(COH), 66.0 and 43.7 (morpholine C's), 25.9 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.12; H, 8.36; N, 7.19.

2-Hydroxy-2-methylpropyl piperazine-1-carboxylate (3c): yield 62.0%;[7] recrystallized from methyl isobutyl ketone/hexane or toluene; mp 80–81 °C; NMR (Me_4Si) δ_{CDCl_3} 1.23 (s, 6, *gem*-CH_3), 2.8 (m, 4, piperazine protons), 3.43 (m, 4, piperazine protons), 3.93 (s, 2, CH_2); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 155.0 (C=O), 72.7 (CH_2), 69.1 (COH), 44.4 and 45.2 (piperazine C), 26.0 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.49; H, 8.71; N, 13.55.

1,1-Dimethyl-2-hydroxyethyl Morpholine-1-carboxylate (2b). A mixture of 1.74 g (0.02 mol) of morpholine and 2.32 g (0.02 mol) of isobutylene carbonate was stirred at room temperature for 3 days. Analysis by NMR spectroscopy showed the mixture containing **2b** and **3b** in a 50:50 ratio and approximately 20% unreacted starting materials. The mixture was chromatographed on a silica gel column with 96:4 methylene chloride–methanol. Fractions found by TLC (silica gel, 8:2 methylene chloride–methanol, I_2 detection) to contain pure product were evaporated to dryness to give 0.96 g (23.6%) of **2b** as a yellow oil which crystallized on standing: mp 68–70 °C; ^1H NMR (Me_4Si) δ_{CDCl_3} 1.4 (s, 6, *gem*-CH_3), 3.3–3.8 (m, 10, morpholine and CH_2 protons), 4.43 (t, 1, OH); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 155.2 (C=O), 83.7 (quaternary C), 69.4 (CH_2), 66.3 and 44.0 (morpholine C's), 23.6 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 52.95; H, 8.15; N, 6.89.

Conversion of 2b to 3b. To a solution of 35 mg of **2b** in 0.4 mL of D_2O in an NMR tube was added approximately 40 mg of morpholine, and the conversion of **2b** to **3b** was monitored by ^1H NMR. Within 20 min at ambient temperature the mixture contained **3b** and **2b** in a 98:2 ratio. Solutions of **2b** in D_2O or $CDCl_3$ containing no base were found to be stable at room temperature for at least 30 min.

Acknowledgment. We thank Dr. G. N. Chmurny for providing the ^{13}C NMR spectra.

Registry No. 1, 4437-69-8; **2a**, 74684-67-6; **2b**, 74684-68-7; **2c**, 73352-30-4; **3a**, 74684-69-8; **3b**, 74684-70-1; **3c**, 71649-29-1; morpholine, 110-91-8; dimethylamine, 124-40-3; piperazine, 110-85-0.

(7) Use of excess piperazine is necessary, in this case, to minimize yield loss due to formation of the diacylated piperazine compound.

A Novel Route for Functionalization of the Bridgehead C-2 Position of Benzomorphans[1]

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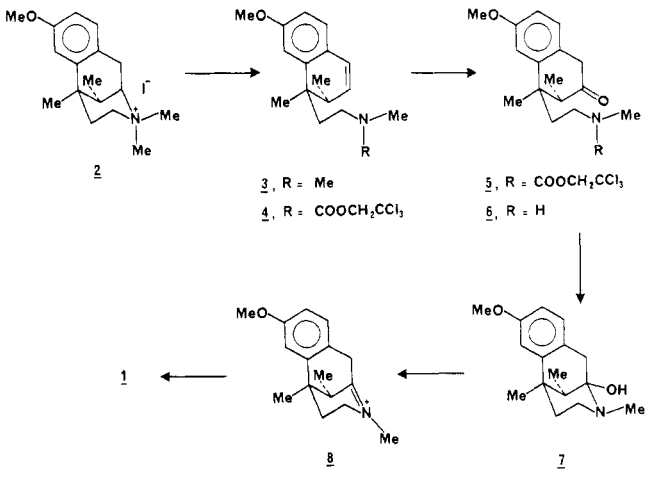
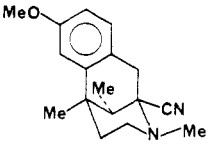
Although hundreds of benzomorphans[1] containing substitution in different positions have been synthesized,[2,3] there is a noteworthy paucity of 2-substituted derivatives in this important class of compounds. The reason for this is the difficulty in creating a quaternary center at the C-2 position through conventional synthetic routes. In this report we describe a novel, practical approach to the attachment of a cyano group at this position, as exemplified by the synthesis of **1**.

Scheme I





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The route to benzomorphan **1** is outlined in Scheme I. A key feature of the synthetic strategy involved the cyclization of tetralone **6** through an intramolecular Strecker-type reaction. In an effort to obtain **6** we subjected the quaternary compound **2** to a Hoffman elimination.[4] The dihydronaphthalene product (**3**) of this reaction was demethylated with trichloroethyl chloroformate[5] to afford the corresponding carbamate **4**, which was subsequently epoxidized with *m*-chloroperbenzoic acid. The product, which was a mixture of the epoxide and benzoate ester (arising from epoxide opening by nucleophilic attack of benzoate anion), was then subjected to acid-catalyzed rearrangement[6] to the ketone **5**.

When the amino group of **5** was deprotected with zinc and acetic acid, the anticipated intermediate **6** was not detected as a product. The infrared spectrum of the compound which was isolated possessed no carbonyl absorption and contained a peak at 3125 cm^{-1} which is attributable to OH. The spectral and analytical data suggest that the deprotected product is the carbinolamine **7**. The facility with which **7** forms is not surprising because there is ample precedent in the literature[7,8] for similar neighboring-group participation which leads to stable carbinolamine formation.

The target compound **1** was prepared in excellent yield by reacting **7** with KCN at pH 5.5. The reaction presumably occurs via the iminium intermediate **8**. Although **8** contains an sp^2-hybridized bridgehead carbon, such an intermediate would not violate Bredt's rule,[9] as the bicyclic system is large enough to accommodate a double bond at the bridgehead center.[8,10]

(1) Although the common name "benzomorphan" is used in our discussion, the numbering system of the chemical name, 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, is employed.

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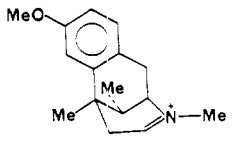
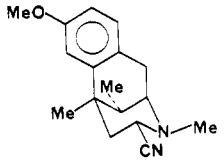
The possibility that iminium intermediate 8 might undergo isomerization to the less strained compound 9, thereby leading to nitrile 10, was ruled out by an independent synthesis of this regioisomer.[11]



9



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The route to C-2 functionalized benzomorphans conceivably can be applied to the morphinans and opiates for preparation of C-9 substituted congeners.

Experimental Section

Melting points were determined by using a Mel-Temp capillary apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 281 instrument. NMR spectra were obtained (Me_4Si, internal standard) with Varian T-60 and FT-80 instruments. An AE1 MS-30 spectrometer (70 eV) was employed for mass spectra. Normetazocine was obtained from Sterling-Winthrop Research Institute.

4-[2-(Dimethylamino)ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydronaphthalene (3). (2α,6α,11α)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (normetazocine,[12] 21.7 g, 0.1 mol) and methyl iodide (125 mL, 2.0 mol) were dissolved in a solution of NaOH (9.0 g, 0.23 mol) in methanol (550 mL). After the mixture was stirred at 25 °C for 15 h and refluxed for 1 h, the volatile components were removed in vacuo. The mixture (68.9 g) of the quaternary salt 2 and NaI which was obtained was dissolved in 10% aqueous NaOH (350 mL) and heated on a steam bath for 2.5 h. Extraction with methylene chloride, washing with water, drying (Na_2SO_4), and removal of solvent gave 3 as an oil (24.6 g, 95%): R_f 0.51 (chloroform/methanol/ammonia, 4:1:0.2); NMR (CCl_4) δ 6.73 (m, 3 H, aromatic), 6.27 (d, 1 H, J = 10 Hz, vinyl), 5.72 (m, 1 H, J = 10 Hz, vinyl); mass spectrum, m/e 259 (M^+). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.40. Found: C, 78.76; H, 10.08; N, 5.31.

4-[2-(((2,2,2-Trichloroethoxy)carbonyl)methylamino)-ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydronaphthalene (4). The amine 3 (44.6 g, 0.15 mol) in benzene (1.4 L) was refluxed with 2,2,2-trichloroethyl chloroformate (80.5 g, 0.3 mol) and K_2CO_3 (26 g, 0.19 mol) for 44 h. The reaction mixture was then stirred with 5% aqueous KOH (250 mL) for 30 min to decompose excess reagent. The organic phase was separated, washed with water, and dried (Na_2SO_4), and the solvent was removed to give 84 g of crude carbamate mixed with bis(2,2,2-trichloroethyl) carbonate. This material was chromatographed on a silica gel column (chloroform/petroleum ether, 1:20) to yield 64.5 g of pure 4 as an oil (91%): R_f 0.66 ($CHCl_3$/EtOAc, 2:1); IR (neat) 1725 cm^{-1} (carbamate); NMR (CCl_4) δ 4.5 (s, 2 H, OCH_2CCl_3), 2.7 (s, 3 H, NCH_3); mass spectrum, m/e 419 (M^+). Anal. Calcd for $C_{19}H_{24}O_3NCl_3$: C, 54.41; H, 5.72; N, 3.34; Cl, 25.41. Found: C, 54.49; H, 5.89; N, 3.08; Cl, 25.27.

4-[2-(((2,2,2-Trichloroethoxy)carbonyl)methylamino)-ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (5). A methylene chloride solution (300 mL) of carbamate 4 (20.8 g, 0.05 mol) was cooled to 5 °C and a solution of *m*-chloroperbenzoic acid (14.85 g, 0.07 mol) in chloroform (140 mL) was added dropwise over a period of 30 min. After being stirred at 25 °C for 2.5 h, the reaction mixture was extracted with cold 5% NaOH and washed with water. After drying of the solution (Na_2SO_4) and removal of the solvent 26.3 g of an oil was obtained. This oil was refluxed in absolute ethanol (210 mL) containing 1.7 g of HCl for 20 min. The ethanol was removed in vacuo and the residue was redissolved in methylene chloride. The solution was washed with aqueous $NaHCO_3$ and then water. Drying (Na_2SO_4) and removal of the solvent gave an oil (19.56 g) which was purified on a silica gel column (chloroform/petroleum ether, 3:2) to provide the ketone 5 (10.19 g, 52%): R_f 0.64 (EtOAc/C_6H_6, 1:1); IR (neat) 1725 (carbamate), 1710 cm^{-1} (ketone). NMR (CCl_4) δ 4.5 (s, 2 H, OCH_2CCl_3), 3.66 (s, 2 H, CH_2Ar); mass spectrum, m/e 435 (M^+). Anal. Calcd for $C_{19}H_{24}O_4NCl_3$: C, 52.17; H, 4.81; N, 3.20. Found: C, 52.09; H, 4.89; N, 2.95.

(2α,6α,11α)-1,2,3,4,5,6-Hexahydro-2-hydroxy-8-methoxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (7). The tetralone 5 (5 g, 0.01 mol) was dissolved in a mixture of THF (100 mL), acetic acid (30 mL), and water (15 mL) and then stirred with Zn dust (1.5 g) for 1 h at 15 °C. The unreacted Zn was removed and the THF was evaporated in vacuo. The residue was redissolved in water, acidified with dilute HCl, and extracted with ether to remove neutral materials. The aqueous layer was basified and extracted with methylene chloride. Drying (Na_2SO_4) and removal of the solvent gave 2.37 g of solid which was crystallized from ethyl acetate/petroleum ether (1:1) to afford 7 (1.2 g, 40%): mp 164–166 °C; R_f 0.56 ($CHCl_3$/CH_3OH/ammonia, 4:1:0.02); NMR (CD_2Cl_2) δ 3.5 (s, 3 H, OCH_3), 2.85 (d, 1 H, J = 16 Hz, benzylic), 2.40 (d, 1 H, J = 16 Hz, benzylic); mass spectrum, m/e 261 (M^+). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.94; H, 9.14; N, 5.05.

(2α,6α,11α)-1,2,3,4,5,6-Hexahydro-2-cyano-8-methoxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (8). A solution of carbinolamine 7 (1.31 g, 5 mmol) in methanol (40 mL) and water (50 mL) was refluxed with KCN (0.6 g, 9.2 mmol) for 40 h, after adjusting to pH 5.5 with dilute HCl. Basification and extraction gave 1.30 g of an oil which was purified on a silica gel column (EtOAc/$CHCl_3$, 9:1) to provide 8 as oil (0.98 g, 75%): R_f 0.61 ($CHCl_3$/EtOAc, 3:2); NMR ($CDCl_3$) δ 6.90 (m, 3 H, aromatic), 3.86 (s, 3 H, OCH_3), 3.38 (d, 1 H, J = 18 Hz, benzylic), 3.04 (d, 1 H, J = 18 Hz, benzylic), 2.72 (s, 3 H, NCH_3), 2.03 (m, 5 H, C_{11}-H, C_4 and C_5 methylene protons), 1.50 (s, 3 H, C_6-CH_3), 1.23 (d, 3 H, C_{11}-CH_3); IR (neat) 2220 cm^{-1} (weak, CN); mass spectrum, m/e 270 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.55; H, 8.15; N, 10.37. Found: C, 75.42; H, 8.25; N, 10.15.

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Registry No. 1, 74752-75-3; 3, 74752-76-4; 4, 74752-77-5; 5, 74752-78-6; 7, 74752-79-7; 8, 74763-40-9; *cis*-normetazocine, 16603-67-1; 2,2,2-trichloroethyl chloroformate, 17341-93-4.

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Lactone Formation via Oxidative Cyclization of an Unsaturated Carboxylic Acid: Application to the Stereoselective Synthesis of (±)-Malyngolide, an Antibiotic from the Marine Blue-Green Alga *Lyngbya majuscula* Gomont

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Recently the isolation and structure determination of malyngolide (8), an antibiotic effective against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, was reported.[1] In view of its activity and to further confirm the assigned structure, we set out to develop a convenient route for total synthesis of this marine natural product. In this note we report such a method, one that should also be adaptable to preparation of other similarly functionalized

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