# Iterative Three-Carbon Annelation. A Stereoselective Total Synthesis of (±)-Hirsutic Acid C

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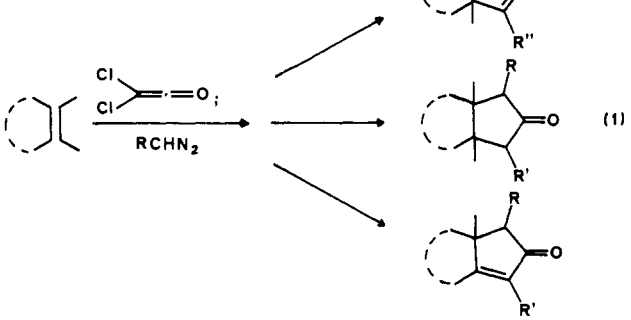
**Abstract:** Iterative olefin annelation has been used for the synthesis of hirsutic acid C, a linearly fused tricyclopentanoid fungal metabolite from *Stereum hirsutum* and *Stereum complicatum*.

The present interest in the development of new techniques for annelatively attaching a three-carbon unit onto a preexisting ring[1] stems, at least in part, from the burgeoning number of natural products found to contain one or more fused five-membered rings. The steroids, guaianes, and pseudoguaianes[2] are representative of the natural products having single five-membered rings incorporated in more complex ring systems; the hirsutanes,[3-5] capnellanes,[6] isocomanes,[7] pentalanes,[8] and propellanes[9] are illustrative of the naturally occurring polyquinanes.[10]

While most of the annelation methods that have been developed offer potential access to the former group of natural products, a great many do not readily lend themselves to iteration and therefore are not generally useful for the construction of the fused polycyclopentanoid skeletons of the latter group. In this paper we demonstrate the effectiveness of our recently described dichloroketene–diazoalkane annelation procedure (generalized in eq 1)[11] in the construction of fused five-membered rings from




(1)

olefins by detailing a new, stereo- and regiocontrolled, iterative approach to hirsutic acid C (**1**).[3]

(1) See: Jung, M. E. *Tetrahedron* **1976**, *32*, 3, and references cited therein. See also: Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 5508. Hayakawa, Y.; Yokoyama, K.; Noyori, R. *Ibid.* **1978**, *100*, 1791. Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217. Hiyama, T.; Shinoda, M.; Nozaki, H. *Ibid.* **1978**, 771. Corey, E. J.; Boger, D. L. *Ibid.* **1978**, 13. Jacobson, R. M.; Abbaspour, A.; Lahm, G. P. *J. Org. Chem.* **1978**, *43*, 4650. Jacobson, R. M.; Lahm, G. P. *Ibid.* **1979**, *44*, 462. Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328. Trost, B. M.; Chan, D. M. T. *Ibid.* **1979**, *101*, 6429. Hiyama, T.; Shinoda, M.; Nozaki, H. *Ibid.* **1979**, *101*, 1599. Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979**, 3279. Ho, T.-L. *J. Chem. Soc., Chem. Commun.* **1980**, 1149. Jacobson, R.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395. Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *Ibid.* **1980**, *45*, 1046. Paquette, L.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *Ibid.* **1980**, *45*, 3017. Marino, J. P.; Ferro, M. P. *Ibid.* **1981**, *46*, 1828. Cohen, T.; Matz, J. R. *Tetrahedron Lett.* **1981**, 2455, 2459. Williams, D. R.; Abbaspour, A.; Jacobson, R. M. *Ibid.* **1981**, 3565. Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. Denmark, S. E.; Jones, T. K. *Ibid.* **1982**, *104*, 2642, and references cited therein.

(2) See: Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972. See also references cited in: Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 472.

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(8) Martin, D. G.; Slomp, G.; Mizak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970**, 4901. Duchamp, D. J.; Chidester, C. G. *Acta Crystallogr., Sect. B* **1972**, *B28*, 173. Connelly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487. Seto, H.; Sasaki, T.; Yonehara, H.; Uzawa, J. *Tetrahedron Lett.* **1978**, 923. Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Ibid.* **1978**, 4411. Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6538. Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973. Parson, W. H.; Schlessinger, R. H.; Quesada, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 889. Paquette, L. A.; Schostarez, H.; Annis, G. D. *Ibid.* **1981**, *103*, 6526. Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355. Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504.

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(10) See also: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41.

(11) (a) Greene, A. E.; Deprês, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. (b) Deprês, J. P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036.

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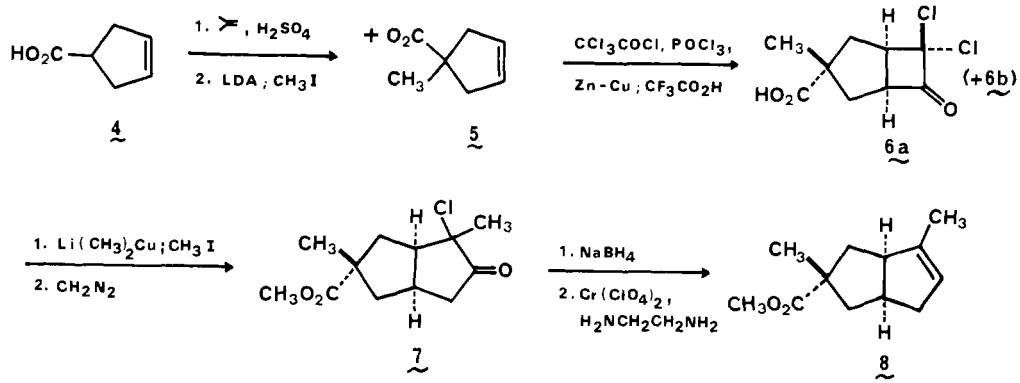
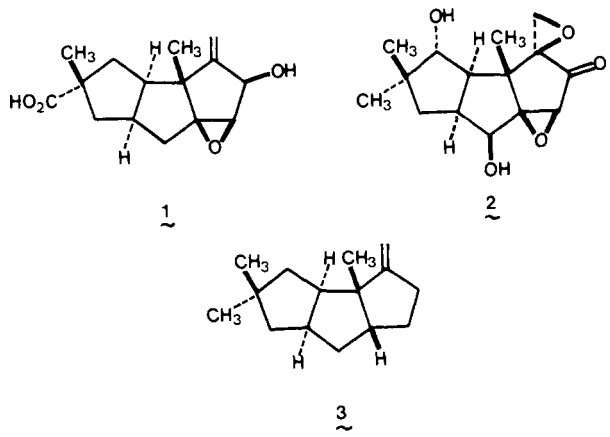
Scheme I



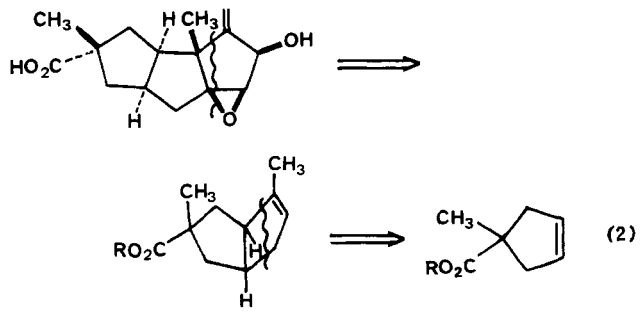
Hirsutic acid C, isolated from *Stereum hirsutum*[3a] and *Stereum complicatum*,[3d] belongs to the synthetically challenging, albeit small, hirsutane group of naturally occurring sesquiterpenes, which also includes the coriolins (e.g., **2**)[4] and the proposed biogenetic precursor of the group, hirsutene (**3**).[5] The considerable synthetic



effort that has recently been focused on these fungal metabolites results not only from their unusual *cis,anti,cis*-tricyclo-[6.3.0.0$^{2,6}$]undecane carbon skeleton but also from the frequently associated significant antibiotic and antitumor properties.[3,4]

## Results and Discussion

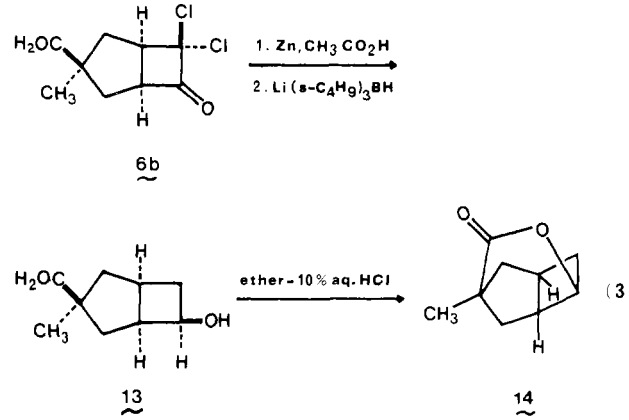
The envisaged approach to hirsutic acid C is outlined retrosynthetically in eq 2. In this approach, the ester group of the



starting olefin and the "open book" shape of the bicyclic intermediate were expected to direct stereoselectivity in the desired sense the respective ketene cycloadditions; attending regioselectivity problems, if any, were expected to be minor owing to the symmetry of the starting olefin and the high degree of selectivity that normally accompanies ketene cycloadditions with trisubstituted olefins.[12]

The readily available acid **4**[13] was converted with isobutylene in ether ($H_2SO_4$ catalysis) to the corresponding *tert*-butyl ester, which, in turn, was methylated to produce ester **5** in 75–80% overall yield (Scheme I). Surprisingly, in light of previous work,[5e,14] chloromethylketene, whether generated in situ from α-chloropropionyl chloride and triethylamine or from α,α-dichloropropionyl chloride and a zinc–copper couple, failed to react with **5**. Fortunately, however, dichloroketene[12] underwent smooth, stereoselective cycloaddition with this olefin and yielded after workup in the presence of trifluoroacetic acid the readily separated crystalline dichloro keto acids **6a** (mp 135–137 °C) and **6b** (mp 129–132 °C) in an ca. 3 to 1 ratio (NMR) in 80% combined yield. In contrast, the methyl and *n*-butyl esters corresponding to **5** were found to produce the isomeric dichloro keto esters in ratios of only ca. 1:1 and 3:2 (NMR), respectively.

The lower field chemical shift of the methyl group of the major isomer (1.40 ppm vs. 1.34 ppm) suggested the indicated stereochemical assignments; however, conclusive evidence could be secured chemically, as shown in eq 3. The minor isomer (**6b**)



was sequentially reduced with zinc in acetic acid and L-Selectride[15] in tetrahydrofuran to give the hydroxy acid **13**, which readily produced the crystalline tricyclic lactone **14**, mp 47–49 °C, on stirring in ether–10% aqueous hydrochloric acid at room temperature. Thus, the minor isomer is clearly the endo acid **6b**.

The chlorine atoms now nicely served to direct the regiochemical outcome of the steps leading to olefin **8**. Addition of ketone **6a** to 3 equiv of lithium dimethylcopper in tetrahydrofuran at −78 °C rapidly generated the α-chloro enolate, which in the presence of excess methyl iodide and hexamethylphosphoric triamide

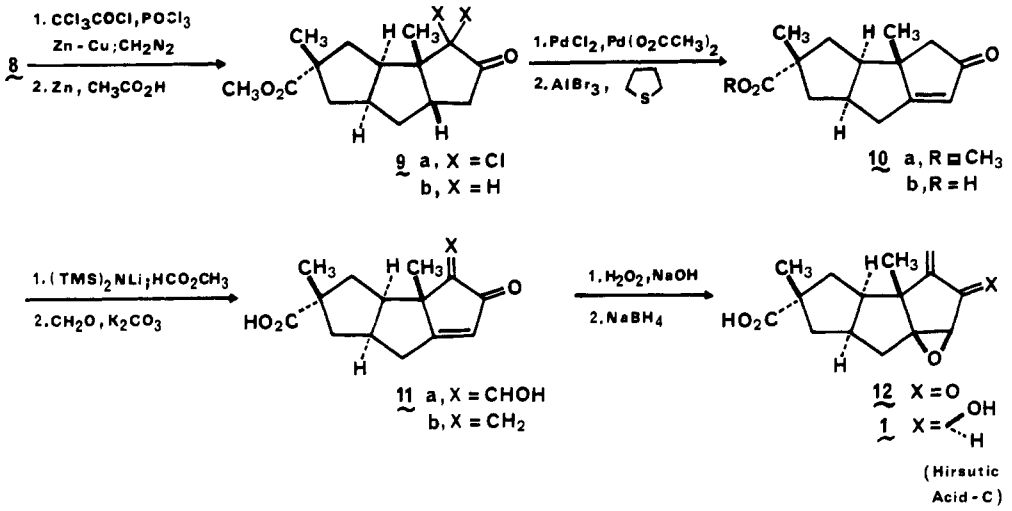
(12) See: Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879, 3173. Bak, D. A.; Brady, W. T. *Ibid.* **1979**, *44*, 107, and references cited therein.

(13) Murdock, K. C.; Angier, R. B. *J. Org. Chem.* **1962**, *27*, 2395. A detailed study of this three-step procedure has resulted in a *4-fold* increase in the overall yield of **4** (73% from dimethyl malonate). This improvement will be discussed in a subsequent paper. For an alternative method of preparation, see: Cremer, S. E.; Blankenship, C. *Ibid.* **1982**, *47*, 1626.

(14) See: Hassner, A.; Pinnick, H. W.; Ansell, J. M. *J. Org. Chem.* **1978**, *43*, 1774, and references cited therein.

(15) L-Selectride is the registered trademark of the Aldrich Chemical Co.

Scheme II




provided the corresponding α-chloro α-methyl ketone in high yield.[11b] Ring expansion (with concomitant esterification) of this cyclobutanone could be cleanly effected with diazomethane in ether–methanol solution[11a] at −35 °C to give regioselectively the cyclopentanone **7**, which could also be secured from cyclobutanone **6a**, but not as effectively, by reversing the order of these last two steps. Treatment of **7** with sodium borohydride in methanol followed by reduction of the resultant chlorohydrin with chromous perchlorate–ethylenediamine in aqueous dimethylformamide[16] then engendered a unique olefin **8** in 38–42% overall yield from acid **6a** (ca. 80%/step).

In the second annelation, as had been hoped, the "open book" shaped olefin **8** suffered a highly stereo- as well as regioselective cycloaddition with dichloroketene[12] to produce, following diazomethane ring enlargement,[11a] the desired *cis,anti,cis*-tricyclopentanoid intermediate **9a** in excellent yield (Scheme II). Enone **10a**, a key intermediate, could be secured from this dichlorocyclopentanone by several different procedures, viz., lithium dimethylcopper reduction followed by dehydrochlorination (lithium carbonate, lithium bromide, dimethylformamide),[11] dehydrochlorination and then zinc–acetic acid reduction, or, most effectively, zinc–acetic acid reduction (→**9b**, 65–70% from **8**, ca. 88%/step) followed by palladium(II) oxidation in dioxane–water at 85 °C (→**10a**, 50–58%).[17,18] Although palladium(II) has only infrequently been used in synthesis to effect this type of direct ketone dehydrogenation,[17] it proved in the present case to be not only more convenient but also higher yielding than the less direct dehydrotrimethylsilylation[19] and the various selenium-based[20] procedures.

The concluding steps of the synthesis commenced with demethylation of the sterically encumbered ester group of **10a** with 3.7 equiv of aluminum bromide in tetrahydrothiophene[21] to produce in excellent yield the acid **10b** (mp 180–182 °C), which was transformed to the dienone acid **11b** via the hydroxymethylene derivative **11a** through successive treatment with lithium bis(trimethylsilyl)amide (3.1 equiv in tetrahydrofuran) and methyl formate,[22] followed by reaction in aqueous acetone with excess formaldehyde in the presence of powdered potassium carbonate (50% overall yield).[23] Stereo- and regioselective basic hydrogen peroxide epoxidation of the dienone acid **11b** in ethanol then afforded dehydrohirsutic acid C (complicatic acid, **12**),[3d,e] which could be conveniently reduced in situ with sodium borohydride to produce highly stereoselectively in 56% yield hirsutic acid C (**1**). The identity of this material, mp 167–169 °C (lit.[3e] racemic mp 168–169 °C) was confirmed through spectroscopic and chromatographic comparison with an authentic sample of the natural product.

In summary, hirsutic acid C has been synthesized in 16 steps in an overall yield of ca. 2%. The significantly greater efficiency of the present synthesis compared with earlier ones is an indication of the synthetic potential of this iterative annelation procedure in the area of fused polycyclopentanoid natural products.

## Experimental Section

Solvents were generally distilled prior to use. Tetrahydrofuran, dioxane, ether, and hydrocarbons were distilled from sodium hydride–lithium aluminum hydride, and hexamethylphosphoric triamide was distilled under reduced pressure from calcium hydride. Methyl formate was distilled twice from phosphorus pentoxide and phosphorus oxychloride was distilled from potassium carbonate. Reactions were generally stirred under a nitrogen or argon atmosphere. Reaction products were isolated by addition of water followed by extraction with the solvent indicated and drying over anhydrous sodium sulfate, magnesium sulfate, or potassium carbonate.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25-mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 230-400 silica gel 60 was employed for dry column chromatography. A Beckman Acculab 4 or a Perkin-Elmer Model 298 or 397 spectrophotometer was used to record IR spectra (as neat liquid films, unless noted otherwise). A JEOL PMX-60 spectrometer was employed for the $^1H$ NMR spectra ($Me_4Si$ as the internal reference in $CCl_4$ solutions, except where noted otherwise). Mass spectra were obtained on a MS-30 AEI mass spectrometer (70 eV, direct insertion probe) or on a VG Micromass 70 70F instrument. Melting points were obtained with a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS.

***tert*-Butyl 3-Cyclopentenecarboxylate.** To 50 mL of distilled isobutylene at −78 °C was added 10.0 g (89.3 mmol) of 3-cyclopentenecarboxylic acid (**4**)[13] in 30 mL of ether followed by 1.0 mL of concen-

(16) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582. Wade, R. S.; Castro, C. E. *Org. Synth.* **1972**, *52*, 62.

(17) Cf.: Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752. von Bierling, B.; Kirschke, K.; Oberender, H. *J. Prakt. Chem.* **1972**, *314*, 170. Wolff, S.; Agosta, W. C. *Synthesis* **1976**, 240. Mincione, E.; Ortaggi, G.; Sirna, A. *Ibid.* **1977**, 773. Other palladium(II) reagents [palladium(II) acetylacetonate, chloride–benzonitrile complex, iodide, nitrate, and trifluoroacetate, and potassium tetrachloropalladate(II)] and other solvents (acetic acid, benzene, diglyme, glyme, tetrahydrofuran, and trifluoroacetic acid) were also examined, with or without added hydrochloric acid, benzoquinone, or dichlorodicyanobenzoquinone, and were found to be much less effective than palladium acetate–palladium chloride in aqueous dioxane.

(18) For less efficient routes to this intermediate, see references 3e–g.

(19) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(20) Branca, S. J.; Lock, R. L.; Smith, A. B., III *J. Org. Chem.* **1977**, *42*, 3165. Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. Reich, H. J.; Renga, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5434. Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130.

(21) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991.

(22) To obtain a high conversion of **10b** to the hydroxymethylene derivative **11a**, the crude reaction product required recycling.

(23) Manson, A. J.; Wood, D. *J. Org. Chem.* **1967**, *32*, 3434. Matsumoto, T.; Shirahama, H.; Tsuzuki, K.; Sakan, F.; Hashimoto, H. *Jpn. Kokai Tokkyo Koho* **1975**, *75 101*,353; *Chem. Abstr.* **1976**, *84*, 59033a.

trated sulfuric acid. After being stirred for 96 h at room temperature (closed system, safety shield!), the reaction mixture was cooled to −78 °C and poured slowly into a stirred mixture of ether and 10% aqueous sodium bicarbonate. After 1 h, the crude product was isolated with ether in the usual manner and then distilled to give 12.64 g (84%) of *tert*-butyl 3-cyclopentenecarboxylate: bp 71–73 °C (15 torr); IR 3060, 1730, 1620, 1370, 1155 $cm^{-1}$; $^1H$ NMR $\delta$ 1.4 (s, 9 H), 2.3–3 (m, 5 H), 5.43 (s, 2 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; $M_r$ 168.11502. Found: C, 71.20; H, 9.40; $M_r$ (mass spectrum) 168.11514.

***tert*-Butyl 1-Methyl-3-cyclopentenecarboxylate (5).** A solution of 8.40 g (50.0 mmol) of *tert*-butyl 3-cyclopentenecarboxylate in 10 mL of tetrahydrofuran was added slowly to 94 mL (52.6 mmol) of a 0.56 M tetrahydrofuran–hexane (2:1) solution of lithium diisopropylamide at −78 °C. After being stirred for 5 min at −78 °C, the reaction mixture was allowed to warm to −10 °C, was stirred for 10 min, and was then recooled to −78 °C and treated rapidly with 5 mL (11.4 g, 80.3 mmol) of methyl iodide. After being allowed to warm slowly to room temperature, the reaction mixture was processed in the usual fashion and the resultant crude product was distilled to afford 8.35 g (92%) of olefin **5**: bp 41–42 °C (4 torr); IR 3055, 1730, 1620, 1370, 1170, 1120 $cm^{-1}$; $^1H$ NMR $\delta$ 1.20 (s, 3 H), 1.40 (s, 9 H), 2.40 (ABq, $J$ = 14 Hz, $\delta_a - \delta_b$ = 44 Hz, 4 H), 5.42 (s, 2 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.26; H, 9.92.

**(1*R**,3*S**,5*S**)-7,7-Dichloro-3-methyl-6-oxobicyclo[3.2.0]heptane-3-carboxylic acid (6a) and 3*R** isomer 6b.** To a well-stirred mixture of 0.945 g (ca. 14 mmol) of zinc–copper couple and 0.945 g (5.19 mmol) of olefin **5** in 12.5 mL of dry ether under argon was added over 40 min a solution of 1.54 g (8.47 mmol) of trichloroacetyl chloride and 1.28 g (8.37 mmol) of phosphorus oxychloride in 9 mL of dry ether.[12a] After 3 h, the ether solution was separated from the excess couple and added to 50 mL of hexane, and the resulting mixture was concentrated under reduced pressure to ca. 40 mL in order to precipitate the zinc chloride. The supernatant was separated and concentrated to 7 mL and then treated with 2.5 mL of trifluoroacetic acid. After the mixture was allowed to stand for 2 h, the crude mixture of **6a** and **6b** was isolated with ether in the usual manner. The NMR spectrum of the mixture showed two signals for the C-3 methyl groups in a ratio of ca. 3:1. Recrystallization of this mixture from hot hexane afforded 0.432 g of **6a**. Dry silica gel chromatography with hexane–ethyl acetate–acetic acid (92.5:5:2.5) of the material remaining in the mother liquor gave 0.311 g (25%) of **6b** and an additional 0.248 g (55% combined yield) of **6a**. In a similar experiment run on 20 times the above scale, 4.5 g (18%) of **6b** and 12.3 g (50%) of **6a** were obtained. Isomer **6a** displayed the following properties: $R_f$ 0.50 [$SiO_2$, hexane–ethyl acetate–acetic acid (8:2:1)]; mp 135–137 °C (hexane); IR (Nujol) 1805, 1690, 1300, 1265, 1220, 945, 790 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 (s, 3 H), 1.6–2.1 (m, 2 H), 2.3–3.0 (m, 2 H), 3.53 (pseudo q, $J$ = 8 Hz, 1 H), 3.9–4.4 (m, 1 H).

Anal. Calcd for $C_9H_{10}O_3Cl_2$: C, 45.59; H, 4.25. Found: C, 45.52; H, 4.20.

The minor isomer **6b** displayed the following properties: $R_f$ 0.44 [$SiO_2$, hexane–ethyl acetate–acetic acid (8:2:1)]; mp 129–132 °C (hexane); IR (Nujol) 1803, 1695, 1290, 1145, 1090 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (s, 3 H), 1.5–2.7 (m, 4 H), 3.2–3.7 (m, 1 H), 3.8–4.3 (m, 1 H).

Anal. Calcd for $C_9H_{10}O_3Cl_2$: C, 45.59; H, 4.25. Found: C, 45.44; H, 4.20.

**(1*R**,3*S**,5*R**,6*S**)-1-Methyl-9-oxatricyclo[3.2.2.0$^{3,6}$]nonan-8-one (14).** A 2.00-g (8.44 mmol) sample of dichloro keto acid **6b** was stirred with 2.00 g (30.6 mmol) of zinc powder and 10 mL of glacial acetic acid at 90 °C for 5 h. The product was isolated with ether in the usual manner and then evaporatively distilled to give 1.18 g (83%) of keto acid: bp ca. 50 °C (0.05 torr); IR 1775, 1695, 1130, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (s, 3 H), 1.4–3.9 (m, 8 H). This material was dissolved in 10 mL of dry tetrahydrofuran and treated at −78 °C with 30 mL (30 mmol) of a 1 M solution of L-Selectride[15] in tetrahydrofuran. After being stirred for 0.5 h at −78 °C, the reaction mixture was treated slowly with 20 mL (32 mmol) of a 1.6 M aqueous sodium hydroxide solution followed by 10 mL (100 mmol) of 30% hydrogen peroxide. The mixture was then allowed to warm to room temperature and excess 10% aqueous hydrochloric acid was added. The product was isolated with ether to give 1.22 g of crude hydroxy acid **13**: IR 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.20 (s, 3 H), 4.50 (m, 1 H). An 0.815-g sample of this material was stirred in 30 mL of ether and 30 mL of 10% aqueous hydrochloric acid at room temperature for 15 h. The product was isolated with ether in the normal manner and then purified by dry silica gel chromatography with 10% ethyl acetate in hexane to yield 0.472 g (55%) of lactone **14**: mp 45–47 °C; IR 1730, 1145, 1125, 1095, 1065, 1015, 945 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (s, 3 H), 4.80 (pseudo q, $J$ = 1.5 Hz, 1 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.76; H, 7.53.

**Methyl (2*R**,3a*S**,6a*R**)-2,4-Dimethyl-1,2,3,3a,6,6a-hexahydropentalene-2-carboxylate (8).** A 2.40-g (10.1 mmol) sample of dichloro keto acid **6a** in 15 mL of dry tetrahydrofuran was added over 2 min to a solution at −78 °C of ca. 27 mmol of lithium dimethylcopper in ether–tetrahydrofuran [from the treatment of 5.34 g (28.0 mmol) of cuprous iodide in 20 mL of tetrahydrofuran at −50 °C with 34.3 mL (55 mmol) of a 1.6 M ether solution of methyllithium, followed by warming of the solution to −20 °C].[11b] Following the addition, the reaction mixture was allowed to warm over ca. 30 min to −50 °C and was then recooled to −78 °C and treated rapidly with a solution of 14.4 g (101 mmol) of methyl iodide in 10 mL of hexamethylphosphoric triamide. After being warmed to 0 °C, the reaction mixture was treated with a saturated solution of aqueous ammonium chloride and the product was isolated with ether to give 2.16 g of the crude $\alpha$-chloro-$\alpha$-methylcyclobutanone: IR 1795, 1705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (s), 1.73 (s).

The above crude product was added to a solution of ca. 3 g of diazomethane in 200 mL of ether and 20 mL of methanol at −35 °C, and the resultant solution was kept at this temperature for 82 h.[11a] Acetic acid was then added to consume the excess diazomethane and the solvents were removed under reduced pressure to leave 2.45 g of crude keto ester **7**: IR 1755, 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 1.33 (s), 1.50 (s), 3.63 (s). The crude keto ester **7** in 50 mL of methanol at 0 °C was treated portionwise with 0.30 g (7.93 mmol) of sodium borohydride over 5 min. After an additional 10 min, the product was isolated in the usual fashion to give 2.50 g of oily chlorohydrin: IR 3440, 1730 $cm^{-1}$. This crude material dissolved in 400 mL of degassed dimethylformamide under argon was treated with 32 mL (51.2 mmol) of a 1.6 M aqueous solution of chromium(II) perchlorate followed by 6.4 mL (95.7 mmol) of ethylenediamine.[16] After 1.5 h, the product was isolated with ether in the usual manner and was purified by dry silica gel chromatography with 5% ether in pentane to give 0.740 g (38% overall from **6a**) of pure olefin **8**: IR 3035, 1735, 1310, 1200, 1170, 1095 $cm^{-1}$; $^1H$ NMR $\delta$ 1.23 (s, 3 H), 1.65 (br s, 3 H), 3.60 (s, 3 H), 5.03 (br s, 1 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.12; H, 9.38.

**Methyl (2*R**,3a*S**,3b*S**,6a*R**,7a*R**)-2,3,3a,3b,4,5,6,6a,7,7a-Decahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (9b).** To a mixture of 2.11 g (ca. 32 mmol) of zinc–copper couple and 0.586 g (3.02 mmol) of olefin **8** in 16 mL of dry ether, stirred under argon at 28 °C, was added over 3 h a solution of 3.44 g (18.9 mmol) of trichloroacetyl chloride and 2.88 g (18.8 mmol) of phosphorus oxychloride in 20 mL of dry ether.[12a] After being stirred at 28 °C for an additional 1.5 h, the mixture was left overnight at 17 °C. The ether solution was then separated from the excess couple and added to hexane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 1.20 g of the crude dichlorocyclobutanone: IR 1800, 1770 $cm^{-1}$; $^1H$ NMR $\delta$ 1.38 (s, 3 H), 1.53 (s, 3 H), 3.73 (s, 3 H). This material was added to a solution of ca. 1 g of diazomethane in 100 mL of ether and 5 mL of methanol at room temperature.[11a] After 30 min, a small amount of acetic acid was added to consume the excess diazomethane and the solvents were removed under reduced pressure to give the crude dichlorocyclopentanone **9a**: IR 1770, 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 1.33 (s, 6 H), 3.67 (s, 3 H). This crude material was stirred with 5 g of zinc powder in 25 mL of glacial acetic acid at 85 °C for 4.5 h. The product was then isolated with ether in the usual manner and purified by dry silica gel chromatography with 10% ether in pentane to yield 0.510 g (68% overall) of ketone **9b**: IR 1735, 1305, 1200, 1170, 1080 $cm^{-1}$; $^1H$ NMR $\delta$ 1.05 (s, 3 H), 1.27 (s, 3 H), 3.58 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_3$: $M_r$ 250.15688. Found: $M_r$ (mass spectrum) 250.15783.

**Methyl (2*R**,3a*S**,3b*R**,7a*R**)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (10a).** A stirred mixture of 210 mg (0.84 mmol) of ketone **9b**, 210 mg (1.18 mmol) of palladium(II) chloride, and 210 mg (0.94 mmol) of palladium(II) acetate in 3.75 mL of 40% aqueous dioxane was heated at 85 °C under an oxygen atmosphere for 5 h.[17] The reaction product was isolated with ether in the normal manner and was purified by dry silica gel chromatography with 20% ethyl acetate in hexane to give 52 mg of starting material and 82 mg (52% based on 75% conversion) of **10a**. A similar experiment run to 86% conversion yielded 58% of **10a**. This material was spectroscopically and chromatographically indistinguishable from an independently prepared sample:[3f] IR 3070, 1730, 1710, 1635, 1310, 1205, 1170, 1095, 845 $cm^{-1}$; $^1H$ NMR $\delta$ 1.10 (s, 3 H), 1.33 (s, 3 H), 3.63 (s, 3 H), 5.60 (br s, 1 H).

**(2*R**,3a*S**,3b*R**,7a*R**)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylic Acid (10b).** An

81-mg (0.33 mmol) sample of ester **10a** in 3.2 mL of tetrahydrothiophene was stirred under argon as 162 mg (0.61 mmol) of aluminum bromide was added over 1 h.[21] After the reaction was stirred for 24 h, an additional 162 mg (0.61 mmol) of aluminum bromide was added over 6 h. After an additional 38 h, the reaction mixture was diluted with methylene chloride and 10% aqueous hydrochloric acid and the product was isolated with methylene chloride in the usual manner to give 76 mg (99%) of **10b**: mp 180–182 °C dec (methylene chloride–cyclohexane); IR (Nujol) 1710, 1670, 1620, 1160 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.12 (s, 3 H), 1.44 (s, 3 H), 5.65 (br s, 1 H).

Anal. Calcd for $C_{14}H_{18}O_3$: $M_r$ 234.12558. Found: $M_r$ (mass spectrum) 234.12656.

**(2*R**,3a*S**,3b*R**,7a*R**)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-4-methylene-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylic Acid (11b).** A 76-mg (0.32 mmol) sample of enone **10b** in 4 mL of tetrahydrofuran at −78 °C under argon was treated with 1.00 mL (1.00 mmol) of a 1 M tetrahydrofuran solution of lithium bis(trimethylsilyl)-amide. The temperature was allowed to reach −35 °C over 1 h, after which 73 mg (1.22 mmol) of methyl formate was rapidly added. After being warmed to room temperature over 45 min, the reaction mixture was recooled to −78 °C and treated with 1.4 mL (1.4 mmol) of the lithium bis(trimethylsilyl)amide solution. The temperature of the reaction was allowed to come to −35 °C over 1 h, after which 730 mg (12.2 mmol) of methyl formate was rapidly added. After being warmed to room temperature over 45 min, the reaction mixture was treated with 10% aqueous hydrochloric acid and then processed in the usual manner with methylene chloride to give a crude mixture of the hydroxymethylene derivative **11a** and some starting material. This mixture was recycled exactly as described above, and the resultant crude product **11a** was stirred rapidly for 30 min in 10 mL of acetone in the presence of 250 mg (1.81 mmol) of potassium carbonate and 250 μL (ca. 2.5 mmol) of 30% formalin.[23] After the addition of methylene chloride and 10% aqueous hydrochloric acid, the product was isolated with methylene chloride in the normal manner and was purified by dry silica gel chromatography with hexane–ethyl acetate–acetic acid (8:1.5:0.5) to give 40 mg (50%) of oily dienone **11b**. This material was spectroscopically the same as an independently prepared sample:[3f] IR 1695, 1645, 1615, 1305, 1260, 1160, 940, 860 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (s, 3 H), 1.40 (s, 3 H), 5.10 (s, 1 H), 5.83 (s, 2 H).

**(1a*R**,2*R**,3a*R**,3b*R**,5*S**,6a*R**,7a*S**)-Decahydro-2-hydroxy-3a,5-dimethyl-3-methylenecyclopenta[4,5]pentaleno[1,6a-*b*]oxirene-5-carboxylic Acid [(±)-Hirsutic Acid C] (1).** A 30-mg (0.12 mmol) sample of dienone **11b** in 1.50 mL of absolute ethanol under argon at −35 °C was treated with 0.50 mL (5.0 mmol) of 30% hydrogen peroxide and then with 0.50 mL (0.50 mmol) of 1 N aqueous sodium hydroxide.[3e] After the mixture was stirred for 4 h at −35 °C, 1.5 mL of absolute ethanol and 80 mg (2.1 mmol) of sodium borohydride were added and the reaction temperature was allowed to reach 0 °C over 35 min. The reaction mixture was then diluted with water, and methylene chloride and 2% aqueous hydrochloric acid were added. Isolation of the product with methylene chloride in the usual manner yielded 28 mg of crude **1**, which was purified by dry silica gel chromatography with hexane–ethyl acetate–acetic acid (8:2:1) to give 18 mg (56%) of pure (±)-hirsutic acid C (**1**): mp 167–169 °C (methylene chloride–cyclohexane) (lit.[3e] mp 168–169 °C); IR ($CHCl_3$) 1700, 1315, 1260, 1220, 1100, 1065, 1030, 1000, 915, 885 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (s, 3 H), 1.37 (s, 3 H), 3.43 (br s, 1 H), 4.57 (m, 1 H), 4.97 (d, $J$ = 2 Hz, 1 H), 5.23 (d, $J$ = 2 Hz, 1 H); mass spectrum $m/e$ 264 ($M^+$). The IR, NMR, and mass spectra were indistinguishable from those of an authentic sample of the natural product. An admixture of the synthetically and naturally derived compounds, as well as an admixture of the corresponding methyl esters obtained with diazomethane in ether, was chromatographically (TLC, silica gel) inseparable with several different solvent systems and multiple developments.

Anal. Calcd for $C_{15}H_{20}O_4$: $M_r$ 264.13614. Found: $M_r$ (mass spectrum) 264.13599.

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**Registry No.** (±)-**1**, 55123-33-6; **4**, 7686-77-3; **5**, 84694-04-2; (±)-**6a**, 84694-05-3; (±)-**6a** (α-chloro-α-methylbutanone derivative), 84694-06-4; (±)-**6b**, 84773-27-3; **7**, 84694-07-5; (±)-**8**, 84694-08-6; (±)-**9a**, 84694-09-7; (±)-**9b**, 84694-10-0; (±)-**10a**, 70004-11-4; (±)-**10b**, 84694-11-1; (±)-**10b**, 55093-82-8; (±)-**14**, 84694-12-2; *tert*-butyl 3-cyclopentenecarboxylate, 84694-13-3; $CCl_3COCl$, 76-02-8.