retical), identical in all respects with the natural material.

Epoxidation of Epoxide 12. A solution of *m*-chloroperbenzoic acid (8 mg, 0.044 mmol) in dry benzene (0.5 mL) was added dropwise to a stirred solution of the epoxide **11** (10 mg, 0.031 mmol) in dry benzene (1.5 mL) at 25 °C. After 5 min, the reaction mixture was diluted with ether (20 mL) and the solution washed with saturated sodium bicarbonate solutions (3 × 5 mL) and water (3 × 5 mL). The extract was dried over magnesium sulfate and the solvent removed to obtain a residue (9.5 mg) that was purified by chromatography on silica gel to obtain the bisepoxide **18** (8 mg, 76% theoretical): oil; IR 3550 (br), 2975, 1710 cm^{-1}; Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.5. Found: C, 71.0; H, 9.87.

Epoxidation of Ketone 5. A solution of *m*-chloroperbenzoic acid (15 mg) in dry benzene (2 mL) was added dropwise to a solution of ketone **5** (20 mg) in dry benzene and the reaction mixture treated as above. The crude product was separated by preparative TLC to obtain a 3,4-epoxide (16 mg) as the major product and the diepoxide **18**, identical in all respects with the material obtained from epoxide **11**.

Oxidation of Aldehyde 13. Silver oxide (60 mg) and sodium cyanide (3 mg) were added to a stirred solution of the aldehyde **13** (8 mg, 0.23 mmol) in methanol (4 mL) at 25 °C. After 3 h, the reaction mixture was filtered, and the product was purified by preparative TLC to obtain the acid **14** (2 mg, 24% theoretical), mp 152–153 °C, identical in all respects with the natural material.

Conversion of Acetate 15 into Ketone 5. A suspension of lithium aluminum hydride (10 mg) in dry ether was added dropwise to a stirred solution of acetate **15** (10 mg) in dry ether (2 mL). After 4 h the reaction was cautiously quenched with water followed by 2 N hydrochloric acid (10 mL). The reaction mixture was extracted with ether (5 × 10 mL), and the combined extracts were washed with water (15 mL) and dried over magnesium sulfate and the ether evaporated to obtain the diol **19** (7 mg) as a colorless oil: IR 3550 (br), 2950, 1150, 1030 cm^{-1}.

Active manganese dioxide (100 mg) was added to a stirred solution of the diol **19** (5 mg) in petroleum ether. After 3 h, the reagent was removed by filtration and the solvent evaporated, giving a residue that was purified by preparative TLC to obtain the ketone **5** (3 mg), mp 93–95 °C, identical in all respects with authentic material.

Epoxidation of Epoxy Acetate 16. A solution of *m*-chloroperbenzoic acid (13 mg) in dry benzene (2 mL) was added to a stirred solution of the epoxy acetate **16** (10 mg, 0.027 mmol) in dry benzene (2 mL) at 25 °C. After 5 min the reaction mixture was worked up as described earlier to obtain the diepoxide **20** (8 mg): mp 130 °C; IR 3500 (br), 2975 (br), 1710–1690 cm^{-1}; Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.02; H, 9.92.

Epoxidation of Acetate 15. A solution of the acetate **15** (5 mg) in dry benzene (1 mL) was treated with *m*-chlorperbenzoic acid (10 mg) as described above to obtain the diepoxide **20** (4 mg), mp 130 °C, identical in all respects with the sample prepared from epoxy acetate **16**.

Acknowledgment. We thank Prof. M. Umamheswara Rao, Department of Botany, Andhra University, for identifying the algae and scientists from the Central Marine Fisheries Research Institute of Mandapam Camp for assistance with collections. This research was generously funded by the Council of Scientific and Industrial Research, New Delhi (to C.B.R.), and the California Sea Grant College Program (NA80AA-D-00120) (to D.J.F.). K.F.A thanks the National Institutes of Health for a postdoctoral fellowship (F32-CAO-7458-02). H.C.-h. and J.C. thank the New York State Sea Grant (NSF INT14133 and NIH CA24487) for financial support.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, and interatomic angles for (1*S**,2*E*,4*R**,7*Z*,11*S**,12*S**)-4,12-dihydroxydolabella-2,7-dien-9-one (**2**) and for (1*R**,3*E*,7*E*,9*S**,11*S**)-9-acetoxydolabella-3,7-12-trien-16-al (**13**) (8 pages). Ordering information is given on any current masthead page.

Total Syntheses of Hirsutic Acid C and Complicatic Acid†

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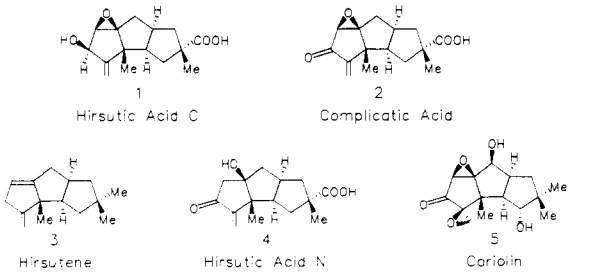
The linearly fused tricyclopentanoids hirsutic acid C (**1**) and complicatic acid (**2**) were synthesized from the methanoindene **12** in a highly stereoselective manner.

Hirsutic acid C (**1**) and an uncharacterized compound called hirsutic acid N were isolated in 1947 from fungal cultures that were thought to be the Basidiomycetes, *Stereum hirsutum*.[4] Later attempts to reisolate hirsutic acid C (**1**) from this culture were unsuccessful. Subsequently, Mellows and Mantle[5] isolated hirsutic acid C (**1**) and a related sesquiterpene, complicatic acid (**2**), from cultures of a related Basidiomycetes, *Stereum complicatum*. These authors have postulated that complicatic acid (**2**) is the same compound as hirsutic acid N.

The structure of hirsutic acid C (**1**) was originally based on spectroscopic and chemical evidence.[6] This was confirmed, and the absolute stereochemistry of **1** was determined by X-ray crystallography of the *p*-bromophenacyl derivative.[7]

Although hirsutic acid C (**1**) shows no biological activity, hirsutic acid N (aka complicatic acid (**2**) ?)[8] showed activity against *Staph. aureus* and *Str. pyogenes*.[4,5]



A large number of publications dealing with methods relating to and the total synthesis of linearly fused cyclo-

† Dedicated to Professor Samuel Danishefsky on the occasion of his election to the National Academy of Sciences.

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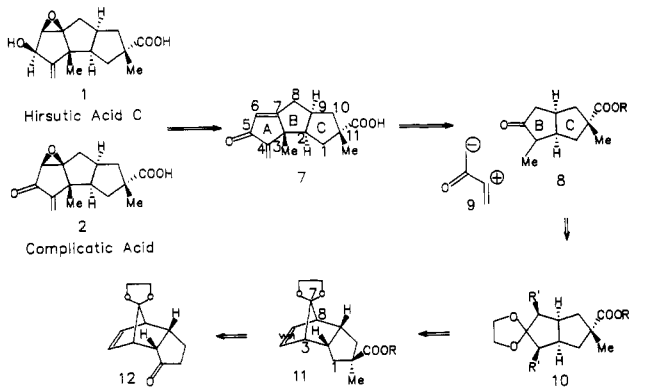
(2) Present address: Union Carbide Agricultural Products, Research Laboratories, P.O. Box 12014, Research Triangle Park, NC 27709. This paper was taken in part from the Ph.D. Thesis of Jennifer L. Phillips; University of Maryland, 1985.

(3) Undergraduate research participant. Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

(4) Heatley, N. G.; Jennings, M. A.; Florey, H. W. *Br. J. Exp. Path.* **1947**, *28*, 35.

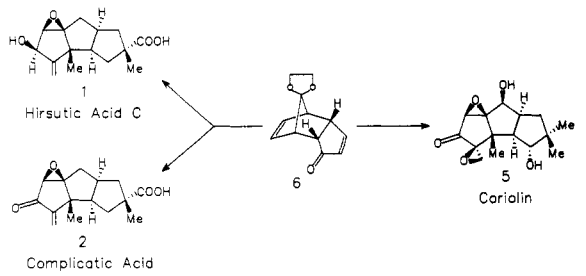
0022-3263/86/1951-2742$01.50/0

Scheme I

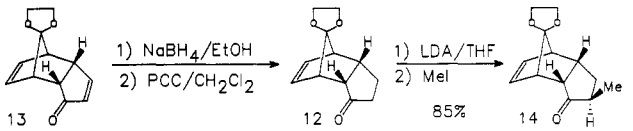


pentanoids (hirsutanes) have appeared in recent years. Targets that have yielded to these efforts include hirsutene (**3**),[9] hirsutic acid C (**1**),[10] isohirsutic acid (**4**),[11] and coriolin (**5**).[12] Several excellent reviews of cyclopentannulation methods have also been published.[13]

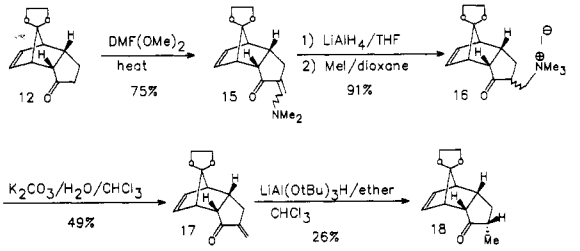
A significant part of our research effort in the past several years has dealt with the conversion of functionalized dicyclopentadiene derivatives, such as **6**, into molecules that contain more than one fused cyclopentane



Scheme II



Scheme III



ring.[14] By using this methodology, we were able to synthesize the highly functionalized and compact hirsutane sesquiterpene coriolin (**5**).[15]

Our attention was also focused on hirsutic acid C (**1**) and complicatic acid (**2**). From examination of the known syntheses of **1**,[10] it was noted that a recurring problem in all but the Trost synthesis[10b] was the lack of stereochemical control at the C11 center. This leads to mixtures early in the sequences that must be separated. The general method developed in these laboratories for the synthesis of coriolin (**5**)[14,15] presents a solution to this problem. Herein we report the total synthesis of hirsutic acid C (**1**) and complicatic acid (**2**).

Our retrosynthetic analysis of the problem is shown in Scheme I. Hirsutic acid C (**1**) and complicatic acid (**2**) could both be synthesized from the "Matsumoto dienone" **7**.[10a] This intermediate has been converted to hirsutic acid C (**1**) by several groups[10a,b,d-f] and is the immediate goal of our synthesis. This would in turn be prepared by annulation of a bicyclic ketone **8** with a charged methyl vinyl ketone synthon **9**. The BC-ring system (**8**) already has three of the seven chiral centers in place. Further, it has been demonstrated[10,11] that the control of these three centers (2, 9, and 11) effectively controls the introduction of the remaining four. Ketone **8** would be synthesized in several steps from ketal **10** (R′ = COOH), which would come from the tricyclic system **11** by oxidative cleavage of the norbornenyl olefin. It is this key intermediate, with the centers at C2, 9, and 11 set, that is prepared from the starting tricyclic ketone **12** in the first stage of our synthesis. Direct comparison of ketone **12** with hirsutic acid C (**1**) shows several advantages to using this as the starting material: (1) 9 of the 15 carbons necessary for a synthesis of **1** and **2** are present, (2) the relative stereochemistry at C2, 3, and 9 is correct, (3) stereochemical control of the crucial C11 geometry is afforded by the rigid tricyclic ring structure and, (4) the masked ketone at C7 will allow for the easy introduction of the A ring at a later time.

The starting ketone **12** was prepared as previously described[14] from the α,β-unsaturated ketone **13**.[14,16] The first stage of the synthesis is concerned with the stereoselective formation of the C11 quaternary center and the C1 de-

(5) Mellows, G.; Mantle, P. G.; Feline, T. C.; Williams, D. J. *Phytochemistry* **1973**, *12*, 2717.

(6) (a) Comer, F. W.; McCapra, F.; Queshri, I. H.; Trotter, J.; Scott, A. J. *Tetrahedron* **1967**, *23*, 4761. (b) Comer, F. W.; McCapra, F.; Queshri, I. H.; Trotter, J.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1965**, 310.

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(8) The structure of hirsutic acid N has never been unambiguously established. Mellows (ref 5) postulates that hirsutic acid N is complicatic acid (**2**) on the basis of in vivo conversion of hirsutic acid C (**1**) to complicatic acid (**2**) and similar reported biological activities. Lansbury states (ref 11b) that isohirsutic acid (**4**) is hirsutic acid N on the basis of partial correspondence of the reported spectroscopic data.

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(12) Hijfte, L. V.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940 and ref 4 and 10 cited therein.

(13) (a) Paquette, L. A. *Aldrichimica Acta* **1984**, *17*, 43. (b) Ramaiah, M. *Synthesis* **1984**, 529. (c) Paquette, L. A. *Top. Curr. Chem.* **1983**, *119*, 1. (d) Paquette, L. A. *Ibid.* **1979**, *79*, 41. (e) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141; (f) *Tetrahedron* **1981**, 4359–4558.

(14) Schuda, P. F.; Ammon, H. L.; Heimann, M. R.; Bhattacharjee, S. *J. Org. Chem.* **1982**, *47*, 3434.

(15) (a) Schuda, P. F.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 4267. (b) Schuda, P. F.; Heimann, M. R. *Tetrahedron* **1984**, *40*, 2365 (see also reprinted paper in Volume #40, issue #21, page 4159 as one page (page 2371) was not printed in the original article).

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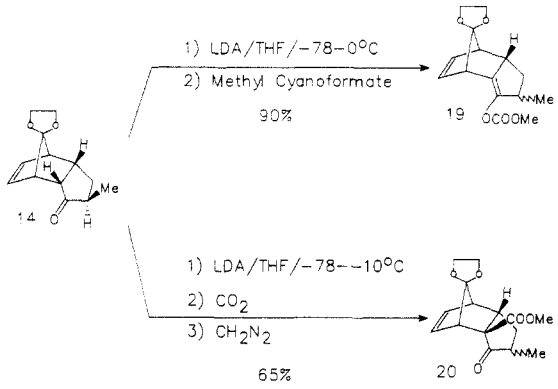
Scheme IV



oxygenation. Alkylation of the C11 enolate should occur from the β-face of the molecule. This dictates that the methyl group at C11 should be introduced first, followed by a carboxyl derived functionality, to give the proper relative stereochemistry in the C ring. Treatment of ketone **12** (Scheme II) with lithium diisopropylamide (LDA; 0.9 equiv) followed by the addition of methyl iodide gave the *exo*-methyl ketone **14** (85%). None of the endo isomer was isolated; however, this compound was prepared by another sequence (Scheme III). Ketone **12** was treated with dimethylformamide dimethyl acetal[17] to afford the enaminone **15** in 75% yield. Reduction with $LiAlH_4$ (1,4 only) followed immediately by quaternization with methyl iodide gave the methiodide **16** in 91% yield (two steps). Elimination to the very unstable enone **17** could be effected with either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/benzene or $K_2CO_3/H_2O/CHCl_3$ (49%). Finally, 1,4-reduction of **17** with $LiAl(O\text{-}t\text{-}Bu)_3H$ gave a 26% yield of the *endo*-methyl compound **18** as the only product.

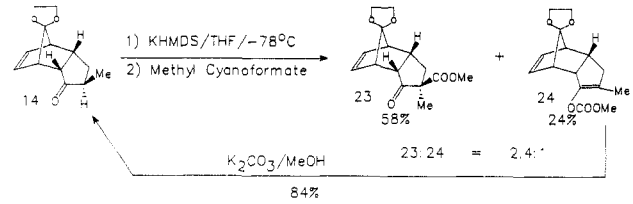
The *exo*- (**14**) and *endo*-methyl (**18**) ketones are clearly different physically and spectroscopically. The exo isomer **14** is an oil while the isomer **18** is a white crystalline solid. Comparison of the 200-MHz NMR spectra of these compounds shows that the C11 methyl signal for the endo isomer **18** occurs at δ 0.78 (d, 3 H, J = 4.1 Hz) while the corresponding signal in the exo isomer **14** is at δ 0.84 (d, 3 H, J = 4.0 Hz). Furthermore, decoupling experiments showed that the C11 methine proton of the endo isomer **18** is part of a complex multiplet at δ 2.25, while the same methine signal in the exo isomer **14** is part of a multiplet at δ 1.76. Examination of models of these compounds shows that these are the expected results. The C11 methyl protons of the endo isomer **18** lie in the shielding cone of the norborneny double bond and thus are shifted slightly upfield in relation to the signal for **14**. Likewise, the C11 methine of the exo isomer **14** lies in the same shielding area and is shifted slightly upfield relative to the C11 methine signal in the endo isomer **18**. These observations support the stereochemical assignments.

The introduction of the C11 carboxyl functionality would seem to be straightforward at this point. This process, however, led to an interesting series of unexpected results. One particularly efficacious way of introducing a carbomethoxy substituent is to use methyl cyanoformate ("Mander's reagent").[18] Treatment of **14** (Scheme IV) with LDA and methyl cyanoformate (MCF) gave a 90% yield of a product that contained a carbomethoxy group by NMR but also had a C11 methyl doublet. An alternative procedure was attempted by using CO_2 to trap the enolate followed by esterification (CH_2N_2). This afforded a product (65%) that also contained both a carbomethoxy group and a C11 methyl doublet. These products were also different from one another. Clearly, the enolate that is reacting in both cases is the C2 enolate as both products have a C11 methyl doublet. The two possible products for the reaction of the C2 enolate are **19** and **20**. Although the possibility for an initial C11 acylation followed by a rearrangement[19] to give the C2 carbomethoxylated product (**20**) exists for the MCF reaction, no such pathway is present for the CO_2 carboxylation. Careful NMR analysis of the products showed that the product of the MCF reaction was in fact the enol carbonate toward C2 (**19**) and that of the CO_2 reaction was the C2 carbomethoxylated product. Both results indicated that the undesired enolate was forming under the reaction conditions.

Table I

ENTRY	STARTING MATERIAL	CONDITIONS	PRODUCT(S)
1.	14	1) LDA/THF/−78–0°C 2) Et_3N/Me_3SiCl	14 + 21 ($OSiMe_3$)
2.	14	1) LDA/THF/−78°C 2) Et_3N/Me_3SiCl	21 ($OSiMe_3$) + 22 ($OSiMe_3$) ca 1:1
3.	14	1) KHMDS/THF/−78°C 2) Et_3N/Me_3SiCl	22 ONLY

Scheme V



A series of enolate trapping experiments was done in order to ascertain whether the C2 or the C11 enolate was the kinetic product. These results are summarized in Table I. These experiments indicate that the C11 enolate is in fact the kinetic product and that the C2 enolate is a result of enolate equilibration,[19] perhaps as a result of a stronger interaction incurred between the C2 enolate p orbitals with those of the norbornenyl double bond. The fact that the C11 enolate can be trapped efficiently by using alkali metal hexamethyldisilazides can perhaps be due to the differing rates of proton transfer between the conjugate acids (diisopropyl amine vs. hexamethyldisilazane).

In any event, it was clear (Table I, entry 3) that potassium hexamethyldisilazide (KHMDS) in THF at −78 °C gave the desired C11 enolate. Therefore, treatment of **14** with KHMDS (−78 °C) followed by the addition of MCF (Scheme V) gave a mixture of the desired C-acylated ester **23** (58%) and the enol carbonate **24** (24%). The enol carbonate **24** was recycled to ketone by hydrolysis with K_2CO_3/MeOH (84%) and resubmitted to the carbometh-

(17) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248.
(18) (a) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486. (b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (c) Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1985**, *26*, 2291.
(19) Sisido, K.; Utimoto, K.; Isida, T. *J. Org. Chem.* **1964**, *29*, 2781.

Scheme VI

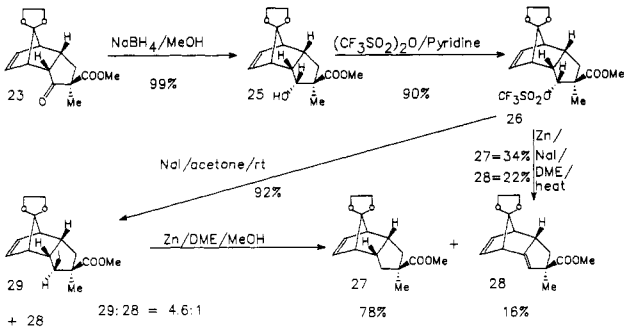
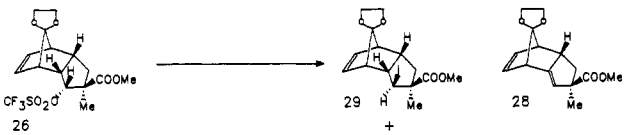


Table II



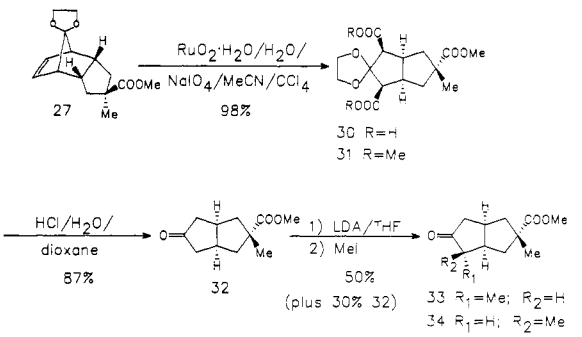
ENTRY	CONDITIONS	RATIO 29:28	YIELD
1	nBu_4NI/C_6H_6/heat	3.4:1	79%
2	NaI/DME/heat	3.4:1	80%
3	NaI/acetone/rt	4.6:1	92%

oxylation procedure. In this manner, an 80% yield of **23** was obtained after three recycles of **24**.

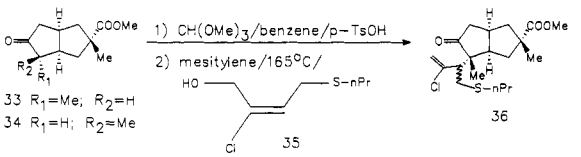
The final transformation necessary for the C ring was the removal of the C1 carbonyl. Strongly basic (Wolff–Kishner) or acidic (Clemmensen) reduction conditions could not be used because of sensitive functionality elsewhere (e.g., ketal; β-keto ester). Attempts at formation of the tosylhydrazone,[20] Zn/HCl(anh.)/ether,[21] and formation of the thioketal were all similarly unsuccessful.

The method that was ultimately successful was a modified multistep procedure that was used in the coriolin (**5**) synthesis.[15] Keto ester **23** was reduced with $NaBH_4$/MeOH to the alcohol **25** (99%). Treatment of **25** with trifluoromethanesulfonic anhydride/pyridine[22] gave triflate **26** (90%). One-step reduction of the C1 triflate was attempted by using NaI/Zn/DME;[23] however, this gave low yields (34%) of the deoxy product **27** and high amounts of the elimination product **28** (22%). To control the formation of the elimination product, we decided to convert the triflate **26** to the iodide **29** and reduce this to **27** in a separate step. Several sets of reaction conditions were examined (Table II). Surprisingly, the use of tetra-*n*-butylammonium iodide (TBAI)/benzene[22] (entry 1) gave similar results to using NaI/DME at reflux (entry 2) (3.4:1 **29**:**28**). The best conditions found were NaI/acetone/room temperature (entry 3). This afforded a 4.6:1 mixture of iodide **29**:olefin **28** in a 92% total yield. These compounds were very difficult to separate chromatographically and usually the crude mixture was submitted to the next step. The mixture was treated with activated zinc dust in refluxing DME/MeOH[25] to give an easily separable mixture of the desired deoxy ester **27** (78% based on iodide **29**) and diene **28** (16%). This process constitutes a 57% overall yield for the C1 deoxygenation process (four steps from **23**).

Scheme VII



Scheme VIII



With the C ring complete, the next stage involved elaboration and functionalization of the B ring. Treatment of olefin **27** (Scheme VII) with $RuO_2/NaIO_4/H_2O$/MeCN/CCl_4[26] afforded the crystalline diacid **30** (98%). This was characterized as the triester **31**, prepared by treatment of **30** with CH_2N_2.

It would be aesthetically pleasing to use one of the carboxyl group (C3 or C8) carbons as a methyl precursor for the synthesis; however, it would require a large number of steps considering ketal hydrolysis, differentiation, decarboxylation, and reduction sequences would be necessary. On the other hand, removal of both carboxyl groups and reintroduction of the methyl carbon via alkylation of the ketone would require only two steps. Therefore, hydrolysis–decarboxylation took place upon treatment of the diacid **30** with 1 N aqueous HCl in refluxing dioxane. Concommitant hydrolysis of the C11 ester also took place. The crude reaction mixture was reacted with CH_2N_2 to give the bicyclic ketone **32** in 87% yield (from diacid **30**). This ketone **32** is an intermediate in the Matsumoto synthesis of hirsutic acid C (**1**)[10a] and the spectroscopic details were in complete agreement.

Monoalkylation of the symmetrical ketone **32** was accomplished with 1 equiv of LDA and methyl iodide to afford a 50% yield of monomethyl ketones **33** and **34** as a mixture of isomers in an 8:1 ratio, along with 30% of the recovered ketone **32** which was recycled. The stereochemistry of the C3 methyl is inconsequential as this center becomes sp^2 hybridized during the A-ring annulation process (vide infra).

The final stage of the synthesis involved the annulation of the A ring and final conversion to hirsutic acid C (**1**) and complicatic acid (**2**). Although a number of excellent methods for cyclopentannulation have been communicated,[13,27] we have found in our studies[15] that the most efficient method of forming the required A-ring dienone was to use the Lansbury chloro olefin annulation process.[11] This process has the advantage of putting in all of the necessary functionality with the requisite number of carbons, in a relatively short and overall high yielding sequence.

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(24) Elimination of **28** probably takes place at the stage of the triflate **26**, because when a small amount of pure iodide **29** was isolated and treated with NaI/acetone, no olefin **28** was detected. Only the starting material (100%) was recovered.
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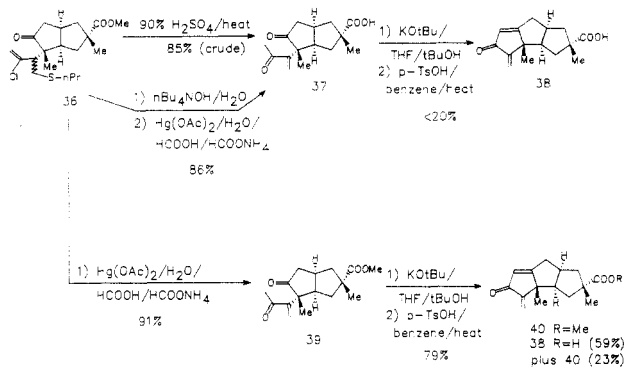
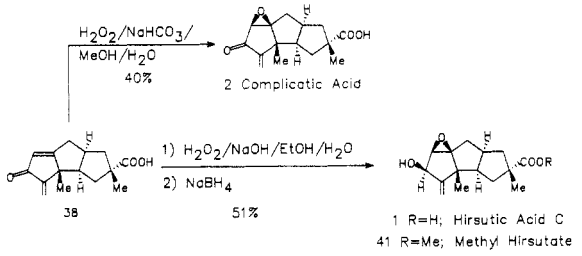
Scheme IX



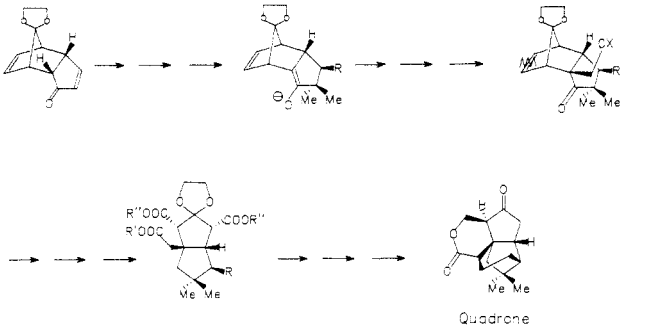
Scheme X



Therefore, methyl ketones **33** and **34** were treated (Scheme VIII) sequentially with $CH(OMe)_3$/MeOH/*p*-TsOH/benzene and 2-chloro-4-(propylthio)-2-buten-1-ol (**35**)[28]/mesitylene. The temperature was raised to 160 °C to effect the Ketal–Claisen reaction.[29] Thus, a four-step process involving ketalization, transketalization, elimination, and Claisen rearrangement occurs in one pot, affording the desired ketone **36** in 85% overall yield. None of the isomeric ketones involving rearrangement of the side chain to the β-surface or toward C8 was detected or isolated.

Two basic routes were examined to give the cyclized A-ring product. Our initial attempts involved the enone acid **37** which could be prepared in two ways from ketone **36** (Scheme IX). Lansbury's route consists of hydrolysis with 90% H_2SO_4 to the enone acid **37** (85% crude).[11b] An alternative route using stepwise hydrolysis of the C11 ester with *n*-Bu_4NOH followed by hydrolysis–elimination of the side chain with $Hg(OAc)_2/HCOOH/HCOONH_4/H_2O$[30] gave purer enone acid **37** in 86% yield. However, subsequent attempts at cyclization with KO-*t*-Bu/THF/*t*-BuOH to the β-hydroxy ketone followed by elimination with *p*-TsOH in refluxing benzene gave the dienone acid **38** in only very low (<20%) yield. All attempts to increase this yield failed. We felt that the low yield was due to a combination of the low solubility and sensitive functionality in the starting material and product and the relatively harsh reaction conditions used. We therefore explored an alternative route which entailed treatment of **36** with $Hg(OAc)_2/HCOOH/HCOONH_4/H_2O$[30] to afford the less polar and much more highly soluble enone ester **39** (91%). This time, cyclization with KO-*t*-Bu/*t*-BuOH/THF followed by elimination with *p*-TsOH/benzene produced the pure dienone ester **40** in 79% yield. This was converted to the key dienone acid **38** in 59% yield (along with 23% recovered ester **40**) with LiI/DMF.[10a,31]

Scheme XI



The dienone acid **38** was converted to hirsutic acid C (**1**) and complicatic acid (**2**) as shown in Scheme X. Reaction of **38** with $H_2O_2/NaHCO_3/H_2O$/MeOH at room temperature gave monoepoxidation at C6 and C7 to afford complicatic acid (**2**) in 40% yield. The 200-MHz NMR and infrared spectra of **2** were in complete agreement with the reported spectroscopic data for complicatic acid (**2**).[5,10a]

Dienone–acid **38** was converted to hirsutic acid C (**1**) in 51% yield by the one-pot procedure developed by Greene[10f] ((1) $H_2O_2/NaOH/H_2O$/EtOH; (2) $NaBH_4$). The physical properties, high field (200 and 300 MHz) NMR, infrared, and mass spectra were in complete agreement with the reported data for hirsutic acid C (**1**).[10] In addition, our sample of **1** was identical in all respects with a sample kindly provided by Professor Barry M. Trost. Methyl hirsutate (**41**) was prepared from hirsutic acid (**1**) by treatment with diazomethane in ether/ethyl acetate. The physical and spectroscopic details were in agreement with those reported.[10a]

The syntheses of hirsutic acid C (**1**) and complicatic acid (**2**) were accomplished in a highly stereoselective manner from the methanoindene **12**. These results further demonstrate the viability of using this methodology for the synthesis of linearly fused polycyclopentanoid natural products of the hirsutane class. Additionally, the interesting results from the enolate formation in the carbomethoxylation sequence (Schemes IV and V; Table I) point to the possibility of using these types of intermediates for the synthesis of quadrone type compounds (Scheme XI) since the alkylation in the junction from the internal enolate is indeed feasible. Studies on this and other uses of this methodology will be reported in due course.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-360A, Varian XL-300, or an IBM WP 200 spectrometer using Me_4Si or $CHCl_3$ as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer and were calibrated with the 1601 cm^{-1} band of polystyrene. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Flash chromatography refers to the method described by Still[32] using E. Merck silica gel 60 (230–400 mesh). Thin layer chromatography was performed on E. Merck glass supported silica gel 60 (0.25 mm, F-254) plates. Silica gel for gravity column chromatography was Baker Reagent grade (60–200 mesh). Analyses for C and H were acquired by Dr. Franz Kasler of the University of Maryland. Low and high resolution mass spectra were obtained by Dr. Joyce Cone of the University of Maryland on a Hitachi RMU-6E (low resolution and VG-7070E (high resolution).

Ethyl acetate, Skellysolve F, and hexanes for chromatography were distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Benzene, diisopropylamine, and hexamethyldisilazane were distilled from CaH_2 prior to use.

(28) This material was prepared from 2,4-dichloro-2-buten-1-ol (cf. Johnson, A. W. *J. Chem. Soc.* **1946**, 1014) and sodium propanethiolate as described in ref 11e.
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4β-Methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo-[5.2.0^{2,6}]dec-8-en-3-one (14). A solution of diisopropylamine (1.40 mL, 10.00 mmol) in 100 mL of dry tetrahydrofuran was cooled to −78 °C under a nitrogen atmosphere. *n*-Butyllithium (8.50 mL, 1.6 M in hexane) was added over a 25-min period via syringe pump, and the resulting solution was stirred at −78 °C for 30 min. At this time, a solution of ketone **12** (2.58 g, 12.50 mmol) in 40 mL of tetrahydrofuran was added dropwise over a 90-min period. The reaction was stirred at −78 °C for 30 min and then placed in an acetone–crushed ice bath and methyl iodide (2.50 mL, 40.00 mmol) was added immediately. The reaction mixture was allowed to warm to room temperature of its own accord and stirred for a total period of 12 h. The solvents were evaporated in vacuo and 60 mL of water was added to the residue. The aqueous was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were washed with 10% HCl (50 mL) and saturated sodium bicarbonate (50 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in hexanes eluant) to give the *exo*-methyl ketone **14** (2.36 g, 85%) as an oil: NMR ($CDCl_3$, 200 MHz) δ 0.84 (d, 3 H, J = 4.0 Hz), 1.37–1.58 (m, 1 H), 1.67–1.85 (m, 2 H), 2.65 (br s, 1 H), 2.83 (m, 1 H), 2.92 (m, 2 H), 3.60–3.81 (m, 4 H), 6.00 (ddd, 1 H, J_1 = 6.2 Hz, J_2 = 3.0 Hz, J_3 = 1.0 Hz), 6.21 (ddd, 1 H, J = 6.2 Hz, J_2 = 3.0 Hz, J_3 = 1.0 Hz); IR (neat) 3000, 1740, 1310, 1095 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: 70.89; H, 7.32. Found: C, 70.89; H, 7.32.

Preparation of Enaminone 15. The method described by Abdulla and Fuhr[17] was used. The ketone **12** (3.00 g, 14.60 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.92 g, 16.10 mmol) were refluxed under a nitrogen atmosphere for 18 h. The reaction was allowed to cool and the methanol and excess *N,N*-dimethylformamide dimethyl acetal were removed under reduced pressure. The resulting solid was triturated with ca. 1:1 ether/petroleum ether to afford the enaminone **15** as golden crystals (2.81 g, 75%): mp 168–172 °C; NMR ($CDCl_3$, 60 MHz) δ 2.10–3.65 (m, 6 H, containing 6 H s at 3.02), 3.85 (m, 4 H), 6.10 (m, 2 H), 7.00 (s, 1 H); IR ($CHCl_3$) 2980, 1660, 1560, 1310, 1100 cm^{-1}.

Preparation of Quaternary Ammonium Salt 16. The enaminone **15** (5.78 g, 22.20 mmol) dissolved in 160 mL of tetrahydrofuran was added dropwise over a 10-min period to a slurry of lithium aluminum hydride (0.59 g, 16.60 mmol) in 45 mL of tetrahydrofuran cooled to 0 °C in an ice bath. After the addition was complete, the reaction was stirred for another minute and then poured rapidly (but carefully!) into 120 mL of ethyl acetate. Water (6 mL) was added all at once and the mixture was stirred vigorously. The mixture was filtered through Celite and the volatiles were evaporated in vacuo. Ether (200 mL) was added, the solution was dried over sodium sulfate, and the volatiles were evaporated in vacuo. The crude amine was not characterized but immediately dissolved in 150 mL of dioxane and 35 mL of methyl iodide. The reaction mixture was stirred at room temperature for 14 h as the crystalline quaternary ammonium salt fell out of solution. The solvents were evaporated in vacuo and the solid was triturated with petroleum ether to give the quaternary ammonium salt **16** (8.23 g, 91% overall) as a yellow powder: mp 154–157 °C; NMR (acetone-d_6, 60 MHz) δ 2.15–3.12 (m, 4 H, containing 9 H s at 2.97), 3.37 (m, 4 H), 3.77–3.82 (m, 5 H), 5.92–6.37 (m, 2 H); IR ($CHCl_3$) 2980, 1750, 1305, 1135 cm^{-1}.

4-Methylene-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo-[5.2.1.0^{2,6}]dec-8-en-3-one (17). The quaternary ammonium salt **16** (0.41 g, 1.00 mmol) was dissolved in 10 mL of chloroform and a solution of 1.22 g of potassium carbonate in 5 mL of water was added. The mixture was vigorously stirred for 24 h. At this time, the aqueous layer was separated and extracted with an additional 20 mL of chloroform. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The crude oil was purified by flash chromatography (15% ethyl acetate in hexanes eluant) to give the α-methylene ketone **17** as a clear oil (0.11 g, 49%): NMR ($CDCl_3$, 200 MHz) δ 1.40–2.30 (m, 2 H), 2.50–3.15 (m, 4 H), 3.40–3.90 (m, 4 H), 5.03 (m, 1 H), 5.69 (m, 1 H), 6.05 (m, 2 H); IR (neat) 2980, 1710, 1630, 1300, 1100 cm^{-1}.

4α-Methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo-[5.2.1.0^{2,6}]dec-8-en-3-one (18). The α-methylene ketone **17** (0.38 g, 1.74 mmol) in 10 mL of chloroform was added all at once to a solution of lithium tri-*tert*-butoxyaluminum hydride (0.99 g, 3.90 mmol) in 25 mL of ether. The reaction mixture was stirred at room temperature under nitrogen for 12 h. Water (12 mL) and 6 N HCl (6 mL) were added. The organic phase was separated and the aqueous layer extracted with an additional 20 mL of ether. The combined ether layers were washed with water (2 × 40 mL), dried over magnesium sulfate, filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography (12% ethyl acetate in hexanes eluant) to yield the *endo*-methyl ketone **18** (100 mg, 26%) as a white crystalline solid: mp 55–56 °C; NMR ($CDCl_3$, 200 MHz) δ 0.78 (d, 3 H, J = 4.1 Hz), 0.91–1.00 (m, 1 H), 2.12–2.35 (m, 2 H), 2.67 (br s, 1 H), 2.82 (br s, 1 H), 3.03 (m, 2 H), 3.72–3.90 (m, 4 H), 6.06 (ddd, 1 H, J_1 = 6.4 Hz, J_2 = 3.2 Hz, J_3 = 1.1 Hz), 6.19 (ddd, 1 H, J_1 = 6.4 Hz, J_2 = 3.2 Hz, J_3 = 1.1 Hz); IR ($CHCl_3$) 2960, 1730, 1290, 1070 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.61; H, 7.28.

Methyl Cyanoformate (MCF). This was prepared by the method described by Weber[18a] and was obtained in 56% yield after distillation: bp 98 °C (25 mmHg) (lit. bp[26] 99 °C).

Preparation of Enol Carbonate 19. A solution of diisopropylamine (0.18 mL, 1.20 mmol) in 5 mL of dry tetrahydrofuran under a nitrogen atmosphere was cooled to −78 °C. A solution of *n*-butyllithium (0.75 mL, 1.6 M in hexane) was added dropwise via syringe pump over a 20-min period. After the addition was complete, the solution was stirred at −78 °C for 30 min. A solution of ketone **14** (0.22 g, 1.00 mmol) in 5 mL of tetrahydrofuran was added dropwise over a 20-min period. The reaction was then warmed to 0 °C and stirred for 60 min. The temperature was again lowered to −78 °C and 0.17 mL (1.00 mmol) of hexamethylphosphoramide and 0.10 g (1.20 mmol) of methyl cyanoformate (MCF) were added all at once. The reaction mixture was stirred at −78 °C for 45 min and then allowed to warm to room temperature of its own accord. The reaction was stirred for 15 h. At this time the mixture was poured into 20 mL of cold water and extracted with ether (2 × 20 mL). The ether extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was purified by flash chromatography (15% ethyl acetate in hexanes eluant) to give enol carbonate **19** (0.56 g, 93%) as a white crystalline solid: mp 125–128 °C; NMR ($CDCl_3$, 200 MHz) δ 0.80–0.95 (two d, 3 H), 1.25–1.60 (m, 2 H), 2.20–2.40 (m, 1 H), 2.40–2.65 (m, 2 H), 2.72–2.95 (m, 1 H), 3.50–3.84 (m, 4 H), 3.75 (s, 3 H), 6.05 (m, 1 H), 6.26 (m, 1 H); IR ($CHCl_3$) 3000, 1765, 1285 cm^{-1}.

Preparation of C2 Acylated Ester 20. A solution of diisopropylamine (0.76 mL, 5.50 mmol) in 40 mL of dry tetrahydrofuran was cooled to −78 °C under a nitrogen atmosphere. A solution of *n*-butyllithium (3.40 mL, 1.6 M in hexane) was added over a 25-min period via syringe pump. After the addition was complete, the solution was stirred at −78 °C for 30 min. The ketone **14** (1.00 g, 4.50 mmol) in 15 mL of tetrahydrofuran was added dropwise over a period of 60 min. The reaction mixture was then stirred at −78 °C for 60 min and then warmed to −10 °C for 60 min. At this time, freshly powdered carbon dioxide (large excess) was added. The mixture was removed from the bath and stirred at room temperature for 45 h. The tetrahydrofuran was evaporated in vacuo and 25 mL of 10% HCl was added. The aqueous phase was extracted with chloroform (3 × 25mL) and the combined organic extracts were dried over magnesium sulfate and evaporated in vacuo. One half of the crude product (0.50 g, 1.89 mmol) was dissolved in 25 mL of ether and ethereal diazomethane was added (ca. 8 mL). The reaction was stirred for 20 min and then the volatiles were removed completely in vacuo. The crude oil was purified by flash chromatography (15% ethyl acetate in Skellysolve-F as eluant) to afford 0.34 g (65%) of the C2-acylated product **20** as an oil: NMR ($CDCl_3$, 60 MHz) δ 1.02 (d, 3 H, J = 7.0 Hz), 1.25–1.43 (m, 1 H), 1.77–2.09 (m, 2 H), 2.57–3.47 (m, 3 H), 3.75 (s, 3 H), 3.87 (s, 4 H), 5.98–6.49 (m, 2 H); IR (neat) 2990, 1750, 1720, 1300, 1230 cm^{-1}.

Enolate Trapping Experiments for Table I. Entry 1. A solution of diisopropylamine (0.420 mL, 3.00 mmol) in 10 mL of tetrahydrofuran under a nitrogen atmosphere was cooled to −78 °C. A solution of *n*-butyllithium (1.88 mL, 1.6 M in hexane) was added dropwise via syringe pump over a period of 20 min, and the resulting mixture was stirred at −78 °C for 30 min. The ketone **14** (0.440 g, 2.00 mmol) in 5 mL of tetrahydrofuran was added dropwise over a 30-min period. After the addition was complete, the temperature of the reaction was raised to 0 °C and the mixture

was stirred at this temperature for 45 min. At this time, the reaction was cooled to −78 °C and 3 mL of a centrifuged 1:1 mixture of triethylamine/trimethylchlorosilane was added all at once. Stirring at −78 °C was continued for 30 min and at −10 °C for 45 min. A solution of cold saturated sodium bicarbonate (20 mL) was added and the mixture was stirred vigorously at room temperature for several minutes. The reaction mixture was extracted with 2 × 20 mL portions of ether. The ether extracts were washed with 20 mL of ice-cold saturated sodium bicarbonate and dried over magnesium sulfate, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography on florisil (14 g florisil using 5% ethyl acetate in hexanes as eluant). The first product eluted was enol ether **21** (0.280 g, 48%), followed by a mixture of *exo*- and *endo*-methyl ketones **14** and **18** (0.150 g, 15%). Silyl enol ether **21**: NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 9 H), 1.11 (d, 3 H, J = 7.0 Hz), 1.21–1.35 (m, 1 H), 1.51 (dd, 1 H, J_1 = 11.8 Hz, J_2 = 5.9 Hz), 2.32 (m, 1 H), 2.63 (m, 1 H), 2.94 (d, 1 H, J = 3.0 Hz), 3.42 (m, 1 H), 3.75–3.94 (m, 4 H), 5.79 (dd, 1 H, J_1 = 6.2 Hz, J_2 = 3.1 Hz), 6.38 (dd, 1 H, J_1 = 6.2 Hz, J_2 = 3.1 Hz); IR (neat) 2970, 1690, 1290 cm^{-1}.

Entry 2. A solution of diisopropylamine (0.330 mL, 2.40 mmol) in 10 mL of tetrahydrofuran was cooled to −78 °C under a nitrogen atmosphere. A solution of *n*-butyllithium (1.50 mL, 1.6 M in hexane) was added dropwise over a 20-min period via syringe pump, and the resulting solution was stirred at −78 °C for 30 min. A solution of ketone **14** (0.440 g, 2.00 mmol) in 5 mL of tetrahydrofuran was added dropwise over a 30-min period. The reaction was maintained at −78 °C for 60 min. At this time, 3 mL of a centrifuged 1:1 mixture of triethylamine/trimethylchlorosilane was added all at once, and the reaction mixture was stirred at −78 °C for 60 min. The reaction was removed from the cooling bath and quenched with 20 mL of ice-cold saturated sodium bicarbonate. The aqueous was extracted with 2 × 25 mL portions of ether. The combined ether was washed with cold saturated sodium bicarbonate (20 mL) and dried with magnesium sulfate, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography on florisil (14 g florisil using 2% ethyl acetate in hexanes as eluant) to give in order of elution: a mixture (1:1 by NMR analysis) of silyl enol ethers **21** and **22** (0.34 g, 58%) and a mixture of *endo*- and *exo*-methyl ketones **14** and **18** (0.11 g, 25%). Representative NMR peaks for mixture of silyl enol ethers **21** and **22**: NMR ($CDCl_3$, 60 MHz) δ 1.11 (d, J = 7.0 Hz), 1.25 (br s), 5.80 (dd, J_1 = 6 Hz, J_2 = 3 Hz), 6.05 (m), 6.40 (dd, J_1 = 6 Hz, J_2 = 3 Hz).

Entry 3. Potassium hydride (0.390 g, 2.40 mmol, 24% in oil) was placed in a dry flask and the oil was removed by washing with 3 × 1 mL aliquots of petroleum ether. Tetrahydrofuran (5 mL) was added and the suspension was cooled to 0 °C under a nitrogen atmosphere in an ice bath. Hexamethyldisilazane (0.510 mL, 2.40 mmol) was added via syringe and the solution was stirred at 0 °C for 15 min and then at room temperature for 30 min. The solution was cooled to −78 °C and ketone **14** (0.440 g, 2.00 mmol) in 5 mL of tetrahydrofuran was added dropwise over a 30-min period. After the addition was complete, the solution was stirred at low temperature for an additional 45 min. At this time 4 mL of a centrifuged 1:1 solution of triethylamine/trimethylchlorosilane was added all at once and stirring was continued for 30 min. The cooling bath was removed and 20 mL of saturated sodium bicarbonate was added. The solution was extracted with 3 × 20 mL of ether. The combined ether extracts were washed with 20 mL of cold saturated sodium bicarbonate and dried over magnesium sulfate, and the volatiles were evaporated in vacuo. The crude oil was purified by flash chromatography on florisil (14 g of florisil using 2% ethyl acetate in hexanes as eluant) to give in order of elution: silyl enol ether **22** (0.218 g, 37%) and a mixture of *endo*- and *exo*-methyl ketones **14** and **18** (0.20 g, 45%). Silyl enol ether **22**: NMR ($CDCl_3$, 200 MHz) δ 0.12 (s, 9 H), 1.31 (s, 3 H), 1.48 (d, 1 H, J = 6 Hz), 2.08 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 2.5 Hz), 2.46–2.78 (m, 3 H), 3.07 (m, 1 H), 3.68–3.88 (m, 4 H), 6.02–6.16 (m, 2 H); IR (neat) 2970, 1690, 1295 cm^{-1}.

4β-Carbomethoxy-4α-methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (23). Potassium hydride (1.15 g, 24% in oil, 7.10 mmol) was placed in a flask and the oil washed off with 4 × 2 mL of petroleum ether. Tetrahydrofuran (10 mL) was added and the suspension cooled to 0 °C under a nitrogen atmosphere. Hexamethyldisilazane (1.40 mL, 6.60 mmol) was added via syringe and the reaction was stirred at 0 °C for 15 min and then at room temperature for 30 min. The solution was cooled to −78 °C and a solution of 1.04 g (4.73 mmol) of ketone **14** in 10 mL of tetrahydrofuran was added dropwise over a period of 30 min. The reaction mixture was stirred for 1 h at this temperature and then treated with methyl cyanoformate (0.800 g, 4.73 mmol). The reaction was allowed to warm to room temperature of its own accord and stirred for a total of 12 h. The mixture was poured into 50 mL of cold water and 50 mL of ether. The layers were separated and the aqueous layer was extracted with an additional 50 mL of ether. The combined ether layers were washed with 50 mL of water and 50 mL of saturated sodium chloride, dried over magnesium sulfate, and concentrated to a yellow oil. The products were separated by flash chromatography (5% ethyl acetate in Skellysolve-F eluant) to yield in order of elution:

O-Acylated product 24 (0.44 g, 24%); NMR ($CDCl_3$, 60 MHz) δ 1.42 (br s, 3 H), 1.65–1.90 (m, 1 H), 2.00–2.30 (br s, 3 H), 2.41–2.72 (m, 2 H), 2.81–3.15 (m, 1 H), 3.44–3.70 (m, 1 H), 3.80 (br s, 7 H), 6.12 (m, 2 H); IR (neat) 2980, 1760, 1245 cm^{-1}.

C-Acylated product 23 (0.76 g, 58%); NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 3 H), 1.16 (dd, 1 H, J_1 = 14.0 Hz, J_2 = 7.6 Hz), 2.48 (dd, 1 H, J_1 = 14.0 Hz, J_2 = 9.4 Hz), 2.68 (m, 1 H), 2.85 (m, 1 H), 3.05–3.16 (m, 1 H), 3.29 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 4.6 Hz), 3.58 (s, 3 H), 3.70–3.87 (m, 4 H), 6.10 (m, 2 H); IR (neat) 2995, 1755, 1725, 1290 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.58; H, 6.51.

Recycling of O-Acylated Compound 24. The enol carbonate **24** (9.18 g, 0.033 mol) was dissolved in 180 mL of absolute methanol and treated with 36 g of potassium carbonate. The reaction mixture was stirred at room temperature for 12 h and then poured into 400 mL of cold water. The aqueous was extracted with 2 × 300 mL portions of ether. The combined ether layers were washed with 100 mL of saturated sodium chloride, dried over magnesium sulfate, and evaporated in vacuo to a yellow oil which was shown to be a mixture of the *exo*- (**14**) and *endo*-methyl (**18**) ketones (6.10 g, 84%). The isolated mixture was sufficiently pure to be resubmitted directly to the acylation reaction described in the previous experiment (vide supra). This process gave the same ratio of **24**:**23** as obtained from pure exo ketone **14**.

3α-Hydroxy-4β-carbomethoxy-4α-methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo[5.2.1.0^{2,6}]dec-8-ene (25). The keto ester **23** (1.00 g, 3.60 mmol) was dissolved in 20 mL of absolute methanol and sodium borohydride (0.274 g, 7.20 mmol) was added in small portions over a 15-min period. After the addition was complete, the reaction was stirred at room temperature for 90 min. The methanol was removed in vacuo and the residue treated with 60 mL of water. The aqueous was extracted with 2 × 60 mL of methylene chloride, which was combined, dried over magnesium sulfate, and evaporated to give alcohol **25** as a clear viscous oil (1.00 g, 99%): NMR ($CDCl_3$, 200 MHz) δ 0.82 (dd, 1 H, J_1 = 12.7 Hz, J_2 = 11.1 Hz), 1.08 (s, 3 H), 1.32 (m, 1 H), 2.04 (dd, 1 H, J_1 = 12.7 Hz, J_2 = 7.2 Hz), 2.54 (m, 1 H), 2.65–2.77 (m, 2 H), 2.94 (m, 1 H), 3.61 (s, 3 H), 3.68–3.86 (m, 4 H), 4.31 (d, 1 H, J = 5.5 Hz), 6.10 (dd, 1 H, J_1 = 6.2 Hz, J_2 = 3.5 Hz), 6.40 (ddd, 1 H, J_1 = 6.2 Hz, J_2 = 3.5 Hz, J_3 = 1.2 Hz); IR (neat) 3520, 2970, 1730, 1290, 1090 cm^{-1}. The alcohol **25** was characterized as the derived acetate by treatment of 0.422 g (1.50 mmol) of **25** with 12 mL of 1:1 acetic anhydride/pyridine for 20 h. The volatiles were evaporated completely in vacuo and the residue was triturated with petroleum ether to give the acetate (0.340 g, 70%) as a light tan crystalline solid: mp 104–106 °C; NMR ($CDCl_3$, 200 MHz) δ 1.00–1.12 (m, 1 H, containing a 3 H s at 1.06), 2.00–2.12 (m, 1 H, containing a 3 H s at 2.02), 2.56 (m, 2 H), 2.74 (m, 1 H), 3.11 (ddd, 1 H, J_1 = 10.6 Hz, J_2 = 6.5 Hz, J_3 = 3.5 Hz), 3.67 (s, 3 H), 3.70–3.88 (m, 4 H), 5.48 (d, 1 H, J = 6.9 Hz), 6.07 (m, 2 H); IR ($CHCl_3$) 2980, 1730, 1245 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.20, H, 6.96.

Preparation of Triflate 26. The method of Binkley was used.[23] A solution of pyridine (4.63 mL, 57.20 mmol) in 240 mL of methylene chloride was cooled to 10 °C in an ice–acetone bath. Trifluoromethanesulfonic anhydride (7.20 mL, 42.90 mmol) was added slowly via syringe and the resulting milky white suspension was stirred at −10 °C for an additional 5 min. At this time, a solution of alcohol **25** (4.00 g, 14.30 mmol) in 25 mL of methylene

chloride was added dropwise over a period of 30 min. After the addition was complete, the reaction was allowed to warm to room temperature of its own accord and stirred for 16 h. The mixture was poured into 400 mL of ice water with vigorous stirring and the organic phase was separated. The aqueous was extracted with 2 × 200 mL of methylene chloride. The combined organic extracts were washed with 200 mL of ice cold 10% HCl and 200 mL of water and dried over sodium sulfate, and the volatiles were evaporated in vacuo to afford triflate **26** (5.28 g, 90%) as a light yellow oil. This material was sufficiently pure to use directly in the next step without purification: NMR ($CDCl_3$, 200 MHz) δ 1.02–1.19 (m, 1 H, containing 3 H s at 1.19), 2.10 (dd, 1 H, J_1 = 12.8 Hz, J_2 = 7.1 Hz), 2.54 (m, 1 H), 2.67–2.75 (m, 2 H), 3.21 (m, 1 H), 3.67 (s, 3 H), 3.70–3.87 (m, 4 H), 5.51 (d, 1 H, J = 6.9 Hz), 6.07 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 3.5 Hz), 6.26 (ddd, 1 H, J_1 = 6.4 Hz, J_2 = 3.5 Hz, J_3 = 1.0 Hz); IR (neat) 3000, 1735, 1420, 1205 cm^{-1}.

3-Iodo-4β-carbomethoxy-4α-methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo[5.2.1.0^{2,6}]dec-8-ene (29). The triflate **26** (0.550 g, 1.33 mmol) was dissolved in 15 mL of acetone and treated with sodium iodide (0.220 g, 1.47 mmol). The reaction mixture was stirred at room temperature for 20 h. At this time the acetone was evaporated in vacuo and the residue treated with 30 mL of ether. The ether solution was washed with water (20 mL), aqueous sodium bisulfite (20 mL), and again with water (20 mL) and dried over magnesium sulfate and the volatiles were evaporated in vacuo to afford 0.480 g (92%) of a yellow oil. Analysis of the NMR spectrum showed the oil to be a mixture of iodide **29** and diene **28** in a ratio of 4.6:1. Separation of **28** and **29** by chromatography was extremely difficult and in general the mixture of products from this reaction was submitted directly to the next reaction (Zn reduction, vide infra). A small sample of pure iodide was obtained for analytical purposes by flash chromatography of the mixture (5% ethyl acetate in Skellysolve-F as eluant). This gave iodide **29** as a white crystalline solid: mp 100–101 °C; NMR ($CDCl_3$, 200 MHz) δ 0.94 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 9.7 Hz), 1.12 (s, 3 H), 1.96 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 9.7 Hz), 2.69 (m, 1 H), 2.76 (m, 1 H), 3.12 (ddd, 1 H, J_1 = 19.0 Hz, J_2 = 9.5 Hz, J_3 = 4.0 Hz), 3.24 (d, 1 H, J = 9.5 Hz), 3.40 (t of d, 1 H, J_1 = 10.0 Hz, J_2 = 4.0 Hz), 3.71 (s, 3 H), 3.77–3.94 (m, 4 H), 6.28 (m, 2 H); IR ($CHCl_3$) 2990, 1730, 1295 cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_4I$: C, 46.17; H, 4.91. Found: C, 46.18; H, 5.00.

4β-Carbomethoxy-4α-methyl-10,10-(ethylenedioxy)-(1α,2β,6β,7α)-tricyclo[5.2.1.0^{2,6}]dec-8-ene (27) (Deoxy ester). The iodide/diene mixture from the previous experiment (0.48 g, 4.6:1 mixture of **28**:**29**, 1.00 mmol of **29**) was dissolved in 20 mL of dimethoxyethane and activated zinc dust (2.17 g, 33.20 mmol) was added immediately followed by 2 mL of methanol. The reaction mixture was heated at reflux and stirred vigorously for 24 h and then cooled to room temperature and filtered through Celite. The pad was washed with 3 × 20 mL of ether. The combined ether was washed with 20 mL of water, dried over magnesium sulfate, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) to give the desired deoxy ester **27** (0.210 g, 78%) as a white crystalline solid mp; 62–64 °C, and the diene **28** (0.058 g, 16%) as an oil.

Deoxy ester 27: NMR ($CDCl_3$, 200 MHz) δ 0.81 (dd, 2 H, J_1 = 13.0 Hz, J_2 = 9.5 Hz), 1.14 (s, 3 H), 2.02 (dd, 2 H, J_1 = 13.0 Hz, J_2 = 6.7 Hz), 2.53 (m, 2 H), 2.78 (m, 2 H), 3.63 (s, 3 H), 3.70–3.88 (m, 4 H), 6.18 (t, 2 H, J = 2.0 Hz); IR ($CHCl_3$) 2970, 1725, 1290, 1090 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.27; H, 7.50.

Diene 28: NMR ($CDCl_3$, 200 MHz) δ 0.83 (t, 1 H, J = 11.2 Hz), 1.17 (s, 3 H), 2.49 (dd, 1 H, J_1 = 11.5 Hz, J_2 = 6.0 Hz), 2.70 (m, 1 H), 3.30 (d, 1 H, J = 3.5 Hz), 3.47–3.65 (m, 1 H containing a 3 H s at 3.63), 3.79–3.93 (m, 4 H), 5.24 (d, 1 H, J = 2.5 Hz), 5.87 (dd, 1 H, J_1 = 6.2 Hz, J_2 = 3.1 Hz), 6.26 (m, 1 H); IR (neat) 2980, 1760, 1325, 1140 cm^{-1}.

Direct Reduction of Triflate 26 to Deoxy Ester 27 Using Sodium Iodide/Zn Dust. The triflate **26** (188 mg, 0.46 mmol) was dissolved in 5 mL of dimethoxyethane and the resulting solution treated with sodium iodide (345 mg, 2.30 mmol), activated zinc dust (301 mg, 4.60 mmol), and methanol (1.00 mL). The reaction mixture was heated at reflux under a nitrogen atmosphere for 5 days and then cooled to room temperature. The mixture was poured into 5 mL of water and 10 mL of ether and the resulting slurry filtered through Celite. The Celite pad was rinsed with ether (50 mL). The aqueous layer was separated and extracted with an additional 10 mL of ether. The combined ether layers were dried over magnesium sulfate and concentrated in vacuo to a yellow oil that was purified by flash chromatography (5% ethyl acetate in Skellysolve-F eluant) to give in order of elution the desired deoxy ester **27** (44 mg, 36%) as a crystalline solid, mp 62–64 °C, and the diene **28** (27 mg, 22%) as an oil.

2β,4β-Dicarboxy-3,3-(ethylenedioxy)-7α-carboxy-7β-methyl-(1α,5α)-bicyclo[3.3.0]octane (30). Deoxy ester **27** (1.00 g, 3.79 mmol) was dissolved in a solvent mixture consisting of carbon tetrachloride (10 mL), acetonitrile (10 mL), and water (15 mL). Sodium metaperiodate (3.31 g, 15.50 mmol) and ruthenium dioxide hydrate (20 mg) were added sequentially. The resulting mixture was stirred vigorously at room temperature for 18 h. At this time, 100 mL of methylene chloride and 40 mL of water were added and the aqueous phase was separated. The aqueous was extracted with 3 × 50 mL of ethyl acetate, and the combined organic layers were dried over magnesium sulfate, filtered through Celite, and concentrated in vacuo to afford the crystalline diacid **30** (1.22 g, 98%). This material was sufficiently pure to use directly in the next reaction (vide infra). A small sample of diacid **30** was characterized via conversion to the triester **31** (diazomethane/ether): mp 105–106 °C; NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 3 H), 1.60–1.72 (m, 2 H), 2.19–2.28 (m, 2 H), 2.86–2.97 (m, 4 H), 3.62 (s, 9 H), 4.05–4.20 (m, 4 H); IR ($CHCl_3$) 2960, 1745, 1730, 1180 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_8$: C, 57.30; H, 6.79. Found: C, 57.19; H, 6.92.

7α-Carbomethoxy-7β-methyl-(1α,5α)-bicyclo[3.3.0]octan-3-one (32). A solution of the diacid **30** in 32 mL of dioxane was treated with 32 mL of 1 N HCl and heated at reflux for 24 h. The solution was cooled to room temperature and diluted with 25 mL of saturated sodium chloride. The resulting solution was extracted with 2 × 100 mL of ethyl acetate. The combined extracts were washed with water (50 mL), dried over magnesium sulfate, and concentrated to ca. 80 mL. This solution was treated with diazomethane in ether until the yellow color remained. After 30 min, the solvents were evaporated in vacuo and the resulting crude oil was purified by flash chromatography (10% ethyl acetate in Skellysolve-F as eluant) to yield the ketone **32** (0.636 g, 87%) as a colorless oil: NMR ($CDCl_3$, 200 MHz) δ 1.10–1.23 (m, 2 H, containing 3 H s at 1.10), 1.82–1.98 (m, 2 H), 2.28–2.50 (m, 4 H), 2.67 (m, 2 H), 3.56 (s, 3 H); IR (neat) 2960, 1730, 1160 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.93; H, 8.35.

2,7β-Dimethyl-7α-carbomethoxy-(1α,5α)-bicyclo[3.3.0]octan-3-ones (33 and 34).[10a] A solution of diisopropylamine (0.46 mL, 3.29 mmol) in dry tetrahydrofuran under a nitrogen atmosphere was cooled to −78 °C. A solution of *n*-butyllithium (2.12 mL, 1.55 M in hexane) was added dropwise over a period of 20 min via syringe pump and the resulting solution was stirred at −78 °C for an additional 30 min. At this time, a solution of ketone **32** (0.644 g, 3.29 mmol) in 20 mL of tetrahydrofuran was added dropwise over a 30-min period. After the addition was complete, the reaction was stirred at −78 °C for 30 min and then at −10 °C for 1 h. Methyl iodide (0.61 mL, 9.87 mmol) was added all at once, and the reaction was allowed to warm to room temperature of its own accord and stirred for 16 h. The solvents were evaporated in vacuo and the residue was partitioned between 50 mL of methylene chloride and 50 mL of water. The aqueous was extracted with an additional 2 × 50 mL of methylene chloride. The combined methylene chloride layers were washed with cold 10% HCl (50 mL), saturated sodium bicarbonate (50 mL), and water (50 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography (4% ethyl acetate in Skellysolve-F as eluant) to afford a mixture of monomethyl ketones **33** and **34** (0.326 g, 48%) in approximately an 8:1 ratio, and the starting ketone **32** (0.169 g, 26%). Physical data is for mixture of **33** and **34**: NMR ($CDCl_3$, 200 MHz) δ 0.92 and 0.97 (ca. 8:1 ratio) (d, 3 H, J = 7.0 Hz), 1.15–1.34 (m, 2 H, containing 3 H s at 1.25), 1.84–2.67 (m, 7 H), 3.59 (s, 3 H); IR (neat) 2980, 1740, 1170 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.47; H, 8.60.

4α-[2-Chloro-4-(propylthio)-1-buten-3-yl]-7α-carbomethoxy-7β,4β-dimethyl-(1α,5α)-bicyclo[3.3.0]octan-3-one (36). A solution of the monomethyl ketones mixture **33** and **34** (0.340 g,

1.62 mmol), trimethyl orthoformate (0.21 mL, 1.94 mmol), methanol (1.34 mL), benzene (15 mL) and *p*-toluenesulfonic acid (5 mg) was stirred at room temperature under a nitrogen atmosphere for 15 h. A 6-in. column packed with glass helices was put on the flask and was topped with a short-path condenser system. The mixture was heated in an oil bath and distilled until the head temperature reached 55 °C. At this time, a solution of 2-chloro-4-(propylthio)-2-buten-1-ol (**35**)[29] (0.320 g, 1.80 mmol) in 15 mL of mesitylene was added and the distillation was continued, heating the reaction mixture slowly over a period of 3 h, until the head temperature reached 162–164 °C. The distillation was discontinued and the oil bath was held at 160 °C for 15 min. The column was removed and the mesitylene was distilled off through the short path until 1–2 mL of pot residue remained. This residue was purified by flash chromatography (1% ethyl acetate in hexanes as eluant) to give the vinyl chloride **36** (0.503 g, 84%) as a pale yellow oil: NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3 H, J = 7.3 Hz), 0.94 (s, 3 H), 1.25–1.65 (m, 4 H, containing 3 H s at 1.28), 2.00–2.14 (m, 1 H), 2.99–3.01 (m, 10 H), 3.65 (s, 3 H), 5.22 (d, 1 H, J = 1.2 Hz), 5.30 (m, 1 H); IR (neat) 2970, 1730, 1165 cm^{-1}. Anal. Calcd for $C_{19}H_{29}O_3ClS$: C, 61.19; H, 7.84; Cl, 9.51. Found: C, 61.50; H, 8.11; Cl, 9.59.

4α-(3-Oxo-1-buten-2-yl)-7α-carboxy-4β,7β-dimethyl-(1α,5α)-bicyclo[3.3.0]octan-3-one (37). A solution of vinyl chloride **36** (0.436 g, 1.15 mmol) in 27 mL of methanol and 6 mL of 40% tetra-*n*-butylammonium hydroxide was heated at reflux for 5 h. The solution was cooled to room temperature, diluted with 40 mL of water, and acidified with 10% HCl (pH 1–2). The aqueous solution was extracted with 3 × 60 mL of ethyl acetate, which was combined, dried over magnesium sulfate, and concentrated in vacuo. The crude oil obtained was dissolved in 115 mL of 88% formic acid and treated with mercuric acetate (1.46 g, 4.58 mmol) and ammonium formate (5.78 g, 92.0 mmol). The mixture was stirred vigorously at room temperature for 41 h. At this time, 75 mL of water and 75 mL of ethyl acetate were added and the layers were separated. The aqueous was extracted with an additional 75 mL of ethyl acetate. The combined ethyl acetate was washed with 2 × 100 mL of water, dried over magnesium sulfate, and concentrated in vacuo. The oil thus obtained was purified by flash chromatography (20% ethyl acetate in hexanes to 50% ethyl acetate in hexanes as eluant) to afford the enone acid **37** (0.264 g, 86%) as a white crystalline solid: mp 109–111 °C; NMR ($CDCl_3$, 200 MHz) δ 0.96–1.24 (m, 2 H, containing 3 H s at 1.10), 1.30–1.44 (m, 1 H, containing 3 H s at 1.36), 2.05–2.33 (m, 2 H, containing 3 H s at 2.30), 2.55–2.71 (m, 2 H), 2.77–2.97 (m, 2 H), 5.88 (d, 1 H, J = 0.5 Hz), 6.18 (broadened s, 1 H); IR ($CHCl_3$) 2900 (br), 1730, 1700, 1675 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.90; H, 7.87.

Cyclization of Enone Acid 37. The enone acid **37** (0.182 g, 0.69 mmol) in 22 mL of 4:1 tetrahydrofuran/*tert*-butyl alcohol was added dropwise to a cold (−20 °C) solution of potassium *tert*-butoxide (Aldrich) (0.155 g, 1.38 mmol) in 11 mL of 4:1 tetrahydrofuran/*tert*-butyl alcohol over a period of approximately 10 min. After the addition was complete, the temperature was raised to −10 °C and stirred at that temperature for 1.5 h. At this time the solution was diluted with 100 mL of water and acidified with 10% HCl. The aqueous solution was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were dried over magnesium sulfate and concentrated in vacuo. The crude β-hydroxy ketone was added to 50 mL of benzene and *p*-toluenesulfonic acid (13 mg) was added. The reaction mixture was heated at reflux for 1 h. The reaction was cooled and the benzene washed with water (20 mL), dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash chromatography (30% ethyl acetate in Skellysolve-F as eluant) to yield in order of elution the dienone acid **38** (29 mg, 17%) and the starting enone acid **37** (19 mg, 10%). (For spectroscopic data of **38** see preparation of that compound (vide infra)).

4α-(3-Oxo-1-buten-2-yl)-7α-carbomethoxy-4β,7β-dimethyl-(1α,5α)-bicyclo[3.3.0]octan-3-one (39). Vinyl chloride **36** (0.266 g, 0.71 mmol) was dissolved in 66 mL of 88% formic acid and treated with 0.91 g (2.86 mmol) of mercuric acetate and 3.56 g (56.5 mmol) of ammonium formate. The reaction mixture was stirred vigorously for 45 h at room temperature. Water (50 mL) was added and stirring was continued for 30 min. An additional 150 mL of water was added and the solution was filtered through Celite. The pad was rinsed with 150 mL of methylene chloride also. The layers were separated and the aqueous was extracted with 2 × 50 mL of methylene chloride. The combined organic layers were washed with saturated sodium bicarbonate (100 mL) and water (100 mL), dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash chromatography (15% ethyl acetate in Skellysolve-F as eluant) to afford the enone ester **39** (0.180g, 91%) as a crystalline solid: mp 78–79 °C; NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 3 H), 1.10–1.20 (m, 1 H), 1.28–1.39 (m, 1 H, containing 3 H s at 1.31), 2.06–2.29 (m, 2 H, containing 3 H s at 2.29), 2.46–2.90 (m, 4 H), 3.62 (s, 3 H), 5.87 (m, 1 H), 6.17 (s, 1 H); IR ($CHCl_3$) 2985, 1740, 1680, 1210, 1175 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.89; H, 7.99.

4α-Carbomethoxy-1β,4β-dimethyl-11-methylene-(2α,6α)-tricyclo[6.3.0.0^{2,6}]undec-8-en-10-one (40).[10a] A solution of enone ester **39** (0.160 g, 0.58 mmol) in 18 mL of 4:1 tetrahydrofuran/*tert*-butyl alcohol was added dropwise over approximately a 10-min period to a cold (−20 °C) solution of potassium *tert*-butoxide (Aldrich) (0.129 g, 1.15 mmol) in 8 mL of 4:1 tetrahydrofuran/*tert*-butyl alcohol. After the addition was complete, the solution was warmed to −10 °C and stirred for 45 min. Water (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with 4 × 50 mL of methylene chloride. The combined organic extracts were washed with water (50 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude β-hydroxy ketone was dissolved in 25 mL of benzene, 5 mg of *p*-toluenesulfonic acid was added, and the reaction was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and the solution was washed with water (15 mL), dried over magnesium sulfate, and evaporated in vacuo. The residual oil was purified by flash chromatography (10% ethyl acetate in Skellysolve-F as eluant) to afford 0.110 g (80%) of the dienone ester **40** as a colorless oil. (See ref 10a for partial spectroscopic data.): NMR ($CDCl_3$, 200 MHz) δ 1.14 (s, 3 H), 1.18–1.39 (m, 1 H, containing 3 H s at 1.34), 1.56 (m, 1 H), 2.21–2.83 (m, 6 H), 3.63 (s, 3 H), 5.54 (s, 1 H), 5.86 (s, 2 H); IR ($CHCl_3$) 2970, 1730, 1700, 1625, 1195 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_3$: M_r, 260.1412. Found: M_r, 260.1410.

4α-Carboxy-1β,4β-dimethyl-11-methylene-(2α,6α)-tricyclo[6.3.0.0^{2,6}]undec-8-en-10-one (38).[10a] A solution of the dienone ester **40** (0.079 g, 0.303 mmol) and dry lithium iodide (0.608 g, 4.55 mmol) in dimethylformamide (12 mL) was heated at reflux under a nitrogen atmosphere for 32 h. The reaction mixture was cooled to room temperature, diluted with 30 mL of water, and acidified with 10% HCl to pH 1–2. The aqueous solution was extracted with methylene chloride (3 × 30 mL) and the combined organic extracts were washed with water (2 × 30 mL), dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash chromatography (25% ethyl acetate in hexanes eluant) to give the starting dienone ester **40** (17.5 mg, 23%) and the dienone acid **38** (44 mg, 59%) as white crystals: mp 113–115 °C (See ref 10a for partial spectroscopic data): NMR ($CDCl_3$, 200 MHz) δ 1.14 (s, 3 H), 1.22–1.39 (m, 1 H, containing 3 H s at 1.39), 1.59 (m, 1 H), 2.24–2.57 (m, 4 H), 2.71–2.84 (m, 2 H), 5.14 (s, 1 H), 5.87 (m, 2 H); IR ($CHCl_3$) 2990 (br), 1700, 1625 cm^{-1}.

4α-Carboxy-1β,4β-dimethyl-8β,9β-oxido-11-methylene-(2α,6α)-tricyclo[6.3.0.0^{2,6}]undecan-10-one (*dl*-Complicatic Acid) (2).[5,10a] The dienone acid **38** (14.0 mg, 0.060 mmol) was dissolved in 4 mL of 1:1 methanol/water and the solution was cooled to 0 °C. Sodium bicarbonate (100 mg, 1.20 mmol) was added, followed by 30% hydrogen peroxide (60 μL, 15.0 mmol). The reaction was warmed to room temperature and stirred at ambient temperature for 1.5 h. The mixture was poured into 20 mL of saturated ammonium chloride and 20 mL of ethyl acetate. The layers were separated and the aqueous layer was extracted with an additional 10 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate and evaporated in vacuo. The crude product was purified by preparative thin layer chromatography (E. Merck silica gel 60-F254, 2-mm glass backed plates) using 8:2:1 petroleum ether/ethyl acetate/acetic acid as the eluant. This afforded complicatic acid (**2**) (see ref 5, 10a) (6.0 mg, 40%) as a colorless oil: NMR ($CDCl_3$, 200 MHz) δ 1.15 (s, 3 H), 1.20 (m, 1 H), 1.38 (s, 3 H), 1.55 (m, 1 H), 1.98 (d, 2 H, J = 8.3 Hz), 2.20–2.82 (m, 4 H), 3.38 (s, 1 H), 5.24 (s, 1 H), 6.02 (s, 1 H); IR ($CHCl_3$) 2980 (br), 2940, 1735, 1705, 1470, 1230 cm^{-1}.

4α-Carboxy-10β-hydroxy-1β,4β-dimethyl-11-methylene-8β,9β-oxido-(2α,6α)-tricyclo[6.3.0.0^{2,6}]undecane (Hirsutic Acid C) (1). The one-pot method of Greene[10f,g] was used to prepare hirsutic acid C (1) from the dienone acid **38**. In this manner, the dienone acid **38** (50 mg, 0.20 mmol) was converted to *dl*-hirsutic acid C (1) (26 mg, 51%), mp 169–171 °C after recrystallization from ether (lit. mp[10a] 168–169 °C): NMR ($CDCl_3$, 200 MHz) δ 1.02 (s, 3 H), 1.18–1.24 (m, 2 H), 1.36 (s, 3 H), 1.46 (m, 1 H), 1.85 (d, 2 H, J = 8.6 Hz), 2.18–2.70 (m, 4 H), 3.45 (d, 1 H, J = 1.8 Hz), 4.58 (m, 1 H), 4.98 (d, 1 H, J = 2.1 Hz), 5.25 (d, 1 H, J = 2.1 Hz); IR (KBr) 3390, 3150–2890 (br), 1695, 1410, 1210, 1160, 1095 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4$: M_r, 264.1362. Found: M_r 264.1360. A sample of synthetic hirsutic acid C (1) was converted to the methyl ester for further comparison purposes (vide infra). In addition, the 300-MHz NMR and infrared spectra were identical with those obtained from a sample of *dl*-hirsutic acid C (1) kindly provided by Professor Barry M. Trost.

4α-Carbomethoxy-10β-hydroxy-1β,4β-dimethyl-11-methylene-8β,9β-oxido-(2α,6α)-tricyclo[6.3.0.0^{2,6}]undecane (Methyl Hirsutate) (41). Hirsutic acid C (1) (10 mg, 0.04 mmol) was dissolved in 3 mL of ethyl acetate and the resulting solution was treated with 3–4 mL of diazomethane/ether. After 5 min, the volatiles were evaporated in vacuo and the residue was purified by flash chromatography (5% ethyl acetate in petroleum ether as eluant) to afford methyl hirsutate (41) (8 mg, 80%) as a white crystalline solid: mp 135–136 °C (after crystallization from ether) (lit. mp[10a] 137–138 °C); NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3 H), 1.46 (m, 1 H), 1.35 (s, 3 H), 1.44 (m, 1 H), 1.65 (br s, 1 H), 1.86 (d, 2 H, J = 8.5 Hz), 2.20–2.35 (m, 2 H), 2.40–2.63 (m, 2 H), 3.44 (d, 1 H, J = 1.9 Hz), 3.64 (s, 3 H), 4.60 (br s, 1 H), 4.98 (d, 1 H, J = 2.6 Hz), 5.25 (d, 1 H, J = 2.3 Hz). This data is in excellent agreement with that reported in the literature for this compound (See lit. ref 10a for published spectroscopic data).

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Biosynthetic Studies of Marine Lipids. 5.[1] The Biosynthesis of Long-Chain Branched Fatty Acids in Marine Sponges

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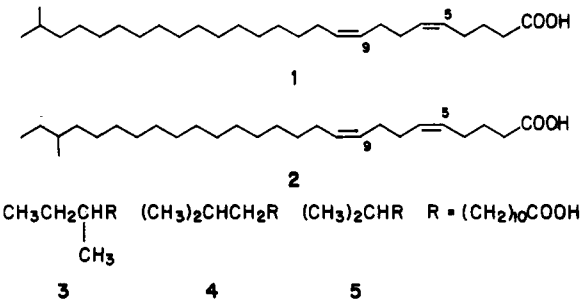
The very long chain branched fatty acids 25-methyl-5,9-hexacosadienoic ($\Delta^{5,9}$-iso-27:2) and 24-methyl-5,9-hexacosadienoic ($\Delta^{5,9}$-anteiso-27:2) acids as well as the straight-chain 5,9-hexacosadienoic ($\Delta^{5,9}$-26:2) acid were shown to originate from the short-chain precursors 13-methyltetradecanoic (iso-15:0), 12-methyltetradecanoic (anteiso-15:0), and palmitic (n-16:0) acids, respectively, by means of ^{14}C incorporation experiments in the marine sponge *Jaspis stellifera*. These results confirm that methyl branching does *not* occur after chain elongation. The unusual $\Delta^{5,9}$ unsaturation probably takes place after chain elongation of short branched or straight-chain fatty acids.

Sponges are the most primitive of the mutlicellular animals with a long, separate evolutionary history. Recent reports[2-5] have shown that they are rich sources of C_{24}–C_{30} fatty acids in contrast to the C_{14}–C_{22} fatty acids typically found in higher animals. Their phospholipids also include numerous branched fatty acids which have been isolated in our laboratory from *Petrosia ficiformis*,[5] *Calix niceaencis*,[6] *Petrosia hebes*,[7] *Aplysina fistularis*,[8] and *Strongylophora durissima*.[9] The first three sponges contain iso and anteiso acids, i.e., (*Z*,*Z*)-25-methyl-5,9-hexacosadienoic (**1**) and (*Z*,*Z*)-24-methyl-5,9-hexacosadienoic (**2**) acids respectively, as their major components, while the other sponges contain fatty acids with branching in the middle of the chain.[5-7]

The origin of terminal methyl branching in short-chain fatty acids has been studied thoroughly.[10,11] The terminal methyl group is generally derived from the three branched amino acids valine, leucine, and isoleucine via transamination to their α-keto acids and oxidative decarboxylation to the branched acyl-CoA primers. Consequently, there are three families of branched fatty acids derived directly from amino acids, i.e., anteiso-odd **3**, iso-odd **4**, and iso-even **5**.



The origin of terminal methyl branching in the very long chain branched fatty acids of marine sponges has so far not been investigated. Terminally branched, short-chain fatty acids, possibly of bacterial origin, may serve as primers for these long-chain acids.[5] However, the terminal methyl group might also arise from unsaturation after chain elongation at the ω3 carbon followed by *S*-

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