High-Pressure Approach to the Total Synthesis of (±)-Ambreinolide and (±)-8-Epiambreinolide

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Ambreinolide (**7a**) and its epimer (**7b**) have been synthesized regioselectively and in a stereocontrolled manner from (±)-*trans*-1,1,4aβ-trimethyldecahydronaphthalen-5-one (**1**) by a route (Scheme I) which relies upon the promotion of a key Diels–Alder reaction under conditions of high pressure.

On account of its fixative properties, ambreinolide (**7a**), a degradation product of ambrein,[1] is widely used in the production of perfumes. For this reason and the fact that this δ-lactone belongs to a chemically interesting group of terpenoids, research into its synthesis[2] has been carried out during the last 30 years. The aim of this investigation was a stereocontrolled synthesis of (±)-ambreinolide (**7a**) starting from simple precursors. Our synthetic strategy was based upon the preparation of compound **4**, which possesses a 1,1-disubstituted buta-1,3-diene unit for subsequent reaction with an activated dienophile, e.g., diethyl mesoxalate.

Results and Discussion

The synthesis was carried out as shown in Scheme I. The starting material for the synthesis of the diene **4** was (±)-*trans*-1,1,4aβ-trimethyldecahydronaphthalen-5-one (**1**) which was obtained after the series of reactions ((i) Robinson annelation, (ii) ketalization, (iii) reductive methylation, (iv) Wolff–Kishner reduction, and (v) hydrolysis)[3] from 2-methylcyclohexane-1,3-dione. Methylation of **1** gave **2** a 7:3 mixture of diastereoisomers which was used directly in the next step without separation.[4] Ethynylation[5] of **2** afforded **3** also as a mixture of two diastereoisomers.[6] The C≡C in the diastereoisomeric mixture was partially hydrogenated over a quinoline modified 10% Pd–$BaSO_4$ catalyst[7] and product was dehydrated to give the diene **4** in good overall yield.

All attempts to effect thermal (4 + 2) cycloaddition of this sterically hindered diene **4** with activated dienophiles such as diethyl mesoxalate, even in the presence of Lewis acid catalysts, were unsuccessful. Hence we decided to investigate the reaction under very high pressure by employing a technique previously described by us.[9]

It is well-known that 1-substituted buta-1,3-dienes with the cis configuration react less readily than trans-dienes even when the dienophile is highly activated. This observation is probably a result of steric hindrance which prevents cis-dienes from acquiring the planar conformation required in the transition states for Diels–Alder reactions. The application of high-pressure conditions enables this unfavorable effect to be overcome and adducts, which cannot be obtained at normal pressure, even in the presence of Lewis acid catalysts, can be prepared.[10]

The choice of diethyl mesoxalate as a highly reactive carbonyl heterodienophile was made on the basis of the expectation that its cycloaddition to the diene **4** would be highly regioselective.[11] In practice, the diene **4** reacted with diethyl mesoxalate under high-pressure conditions (20 kbar at 55 °C) to afford a mixture of two diastereoisomeric adducts **5** with complete regioselectivity. The yield of chromatographically isolated products (**5a** + **5b**) was 35% counting on starting diene **4**; 30% of the diene was recovered by chromatography and the rest has been polymerized. The formation of the two diastereoisomers **5a** and **5b** results from the different approaches (A and B) of the dienophile to the diastereotopic faces of the diene as shown in Scheme II.

Obviously, approach A of the dienophile anti to the angular methyl group is expected to be the preferred one. On account of the chromatographic instability of the alkenes **5a** and **5b**, the ratio of the diastereoisomers was determined after hydrogenation of the mixture to give **6a** and **6b** in the proportions of 65:35, respectively. The diastereoisomers **6a** and **6b** were separated by column chromatography and were hydrolyzed separately to yield the corresponding dicarboxylic acids. Transformation of these acids into acid chlorides, followed by the reaction with activated sodium azide, Curtius rearrangement[12] of the resulting azides and hydrolysis afforded **7a** and **7b** in 26% and 24% yields, respectively.

In this way, both (±)-ambreinolide (**7a**) and (±)-8-epiambreinolide (**7b**) were synthesized from (±)-*trans*-1,1,4aβ-trimethyldecahydronaphthalen-5-one (**1**) in a stereocontrolled manner with the satisfactory overall yields of 0.72% and 0.28%, respectively.[13] The preparation of these two nor-diterpenoic δ-lactones illustrates the unique

(1) Ruzicka, L.; Lardon, F. *Helv. Chim. Acta* **1946**, *29*, 912. Lederer, E.; Marx, F.; Mercier, D.; Perot, G. *Ibid.* **1946**, *29*, 1354.

(2) Dietrich, P.; Lederer, E. C. R. *Hebd. Seances Acad. Sci.* **1952**, *234*, 637. Wolff, R. E. *Ibid.* **1954**, *238*, 1041. Schenk, H. R.; Gutman, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* **1952**, *35*, 817. Lederer, E.; Stoll, H. *Ibid.* **1950**, *33*, 1345. Combie, R. C.; Palmer, B. D. *Aust. J. Chem.* **1981**, *34*, 1265.

(3) Snitman, D. L.; Mei-Yuan Tsai; Watt, D. S.; Edwards, C. L.; Stater, P. L. *J. Org. Chem.* **1979**, *44*, 2838.

(4) Diastereoisomers **2** need not to be separated as the center of chirality at carbon atom C-8 is lost in a subsequent step in the synthesis.

(5) Coisne, J. M.; Pecher, J.; Declerq, J. P.; Germain, G.; Van Meersche, M. *Bull. Soc. Chim. Belg.* **1980**, *89*, 551. Cohen, N.; Banner, B.; Eichel, W. F.; Valenta, Z.; Dickinson, R. A. *Synth. Commun.* **1978**, *8*, 427.

(6) In the absence of diastereoselectivity, the formation of four diastereoisomers would be expected. The fact that only two diastereoisomers are observed in the ratio 9:1 can be explained if the ethynylation is highly diastereoselective following the equilibration of the methyl group at C-8.

(7) Dobson, N. A.; Eglinton, G.; Krishnamurti, M.; Raphael, R. A.; Willis, R. G. *Tetrahedron* **1961**, *16*, 16. Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(8) For the sake of simplicity we represent all compounds as enantiomers, when in fact they are racemic modifications.

(9) For the high-pressure experiments we used the piston–cylinder type apparatus for pressures of about 30 kbar; the initial working volume was 70 mL. The details of this apparatus are described in Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41.

(10) Asano, T.; leNoble, W. *J. Chem. Rev.* **1978**, *78*, 407. Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1, and references quoted therein.

(11) Konował, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1968**, *42*, 2045.

(12) Ruden, R. A.; Bonjouklian, R. *J. Am. Chem. Soc.* **1975**, *97*, 6892. Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.* **1977**, *42*, 4095.

(13) The spectroscopic properties of compounds **7a** and **7b** are in good agreement with those published in the literature.[2]

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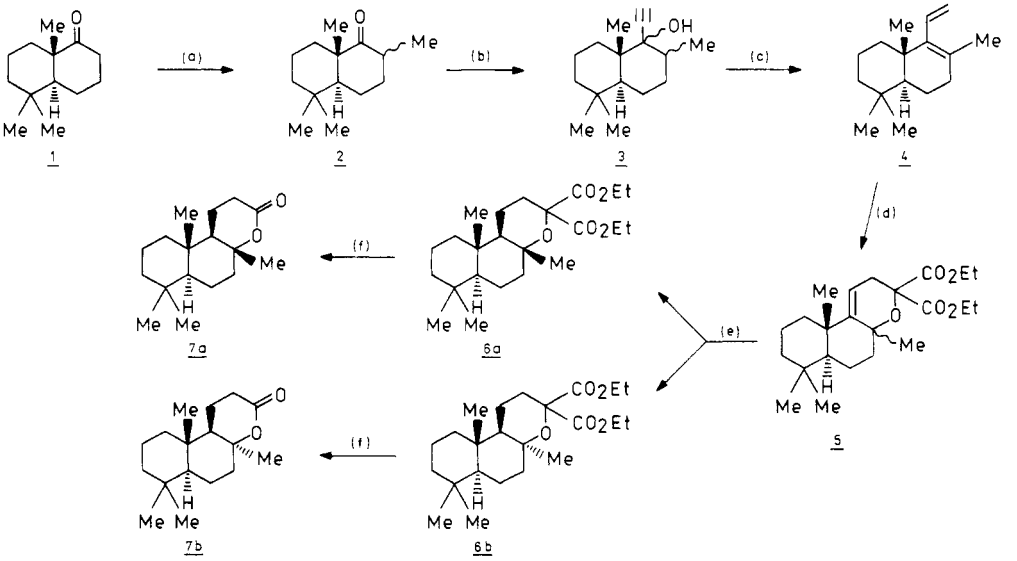
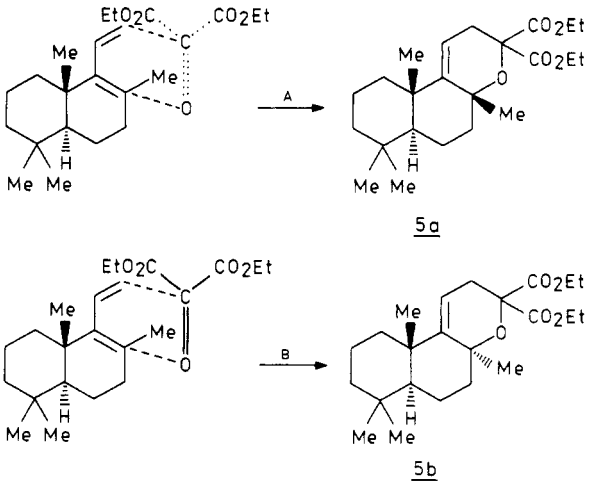
Scheme I.[8a] Synthesis of (±)-Ambreinolide (7a) and (±)-Epiambreinolide (7b)



[a] Reagents and reaction conditions: (a) LDA, MeI (HMPA/THF), −78 °C, 1 h; (b) i, Li, NH_3, −78 °C, 0.5 h; ii, CH≡CH (Et_2O), −78 °C, 4 h; (c) i, H_2, 10% Pd-$BaSO_4$, quinoline (dioxane), room temperature, 4 h; ii, BF_3·Et_2O (THF/xylene), reflux, 3.5 h; (d) EtO_2CCOCO_2Et (CH_2Cl_2), 20 kbar, 55 °C, 20 h; (e) i, H_2, 10% Pd-C (MeOH), room temperature, 20 h; ii, chromatographic separation (hexane–ethyl acetate, 95:5, 9:1, 8:2 v/v); (f) i, KOH (MeOH), reflux, 4 h; ii, $(COCl)_2$ (pyridine/benzene), reflux, 1.5 h; iii, NaN_3 (MeCN), room temperature, 2 h; iv, 5% $(CO_2H)_2$ (H_2O/THF), room temperature, 1 h.

Scheme II.[8] Approaches (A and B) of the Dienophile to the Diastereotopic Faces of the Diene



usefulness of applying high-pressure techniques to Diels–Alder reactions during organic synthesis.

Experimental Section

All melting points were taken with a Kofler hot-stage instrument and are uncorrected. UV spectra were obtained in ethanolic solutions with a Beckman Acta M-VI spectrophotometer. Infrared (IR) spectra were determined on a Beckman Acculab spectrophotometer. ^1H NMR spectra were measured in $CDCl_3$ solutions with a JEOL JNM-4H-100 spectrometer at 100 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0) as an internal standard. Low-resolution mass spectra were recorded on an LKB-2091 spectrometer. The reported yields correspond to chromatographically pure compounds. Gravity column chromatography was performed on Merck Kieselgel 60 (100–200 mesh). All chromatographic separations were monitored by TLC and/or HPLC.

(±)-*trans*-1,1,4aβ,6ξ-Tetramethyldecahydronaphthalen-5-one (2). Lithium diisopropylamide (3 mmol) was treated with hexamethylphosphoramide (0.125 mL, 3 mmol) and a few crystals of dipyridyl were added. Subsequently, (±)-*trans*-1,1,4aβ-trimethyldecahydronaphthalen-5-one (1) (0.58 g, 3 mmol) dissolved in tetrahydrofuran (1.5 mL) was added dropwise to the reaction mixture cooled to −78 °C until the yellow color disappeared. The reaction mixture was allowed to warm up to −10 °C over a period of 1 h and then methyl iodide (4.26 g, 30 mmol) was added and the stirring was continued at room temperature for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of potassium bicarbonate (20 mL), and pentane (50 mL) was added to the reaction mixture. The organic layer was washed with a saturated aqueous solution of potassium bicarbonate and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by chromatography (pentane–ethyl acetate, 98:2 v/v) and compound **2** (0.525 g, 84% yield) was obtained as a mixture of two epimers. The epimers were separated by HPLC using the same eluting system and their ratio was 7:3. The spectral data of the major epimer were as follows: ^1H NMR δ 1.28 (d, 3 H, C-6, CH_3, J = 6.8 Hz), 1.10 (s, 3 H, C-4, CH_3), 0.95 and 0.93 (2 × s, 2 × 3 H, 2 × C-1 CH_3); IR (Nujol) 1710 cm^{-1} (C=O); mass spectrum (70 eV), m/e 208, 81.

(±)-*trans*-1,1,4aβ,6ξ-Tetramethyl-5ξ-ethynyldecahydronaphthalen-5ξ-ol (3). A three-necked flask fitted with a mechanical stirrer, thermometer, and dry ice condenser was charged with redestilled liquid ammonia (150 mL). Subsequently, at −78 °C, lithium metal (0.035 g, 5 mmol) was added to the flask. The stirring was continued for 0.5 h to dissolve lithium and then dry acetylene was passed into the solution, the blue color disappeared, and the bubbling of acetylene was continued for additional 0.5 h. Subsequently, compound **2** (0.50 g, 2.4 mmol) dissolved in anhydrous ethyl ether (10 mL) was added, the cooling bath was removed, and the reaction mixture was stirred for 4 h. The reaction mixture was treated with diethyl ether (100 mL) and solid ammonium chloride (5 g), and liquid ammonia was allowed to evaporate. The ethyl ether solution was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by chromatography (hexane–ethyl acetate 9:1 v/v) to give **3** (0.31 g, 55% yield) as a mixture of diastereoisomers in the ratio 9:1 (HPLC). Small samples of both pure isomers were isolated by HPLC and their ^1H NMR spectra were measured, however no stereochemical assignment could be made. The spectral data of the major diastereoisomer were as follows: ^1H NMR δ 2.50 (s, 1 H, C≡CH), 1.25 (d, 3 H, C-6 CH_3, J = 6.8 Hz), 1.05 (s, 3 H, C-4 CH_3), 0.87 and 0.84 (2 × s, 2 × 3 H, 2 × C-1 CH_3); IR (Nujol) 3605, 3300 cm^{-1} (OH); mass spectrum (70 eV), m/e 234, 136, 109.

(±)-*trans*-1,1,4aβ,6-Tetramethyl-5-ethenyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (4). Compound **3** (0.1 g, 0.42 mmol)

dissolved in dioxane (40 mL) was hydrogenated over palladium-on-barium sulfate catalyst (0.02 g) in the presence of quinoline (0.2 g). When the hydrogen absorption ceased, the catalyst was filtered off and the solvent was removed in vacuo, leaving a residue (0.081 g), which was dehydrated in xylene–tetrahydrofuran (4:1 v/v) solution with boron trifluoride etherate (0.9 mL) in the presence of hydroquinone (0.02 g) by boiling in a reflux condenser during 3.5 h. After cooling, the reaction mixture was treated with 10% aqueous sodium hydroxide (4 mL), taken in ethyl ether (150 mL), washed with water, and dried over anhydrous magnesium sulfate. Upon removal of the solvent the residue was purified by chromatography which gave **4** oil (0.052 g, 56% yield): ^{1}H NMR δ 6.25, 5.20, 4.90 (3 × dd, 3 × 1 H, olefin, J_1 = 2.0, J_2 = 10.9, J_3 = 17.3 Hz), 1.51 (s, 3 H, C-6 CH_3), 0.98 (s, 3 H, C-4 CH_3), 0.88 and 0.85 (2 × s, 2 × 3 H, 2 × C-1 CH_3); IR (Nujol) 1640, 1600 cm^{-1} (C=C); UV (EtOH, *c* 1) λ_{max} 228 nm (ϵ 21 500); mass spectrum (70 eV), *m/e* 218, 136, 128. Anal. Calcd for $C_{16}H_{26}$: C, 88.10; H, 11.80. Found: C, 88.01; H, 11.98.

(±)-8ξ,13-Epoxy-13,13-dicarbethoxy-14,15,16-trisnorlabd-9(11)-ene (5). Compound **4** (0.05 g, 0.23 mmol), diethyl mesoxalate (0.044 g, 0.27 mmol), and dry methylene chloride (15 mL) were charged in special Teflon-brand vessel which was placed in very high-pressure apparatus. The pressure was set for 20 kbar. After stabilization of pressure, the temperature was set to 55 °C. The reaction mixture was kept under these conditions during 20 h. After decompression, the solvent was removed in vacuo and the residue was chromatographed by using hexane–ethyl acetate (95:5 v/v) solution. Pure **5**, oil (0.033 g, 35% yield), was obtained as a mixture of diastereoisomers, homogeneous by TLC analysis: ^{1}H NMR δ 5.65 (m, 1 H, C-11 H), 4.35 (m, 4 H, 2 × OCH_2CH$_3$), 2.45 (m, 2 H, C=CCH_2), 1.40–0.75 (m, 29 H, among them C-4 CH_3, C-8 CH_3, C-10 CH_3, OCH$_2$CH_3); IR (Nujol) 1740 (C=O), 1620 cm^{-1} (C=C); mass spectrum (70 eV), *m/e* 392, 350, 111, 109. Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.40; H, 9.19. Found: C, 70.43; H, 9.35.

(±)-8ξ,13-Epoxy-13,13-dicarbethoxy-14,15,16-trisnorlabdan (6). Compound **5** (0.05 g, 0.12 mmol) was hydrogenated in methanol over 10% palladium-on-charcoal catalyst during 20 h. After removal of the catalyst and the solvent, the residue was separated into **6a** and **6b** by preparative HPLC (hexane–ethyl acetate, 95:5 v/v). The ratio of **6a**:**6b** was 65:35 (total yield 90%). Compound **6a**: ^{1}H NMR δ 4.30 (q, 4 H, 2 × OCH_2CH$_3$, *J* = 7.5 Hz), 1.35 (s, 3 H, C-8 CH_3), 1.30 (t, 6 H, 2 × OCH$_2$CH_3, *J* = 7.5 Hz), 1.20 (s, 3 H, C-10 CH_3), 0.85 (s, 6 H, 2 C-4 CH_3); IR (film) 1740 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* 394, 350, 109. Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.06; H, 9.64. Found: C, 70.40; H, 9.70. Compound **6b**: ^{1}H NMR δ 4.35 (q, 4 H, 2 × OCH_2CH$_3$), 1.25 (t, 6 H, 2 × OCH$_2$CH_3), 1.25 (s, 3 H, C-8 CH_3), 0.95 (s, 3 H, C-10 CH_3), 0.80 (s, 6 H, 2 × C-4 CH_3); IR (film) 1740 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* 394, 350, 126, 111. Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.06; H, 9.64. Found: C, 70.25; H, 9.78.

(±)-8α,13-Epoxy-14,15,16-trisnorlabdan-13-one (7a, Ambreinolide). Compound **6a** (0.05 g, 0.12 mmol) was dissolved in 5% methanolic potassium methoxide solution (20 mL), and the reaction mixture was boiled on a reflux condenser during 4 h. After cooling, the mixture was neutralized with dilute hydrochloric acid, treated with water (50 mL), and extracted with ethyl ether. The ether extract was dried over anhydrous magnesium sulfate. Upon removal of the solvent the residue was dissolved in benzene (12 mL) and treated with oxalyl chloride (0.015 g, 0.12 mmol) and pyridine (0.009 g, 0.11 mmol). The reaction mixture was boiled on a reflux condenser during 1.5 h. Subsequently, the solvent and an excess of oxalyl chloride were removed in vacuo. The residue was dissolved in dry acetonitrile (8 mL), treated with sodium azide (0.014 g, 0.21 mmol), and stirred at room temperature for 2 h. Subsequently, acetonitrile was removed in vacuo and the residue was treated with cyclohexane (8 mL) and heated to boiling under nitrogen for 2 h. After removal of the solvent, the residue was treated with 5% tetrahydrofuran oxalic acid solution (15 mL) and the stirring was continued at room temperature for 1 h. The reaction mixture was taken in ethyl ether (60 mL), washed with diluted aqueous sodium hydroxide solution, water, and dried over anhydrous magnesium sulfate. Upon removal of the solvent the residue was chromatographed using hexane–ethyl acetate gradient system and gave **7a** (0.0047 g, 20% yield): solid, mp 139–141 °C; ^{1}H NMR δ 1.05 (s, 3 H, C-8 CH_3), 0.85 (s, 3 H, C-10 CH_3), 0.80 (s, 6 H, 2 × C-4 CH_3); IR ($CHCl_3$) 1720 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* 264, 192, 109, 82.

(±)-8β,13-Epoxy-14,15,16-trisnorlabdan-13-one (7b,8-Epiambreinolide). Compound **7b** was prepared from **6b** in an analogous manner as **7a** from **6a**. Thus from **6b** (0.03 g, 0.076 mmol), **7b** (0.002 g, 18% yield) solid, mp 140–150 °C, was obtained: IR ($CHCl_3$) 1720 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* 264, 221, 191, 126, 111.

Registry No. (±)-**1**, 65556-24-3; (±)-**2** (isomer 1), 98048-49-8; (±)-**2** (isomer 2), 98048-50-1; **3**, 97974-42-0; dihydro-**3**, 97974-46-4; (±)-**4**, 97974-43-1; (±)-**5** (isomer 1), 97974-44-2; (±)-**5** (isomer 2), 98048-51-2; (±)-**6a**, 97974-45-3; (±)-**6a** (diacid), 97974-47-5; (±)-**6a** (diacid chloride), 97974-48-6; (±)-**6a** (diazide), 97974-49-7; (±)-**6a** (diisocyanate), 97974-50-0; (±)-**6b**, 98048-52-3; (±)-**6b** (diacid), 98048-54-5; (±)-**6b** (diacid chloride), 98048-55-6; (±)-**6b** (diazide), 98048-56-7; (±)-**6b** (diisocyanate), 98048-57-8; (±)-**7a**, 7663-46-9; (±)-**7b**, 98048-53-4; CH≡CH, 74-86-2; diethyl mesoxalate, 609-09-6.

Structural and Stereochemical Studies of Naturally Occurring Longipinene Derivatives

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The introduction of a double bond into the six-membered ring of the rastevione (**1**) skeleton gave a compound (**8**) whose spectral data are in excellent agreement with those of a substance previously thought to be **12**. Further selective elimination of the oxygen atom from C-8 gave **14**, previously formulated as **16**. This allows us to reassign the structures of several longipinenetriolones and longipinenediolones found as constituents of *Stevia* and *Polypteris*. The selective derivatization of **14** followed by controlled cleavage of the seven-membered ring permitted us to assign the H-7 and H-9 NMR signals, which in turn allows us to ascertain the positions at which ester residues are placed by nature. Some NMR signals are reassigned in view of the results of a ^{13}C/^{1}H heteronuclear chemical shift correlation experiment.

Extensive studies of the genus *Stevia*, which is widely distributed through the American continent, have led to isolation and structural elucidation of a variety of sesquiterpene lactones,[2] diterpenes,[3] flavones,[4] and longipi-

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