 875 cm^{-1}; ^1H NMR δ 4.0 (4 H, br s), 3.36–3.04 (1 H, m), 2.6–1.2 (10 H, m), 1.28 (3 H, s, $-CCH_3$), 1.06 (3 H, d, J = 7 Hz, $-CHCH_3$), 1.0 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 204.5, 164.3, 138.7, 113.9, 65.2, 65.0, 57.1, 43.4, 33.8, 33.7, 29.1, 28.2, 23.2, 21.0, 19.3. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.56; H, 9.20.

Li–NH_3 Reduction of (+)-55. Formation of 56 and 57. Enone acetal **55** (200 mg, 0.72 mmol) was reduced with Li–NH_3(liq) as described above for enedione **50**. Usual workup and chromatography furnished *cis*-acetal **56**: 125 mg, 65%; bp 165 °C (0.1 Torr); $[\alpha]_D$ 17.5° (*c* 1.6, $CHCl_3$); IR (neat) 1700, 1380, 1120 cm^{-1}; ^1H NMR δ 4.0 (4 H, m, $-OCH_2CH_2O-$), 3.72 (1 H, br d, J = 9 Hz), 2.6–1.2 (12 H, m), 0.9 (3 H, s, $-CCH_3$), 0.84 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.72 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 212.8, 113.1, 65.4 (2 C), 52.7, 52.0, 50.8, 44.0, 34.4, 33.5, 30.0, 28.0, 23.5, 22.1, 21.8, 19.4. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.09; H, 9.79. Further elution of the column gave *trans*-acetal **57**: 17 mg, 9%; bp 176 °C (0.1 Torr); $[\alpha]_D$ −15.5° (*c* 1.0, $CHCl_3$); ^1H NMR δ 4.0–3.6 (4 H, m, $-OCH_2CH_2O-$), 2.8–1.4 (13 H, series of m), 1.29 (3 H, s, $-CCH_3$), 0.85 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.76 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 210.8, 113.4, 65.3, 64.6, 62.6, 54.1, 45.9, 40.7, 33.8, 33.0, 32.7, 26.3, 24.7, 21.7, 19.7, 18.8. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.98; H, 9.74.

(1*S*,7*R*,8*R*)-5-Carbomethoxy-8-isopropyl-1-methylbicyclo[5.3.0]decane-2,6-dione 2-Ethylene Ketal (58). Hexamethyldisilazane (0.25 mL, 1.2 mmol) was added to *n*-butyllithium (0.6 mL, 0.6 mmol, 1.0 M in hexane) at −78 °C under N_2, and the resulting slurry was dissolved by the addition of THF (2 mL). A solution of *cis*-acetal **56** (100 mg, 0.3 mmol) in THF (2 mL) was added and stirred for 30 min at −78 °C. The resulting enolate was quenched by the addition of methyl chloroformate (0.5 mL, excess), and the stirring was continued for 10 min. The reaction mixture was diluted with brine and extracted with ether (50 mL × 3). The crude product was charged on a silica gel column (5 g). Elution with 5% ethyl acetate–petroleum ether furnished the ketoester **58** (105 mg, 86%) as a diastereomeric mixture: bp 163 °C (0.1 Torr); IR (neat) 1730, 1720, 1160 cm^{-1}; ^1H NMR δ 4.05–3.8 (8 H, m, $-OCH_2CH_2O-$), 3.78 (3 H, s, $-OCH_3$), 3.73 (3 H, s, $-OCH_3$), 3.6–1.0 (24 H, series of m), 0.98–0.64 (18 H, series of s and d). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.01; H, 8.29.

Reduction of 58 with Sodium Borohydride. Sodium borohydride (100 mg, excess) was added to ketoester **58** (100 mg, 0.3 mmol) in dry methanol (5 mL), and the contents were stirred for 30 min. Methanol was removed, and the residue was diluted with water (10 mL) and extracted with ether (50 mL × 3). The combined ethereal extract was washed and dried, and the crude product was charged on a silica gel (5 g) column. Elution with 50% ethyl acetate–petroleum ether furnished the diol **59**: 55 mg, 62%; IR (neat) 3450, 1460 cm^{-1}; ^1H NMR δ

4.16–4.02 (1 H, m, –CHOH), 3.92 (4 H, br s, OCH_2CH_2O), 3.68–3.44 (2 H, m, $-CH_2OH$), 2.56–1.28 (14 H, m), 1.30 (3 H, s, $-CCH_3$), 0.96 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.86 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 114.7, 75.0, 69.1, 65.2, 65.0, 53.8, 51.7, 50.2, 44.2, 35.7, 34.8, 29.7, 28.2, 24.7, 23.2, 23.0, 22.5. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.39; H, 10.09.

Swern Oxidation[30] of 59. Formation of Hydroxy Aldehyde 60. Oxalyl chloride (0.1 mL, 1.0 mmol) in dichloromethane (2 mL) was cooled to –60 °C under N_2. DMSO (0.2 mL) in dichloromethane (2 mL) was added, and the stirring was continued for 15 min. Then the diol **59** (50 mg, 0.16 mmol) in dichloromethane was introduced over a period of 5 min. After stirring for an additional 10 min, triethyl amine (1 mL) was added at –60 °C. The reaction mixture was brought to ~30 °C, quenched with water (10 mL), and extracted with ether (5 mL × 3). The combined organic layer was washed and dried, and the crude product was filtered through a silica gel (5 g) column. Elution with 10% ethyl acetate–petroleum ether furnished the hydroxy aldehyde **60**: 35 mg, 70%; IR (neat) 2720, 1690, 800 cm^{-1}; ^1H NMR δ 9.72 (1 H, s, O=C*H*), 4.48–4.72 (1 H, m, –C*H*OH), 4.08–3.84 (m, 4 H, $-OCH_2CH_2O-$), 2.68–1.12 (13 H, m), 1.28 (3 H, s, $-CCH_3$), 1.02 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.92 (3 H, d, J = 7 Hz, $-CHCH_3$). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.79; H, 9.46.

(+)-2-Oxoisodauc-5-en-12-al (46). A solution of the hydroxy aldehyde **60** (10 mg, 0.034 mmol) and a catalytic amount of PTS in benzene (5 mL) was refluxed for 2 h and quenched with $NaHCO_3$ (satd) solution. The benzene layer was washed and dried to give an oily residue. Filtration through a small silica gel (1 g) column using 5% ethyl acetate–petroleum ether furnished (+)-**46** (4 mg, 37%), $[\alpha]_D$ 33° (*c* 0.5, $CHCl_3$); IR (neat) 2950, 2740, 1680, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.35 (1 H, s, O=C*H*), 6.63 (1 H, br d, –C=C*H*–), 2.8–1.5 (11 H, series of m), 1.33 (3 H, s, $-CCH_3$), 0.91 (6 H, d, J = 7 Hz, $-CHCH_3$); ^1H NMR (C_6D_6) δ 9.15 (1 H, s, O=C*H*), 6.01 (1 H, br d, –C=C*H*–), 2.7–1.1 (11 H, series of m), 0.89 (3 H, s, $-CCH_3$), 0.73 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.71 (3 H, d, J = 7 Hz, $-CHCH_3$). The ^1H NMR spectral data of this product (both in $CDCl_3$ and C_6D_6) was found to be exactly identical with those reported in the literature.[25]

(+)-Aphanamol I (2). To a solution of (+)-2-oxoisodauc-5-en-12-al (**46**) (14 mg) in dry methanol (2 mL) was added $CeCl_3 \cdot 7H_2O$ (15 mg) at 5 °C. Sodium borohydride (5 mg) was added, and the reaction was followed by TLC. When the starting material was completely consumed, the reaction was quenched by addition of acetone (0.1 mL) followed by water (5 mL). Extraction with ether (10 mL × 3) and filtration through a silica gel column furnished (+)-aphanamol I (**2**): 14 mg, quantitative; $[\alpha]_D$ 10° (*c* 0.7, $CHCl_3$); IR (neat) 3400, 1690 cm^{-1}; ^1H NMR δ 5.51 (1 H, br d, –C=C*H*), 4.0 (2 H, br s, $-CH_2OH$), 3.0–1.4 (11 H, series of m), 1.22 (3 H, s, $-CCH_3$), 0.9 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.91 (3 H, d, J = 7 Hz, $-CHCH_3$). Direct comparison of our spectra with those supplied by Professor nishizawa established the identity of our synthetic material with the natural product.[4]

(–)-(1*S*,4*S*)-8-Isopropyl-1-methyl-4-[5-(triisopropylsilyl)pent-4-ynyl]bicyclo[5.3.0]dec-7(8)-en-3-one (65). A solution of ketone **31** (500 mg, 2.4 mmol) in THF (2 mL) was added to a solution of lithium hexamethyldisilamide (3.0 mmol), and the resulting solution was brought to –10 °C and stirred for 30 min. The enolate thus obtained was quenched by the addition of excess alkyl iodide (1.5 g) in HMPA (4 mL) at –10 °C. After further stirring at –10 °C for 45 min, the reaction mixture was quenched by the addition of water and extracted with ether (50 mL × 3). The ethereal extract was washed, dried, and charged on a silica gel column. Elution with 10% ethyl acetate–petroleum ether furnished the alkylated ketone **65**: 1.1 g, 80%; $[\alpha]_D$ –53.3° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 2200, 1710 cm^{-1}; ^1H NMR δ 2.8–1.2 (18 H, series of m), 1.05 (21 H, s, $-Si(CH(CH_3)_2)_3$), 0.97 (s, 3 H, $-CCH_3$), 0.96 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.91 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 213.7, 141.5, 139.6, 108.8, 80.5, 54.0, 53.5, 47.4, 37.5, 32.6, 31.4, 27.4, 26.7, 26.5, 24.8, 23.3, 21.5, 21.1, 19.8, 18.64 (6 C), 11.3 (3 C). Analytical data was not obtained as it could not be distilled due to its high boiling point.

(–)-(1*S*,4*R*)-1,4-Dimethyl-8-isopropyl-4-(pent-4-ynyl)bicyclo[5.3.0]-dec-7(8)-en-3-one (67). To a suspension of sodium hydride (72 mg, 1.5 mmol) in dimethoxyethane (5 mL) was added **65** (500 mg, 1.25 mmol) in dimethoxyethane (5 mL), and stirring was continued for 2 h at 30 °C under N_2. The resulting pale yellow enolate solution was quenched with an excess of methyl iodide (0.5 mL), and stirring was continued for an additional 10 h at 30 °C. The reaction mixture was quenched by addition of water and then extracted with ether (50 mL × 3). The combined ethereal extract was washed, dried, and chromaotgraphed on a silica gel (10 g) column. Elution with 5% ethyl acetate–petroleum ether furnished the methylated product **66**: 325 mg, 65%; $[\alpha]_D$ –42° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 2200, 1695 cm^{-1}; ^1H NMR δ 2.8–1.2 (17 H, series of m), 1.08 (24 H, s, $-CCH_3$ and $Si(CH(CH_3)_2)_3$, 0.95 (3 H, s, $-CCH_3$), 0.94 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.89 (3 H, d, J = 7 Hz, $-CHCH_3$); ^{13}C NMR δ 215.3, 142.7, 137.0, 108.7, 80.5, 51.3, 49.7, 48.1, 38.2, 37.5, 35.7, 27.7, 26.8, 26.5, 25.4, 23.3, 21.2, 20.7, 20.4, 18.6 (6 C), 11.2 (3 C). The bicyclic ketone **66** (300 mg, 0.725 mmol) was placed in THF (5 mL), tetra-*n*-butylammonium fluoride (260 mg, 1.0 mmol) was added, and the mixture was stirred for 2 min at 30 °C. The reaction mixture was diluted with water (5 mL) and extracted with ether (25 mL × 3). The combined ethereal extract was washed, dried, and filtered through a small silica gel (5 g) column to furnish the ketoacetylene **67**: 195 mg, quantitative; bp 190 °C (0.1 Torr); $[\alpha]_D$ –21° (*c* 1.0, $CHCl_3$); IR (neat) 3250, 2950, 1695, 1450, 1060 cm^{-1}; ^1H NMR δ 2.8–1.2 (18 H, series of m), 1.02 (3 H, s, $-CCH_3$), 0.93 (3 H, s), 0.92 (3 H, s), 0.92 (3 H, d, J = 7 Hz), 0.88, (3 H, d, J = 7 Hz); ^{13}C NMR δ 215.1, 142.5, 136.9, 114.4, 84.0, 68.6, 51.4, 49.7, 48.1, 38.1, 37.5, 35.4, 27.6, 26.7, 25.3, 23.0, 21.2, 21.0, 20.7, 18.9. Anal. Calcd for $C_{20}H_{30}O$: C, 83.85; H, 10.55. Found: C, 83.42; H, 10.50.

(–)-Dolasta-1(15),7-dien-14-ol (68). The ketoacetylene **67** (100 mg, 0.35 mmol) was placed in THF (5 mL) under a N_2 blanket, and a THF solution of sodium naphthalenide was added slowly with stirring until a pale green color persisted. The THF was removed, and the residue was diluted with water (5 mL) and extracted with ether (25 mL × 3). The ethereal extract was washed and dried, and the crude product (150 mg) was charged on a silica gel column. Elution with petroleum ether removed the less polar naphthalene impurities, and further elution with 5% ethyl acetate–petroleum ether furnished the cyclized product **68**: 40 mg, 40%; mp 105 °C; $[\alpha]_D$ –12° (*c* 0.1, $CHCl_3$); IR (KBr) 3450, 2950, 1450, 1110, 890 cm^{-1}; ^1H NMR δ 4.81 (1 H, t, J = 1.5 Hz), 4.76 (1 H, br s), 2.6–1.4 (17 H, series of m), 1.34 (3 H, s), 0.94 (3 H, d, J = 7 Hz), 0.92 (3 H, d, J = 7 Hz), 0.78 (3 H, s). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.62; H, 11.21.

(+)-Isoamijiol (63), (+)-Dolasta-1(15),7,9-trien-14-ol (64), and (+)-Dolasta-1(15),7,9-triene-2,4-diol (69). To a solution of the hydroxy compound **68** (10 mg, 0.035 mmol) in dichloromethane (2 mL) were added selenium dioxide (0.3 mg) and *t*-butyl hydroperoxide (0.011 mL, 0.035 mmol) at 0 °C under N_2. The reaction mixture was kept in the freezer for 8 h. Then it was diluted with dichloromethane (25 mL) washed with 5% KOH solution followed by water, and dried. The crude product was charged on a silica gel (5 g) column. Elution with 3% ethyl acetate–petroleum ether gave (+)-dolasta-1(15),7,9-trien-14-ol (**64**): 2 mg, 20%; mp 103–105 °C (lit.[34] mp 105 °C); $[\alpha]_D$ 200° (*c* 0.25, $CHCl_3$); IR (KBr) 3400, 1000, 890 cm^{-1}; ^1H NMR δ 5.54 (1 H, br s, –C*H*=C), 5.46 (1 H, dd, J_1 = 9.5 Hz, J_2 = 4.5 Hz, –C=C*H*), 4.84 (1 H, br s, $-C=CH_2$), 4.70 (1 H, br s, $-C=CH_2$), 3.2–1.4 (13 H, series of m), 1.37 (3 H, s, $-CCH_3$), 1.14 (3 H, d, J = 7 Hz, $-CHCH_3$), 1.11 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.88 (3 H, s, $-CCH_3$). The spectral data of this product were found to be identical with those reported in the literature,[34] and a direct comparison with the authentic spectra provided by Professor Piers further established its identity with the natural product. Further elution of the column with 10% ethyl acetate–petroleum ether furnished (+)-isoamijiol (**63**): 3 mg, 30%; mp 126–8 °C; $[\alpha]_D$ 45° (*c* 0.1, $CHCl_3$) (lit.[33] $[\alpha]_D$ –45°); IR (KBr) 3400, 2950, 1000, 890 cm^{-1}; ^1H NMR δ 5.08 (1 H, m, $-C=CH_2$), 4.29 (1 H, t, J = 3 Hz), 2.68–1.5 (17 H, m), 1.34 (3 H, s, $-CCH_3$), 0.94 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.92 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.77 (3 H, s, $-CCH_3$). A direction comparison of our spectra with those supplied by Professor Ochi established the identity of our synthetic material with the natural product. Further elution of the column afforded **69**: 1 mg, 10%: mp 109 °C; $[\alpha]_D$ 75° (*c* 0.05, $CHCl_3$); IR (KBr) 3400, 2950, 1020, 890 cm^{-1}; ^1H NMR δ 5.55 (1 H, br s, –C*H*=C), 5.4 (1 H, dd, J_1 = 9 Hz, J_2 = 5 Hz, –C=C*H*–), 5.04 (1 H, s, $-C=CH_2$), 4.9 (1 H, s, $-C=CH_2$), 4.3 (1 H, m, –C*H*OH), 3.2–1.4 (11 H, series of m), 1.28 (1 H, s, $-CCH_3$), 1.05 (3 H, d, J = 7 Hz, $-CHCH_3$), 1.01 (3 H, d, J = 7 Hz, $-CHCH_3$), 0.8 (3 H, s, $-CCH_3$). Due to paucity of the material, analytical data could not be obtained and its structure should be regarded as tentative.

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Registry No. 2, 91410-61-6; (–)-**11**, 117152-55-3; (–)-**12a**, 134107-43-0; **12b**, 134031-61-1; **13**, 5989-27-5; **14**, 62994-35-8; **15**, 105576-35-0; **16**, 117152-54-2; **20**, 134031-62-2; (+)-**21**, 134031-63-3; **22**, 134031-64-4; **23**, 134031-65-5; (*E*)-**24**, 134031-66-6; (*Z*)-**24**, 134107-44-1; **26a**, 134031-67-7; **26b**, 134031-68-8; **27a**, 134031-69-9; **27b**, 134031-70-2; **28**, 134031-71-3; **29**, 134031-72-4; (–)-**30**, 134031-73-5; (–)-**31**, 117182-78-2; (+)-**32**, 134031-74-6; (–)-**33**, 117152-59-7; **34**, 117152-56-4; **35**, 134031-75-7; **36**, 134031-76-8; **37** (isomer 1), 117181-70-1; **37** (isomer 2), 117133-37-6; **38** (isomer 1), 117182-85-1; **38** (isomer 2), 117152-57-5; **39**, 117152-58-6; **40** (isomer 1), 134031-77-9; **40** (isomer 2),

134031-84-8; **41** (isomer 1), 134031-78-0; **41** (isomer 2), 134031-85-9; (+)-**42**, 134031-79-1; (+)-**46**, 125136-27-8; **49**, 124764-75-6; (+)-**50**, 125315-19-7; **51**, 134031-80-4; **52**, 134031-81-5; **53**, 134031-82-6; **54**, 134031-83-7; **55**, 125315-20-0; **56**, 125315-21-1; **57**, 125409-70-3; **58** (isomer 1), 125409-69-0; **58** (isomer 2), 125315-22-2; **59**, 125315-24-4; **60**, 125315-23-3; (+)-**63**, 117182-82-8; (+)-**64**, 80243-67-0; **65**, 117182-79-3; **66**, 117182-80-6; **67**, 117182-86-2; (-)-**68**, 117182-81-7; (+)-**69**, 117182-84-0.

C-Glycosylanthraquinone Synthesis: Total Synthesis of Vineomycinone B2 Methyl Ester

Marcus A. Tius,*[1] Jorge Gomez-Galeno, Xue-qin Gu, and Javid H. Zaidi[2]

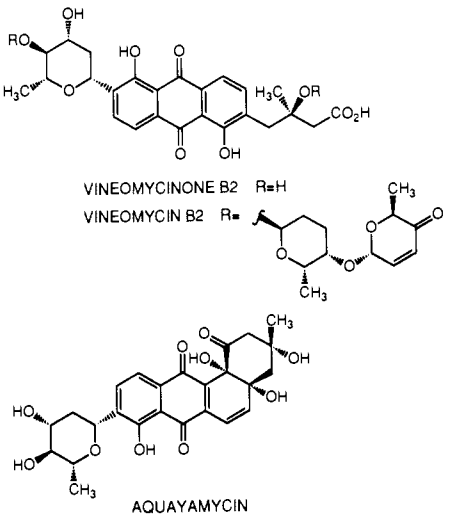
Contribution from the Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822. *Received December 14, 1990*

Abstract: A synthesis of substituted anthraquinones has been developed. Commercially available anthrarufin and 1,8-dihydroxyanthraquinone were converted to the corresponding (methoxymethoxy)anthracenes. Directed metalation followed by stannylation produced stable intermediates that were either alkylated, arylated, acylated, and/or C-glycosylated. The value of this new methodology was demonstrated by the triply convergent total synthesis of vineomycinone B2 methyl ester, a representative *C*-glycosylanthraquinone antibiotic.

Introduction

The clinical utility of the anthracyclines and their analogues in the chemotherapy of acute leukemia and solid tumors of the breast, lung, bladder, and ovary, as well as their interesting structures, has brought these compounds to the forefront of chemical synthesis.[3] Anthracyclines consist of an anthraquinone nucleus embedded within a hydrotetracene. Typically, one or more sugars are attached through *O*-glycosyl bonds. A fascinating class of structurally related compounds exists in which the anthraquinone portion of the molecule is linked to a carbohydrate through a C-glycosidic bond.[4] Two representatives of this class of compounds are vineomycin B2[5] and aquayamycin.[6] Aquayamycin is a powerful tyrosine hydroxylase and dopamine β-hydroxylase inhibitor.[6] The vineomycins are antitumor antibiotics that were first isolated from a culture of *Streptomyces matensis* subsp. *vineus*, which was active against Gram-positive bacteria and against sarcoma-180 solid tumors in mice.[5] Vineomycinone B2 methyl ester is derived from the acid-catalyzed methanolysis of vineomycin B2.

The characteristic structural features of vineomycinone B2 methyl ester (**1**) are the *C*-glycosyl bond to the olivose derivative and the alkyl side chain bearing a stereogenic center on the opposite end of the molecule. This combination of challenging structure and the interesting pharmacological properties has motivated efforts in organic synthesis. To date three groups in addition to our own have reported total syntheses of **1**.[7-9] Results



from our research have demonstrated the utility of a triply convergent approach to the synthesis of this structural type.[10,11] The experimental detail that was lacking in the preliminary communication,[11] as well as some new results, will be described.

Results and Discussion

The target molecule **1** was quite simple; therefore, it was felt that the retrosynthesis should also reflect this fact. The total synthesis that was devised was an opportunistic one, in the sense that it exploited the features peculiar to the molecule. The most obvious feature of **1** is the symmetry of the aromatic core, and it was felt that any successful synthesis would have to take advantage of this. Indeed, Danishefsky's inspired first total synthesis[7] made use of this feature and also demonstrated, unsurprisingly, that no transmission of stereochemical information took place

(1) Fellow of the Alfred P. Sloan Foundation, 1988-1991.
(2) Current address: Federal Government College, Department of Chemistry, H8, Islamabad, Pakistan.
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