Efficient Synthesis of *dl*-Malyngolide

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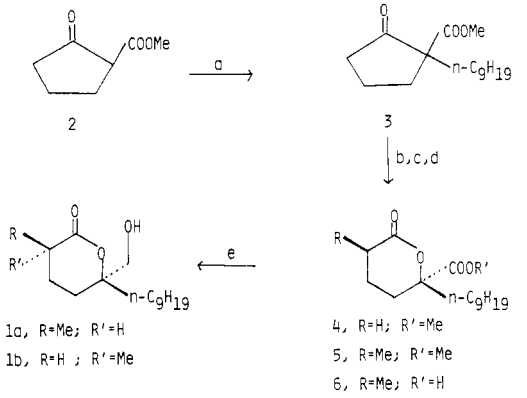
Recently the isolation and structure determination of malyngolide, an antibiotic from the marine blue-green alga *Lyngbya majuscula* Gomont, was reported.[1]

Recent reports on the synthesis of malyngolide prompt us to disclose our efficient five-step synthesis which has been achieved with an entirely different approach (Scheme I), compared to previous syntheses.[2,3]

Reaction of the potassium salt of 2-(carbomethoxy)-cyclopentanone[4] with *n*-nonyl bromide in dimethyl sulfoxide at room temperature for 6 h provided the alkylated keto ester **3** along with a small amount of a byproduct, presumably O-alkylated product.[5,6] Without separation of the byproduct, the mixture was subjected to Baeyer–Villiger oxidation conditions with *m*-chloroperoxybenzoic acid and sodium bicarbonate in chloroform at room temperature for 48 h to afford δ-lactone **4** in an 85% overall yield from **2** after separation by silica gel column chromatography. **4** was treated with 1.1 equiv of lithium diisopropylamide at −78 °C and methylated with 5 equiv of methyl iodide and 1.2 equiv of hexamethylphosphoramide at −45 °C to afford the desired methyl lactone **5** in 91% yield.[7,8] Hydrolysis of **5** with lithium iodide in pyridine at reflux for 8 h provided the acid **6**.[9] **6** was converted to the mixed anhydride with ethyl chloroformate and triethylamine in ether at 0 °C, followed by reduction with zinc borohydride in ether to afford a 70:30 mixture of malyngolide and its C-2 epimer in 80% yield after separation by silica gel column chromatography.[10,11] The C-2 epimer **1b** was epimerized to an approximate 1:1 mixture of **1a** and **1b** on treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene in toluene at reflux for 10 h.

In view of the few steps required, the high yield, and the use of readily available starting materials, we regard the synthesis presented here as an efficient alternative for the synthesis of malyngolide and its analogues.

Scheme I[a]



[a] (a) KOH, n-$C_9H_{19}Br/Me_2SO$; (b) MCPBA, $NaHCO_3$ (85% overall yield from **2**); (c) LDA, MeI/HMPA-THF (91%); (d) LiI/pyridine (98%); (e) $ClCOOEt/Et_3N$, $Zn(BH_4)_2$ (80%).

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 267, and the frequences are given in reciprocal centimeters. NMR spectra were recorded with a Varian T-60A spectrometer, and chemical shifts are expressed as δ units relative to tetramethylsilane. GLC analysis was performed on a Varian 2800 gas chromatograph. Analytical thin-layer chromatography was performed on precoated silica gel glass plates (0.25 mm, 60F-254, E. Merck), and silica gel (activity III, 04526, ICN) was used for column chromatography.

2-Nonyl-2-(carbomethoxy)cyclopentanone (3). To the potassium salt of **2** (4.30 g, 23.9 mmol)[4] in dry dimethyl sulfoxide (25 mL) was added freshly distilled *n*-nonyl bromide (5.94 g, 28.7 mmol). After 6 h of stirring at room temperature, the reaction mixture was poured into water and extracted with hexane. The hexane extracts were combined, washed with water and brine, dried ($MgSO_4$), and evaporated. Distillation provided 5.97 g of a 95:5 mixture of 2-nonyl-2-(carbomethoxy)cyclopentanone and O-alkylated product (132–135 °C at 0.9 torr):[6] ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, CH_3), 1.26 (br s, 16 H, CH_2), 1.60–2.20 (m, 4 H, CH_2), 2.20–2.60 (m, 2 H, $COCH_2$), 3.76 (s, 3 H, $COOCH_3$); IR (neat) 1750, 1735 (C=O) cm^{-1}.

5-Nonyl-5-(carbomethoxy)pentanolide (4). To a solution of **3** containing a small amount of O-alkylated product (5.97 g, 22.3 mmol) in chloroform (40 mL) were added *m*-chloroperoxybenzoic acid (7.77 g, 45.0 mmol) and sodium bicarbonate (3.78 g, 45.0 mmol). After the reaction mixture was stirred at room temperature for 48 h, hexane (40 mL) was added to the reaction mixture, and the precipitate was filtered off. The filtrate was washed with 1 N sodium hydroxide, saturated sodium hydrogen sulfite solution, and water. The organic layers were dried ($MgSO_4$) and evaporated. The residue was subjected to silica gel column chromatography with petroleum ether–acetone (85:15) as an eluant to yield **4** (5.76 g, an 85% overall yield from **2**) as a colorless oil: ^1HNMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_3), 1.26 (br s, 12 H, CH_2), 1.45–2.15 (m, 6 H, CH_2), 2.15–2.70 (m, 4 H, CH_2COO and CH_2), 3.78 (s, 3 H, $COOCH_3$); IR (CCl_4) 1750 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.46; H, 9.85.

2-Methyl-5-nonyl-5-(carbomethoxy)pentanolide (5). To a solution of **4** (950 mg, 3.34 mmol) in THF (3 mL) at −78 °C under nitrogen was added lithium diisopropylamide (0.9 M, 4.0 mL, 3.60 mmol) in THF–hexane. The reaction mixture was stirred at −78 °C for 10 min and allowed to warm to −45 °C over 0.5 h. A mixture of dry HMPA (719 mg, 4.01 mmol) and methyl iodide (2.37 g, 16.70 mmol) in THF (2 mL) was added dropwise to the enolate solution

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(2) (a) Babler, J. H.; Invergo, B. J.; Sarussi, S. J. *J. Org. Chem.* **1980**, *45*, 4241. (b) Sakito, Y.; Tanaka, S.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 1223. (c) Cardillo, G.; Orena, M.; Prozi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2439. (d) Torii, S.; Inokuchi, T.; Yoritaka, K. *Ibid.* **1981**, *46*, 5030.

(3) After the completion of our synthesis, two recent syntheses of *dl*-malyngolide, which are similar to our synthesis in many respects, have been reported: (a) Matsuo, K.; T.; Tanaka, K. *Chem. Pharm. Bull.* **1981**, *29*, 3047. (b) Matsuo, K.; Tanaka, K. *Ibid.* **1981**, *29*, 3070.

(4) Meyer, R.; Wenschuh, G.; Töpelmann, W. *Chem. Ber.* **1958**, *91*, 1616.

(5) Pond, D. M.; Cargill, R. L. *J. Org. Chem.* **1967**, *32*, 4064.

(6) Attempted separation of a byproduct by means of fractional distillation or silica gel chromatography failed. However, GLC analysis (a 7-ft, 10% Carbowax 20M column at 180 °C) revealed a 95:5 mixture of two products.

(7) Our original plan was to utilize selective reduction of the methyl ester via enolate protection of the lactone. However, treatment of **4** with 1.1 equiv of LDA and 1.2 equiv of MeI in THF–HMPA followed by the addition of 1 equiv of LDA and subsequent reduction with $LiAlH_4$ or i-Bu_2AlH resulted in the formation of complex mixtures of products: Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4262.

(8) Treatment of **5** with DBU or diisopropylethylamine in refluxing toluene for 10 h failed to epimerize the methyl group at C-2. The configuration at C-2 in **5** was supported further by conversion of malyngolide into the methyl ester **5**. Oxidation of malyngolide with pyridinium dichromate in DMF at room temperature for 24 h, followed by treatment with diazomethane, gave only **5**. See also ref 1.

(9) Epimerization at C-2, characterized as the methyl ester, did not occur during hydrolysis of 5.

(10) Epimerization at C-2 might occur during either the reduction or workup. Treatment of the acid **6** with equimolar amounts of BH_3 in THF or BH_3–Me_2S in CH_2Cl_2 resulted in 30–40% of triol, resulting from overreduction of the δ-lactone ring, along with a mixture of **1a**, **1b**, and the original acid. Moreover, reduction of the mixed anhydride with $NaBH_4$ in THF gave lower yields (50–60%).

(11) The spectral data (IR, NMR) and chromatographic behavior (R_f values in TLC) of malyngolide and the C-2 epimer **1b** were virtually identical with those previously reported for malyngolide and its C-2 epimer.

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at −45 °C, and the resulting solution was warmed to −20 °C for 0.5 h, quenched with saturated ammonium chloride, and extracted with ether. The combined extracts were washed with saturated ammonium chloride, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel column chromatography with hexane–ether (3:1) as an eluant to yield **5** (906 mg, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, CH_2CH_3), 1.27 (br s, 12 H, CH_2), 1.26 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.45–2.20 (m, 6 H, CH_2), 2.20–2.65 (m, 3 H, $CHCH_3$ and CH_2), 3.79 (s, 3 H, $COOCH_3$); IR (CCl_4) 1745, 1765 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.52; H. 10.37.

2-Methyl-5-nonyl-5-carboxypentanolide (6). To a solution of **5** (475 mg, 1.59 mmol) in dry pyridine (5 mL) was added lithium iodide (1.50 g, 11.21 mmol). The resulting solution was refluxed for 8 h, poured into water, acidified with 0.1 N hydrochloric acid, and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to yield **6** (440 mg, 98%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 15 H, CH_2 and $CHCH_3$), 1.45–2.20 (m, 6 H, CH_2), 2.20–2.65 (m, 3 H, CH_2 and $CHCH_3$), 9.40 (br, 1 H, COOH); IR (CCl_4) 3150 (OH), 1730, 1710 (C=O) cm^{-1}.

***dl*-Malyngolide (1a) and 2-Epimalyngolide (1b).** To a solution of **6** (246 mg, 0.86 mmol) in ether (5 mL) at 0 °C were added triethylamine (104 mg, 1.03 mmol) and ethyl chloroformate (118 mg, 1.03 mmol). After 0.5 h of stirring at 0 °C, freshly prepared zinc borohydride in ether (0.45 M, 2.3 mL, 1.04 mmol) was added. The resulting solution was stirred at 0 °C for 0.5 h, poured into saturated ammonium chloride, and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel column chromatography with hexane–ethyl acetate (7:3) to yield 129 mg (55%) of **1a** (R_f 0.35; hexane–ethyl acetate, 6:4) and 58 mg (25%) of **1b** (R_f 0.47; hexane–ethyl acetate, 6:4). **1a**: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 16 H, CH_2), 1.26 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.45–2.25 (m, 4 H, CH_2), 2.25–2.65 (m, 1 H, $CHCH_3$), 2.80 (br s, 1 H, OH), 3.46 (d, J = 12 Hz, 1 H, CH_2OH), 3.70 (d, J = 12 Hz, 1 H, CH_2OH); IR (neat) 3420 (OH), 1730, 1715 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.49; H, 11.28. **1b**: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 19 H, CH_2 and $CHCH_3$), 1.45–2.25 (m, 4 H, CH_2), 2.25–2.65 (m, 1 H, $CHCH_3$), 2.86 (br s, 1 H, OH), 3.58 (s, 2 H, CH_2OH); IR (neat) 3400 (OH), 1730, 1715 (C=O) cm^{-1}.

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Registry No. 1a, 74742-19-1; **1b**, 76984-84-4; **2** K salt, 62791-43-9; **3**, 82798-02-5; **4**, 82808-05-7; **5**, 82838-26-4; **6**, 82838-27-5; *n*-nonyl bromide, 693-58-3.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy and Conformational Analysis of the Daphnoline–Repandine Class of Bis(benzylisoquinoline) Alkaloids

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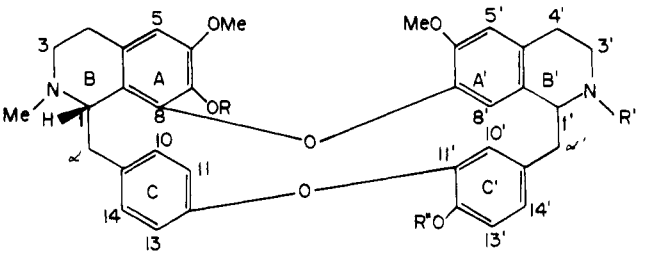
The conformation of macrocyclic compounds are a challenge which has normally been solved by using X-ray crystallography. On the basis of previous works on bis(benzylisoquinoline) alkaloids[1b,2] and conscious that ^1H and ^{13}C NMR data are reliable tools for conformational analysis, we decided to carry out a careful analysis of the 18-membered macrocyclic alkaloids of the dapnoline–repandine class in order to contribute to the determination of related unknown compounds as well as to stimulate similar studies on other macrocyclic compounds.

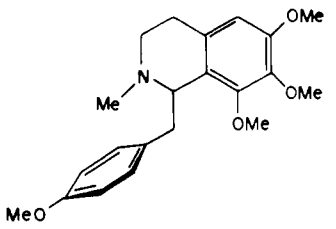
The ^{13}C NMR shifts for daphnoline and some of its derivatives (**1–4**) are listed in Table I. Assignments for



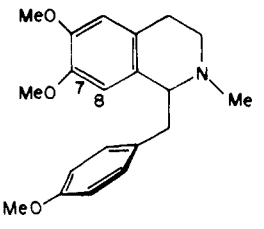
(1) R=R'=R"=H, 1'= R
(2) R=R"=H,R'=Me, 1'= R
(3) R=R'=H,R"=Me, 1'= R
(4) R=R"=Me,R'=H, 1'= R
(5) R=R'=Me,R"=H, 1'= S
(6) R=R'=R"=Me, 1'= S
(13) R=R'=R"=Me, 1'= R

two alkaloids which belong to a diastereomeric series, repandine (**5**) and *O*-methylrepandine (**6**), are also listed. The values have been derived from standard chemical shift theory and from a study of the SFORD and the fully coupled ^{13}C NMR spectra. We have also taken into account analyses which have been reported previously for various mono-[1] and bis(benzylisoquinoline)[1b,2] alkaloids. It has been possible to resolve most of the uncertainties in assignment by selective heteronuclear irradiations and by a consideration of the known effects of O- and N-alkylation.

In the case of monobenzylisoquinoline alkaloids, it is known from ^1H NMR data[3] that a base such as *N,O,O*-trimethylcoclaurine (**7**) preferentially adopts a folded conformation in solution, but if a substituent such as methoxyl is inserted at C-8 as in **8**, an extended conformation is preferred.



(8)



(7)

These facts can only be used for the bis(benzylisoquinoline) conformational analysis, taking into consideration that new steric interactions arise when the macrocycle is formed by the coupling of two benzylisoquinoline

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