A Total Synthesis of the Racemic Sesquiterpene Parvifoline†

Adrián Covarrubias-Zúñiga, Fernando Cantú, and Luis A. Maldonado*

Instituto de Química and División de Estudios de Posgrado, Facultad de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México D. F., México

Received November 14, 1997

A total synthesis of the sesquiterpene (±)-parvifoline **1** from the symmetrical naphthalene **4** is reported. The key step of the synthesis was a Stork−Landesman two-carbon ring expansion of β-tetralone **5,** which affords **9a** with the complete framework of the target. Although many reactions are involved in the sequence, the whole synthesis can be executed in only five synthetic operations and in ≈18% overall yield.

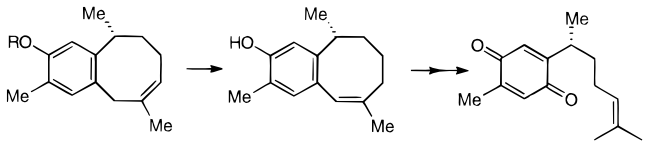
The benzocyclooctene parvifoline (**1**) is a phenolic sesquiterpene isolated from *Coreopsis parvifolia, Pereziae carpholepsis, Pereziae alamani* var. *oolepis,* and *Pereziae longifolia* Blake.[1] Its structure was proposed from spectral data[1a] and the absolute configuration established by conversion (via isoparvifoline **2**) to curcuquinone (**3**), a natural product of known absolute configuration[2] (Scheme 1).

It has been suggested that **1** is formed biogenetically, by cyclization of an activated phenolic bisabolene precursor such as a hydroxylated xanthorrizol, although its attempted synthesis along this biomimetically modeled route failed.[3] To our knowledge, two total syntheses of **1** have been described, one in which the cyclooctane ring was constructed by a Dieckmann-type intramolecular cyclization of an ester sulfone[4] and the other employing a Grob fragmentation of a bicyclo[3.3.0]octane γ-hydroxymesylate.[5] In both cases, a product with a C_{14} skeleton was obtained which was conveniently handled to introduce the lacking CH_3 group.

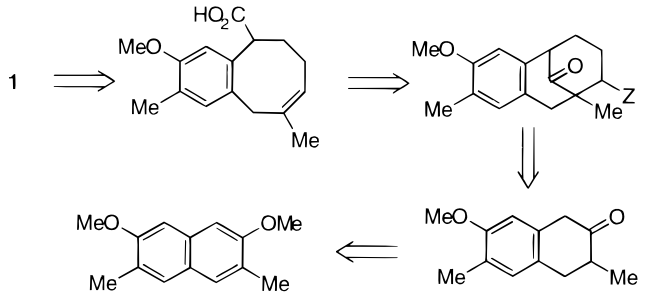
In this paper we wish to report another Grob fragmentation-based total synthesis of **1**[6] which has as the salient features: (1) the starting material contains 80% (C_{12}) of the carbon atoms of the target skeleton and is readily available, (2) in the cyclooctene ring formation, the complete framework of **1** is delivered, and (3) though it involves 12 chemical steps, it can be executed in only five synthetic operations.

Cyclohexanones can be converted into 4-cyclooctene carboxylic acids via Grob fragmentation of a bicyclo[3.3.1]-nonane intermediate (the Stork−Landesman two-carbon ring expansion[7]). From the recognition of this system in the B ring of **1**, it follows that by appropriate substitution in the starting cyclohexanone a simple synthesis of **1** via the Stork−Landesman two-carbon ring expansion would be at hand.[8] Our retrosynthetic analysis is depicted in Scheme 2.

Scheme 1



Scheme 2



β-Tetralone **5** was easily obtained from the known symmetrical naphthalene **4**[9] by Na/EtOH reduction, followed by acid-catalyzed hydrolysis of the intermediate enol ether in 95% yield (Scheme 3). Due to the sensitive nature of the intermediates involved in the Stork−Landesman ring expansion sequence (as has been reported for other substrates[10]), the conversion **5** → **9a** was first attempted without the isolation of intermediates. By careful spectroscopic monitoring of the reaction steps,

† Contribution no. 1635 of Instituto de Química, UNAM.

(1) (a) Bohlmann, F.; Zdero, Ch. *Chem. Ber.* **1977**, *110,* 468. (b) Joseph-Nathan, P.; Hernández, J. D.; Román, L. U.; García, E.; Mendoza, V. *Phytochemistry* **1982**, *21,* 669. (c) Joseph-Nathan, P.; Hernández, J. D.; Román, L. U.; García, E.; Mendoza, V.; Mendoza, S. *Phytochemistry* **1982**, *21,* 1129. (d) García, E.; Mendoza, V.; Guzmán, J. A. *J. Nat. Prod.* **1988**, *51,* 150.

(2) (a) García, E.; Mendoza, V.; Guzmán, J. A. *J. Nat. Prod.* **1987**, *50,* 1055. (b) Joseph-Nathan, P.; Hernández-Medel, M. del R.; Martínez, E.; Rojas-Gardida, M.; Cerda, C. M. *J. Nat. Prod.* **1988**, *51,* 675.

(3) Krause, W.; Bohlmann, F. *Tetrahedron Lett.* **1987**, *28,* 2575.

(4) Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994**, *35,* 5369.

(5) (a) Villagómez-Ibarra, R.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35,* 4771. (b) Villagómez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, *51,* 9285.

(6) Covarrubias, A.; Maldonado, L. A. *4th Chemical Congress of North America* **1991**, Abs. Org. 176.

(7) (a) Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, *78,* 5129. (b) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 555.

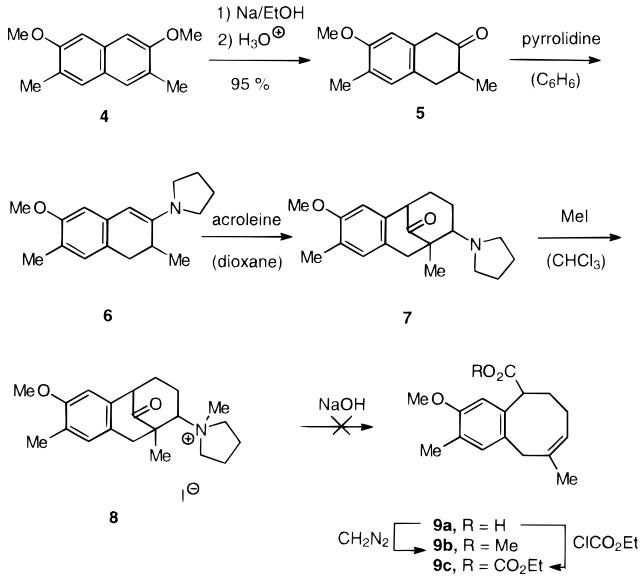
(8) For a review on the syntheses of cyclooctanes, which includes fragmentation reactions of bicyclic systems, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48,* 5757.

(9) Johansson, A. M.; Mellin, Ch.; Hacksell, U. *J. Org. Chem.* **1986**, *51,* 5252.

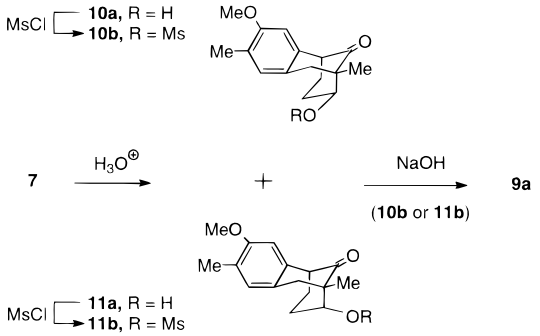
(10) For a reference in which a bicyclo[3.3.1]nonane pyrrolidinoketone closely related to **7** was isolated, but not characterized, see: Mitsuhashi, K.; Shiotani, S. *Chem. Pharm. Bull.* **1970**, *18,* 75.

S0022-3263(97)02092-6 CCC: $15.00
Published on Web 04/14/1998

Scheme 3



Scheme 4



we could tentatively identify the following: enamine **6** [IR 1610 cm^{-1} (C═CN), no absorption for C═O], bridged amino ketone **7**[11] [IR 1715 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ ppm 1.15 (s, CCH_3)], and the quaternary ammonium salt **8** [^1H NMR ($CDCl_3$) δ 3.56 (s, N^+CH_3)]. However, treatment of **8** with 15% aqueous NaOH solution to induce cleavage of the bicyclo[3.3.1]nonane ring system gave only traces of acidic material; the main product was extracted into the organic solvent from the original alkaline solution and identified as impure **7**.[11]

Since NaOH apparently induced the N-demethylation of **8** to give back amino ketone **7**,[12] an alternative plan became necessary. Mild acid treatment of **7** gave a mixture of ketols[13] that could be separated by column chromatography and characterized by spectroscopy and (in the case of **11a**) by single-crystal X-ray analysis[14] as the equatorial and axial isomers **10a** and **11a** in a 3:2 ratio (57% combined yield, Scheme 4). The MS (EI) spectra of the ketols are also in accord with the assigned structures, since an important (41% of relative intensity) $M^+ - 18$ peak is observed in the axial isomer, but is almost absent (10%) in the equatorial isomer.

As expected from stereoelectronic considerations, the mesylate **10b** derived from the equatorial ketol **10a**, upon treatment with refluxing 15% aqueous NaOH solution[15] under a N_2 atmosphere, gave cleanly (82% yield) the benzocyclooctene carboxylic acid **9a.** Under the same reaction conditions, the isomeric derived mesylate **11b** from the axial ketol **11a** gave also carboxylic acid **9a** but only in 41% yield.[16]

At this point, it was gratifying to find that the ^1H NMR spectrum of **9a** matched very closely with that of parvifoline methyl ether **13**, with the exception of the chemical shift and splitting pattern of the benzylic methine. Thus, the CO_2H substituent in **9a** induces a low field shift of the CH signal as compared with **13** and is seen at δ 4.11 as a doublet of doublets (J = 4.8, 13.5) due to coupling with the vicinal CH_2. In **13**, the benzylic CH is observed as a complex signal (additional coupling with the CH_3 substituent) at δ 3.20. The structure of **9a** was confirmed later unambiguously, by single-crystal X-ray analysis.[17]

For practical purposes, the β-tetralone **5** could be converted into **9a** by consecutive (1) enamine formation (pyrrolidine, C_6H_6, reflux with H_2O separator), (2) treatment of a dioxane solution of crude **6** with 3 equiv of acrolein, (3) shaking of the ethereal solution of crude **7** with 10% aqueous HCl, (4) after column chromatography purification, mesylation of the mixture of ketols **10a** and **11a** (1.3 equiv of MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h), and (5) fragmentation of the derived mesylates **10b** and **11b** with 15% aqueous NaOH solution. In this way, consistent yields of **9a** were obtained in ≈40% overall yield from **5**.

In completing the synthesis of **1**, the apparently trivial $CO_2H \rightarrow CH_3$ conversion was not an uncomplicated event. Thus, $LiAlH_4$ reduction of both carboxylic acid **9a**, as well as its derived methyl ester **9b** (CH_2N_2, Et_2O), gave appreciable amounts of overreduced (saturated) products. Since transannular reactions in the cyclooctane ring are common,[18] very probably intramolecular hydroalumination from an alkoxy organoaluminum hydride intermediate explains this unusual reduction of an isolated C═C double bond.

Fortunately, this undesirable side reaction could be avoided by $NaBH_4$ reduction of either the methyl ester **9b** in *t*-BuOH−MeOH[19] or the mixed ethyl carbonic anhydride **9c** (prepared in situ from **9a** with $ClCO_2Et$

(11) Although isolated in ≈90% yield, crude **7** was unstable on attempted purification by column chromatography. The complete ^1H NMR data for the crude product is ($CDCl_3$) δ 1.15 (s, 3H), 2.15 (s, 3H), 3.78 (s, 3H), 6.35 (s, 1H), 6.78 (s, 3H). The aliphatic CH_2 and CH protons are shown in the range of δ ≈1.0−4.0.

(12) As a referee has pointed out, since the conversion **7** → **8** was followed only by TLC, an incomplete *N*-methylation reaction can also (partially) explain the observed results.

(13) Aqueous acid treatment of bridged β-amino ketones gives bridged ketols by a reaction mechanism involving (1) acid-catalyzed opening of the bridged system, (2) hydrolysis of the immonium salt intermediate, and (3) acid-catalyzed aldol recyclization of the 1,5-keto aldehyde. See, for instance: (a) Allan, R. D.; Cordiner, B. G.; Wells, R. J. *Tetrahedron Lett.* **1968**, 6055. (b) Momose, T.; Kinoshita, M.; Imanishi, T. *Heterocycles* **1979**, *12*, 243. (c) Boucher, R. J.; Campbell, M. M.; Rae, D. *Tetrahedron* **1990**, *46*, 6839.

(14) Soriano-García, M.; Villena, R.; Covarrubias, A.; Olguin, J. S.; Maldonado, L. A. *Acta Crystallogr.* **1993,** C49, 2140.

(15) Hendrickson, J. B.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1307.

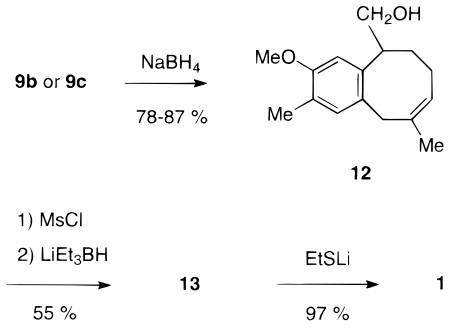
(16) Low-polarity compounds (unidentified) were also formed in this experiment. The successful (although modest yielding) formation of carboxylic acid **9a** from the axial isomer **11a**, very probably involves a nonconcerted carbonium ion initiated fragmentation. The alternative, concerted fragmentation of mesylate **11b** from a boat ring C conformation is ruled out, since a strained (*E*)-cyclooctene double bond should be obtained.

(17) Soriano-García, M.; Villena Iribe, R.; Covarrubias, A.; Cantú, F.; Maldonado, L. A. *Anal. Sci.* **1993**, *9*, 439.

(18) Harrowven, D. C.; Pattenden, G. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3 pp 379−385 and references therein.

(19) Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.

Scheme 5



and Et_3N in dry THF) in THF−H_2O. The primary alcohol **12** was thus obtained in 87 and 78% yields, respectively (Scheme 5).

Mesylation of alcohol **12** (1.3 equiv of MsCl, Et_3N, CH_2Cl_2), followed by reduction of the crude mesylate with $LiEt_3BH$ gave racemic **13** in 55% overall yield. The synthetic material was spectroscopically identical with an authentic sample prepared (Me_2SO_4, K_2CO_3, Me_2CO) from natural **1**.[20] Finally, cleavage of the methyl ether in **13** with EtSLi in dry DMF (105 °C, 48 h) gave racemic **1** (97%) whose spectroscopic properties were identical with those reported for the natural product.[20]

Since the easily obtained carboxylic acid **9a** should be amenable to enantiomeric resolution, a total synthesis of natural **1** by the approach described in this paper is in principle conceivable. Work along this way is being pursued at present in our laboratory and will be reported in due course.

Experimental Section

Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV irradiation; column chromatography purifications were carried out using silica gel (70−230 mesh). ^{1}H NMR spectra were recorded at either 200 or 300 MHz, while ^{13}C NMR were run at 75 MHz. Low- and high-resolution mass spectra were measured at 70 eV (EI). Elemental analyses were performed by Galbraith Laboratories, Inc.

1,4-Dihydro-2,7-dimethoxy-3,6-dimethylnaphthalene (4a) was prepared as indicated in ref 9 for the synthesis of other 1,4-dihydronaphthalenes: mp 103−105 °C; yield 95%; ^{1}H NMR δ 1.59 (s, 3H), 2.01 (s, 3H), 3.05−3.18 (m, 2H), 3.24−3.42 (m, 2H), 3.43 (s, 3H), 3.63 (s, 3H), 6.40 (s, 1H), 6.72 (s, 1H); ^{13}C NMR δ 14.98, 15.82, 29.56, 35.03, 55.30, 56.50, 109.27, 112.38, 124.58, 125.33, 129.83, 131.85, 145.21, 155.92; MS *m*/*z* (relative intensity) 218 (M^+, 72), 203 (43), 187 (100), 172 (38); HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1303. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8,25. Found: C, 76.87; H, 8.12.

7-Methoxy-3,6-dimethyl-2-tetralone (5) was prepared by the same procedure of ref 9 for the synthesis of other tetralones: mp 84−85 °C; yield quantitative; IR (KBr) 1708 cm^{-1}; ^{1}H NMR δ 1.18 (d, 3H, J = 6.9), 2.19 (s, 3H), 2.45−2.62 (m, 1H), 2.73 (dd, 1H, J = 15.1, 10.7), 3.00 (dd, 1H, J = 15.2, 5.7), 3.55 (s, 2H), 3.80 (s, 3H), 6.55 (s, 1H), 6.95 (s, 1H); ^{13}C NMR δ 14.90, 15.72, 36.12, 42.81, 43.96, 55.42, 109.67, 124.97, 127.48, 130.02, 131.57, 156.65, 212.05; MS *m*/*z* (relative intensity) 204 (M^+, 86), 175 (11), 161 (21), 148 (100); HRMS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1156. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.40; H, 7.95.

10-(equatorial and axial)-Hydroxy-40-methoxy-5,9-dimethyltricyclo[7.3.1.0^{2,7}]tridec-2,4,6-triene-13-one (10a and 11a). A mixture of **5** (5.50 g, 0.027 mol) and pyrrolidine (5 mL, 0.058 mol) in benzene (75 mL) was refluxed under a water separator for 2.25 h. After removal of solvent and excess pyrrolidine in vacuo, the crude crystalline enamine was dissolved in dioxane (45 mL). To this solution was added freshly distilled acrolein (2.0 g, 0.0357 mol) in dioxane (5 mL) with ice cooling and stirring; the cooling bath was removed and stirring was continued for 12 h at room temperature. After evaporation of the solvent, the residual syrup was dissolved in ether (100 mL). The ethereal extract was washed with 50 mL each of 10% aqueous HCl and water, dried over Na_2SO_4, filtered, and concentrated to give 4.70 g of residue which was purified by column chromatography with ethyl acetate/hexanes 1:6 as eluent to give 2.25 g of ketol **10a** (equatorial isomer) and 1.73 g of ketol **11a** (axial isomer) in 57% combined yield.

10a (equatorial isomer): IR (neat) 3450, 1715 cm^{-1}; ^{1}H NMR δ 1.17 (s, 3H), 1.50−1.90 (m, 4H), 2.05−2.20 (m, 1H), 2.13 (s, 3H), 3.45 (t, 1H, J = 3.3), 3.63 (br d, 1H, J = 6), 2.60 and 3.55 (AB system, 2H, J = 16.8), 3.79 (s, 3H), 6.37 (s, 1H), 6.86 (s, 1H); ^{13}C NMR δ 15.87, 19.97, 26.89, 31.14, 37.16, 51.26, 52.70, 55.42, 78.66, 108.76, 125.23, 127.23, 129.09, 136.25, 156.79, 213.57; MS *m*/*z* (relative intensity) 260 (M^+, 100), 216 (88), 203 (95), 188 (45); HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1395. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.92; H, 7.76.

11a (axial isomer): mp 164.5−166.5 °C; IR (KBr) 3400, 1710 cm^{-1}; ^{1}H NMR δ 1.21 (s, 3H), 1.63 (dm, 1H, J = 14), 1.75−1.95 (m, 3H), 2.17 (s, 3H), 2.48 (tt, 1H, J = 4, 13), 2.95 and 3.15 (AB system, 2H, J = 17.4), 3.46 (br t, 1H, J = 3.3), 3.80 (s, 3H), 4.00 (br dd, 1H, J = 2.7, 2.4), 6.41 (s, 1H), 6.83 (s, 1H); ^{13}C NMR δ 15.84, 19.73, 25.64, 31.66, 43.14, 50.73, 53.39, 55.38, 81.69, 108.87, 125.68, 126.29, 128.88, 136.79,156.78, 213.91; MS *m*/*z* (relative intensity) 260 (M^+, 62), 242 (41), 203 (43), 186 (100); HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1397. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.89; H, 7.73.

10-Carboxy-5,8,9,10-tetrahydro-2-methoxy-3,6-dimethylbenzocyclooctene (9a). To a mixture of **10a** (0.18 g, 0.69 mmol) and anhydrous Et_3N (0.15 mL, 1.04 mmol) in dry CH_2Cl_2 (10 mL) was added MsCl (0.10 mL, 0.865 mmol). The solution was stirred at 25 °C for 1.5 h and then poured into ice−water (20 mL) and extracted with ether. Drying, filtration, and concentration of the ether layer gave a residue which was boiled for 2.5 h with 15% aqueous NaOH solution (10 mL) under a N_2 atmosphere. The reaction mixture was poured into ice−water (20 mL) and extracted with ether. The aqueous layer was acidified with 15% HCl solution to pH 3, extracted with ether, washed with water, and dried (Na_2SO_4). Concentration of the ether layer gave a solid residue which was recrystallized from ethyl acetate/hexanes to afford 148 mg (82%) of **9a**.

9a: mp 155−156 °C; IR (KBr) 3500, 1705 cm^{-1}; ^{1}H NMR δ 1.76 (s, 3H), 1.85−2.10 (m, 4H), 2.16 (s, 3H), 3.15 and 3.55 (AB system, 2H, J = 18.3), 3.76 (s, 3H), 4.11 (dd, 1H, J = 4.8, 13.5), 5.36 (br t, 1H, J = 7.8), 6.69 (s, 1H), 6.93 (s, 1H), 9.80 (br signal, 1H, exchanges with D_2O); ^{13}C NMR δ 15.70, 22.28, 26.33, 32.89, 41.40, 46.15, 55.47, 108.21, 122.86, 125.08, 130.41, 132.22, 135.45, 138.07, 157.22, 180.15; MS *m*/*z* (relative intensity) 260 (M^+, 100), 245 (13), 215 (45), 173 (33); HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1406. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.95; H, 7.76.

5,8,9,10-Tetrahydro-10-hydroxymethyl-2-methoxy-3,6-dimethylbenzocyclooctene (12). (a) From 9b. A solution of **9a** (0.956 g, 3.68 mmol) in dry Et_2O (25 mL) cooled in an ice bath was treated with an ethereal solution of CH_2N_2 (prepared from 1.136 g, 0.011 mol, of *N*-nitroso-*N*-methylurea). After allowing the mixture to stand for 2 h in the cooling bath, excess CH_2N_2 was destroyed by dropwise addition of AcOH (0.3 mL), the volatiles were removed in vacuo, and crude **9b** was kept at 50 °C for 1 h under reduced pressure (0.1 Torr).

To a refluxing mixture of crude methyl ester **9b** (3.68 mmol) and $NaBH_4$ (0.35 g, 9.26 mmol) in dry *t*-BuOH (20 mL) was

(20) We thank M. Sc. José Agustín Guzmán, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás Hidalgo, Morelia, Michoacán, México, for a generous gift of natural **1** and related spectral data.

added dry MeOH (2.9 mL) over a period of 1 h. The addition of a fresh portion of $NaBH_4$ and the slow addition of dry MeOH were repeated twice, and the reflux was continued for an additional 1 h (the total amounts of $NaBH_4$ and MeOH were 1.05 g (27.78 mmol) and 7.8 mL, respectively). The reaction mixture was cooled, water was added to quench the reaction, and the MeOH and *t*-BuOH were removed under reduced pressure. After extracting with ether, the combined extracts were dried (Na_2SO_4), and the ether was evaporated. The residue was purified by column chromatography using ethyl acetate/hexanes (0.5:9.5) as eluent and **12** (0.79 g) was obtained in 87% yield.

(b) From 9c. To acid **9a** (0.1 g, 0.384 mmol) in dry THF (2 mL) and Et_3N (0.06 mL, 0.403 mmol), cooled in an ice bath, was added with stirring $ClCO_2Et$ (0.05 mL, 0.403 mmol). After 15 min the cooling bath was removed and stirring was continued for 45 min at room temperature. The suspension was filtered off and washed with dry THF (5 mL) and the combined THF solution was added dropwise over a period of 30 min to a stirred solution of $NaBH_4$ (0.0364 g, 0.963 mmol) in H_2O (0.4 mL) at room temperature. After 3.5 h the reaction mixture was acidified with 5% HCl to pH 2, extracted with ether, washed with brine, dried (Na_2SO_4), and evaporated. The oily residue was purified by column chromatography using ethyl acetate/hexanes (0.5:9.5) as eluent to give pure **12** (73.4 mg, 78%).

12: IR (neat) 3350 cm^{-1}; ^1H NMR δ 1.40−2.00 (m, 5H), 1.70 (s, 3H), 2.20 (s, 3H), 3.05−3.35 (X part of a ABX system, 1H), 3.15 and 3.50 (AB system, 2H, J = 18), 3.80 (s, 3H), 3.70−4.05 (AB part of a ABX system, 2H), 5.35 (br t, 1H, J = 7), 6.60 (s, 1H), 6.90 (s, 1H); ^{13}C NMR δ 15.73, 22.24, 26.35, 32.84, 38.79, 41.37, 55.44, 76.61, 108.06, 122.81, 125.00, 130.37, 132.20, 135.43, 138.04, 157.15; MS *m*/*z* (relative intensity) 246 (M^+, 1), 55 (35), 43 (100), 41 (32). Anal. Calcd for $C_{15}H_{22}O_2$: C, 78.04; H, 8.94. Found C, 78.12; H, 8.97.

5,8,9,10-Tetrahydro-2-methoxy-3,6,10-trimethylbenzocyclooctene [(±)-Parvifoline Methyl Ether] (13). To alcohol **12** (0.48 mmol) in dry CH_2Cl_2 (5 mL) cooled in an ice bath was added with stirring dry Et_3N (0.1 mL, 0.73 mmol) and MsCl (0.05 mL, 0.61 mmol). The solution was stirred at 25 °C for 2.5 h and then poured into water (10 mL) and extracted with ether. The ether extract was dried (Na_2SO_4), filtered, and concentrated to give a residue which was dissolved under a N_2 atmosphere in dry THF (5 mL) and cooled in an ice bath. To this solution was added a 0.98 M solution of $LiBHEt_3$ in THF (1.05 mL, 1.03 mmol). The reaction mixture was stirred for 10 h at 25 °C, poured into ice−water (10 mL), and extracted with ether. Drying, filtration, and concentration of the organic layer gave an oily residue which was purified by column chromatography using ethyl acetate/hexanes (0.5:9.5) as eluent. **13** (44 mg) was obtained in 55% yield.

13: The synthetic material was spectroscopically identical with an authentic sample prepared (Me_2SO_4, K_2CO_3, Me_2CO) from natural **1**.[5,20]

5,8,9,10-Tetrahydro-3,6,10-trimethylbenzocyclooctene [(±)-Parvifoline] (1). To a solution of EtSLi, prepared by addition of *n*-BuLi (1.6 M in hexanes, 16 mmol, 10 mL) to a mixture of EtSH (3 mL, 39 mmol) and dry DMF (10 mL) at −78 °C, was added **13** (186 mg, 0.81 mmol) in DMF (5 mL). The mixture was stirred at 105 °C for 48 h, cooled to room temperature, poured into dilute HCl (20 mL), and extracted with EtOAc. After drying (Na_2SO_4), filtration, and concentration of the organic layer, the crude product was purified by column chromatography using ethyl acetate/hexanes (0.5:9.5) as eluent. **1** (0.17 g) was obtained in 97% yield, identical with the reported data for the natural product.[1,21]

Acknowledgment. We are grateful to Q Alejandrina Acosta, Q Marisela Gutiérrez, QFB Graciela Chávez, MC Claudia Contreras, Q Rocío Patiño, IQ Luis Velasco, MC Javier Pérez Flores, and MC Rubén Gaviño, for their assistance in acquiring spectral data. We also thank a referee for the thorough and critical revision of our manuscript which made this work readable.

JO972092P

(21) Interestingly, cleavage of **13** with *n*-BuSNa in dry DMF gave a 7:3 mixture of **1** and **2** (95%).