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Highly Stereocontrolled Synthesis of Natural Barbacenic Acid, Novel Bisnorditerpene from *Barbacenia flava*

Amaury Patin, Alice Kanazawa,* Christian Philouze,† and Andrew E. Greene*

Université Joseph Fourier, LEDSS, BP 53X, 38041 Grenoble Cedex, France

Estela Muri, Eliezer Barreiro, and Paulo C. C. Costa

Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, RJ, 21.944 Brazil

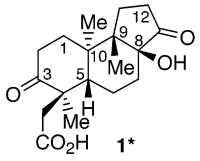
alice.kanazawa@ujf-grenoble.fr; andrew.greene@ujf-grenoble.fr

Received January 3, 2003

Barbacenic acid, a bisnorditerpene with five contiguous asymmetric centers (four fully substituted), has been prepared for the first time through a highly stereocontrolled route in 5.2% overall yield from a known octalone. The synthesis serves to define the absolute configuration of the natural product.

Introduction

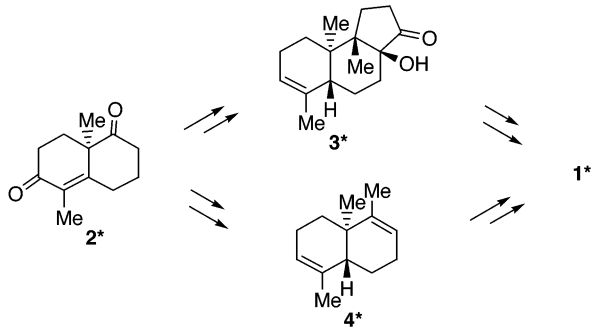
Barbacenia flava (Velloziaceae), a hummingbird-pollinated perennial found in xeric areas of South America, generally grows singly and can reach a height of up to 100 cm.[1] From the ethanol extract of the stem, roots, and leaf sheaths of this attractive plant a Brazilian group was able to isolate and, with the help of Belgian crystallographers, elucidate the structure and relative stereochemistry of a novel bisnorditerpene, barbacenic acid (**1***[2]).[3]



Barbacenic Acid

Because of our interest in applications of dichloroketene in natural product synthesis,[4] we were attracted to barbacenic acid as a synthetic target. It appeared that a route to this compound could involve enantioselective annelation[5] of 2-methylcyclohexane-1,3-dione with ethyl vinyl ketone to provide the known[5a,c,d] octalone **2***, which might be converted into tricycle **3*** (Scheme 1).[6] The carbon−carbon double bond in **3*** could then be used to access, through dichloroketene−dichlorocyclobutanone chemistry, the A-ring functionality and the correct C-4 configuration of barbacenic acid.[7] A related, but bolder, alternative was envisaged to involve double, stereoselective cycloaddition of dichloroketene to diene **4*** and subsequent discrimination between the dichlorocyclobutanones to produce ultimately **1***. While neither of these ap-

SCHEME 1



* To whom general correspondence should be addressed. Phone: (33)-4-76-51-46-86. Fax: (33)-4-76-51-44-94.

† To whom inquiries concerning the X-ray structure analyses should be addressed (christian.philouze@ujf-grenoble.fr).

(1) Sazima, M. *Flora, Bd.* **1977**, *166*, 239−247 and references therein.

(2) An asterisk with a compound number signifies that a single enantiomer is depicted with the absolute stereochemistry as indicated. Steroid-type numbering is used in the text of this paper. The stereochemical descriptors α and *β* refer to orientations below the plane of the molecule (cis to the C-10 Me) and above the plane (trans to the C-10 Me), respectively.

(3) (a) Pinto, A. C.; Frechiani, M. C.; Tinant, B.; Declercq, J.-P.; Van Meerssche, M. *J. Chem. Soc., Chem. Commun.* **1985**, 446−447. (b) Pinto, A. C.; Frechiania, M. C.; Pereira, A. L. *Phytochemistry* **1988**, *27*, 3917−3918.

(4) For leading references, see: Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443.

(5) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (c) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308−2311. (d) Takahashi, S.; Oritani, T.; Yamashita, K. *Tetrahedron* **1988**, *44*, 7081−7088. For a general review of annelation routes to *trans*-decalins, see: Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867−13886.

(6) Since the absolute configuration of barbacenic acid was unknown, the choice of the starting octalone was arbitrary. Only the correct series (used subsequently!) is shown.

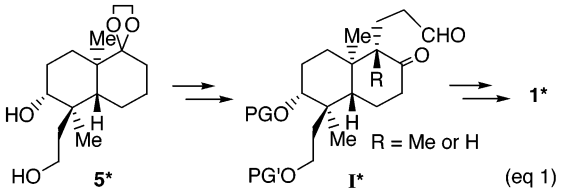
(7) For reviews on dichloroketene, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995. For a review on dichlorocyclobutanones, see: Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed., Engl.* **1988**, *27*, 797−827. For discussions on the stereochemical outcome of dichloroketene cycloaddition to cyclohexenes, see: Hassner, A.; Fletcher, V. R.; Hamon, D. P. G. *J. Am. Chem. Soc.* **1971**, *93*, 264−265. Hassner, A.; Krepski, L. R. *J. Org. Chem.* **1979**, *44*, 1376−1379.

10.1021/jo0340049 CCC: $25.00
Published on Web 04/11/2003

proaches, unfortunately, could be reduced to practice,[8] we nonetheless felt that barbacenic acid with its five contiguous asymmetric centers, of which four are fully substituted, presented a challenge worthy of additional investigation.

Results and Discussion

The subsequent synthetic plan called for installation of A-ring functional equivalents now prior to construction of the C-ring, which was expected to be sensitive due to the presence of the α-hydroxy carbonyl. A potentially useful intermediate for this synthetic strategy appeared to be diol **5*** (eq 1), which had previously been secured

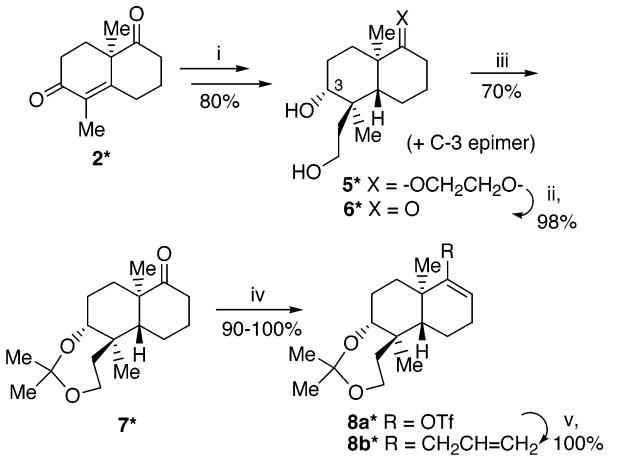


by Hagiwara and co-workers[9] in high yield from the octalone derivative **2*** through a standard sequence of reactions. Protection of the hydroxyl groups and B-ring transformations could then afford **I***, which under pinacol cyclization conditions might provide an advanced precursor of barbacenic acid. Described below is the first synthesis of this novel bisnorditerpene, which has been accomplished along these general lines. We note in advance that the synthesis is highly stereocontrolled and permits the assignment of absolute configuration to the natural product.

The starting octalone derivative **2*** was obtained in enantiopure form (≥99.9% ee) and in good yield by using a modification[5d] of the Hajos−Parrish procedure[5b] and then converted into a 4:1 mixture of diol **5*** and its C-3 epimer by acetalization, Birch reduction−allylation, and ozonolysis−reduction (Scheme 2).[9] The epimeric mixture was most conveniently separated after deacetalization and transformation of the resulting keto diols into the corresponding acetonides, which provided pure **7*** in 55% overall yield from dione **2*** (89%/step). The ketone was next converted in high yield into its enol triflate **8a***, which underwent Stille coupling[10] with allyltributyltin in quantitative yield to produce diene **8b***.

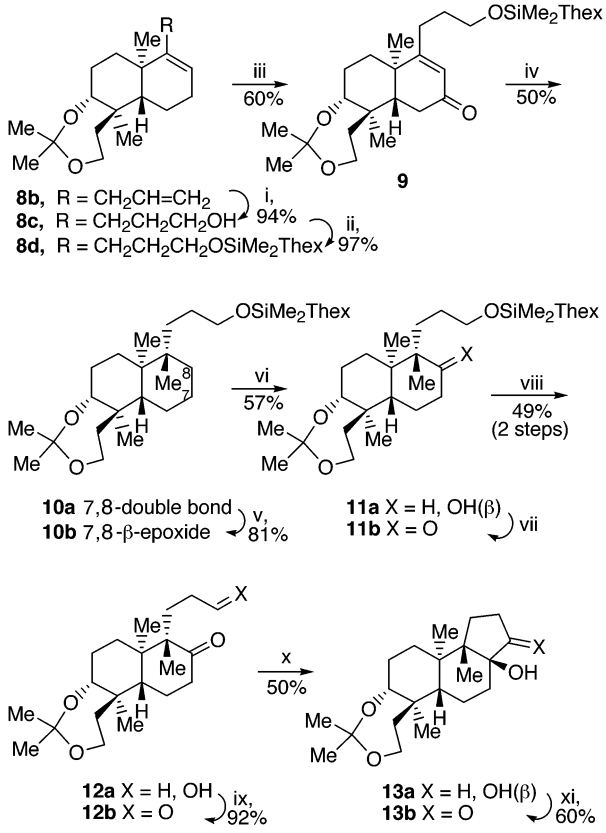
In preliminary work with this diene (Scheme 3),[11] we opted to examine an approach that would involve conjugate addition for the creation of the third quaternary center prior to C-ring closure. Thus, the diene was subjected to selective hydroboration−oxidation to provide the expected alcohol **8c** (94%), which was protected[12] to give the corresponding silyl ether **8d** (97%). Allylic oxidation with *tert*-butyl hydrogen peroxide in the presence of cuprous bromide[13] then proceeded smoothly and

SCHEME 2[a]



[a] Reagents and conditions: (i) Reference 9. (ii) $MeCO_2H-H_2O$, Δ. (iii) Me_2CO, PPTS, $CuSO_4$, 20 °C; separation. (iv) Tf_2O, *t*-Bu_2MePyr, 20 °C. (v) $AllylSnBu_3$, LiCl, $Pd(PPh_3)_4$, THF, Δ.

SCHEME 3[a]



[a] Reagents and conditions: (i) 9-BBN, THF, 20 °C; NaOH, H_2O_2, EtOH, 20 °C. (ii) $ThexMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 20 °C. (iii) *t*-BuOOH, CuBr, PhH, 45 °C. (iv) $AlMe_3$, $Ni(acac)_2$, THF, Et_2O, −30 to 20 °C; $ClPO(OEt)_2$, 20 °C; Li, $MeNH_2$, *t*-BuOH, THF, −30 °C. (v) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 0−20 °C. (vi) $LiBEt_3H$, THF, reflux. (vii) PCC, 3 Å MS, CH_2Cl_2, 20 °C. (viii) HF·Pyr, Pyr, THF, 20 °C. (ix) DMSO, $(ClCO)_2$, CH_2Cl_2, −60 to −40 °C; Et_3N, −40 to 20 °C. (x) SmI_2, THF, 0 °C. (xi) Pyr·SO_3, DMSO, Et_3N, 20 °C.

regioselectively to provide in 60% yield enone **9**. While lithium dimethylcuprate with or without boron trifluoride etherate was found, as expected, to be ineffective in achieving conjugate addition to enone **9**, an excess of

(8) A satisfactory route to olefin **3*** could not be developed and it was found, in a model system, that the B-ring trisubstituted double bond of **4*** resisted dichloroketene cycloaddition.

(9) Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 757−764 and references therein. See, also: Ling, T.; Rivas, F.; Theodorakis, E. A. *Tetrahedron Lett.* **2002**, *43*, 9019−9022.

(10) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(11) Racemic material was used for the work shown in Scheme 3.

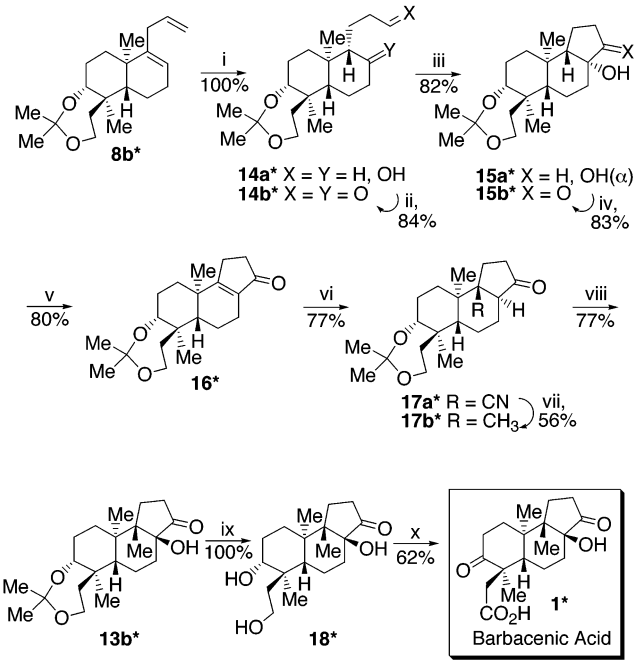
(12) Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515−5518.

trimethylaluminum together with a catalytic amount of nickel acetylacetonate[14] was effective and, following enolate trapping with diethyl chlorophosphate and reduction of the resulting enol phosphate with lithium in methylamine-*tert*-butyl alcohol,[15] the desired olefin **10a** was obtained in 50% overall yield.

Epoxidation of olefin **10a** with *m*-chloroperbenzoic acid provided in 81% yield uniquely epoxide **10b**, which was assigned the β configuration from consideration of the relative steric impediment to peracid approach on the two faces of the olefin. Treatment of **10b** with lithium aluminum hydride afforded exclusively the product of trans diaxial epoxide opening through hydride attack at the neopentyl carbon; however, the bulkier lithium triethylborohydride[16] partially overrode this usual mode[17] to give predominantly (ca. 2:1) the desired alcohol **11a** in 57% isolated yield.[18] A three-step sequence, which involved oxidation of **11a**, followed by deprotection and a second oxidation, then afforded the cyclization substrate, keto aldehyde **12b**.

The best of several reagents tested for pinacol cyclization of **12b** proved to be samarium(II) iodide.[19] This reagent in THF at 0 °C produced a single diol, which was shown through X-ray diffraction analysis[20] to be **13a**, in which the tertiary hydroxyl had been installed with the correct configuration. The selective formation of this cis diol can readily be understood on the basis of steric shielding of the top face of the carbonyl by the adjacent C-9 methyl, which makes bottom-face approach of the side chain preferred despite the hindrance due to the angular methyl at C-10. Acyloin **13b** could be secured in 60% yield from diol **13a** by using the Parikh−Doering reagent,[21] thereby completing the C-ring portion of the molecule.

SCHEME 4[a]



[a] Reagents and conditions: (i) 9-BBN, THF, 20 °C; BH_3, THF, 0−20 °C; EtOH, NaOH, H_2O_2, 0−20 °C. (ii) DMSO, $(ClCO)_2$, CH_2Cl_2, −60 to −40 °C; Et_3N, −40 to 20 °C. (iii) SmI_2, THF, −70 to −40 °C. (iv) Pyr·SO_3, DMSO, Et_3N, 20 °C. (v) $SOCl_2$, Pyr, 0 °C. (vi) Et_2AlCN, PhMe, 20 °C. (vii) *i*-Bu_2AlH, PhMe, −60 to −40 °C; N_2H_4, KOH, $(HOCH_2CH_2)_2O$, 195 °C; Pyr·SO_3, DMSO, Et_3N, 20 °C. (viii) Et_3SiOTf, Et_3N, Et_2O, 20 °C; *m*-CPBA, CH_2Cl_2, −30 °C; Bu_4NF, CH_2Cl_2−THF, 20 °C. (ix) $MeCO_2H-H_2O$, 20 °C. (x) DMSO, $(ClCO)_2$, CH_2Cl_2, −60 to −40 °C; Et_3N, −40 to 20 °C; $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH−THF−H_2O, 20 °C.

While pleased to have this apparently viable route to barbacenic acid, we found the pinacol cyclization to be highly irreproducible and to afford at best (but rarely) yields of ca. 50%. It thus seemed desirable to explore an alternative route to **13b** in which pinacol cyclization would precede conjugate addition. This could lead to a more effective cyclization due to the absence of the encumbering C-9 methyl and, in addition, might reduce the number of steps in the synthesis.

Diene **8b*** was converted in excellent yield into the new cyclization substrate, keto aldehyde **14b***, by hydroboration−oxidation, followed by Swern oxidation (Scheme 4). Hydroboration was best achieved by one-pot treatment of **8b*** with 9-BBN and then BH_3, rather than with BH_3 alone. Cyclization of this derivative with samarium(II) iodide in THF now proceeded quite readily at low temperature to deliver in 82% yield only the cis diol **15a***, which was shown to have the indicated stereochemistry by X-ray diffraction analysis.[22] Oxidation of **15a*** was next accomplished, as in the case of the related diol **13a**, with the Parikh−Doering reagent to provide in 83% yield acyloin **15b***, which underwent smooth dehydration in the presence of thionyl chloride to generate only the

(13) Salvador, J. A. R.; Melo, M. L. S.; Campos Neves, A. S. *Tetrahedron Lett.* **1997**, *38*, 119−122. Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259−8260.

(14) For the use of trimethylaluminum with nickel acetylacetonate, see: Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 801−815. Atwal, K. S.; Sahoo, S. P.; Tsai, T. Y. R.; Wiesner, K. *Heterocycles* **1982**, *19*, 641−646. Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Synthesis* **1995**, 317−320. Chavan, S. P.; Patil, S. S.; Ravindranathan, T. *Tetrahedron* **1999**, *55*, 13417−13422. Dimethylzinc in the presence of nickel acetylacetonate (Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931−932) surprisingly provided only a trace amount of the desired adduct. See: Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761−5768.

(15) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, *20*, 2145−2148.

(16) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1−12.

(17) Phillips, J. G.; Parker, V. D. In *Steroid Reactions*; Djerassi, C., Ed.; Holden-Day, Inc.: San Francisco, CA, 1963; Chapter 14.

(18) Initial plans were to convert the epoxide into the C-8 allylic alcohol, which on hydrogenation would have produced alcohol **11a**. Unfortunately, however, this transformation could not be cleanly accomplished under a variety of conditions.

(19) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765−766. Deng, Y.; Snyder, J. K. *J. Org. Chem.* **2002**, *67*, 2864−2873 and references therein.

(20) Crystal data for **13a**: $C_{21}H_{36}O_4$ triclinic, $P\bar{1}$. a = 7.3176(7) Å, b = 12.220(2) Å, c = 21.946(3) Å, α = 96.27(1)°, β = 95.08(1)°, γ = 97.77(1)°, V = 1939.7(4) Å^3. Z = 4, D = 1.21 Mg·m^{-3}. λ = 1.54178 Å. F(000) = 776.00. Θ range = 2−55°. 5018 measured reflections, 4866 [R(int) = 0.03] independent reflections. 451 parameters. Reflections/parameters ratio 6.5. R(1)[$I > 2.00\sigma(I)$] = 7.1%. WR(2)[all data] = 11.1%. G.O.F.(all data) = 1.92.

(21) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507. See, also: Muri, E.; Kanazawa, A.; Barreiro, E.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 731−735.

(22) Crystal data for **15a*** (C-3 epimer): $C_{20}H_{34}O_4$ triclinic, $P\bar{1}$. a = 7.073(6) Å, b = 15.128(4) Å, c = 20.629(2) Å, α = 108.14(2)°, β = 90.11(3)°, γ = 116.72(3)°, V = 1847(2) Å^3, Z = 4, D = 1.22 Mg·m^{-3}. λ = 1.54178 Å. F(000) = 744.00. Θ range = 2.3−70.5°. 7728 measured reflections, 7344 [R(int) = 0.03] independent reflections. 433 parameters. Reflections/parameters ratio 12.8. R(1)[$I > 1.10\sigma(I)$] = 6.0%. WR(2)[all data] = 10.8%. G.O.F.(all data) = 2.00.

desired conjugate addition substrate, enone **16*** (80%).

To our dismay, though, the previously successful reagent, trimethylaluminum, totally failed to effect conjugate addition to enone **16***. Other attempts to install directly the second angular methyl group, for example by using dimethylzinc, likewise failed.[14] Fortunately, however, diethylaluminum cyanide[23] cleanly achieved 1,4-addition to give the desired adduct **17a*** in 77% yield, albeit at 60% conversion. Larger amounts of reagent improved the conversion, but at the expense of the yield, and therefore we opted to recycle the easily recovered **16***. The transformation of the angular cyano group of **17a*** into a methyl group was best realized[24] through a 3-step sequence: Dibal-H reduction, Wolff−Kishner reduction, and Parikh−Doering oxidation (56% brsm). Pleasingly, the resulting trans-, anti-, trans-fused ketone **17b***,[25,26] on regioselective triethylsilyl enol ether formation followed by oxidation[28] and desilylation, produced stereoselectively in 77% yield material that was spectroscopically and chromatographically identical with the previously prepared acyloin **13b**.[29] This alternative route to **13b*** in practice required approximately the same number of steps as before from the octalone, but was substantially more efficient and reproducible and, therefore, preferred.

The completion of the synthesis was accomplished uneventfully. The hydroxyl groups were deprotected with aqueous acetic acid to give **18***, which was then converted by Swern oxidation into the corresponding keto aldehyde. The final oxidation was achieved through treatment of the keto aldehyde with sodium chlorite in the presence of sodium dihydrogenphosphate and 2-methyl-2-butene to afford barbacenic acid (**1***) in 62% yield. Synthetically derived barbacenic acid and methyl barbacenoate (mp 136−137 °C, $[\alpha]_D$ +41), prepared with diazomethane, provided spectral data in excellent accord with those for naturally derived barbacenic acid and its methyl ester (lit.[3] mp 137−139 °C, $[\alpha]_D$ +40).[3] The identity of the synthetic material was further confirmed through single-crystal X-ray analysis of methyl barbacenoate.[30,31]

In summary, this first synthesis of barbacenic acid, which serves to define the absolute configuration of the natural product, has been accomplished in 5.2% overall yield from octalone **2*** via cyclopentenone **16*** (21 steps, 87%/step) with an excellent level of stereocontrol at each of the five contiguous asymmetric centers.

Experimental Section

The reaction mixture was generally poured into water and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhydrous Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Toluene, ether, and THF were distilled from sodium−benzophenone and pentane, dichloromethane, pyridine, triethylamine, DMF, and DMSO were distilled from calcium hydride.

(4a*R*,5*R*,6*R*,8a*R*)-6-Hydroxy-5-(2-hydroxyethyl)-5,8a-dimethyloctahydronaphthalen-1(2*H*)-one (6*). A solution of 3.12 g (11.0 mmol) of diol **5*** and its OH-epimer (4:1), prepared from octalone **2***[5d] (ee ≥99.9% by HPLC) in 80% overall yield according to a literature procedure,[9] in 120 mL of 85% aqueous acetic acid was refluxed for 30 min, whereupon the solvent was evaporated under reduced pressure. The crude product was isolated with ethyl acetate in the usual manner and purified by silica gel chromatography with ethyl acetate to give 2.58 g (98%) of diol **6*** and its epimer: major isomer (from a chromatographic fraction); mp 147−148 °C; $[\alpha]^{25}_D$ +37 (*c* 1.0, $CHCl_3$); IR 3700−3050, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (t, J = 5.8 Hz, 2 H), 3.48−3.39 (m, 1 H), 2.88−2.45 (br s, 2 H), 2.55 (td, J = 13.8, 5.9 Hz, 1 H), 2.25−2.15 (m, 1 H), 2.12−2.01 (m, 1 H), 1.89−1.78 (dt, J = 15.0, 5.0 Hz, 1 H), 1.78−1.41 (m, 9 H), 1.16 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 215.2 (C), 75.5 (CH), 58.2 (CH_2), 50.3 (CH), 48.6 (C), 42.7 (CH_2), 42.0 (C), 37.3 (CH_2), 31.1 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 20.7 (CH_2), 19.1 (CH_3), 14.4 (CH_3); MS (EI) m/z 240 (M^+), 41 (100%). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.74; H, 10.06.

(4a*R*,6a*R*,11a*R*,11b*R*)-4a,8,8,11a-Tetramethyldecahydro-7,9-dioxa-cycloheptanaphthalen-4-one (7*). A mixture of diol **6*** and its OH-epimer (ca. 4:1, 4.56 g, 19.0 mmol), pyridinium *p*-toluenesulfonate (160 mg, 0.64 mmol), and copper sulfate (11.75 g, 73.6 mmol) in 145 mL of dry acetone was stirred overnight at 20 °C, whereupon the reaction mixture was filtered through Celite and the acetone was removed under reduced pressure. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in pentane to give 3.73 g (70%) of ketone **7*** and 933 mg (17.5%) of its epimer. Ketone **7***: mp 97 °C; $[\alpha]^{25}_D$ +53 (*c* 1.4, $CHCl_3$); IR 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (t, J = 12.5 Hz, 1 H), 3.48 (dt, J = 12.5, 3.5 Hz, 1 H),

(23) Nagata, W. *Org. React.* **1977**, *25*, 255−476.

(24) See: Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031−12040. (brsm = based on recovered starting material.)

(25) Crystal data for **17b***: $C_{21}H_{34}O_3$ orthorhombic. $P2_12_12_1$. a = 10.319(3) Å, b = 12.142(6) Å, c = 14.861(5) Å, V = 1861(1) Å^3. Z = 4. D = 1.19 Mg·m^{-3}. λ = 0.71073 Å. F(000) = 736.00. Θ range = 1.3−30°. 2239 measured reflections, 5846 independent reflections. 217 parameters. Reflections/parameters ratio 10.4. $R(1)[I > 2.00\sigma(I)]$ = 4.8%. WR(2)[all data] = 5.6%. G.O.F.(all data) = 1.61.

(26) The ketone **17b*** was also converted through diol deprotection, oxidation, and esterification into the C-8 epimer[27] of methyl deoxybarbacenoate.[3b] On DBU epimerization, this isomer was partially transformed into the natural product (methyl ester), thereby confirming the previously assigned[3b] structure and relative stereochemistry of the barbacenic acid congener.

(27) Crystal data for the C-8 epimer of methyl deoxybarbacenoate: $C_{19}H_{28}O_4$ orthorhombic. $P2_12_12_1$. a = 11.691(3) Å, b = 11.750(2) Å, c = 12.767(3) Å, V = 1753.8(5) Å^3. Z = 4. D = 1.21 Mg·m^{-3}. λ = 1.54178 Å. F(000) = 696.00. Θ range = 3.4−75°. 1810 measured reflections, 1810 independent reflections. 208 parameters. Reflections/parameters ratio 7.3. $R(1)[I > 1.10\sigma(I)]$ = 6.4%. WR(2)[all data] = 10.2%. G.O.F.(all data) = 1.99.

(28) For a similarly selective epoxidation in a closely related system, see: Nakajima, Y.; Satoh, Y.; Katsumata, M.; Tsujiyama, K.; Ida, Y.; Shoji, J. *Phytochemistry* **1994**, *36*, 119−127.

(29) While the enolate from CN conjugate addition to **16*** could be trapped with trimethylsilyl chloride to give the trimethylsilyl enol ether, which in turn could be transformed with peracid into the acyloin corresponding to **13b*** (CN replaces Me at C-9), the final CN → Me conversion to give **13b*** could not be satisfactorily accomplished. In the subsequent work, it was found that the trimethylsilyl enol ether of **17b*** suffered partial cleavage during the peracid oxidation (in the presence of base α,α′-dihydroxylation became significant), and for this reason the more robust triethylsilyl enol ether was used.

(30) Crystal data for **1*** (methyl ester): Crystal data for $C_{19}H_{28}O_5 \cdot 0.5(H_2O) \cdot 0.35(CH_2Cl_2)$: monoclinic. *C*2. a = 17.9204(12) Å, b = 7.3606(5) Å, c = 17.2855(12) Å, β = 115.56(22)°, V = 2056(2) Å^3. Z = 4. D = 1.20 Mg·m^{-3}. λ = 0.71073 Å. F(000) = 798.80. Θ range = 1−30°. 11521 measured reflections, 2915 [R(int) = 0.07] independent reflections. 233 parameters. Reflections/parameters ratio 8.5. $R(1)[I > 1.20\sigma(I)]$ = 8.8%. WR(2)[all data] = 11.6%. G.O.F.(all data) = 1.99.

(31) Since no studies of the biological properties of barbacenic acid have been reported, the synthetically derived material was tested; barbacenic acid was found to be devoid of significant antibacterial, antifungal, antinematicidal, and cytotoxic activity.

3.50−3.40 (m, 1 H), 2.55 (td, J = 14.0, 6.9 Hz, 1 H), 2.19 (dd, J = 14.0, 3.8 Hz, 1 H), 2.14−1.99 (m, 1 H), 1.77−1.41 (m, 9 H), 1.27 (s, 6 H), 1.23−1.04 (m, 1 H), 1.12 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 214.9 (C), 100.6 (C), 75.0 (CH), 58.4 (CH), 53.8 (CH), 48.3 (C), 45.0 (CH_2), 41.0 (C), 37.5 (CH_2), 31.6 (CH_2), 26.2 (CH_2), 25.2 (CH_2), 24.7 (CH_3), 24.6 (CH_3), 21.1 (CH_2), 18.7 (CH_3), 14.1 (CH_3); MS (EI) *m*/*z* 280 (M^+), 55 (100%). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.89; H, 10.12.

(4a*R*,6a*R*,11a*R*,11b*R*)-Trifluoromethanesulfonic Acid 4a,8,8,11a-Tetramethyl-1,2,4a,5,6,6a,10,11,11a,11b-decahydro-7,9-dioxa-cyclohepta[α]naphthalen-4-yl Ester (8a*). To a solution of 2.85 g (10.2 mmol) of ketone **7*** and 5.55 g (27.0 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine in 62 mL of dichloromethane at 20 °C was added 3.60 mL (6.04 g, 21.4 mmol) of trifluoromethanesulfonic anhydride. After the solution was stirred for 2 h, pentane was added and stirring was continued at 0 °C for an additional 10 min, whereupon the pyridinium salt was removed by filtration through a pad of Celite. The solids were washed with pentane and the combined organic filtrates were concentrated to afford a tan solid, which was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in pentane to afford 275 mg (10%) of recovered **7*** and 3.80 g (90%) of triflate **8a***: mp 96 °C; $[\alpha]^{25}_D$ −18 (*c* 1.3, $CHCl_3$); IR 3053, 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dd, J = 4.8, 2.9 Hz, 1 H), 3.82 (t, J = 11.9 Hz, 1 H), 3.53 (dd, J = 11.7, 5.1 Hz, 1 H), 3.51 (dd, J = 16.3, 3.3 Hz, 1 H), 2.35−2.00 (m, 2 H), 1.81 (dt, J = 12.6, 3.3 Hz, 1 H), 1.72−1.41 (m, 4 H), 1.41−1.19 (m, 4 H), 1.30 (s, 6 H), 1.12 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.5 (C), 118.4 (q, J = 320 Hz, CF_3), 114.8 (CH), 100.7 (C), 75.1 (CH), 58.5 (CH_2), 52.0 (CH), 44.6 (CH_2), 40.0 (C), 38.7 (C), 33.1 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.7 (CH_3), 24.6 (CH_3), 19.6 (CH_3), 18.0 (CH_2), 13.8 (CH_3); MS (CI) *m*/*z* 413 (MH^+), 205 (100%). Anal. Calcd for $C_{18}H_{27}O_5F_3S$: C, 52.41; H, 6.60. Found: C, 52.82; H, 6.70.

(4a*R*,6a*R*,11a*R*,11b*S*)-4-Allyl-4a,8,8,11a-tetramethyl-1,2,4a,5,6,6a,10,11,11a,11b-decahydro-7,9-dioxa-cyclohepta[α]naphthalene (8b*). To a mixture of 3.50 g (8.49 mmol) of triflate **8a***, 1.07 g (25.2 mmol) of lithium chloride, and 200 mg (0.17 mmol) of $Pd(PPh_3)_4$ was added a solution of 3.05 g (9.21 mmol) of allyltributyltin in 60 mL of THF. The reaction mixture was heated at reflux for 14 h and then cooled to 20 °C, diluted with hexane, and washed several times with 10% aq ammonium hydroxide. The crude product was isolated in the usual manner and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in pentane to afford 2.59 g (100%) of diene **8b***: mp 76−77 °C; $[\alpha]^{25}_D$ −33 (*c* 1.2, $CHCl_3$); IR 3090, 3058, 1640 cm^{-1}; ^{1} H NMR (300 MHz, $CDCl_3$) δ 5.86−5.68 (m, 1 H), 5.17 (br s, 1 H), 5.00 (s, 1 H), 4.98−4.93 (m, 1 H), 3.83 (t, J = 12.3 Hz, 1 H), 3.58−3.44 (m, 2 H), 2.76−2.51 (m, 2 H), 2.19−1.95 (m, 2 H), 1.85−1.37 (m, 7 H), 1.30 (s, 6 H), 1.30−1.18 (m, 1 H), 1.15 (dd, J = 12.0, 2.3 Hz, 1 H), 1.02 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.6 (C), 138.1 (CH), 120.9 (CH), 115.4 (CH_2), 100.8 (C), 75.7 (CH), 58.7 (CH_2), 52.2 (CH), 44.9 (CH_2), 40.2 (C), 37.8 (C), 35.1 (CH_2), 35.0 (CH_2), 27.0 (CH_2), 25.8 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 20.2 (CH_3), 18.8 (CH_2), 13.8 (CH_3); MS (CI) *m*/*z* 305 (MH^+), 247 (100%). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.72; H, 10.71.

(3*S*,4*S*,4a*R*,6a*R*,11a*R*,11b*S*)-4-(3-Hydroxypropyl)-4a,8,8,-11a-tetramethyldodecahydro-7,9-cyclohepta[α]-naphthalen-3-ol (14a*). A solution of 2.58 g (8.47 mmol) of diene **8b*** and 2.75 g (11.3 mmol) of recrystallized 9-BBN dimer in 30 mL of THF under argon was stirred at 20 °C for 1.5 h, after which 19.4 mL (19.4 mmol) of a 1 M solution of BH_3 in THF was slowly added at 0 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 2 h. Ethanol (33 mL), 3 M NaOH (33 mL), and then 30% H_2O_2 (33 mL) were added at 0 °C, and the resulting mixture was stirred at 20 °C for 5 h. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ethyl acetate to give 2.88 g (100%) of diol **14a***: mp 165 °C; $[\alpha]^{25}_D$ +61.5 (*c* 1.1, $CHCl_3$); IR 3650−3100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (t, J = 12.5 Hz, 1 H), 3.73−3.53 (m, 2 H), 3.53−3.42 (m, 3 H), 2.08−1.98 (m, 1 H), 1.75 (dt, J = 13.0, 3.4 Hz, 1 H), 1.72−1.32 (m, 9 H), 1.29 (2s, 6 H), 1.32−1.17 (m, 2 H), 1.07 (td, J = 13.0, 4.0 Hz, 1 H), 0.94−0.82 (m, 2 H), 0.81 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 100.6 (C), 75.8 (CH), 72.6 (CH), 61.8 (CH_2), 58.7 (CH_2), 56.9 (CH), 55.2 (CH), 45.2 (CH_2), 40.1 (C), 38.4 (C), 37.1 (CH_2), 36.7 (CH_2), 33.8 (CH_2), 25.3 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 22.7 (CH_2), 20.8 (CH_2), 14.5 (CH_3), 13.7 (CH_3); MS (CI) *m*/*z* 341 (MH^+), 265 (100%). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.47; H, 10.84.

(4*S*,4a*R*,6a*R*,11a*R*,11b*S*)-3-(4a,8,8,11a-Tetramethyl-3-oxo-dodecahydro-7,9-cyclohepta[α]naphthalen-4-yl)propionaldehyde (14b*). To a stirred solution of 6.25 mL (6.88 g, 88.1 mmol) of dimethyl sulfoxide in 65 mL of dichloromethane at −60 °C under argon was added 4.00 mL (5.82 g, 45.9 mmol) of oxalyl chloride. After being stirred for 10 min at −60 °C, the reaction mixture was treated dropwise with a solution of 2.95 g (8.66 mmol) of diol **14a*** in 100 mL of dichloromethane. The mixture was allowed to warm to −40 °C, stirred for 1.5 h at this temperature, and then treated with 27.0 mL (19.6 g, 194 mmol) of triethylamine. The reaction mixture was allowed to warm to 20 °C and was processed with dichloromethane in the normal manner. Purification of the resulting crude material by filtration through silica gel (pretreated with 2.5% (v/v) of Et_3N) with ethyl acetate in pentane gave 2.44 g (84%) of keto aldehyde **14b***: mp 119 °C; $[\alpha]^{25}_D$ +65 (*c* 1.1, $CHCl_3$); IR 1711, 1699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, 1 H), 3.76 (t, J = 11.8 Hz, 1 H), 3.54 (dd, J = 12.0, 4.7 Hz, 1 H), 3.46 (dt, J = 12.9, 3.3 Hz, 1 H), 2.51 (dddd, J = 17.9, 7.9, 5.5, 1.0 Hz, 1 H), 2.34 (ddd, J = 13.4, 5.1, 2.1 Hz, 1 H), 2.29−2.11 (m, 2 H), 2.01 (d, J = 10.5 Hz, 1 H), 1.98−1.22 (m, 11 H), 1.27 (s, 3 H), 1.26 (s, 3 H), 0.82 (s, 3 H), 0.71 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.2 (C), 202.2 (C), 100.6 (C), 75.2 (CH), 62.7 (CH), 58.5 (CH_2), 54.6 (CH), 45.3 (CH_2), 43.0 (CH_2), 42.1 (C), 42 (CH_2), 40.4 (C), 37.3 (CH_2), 25.7 (CH_2), 24.6 (2 CH_3), 23.5 (CH_2), 14.6 (CH_3), 14.5 (CH_2), 13.7 (CH_3); MS (CI) *m*/*z* 337 (MH^+). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.84.

(1*S*,3a*S*,3b*R*,5a*R*,10a*R*,10b*S*,12a*R*)-3b,7,7,10a-Tetramethyltetradecahydro-6,8-dioxa-cyclohepta[α]cyclopenta[*f*]-naphthalene-1,12a-diol (15a*). To 2.92 g (8.68 mmol) of keto aldehyde **14b*** under argon and at −70 °C was added 200 mL (20 mmol) of a 0.1 M solution of SmI_2 in THF. The reaction mixture was allowed to warm to −40 °C over 1.5 h, treated with saturated aqueous $NaHCO_3$, and then extracted with EtOAc. The organic layer was washed with aqueous saturated $NaHCO_3$, a 10% $Na_2S_2O_3$ solution, and then brine and dried (Na_2SO_4). After evaporation of the solvents in vacuo, the residue was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in dichloromethane to provide 2.41 g (82%) of diol **15a***: mp 183−184 °C; $[\alpha]^{25}_D$ +56 (*c* 1.1, $CHCl_3$); IR 3600−3150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (t, J = 12.4 Hz, 1 H), 3.69 (t, J = 7.9 Hz, 1 H), 3.52−3.39 (m, 2 H), 2.42−2.20 (br s, 2 H), 2.11−1.96 (m, 1 H), 1.83 (dt, J = 13.2, 3.0 Hz, 1 H), 1.78−1.56 (m, 3 H), 1.56−1.32 (m, 6 H), 1.27 (s, 6 H), 1.24−0.96 (m, 4 H), 1.00 (s, 3 H), 0.86 (s, 3 H), 0.75 (dd, J = 11.9, 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 100.5 (C), 78.4 (CH), 77.3 (C), 76.1 (CH), 58.8 (CH_2), 57.0 (CH), 56.7 (CH), 45.4 (CH_2), 40.1 (C), 38.3 (CH_2), 36.5 (CH_2), 36.3 (C), 30.6 (CH_2), 25.2 (CH_2), 24.7 (2 CH_3), 19.9 (CH_2), 18.6 (CH_2), 15.2 (CH_3), 13.8 (CH_3); MS (CI) *m*/*z* 339 (MH^+). An X-ray crystallographic structure determination supports the assignment.[22] Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 71.17; H, 10.27.

(3a*S*,3b*R*,5a*R*,10a*R*,10b*S*,12a*R*)-12a-Hydroxy-3b,7,7,-10a-tetramethyltetradecahydro-6,8-dioxa-cyclohepta[α]-cyclopenta[*f*]naphthalen-1-one (15b*). A solution of 555 mg (3.49 mmol) of pyridine−sulfur trioxide complex in 1.50 mL of DMSO was added to a stirred solution at 20 °C of 350 mg

(1.03 mmol) of diol **15a*** in 1.50 mL of DMSO and 1.50 mL (1.09 g, 10.8 mmol) of triethylamine. The reaction mixture was stirred for 2 h, after which aqueous ammonium chloride was added. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in pentane to yield 290 mg (83%) of the hydroxy ketone **15b***: mp 243−245 °C; $[\alpha]^{25}_D$ +161 (*c* 1.2, $CHCl_3$); IR 3500−3300, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (t, J = 12.2 Hz, 1 H), 3.53−3.43 (m, 2 H), 2.54 (dd, J = 18.9, 8.3 Hz, 1 H), 2.11−1.57 (m, 9 H), 1.57−1.39 (m, 2 H), 1.29 (s, 6 H), 1.28−1.04 (m, 3 H), 1.09 (s, 3 H), 0.89 (s, 3 H), 0.83 (dd, J = 12.4, 2.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 215.4 (C), 100.5 (C), 75.9 (C), 75.9 (CH), 58.7 (CH_2), 57.9 (CH), 56.8 (C), 45.3 (CH_2), 40.2 (C), 37.8 (CH_2), 37.0 (C), 35.3 (CH_2), 32.3 (CH_2), 25.1 (CH_2), 24.7 (CH_3), 24.7 (CH_3), 18.1 (CH_2), 18.1 (CH_2), 16.4 (CH_3), 13.7 (CH_3); MS (CI) *m*/*z* 337 (MH^+). HRMS calcd for $C_{20}H_{33}O_4$: 337.2379. Found: 337.2398 (MH^+).

(3b*R*,5a*R*,10a*R*,10b*S*)-3b,7,7,10a-Tetramethyl-2,3,3b,4,5,-5a,9,10,10a,10b,11,12-dodecahydro-6,8-dioxa-cyclohepta[α]-cyclopenta[*f*]naphthalen-1-one (16*). To a solution of 1.59 g (4.73 mmol) of hydroxy ketone **15b*** in 130 mL of pyridine at 0 °C was added 6.00 mL (9.79 g, 82.3 mmol) of freshly distilled thionyl chloride. After 45 min, water was added and the mixture was extracted with ether, which was washed with a saturated solution of copper sulfate, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to leave the crude reaction product, which was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in dichloromethane to give 1.20 g (80%) of enone **16***: mp 119 °C; $[\alpha]^{25}_D$ +11 (*c* 1.3, $CHCl_3$); IR 1698, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (t, J = 12.2 Hz, 1 H), 3.58−3.33 (m, 2 H), 2.53−2.18 (m, 5 H), 2.11−1.84 (m, 1 H), 1.81−1.65 (m, 3 H), 1.57−1.28 (m, 3 H), 1.48 (dd, J = 14.0, 3.0 Hz, 1 H), 1.26−1.13 (m, 1 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 1.12−1.03 (m, 1 H), 1.06 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.3 (C), 181.1 (C), 136.1 (C), 100.5 (C), 75.2 (CH), 58.5 (CH_2), 51.6 (CH), 44.7 (CH_2), 40.2 (C), 37.6 (CH_2), 34.5 (CH_2), 34.2 (C), 25.4 (CH_2), 24.6 (CH_3), 24.5 (CH_3), 23.8 (CH_2), 23.1 (CH_2), 19.7 (CH_3), 18.0 (CH_2), 13.8 (CH_3); MS (CI) *m*/*z* 319 (MH^+). HRMS calcd for $C_{20}H_{31}O_3$: 319.2273. Found: 319.2270 (MH^+).

(3a*S*,3b*R*,5a*R*,10a*R*,10b*S*,12a*S*)-3b,7,7,10a-Tetramethyl-1-oxo-tetradecahydro-6,8-dioxa-cyclohepta[α]cyclopenta[*f*]naphthalene-3a-carbonitrile (17a*). To a solution of 930 mg (2.92 mmol) of enone **16*** in 40 mL of dry toluene at 20 °C was added 8.8 mL (8.8 mmol) of a 1 M solution of Et_2-AlCN in toluene. After being stirred at 20 °C for 24 h, the reaction mixture was diluted with ether and treated with saturated aqueous $NaHCO_3$. The crude product was isolated with ether in the usual way and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in dichloromethane to provide 370 mg (40%) of recovered starting material and 470 mg (47%, 77% brsm) of nitrile **17a***: mp 214−215 °C; $[\alpha]^{25}_D$ +151 (*c* 1.0, $CHCl_3$); IR 2305, 1748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (br t, J = 13 Hz, 1 H), 3.60 (dd, J = 11.5, 4.6 Hz, 1 H), 3.51 (dt, J = 13.0, 3.3 Hz, 1 H), 2.48 (dd, J = 10.7, 7.1 Hz, 2 H), 2.23−2.09 (m, 3 H), 1.98 (ddd, J = 13.0, 10.5, 9.0 Hz, 1 H), 1.99−1.68 (m, 3 H), 1.68−1.41 (m, 5 H), 1.40−1.23 (m, 2 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.04 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.2 (C), 121.4 (C), 100.7 (C), 74.8 (CH), 58.5 (CH_2), 56.2 (CH), 52.3 (CH), 51.0 (CH), 45.0 (CH_2), 40.2 (C), 38.9 (C), 35.3 (CH_2), 34.0 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.7 (CH_3), 24.6 (CH_3), 22.6 (CH_2), 20.9 (CH_2), 14.1 (CH_3), 13.7 (CH_3); MS (CI) *m*/*z* 346 (MH^+), 305 (100%). Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.97; H, 9.22; N, 4.08.

(3a*R*,3b*R*,5a*R*,10a*R*,10b*S*,12a*S*)-3a,3b,7,7,10a-Pentamethyltetradecahydro-6,8-dioxa-cyclohepta[α]cyclopenta[*f*]naphthalen-1-one (17b*). To a stirred solution of 470 mg (1.36 mmol) of nitrile **17a*** in 40 mL of toluene at −60 °C was added 7.0 mL (10.5 mmol) of a 1.5 M solution of Dibal-H in toluene, and the resulting solution was allowed to warm to −40 °C over 1 h. The reaction was quenched by successive addition of 3 mL of methanol and 30 mL of 2 M NaOH. The resulting mixture was stirred at 20 °C for 30 min and then extracted several times with dichloromethane. The combined organic layers were washed with brine, dried, and filtered. Concentration of the filtrate afforded 570 mg of the crude α-amino ether as a viscous oil, which was used directly below: IR 3600−3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (br s, 1 H), 1.28 (s, 6 H), 1.06 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 100.6 (C), 85.6 (CH), 78.7 (CH), 75.9 (CH), 58.8 (CH_2), 56.0 (C), 49.3 (CH), 48.6 (CH), 46.0 (CH_2), 40.4 (C), 36.6 (C), 34.6 (CH_2), 30.9 (CH_2), 25.7 (CH_2), 24.7 (2 CH_3), 22.9 (CH_2), 21.6 (CH_2), 19.3 (CH_2), 17.6 (CH_3), 14.5 (CH_3). HRMS calcd for $C_{21}H_{36}NO_3$: 350.2695. Found: 350.2716 (MH^+).

The above crude α-amino ether in 25 mL of ethylene glycol and 6.0 mL (6.2 g, 124 mmol) of hydrazine monohydrate was heated at 195 °C for 30 min. The reaction mixture was cooled to 0 °C, 1.30 g (23.2 mmol) of potassium hydroxide pellets was carefully added, and the resulting mixture was heated at 195 °C for an additional 16 h. After being allowed to cool to 20 °C, the reaction mixture was processed with ethyl acetate−ether in the usual way to give the crude product, which was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in dichloromethane to give 120 mg (25%) of hydroxy nitrile (recycled by oxidation to **17a*** with PCC in dichloromethane; 85% yield) and 230 mg (50%, 64% brsm) of the desired alcohol: mp 162 °C; $[\alpha]^{25}_D$ −52 (*c* 1.0, $CHCl_3$); IR 3600−3100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (m, 1 H), 3.80 (t, J = 12.0 Hz, 1 H), 3.53−3.40 (m, 2 H), 2.14 (dt, J = 14.3, 8.3 Hz, 1 H), 1.78−1.14 (m, 15 H), 1.30 (s, 3 H), 1.29 (s, 3 H), 1.05 (s, 3 H), 0.92 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 100.5 (C), 76.1 (CH), 73.9 (CH), 58.9 (CH_2), 48.4 (C), 47.1 (CH), 47.1 (CH), 45.9 (CH_2), 40.3 (C), 39.7 (C), 33.7 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 26.1 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 22.6 (CH_2), 21.9 (CH_2), 16.5 (CH_3), 15.1 (CH_3), 13.8 (CH_3); MS (CI) *m*/*z* 337 (MH^+), 279 (100%). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.13; H, 10.92.

To a stirred solution of 230 mg (0.68 mmol) of the above alcohol in 2.5 mL of DMSO and 0.925 mL (672 mg, 6.64 mmol) of triethylamine at 20 °C was added a solution of 375 mg (2.36 mmol) of pyridine−sulfur trioxide complex in 2.5 mL of DMSO. The reaction mixture was stirred for 2 h, after which aqueous ammonium chloride was added. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in dichloromethane to provide 200 mg (87%) of ketone **17b***: mp 201−202 °C; $[\alpha]^{25}_D$ +121 (*c* 1.4, $CHCl_3$); IR 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (td, J = 12.4, 1.3 Hz, 1 H), 3.53−3.40 (m, 2 H), 2.30−2.03 (m, 3 H), 1.96 (t, J = 11.1 Hz, 1 H), 1.94−1.82 (m, 1 H), 1.80−1.66 (m, 1 H), 1.63−1.12 (m, 10 H), 1.31−1.30 (s, 6 H), 1.06 (s, 3 H), 0.88 (d, J = 0.9 Hz, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 217.9 (C), 100.6 (C), 75.9 (CH), 58.2 (CH_2), 53.8 (CH), 47.9 (CH), 46.5 (C), 45.9 (CH_2), 40.3 (C), 39.4 (C), 34.8 (CH_2), 31.4 (CH_2), 27.8 (CH_2), 25.9 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 21.6 (CH_2), 20.6 (CH_2), 16.5 (CH_3), 15.1 (CH_3), 13.9 (CH_3); MS (CI) *m*/*z* 335 (MH^+), 294 (100%). An X-ray crystallographic structure determination supports the assignment.[25] HRMS calcd for $C_{21}H_{35}O_3$: 335.2586. Found: 335.2573 (MH^+).

(3a*S*,3b*R*,5a*R*,10a*R*,10b*S*,12a*S*)-12a-Hydroxy-3a,3b,7,7,-10a-pentamethyltetradecahydro-6,8-dioxa-cyclohepta[α]-cyclopenta[*f*]naphthalen-1-one (13b*). A solution of 103 mg (0.31 mmol) of ketone **17b*** and 0.270 mL (196 mg, 1.94 mmol) of triethylamine in 4.0 mL of ether was treated with 0.300 mL (351 mg, 1.33 mmol) of triethylsilyl triflate. After being stirred for 1.5 h, the mixture was processed with ether in the usual way and the crude product was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ether in pentane to afford 133 mg (96%) of a 92:8 mixture of tetra- and trisubstituted silyl enol ethers, respectively: IR 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 3.81

(t, J = 12.0 Hz, 1 H), 3.52−3.42 (m, 2 H), 2.43 (ddd, J = 13.8, 5.1, 1.7 Hz, 1 H), 2.37−2.24 (m, 1 H), 2.21−2.08 (m, 1 H), 1.87 (ddd, J = 15.8, 10.4, 5.4 Hz, 1 H), 1.80−1.55 (m, 2 H), 1.55−1.37 (m, 5 H), 1.31 (3 H), 1.30 (3 H), 1.30−1.16 (m, 4 H), 1.05 (s, 3 H), 0.96 (t, J = 7.8 Hz, 9 H), 0.87 (s, 3 H), 0.86 (s, 3 H), 0.62 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, major isomer) δ 142.5 (C), 120.9 (C), 100.5 (C), 76.2 (CH), 58.9 (CH_2), 51.6 (C), 47.8 (CH), 45.7 (CH_2), 40.4 (C), 40.3 (C), 32.7 (CH_2), 32.0 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 24.8 (2 CH_3), 22.8 (CH_3), 22.3 (CH_2), 21.1 (CH_2), 16.4 (CH_3), 14.0 (CH_3), 6.7 (3 CH_3), 5.3 (3 CH_2); MS (CI) m/z 449 (MH^+). HRMS calcd for $C_{27}H_{49}O_3Si$: 449.3451. Found: 449.3411 (MH^+).

A stirred solution of 126 mg (0.28 mmol) of the above mixture of silyl enol ethers in 8.0 mL of dichloromethane was cooled to −30 °C and treated with 240 mg (1.39 mmol) of purified *m*-chloroperbenzoic acid. After being stirred for 1 h, the mixture was filtered through Celite, which was washed with ether. The solvents were evaporated and the resulting residue was dissolved in 8.0 mL of dichloromethane and treated at 20 °C with 1.2 mL (1.2 mmol) of a 1 M solution of Bu_4NF in THF. After being stirred for 1.5 h, the reaction mixture was worked up with dichloromethane in the usual way and the crude product was purified by silica gel chromatography (SiO_2 pretreated with 2.5% (v/v) of Et_3N) with ethyl acetate in dichloromethane to provide 79 mg (80%) of α-hydroxy ketone **13b***: mp 175−176 °C; $[\alpha]^{25}_D$ +7 (*c* 1.1, $CHCl_3$); IR 3700−3100, 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (t, J = 12.0 Hz, 1 H), 3.48 (dt, J = 12.8, 3.3 Hz, 1 H), 3.45 (dd, J = 12.0, 4.1 Hz, 1 H), 2.54 (ddd, J = 19.5, 11.8, 2.8 Hz, 1 H), 2.17−2.01 (m, 2 H), 1.86 (ddd, J = 13.8, 6.8, 2.9 Hz, 1 H), 1.73−1.54 (m, 3 H), 1.53−1.35 (m, 5 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 1.32−1.15 (m, 3 H), 1.10 (s, 3 H), 0.80 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 216.5 (C), 100.6 (C), 78.2 (C), 75.7 (CH), 58.8 (CH_2), 49.1 (C), 47.4 (CH), 45.8 (CH_2), 40.1 (C), 39.5 (C), 34.5 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 25.2 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 19.6 (CH_2), 17.3 (CH_3), 16.4 (CH_3), 14.3 (CH_3); MS (CI) m/z 351 (MH^+), 275 (100%). HRMS calcd for $C_{21}H_{35}O_4$: 351.2535. Found: 351.2539 (MH^+).

(3a*S*,5a*S*,6*R*,7*R*,9a*R*,9b*S*)-3a,7-Dihydroxy-6-(2-hydroxyethyl)-6,9a,9b-trimethyldodecahydrocyclopenta[α]naphthalen-3-one (18*). A solution of 82 mg (0.23 mmol) of α-hydroxy ketone **13b*** in 4.5 mL of 85% aqueous acetic acid was stirred at 20 °C for 45 min, after which the solvents were evaporated and the residue was purified by silica gel chromatography with methanol in dichloromethane to give 72 mg (100%) of triol **18***: mp 191 °C; $[\alpha]^{25}_D$ −11 (*c* 1.3, MeOH); IR 3600−3100, 1725 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 3.63 (t, J = 7 Hz, 2 H), 3.29−3.45 (m, 1 H), 2.53 (ddd, J = 19, 12, 2.5 Hz, 1 H), 2.19−1.98 (m, 2 H), 1.96−1.78 (m, 2 H), 1.72−1.56 (m, 4 H), 1.56−1.32 (m, 5 H), 1.25−1.12 (m, 1 H), 1.11 (s, 3 H), 0.79 (s, 6 H);^{13}C NMR (75.5 MHz, MeOD) δ 218.8 (C), 78.6 (C), 76.2 (CH), 59.0 (CH_2), 50.6 (C), 43.4 (CH), 43.1 (CH_2), 42.1 (C), 40.9 (C), 35.4 (CH_2), 32.4 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 27.3 (CH_2), 20.3 (CH_2), 18.2 (CH_3), 17.1 (CH_3), 16.3 (CH_3); MS (CI) m/z 311 (MH^+), 275 (100%). HRMS calcd for $C_{18}H_{34}NO_4$: 328.2487. Found: 328.2494 (MNH_4^+).

(3a*S*,5a*S*,6*R*,9a*R*,9b*S*)-(3a,7-Hydroxy-6,9a,9b-trimethyl-3,7-dioxo-dodecahydrocyclopenta[α]naphthalen-6-yl)-acetic Acid (1*) and Methyl Ester. To a stirred solution of 0.780 mL (859 mg, 11.0 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane at −60 °C under argon was added 0.550 mL (800 mg, 6.30 mmol) of oxalyl chloride. After being stirred for 10 min at −60 °C, the reaction mixture was treated dropwise with a solution of 36 mg (0.12 mmol) of triol **18*** in 5 mL of dichloromethane and 0.5 mL of dimethyl sulfoxide. The reaction mixture was allowed to warm to −40 °C, stirred for 1.5 h at this temperature, and then treated with 1.60 mL (1.16 g, 11.5 mmol) of triethylamine. The reaction mixture was allowed to warm to 20 °C and processed with dichloromethane in the usual way to afford 30 mg of the crude keto aldehyde, which was used directly below: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 1.09 (s, 3 H), 0.98 (s, 3 H), 0.88 (s, 3 H).

To a solution of 30 mg of the above crude keto aldehyde in 2.0 mL of *tert*-butyl alcohol, 1.0 mL of THF, and 0.630 mL (417 mg, 5.95 mmol) of 2-methyl-2-butene was added 43 mg (0.48 mmol) of $NaClO_2$ and 115 mg (0.83 mmol) of $NaH_2PO_4 \cdot H_2O$ in 1.0 mL of water. The mixture was stirred overnight and then treated with 3 mL of 1 M HCl. Extraction of the reaction mixture with ethyl acetate yielded the crude product, which was purified by methylation (CH_2N_2, SiO_2 chromatography, 62%) and hydrolysis (LiOH, THF−H_2O, 20 °C, 100%) to give 23 mg (62%) of barbacenic acid (**1***) as a white solid: $[\alpha]^{25}_D$ +7 (*c* 1.0, MeOH); IR 3600−3100, 1736, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (d, J = 17.4 Hz, 1 H), 2.32 (d, J = 16.4 Hz, 1 H), 1.06 (s, 3 H), 1.00 (s, 3 H), 0.75 (s, 3 H); MS (CI) m/z 340 (MNH_4^+, 100%). HRMS calcd for $C_{18}H_{26}NaO_5$: 345.1678. Found: 345.1647 (MNa^+). The methyl ester:[3] mp 136−137 °C; $[\alpha]^{25}_D$ +41 (*c* 0.9, $CHCl_3$); IR 3600−3100, 1738, 1732, 1698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 3 H), 2.88 (d, J_{AB} = 17.3 Hz, 1 H), 2.60 (ddd, J = 19.3, 11.8, 2.8 Hz, 1 H), 2.49−2.40 (m, 2 H), 2.38 (d, J_{AB} = 17.3 Hz, 1 H), 2.26−2.06 (m, 4 H), 1.94 (ddd, J = 13.0, 9.6, 2.7 Hz, 1 H), 1.75 (ddd, J = 13.9, 11.7, 7.6 Hz, 1 H), 1.59 (dt, J = 13.2, 4.1 Hz, 2 H), 1.44 (ddd, J = 12.5, 12.5, 3.6 Hz, 1 H), 1.35−1.21 (m, 2 H), 1.12 (s, 3 H), 0.95 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 216.4 (C), 215.2 (C), 172.5 (C), 77.9 (C), 51.6 (CH_3), 49.0 (C), 48.0 (C), 44.0 (CH_2), 41.8 (CH), 38.9 (C), 34.9 (CH_2), 34.4 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 27.3 (CH_2), 23.0 (CH_3), 20.3 (CH_2), 16.5 (CH_3), 16.0 (CH_3); MS (CI) m/z 337 (MH^+), 322 (100%). These spectral data are in excellent accord with the literature values[3] for natural **1*** and its methyl ester. The structure of **1*** (methyl ester) was further confirmed by an X-ray crystallographic determination.[30] HRMS calcd for $C_{19}H_{29}O_5$: 337.2015. Found: 337.2011 (MH^+).

Acknowledgment. We thank Professor Y. Vallée for his interest in our work, Prof. H. Anke and Drs. S. Omura and M. Kashimura for the biological tests, and Prof. A. Pinto for the spectra of natural barbacenic acid and its methyl ester. We also gratefully acknowledge financial support from the Université Joseph Fourier, the CNRS (UMR 5616), and the CNPq and fellowship awards from the MESR (to A.P.) and the CAPES (to E.M.).

Supporting Information Available: X-ray data for compounds **1*** (methyl ester), **13a**, **15a** (C-3 epimer), **17b***, and methyl deoxybarbacenoate (C-8 epimer), and ^{1}H and ^{13}C NMR spectra of compounds **1*** (methyl ester), **13b***, **15b***, **16***, **17b***, **17b*** (enol ether), and **18***. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0340049