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A Novel Synthesis of [O-methyl-^{14}C]Dextromethorphan: Utility of the Vinyloxycarbonyl Group

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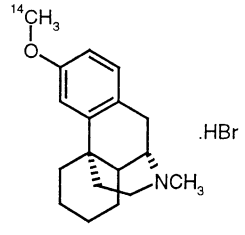
Summary

A novel, selective approach to [O-methyl-^{14}C]Dextromethorphan is presented. The key feature is protection of 3-hydroxymorphinan at nitrogen and oxygen with the vinyloxycarbonyl group. This allows selective O-deprotection and methylation without competing nitrogen quaternization. The N-vinyloxy carbonyl group is converted to the desired methyl group by lithium aluminum hydride reduction.

Key Words: Carbon-14, Dextromethorphan, morphinan, vinyloxycarbonyl protecting group, vinyl chloroformate

Introduction

Dextromethorphan hydrobromide, labeled with carbon-14 in the O-methyl group ([**^{14}C**]**1**), was required by the Drug Metabolism Department.



[**^{14}C**]**1**

[O-methyl-^{14}C]Dextromethorphan Hydrobromide

A previous synthesis of [**^{14}C**]**1** in our laboratory by direct alkylation of 3-hydroxy N-methylmorphinan **3** with [^{14}C]methyl iodide (Scheme 1) was complicated by competitive N-alkylation, leading to extensive quaternary ammonium salt formation and very low yield after laborious purification. A new synthesis was developed to address this problem.

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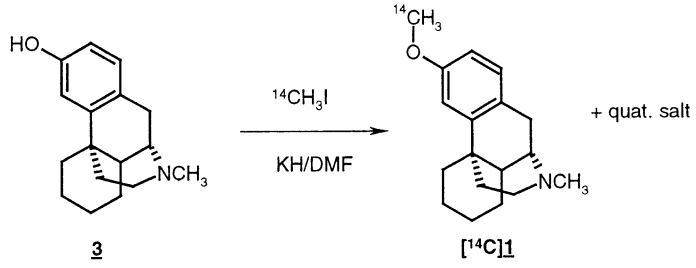
Scheme 1

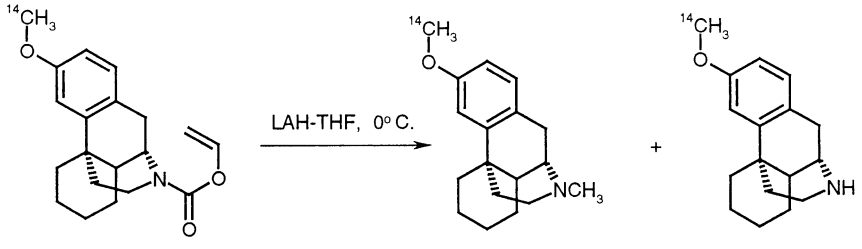


3 [14C]1

Results and Discussion

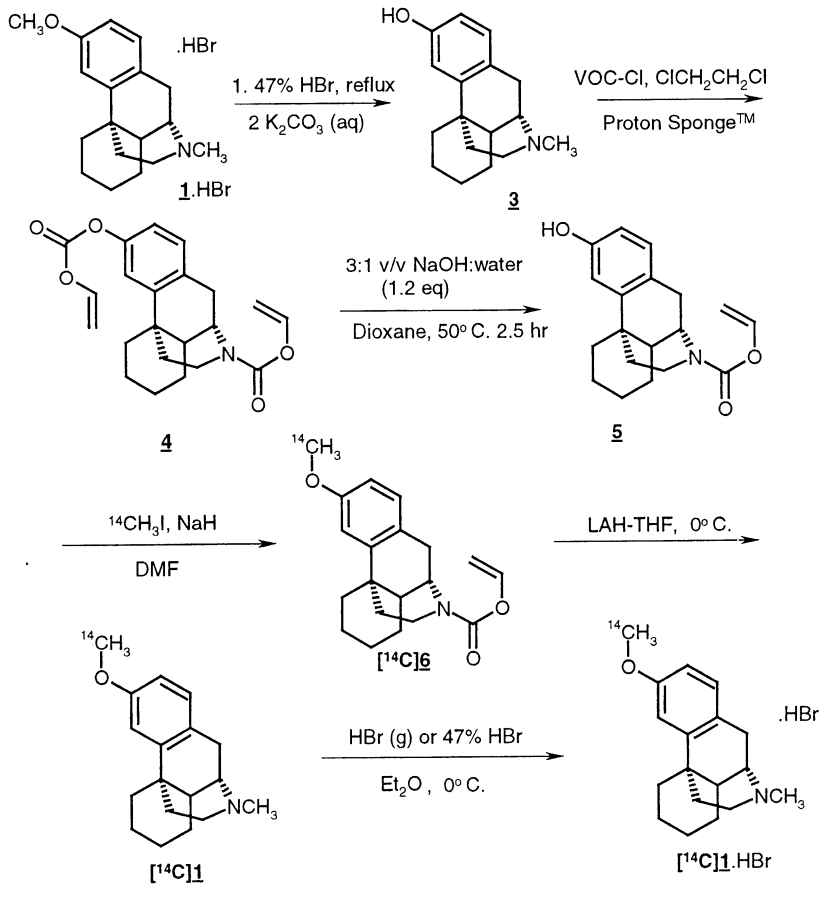
Protection of the nitrogen and oxygen of dextromethorphan in a manner allowing selective O-deprotection would lead to a substrate that could be O-alkylated without competing N-alkylation. Literature precedent suggested that the vinyloxycarbonyl (VOC) group would afford excellent N and O differentiation in this system.[1] The phenolic VOC function is easily removed by mild basic hydrolysis, while the N-VOC function is refractory to cleavage under these conditions.[1] Conversely, mild acid hydrolysis converts the N-VOC function to an amine with no effect on the phenolic VOC function.[1] Although the N-methyl group would be removed by carbamate formation in the generation of key intermediate N,3-O bis VOC morphinan,[2] the literature suggested that the carbamate could be converted efficiently back to the desired N-methyl moiety by lithium aluminum hydride reduction,[3] obviating the need for re-alkylation. The synthesis is shown in Scheme 2.

Dextromethorphan hydrobromide **1** was O-demethylated in 87% yield by treatment with 47% aqueous hydrobromic acid at reflux. The resulting O-desmethyl dextromethorphan hydrobromide (**2**, not shown) was converted to the free base **3** and treated with 2.25 eq of vinylchloroformate and Proton Sponge™ in 1,2-dichloroethane to give bis-VOC derivative **4** in 70-89% yield after silica gel chromatography. Compound **4** was selectively O-deprotected in 94% yield by hydrolysis with 3:1 dioxane:aqueous sodium hydroxide (1.2 eq) at 50° C. The resulting N-VOC phenol **5** was treated with 100 mCi of [^{14}C]methyl iodide and sodium hydride in DMF at RT to give 96 mCi (solution yield) of [**^{14}C**]**6** at a radiochemical purity of 84%. This material was treated with lithium aluminum hydride in THF at 0° C to give 86 mCi (solution yield) of [**^{14}C**]**1** free base at 94% radiochemical purity. The crude chemical yield of the free base was over 100%. The product was contaminated with ca 1% of the N-desmethyl analog [**^{14}C**]**7**, which was



[14C]6 [14C]1 [14C]7

Scheme 2



formed in amounts as great as 10-15% if initial reduction temperature and reductant addition rate were not carefully controlled. This material was identified by chromatographic isolation, mass spectrometry, and ^{1}H-NMR spectroscopy (unpublished results).

The synthesis of [^{14}C]1 was completed by treatment of a 20 mCi portion (solution determination by LSC) of free base in diethyl ether with 47% hydrogen bromide and recrystallization. The final chemical yield after recrystallization from diethyl ether was 120 mg. The final specific activity was 50 mCi/mmol, with chemical and radiochemical purities greater than 99%. Thus, the radiochemical yield was 17 mCi. Purification of small amounts of [^{14}C]1 could be done by semi-preparative RP-HPLC, providing solutions of the TFA salt.

Conclusion

A novel approach for labeling Dextromethorphan with carbon-14 at the methyl carbon of the methoxy group has been described in which N and O differentiation is achieved with the VOC group. The N-vinyloxycarbonyl group has been used as both a nitrogen protecting group to eliminate quaternary salt formation during O-alkylation and as an N-methyl precursor. The flexibility of this approach is attractive. Alkylation of N-VOC phenol **5** with [^{3}H]methyl iodide could produce after N-methyl regeneration the 3-methoxy tritiated analog of dextromethorphan. In addition, the use of lithium aluminum [^{3}H]hydride in the reduction of **[^{14}C]6** could produce dual labeled [O-methyl-^{14}C, N-methyl-^{3}H]Dextromethorphan.

Experimental Section

All reagents and solvents were obtained from Aldrich unless otherwise noted. Proton NMR spectra (^{1}H-NMR) were obtained on a Bruker instrument at 300 MHz in the designated solvent. Only diagnostic peaks are reported. Mass spectra (MS) were evaluated by FIA/ESI/MS on a HP 1100 MSD. The samples were solubilized in 70:30 v/v acetonitrile:water prior to analysis. Radiochemicals were obtained from ARC, St. Louis, MO. Radio-HPLC detection employed a Ramona Classic instrument with a 0.75 mL cell using Tru-Count scintillant. TLC scanning was done on a Berthold instrument. Specific activities of [O-methyl-^{14}C]Dextromethorphan hydrobromide were determined by liquid scintillation counting (Beckman LS 6500, Tru-Count scintillant) of ethanol solutions

3-(O-Desmethyl) Dextromethorphan 2: Dextromethorphan hydrobromide (5.0 g, 14.2 mmol, Sigma) was dissolved in 47% aqueous hydrobromic acid. The solution was heated at reflux for 18 hours. The mixture was poured on crushed ice, and treated with saturated potassium carbonate until pH=10. The mixture was extracted with 3 x 50 mL of chloroform. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and solvent was removed at reduced pressure to give a solid (3.2 g, 87%). HPLC assay showed a single component (Beckman C-18 column, 5 micron packing, 4.6 x 250 mm, 1 mL/min flow rate, 30-50% v/v linear gradient of methanol in water over 40 minutes, UV 280 nm, 97.3% par, Rt=14.8 min). The material was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$):
δ6.95 (d, J=6.9 Hz, 1H, C1-H); δ6.70 (s, 1H, C4-H); δ6.60 (dd, *J*=1.2, 6.6 Hz, 1H, C2-H); δ2.45 (s, 3H, N-CH_3)

MS: m/e (intensity) calcd for $C_{17}H_{23}NO$, 258; found 258 (100) $M+H^{+}$

N, 3-O bis-VOC morphinan 4:
Under dry argon, 3-(O-desmethyl) dextromethorphan (1.0 g, 3.9 mmol) was dissolved in 1,2-dichloroethane (15 mL, freshly distilled from calcium hydride) at RT. To the solution was added Proton Sponge (1,8-bis(dimethylamino)napthalene, 1.01 g, 4.7 mmol) and vinyl chloroformate (953 mg, 8.4 mmol). The solution was heated at 60^{o} overnight. TLC assay (silica gel, methylene chloride) revealed no starting material remaining. The mixture was concentrated in vacuo, and the residue was passed through a short silica gel column, eluting with methylene chloride. Combination of the desired highly UV active fractions was followed by solvent removal at reduced pressure. An oil was isolated (1.34 g, 89%). A second preparation on 7.3 mmol scale gave 1.93 g (70%). These lots were combined and used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$):
δ7.35 (d, J=7.0 Hz, 1H, C1-H); δ7.2 (m, 2H, H_2C=CHO-COR, R=N and O); δ7.10 (s, 1H, C4-H); δ7.0 (dd, *J*=1.3, 6.8 Hz, 1H, C2-H); δ5.02 (dd, *J*=1.4, 13.9 Hz, 1H, trans-H_2C=CHO-COO), δ4.81 (dd, *J*=1.5. 14.0 Hz, 1H, trans-H_2C=CHO-CON); δ4.70 (d, *J*=6.0 Hz, 1H, cis-H_2C=CHO-COO), δ4.40 (d, *J*=6.0 Hz, 1H, cis-H_2C=CHO-CON)

3-Hydroxy N-VOC morphinan 5:
N,3-O bis VOC morphinan (3.27 g, 8.5 mmol) was dissolved in dioxane (36 mL) and water (12 mL) containing 408 mg (10.2 mmol) of sodium hydroxide. The solution was heated at 50° for 4 hr. TLC assay (silica gel, methylene chloride) revealed no starting material present. The mixture was cooled to RT, poured into brine, and extracted with 3 x 50 mL of ether. The combined ether extracts were dried over sodium sulfate, filtered, and solvent was removed under reduced pressure to give a glass (2.50 g, 94%). The material was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$):
δ7.2 (m, 1H, H_2C=CHO-CON); δ6.95 (d, *J*=6.9 Hz, 1H, C1-H); δ6.70 (s, 1H, C4-H); δ6.60 (dd, 1.2, *J*=6.6 Hz, 1H, C2-H); δ4.81 (dd, *J*=1.5. 14.0 Hz, 1H, trans-H_2C=CHO-CON); δ4.40 (d, *J*=6.0 Hz, 1H, cis-H_2C=CHO-CON)

MS: m/e (% intensity of base peak) calcd for $C_{19}H_{23}NO_3$, 314; found 314 (100) M^++H^+, 244 M^++H^++-$C_3H_3O_2$ (VOC)+H

3-[^{14}C]Methoxy N-VOC morphinan 6:
Under dry argon, 3-hydroxy N-VOC morphinan (572 mg, 1.82 mmol) was dissolved in dry DMF (12 mL). To the rapidly stirred solution was added sodium hydride (76 mg of a 60% oil dispersion, 1.91 mmol). The mixture was stirred at RT for one hour. To the mixture was added 100 mCi of [^{14}C]methyl iodide (nominal specific activity 55 mCi/mmol) in 7 mL of DMF. The mixture was sealed and stirred at RT overnight. Radio-TLC assay (silica gel, 2:1:0.1 v/v/v acetone/methanol/ammonia) revealed a single major component (80% of total activity). The mixture was poured into 100 mL of brine, and the mixture was extracted with 4 x 30 mL of ether. The combined organic extracts were dried over sodium sulfate, filtered (nominal solution radiochemical yield=96 mCi), and solvent was removed at reduced pressure to give an oil (615 mg, over 100%). The material was used without further purification in the next reaction

[O-methyl-^{14}C]Dextromethorphan 1:
Under dry argon, 3-[^{14}C]methoxy N-VOC morphinan (1.82 mmol) was dissolved in dry THF (25 mL). The solution was cooled to 0° over 30 minutes. Solid lithium aluminum hydride (277 mg, 7.3 mmol) was added in small portions over 15 minutes with rapid stirring and diligent maintenance of cooling. The mixture was stirred under argon at 0° for 30 minutes, and then from 0°-RT overnight. To the mixture was added sequentially 0.3 mL of water, 0.3 mL of 15% aqueous sodium hydroxide and 0.9 mL of water. The mixture was filtered, and the filtrate was poured into 75 mL of water. The mixture was extracted with 4 x 30 mL of ether. The combined organic extracts were dried over sodium sulfate and filtered. The nominal solution radiochemical yield was 86 mCi. The solvent was removed under reduced pressure, and the the oily solid free base (510 mg, over 100%) was stored at -80° under argon. Radio-HPLC assay (50:50:0.1 v/v/v

methanol/water/TFA, 1 mL/min Beckman C-18 column, 4.6 x 250 mm, 5 micron particle size, UV 280 nm, radiodetection by Ramona Classic flow detector) showed single major mass (94% par) and radioactive (94% RCP) components that co-migrated with authentic (Sigma) standard (R_t=11.3 min). A 20 mCi portion of crude free base was dissolved in diethyl ether and treated with 47% aqueous hydrogen bromide. The resulting white solid was recrystallized from diethyl ether to give 120 mg of the hydrobromide. The specific activity was 50 mCi/mmol, with chemical and radiochemical purities greater than 99%. Thus, the radiochemical yield was 17 mCi.

Small scale (ca 1-5 mCi) purification of material intended for blending with carrier was obtained by semi-preparative HPLC (Zorbax SB-CN column, 20 x 250 mm, 7 micron particle size, 15 mL/min linear gradient: 90:10:0.2 water/acetonitrile/TFA to 30:70:0.2 water/acetonitrile/TFA over 70 min, UV 275 nm, R_t=33 min. Solvent removal and reconstitution of the residue in absolute ethanol provided the TFA salt.

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