was removed under reduced pressure. The residue was triturated with ethyl acetate and gave a solid compound which was filtered off and heated for 1 h at 60 °C with KOH (0.61 g, 11 mmol) in methanol (10 mL). The cooled solution was filtered on alumina. Evaporation of solvent gave 285 mg (23% from c) of (±)-**3m** as a viscous material.

S-(-)-Carbamalactic acid was used as resolving agent[36] for racemic **3m**. The salt obtained from **3m** (285 mg, 1.4 mmol) presented a constant optical rotation after two crystallizations (MeOH/ether): $[\alpha]_D$ -43° (*c* = 1.1, CH_2Cl_2) and led to (+)-**3m** (89 mg, 0.43 mmol); $[\alpha]_D$ +2.5° (*c* = 2.4, CH_2Cl_2); mp (salt from benzoic acid, CH_2Cl_2) 170 °C; IR 3600-3200, 2960, 1450, 1360, 1130, 970; ^1H NMR 0.78 (d, *J* = 6.6, 3 H), 1.15 (s, 9 H), 1.73 (dq, *J* = 6.3, 4.2, 1 H), 7.19-7.31 (m, 5 H); ^{13}C NMR 17.93 (q), 30.03 (q), 51.11 (s), 51.93 (d), 74.79 (d), 126.12 (d), 126.74 (d), 127.83 (d), 141.82 (s); MS *m/e* 208 (M^+ + 1, 43), 174 (21), 100 (100).

The configuration of (+)-**3m** was established as 1-*R*, 2-*S* by comparison of its circular dichroism spectrum with those of **3b** and **3g**. Observed molar ellipticity were the following: (+)-(1*S*,2*R*)-ephedrine (**3b**) $[\theta]^{20}_{267.5}$ = -1062, $[\theta]^{20}_{261}$ = -1136; (-)-(1*R*,2*S*)-2-(isopropylamino)-1-phenyl-1-propanol (**3g**) $[\theta]^{20}_{267.5}$ = +1437, $[\theta]^{20}_{261}$ = +1555, and (+)-(1*R*,2*S*)-2-(*tert*-butylamino)-1-phenyl-1-propanol (**3m**) $[\theta]^{20}_{267.5}$ = + 1666, $[\theta]^{20}_{261}$ = +1825.

(*R*)-2-(Isopropylamino)-1-phenylethanol (8). The procedure reported in ref 37 was used. Isopropylamine (6.8 mL, 79.3 mmol) in dry ether (20 mL) was added to an ice-cooled solution of acetylmandelyl chloride (8.43 g, 39.6 mmol)[38] in ether (30 mL). The mixture was stirred for 12 h, hydrolyzed with saturated brine, extracted with CH_2Cl_2 and dried over magnesium sulfate. After evaporation the residue was crystallized from hexane to afford 6.4 g (27.2 mmol, 69%) of *N*-isopropyl-*O*-acetylmandelamide: mp 98 °C; IR 3420, 2980, 1745, 1675, 1520, 1460, 1375, 1230-1210, 1030; $[\alpha]_D$ -105.4 (*c* = 0.46, CH_2Cl_2); ^1H NMR 1.13 (d, *J* = 6.6, 3 H), 1.15 (d, *J* = 6.5, 3 H), 2.16 (s, 3 H), 4.08 (m, 1 H), 6.02 (s, 1 H), 7.32-7.43 (m, 5 H).

The mandelamide (2.5 g, 10.6 mmol) in THF was added at 0 °C to a stirred suspension of $LiAlH_4$ (1.61 g, 42.5 mmol) in THF. The mixture was refluxed overnight, cooled, and carefully hydrolyzed with wet ether. The product was isolated after filtration of the ether layer, evaporation, and crystallization from hexane to give 838 mg (44% yield) of **8**: mp 91 °C; IR 3620, 3540-3200, 3020, 2980, 1490, 1450, 1230-1200, 1060; $[\alpha]_D$ -2° (*c* = 0.2, $CHCl_3$); ^1H NMR 1.03 (d, *J* = 6.2, 3 H), 1.04 (d, *J* = 6.2, 3 H), 2.63 (dd, *J* = 12, 9.1, 1 H), 2.78 (qq, *J* = 6.2, 6.2, 1 H), 2.86 (dd, *J* = 12, 3.7, 1 H), 4.68 (dd, *J* = 9.1, 3.7, 1 H), 7.28-7.36 (m, 5 H); ^{13}C NMR 23.13 (q), 48.81 (d), 54.93 (t), 72.19 (d), 125.96 (d), 127.52 (d), 128.47 (d), 143.28 (s); MS *m/e* 180 (M^+ + 1.76), 146 (50), 91 (37), 79 (63), 77 (100), 73 (14), 72 (100). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.93; H, 9.50; N, 7.83.

Acknowledgment. Financial Support from C.N.R.S. (contrat ATP) is gratefully acknowledged. R.M. and O.P. thank, respectively, the Région Champagne-Ardenne and the Ministère de la Recherche et de la Technologie for research grants. We are also grateful to Dr. G. Bird (ICI Pharma, Reims) for his aid during translation of this manuscript.

Supplementary Material Available: Tables showing the influence of temperature on the enantioselectivity of various photodeconjugations (8 pages). Ordering information is given on any current masthead page.

(36) Brown, E.; Viot, F.; Le Floc'h, Y. *Tetrahedron Lett.* **1985**, *26*, 4451.
(37) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114.
(38) Thayer, F. K. *Organic Syntheses*; J. Wiley: New York, 1961; Collect. Vol. 1, p, 12.

New Tandem Radical Cyclizations Directed toward the Synthesis of Crinipellin A

C. Eric Schwartz and Dennis P. Curran*

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15208. *Received April 23, 1990*

Abstract: We describe a new tandem radical cyclization strategy for the construction of the congested angular triquinane portion of the naturally occurring tetraquinane crinipellin A. The preparation and cyclization of three 5,5-disubstituted-1,4-dimethyl-1,3-cyclopentadienes are detailed. This cyclization strategy results in a 1,4-functionalization of the cyclopentadiene nucleus, mediated by an allylic radical cyclization. Each tandem cyclization produces two diastereomeric triquinanes in a ratio of 5:1. The minor diastereomer possesses the correct relative stereochemistry for the D-ring isopropyl group of crinipellin A. A tandem cationic cylization, paralleling the radical cyclizations, is also described. The generation and subsequent addition or cyclization reactions of acyl radicals has been accomplished by the reduction of acyl methyl selenides with tin hydride. This new method is the most direct route for conversion of a methyl ester to an acyl radical.

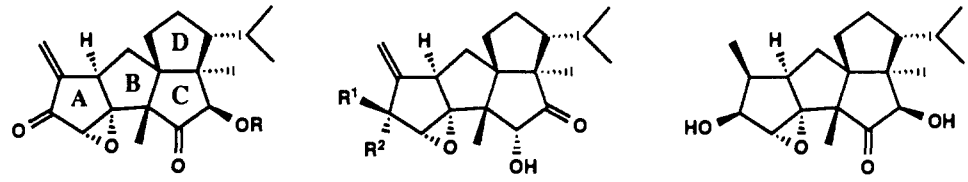
Introduction

Several years ago, we initiated a program to develop a unified approach to the synthesis of triquinane natural products.[1] Our strategy is based on tandem radical cyclizations, wherein the two outer rings of a triquinane (linear or angular) are formed around a central, preformed cyclopentene ring. Variations in both the placement and degree of functionality of the side chains on the central ring allow for an efficient entry to a variety of cyclopentanoids, as demonstrated by the syntheses of the linear triquinanes hirsutene,[2] capnellene,[3] coriolin, and hypnophilin,[4] the angular triquinane silphiperfolene,[5] and the propellane triquinane modhephene.[6] We now report our initial studies on a new tandem radical cyclization strategy directed toward the synthesis of the tetraquinane crinipellin A (**1a**, Figure 1).

Crinipellis stipitaria (Agaricales) is a fungus that grows on both the dead and living parts of grasses. It produces an antibacterial metabolite that was isolated and named crinipellin.[7a]

(1) For an overview of the tandem radical cyclization strategy, see: Curran, D. P. *Advances in Free Radical Chemistry*, Tanner, D., Ed.; JAI: Greenwhich, 1990, p 157.
(2) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.
(3) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.
(4) Curran, D. P.; Fevig, T. L.; Elliott, R. L. *J. Am. Chem. Soc.* **1988**, *110*, 5064.
(5) Curran, D. P.; Duo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106.
(6) Curran, D. P.; Jasperse, C. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.
(7) (a) Kupka, J.; Anke, T.; Oberwinkler, F.; Schranem, G.; Steglich, W. *J. Antibiot.* **1979**, *32*, 130. (b) Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *8*, 709.

0002-7863/90/1512-9272$02.50/0

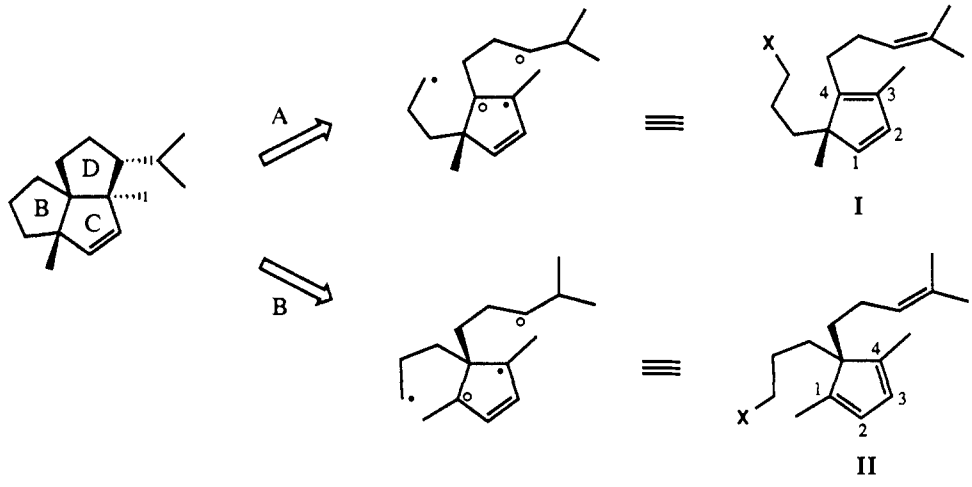


1a R = H **2a** $R^1 = R^2 = O$ **3**

1b R = Ac **2b** $R^1 = OH$, $R^2 = H$

Figure 1.

Scheme I

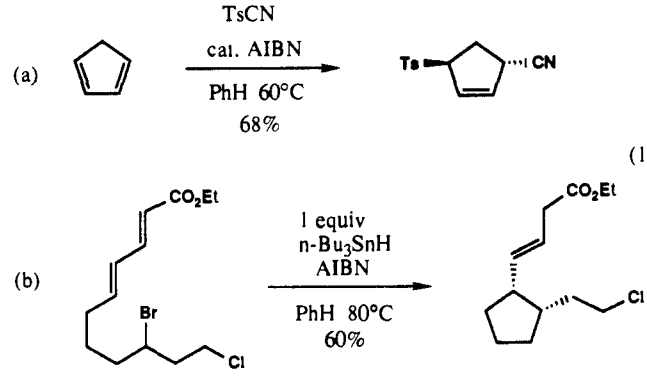


Several years later, an investigation[7b] of different strains of the fungus led to the isolation and structural determination of the antibiotics crinipellin A (**1a**), crinipellin B (**2a**), and *O*-acetylcrinipellin A (**1b**). *O*-Acetylcrinipellin A was identical with the earlier crinipellin. In addition to these antibiotics, two inactive substances, dihydrocrinipellin B (**2b**) and tetrahydrocrinipellin A (**3**), were also found. *O*-Acetylcrinipellin A was not active against Gram-negative bacteria, while Gram-positive bacteria were inhibited at an average minimum concentration of 5 μg/mL. *O*-Acetylcrinipellin A also showed antineoplastic properties. The inhibitory effect on cellular DNA, RNA, and protein synthesis was examined in Ehrlich carcinoma cells by determining the reduced incorporation of ^{14}C-labeled thymidine, uridine, and leucine relative to controls. At low concentrations of 0.5–1 μg/mL, **1b** inhibited the synthesis of both RNA and DNA, while at 5 μg/mL all macromolecular synthesis was completely stopped. Evidence suggested that these antineoplastic effects arise from the interaction of **1b** with cytoplasmic membrane components involved in macromolecular precursor transport.[7b]

The crinipellins are the first tetraquinanes of the diterpenoid type to be discovered, and none have yet been synthesized.[8] This challenge, coupled with the biological activity and unique structural features of these molecules, makes them attractive targets for synthetic endeavors. The dense array of stereocenters, including three contiguous quaternary carbons, provides a challenging test for new or existing methods.

Our approach to the synthesis of crinipellin A is based on the preparation of the angular triquinane portion (BCD rings), followed by A-ring annulation. Two potential tandem radical cyclizations for the BCD segment are illustrated in Scheme I. We use a new notation for radical reactions in which bonds are disconnected in a retrosynthetic fashion to give radical donors (●) and radical acceptors (○).[6] In both paths, an additional double bond is incorporated into ring C as a precursor of the vicinal oxygens in the crinipellins. The strategy of path A is identical with that used in our silphiperfolene synthesis,[5] but this approach is doomed to fail because the initial radical will cyclize to the less-substituted terminus of the cyclopentadiene I (C_1 rather than C_4). However, the presence of the C-ring olefin suggests a new strategy (path B) in which the tandem cyclization is conducted through the diene of II.

Several features of this strategy are important. First, the diene termini (C_1 and C_4) of II are enantiotopic, eliminating the need to discriminate between the double bonds of the diene in the first ring closure. Second, the plane of symmetry in II should simplify its preparation. Third, this tandem cyclization results in a 1,4-functionalization of ring C, whereas all previous tandem cyclizations have formed the two new C–C bonds in a 1,2-fashion (as in path A). Examples[9] of 1,4-additions across 1,3-butadiene and cyclopentadiene under free radical conditions are known (eq 1a[9g]), as are radical cyclizations to conjugated dienes (eq 1b[10]). To

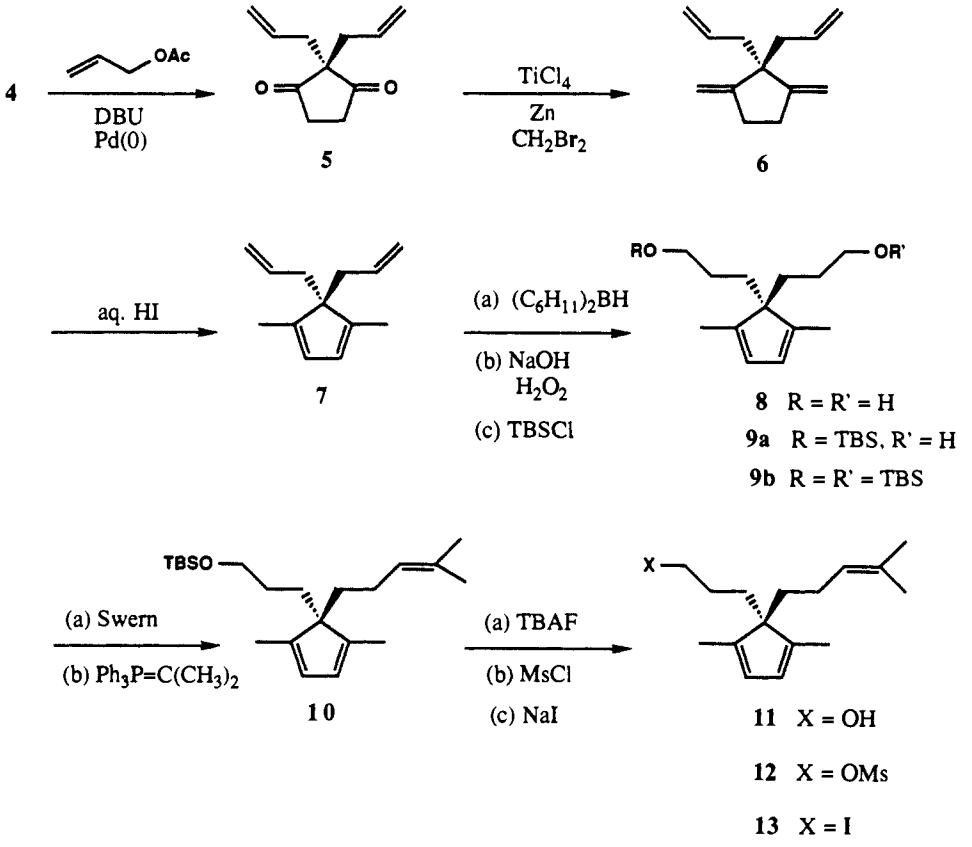


(1)

(8) For an approach to the crinipellin skeleton, see: Mehta, G.; Rao, K. S.; Reddy, M. S. *Tetrahedron Lett.* **1988**, *29*, 5025.

(9) For additions to 1,3-butadiene, see: (a) Kharasch, M. S.; Margolis, E. T.; Mayo, F. R. *J. Org. Chem.* **1936**, *1*, 393. (b) Kharasch, M. S.; Sage, M. *Ibid.* **1949**, *14*, 537. (c) Kharasch, M. S.; Nudenberg, W.; Kawahara, F. *Ibid.* **1955**, *20*, 1550. (d) Gendron, L. J.; Nicholls, R. V. V. *Can. J. Chem.* **1957**, *35*, 1467. For additions to cyclopentadiene, see: (e) Kharasch, M. S.; Simon, E.; Nudenberg, W. *J. Org. Chem.* **1953**, *18*, 328. (f) Skinner, W. A.; Bishop, E.; Tieszen, D.; Johnston, J. D. *Ibid.* **1958**, *23*, 1710. (g) Fang, J.-M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, *28*, 2853.

Scheme II



our knowledge, there are no examples of cyclizations across a cyclic, conjugated diene where two new C–C bonds are formed. Connected with the radical cyclization of the cyclopentadiene is the intermediacy of a bicyclic allylic radical. Only recently have there been examples of allylic radical cyclizations,[11] and at the outset of this work it was not clear whether cyclization of the resonance-stabilized radical would compete effectively with dimerization or hydrogen atom abstraction. Another point of concern was the stereochemistry. While we were certain that only cis-fused rings would form, available precedent[12,13] gave conflicting predictions regarding the stereochemical disposition of the isopropyl group in the second cyclization.

Substrate Preparation

The preparation of the cyclization precursors is shown in Scheme II. The diallyl-1,3-cyclopentanedione (**5**) is a new compound, but is readily available from palladium-catalyzed alkylation[14] of 1,3-cyclopentanedione (**4**). Treatment of the dione (100 mmol) with 3 equiv of allyl acetate, 2.4 equiv of DBU, and 0.8 mol % $(Ph_3P)_4Pd$ (THF, 25 °C, 5 h) provided the diallylated dione **5** in 84% distilled yield. Similar yields were obtained on small scale by using catalytic $(dba)_3{\cdot}CHCl_3$ and excess diallyl carbonate;[15] however, this procedure gave considerably lower yields upon scaleup. Reaction of dione **5** with the reagent[16] formed from $TiCl_4/CH_2Br_2/Zn$ (THF, 0 °C) afforded the tetraene **6**,[17] which was isomerized with aqueous hydriodic acid (PhH, 25 °C) to the cyclopentadiene **7**. Compound **7** could be isolated in about 40% yield (based on **5**) either by flash chromatography or vacuum distillation. Compound **7**, like all other cyclopentadienes prepared in this work, is a stable, easily isolable compound.[18,19] Diels–Alder dimerization is inhibited by the alkyl substituents on the ring, and double bond migration by a 1,5-hydrogen shift is not possible due to the 5,5-disubstitution.

Elaboration of the side chains of **7** began with hydroboration–oxidation of the terminal olefins to provide the diol **8**. The hydroboration was initially carried out with 9-BBN, but chromatographic separation of **8** from the 1,5-cyclooctanediol byproduct was tedious. However, the use of dicyclohexylborane (generated in situ) eliminated this problem. Selective monoprotection of the symmetrical diol **8** (1 equiv NaH, THF; 1 equiv TBSCl)[20] was unsuccessful. However, the statistical mixture of

(10) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.

(11) Cyclizations of allylic radicals formed by 1,5-hydrogen abstraction: (a) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (b) Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988**, *29*, 837. By halogen abstraction: (c) Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911. (d) Chang, C.-T., Ph.D. Thesis, University of Pittsburgh, 1988. (e) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 921. (f) Cox, N. J. G.; Pattenden, G.; Mills, S. D. *Tetrahedron Lett.* **1989**, *30*, 621. (g) For an unsuccessful cyclization involving an allylic radical, see: Subba Rao, G. S. R.; Bhaskar, K. V. *Tetrahedron Lett.* **1989**, *30*, 225.

(12) For examples of endo selectivity, see: (a) References 3 and 6. (b) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (c) Fallis, A. G.; Yadav, V. K. *Tetrahedron Lett.* **1988**, *29*, 897. (d) Cossy, J.; Belotti, D.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196. (e) Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311. (f) Hart, D. J.; Burnett, D. A.; Choi, J.-K.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (g) Wolff, S.; Agosta, W. C. *J. Chem. Res., Synop.* **1981**, *3*, 78. (h) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811.

(13) For examples of exo selectivity, see: (a) Livinghouse, T.; Leonard, W. R. *Tetrahedron Lett.* **1985**, *26*, 6431. (b) Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966. (c) Nagarajan, M.; Rao, Y. K. *Tetrahedron Lett.* **1988**, *29*, 107. (c) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296. (d) Reference 11c.

(14) For reviews of Pd-catalyzed allylations, see: (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(15) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.

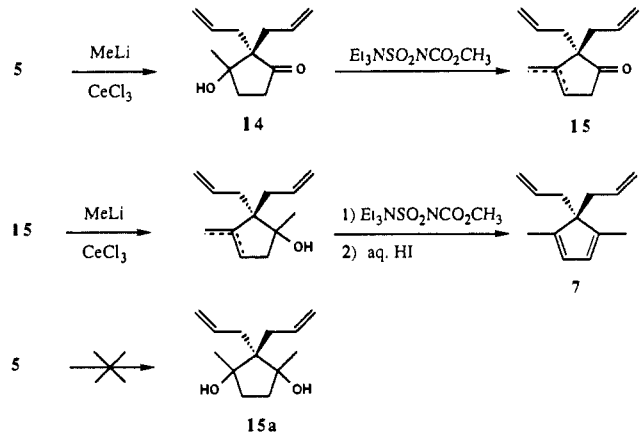
(16) (a) Lombardo, L. *Org. Syn.* **1987**, *65*, 81. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417. (c) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.

(17) Reaction of dione **5** with excess methylidenetriphenylphosphorane produced a mixture of **5**, **6**, and the corresponding mono-olefinated ketone. Enolization of the sterically hindered ketones by the ylide presumably competes with olefination.

(18) Vacuum distillation of **7** results in tar formation if any acid is present in the crude product mixture. Polymerization of **7** during the acid-catalyzed isomerization of **6** is suspected to be the primary reason for the modest isolated yield of **7**.

(19) For examples of other highly substituted cyclopentadienes, see: Winterfeldt, E.; Matcheva, K.; Beckmann, M.; Schomburg, D. *Synthesis* **1989**, 814, and references therein.

Scheme III



mono(silyl ether) **9a**, bis(silyl ether) **9b**, and unreacted **8** obtained from treatment of **8** with TBSCl (1 equiv) and imidazole (1.3 equiv, CH_2Cl_2, 25 °C) was easily separated by chromatography. Recycling of the bis(silyl ether) **9b** and the recovered diol **8** eventually led to an overall 70–80% yield of the desired alcohol **9a**. The problem of differentiating the two side chains could probably be solved by using two different alkylating agents in the reaction with **4**. However, at this point we were more concerned with flexibility than brevity, and monoprotected diol **9a** is a useful precursor for a diverse collection of cyclization substrates. Assembly of one side chain was completed by oxidation of the alcohol **9a** to the aldehyde, followed by Wittig olefination ($PhCH_3$, −78 °C to 0 °C, 66% overall), to afford **10**. Desilylation of **10** (TBAF, THF, 94%) gave alcohol **11**, and formation of the mesylate **12** with subsequent nucleophilic displacement (NaI, acetone, 25 °C, 74% overall) provided the first radical precursor **13**.

Another route[21] for conversion of **5** to **7** is shown in Scheme III. Addition of methyllithium to **5** to provide **14** was best carried out in the presence of anhydrous $CeCl_3$[22] (THF, −78 °C), as enolization of the neopentyl ketone competed with nucleophilic addition when either MeLi, MeLi–LiBr, or MeMgBr was used. Dehydration of the tertiary alcohol **14** was smoothly accomplished with the Burgess reagent[23,24] ($Et_3NSO_2NCO_2CH_3$, PhH, 55 °C) to provide a mixture of exo- and endocyclic olefins **15**. A second addition of the methylcerium reagent to **15**, followed by dehydration and acid-catalyzed isomerization, gave **7** in a somewhat better overall yield than the methylenation-isomerization sequence described in Scheme II. However, due to the brevity of the Scheme II sequence, the lower yield was acceptable. Dehydration of the diol **15a** under acidic conditions was anticipated to produce tetracene **7** directly. However, formation of **15a** from either dione **5**, or ketone **14**, or its derived silyl ether, was unsuccessful under a variety of conditions. The case of addition of methyl anion to **5** or **15** suggests that the tertiary alcohol center of **14** impedes the approach of the incoming nucleophile along the Dunitz–Bürgi trajectory[25] to the carbonyl carbon.

Tandem Cyclizations

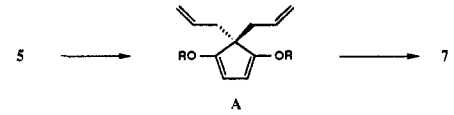
With the alkyl iodide **13** in hand, we investigated the proposed tandem radical cyclization (Scheme IV). To our delight, reduction of **13** with tributyltin hydride under standard conditions (1.2 equiv of Bu_3SnH, catalytic AIBN, PhH, 80 °C, 0.02 M) resulted in smooth conversion to the tricyclic products **16** and **17**, in a ratio of 1:5 as determined by ^1H NMR integration of the corresponding vinyl hydrogen signals. The crude yield for **16/17** was estimated (by GC and ^1H NMR) to be 85–90%, while the isolated yield was somewhat lower (65%) due to the difficulty in removing nonpolar tin-containing products from the tricyclic hydrocarbons. Products derived from tin hydride reduction of either the initial alkyl radical (not shown) or the allylic radical **18** were not observed, nor were bridged products resulting from 6-exo cyclization to the least-substituted terminus of the allylic radical obtained. Unfortunately, we could not separate isomers **16/17** by silica gel chromatography, nor could we determine the relative stereochemistry from examination of the ^1H NMR spectrum.[26] Correlation of **16** and **17** with a compound of known relative stereochemistry (see below) ultimately provided the stereochemical assignments: the minor tricyclic product **16** possesses the correct relative isopropyl group stereochemistry of the crinipellins.

This tandem cyclization is particularly notable for the ease with which the two new quaternary centers are created on either side of the existing quaternary carbon. Although substitution at C_5 of 5-hexenyl radicals retards the rate of 5-exo cyclization relative to 6-endo cyclization,[27] this effect is not manifested in the cyclization of our initial alkyl radical, possibly due to activation of the reacting double bond by the conjugated π-system. 6-Endo cyclization is certainly disfavored due to the angle strain and nonbonded interactions present in formation of the resulting bridged product (not shown). Two cyclization pathways (a and b) are also available to the allylic radical **18**, and 5-exo cyclization (a) is favored over 6-exo cyclization (b) even though the 5-exo cyclization forms a third, contiguous quaternary center.[28] Entropy generally favors 5-exo closure over 6-exo closure, and ring strain may also disfavor the 6-exo closure of **18**. Substitution at the radical center often does not retard 1,5-ring closure,[27] and thus ring closure at the tertiary allylic site is not disfavored relative to ring closure at the secondary site. That this tandem cyclization succeeds in forming two new quaternary centers flanking a third is testament to the early transition states of these radical cyclizations. Cyclization of resonance stabilized allylic radical **18** presumably has a later transition state than cyclization of a simple alkyl radical; however, the tertiary substitution at the reacting radical center is not detrimental.

Two reasonable transition states for the allylic radical cyclization are illustrated in Figure 2. Transition state **21** leads to the tricyclic radical **20**, which in turn provides the major product **17**. In this chair-like transition state (TS), the isopropylidene group is in an endo orientation relative to the newly forming bicyclooctane, and the smaller vinyl hydrogen is in the apparently more sterically demanding exo orientation. This endo selectivity is in accord with the cis stereoselectivity of 1-alkylhex-5-enyl radicals[29] and con-

(20) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(21) Another route to **7** would be the coupling of a bisenol derivative of **5** (see A) with either MeLi or MeMgBr under transition-metal catalysis. Early attempts to form the bis(trimethylsilyl)enol ether (A, R = TMS) were unsuccessful, and this route was not pursued.



A

R = TMS, SO_2CF_3, $PO(OR')_2$

(22) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(23) Alcohol **14** was surprisingly resistant to dehydration under acidic conditions. Base-induced eliminations of the corresponding mesylate or triflate were also unsuccessful.

(24) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(25) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *Ibid.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(26) The results of ^1H NMR NOE experiments were ambiguous. Irradiation of either of the methyl doublets of the major diastereomer gave no enhancement (<1%) for either of the vinyl signals of the major diastereomer.

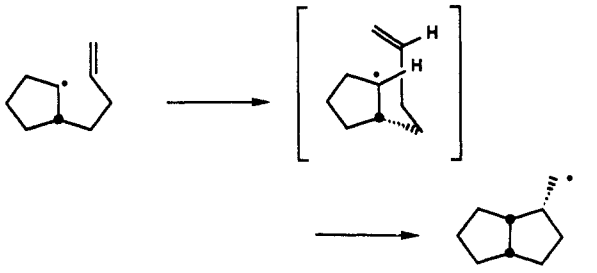
(27) (a) Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073, and references therein.

(28) Quaternary centers have been formed in the cyclizations of secondary allylic radicals. See ref 11c.

(29) The 1-methyl-5-hexenyl radical cyclizes to afford a 2:1 cis/trans mixture of 1,2-dimethylcyclopentane. See: (a) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711. (b) Beckwith, A. L. J.; Phillipou, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 1613.

sistent with other cyclizations forming bicyclooctanes[12] (eq 2a[12g]).

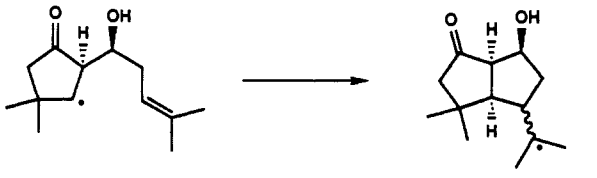
(a)



endo : exo = 8.3

(2)

(b)



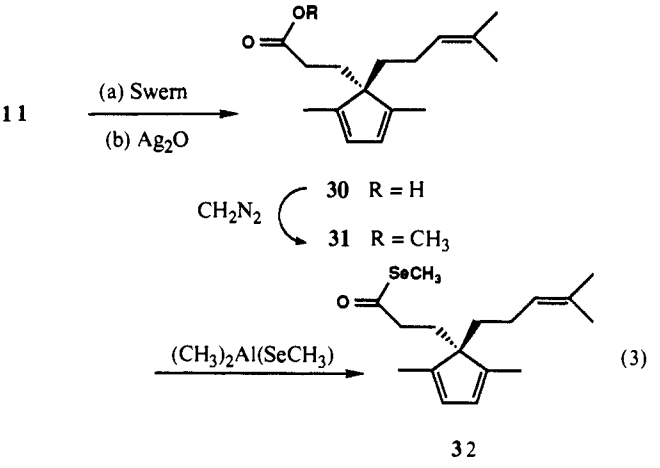
endo : exo = 1

We had hoped that the syn methyl group on our isopropylidene terminus would encounter nonbonded interactions with the bicyclic nucleus in the normally preferred endo TS, thus favoring cyclization via the boat-like exo TS[13] (eq 2b[13a]) which leads to the desired isopropyl group stereochemistry. That this does not occur may be because the steric interactions introduced in the endo transition state by the disubstituted olefin terminus are effectively negated by the presence of the "flat" allylic radical. Another pair of chair-like and boat-like transition states (not shown) are possible, leading to **17** and **16**, respectively. However, these transition states appear to be more strained than **21** or **22** due to the tricyclic nature of the cyclization. We have recently examined a related tandem cyclization in which the D ring of the crinipellin skeleton is formed first. This "reverse" cyclization was, unfortunately, also endo selective.[30]

In the above tin hydride mediated tandem cyclization, a carbon–heteroatom bond serves as the initial alkyl radical precursor. Carbon–hydrogen bonds cannot be directly used as radical precursors because hydrogen atom transfer to a stannyl radical is endothermic. However, we have recently developed a method that permits the indirect use of a C–H bond as a radical precursor by initial generation of a carbon-centered radical at a remote site, followed by 1,5-hydrogen atom transfer.[31] Application of this tactic to the synthesis of the BCD rings of crinipellin A is illustrated in Scheme V. The cyclization substrate **23** was prepared in 70% purified yield by reaction of alcohol **11** with (2-bromophenyl)chlorodimethylsilane in the presence of imidazole (CH_2Cl_2, 0 °C to 25 °C). Treatment of bromide **23** with tin hydride (1.2 equiv, catalytic AIBN, PhH, 80 °C) produced a mixture of 4 diastereomeric tricycles **25**, along with a small amount (about 10%) of the cyclopentadiene corresponding to **24**. This reaction presumably involves initial generation of an aryl radical (not shown) which undergoes a 1,5-hydrogen atom transfer to generate the α-alkoxy radical **24**. Tandem cyclization then provides **25**. We do not know whether the cyclopentadiene product is produced by reduction of **24** or of the initial aryl radical.

The alcohols **26** (diastereomeric ratio of 1:1:3.5:4.8) were isolated in 65% yield (based on **23**) after fluoride-induced desilylation of **25**. Similar to the cyclization of iodide **13**, bicyclic products (**27**) were not observed. Oxidation of the alcohols **26** (PDC, DMF, 25 °C) proceeded smoothly to provide the ketones **28**/**29** in a ratio of 1:4.5. This ratio corresponds to the ratio of the two minor and two major diastereomers for **26** (2:8.3). As expected, the stereoselectivity at the isopropyl-bearing center is essentially identical with that in the cyclization of iodide **13**. The carbinol center is formed without appreciable stereoselectivity, and this is somewhat surprising.[4,12] As with the hydrocarbons **16** and **17**, the ketones **28** and **29** were inseparable by analytical HPLC, and the relative stereochemistry of each was assigned by correlation with a compound of known relative stereochemistry (see below).

Methyl Selenol Esters. The carbonyl group in **28** is ideally located to assist in annulation of the A ring by traditional methods. Therefore, in parallel with efforts to assign the stereochemistry of **16** and **17** (and **28** and **29**), we proceeded with a more direct construction of ketone **28** (Scheme VI) by using a tandem cyclization of an acyl radical.[32] Accordingly, the acyl methyl selenide **32** was prepared as shown in eq 3. Oxidation of the

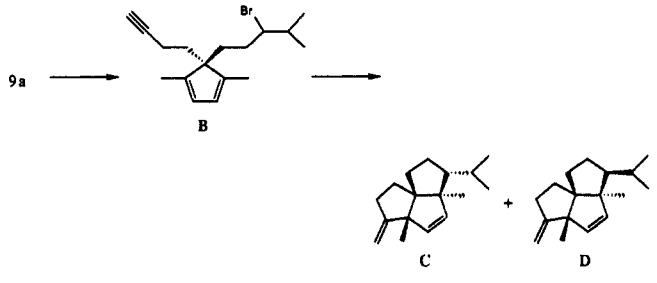


(3)

32

alcohol **11** to the aldehyde, followed by silver oxide oxidation, produced carboxylic acid **30** in excellent yield. Attempts to convert the carboxylic acid to the corresponding phenyl selenol ester by using *N*-phenylselenophthalimide[33] (Bu_3P, THF, 25 °C) met with limited success (yields were low and irreproducible). However, esterification of **30** (CH_2N_2, Et_2O, 0 °C) and subsequent treatment of the ester **31** with dimethylaluminum methaneselenolate[34] ($PhCH_3$, 0 °C to 25 °C) provided the methyl selenol ester **32** in high yield (90%) after chromatographic purification.

(30) The secondary bromide B was prepared in six steps from alcohol **9a**. Treatment of B with Bu_3SnH (catalytic AIBN, benzene-d_6, 80 °C, 0.02 M) provided the tricycles C and D in a ratio of about 1:10. The relative isopropyl group stereochemistry of C and D was determined by ^1H NMR comparison to a mixture of C/D (1:4) prepared by olefination ($TiCl_4$, CH_2Br_2, Zn, THF) of a mixture (1:4.5) of ketones **28**, **29**.



(31) (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Sniekus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H. T.; Curran, D. P. *Ibid* **1990**, *112*, 896.

(32) (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295. For leading references on the generation and reaction of acyl radicals, see footnotes 3 and 4. (b) Vinogradov, M. G.; Nikishin, G. I. *Russ. Chem. Rev.* **1971**, *40*, 916. (c) Crich, D.; Fortt, S. M. *Tetrahedron* **1989**, *45*, 6581. (d) Crich, D.; Forti, S. M.; Ritchie, T. J. *Free Radicals in Synthesis and Biology*; Minisoi, F., Ed.; Kluwer Academic Publishers: Boston, 1989; pp 135–143. (e) Bachi, M. D.; Bosch, E.; Denenmark, D.; Girsh, D. *Ibid.* pp 125–134. (f) Zard, S. Z.; Tailhan, C. *Ibid.* pp 263–268. (g) Kagan, H. B.; Sasaki, M.; Collin, J. *Tetrahedron Lett.* **1988**, *29*, 6105. (h) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377. (i) Boger, D. L.; Mathvink, R. J. *Ibid.* **1989**, *54*, 1777. (j) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *1102* 4004; 4008. (k) Corey, E. J.; Singh, A. K.; Bakshi, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (l) Wiberg, K. B.; Waddell, S. T. *Ibid.* **1990**, *112*, 2194.

(33) Grieco, P. A.; Jaw, J. Y.; Claremon, D. A.; Nicolaou, K. C. *J. Org. Chem.* **1981**, *46*, 1215.

(34) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735.

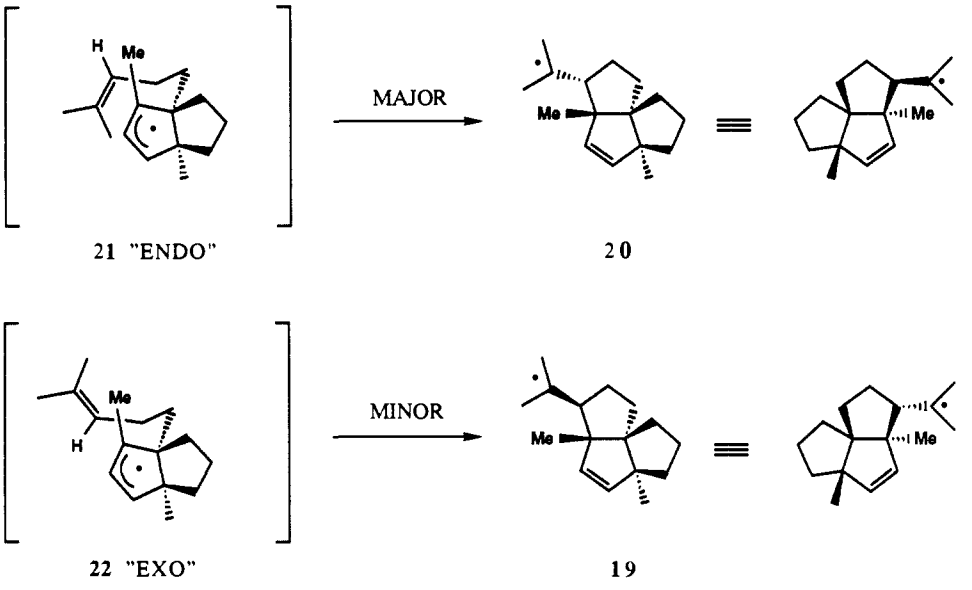
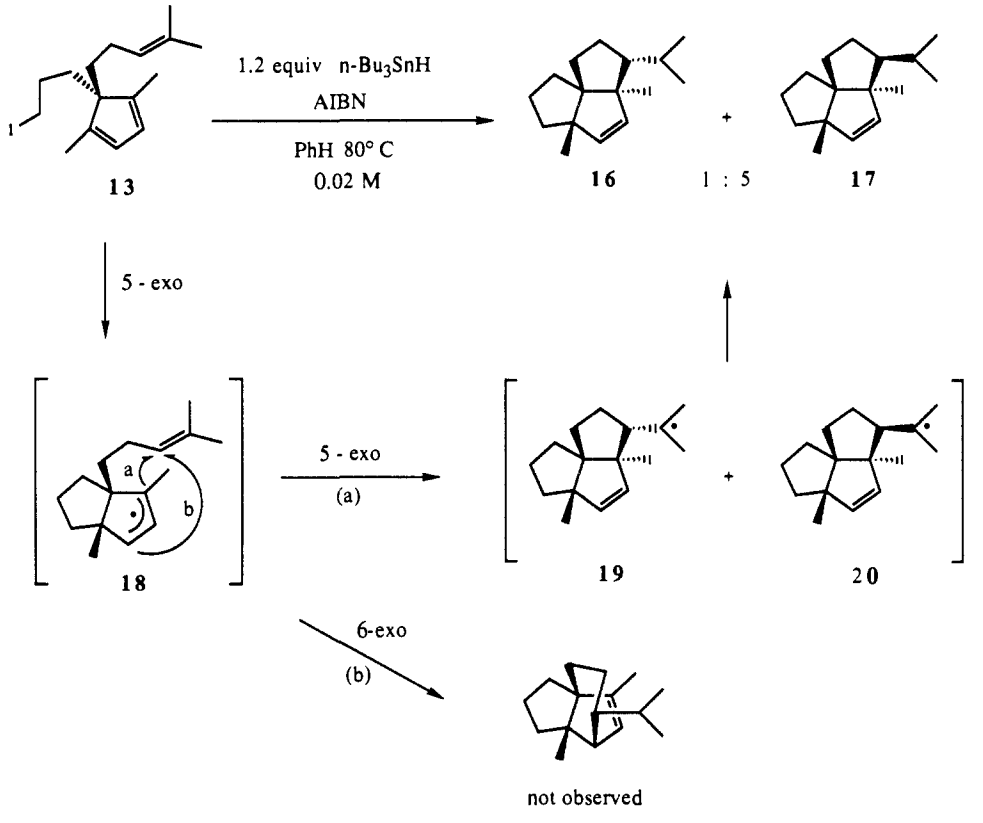


Figure 2.

Scheme IV

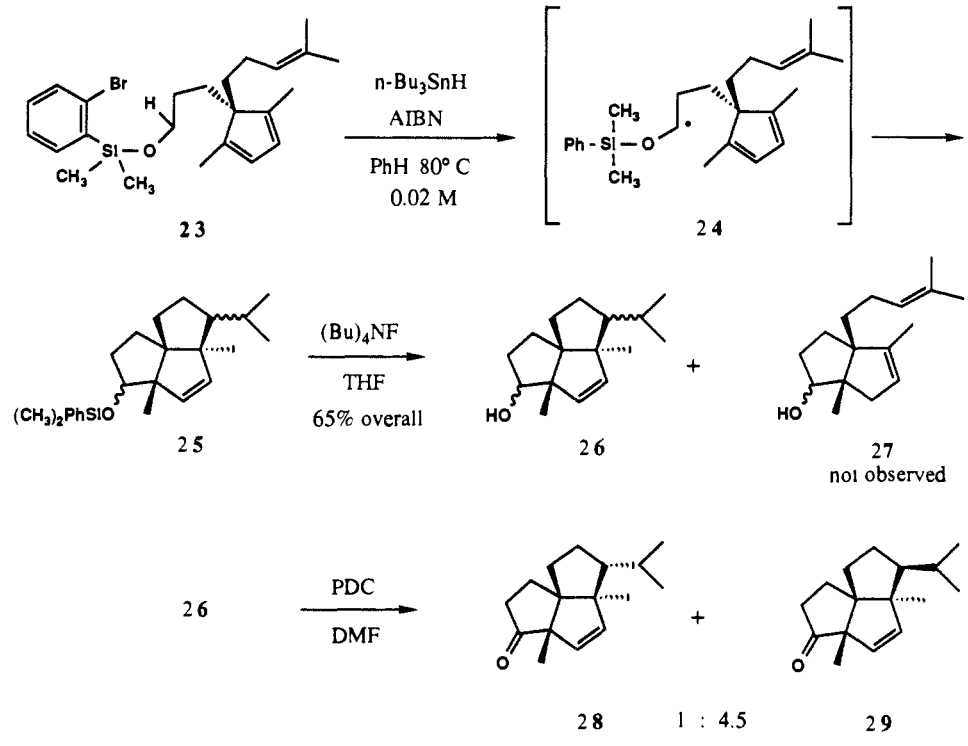


While only phenyl-substituted selenol esters have been used for the tin hydride mediated generation of acyl radicals,[32c-e,h-l] we have found that the acyl methyl selenides are also useful acyl radical precursors. Reaction of **32** with Bu_3SnH (2.2 equiv, catalytic AIBN, PhH, 80 °C) afforded the cyclized products **28**, **29**, and **35** in good yield after chromatography (Scheme VI).[35] The ratio of tricyclic diastereomers (**28**:**29**) was again 1:5. The aldehyde corresponding to direct tin hydride reduction of the acyl radical **33** was not observed (by GC or NMR).[36] However, unlike the cyclization of iodide **13** or silyl ether **23**, about 25% of this product mixture was the bicyclic compound **35** derived from reduction of the allylic radical **34**. One possible explanation for the formation of **35** is that the carbonyl group in **34** inductively deactivates the allylic radical, slowing the rate of cyclization relative to hydrogen atom abstraction from tin hydride. However, attempts to minimize the amount of bicyclic ketone **35** by decreasing the tin hydride concentration (0.003 M fixed concentration, or syringe pump addition of Bu_3SnH) met with no success; ketone **35** consistently accounted for about 25% of the cyclized

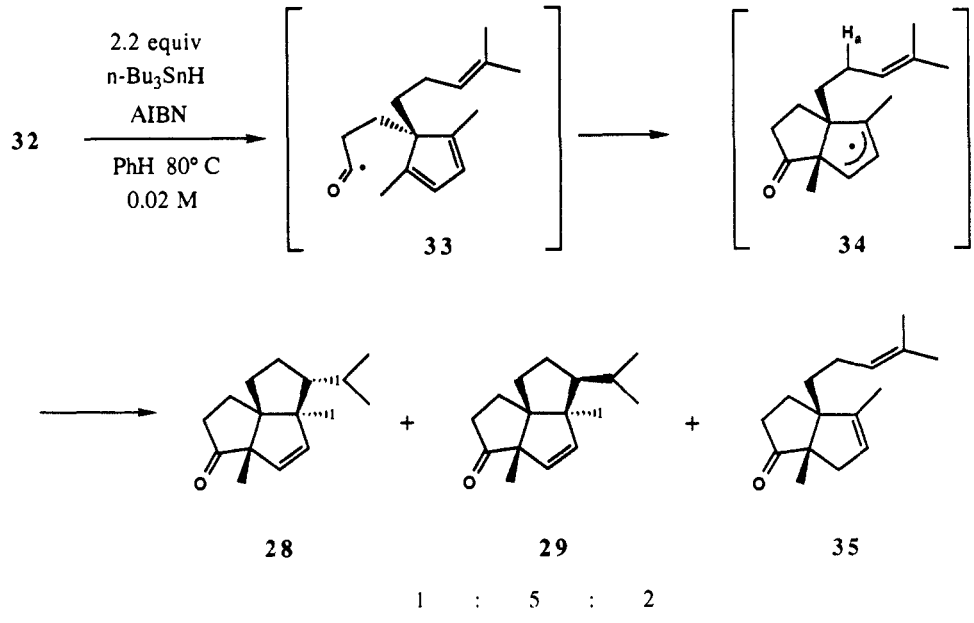
(35) Unfortunately, products **28**, **29**, and **35** were inseparable by analytical HPLC. However, the olefinic signals were resolved in the ^1H NMR spectrum of the mixture, allowing for reliable determination of ratios by integration, and also allowing for a tentative structural assignment for compound **35**. Treatment of the mixture with MCPBA (CH_2Cl_2, 25 °C) resulted in selective epoxidation of the acyclic olefin of **35**. The epoxide was easily separated from **28**/**29** by flash chromatography. The stereochemical assignments for **28**/**29** are by correlation with a compound of known stereochemistry (Scheme X).

(36) This aldehyde is a potential acyl radical precursor by hydrogen atom abstraction (see refs 32b,l). Treatment of the aldehyde with 1–2 equiv of $(t\text{-BuO})_2$ in cyclohexane (80–120 °C) provided no cyclized materials, and ultimately resulted in destruction of the substrate.

Scheme V



Scheme VI



products. These results suggest that H-atom transfer to the allylic radical does not involve a bimolecular reaction with tin hydride. An intramolecular 1,5-hydrogen atom transfer of H_a to the least-substituted terminus of **34** is possible, but it seems unlikely due to the constraints of the bridged transition state. We did not conduct further experiments to determine the origin of **35**.

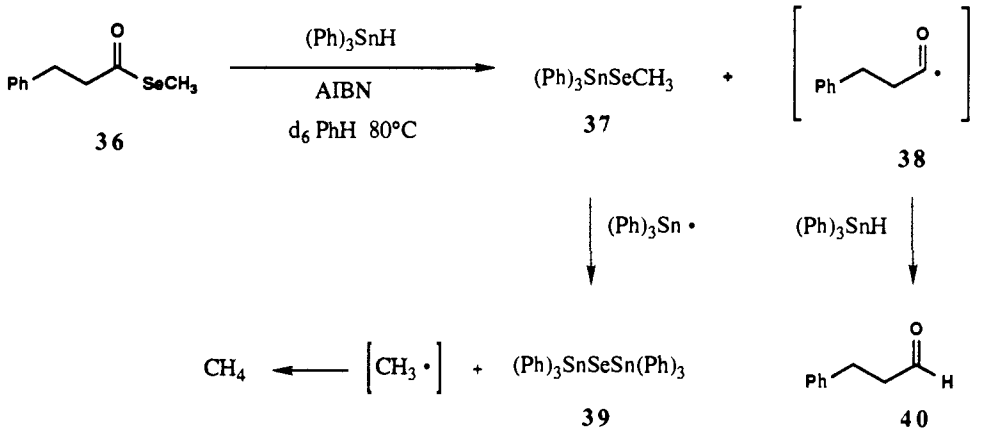
While phenyl selenol esters require only 1 equiv of tin hydride for conversion to the acyl radical, we found that 2 equiv of Bu_3SnH was required for complete consumption of the methyl selenide **32**. The reason for this difference became clear upon examination of the reduction of the simple methyl acyl selenide **36** (Scheme VII). In this case, cyclization of the acyl radical **38** onto the phenyl ring is slow, and hydrogen abstraction provides dihydrocinnamaldehyde (**40**). Reductions of **36** were monitored by ^1H NMR in benzene-d_6, and, to simplify the alkyl region of the ^1H NMR spectrum, Bu_3SnH was replaced by Ph_3SnH. Treatment of **36** with 1 equiv of Ph_3SnH resulted in complete consumption of tin hydride, and the ratio of **40**:**36** was about 1:1. During the reaction, we also observed a singlet at 1.74 ppm, which was assigned to the stannyl selenide **37**.[37] This selenide apparently competes efficiently with **36** for stannyl radical,[38] producing the distannyl selenide **39** and methyl radical, which forms methane[39] upon hydrogen abstraction from tin hydride. Addition of a second equivalent of Ph_3SnH to the reaction mixture completely consumed the acyl selenide and nearly consumed **37**. A preparative reaction (with 2.2 equiv of Bu_3SnH) provided an 85% yield of **40** after chromatography. The reactivity of stannyl selenide **37** parallels that of stannyl sulfides

(37) The selenide **37** was independently prepared (but not isolated) by reaction of $(Ph)_3SnH$ with 3 equiv of $(CH_3Se)_2$ (benzene-d_6, catalytic AIBN, 80 °C).

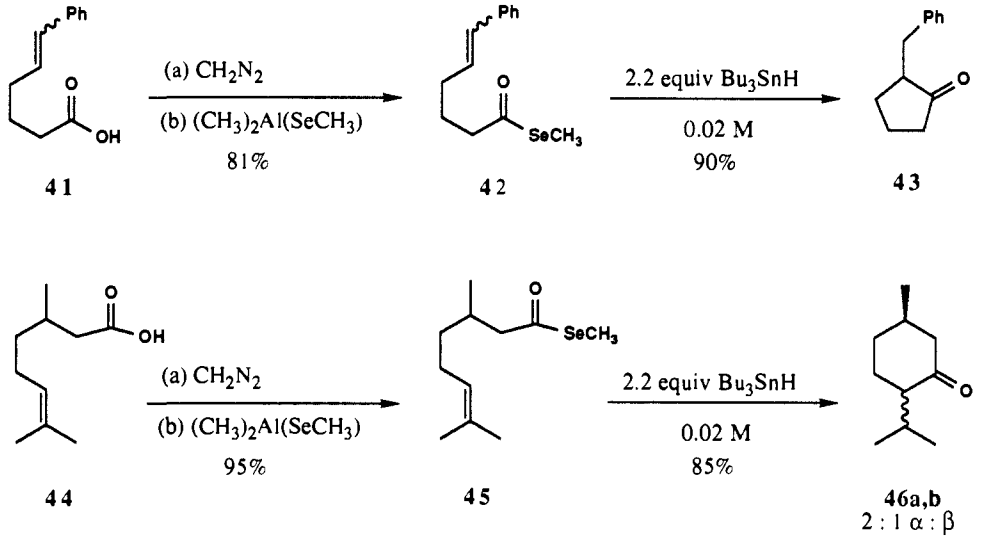
(38) For the tin hydride reduction of unsymmetrical sulfides and stannyl sulfides, see: Gutierrez, C.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206.

(39) In a sealed NMR tube experiment (C_6D_6), a small singlet at 0.18 ppm was observed.

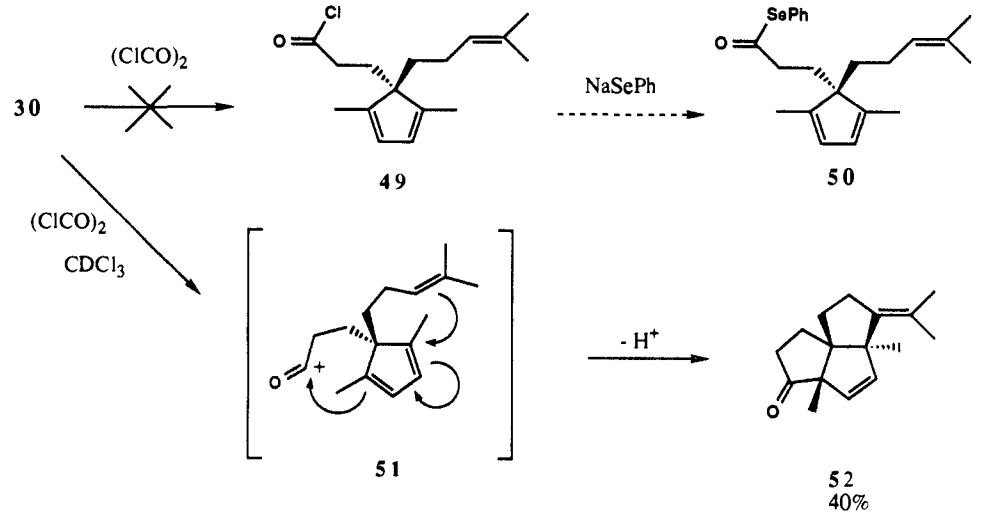
Scheme VII



Scheme VIII



Scheme IX



(RSSnBu$_3$), which show enhanced reactivity toward stannyl radical relative to dialkyl sulfides.[38]

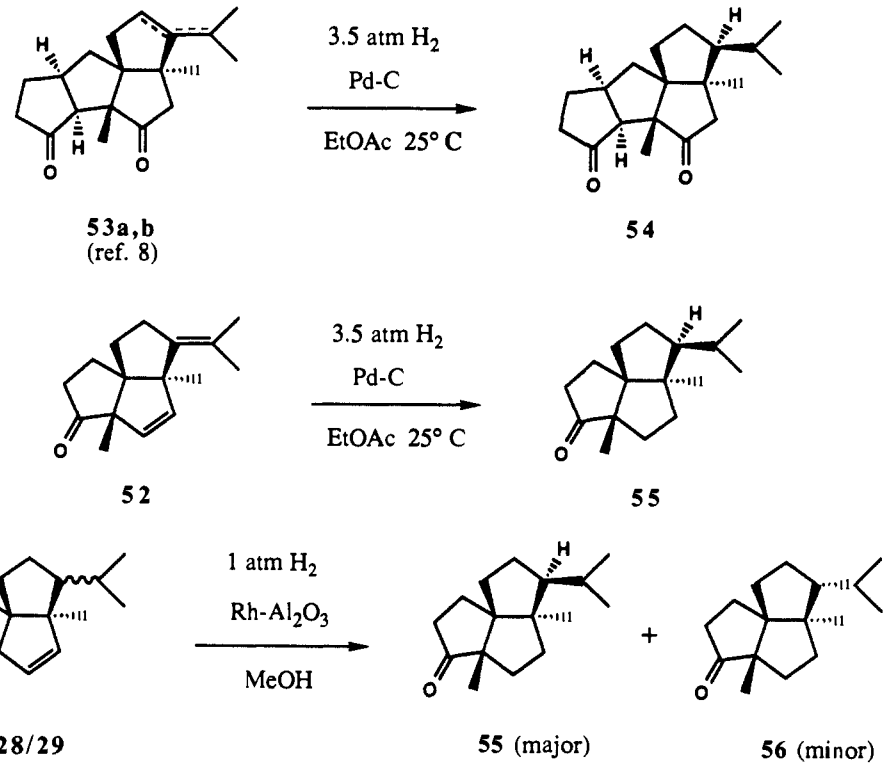
To further illustrate the synthetic utility of the methyl selenol esters, two simple cyclization substrates were prepared (Scheme VIII). Esterification of acid **41**[40] was followed by reaction with dimethylaluminum methaneselenolate to afford **42** in 81% isolated yield. Tin hydride mediated cyclization proceeded cleanly to give cyclopentanone **43** in 90% purified yield. Similarly, preparation and cyclization of **45**, derived from citronellic acid (**44**), proceeded cleanly to provide menthone (**46a**), and isomenthone (**46b**) in a 2:1 ratio and in 80% combined overall yield. These yields compare very favorably with related cyclizations of phenyl selenol esters.[32d,h]

An intermolecular addition[32i] of the dihydrocinnamyl radical to methyl acrylate was also successful (eq 4).[41] When acyl

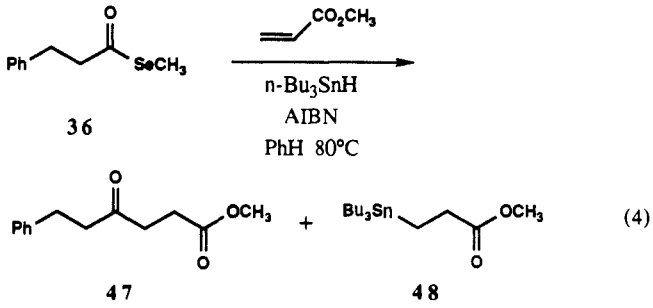
(40) Acid **41** was prepared as follows: (a) DIBAL reduction of δ-valerolactone to the lactol (THF, −78 °C); (b) Wittig reaction with (Ph)$_3$P=CH-(Ph) (PhCH$_3$, 0 °C); (c) PDC oxidation of the alcohol to the acid (DMF, 25 °C).

(41) In these experiments, Bu$_3$SnH was added via syringe pump to a mixture of **36** and methyl acrylate, following Boger and Mathvink's general procedure (see ref 32i).

Scheme X



selenide **36** was treated with 5.3 equiv of methyl acrylate and 2.2 equiv of Bu_3SnH, a 41% yield of the ketone **47** was obtained.



(4)

equiv acrylate	equiv hydride	% yield **47**
5.3	2.2	41
1.3	2.2	64
7.0	5.1	97

Unreacted **36** was present, even though all of the tin hydride was consumed. The recovery of **36** is due to the competition for the stannyl radical between selenium group abstraction (from **36** or **37**) and addition to methyl acrylate to give **48**.[42] The use of less acrylate (1.3 equiv) actually improved the yield of ketone **47** to 64%. A nearly quantitative conversion of **36** to **47** was obtained by using 7 equiv of methyl acrylate and 5 equiv of tin hydride. Again, all of the tin hydride was consumed and a large amount of **48** was present; however, this hydrostannylation product is easily separated from the ketone **47** by chromatography. These results demonstrate that methyl selenol esters should prove useful as acyl radical precursors when a methyl ester and not a carboxylic acid (the usual precursor of a phenyl selenol ester[32c,h,i,33]) is provided by a synthetic sequence.

As mentioned previously, early attempts to convert the acid **30** to the phenyl selenol ester **50** (Scheme IX) were unsuccessful. Conversion of dihydrocinnamic acid to the corresponding acid chloride ($(ClCO)_2$, CH_2Cl_2), and subsequent reaction of the crude material with sodium (phenylseleno)(triethoxy)borate[43,44] gave moderate yields of the phenyl selenol ester. However, the same reactions with acid **30** did not produce significant amounts of **50**. In an effort to ascertain what had occurred, we monitored the reaction of **30** and oxalyl chloride (1.1 equiv, $CDCl_3$, 25 °C) by ^1H NMR. The acid was consumed after several hours, and several new compounds were produced. Flash chromatography led to the isolation of the major product, tricyclic ketone **52**, in 40% yield. This ketone probably arises from a tandem cationic cylization.[45] This is a rare example of a cationic cylization that parallels the regiochemistry of the corresponding radical cyclization.[46] The cyclization is presumably initiated by the acylium ion **51** (or its equivalent). Reexamination of the crude ^1H NMR spectra for the reactions of **30** with $(ClCO)_2/Na(PhSe)B(OEt)_3$ revealed the presence of ketone **52** among the other unidentified products, explaining at least in part the failure of the phenyl selenide acylation reaction.

Stereochemical Correlation

While the above cationic cyclization is intriguing in its own right, the isolation of ketone **52** provided us with a fortuitous opportunity to assign stereochemistry to the radical cyclization products **16**/**17** and **28**/**29**. In a recent report by Mehta and co-workers,[8] hydrogenation of olefins **53a,b** (Scheme X) gave a single product **54**, the relative stereochemistry of which was assigned by X-ray analysis. Given the structural similarity of **52** and **53a,b**, we felt confident that the hydrogenation product (3.5 atm H_2, EtOAc, 25 °C) of **52**, ketone **55**, possessed the designated relative stereochemistry. Hydrogenation of the mixture of tandem radical cyclization products **28** and **29** (1:4.5) produced as the

(42) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press: Oxford, **1986**; pp 10–11. (b) Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 343.

(43) For the initial preparation of this reagent, see: (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. For the subsequent characterization of the reagent, see: (b) Miyashita, M.; Hoshino, H.; Yoshikoshi, A. *Tetrahedron Lett.* **1988**, *29*, 347.

(44) For a recent example of the preparation of phenyl selenol esters from carboxylic acid chlorides and $Na(PhSe)B(OEt)_3$, see: Crich, D.; Eustace, K. A.; Ritchie, T. J. *Heterocycles* **1989**, *28*, 67.

(45) (a) For a review of biomimetic polyene cyclizations, see: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) For a recent example involving an allylic cation, see: Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852.

(46) For a tandem radical cyclization that resembles some cationic polyolefin cyclizations, see: Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837.

major product a compound identical (by ^1H and ^{13}C NMR comparison) with **55**. The stereochemistry of hydrocarbon **17** was then assigned by analogy.[47] This stereochemical correlation does not provide a direct structural assignment for the minor cyclization products **16** and **28**. However, given the spectroscopic similarities of **28** and **29** (and **16** and **17**), we are confident that these pairs are stereoisomeric.

Conclusions

We have demonstrated the usefulness of our new tandem cyclization strategy for construction of the congested angular triquinane portion of the crinipellins. Several features of this new chemistry are noteworthy. First, the tandem cyclizations result in a 1,4-functionalization of the cyclopentadiene nucleus, whereas all previous tandem cyclizations accomplished a vicinal functionalization of an olefin. Second, we have demonstrated that cyclizations of allylic radicals are possible even in a complex, crowded environment. Third, the tandem cyclization of an acyl radical proceeded efficiently to provide an angular triquinane that was suitably functionalized for annulation of the A ring of the crinipellins. Connected with the acyl radical cyclization is the facile generation of acyl radicals from the readily accessible methyl selenol esters. With the flexibility available in the design of cyclization substrates, we are currently directing our efforts toward the preparation of cyclopentadiene substrates that will allow for control of the isopropyl stereocenter of the crinipellins.

Experimental Section

Proton nuclear magnetic resonance spectra were recorded on either a Bruker AC-300 300 MHz or a Bruker AM-500 500 MHz spectrometer, and all chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.24 ppm). Carbon nuclear magnetic resonance spectra were recorded on a Bruker AM-500 spectrometer at 125 MHz, and all chemical shifts are reported relative to residual $CHCl_3$ (77.09 ppm). Infrared spectra were recorded on either a Mattson Cygnus 100 or IBM IR/32 FT-IR spectrophotometer. Mass spectra (high resolution) were run on a Varian Match-5 DF spectrometer.

Benzene (PhH) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) was freshly distilled from CaH_2. Dimethyl sulfoxide (DMSO), toluene ($PhCH_3$), *N,N*-dimethylformamide (DMF), and triethylamine (Et_3N) were distilled from CaH_2. Acetone and methanesulfonyl chloride were distilled under N_2 from P_2O_5 prior to use. Isopropyltriphenylphosphonium bromide was dried prior to use by stirring under vacuum at 80 °C for 15 h. All other reagents were used as received. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates (Merck 60F-254), and flash chromatography was performed with use of Merck 60 230–400 mesh silica gel. All reactions were carried out in flame-dried flasks under a nitrogen atmosphere with positive pressure maintained throughout, unless otherwise noted.

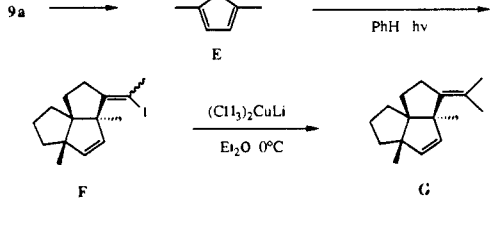
2,2-Bis(2-propenyl)-1,3-cyclopentanedione (5). To a solution of 1,3-cyclopentanedione (**4**) (10.0 g, 0.101 mol) in THF (200 mL) was added allyl acetate (33.0 mL, 0.306 mol), DBU (33.0 mL, 0.240 mol), and tetrakis(triphenylphosphine)palladium (545 mg, 0.471 mmol).[14] The reaction vessel was purged with N_2 for 10 min, and the mixture was stirred at room temperature for 23 h. The red solution was diluted with ether (200 mL), washed with saturated aqueous NH_4Cl (2 × 150 mL), water (150 mL), brine (150 mL), and the organic phase was dried ($MgSO_4$). After filtration and solvent evaporation, the residue was purified by vacuum distillation (short path, bp = 77–80 °C at 0.8 mmHg) to afford 15.3 g (84%) of the diallyl cyclopentanedione **5**: IR (thin film) 1726, 1417, 1194, 993, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (2 H, ddt, J = 14.5, 11.9, 7.4 Hz), 5.04 (2 H, d, J = 14.5 Hz), 5.03 (2 H, d, J = 11.9 Hz), 2.59 (4 H, s), 2.35 (4 H, d, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.12 (s), 131.22 (d), 119.76 (t), 61.00 (s), 39.15 (t), 36.22 (t); HRMS m/e calcd for $C_{11}H_{14}O_2$ (M^+) 178.0994, obsd 178.0994; LRMS m/e 178 (M^+), 137, 107.

1,4-Dimethyl-5,5-bis(2-propenyl)-1,3-cyclopentadiene (7). Titanium tetrachloride[16] (19.0 mL, 0.173 mol) was added dropwise via cannula to a well-stirred, 0 °C suspension of zinc dust (45.5 g, 0.696 mol) and dibromomethane (15.8 mL, 0.225 mol) in THF (350 mL), and the mixture was stirred at 0 °C for 5 h. A solution of dione **5** (7.74 g, 0.434 mol) in THF (50 mL) was added rapidly via cannula to the dark brown suspension, and the reaction was allowed to slowly warm to room temperature. After 18 h, acetone (10 mL, reagent grade) was added, and, after stirring an additional 1 h, the mixture was diluted with ether (400 mL), washed with 10% aqueous HCl (2 × 200 mL), water (200 mL), brine (200 mL), and saturated aqueous $NaHCO_3$ (2 × 100 mL). The combined aqueous phase was extracted with ether (2 × 50 mL), and the combined organic phase was dried over $MgSO_4$, Celite, $NaHCO_3$, and Norit. After filtration through a pad of Celite and solvent evaporation, the residue was eluted through a plug of silica gel with pentane, and the solvent was removed to yield the crude tetraene 6, as a pale yellow oil. This was dissolved in PhH (20 mL), and 57% aqueous HI (1.8 mL) was added. After stirring for 17 h, aqueous HI (0.8 mL) was added, and after an additional 7 h the dark reaction was diluted with hexane (30 mL), washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), aqueous $Na_2S_2O_3$ (2 × 20 mL), and brine (20 mL), and the organic phase was dried over a mixture of $MgSO_4$, $NaHCO_3$, Celite, and Norit. After filtration through a pad of Celite and solvent removal, the residue was purified by flash chromatography (100% hexane) to yield 3.08 g (41% based on dione **5**) of cyclopentadiene **7**, as a pale yellow liquid: IR (thin film) 2920, 1641, 1442, 989, 910, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (2 H, s), 4.98 (2 H, ddt, J = 15.9, 9.8, 6.6 Hz), 4.82 (2 H, d, J = 15.9 Hz), 4.68 (2 H, d, J = 9.8 Hz), 2.11 (4 H, d, J = 6.6 Hz), 1.67 (6 H, s); HRMS m/e calcd for $C_{13}H_{18}$ (M^+) 174.1404, obsd 174.1389; LRMS m/e 174 (M^+), 162, 151, 131, 105.

1,4-Dimethyl-5,5-bis(3-hydroxypropyl)-1,3-cyclopentadiene (8). Borane/dimethyl sulfide (4.0 mL, 10 M in BH_3) was added by syringe to a 0 °C solution of cyclohexene (8.4 mL, 82.9 mmol) in ether (30 mL), and after several minutes, a thick white precipitate formed. The mixture was vigorously stirred at 0 °C for 2 h, and a solution of tetraene **7** (3.00 g, 17.2 mmol) in ether (15 mL) was added over 15 min via cannula. The reaction was stirred 4.5 h, and ethanol (5 mL) was added slowly by syringe. After the solution was stirred for 1 h, aqueous NaOH (15 mL, 3 M) was added, and, after 5 min, 30% aqueous H_2O_2 (15 mL) was added slowly by syringe. After stirring 1 h at 0 °C, the two-phase mixture was warmed to room temperature and stirred an additional 2.5 h. The reaction was acidified to ca. pH 4 with 10% aqueous HCl, transferred to a separatory funnel with ether and water, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic phase was washed with brine (30 mL), and dried ($MgSO_4$). After filtration and solvent removal, the residue was purified by flash chromatography (55% EtOAc/hexane) to provide 2.38 g (66%) of the diol **8**, as a colorless, viscous oil: IR (thin film) 3329, 2936, 1437, 1057, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (2 H, s), 3.55–3.40 (4 H, m), 1.72, (6 H, s), 1.50–1.44 (4 H, m), 1.11 (2 H, br s), 0.98–0.88 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.14 (s), 126.69 (d), 63.08 (t), 59.46 (s), 31.15 (t), 26.24 (t), 12.80 (t); HRMS m/e calcd for $C_{13}H_{22}O_2$ (M^+) 210.1614, obsd 210.1620; LRMS m/e 210 (M^+), 179, 166, 153, 133, 121, 107.

1,4-Dimethyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-5-(3-hydroxypropyl)-1,3-cyclopentadiene (9a). To a 0 °C solution of diol **8** (2.38 g, 11.3 mmol) and imidazole (1.01 g, 14.8 mmol) in CH_2Cl_2 (100 mL) was added *tert*-butylchlorodimethylsilane (1.88 g, 12.4 mmol). A thick, white precipitate formed within several minutes. The well-stirred suspension was allowed to slowly warm to room temperature. After 12.5 h, the mixture was transferred to a separatory funnel with CH_2Cl_2, washed with saturated aqueous NH_4Cl (2 × 50 mL), water (50 mL), and brine (50 mL), and the organic phase was dried ($MgSO_4$). Filtration and solvent removal gave a viscous oil consisting of a mixture of bis(silyl ether) **9b**, alcohol **9a**, and diol **8**. The oil was applied to a silica gel plug, and elution with 5% EtOAc/hexane, followed by solvent removal gave 1.51 g (30%) of the bis(silyl ether) **9b**. Elution with 15% EtOAc/hexane afforded 1.68 g (46%) of the alcohol **9a**, and elution with ether provided 0.47 g (20%) of the diol **8**. The bis(silyl ether) (1.51 g, 3.45 mmol) was dissolved in

(47) By analogy to ketone **52**, the tricyclic diene G was viewed as a useful target for the stereochemical correlation of hydrocarbons **16**/**17**. Alcohol **9a** was converted to the iodide E and iodine-atom transfer cyclization provided the vinyl iodide F, which was converted to G by reaction with CH_3MgBr/catalytic CuI. Unfortunately, the yield of the atom transfer cyclization was extremely low (<10%) under a variety of conditions. The reasons for the failure of this cyclization are not clear. The difficulty in obtaining any reasonable amount of purified F resulted in the postponement of the stereochemical assignments for **16**/**17**.



THF (30 mL), cooled to 0 °C, and tetra-*n*-butylammonium fluoride (8.2 mL, 1.0 M in THF) was added rapidly dropwise by syringe. The reaction was allowed to slowly warm to room temperature, and after 2.5 h, the mixture was diluted with ether (50 mL), washed with saturated aqueous NH_4Cl (2 × 30 mL), water (30 mL), and brine (30 mL), and the organic phase was dried ($MgSO_4$). After filtration and solvent removal, the residue was applied to a silica gel plug, which was eluted with 30% EtOAc/hexane to remove nonpolar impurities. Elution with ether and solvent removal afforded 720 mg of diol **8**, which was combined with the previously recovered diol (1.68 g total, 8.032 mmol). The diol was resubmitted to the silylation conditions (1.21 g, 8.03 mmol TBSCl; 0.72 g, 10.5 mmol imidazole; 45 mL CH_2Cl_2) to afford, after workup and chromatographic separation, 1.10 g of **9b**, 0.95 g of **9a**, and 0.26 g of **8**. The bis(silyl ether) **9b** was desilylated (6.0 mL TBAF; 20 mL THF) to provide 540 mg of diol **8**. The recovered diol (790 mg total, 3.756 mmol) was resubjected to the silylation reaction (633 mg, 4.20 mmol TBSCl; 339 mg, 4.97 mmol imidazole; 30 mL CH_2Cl_2) to yield 690 mg of the bis(silyl ether) **9b**, 442 mg of alcohol **9a**, and 121 mg of diol **8**. The combined yield of alcohol **9a** was 3.06 g (83%): IR (thin film) 3047, 2930, 1255, 1099, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (2 H, s), 3.51–3.42 (2 H, m), 3.44 (2 H, t, J = 6.2 Hz), 1.71 (6 H, S), 1.49–1.42 (4 H, m), 1.07 (1 H, t, J = 5.4 Hz), 0.98–0.82 (4 H, m), 0.85 (9 H, s), 0.01 (6 H, s); HRMS m/e calcd for $C_{19}H_{36}O_2Si$ (M^+) 324.2482, obsd 324.2482; LRMS m/e 324 (M^+), 267, 225, 192, 153.

Swern Oxidation of Alcohol 9a. DMSO (0.50 mL, 7.04 mmol) was added rapidly via syringe to a −78 °C solution of oxalyl chloride (0.30 mL, 3.43 mmol) in CH_2Cl_2 (25 mL). After 3 min, a solution of alcohol **9a** (875 mg, 2.69 mmol) in CH_2Cl_2 (7 mL) was added dropwise via cannula. After 20 min, Et_3N (1.50 mL, 10.76 mmol) was added rapidly by syringe, and the mixture was stirred an additional 20 min. The cold bath was removed, and the reaction was stirred for 30 min, diluted with ether (60 mL), washed with saturated aqueous NH_4Cl (2 × 30 mL), water (30 mL), and brine (30 mL), and the organic phase was dried ($MgSO_4$). After filtration and solvent evaporation, the residue was purified by flash chromatography (10% EtOAc/hexane) to provide 759 mg (87%) of the aldehyde, as a colorless oil: IR (thin film) 2930, 1728, 1235, 1099, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (1 H, s), 5.94 (2 H, s), 3.44 (2 H, t, J = 6.4 Hz), 1.85–1.79 (1 H, m), 1.75–1.69 (1 H, m), 1.69 (6 H, s), 1.53–1.46 (2 H, m), 0.91–0.78 (4 H, m), 0.85 (9 H, s), 0.01 (6 H, s); HRMS m/e calcd for $C_{19}H_{34}O_2Si$ (M^+) 322.2324, obsd 322.2324; LRMS m/e 322 (M^+), 265, 221, 209, 171, 151.

1,4-Dimethyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-5-(4-methyl-3-pentenyl)-1,3-cyclopentadiene (10). To a well-stirred, 0 °C suspension of isopropyltriphenylphosphonium bromide (545 mg, 1.41 mmol) in $PhCH_3$ (10 mL) was added *n*-BuLi (1.10 mL, 1.2 M in hexane). The red-orange suspension was stirred at 0 °C for 30 min and cooled to −78 °C, and a solution of the above aldehyde (405 mg, 1.25 mmol) in $PhCH_3$ (5 mL) was added dropwise via cannula. The reaction was allowed to warm to 0 °C over 1 h, the cold bath was removed, and the reaction was stirred at room temperature for 1.75 h. The reaction was quenched with glacial acetic acid (0.25 mL), and the solvent was evaporated. The residue was purified by flash chromatography (2% EtOAc/hexane) to afford 335 mg (76%) of the olefin **10**, as a clear, colorless oil: IR (thin film) 2928, 2856, 1255, 1101, 835, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (2 H, s), 5.00 (1 H, t, J = 6.7 Hz), 3.44 (2 H, t, J = 6.3 Hz), 1.72 (6 H, s), 1.62 (3 H, s), 1.48 (3 H, s), 1.45–1.30 (4 H, m), 0.92–0.82 (4 H, m), 0.85 (9 H, s), −0.01 (6 H, s); HRMS m/e calcd for $C_{22}H_{40}OSi$ (M^+), 348.2860, obsd 348.2860; LRMS m/e 348 (M^+), 333, 291, 279, 262, 251, 209, 171.

1,4-Dimethyl-5-(3-hydroxypropyl)-5-(4-methyl-3-pentenyl)-1,3-cyclopentadiene (11). To a 0 °C solution of silyl ether **10** (914 mg, 2.62 mmol) in THF (25 mL) was added tetra-*n*-butylammonium fluoride (3.5 mL, 1.0 M in THF). The ice bath was removed, and the reaction was stirred 17 h. The mixture was diluted with ether (50 mL), washed with saturated aqueous NH_4Cl (2 × 30 mL), water (30 mL), and brine (30 mL), and the organic phase was dried ($MgSO_4$). Filtration and solvent removal gave a residue which was eluted through a silica gel plug with 3% EtOAc/hexane to remove nonpolar impurities. Elution with 50% EtOAc/hexane and solvent evaporation gave 576 mg (94%) of the alcohol **11**, as a colorless oil: IR (thin film) 3314, 2910, 2847, 1437, 1375, 1057, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (2 H, s), 4.99 (1 H, br t, J = 7.2 Hz), 3.50–3.43 (2 H, m), 1.73 (6 H, s), 1.61 (3 H, s), 1.48 (3 H, s), 1.46–1.39 (4 H, m), 1.35–1.32 (2 H, m), 1.06 (1 H, v br s), 0.96–0.84 (2 H, m); HRMS m/e calcd for $C_{16}H_{26}O$ (M^+) 234.1968, obsd 234.1968; LRMS m/e 234 (M^+), 165, 152, 121.

1,4-Dimethyl-5-(3-iodopropyl)-5-(4-methyl-3-pentenyl)-1,3-cyclopentadiene (13). To a 0 °C solution of alcohol **11** (84.3 mg, 0.359 mmol) and Et_3N (200 μL, 1.43 mmol) in ether (4 mL) was added methanesulfonyl chloride (84 μL, 1.08 mmol) by syringe. The reaction, containing white precipitate, was stirred 1.15 h, diluted with ether (20 mL), washed with saturated aqueous NH_4Cl (2 × 15 mL), water (15 mL), and brine (15 mL), and the organics were dried ($MgSO_4$). Filtration and solvent removal gave the crude mesylate **12**, as a cloudy oil. This was dissolved in acetone (4 mL), NaI (246 mg, 1.64 mmol) was added, the flask was covered with foil, and the mixture was stirred at room temperature. After 21 h, the reaction was diluted with ether (20 mL), washed with water (3 × 10 mL), aqueous $Na_2S_2O_3$ (10 mL), and brine (10 mL), and the organics were dried ($MgSO_4$). Filtration and solvent evaporation gave a residue which was purified by flash chromatography (3% EtOAc/hexane) to provide 91.7 mg (74%) of the iodide **13**, as a colorless oil: IR (thin film) 2963, 2916, 2853, 1437, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (2 H, s), 4.99 (1 H, br t, J = 6.9 Hz), 3.05 (2 H, t, J = 6.6 Hz), 1.74 (6 H, s), 1.61 (3 H, s), 1.53–1.48 (2 H, m), 1.48 (3 H, s), 1.45–1.39 (2 H, m), 1.36–1.30 (2 H, m), 1.23–1.16 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.06 (2 C, s), 131.17 (s), 126.82 (2 C, d), 124.72 (d), 59.64 (s), 35.75 (t), 35.19 (t), 27.19 (t), 25.75 (q), 21.51 (t), 17.56 (q), 12.94 (2 C, q), 8.49 (t); HRMS m/e calcd for $C_{16}H_{25}I$ (M^+) 344.1001, obsd 344.1002; LRMS m/e 344 (M^+), 275, 262, 246, 133.

(1*R,4*R**,8*R**)-1,4-Dimethyl-5-(methylethyl)tricyclo[6.3.0.0^{4,8}]undec-2-ene (16/17).** Argon was bubbled for 10 min through a solution of iodide **13** (100 mg, 0.291 mmol), Bu_3SnH (94 μL, 0.349 mmol), and AIBN (1.0 mg, 0.042 mmol) in PhH (14 mL), and the solution was heated to reflux for 1.5 h. After cooling, the reaction was diluted with ether (15 mL), and treated with DBU (100 μL, 0.727 mmol), resulting in formation of a heavy, white precipitate. A solution of I_2 in ether was added dropwise to the stirred mixture until the yellow color of I_2 persisted. The mixture was directly applied to a silica gel plug and eluted with ether. Solvent removal afforded 49.7 mg of crude tricycles **16** and **17** (1:5 by ^1H NMR integration). Flash chromatography (100% hexane) provided 38.7 mg (61%) of **16** and **17**, as a clear, sweet smeeling oil: IR (thin film) 2953, 2866, 1458, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 5.38 (1 H, d, J = 5.7 Hz), 5.28 (1 H, d, J = 5.7 Hz), 1.80 (1 H, br d, J = 17.7 Hz), 1.69 (1 H, dd, J = 12.8, 5.1 Hz), 1.58–1.42 (3 H, m), 1.41–1.15 (7 H, m), 1.08 (3 H, s), 1.05 (3 H, s), 0.98 (3 H, d, J = 6.5 Hz), 0.82 (3 H, d, J = 6.6 Hz); partial ^1H NMR (minor diastereomer) δ 5.51 (1 H, d, J = 5.7 Hz), 5.13 (1 H, d, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 138.59, 134.40, 61.78, 60.39, 60.01, 58.14, 42.61, 37.69, 34.64, 29.85, 29.47, 27.52, 24.75, 24.26, 23.72, 23.35, 22.51; LRMS m/e 218 (M^+), 190, 175, 134. The sample was too volatile for high-resolution MS.

1,4-Dimethyl-5-[3-[[(*o*-bromophenyl)dimethylsilyl]oxy]propyl]-5-(4-methyl-3-pentenyl)-1,3-cyclopentadiene (23). (2-Bromophenyl)chlorodimethylsilane (287 mg, 1.15 mmol) was added to a 0 °C solution of alcohol **11** (230 mg, 0.982 mmol) and imidazole (85.2 mg, 1.25 mmol) in CH_2Cl_2 (15 mL). The reaction was allowed to slowly warm to room temperature, and, after 16.5 h, the mixture was diluted with ether (50 mL), washed with saturated aqueous NH_4Cl, water, and brine (20 mL each), and the organic phase was dried ($MgSO_4$). Filtration and solvent removal gave an oil which was purified by flash chromatography (2% EtOAc/hexane) to yield 309 mg (70%) of the silyl ether **23**, as a cloudy, viscous oil: IR (thin film) 2916, 1577, 1552, 1406, 1249, 1095, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (2 H, t, J = 7.2 Hz), 7.30–7.18 (2 H, m), 5.92 (2 H, s), 5.00 (1 H, br t, J = 8.0 Hz), 3.53 (2 H, t, J = 6.5 Hz), 1.72 (6 H, s), 1.62 (3 H, s), 1.50–1.35 (5 H, m), 1.49 (3 H, s), 1.01–0.90 (3 H, m), 0.43 (6 H, s); HRMS m/e calcd for $C_{24}H_{35}BrOSi$ (M^+) 446.1642, obsd 446.1642; LRMS m/e 446 (M^+), 366, 271, 215, 177, 147, 134.

(1*R,4*R**,8*R**)-1,4-Dimethyl-5-(methylethyl)tricyclo[6.3.0.0^{4,8}]undecan-11-ol (26).** A solution of silyl ether **23** (30.0 mg, 0.067 mmol), Bu_3SnH (22 μL, 0.082 mmol), and AIBN (1.6 mg, 0.009 mmol) in C_6D_6 (1.7 mL) was heated at 85 °C. After 1.5 h, additional portions of Bu_3SnH (12 μL, 0.044 mmol) and AIBN (1 mg, 0.006 mmol) were added, and the mixture was heated for 1 h. After cooling, the reaction was diluted with THF (3 mL), tetra-*n*-butylammonium fluoride (0.4 mL, 1.0 M in THF) was added, and the mixture was stirred at room temperature. After 15 h, the reaction was diluted with ether (15 mL), washed with saturated aqueous NH_4Cl (2 × 10 mL), water (10 mL), and brine (10 mL), and dried ($MgSO_4$). Filtration and solvent removal gave an oil which was purified by flash chromatography (15% EtOAc/hexane) to afford 10.1 mg (64%) of the tricyclic alcohols **26** as a clear, sweet-smelling oil: IR (thin film) 3362, 2957, 2868, 1460, 1047, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, partial) δ 5.76 (0.10 H, d, J = 5.7 Hz), 5.62 (0.47 H, d, J = 5.9 Hz), 5.56 (0.10 H, d, J = 5.6 Hz), 5.43 (0.33 H, d, J = 5.8 Hz), 5.37 (0.47 H, d, J = 5.9 Hz), 5.30 (0.33 H, d, J = 5.8 Hz), 5.20 (0.10 H, d, J = 5.6 Hz), 5.15 (0.10 H, d, J = 5.7 Hz); HRMS m/e calcd for $C_{16}H_{26}O_1$ (M^+) 234.1984, obsd 234.1984; LRMS m/e 234 (M^+), 190, 177, 1512, 137.

The mixture of the tricyclic alcohols **26** (14.0 mg, 0.059 mmol) was dissolved in DMF (2 mL), and pyridinium dichromate (43.9 mg, 0.116

mmol) was added. The solution was stirred at room temperature for 17 h, diluted with ether (20 mL), and then washed with water (3 × 15 mL) and brine (15 mL), and dried ($MgSO_4$). Filtration and solvent removal afforded 11.0 mg (80%) of the tricyclic ketones **28** and **29** in a ratio of 1:4.5, as determined by ^1H NMR integration.

Swern Oxidation of Alcohol 11. Oxidation of alcohol **11** (576 mg, 2.46 mmol) was carried out by using the procedure described above for the oxidation of alcohol **9a**. Purification by flash chromatography (7% EtOAc/hexane) afforded 522 mg (91%) of the aldehyde as a clear, colorless oil: IR (thin film) 2919, 1726, 1437, 1379, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (1 H, t, J = 1.3 Hz), 5.96 (2 H, s), 4.98 (1 H, br t, J = 6.1 Hz), 1.84–1.78 (2 H, m), 1.73–1.68 (2 H, m), 1.71 (6 H, s), 1.61 (3 H, s), 1.50–1.41 (2 H, m), 1.48 (3 H, s), 1.37–1.30 (2 H, m); HRMS m/e calcd for $C_{16}H_{24}O$ (M^+) 232.1827, obsd 232.1828; LRMS m/e 232, 189, 163, 150, 119.

1,4-Dimethyl-5-(2-carboxyethyl)-5-(4-methyl-3-pentenyl)-1,3-cyclopentadiene (30). To a solution of the above aldehyde (522 mg, 2.24 mmol) in CH_2Cl_2 (10 mL) was added water (10 mL), silver oxide (614 mg, 2.65 mmol), and sodium hydroxide (378 mg, 9.45 mmol). The two-phase mixture was stirred at room temperature for 47 h (metallic silver plated out), and acidified to ca. pH 4 with concentrated HCl. Solids were removed by filtration through a pad of Celite, and the filtrate was transferred to a separatory funnel with CH_2Cl_2 and water. The layers were separated, the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phase was dried ($MgSO_4$). Filtration and solvent removal afforded 560 mg (100%) of the acid **30**, as a viscous oil: IR (thin film) 3051, 2918, 1716, 1456, 1302, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (2 H, s), 4.98 (1 H, br t, J = 5.4 Hz), 1.77–1.65 (4 H, m), 1.72 (6 H, s), 1.61 (3 H, s), 1.48 (3 H, s), 1.48–1.41 (2 H, m), 1.37–1.27 (2 H, m); hydroxy proton not observed; HRMS m/e calcd for $C_{16}H_{24}O_2$ (M^+) 248.1776, obsd 248.1777; LRMS m/e 248 (M^+), 232, 205, 179, 166, 119.

1,4-Dimethyl-5-(4-methyl-3-pentenyl)-5-[2-(methoxycarbonyl)ethyl]-1,3-cyclopentadiene (31). An ethereal solution of diazomethane was added dropwise to a well-stirred, 0 °C solution of carboxylic acid **30** (257 mg, 1.03 mmol) in ether (15 mL) until the yellow color of CH_2N_2 persisted. Glacial acetic acid (0.50 mL) was added, and after 5 min, the solvent was evaporated. The residue was purified by flash chromatography (5% EtOAc/hexane) to yield 196 mg (72%) of the methyl ester **31**: IR (thin film) 2918, 1737, 1433, 1163, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (2 H, s), 4.98 (1 H, br t, J = 7.1 Hz), 3.58 (2 H, s), 1.75–1.60 (4 H, m), 1.72 (6 H, s), 1.61 (3 H, s), 1.50–1.41 (2 H, m), 1.48 (3 H, s), 1.37–1.31 (2 H, m); HRMS m/e calcd for $C_{17}H_{26}O_2$ (M^+) 262.1933, obsd 262.1933; LRMS m/e 262 (M^+), 193, 180, 119.

Dimethylaluminum Methaneselenolate.[34] Selenium powder (2.00 g, 25.3 mmol) was placed in a dry, N_2-purged flask fitted with a magnetic stir bar and condenser. Trimethylaluminum (12.2 mL, 2 M in $PhCH_3$) was added by syringe, and the mixture was heated at reflux for 2 h. The initial gray-black suspension turned to a yellow solution containing some gray precipitate after about 30 min. The mixture was cooled to room temperature, the condenser was replaced with a septum, and the contents were allowed to settle. The clear, yellow solution (ca. 2 M in $(CH_3)_2Al(SeCH_3)$) was stored at room temperature in the dark.

1,4-Dimethyl-5-[4-methyl-3-pentenyl]-5-[3-(methylseleno)-3-oxopropyl]-1,3-cyclopentadiene (32). Nitrogen was bubbled for 25 min through a stirred solution of methyl ester **31** (245 mg, 0.934 mmol) in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C, and an aliquot of $(CH_3)_2Al(SeCH_3)$ solution (0.6 mL, ca. 2 M in $PhCH_3$) was added by syringe. After 30 min, the cold bath was removed, and after an additional 30 min the reaction was quenched with moist $Na_2S_2O_3$. After the gas evolution ceased, the mixture was diluted with ether (30 mL) and washed with water (2 × 15 mL) and brine (15 mL), and the organic layer was dried ($MgSO_4$). Filtration and solvent removal gave a residue which was purified by flash chromatography (3% EtOAc/hexane) to afford 264 mg (87%) of the methyl selenol ester **32** as a clear, colorless oil: IR (thin film) 29818, 1707, 1558, 1437, 1377, 1005, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (2 H, s), 4.98 (1 H, br t, J = 5.2 Hz), 2.14 (3 H, s), 1.99–1.94 (2 H, m), 1.77–1.70 (2 H, m), 1.72 (6 H, s), 1.61 (3 H, s), 1.50–1.40 (2 H, m), 1.48 (3 H, s), 1.36–1.30 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.24, 146.40 (2 C), 131.28, 127.48 (2 C), 124.55, 59.32, 42.07, 34.84, 29.53, 25.72, 21.65, 17.55, 12.79 (2 C), 4.94; HRMS m/e calcd for $C_{17}H_{26}O_1Se_1$ (M^+) 326.1149, obsd 326.1149; LRMS m/e 326 (M^+), 244, 231, 163, 149, 133, 119.

(1*R,4*R**,8*R**)-1,4-Dimethyl-5-(methylethyl)tricyclo[6.3.0.0^{4,8}]undec-2-en-11-one (28/29).** A solution of methyl selenol ester **32** (47.3 mg, 0.145 mmol), Bu_3SnH (90 μL, 0.334 mmol), and AIBN (3.4 mg, 0.021 mmol) in PhH (8 mL) was heated at 85 °C for 5 h, and then Bu_3SnH (40 μL, 0.148 mmol) and AIBN (1.5 mg, 0.009 mmol) were added. After heating at 85 °C for an additional 3.5 h, the mixture was cooled, the solvent was removed, and the residue was purified by flash chromatography (4% EtOAc/hexane) to provide 20.4 mg (62%) of an oil consisting of tricycles **28** and **29** and bicycle **35**, in a ratio of 5.5:1:2.2, as determined by ^1H NMR integration. The mixture of cyclized products was dissolved in CH_2Cl_2 (3 mL), cooled to 0 °C, and a solution of *m*-chloroperbenzoic acid (82% peracid, 9.9 mg, 0.047 mmol) in CH_2Cl_2 (2 mL) was added via cannula. After 3.75 h, the mixture was diluted with ether (20 mL), and washed with aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine (15 mL each). The organic phase was dried ($MgSO_4$), and filtration and solvent evaporation gave a residue which was purified by flash chromatography (10% EtOAc/hexane) to afford 11.4 mg of **28** and **29**, in a ratio 1:7.5, as determined by ^1H NMR integration: IR (thin film) 2959, 2868, 1738, 1487, 1084, 796 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 5.54 (1 H, d, J = 5.6 Hz), 5.30 (1 H, d, J = 5.6 Hz), 2.40 (1 H, dd, J = 14.6, 8.8 Hz), 2.35 (1 H, dd, J = 14.6, 8.7 Hz), 2.10–2.04 (2 H, m), 1.79 (1 H, dd, J = 13.2, 5.3), 1.61–1.47 (3 H, m), 1.29 (1 H, ddd, J = 13.6, 13.6, 5.6), 1.25–1.20 (1 H, m), 1.21 (3 H, s), 1.07 (3 H, s), 0.99 (3 H, d, J = 6.6 Hz), 0.82 (3 H, d, J = 6.6 Hz); partial ^1H NMR (minor diastereomer) δ 5.64 (1 H, d, J = 5.5 Hz), 5.54 (1 H, d, J = 5.5 Hz), 1.10 (3 H, s), 0.91 (3 H, d, J = 6.4 Hz), 0.85 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 221.43, 138.10, 133.28, 65.21, 61.34, 60.42, 59.71, 36.58, 36.00, 29.22, 29.01, 28.94, 23.63, 23.05, 22.42, 16.29; HRMS m/e calcd for $C_{16}H_{24}O_1$ (M^+) 232.1827, obsd 232.1828; LRMS m/e 232 (M^+), 204, 190, 176, 149, 133, 122, 107.

***Se*-Methyl 6-Phenyl-5-hexenselenoate (42).** Conversion of 6-phenyl-5-hexenoate (**41**)[40] (270 mg, 1.32 mmol) to the selenide **42** followed the procedure described above for the preparation of selenide **32**. Purification of the crude selenide by flash chromatography (5% EtOAc/hexane) afforded 286 mg (81%) of the methylselenol ester **42** (3:1 *E*:*Z* mixture) as a colorless oil: IR (thin film, *E*:*Z* mixture) 3024, 2932, 1711, 1496, 1443, 966, 767, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *E*:*Z* mixture) δ 7.30–7.18 (5 H, m), 6.44 (0.25 H, d, J = 11.3 Hz), 6.38 (0.75 H, d, J = 16.1 Hz), 6.14 (0.75 H, dt, J = 16.1, 6.8 Hz), 5.59 (0.25 H, dt, J = 11.3, 6.8 Hz), 2.79–2.54 (2 H, m), 2.36 (0.50 H, dt, J = 7.1, 7.1 Hz), 2.28–2.15 (3 H, s), 1.89–1.80 (2 H, m); HRMS m/e calcd for $C_{13}H_{16}OSe$ ($M - SeCH_3$) 173.0966, obsd 173.0996; LRMS m/e 173 ($M - SeCH_3$), 145, 129, 117.

2-(Phenylmethyl)cyclopentanone (43). A solution of methyl selenol ester **42** (84.6 mg, 0.316 mmol), Bu_3SnH (190 μL, 0.706 mmol), and AIBN (7.5 mg, 0.045 mmol) in PhH (8 mL) was heated at reflux for 1.5 h. After cooling, the solvent was evaporated, and the residue was purified by flash chromatography (10% EtOAc/hexane) to provide 49.5 mg (90%) of a mixture of cyclopentanone **43** and 6-phenyl-5-hexenal (≥18:1 by ^1H NMR integration). **43**: IR (thin film) 2961, 1737, 1160, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.13 (5 H, m), 3.13 (1 H, dd, J = 13.7, 3.9 Hz), 2.51 (1 H, dd, J = 13.7, 9.4 Hz), 2.37–2.27 (2 H, m), 2.15–2.02 (2 H, m), 1.99–1.89 (1 H, m), 1.75–1.67 (1 H, m), 1.59–1.46 (1 H, m); HRMS m/e calcd for $C_{12}H_{14}O$ (M^+) 174.1045, obsd 174.1044; LRMS m/e 174 (M^+), 156, 146, 130, 117.

***Se*-Methyl Citronellselenoate (45).** Conversion of methyl citronellate (210 mg, 1.23 mmol) to the selenide **45** followed the procedure described above for the preparation of selenide **32**. Purification of the crude selenide by flash chromatography (1% EtOAc/hexane) afforded 292 mg (95%) of the methyl selenol ester **45** as a clear, colorless oil. Use of a 3-week-old solution of dimethylaluminum methaneselenolate resulted in a 77% yield of **45**: IR (thin film) 2964, 2930, 1705, 1450, 1377, 995, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (1 H, br t, J = 6.9 Hz), 2.60 (1 H, dd, J = 14.7, 5.8 Hz), 2.42 (1 H, dd, J = 14.7, 8.2 Hz), 2.19 (3 H, s), 2.07–1.89 (3 H, m), 1.66 (3 H, s), 1.58 (3 H, s), 1.41–1.29 (1 H, m), 1.26–1.16 (1 H, m), 0.93 (3 H, d, J = 6.6 Hz); HRMS m/e calcd for $C_{10}H_{17}O$ ($M - SeCH_3$) 153.1279, obsd 153.1279; LRMS m/e 153 (M^+), 109.

Menthone (46a) and Isomenthone (46b). A solution of *Se*-methyl citronellselenoate (**45**) (84.8 mg, 0.343 mmol), Bu_3SnH (205 μL, 0.762 mmol), and AIBN (11.2 mg, 0.068 mmol) in PhH (17 mL) was heated at reflux for 2.5 h. After cooling, the solvent was evaporated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to afford 45.8 mg (87%) of a mixture of menthone (**46a**) and isomenthone (**46b**), 2.2:1 by GC analysis.

***Se*-Methyl Selenohydrocinnamate (36).** Conversion of methyl hydrocinnamate (272 mg, 1.65 mmol) to the selenide **36** followed the procedure described for the preparation of selenide **32**. Purification of the crude selenide by flash chromatography (5% EtOAc/hexane) afforded 327 mg (100%) of the methyl selenol ester **36** as a clear, colorless oil. Use of a 3-week-old solution of dimethylaluminum methaneselenolate resulted in a 65% yield of **36**: IR (thin film) 3076, 2951, 1703, 1503, 1462, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.29 (2 H, m), 7.26–7.21 (3 H, m), 3.04–2.95 (4 H, m), 2.26 (3 H, s); HRMS m/e calcd for $C_{10}H_{12}OSe$ (M^+) 228.0053, obsd 228.0053; LRMS m/e 228 (M^+), 133, 105.

Dihydrocinnamaldehyde (40). A solution of methyl selenoester **36**

(69.7 mg, 0.307 mmol), Bu_3SnH (182 μL, 0.676 mmol), and AIBN (10.0 mg, 0.061 mmol) in PhH (10 mL) was heated at reflux for 54 min. After cooling, the solvent was evaporated and the residue was purified by flash chromatography (5% EtOAc/hexane) to provide 35.0 mg (85%) of dihydrocinnamaldehyde (**40**), identical with an authentic sample (Aldrich) by ^1H NMR and GC comparison.

Methyl 4-Oxo-6-phenylhexanoate (47). A solution of Bu_3SnH (520 μL, 0.1.93 mmol) in PhH (4 mL) was added via syringe pump over 2.5 h to a refluxing solution of methyl selenide **36** (86.3 mg, 0.380 mmol), methyl acrylate (240 μL, 2.66 mmol), and AIBN (13.0 mg, 0.08 mmol) in PhH (6 mL). After the addition was complete, the reaction was heated an additional 45 min and cooled to room temperature. After solvent removal, the residue was applied to a silica gel plug and the nonpolar tin-containing products eluted with 10% EtOAc/hexane. Subsequent elution with ether gave the crude keto ester **47**, which was purified by flash chromatography (20% EtOAc/hexane) to provide 81.5 mg (97%) of pure **47**: IR (thin film) 2953, 1738, 1718, 1437, 1365, 1207, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.24 (2 H, m), 7.18–7.14 (3 H, m), 3.65 (3 H, s), 2.88 (2 H, t, J = 7.7 Hz), 2.76 (2 H, t, J = 7.7 Hz), 2.69 (2 H, J = 6.3 Hz), 2.56 (2 H, t, J = 6.3 Hz); HRMS m/e calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, obsd 220.1100; LRMS m/e 220 (M^+), 188, 160, 146, 133.

(1*R,4*R**,8*R**)-1,4-Dimethyl-5-isopropylidenetricyclo[6.3.0.0^{4,8}]undec-2-en-11-one (52).** To a solution of carboxylic acid **30** (17.1 mg, 0.069 mmol) in $CDCl_3$ (1.5 mL, distilled under N_2 from P_2O_5) was added oxalyl chloride (6.6 μL, 0.075 mmol). The solution was allowed to stand at room temperature for 23 h (^1H NMR analysis indicated the starting material was completely consumed). The solvent was removed, and the residue was purified by flash chromatography (8% EtOAc/hexane) to afford 6.9 mg (44%) of the tricyclic diene **52**: IR (thin film) 2972, 2872, 1729, 1451, 1051, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (1 H, d, J = 5.6 Hz), 5.30 (1 H, d, J = 5.6 Hz), 2.37 (1 H, ddd, J = 17.5, 13.8, 8.7), 2.16–2.04 (2 H, m), 1.97–1.85 (2 H, m), 1.81–1.31 (2 H, m), 1.65 (3 H, s), 1.64 (3 H, s), 1.36 (3 H, s), 1.12 (3 H, s); HRMS m/e calcd for $C_{16}H_{22}O_1$ (M^+) 230.1671, obsd 230.1671; LRMS m/e 230 (M^+), 162, 148, 133, 120, 106.

(1*R,4*R**,5*S**,8*R**)-1,4-Dimethyl-5-(methylethyl)tricyclo[6.3.0.0^{4,8}]undecan-11-one (55).** To a solution of ketone **52** (17.0 mg, 0.074 mmol) in EtOAc (2 mL) was added 10% Pd/C (6 mg). The suspension was then shaken at 25 °C under 3.5 atm H_2 for 24 h. The reaction mixture was filtered through a pad of Celite, the solvent was evaporated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to yield 9.6 mg (56%) of ketone **55** as a clear, sweet-smelling oil: IR (thin film) 2957, 2867, 1737, 1465, 1367, 1253, 1113, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (1 H, dd, J = 18.8, 10.2 Hz), 2.12–1.99 (2 H, m), 1.92–1.87 (2 H, m), 1.76 (1 H, dd, J = 13.1, 5.8 Hz), 1.71–1.59 (2 H, m), 1.53–1.48 (1 H, m), 1.37 (1 H, ddd, J = 13.1, 13.1, 6.3 Hz), 1.29–1.21 (3 H, m), 1.07 (3 H, s), 1.01–0.90 (1 H, m), 0.96 (3 H, d, J = 8.4 Hz), 0.95 (3 H, s), 0.87 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 227.40, 68.28, 62.76, 59.82, 59.26, 38.90, 38.19, 35.32, 35.19, 31.31, 29.15, 28.18, 27.93, 23.44, 22.78, 17.64; HRMS m/e calcd for $C_{16}H_{26}O_1$ (M^+) 234.1984, obsvd 234.1984; LRMS m/e 234 (M^+), 191, 177, 163, 149, 109.

Hydrogenation of Ketones 28/29. The above mixture of ketones **28/29** (11.0 mg, 0.047 mmol, ratio of 1:4.5) was dissolved in MeOH (2 mL) and rhodium on alumina (8.9 mg, 5% Rh content) was added. The suspension was stirred at 25 °C under a balloon of H_2 for 24 h, and then the reaction mixture was filtered through a pad of Celite. Solvent evaporation afforded 10.4 mg (94%) of the ketones **55/56**. The diastereomer ratio was not easily determined by ^1H NMR integration due to overlap of signals, nor could the ratio be determined by GC as both ketones overlapped as a single, sharp peak. The major product was clearly identical with ketone **55** by comparison of the ^1H and ^{13}C NMR data. Additionally, the IR and MS data for the mixture of **28/29** was essentially identical with that for ketone **55**.

Acknowledgment. We thank the National Institutes of Health (Grant No. GM 33378 and Career Development Award to D. P.C.), ICI Pharmaceuticals, the Dreyfus Foundation, and the American Chemical Society (through a Cope Scholar award to D.P.C.) for funding of this work. We also thank Dr. Richard Soll (Wyeth-Ayerst) for carrying out the hydrogenation of **52**.

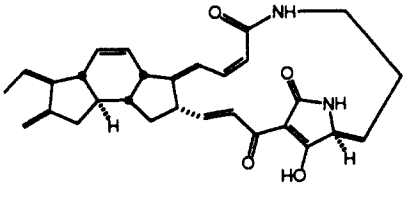
Total Synthesis of (+)-Ikarugamycin. 1. Stereocontrolled Construction of the Decahydro-*as*-indacene Subunit

Leo A. Paquette,* Jeffrey L. Romine, Ho-Shen Lin, and Jonathan Wright

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received April 27, 1990*

Abstract: A concise synthesis of the carbotricyclic decahydro-*as*-indacene portion of ikarugamycin is described. Anionic oxy-Cope rearrangement of alcohol **15** leads directly to **18** under the proper workup conditions. Ensuing ketone reduction, ketal hydrolysis, and K_2CO_3-promoted double bond isomerization provides **20**. Dissolving metal reduction of this intermediate generates the pivotal hydroxy ketone **12**. The six contiguous stereocenters in **12** are shown to be capable of substantive purposeful variation. The stereochemical assignments rest on ^1H NMR data and X-ray crystallographic analysis of the *p*-nitrobenzoate of **25**.

Ikarugamycin (**1**), an architecturally unusual macrocyclic antibiotic first isolated in 1972 from a sample of Japanese soil,[1] has also been produced in the culture broths of *Streptomyces phaeochromogenes* var. *ikaruganensis* Sakai. Interest in this substance arose quickly because of its powerful and specific antiprotozoal and antiamoebic activity against such strains as *Tetrahymena pyriformis W*, *Entamoeba histolytica*, and *Trichomonas vaginalis*. In addition, **1** is bacteriocidal against select gram-positive organisms. Unfortunately, however, ikarugamycin is not active against yeast or fungi, is quite toxic to mice (the lethal dose is 6 mg/kg), and causes hemolysis at low concentrations (3.5 mcg/mL) in rabbit blood.



1

Nonetheless, **1** merits serious consideration as a synthetic target because of its unusual bioactivity spectrum and its infrequently encountered combination of structural features. The uncommon *trans,anti,cis*-decahydro-*as*-indacene subunit is endowed with *eight* consecutive stereogenic centers. The macrocyclic lactam to which this building block is fused contains the ninth asymmetric carbon.

(1) Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271.

0002-7863/90/1512-9284$02.50/0