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An Efficient, Enantioconvergent Total Synthesis of Natural Hirsutic Acid C

Andrew E. Greene,* Marie-Jacqueline Luche, and A. Aarao Serra

Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, Université Scientifique et Médicale de Grenoble, Bat. 52—Chimie Recherches BP 68, 38402 Saint Martin d'Heres Cedex, France

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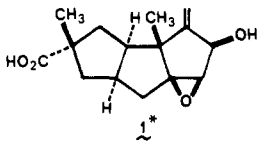
A stereocontrolled total synthesis of natural hirsutic acid C, a linearly fused triquinane from *Stereum hirsutum*, has been achieved through the use of an efficient asymmetric hydroboration and two highly selective three-carbon annelations.

Among the many syntheses that have been reported to date of triquinane natural products, there are exceedingly few that selectively produce the naturally occurring enantiomer or readily could.[1] We now detail an effective, enantioconvergent total synthesis of the linearly fused triquinane (+)-hirsutic acid C (**1***[2]), the naturally occurring antipode, which we have been able to achieve through adjustment of our synthesis of racemic hirsutic acid C.[3]



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(+)-Hirsutic acid C was first isolated in 1947 from the metabolism fluid of the fungus *Stereum hirsutum* by Heatley, Jennings, and Florey, who, in addition, studied some of the biological properties of this and related metabolites.[4] Some 18 years later, Scott and co-workers through chemical and crystallographic studies correctly determined the structure and stereochemistry of (+)-hirsutic acid C to be that indicated by formula **1***.[5] Since this determination, four different syntheses of racemic hirsutic acid C have appeared (with overall yields ranging from 2 to 0.2%)[3,6] and one of (+)-hirsutic acid C has recently been published (ca. 0.15% overall yield).[7]

Discussion

The readily available intermediate from our previous synthesis[3] racemic keto acid **2** (Chart I) seemed an ideal starting material for use in an enantioconvergent approach to natural hirsutic acid C (**1***). Through simple manipulations at the C-6 and C-7 positions,[3,8] it appeared it might be possible to merge the individual enantiomers **2*** and **2***′ into the "correct" enantiomer (**4***) of a known[3] racemic hirsutic acid C precursor or to convert racemic **2** into the meso compound **5**, a substrate with which chiral induction could be quite successful. These two approaches are outlined in Chart I.

In hoping to transfer as much of the efficient methodology of the racemic synthesis as possible to the synthesis of (+)-hirsutic acid C, we first examined the resolution of **2** with various amines. Unfortunately, large material loss generally attended the crystallizations, a consequence not only of the inherent inefficiency of the process but also of the instability of the compounds. Nevertheless, with cinchonidine, the best of several amines tested, it was possible to secure enough of the dextro acid to be able to determine unequivocally its absolute configuration (**2***, eq 1). The circular dichroism curves of **2***, its methyl ester,

(1) For an excellent review of recent synthetic developments in polyquinane chemistry, see: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1–163. See also publications cited in ref 3.

(2) An asterisk with a compound number signifies that a single enantiomer is being depicted with absolute stereochemistry as indicated.

(3) Greene, A. E.; Luche, M.-J.; Deprês, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435–2439.

(4) (a) Heatley, N. G.; Jennings, M. A.; Florey, H. W. *Br. J. Exp. Pathol.* **1947**, *28*, 35–46. Hirsutic acid C has also been isolated from the fermentations of *Stereum complicatum* (Fr.) Fr. See: (b) Feline, T. C.; Mellows, G.; Jones, R. B.; Phillips, L. *J. Chem. Soc., Chem. Commun.* **1974**, 63–64.

(5) (a) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Trotter, J.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1965**, 310–311. (b) Comer, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, 11–18. (c) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4761–4768.

(6) (a) Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, *15*, 3745–3748. (b) Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284–1285. (c) Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245–1248. See also: (d) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1972**, *13*, 2053–2056.

(7) (a) Shibasaki, M.; Yamazaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1982**, *23*, 5311–5314. (b) See also: Yamazaki, M.; Shibasaki, M.; Ikegami, S. *J. Org. Chem.* **1983**, *48*, 4402–4404.

(8) See, for example: Hassner, A.; Fletcher, V. R. *Tetrahedron Lett.* **1970**, *11*, 5053–5056.

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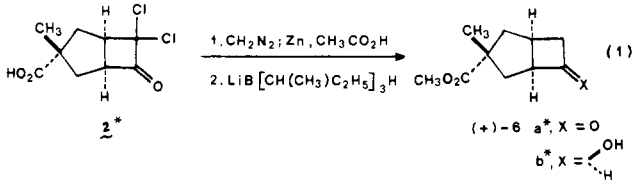
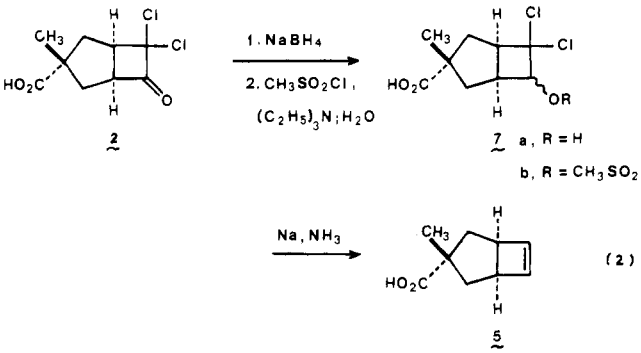


and the derived ketone **6a*** displayed strongly positive Cotton effects;[8,9] furthermore, Horeau's method[10] on the derived endo alcohol **6b*** yielded (+)-α-phenylbutyric acid. These concordant results clearly indicated the dextro acid to be the depicted 1*R*,3*S*,5*S* antipode **2***.

The disappointing resolution of **2** coupled with the mediocre yields obtained in a study (racemic material) of the transformation of **2*'** to the vinyl chloride **3*** (CH_2N_2; CH_3MgBr; CH_3SO_2Cl; Zn–Cu[8]) prompted an investigation of the alternative, ultimately successful approach based on the meso compound **5** (Chart I). This material could be easily obtained in high yield from the racemic keto acid **2**, as shown in eq 2. Sodium borohydride reduction of **2**

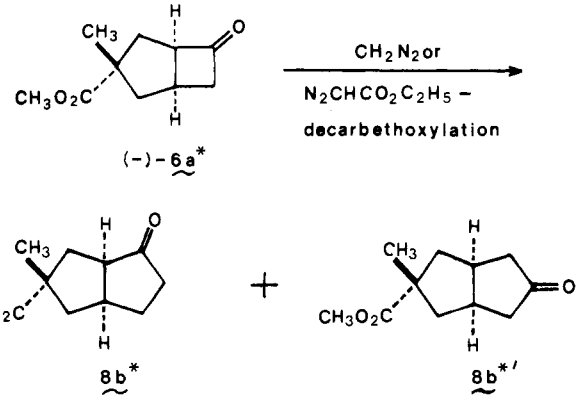


in ethanol furnished an epimeric mixture of hydroxy acids **7a**, which was converted to the mesylate acids **7b** by reaction with methanesulfonyl chloride followed by treatment with aqueous tetrahydrofuran (to hydrolyze the mixed anhydrides). The crude product **7b** was then added to excess sodium in liquid ammonia to furnish the crystalline cyclobutene **5** in 82% overall yield from **2**.

Of the methods currently available for inducing asymmetry in prochiral olefins, it appeared that the hydroboration–oxidation procedure recently developed by Brown and co-workers[11] would be the most likely to provide a direct and effective means for creating asymmetry in the meso olefin **5**. Once obtained, the cyclobutanol, hopefully of high optical purity, might then be converted in a few steps to an olefin that had been employed in racemic form in the previous synthesis. The successful synthesis through this approach of the olefin **9*** is shown in Scheme I.

Acid **5** was converted with ethereal diazomethane to its methyl ester, which was asymmetrically hydroborated with excess (+)-diisopinocampheylborane in tetrahydrofuran to give, following alkaline hydrogen peroxide oxidation, the exo alcohol **6c*** in 73% yield.[11] The optical purity of the product could be conveniently measured by proton NMR (80 MHz) with the chiral shift reagent Eu(hfc)$_3$ and was

Table I. Ring Expansion of Cyclobutanone (–)-6a*



reagent	ring-expansion conditions	8b*:8b*' ratio[a]
CH_2N_2 (large excess)	$(C_2H_5)_2O$–CH_3OH (4:1), 0 °C, 5 h	50:50[b]
$N_2CHCO_2C_2H_5$ (1.7 equiv)	$(C_2H_5)_2O$, $BF_3{\cdot}O(C_2H_5)_2$ (1.7 equiv), 0 °C, 1 h	68:32
$N_2CHCO_2C_2H_5$ (1.7 equiv)	CH_2Cl_2, $(C_2H_5)_3O^+$ BF_4^- (1.7 equiv), –30 °C, 48 h	67:33[c]
$N_2CHCO_2C_2H_5$ (2.1 equiv)	CH_2Cl_2, $SbCl_5$ (0.44 equiv), –78 °C, 2 h	98:2

[a] 10% Carbowax 20M on Chromosorb, 180 °C. Decarbethoxylation occurs under the VPC conditions. The same ratios (VPC) are obtained after decarbethoxylation in refluxing wet dimethoxyethane or dioxane.[16] [b] Ca. 15% starting material remained. [c] Ca. 50% starting material remained.

found to be a highly satisfying 92 ± 5%.[12] It had been anticipated, on the basis of Brown and co-workers' results with simple prochiral olefins,[11a,c] that (+)-diisopinocampheylborane (derived from (–)-α-pinene, 90% ee, obtained by isomerization of (–)-β-pinene[11b]) would afford the required 1*R*,3*S*,5*R*,6*R* enantiomer. That this was in fact the case was evidenced by the negative sign of the α_D of the corresponding ketone (–)-**6a***, obtained from **6c*** in high yield by Collins oxidation. The dextro isomer had earlier been shown to have the absolute stereochemistry depicted in (+)-**6a*** (vide supra).

With the desired cyclobutanone (–)-**6a*** of high optical purity in hand, a selective transformation to the cyclopentanone **8b*** was next sought. On the basis of previous experience,[13] the lack of selectivity observed on treatment of the cyclobutanone with diazomethane came as no surprise (Table I); what was surprising, though, was the relatively poor selectivity obtained with ethyl diazoacetate in the presence of either boron trifluoride etherate[14] or triethyloxonium tetrafluoroborate.[15] Fortunately, however, the cyclobutanone on exposure to ethyl diazoacetate and antimony pentachloride in methylene chloride[15] underwent a highly regioselective ring expansion to give almost exclusively the desired β-keto ester **8a***. Quite conveniently, on heating the crude product in wet dimethoxyethane[16] it suffered smooth decarbethoxylation to provide a ca. 98:2 mixture (VPC) of the ketones **8b*** and

(9) See: Crabbé, P. "Applications de la Dispersion Rotatoire Optique et du Dichroïsme Circulaire Optique en Chimie Organique"; Gauthier-Villars: Paris, 1968; pp 158–160 and references cited therein.

(10) Horeau, A. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. III, Chapter 3 and references cited therein.

(11) (a) Brown, H. C.; Jadhav, P. K. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. II, Chapter 1. (b) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583–4584. (c) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *Ibid.* **1982**, *47*, 5065–5069. (d) Brown, H. C.; Singaram, B. *Ibid.* **1984**, *49*, 945–947.

(12) For use in this determination, the corresponding racemic alcohol was prepared from the methyl ester of **5** by using 9-BBN and basic hydrogen peroxide.

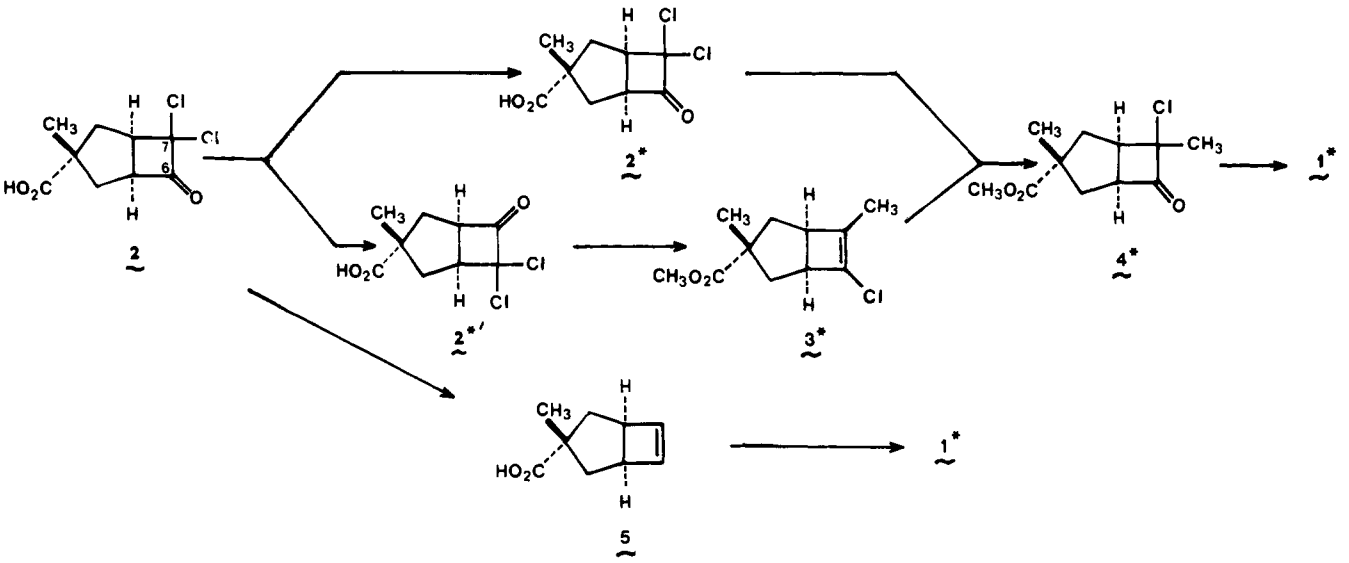
(13) Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003–4005 and references cited therein.

(14) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, *14*, 4937–4940. However, see also: Liu, H. J.; Chan, W. H. *Can. J. Chem.* **1982**, *60*, 1081–1091.

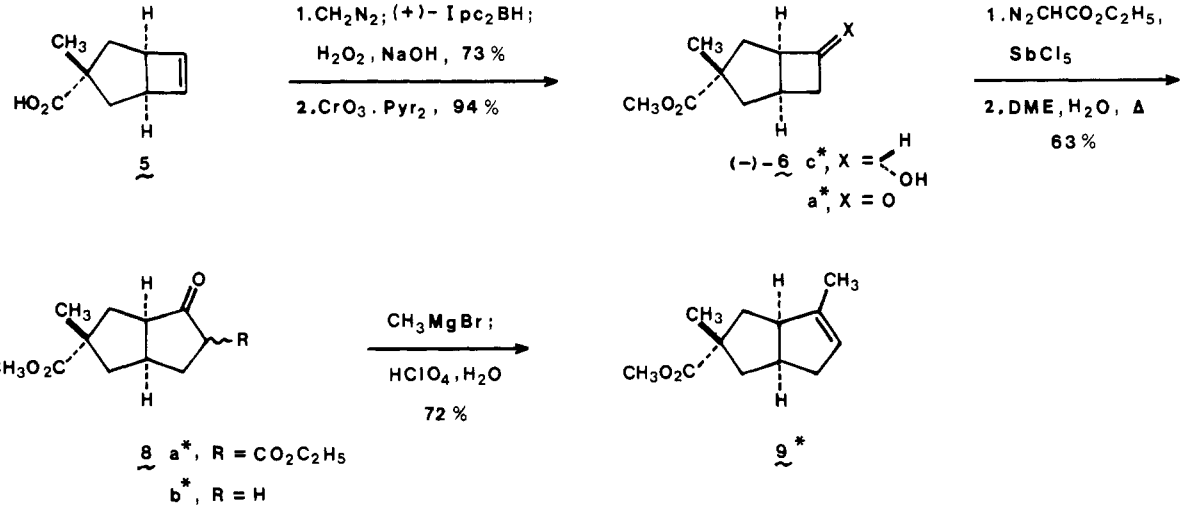
(15) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459–465, 466–472.

(16) Greene, A. E.; Cruz, A.; Crabbé, P. *Tetrahedron Lett.* **1976**, *17*, 2707–2708.

Chart I



Scheme I



8b*′, from which pure **8b*** could be isolated by silica gel chromatography in 63% overall yield. The ketone attribution could easily be made on the basis of the optical rotation of isomer **8b*** (**8b*′** is meso) and from the carbon-13 NMR spectra: viz., the minor ketone isomer **8b*′**, because of symmetry, affords a relatively simple eight-line spectrum, whereas the major isomer **8b*** produces a spectrum displaying 11 resonances. The optical purity of ketone **8b*** was found by proton NMR with $Eu(hfc)_3$ to be 90 ± 5%,[17] thus confirming the previously determined high enantiomeric excess of the cyclobutanol.

The conversion of cyclopentanone **8b*** to cyclopentene **9***, the remaining transformation needed to rejoin the racemic synthesis, could be nicely accomplished in one pot by reaction first with methylmagnesium bromide in tetrahydrofuran at 0 °C and then with aqueous perchloric acid. Olefin **9***, produced in 72% yield, was chromatographically and spectroscopically homogeneous[18] and identical with the racemic compound, which had been obtained by an alternative route.[3]

The concluding steps of the synthesis from olefin **9*** were executed as they had been from the racemic material[3] (Scheme II). A highly stereo- and regioselective three-carbon annelation[13] of **9*** produced **10a***, which was reduced with zinc in acetic acid to give the *cis,anti,cis*-tricyclopentanoid derivative **10b*** in 81% overall yield. Palladium(II) oxidation[19] of **10b*** in hot aqueous dioxane provided the enone ester **11a*** (60% yield), which was converted to the corresponding free acid **11b*** in excellent yield with aluminum bromide in tetrahydrothiophene.[20] The dienone acid **12b*** was next obtained, as indicated, from the enone acid **11b*** via the hydroxymethylene derivative **12a*** in 62% yield.[21]

Basic hydrogen peroxide epoxidation of the dienone acid **12b*** in ethanol selectively engendered dehydrohirsutic acid C (**13***),[4b,6a] which was reduced in situ with sodium

(17) For use in this determination, the corresponding racemic cyclopentanone was prepared by similar ring expansion–decarbethoxylation of the racemic cyclobutanone, which was obtained from the methyl ester (CH_2N_2) of **2** by reduction with zinc in acetic acid.

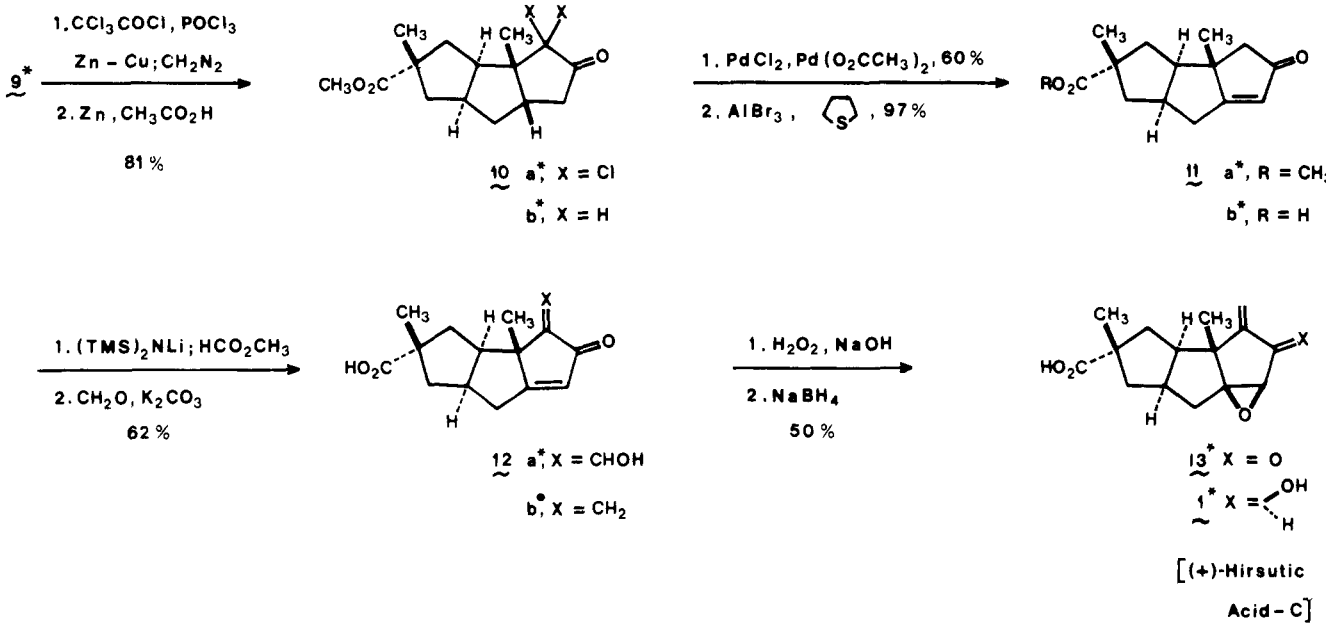
(18) See: Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S. *Synth. Commun.* **1977**, *7*, 355–362 and ref 7a.

(19) Cf.: Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752–757. von Bierling, B.; Kirschke, K.; Oberender, H. *J. Prakt. Chem.* **1972**, *314*, 170–180. Wolff, S.; Agosta, W. C. *Synthesis* **1976**, 240–241. Mincione, E.; Ortaggi, G.; Sirna, A. *Ibid.* **1977**, 773–774.

(20) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991–1993.

(21) Manson, A. J.; Wood, D. *J. Org. Chem.* **1967**, *32*, 3434–3437. Matsumoto, T.; Shirahama, H.; Tsuzuki, K.; Sakan, F.; Hashimoto, H. *Jpn. Kokai Tokkyo Koho* **1975**, *75–101*, 353; *Chem. Abstr.* **1976**, *84*, 59033*a*. To obtain a high conversion of **11b*** to the hydroxymethylene derivative **12a***, the crude reaction product required recycling.

Scheme II



borohydride to produce highly stereoselectively in 50% yield after chromatography (+)-hirsutic acid C (1*). Recrystallization of the chromatographed material from methylene chloride–cyclohexane gave (+)-hirsutic acid C [mp 175–177 °C, $[\alpha]^{23}_D$ +117° (lit.[5c] mp 179–180 °C, $[\alpha]^{23}_D$ +116°)], having spectral (IR, NMR, MS) and chromatographic (TLC, multiple developments) characteristics indistinguishable from those of the naturally derived substance.

In summary, an enantioconvergent total synthesis of natural hirsutic acid C, based on an efficient asymmetric hydroboration and two highly selective three-carbon annelations, has been achieved. The synthesis requires only 18 steps from the racemic keto acid **2** and proceeds in an overall yield of ca. 3% (1% from dimethyl malonate[3,22]).

Experimental Section

Solvents were generally distilled prior to use. Tetrahydrofuran, dioxane, ether, and hydrocarbons were distilled from sodium hydride–lithium aluminum hydride, hexamethylphosphoric triamide and pyridine were distilled under reduced pressure from calcium hydride, and methylene chloride was distilled from calcium chloride or 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 70-230 silica gel 60 was employed for dry column chromatography. 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 or a Bruker WP 80 SY spectometer was employed for the ^1H NMR spectra. The ^{13}C NMR spectra were taken in $CDCl_3$ solution at 20.15 MHz on the Bruker instrument. Optical rotations were measured with a Perkin-Elmer 141 polarimeter, and the circular dichroism curves were recorded on a Jouan 3 dichrograph instrument. Mass spectra were obtained on a MS-30 AEI mass spectrometer (70 eV, direct insert probe) or on a VG Micromass 70 70F instrument. Melting points were obtained with a Buchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS.

(1*R*,3*S*,5*S*)-7,7-Dichloro-3-methyl-6-oxobicyclo[3.2.0]heptane-3-carboxylic Acid (2*). A 2.53-g (10.67 mmol) sample of racemic **2**[3] and 3.14 g (10.66 mmol) of cinchonidine were disssolved in 60 mL of warm absolute ethanol. On cooling, there was deposited 1.42 g of salt, 50 mg of which was converted with dilute hydrochloric acid to the free acid: $[\alpha]^{20}_D$ +98° (*c* 2.18, chloroform). The remaining sample was recrystallized from 50 mL of ethanol to give 0.470 g of salt, which yielded 216 mg (9%) of acid **2***: $[\alpha]^{20}_D$ +112°, $[\alpha]^{20}_{578}$ +119°, $[\alpha]^{20}_{546}$ +146° (*c* 1.76, chloroform); CD (*c* 0.87 × 10^{-3}, dioxane; 20 °C) $[\theta]_{360}$ 0, $[\theta]_{320}$ +10 580, $[\theta]_{270}$ 0. The corresponding methyl ester was prepared by reaction with a small excess of diazomethane at −78 °C and was purified by dry silica gel chromatography (4% ethyl acetate in hexane): $[\alpha]^{20}_D$ +131°, $[\alpha]^{20}_{578}$ +140°, $[\alpha]^{20}_{546}$ +169° (*c* 1.76 chloroform); CD (*c* 1.12 × 10^{-3}, cyclohexane; 20 °C) $[\theta]_{360}$ 0, $[\theta]_{320}$ +14 440, $[\theta]_{270}$ 0; IR 1810, 1730, 1470–1430, 1250, 1200, 1180, 1100, 800 cm^{-1}; ^1H NMR (CCl_4) δ 1.40 (s, 3 H), 1.5–2 (m, 2 H), 2.3–2.8 (m, 2 H), 3.3 (pseudo q, *J* = 8 Hz, 1 H), 3.7 (s, 3 H), 3.9–4.3 (m, 1 H).

Methyl (1*S*,3*R*,5*S*)-3-Methyl-6-oxobicyclo[3.2.0]heptane-3-carboxylate ((+)-6a*). A 149-mg (0.59 mmol) sample of the above ester and 462 mg (7.06 mmol) of zinc powder in 1.47 mL of glacial acetic acid were stirred at 90 °C for 6 h. The reaction mixture was then processed in the usual manner to give 100 mg (92%) of keto ester (+)-**6a***: $[\alpha]^{20}_D$ +72°, $[\alpha]^{20}_{578}$ +76°, $[\alpha]^{20}_{546}$ +90°, $[\alpha]^{20}_{436}$ +197° (*c* 2.1, chloroform); CD (*c* 4.1 × 10^{-3}, cyclohexane; 20 °C) $[\theta]_{340}$ 0, $[\theta]_{322}$ +4160, $[\theta]_{310}$ +6620, $[\theta]_{301}$ +6060, $[\theta]_{250}$ 0; IR 1780, 1730, 1460–1430, 1380, 1300, 1250, 1200, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.4–3.5 (m, 8 H), 3.68 (s, 3 H).

Methyl (1*S*,3*R*,5*S*,6*R*)-3-Methyl-6-hydroxybicyclo[3.2.0]heptane-3-carboxylate ((+)-6b*). A stirred solution of 100 mg (0.54 mmol) of keto ester (+)-**6a*** in 650 μL of tetrahydrofuran at −78 °C was treated with 975 μL (0.97 mmol) of a 1.0 M solution of L-Selectride[23] in tetrahydrofuran. After 45 min, 650 μL (1.0 mmol) of 1.6 M aqueous sodium hydroxide was added followed by 330 μL (3.3 mmol) of 30% hydrogen peroxide. After warming to room temperature, the reaction mixture was treated with dilute aqueous hydrochloric acid, and the product was isolated with ether in the usual manner. Purification of the product by dry silica gel chromatography (20% ethyl acetate in hexane) yielded in 63 mg (62%) of hydroxy ester (+)-**6b***: $[\alpha]^{20}_D$ +21.6°, $[\alpha]^{20}_{578}$ +23.3°, $[\alpha]^{20}_{546}$ +26.4°, $[\alpha]^{20}_{436}$ +42.8° (*c* 2.1, methanol); IR 3440, 1735, 1420, 1345, 1210, 1170, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 1.38 (s, 3 H), 1.75–3.25 (m, 9 H), 3.60 (s, 3 H), 4.2–4.75 (m, 1 H). Horeau's method:[10] A solution of 22.5 mg (0.12 mmol) of

(22) Deprês, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928–931.

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

(+)-**6b*** and 75 mg (0.24 mmol) of α-phenylbutyric anhydride in 600 μL of pyridine was stirred for 43 h at 20 °C. Water (50 μL) was then added, and the solution was stirred for 30 min at 75 °C. The reaction mixture, after cooling, was treated with benzene and dilute aqueous sodium hydroxide, and then the aqueous phase was separated, acidified, and extracted with ether, which was processed as usual to produce 63 mg of α-phenylbutyric acid: $[\alpha]^{20}_{D}$ +5.3°, $[\alpha]^{20}_{578}$ +5.4° (*c* 5.6, benzene).

(1*R*,3*r*,5*S*)-3-Methylbicyclo[3.2.0]hept-6-ene-3-carboxylic Acid (5). A 500-mg (2.11 mmol) sample of keto acid **2** in 15 mL of methanol at 0 °C was treated over 1 h with 500 mg (13.22 mmol) of sodium borohydride. The reaction mixture was poured into ether–10% aqueous hydrochloric acid and the product was isolated with ether to give 520 mg of crude hydroxy acid **7a**: IR 3300, 2700, 1700, 1150, 980, 925, 820 cm^{-1}. Over 1 min, 530 μL (784 mg, 6.85 mmol) of distilled methanesulfonyl chloride was added to a stirred solution at 0 °C of the above sample of **7a** in 30 mL of methylene chloride and 1.30 mL (944 mg, 9.33 mmol) of triethylamine. After being stirred for 30 min at 0 °C and for 30 min at 20 °C, the reaction mixture was treated with 30 mL of tetrahydrofuran and 2 mL of water and then stirred vigorously for 30 min. After acidification of the mixture with 10% aqueous hydrochloric acid, the product was isolated with ether in the usual manner to afford 790 mg of crude mesylate **7b** as a semisolid: IR 3300, 2700, 1700, 1350, 1190 cm^{-1}. The crude mesylate in 24 mL of tetrahydrofuran was added over 5 min to 1.8 g (78.3 mmol) of sodium in 150 mL of refluxing ammonia. After being stirred for 45 min, the reaction mixture was carefully treated until no longer blue with solid ammonium chloride, and the ammonia was allowed to evaporate. The salts were dissolved in water, and the aqueous solution was extracted with ether and then acidified with 10% aqueous hydrochloric acid. Isolation of the product with ether in the usual manner produced 342 mg of crude olefin. Trituration of this material with hot hexane, concentration of the hexane solution, and evaporative distillation (~50 °C, 0.005 torr) of the residue gave 264 mg (82% overall) of olefin **5**: mp 80–84 °C; IR (Nujol) 3040, 1690, 1315, 1255, 1125, 955, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 2.14, 1.64, 3.41 (~ABX, J_{AB} = 13 Hz, J_{AX} = 8 Hz, J_{BX} < 3 Hz, 6 H), 6.17 (s, 2 H), 7.31 (s, 1 H). A small sample of olefin **5** was converted to the dihydro derivative (ethyl acetate, H_2, 10% Pd–C), which was shown by TLC and VPC (methyl esters) analysis to be absent from the above sample.

Anal. Calcd from $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.74; H. 7.90.

Methyl (1*R*,3*S*,5*R*,6*R*)-3-Methyl-6-hydroxybicyclo-[3.2.0]heptane-3-carboxylate ((–)-6c*). A suspension of 987 mg (6.49 mmol) of **5**, comparable to that above, in 2.0 mL of ether was esterified with a slight excess of ethereal diazomethane, and the resultant solution was then concentrated. The residual oil was dissolved in 22 mL of tetrahydrofuran and added to a stirred mixture at –50 °C of (+)-diisopinocampheylborane in tetrahydrofuran [from treatment at 0 °C of 1.1 mL (ca. 11 mmol) of ca. 10 M borane–dimethyl sulfide complex in 3 mL of tetrahydrofuran with 3.46 mL (2.97 g, 21.8 mmol) of (–)-α-pinene ($[\alpha]^{20}_{D}$ –46.2°, neat; ee 90%)[11b] for 3 h followed by distillation of 2.6 mL of solvents under reduced pressure, addition of 4 mL of tetrahydrofuran and 520 μL 520 μL (447 mg, 3.28 mmol) of α-pinene, and refrigeration at 0 °C for 72 h].[11] After being stirred for 5 h at –50 °C, the reaction mixture was treated with 500 μL of methanol and then with 2.71 mL (8.13 mmol) of 3 M aqueous sodium hydroxide and 3.28 mL (ca. 33 mmol) of 30% hydrogen peroxide. Following 1 h of stirring at 55 °C, the reaction mixture was cooled and then processed with ether in the normal manner. Dry column chromatography on silica gel of the crude product with ethyl acetate in hexane (0–30%) gave 870 mg (73%) of ester alcohol (–)-**6c***: $[\alpha]^{20}_{D}$ –8.8°, $[\alpha]^{20}_{578}$ –9.3°, $[\alpha]^{20}_{546}$ –10.5°, $[\alpha]^{20}_{436}$ –17.1° (*c* 2.4, methanol); IR 3400, 1730, 1470–1440, 1380, 1330, 1310, 1250, 1210, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (s, 3 H), 1.5–2.75 (m, 8 H), 3.63 (s, 3 H), 3.80–4.25 (m, 1 H) [the addition of Eu(hfc)$_3$ split the CH_3C and CH_3O resonances, giving an enantiomeric purity for (–)-**6c*** of 92 ± 5%[12]]; mass spectrum, *m/e* 185 (M^+ + 1).

Anal. Calcd for $C_{10}H_{17}O_3$: M_r, 185.1178. Found: M_r (mass spectrum), 185.1189 (M^+ + 1).

Methyl (1*R*,3*S*,5*R*)-3-Methyl-6-oxobicyclo[3.2.0]heptane-3-carboxylate ((–)-6a*). A solution of alcohol (–)-**6c*** (870 mg, 4.72 mmol) in 20 mL of methylene chloride was added to a stirred suspension of 10.0 g (32.2 mmol) of Collins reagent[24] in 80 mL of methylene chloride at 0 °C. After being stirred for 45 min, the mixture was filtered through Florisil. The filtrate was washed with 10% aqueous hydrochloric acid, aqueous sodium bicarbonate, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 810 mg (94%) of ketone (–)-**6a***: $[\alpha]^{20}_{D}$ –95° (*c* 4.1, chloroform). The analytical sample was prepared by dry silica gel chromatography of comparable material with 10% ether in pentane: $[\alpha]^{20}_{D}$ –101°, $[\alpha]^{20}_{578}$ –106°, $[\alpha]^{20}_{546}$ –125°, $[\alpha]^{20}_{436}$ –237° (*c* 2.2, chloroform); the IR and ^1H NMR spectra were superimposable with those of (+)-**6a***; mass spectrum, *m/e* 182 (M^+).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74; M_r, 182.0943. Found: C, 66.04; H, 7.75; M_r (mass spectrum), 182.0943.

Methyl (2*S*,3a*R*,6a*S*)-1,2,3,3a,4,5,6,6a-Octahydro-2-methyl-4-oxopentalene-2-carboxylate (8b*) and Isomer 8b*'. The above 810-mg (4.44 mmol) sample of ketone (–)-**6a*** was dissolved in 52 mL of methylene chloride and at –78 °C treated with 290 μL (677 mg, 2.27 mmol) of antimony pentachloride and 10 min later with 970 μL (1.06 g, 9.29 mmol) of ethyl diazoacetate. After being stirred for 2 h at –78 °C, the reaction mixture was allowed to warm to 0 °C and was then poured into a stirred mixture of methylene chloride and aqueous sodium bicarbonate. After 45 min, the mixture was filtered, and the crude product was isolated with methylene chloride in the usual fashion and then filtered with ether through a small pad of silica gel to afford impure **8a***: IR 3500, 1750, 1730, 1660, 1620, 1460, 1440, 1370, 1240–1160 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (s, 3 H), 1.27 (t, *J* = 7 Hz, 3 H), 1.5–2.8 (m, 8 H), 3–3.5 (m, 1 H), 3.63 (s, 3 H), 4.15 (br q, *J* = 7 Hz, 2 H). A solution of this material in 20 mL of dimethoxyethane containing 300 μL of water was refluxed for 48 h and then concentrated under reduced pressure. VPC analysis (10% Carbowax 20M on Chromosorb, 180 °C) of the residue showed the presence of **8b*** and **8b*'** in a ratio of ca. 98:2. Dry silica gel chromatography of the residue with ether in pentane (0–10%) gave 554 mg (63%) of pure **8b***: $[\alpha]^{20}_{D}$ –155°, $[\alpha]^{20}_{578}$ –163°, $[\alpha]^{20}_{546}$ –190°, $[\alpha]^{20}_{436}$ –389° (*c* 3.3, chloroform) [lit. (ee 80%)[7a] $[\alpha]^{25}_{D}$ –137° (*c* 0.99, chloroform)]; IR 1730, 1460, 1440, 1420, 1290, 1240, 1200, 1160, 1120, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.5–2.75 (m, 10 H), 3.68 (s, 3 H) [the addition of Eu(hfc)$_3$ split the CH_3O resonance, giving an enantiomeric purity for **8b*** of 90 ± 5%[17]]; ^{13}C NMR ($CDCl_3$) δ 24.43 (2×), 35.81, 39.42, 40.71, 44.01, 51.60, 51.87 (2×), 177.35, 221.43; mass spectrum, *m/e* 196 (M^+).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; M_r, 196.1099. Found: C, 67.51; H, 7.96; M_r (mass spectrum), 196.1111.

A small amount could also be isolated of pure **8b*'**: IR 1730, 1460, 1400, 1370, 1305, 1200, 1160, 1030, 985, 810, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.75–2.8 (m, 10 H), 3.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 25.26, 38.99, 44.51, 45.30, 51.73, 51.94, 177.60, 219.79.

Methyl (2*S*,3a*R*,6a*S*)-1,2,3,3a,6,6a-Hexahydro-2,4-dimethylpentalene-2-carboxylate (9*). A stirred solution of 536 mg (2.73 mmol) of the above ketone **8b*** in 50 mL of tetrahydrofuran at 0 °C was treated over 3 h with 13.0 mL (ca. 13 mmol) of a ca. 1.0 M solution of methylmagnesium bromide in ether. (The reaction was carefully monitored by TLC with 30% ethyl acetate in hexane. R_f **8b***, 0.50; R_f product, 0.43.) Following the addition, 10 mL of 70% aqueous perchloric acid was slowly added, and the resulting solution was heated at 40 °C for 1 h. The crude product was isolated with pentane in the normal manner and purified by dry silica gel chromatography with 5% ether in pentane to yield 380 mg (72%) of olefin **9***: $[\alpha]^{28}_{D}$ ~0°, $[\alpha]^{28}_{578}$ ~0°, $[\alpha]^{28}_{546}$ +1°, $[\alpha]^{28}_{436}$ +5°, $[\alpha]^{28}_{365}$ +13.8° (*c* 3.3, chloroform); IR 3035, 1735, 1310, 1200, 1170, 1095 cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (s, 3 H), 1.65 (br s, 3 H), 3.60 (s, 3 H), 5.03 (br s, 1 H).[25]

Anal. Calcd for $C_{12}H_{18}O_2$: M_r, 194.13067. Found: M_r (mass spectrum), 194.13062.

Methyl (2*S*,3a*R*,3b*R*,6a*S*,7a*S*)-2,3,3a,3b,4,5,6,6a,7,7a-Decahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (10b*). To a mixture of 1.20 g (ca. 18 mmol)

(24) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587–3592.

(25) The IR and ^1H NMR spectra of this optically active compound were identical with those of the racemic material.[3]

of zinc–copper couple and 314 mg (1.62 mmol) of olefin **9*** in 9 mL of dry ether, stirred under argon at 29 °C, was added over 3 h a solution of 1.92 g (10.6 mmol) of trichloroacetyl chloride and 1.61 g (10.5 mmol) of phosphorus oxychloride in 11 mL of dry ether.[26] After being stirred at 29 °C for an additional 1.5 h, the mixture was left overnight at 17 °C. The ether solution was 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 590 mg of the crude dichlorocyclobutanone: IR 1800, 1770 cm^{-1}; ^1H NMR (CCl_4) δ 1.38 (s, 3 H), 1.53 (s, 3 H), 3.73 (s, 3 H). This material was added to a solution of ca. 0.5 g of diazomethane in 50 mL of ether and 2.5 mL of methanol at room temperature.[13] After 25 min, acetic acid was added to consume the excess diazomethane, and the solvents were removed under reduced pressure to give the crude dichlorocyclopentanone **10a***. This crude material was stirred with 2.5 g of zinc powder in 12.5 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 326 mg (81% overall) of ketone **10b***: $[\alpha]^{27}_D$ −125°, $[\alpha]^{22}_{578}$ −131°, $[\alpha]^{27}_{546}$ −153°, $[\alpha]^{27}_{436}$ −308°, $[\alpha]^{27}_{365}$ −676° (*c* 1.2, chloroform); IR 1735, 1305, 1200, 1170, 1080 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (s, 3 H), 1.27 (s, 3 H), 3.58 (s, 3 H).[25]

Anal. Calcd for $C_{15}H_{22}O_3$: M_r, 250.156 88. Found: M_r (mass spectrum), 250.150 16.

Methyl (2*S*,3a*R*,3b*S*,7a*S*)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (11a*). A stirred mixture of 215 mg (0.86 mmol) of ketone **10b***, 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.[19] 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 47 mg of starting material and 100 mg (60% based on 78% conversion) of **11a***. A similar experiment run to 82% conversion yielded 59% of **11a***. This material was spectroscopically and chromatographically indistinguishable from an independently prepared sample:[6b] $[\alpha]^{28}_D$ +57°, $[\alpha]^{28}_{578}$ +61°, $[\alpha]^{28}_{546}$ +72°, $[\alpha]^{28}_{436}$ +133° (*c* 0.65, chloroform) [lit. (ee 80%)[7a] $[\alpha]^{25}_D$ +50° (*c* 1.87, chloroform)]; IR 3070, 1730, 1710, 1635, 1310, 1205, 1170, 1095, 845 cm^{-1}; ^1H NMR (CCl_4) δ 1.10 (s, 3 H), 1.33 (s, 3 H), 3.63 (s, 3 H), 5.60 (br s, 1 H).[25]

Anal. Calcd for $C_{15}H_{20}O_3$: M_r, 248.1412. Found: M_r (mass spectrum), 248.1414.

(2*S*,3a*R*,3b*S*,7a*S*)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylic Acid (11b*). A 92-mg (0.37 mmol) sample of ester **11a*** in 3.6 mL of tetrahydrothiophene was stirred under argon as 184 mg (0.69 mmol) of aluminum bromide was added over 1 h.[20] After the reaction was stirred for 24 h, an additional 184 mg (0.69 mmol) of aluminum bromide was added over 6 h, and after a total of 68 h of stirring, a third portion (184 mg, 0.69 mmol) of aluminum bromide was added. After an additional 6 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 afford 84 mg (97%) of **11b***: mp ~210 °C dec (methylene chloride–cyclohexane); $[\alpha]^{28}_D$ +54°, $[\alpha]^{28}_{578}$ +58°, $[\alpha]^{28}_{546}$ +67°, $[\alpha]^{28}_{436}$ +124°, $[\alpha]^{28}_{365}$ +141° (*c* 0.4, chloroform); IR (Nujol) 1710, 1670, 1620, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.44 (s, 3 H), 5.65 (br s, 1 H).[25]

Anal. Calcd for $C_{14}H_{18}O_3$: M_r, 234.1256. Found: M_r (mass spectrum), 234.1254.

(2*S*,3a*R*,3b*S*,7a*S*)-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-4-methylene-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylic Acid (12b*). An 89-mg (0.38 mmol) sample of enone **11b***, comparable to that described above, in 4.8 mL of tetrahydrofuran at −78 °C under argon was treated with 1.17 mL (1.17 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 86 mg (1.43 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 1.64 mL (1.64 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 860 mg (14.3 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 **12a*** and some starting material. This mixture was recycled exactly as described above, and the resultant crude product **12a*** was then stirred rapidly for 30 min in 11.7 mL of acetone in the presence of 293 mg (2.12 mmol) of potassium carbonate and 293 μL (ca. 2.9 mmol) of 30% formalin.[21] After the addition of methylene chloride and 10% 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 58 mg (62%) of dienone **12b***. This material was spectroscopically the same as an independently prepared sample:[6b] $[\alpha]^{25}_D$ +74°, $[\alpha]^{25}_{578}$ +85°, $[\alpha]^{25}_{546}$ +92°, $[\alpha]^{25}_{436}$ +118° (*c* 0.4, chloroform) [lit. (ee 80%)[7a] $[\alpha]^{25}_D$ +67.7° (*c* 0.42, chloroform)]; IR 1695, 1645, 1615, 1305, 1260, 1160, 940, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.40 (s, 3 H), 5.10 (s, 1 H), 5.83 (s, 2 H).[25]

(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 56-mg (0.23 mmol) sample of dienone **12b*** in 3.0 mL of absolute ethanol under argon at −35 °C was treated with 1.0 mL (10.0 mmol) of 30% hydrogen peroxide and then with 1.0 mL (1.0 mmol) of 1 N aqueous sodium hydroxide.[6a] After the mixture was stirred for 4 h at −35 °C, 3.0 mL of absolute ethanol and 160 mg (4.2 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 54 mg of crude **1***, which was purified by dry silica gel chromatography with hexane–ethyl acetate–acetic acid (8:2:1) to give 30 mg (50%) of (+)-hirsutic acid C (**1***), which was recrystallized from methylene chloride–cyclohexane: mp 175–177 °C (lit.[5c] mp 179–180 °C); $[\alpha]^{23}_D$ +117° (*c* 0.31, chloroform) [lit.[5c] $[\alpha]^{23}_D$ +116° (*c* 1.05, chloroform)]; IR (Nujol) 3385, 1705, 1215, 1165, 1110, 1000, 890, 850, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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, 264.1361. Found: M_r (mass spectrum), 264.1346.

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Registry No. **1***, 3650-17-7; (±)-**2**, 84694-05-3; **2***, 97673-14-8; **2***-cinchonidine, 97718-43-9; **2*** (methyl ester), 97673-15-9; **5**, 97634-77-0; **5** (methyl ester), 97634-78-1; (+)-**6a***, 97634-73-6; (−)-**6a***, 97673-17-1; (+)-**6b***, 97634-74-7; (−)-**6c***, 97673-16-0; **7a** (isomer 1), 97634-75-8; **7a** (isomer 2), 97673-22-8; **7b** (isomer 1), 97634-76-9; **7b** (isomer 2), 97673-23-9; **8a***, 97634-79-2; **8b***, 85798-98-7; **9***, 84694-08-6; **10a***, 97673-18-2; **10b***, 97673-19-3; **11a***, 85799-03-7; **11b***, 97673-20-6; **12a***, 97673-21-7; **12b***, 85799-05-9; $N_2CHCO_2C_2H_5$, 623-73-4; CH_3Br, 74-83-9; CCl_3COCl, 76-02-8; cinchonidine, 485-71-2; methyl (2a*R*,2b*R*,4*S*,5a*S*,6a*S*)-decahydro-2,2-dichloro-2a,4-dimethyl-1-oxocyclobuta[*a*]pentalene-4-carboxylate, 97634-80-5.

(26) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879–2882.