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SYNTHESIS OF CARBON-11 LABELED DIPRENORPHINE: A RADIOLIGAND FOR POSITRON EMISSION TOMOGRAPHIC STUDIES OF OPIATE RECEPTORS

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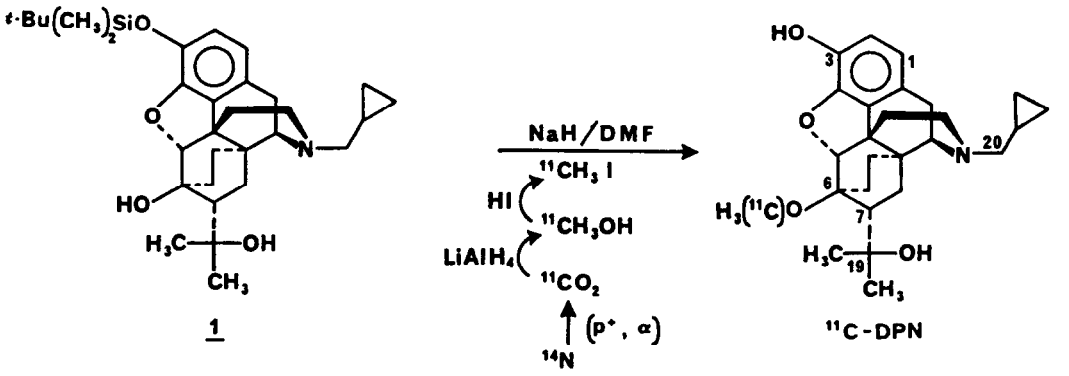
Summary: Selective alkylation of 3-(O-t-butyldimethylsilyl)-6-(O-desmethyl)-diprenorphine with [^{11}C]-methyl iodide followed by desilylation affords [^{11}C]-diprenorphine labeled at the 6-methoxy position in 10% yield with a specific activity of 1740 mCi/μmol at the end of a 30 minute synthesis.

Diprenorphine (DPN), a semi-synthetic morphinan, is a potent and pharmacologically well-defined opiate antagonist which has proved particularly useful for in vivo studies of opiate receptors in rodents[1] and sub-human primates.[2] Accordingly, there is considerable interest in the development of an efficient synthesis of DPN isotopically labeled with carbon-11, a short-lived radionuclide, for non-invasive visualization and quantification of human cerebral opiate receptors by positron emission tomography.[3] Routes to [^{11}C]-DPN have used either [^{11}C]-methyllithium[4] to label a C-19 methyl group or [^{11}C]-cyclopropanecarbonyl chloride[5] to label the C-20 methylene position; however, radiochemical yields are low, < 3%, at end of synthesis.[4b,5c] Therefore, we have developed a new method which provides [^{11}C]-DPN of high specific activity in significantly greater radiochemical yield. The procedure employs a novel precursor, diol 1, and a readily prepared labeled reagent, [^{11}C]-methyl iodide. As indicated in Scheme 1, selective O-alkylation of 1 with [^{11}C]-methyl iodide followed by desilylation gives [^{11}C]-DPN labeled at the 6-methoxy position in 10% yield with a specific activity of 1740 mCi/μmol at the end of a 30 minute synthesis.[6]



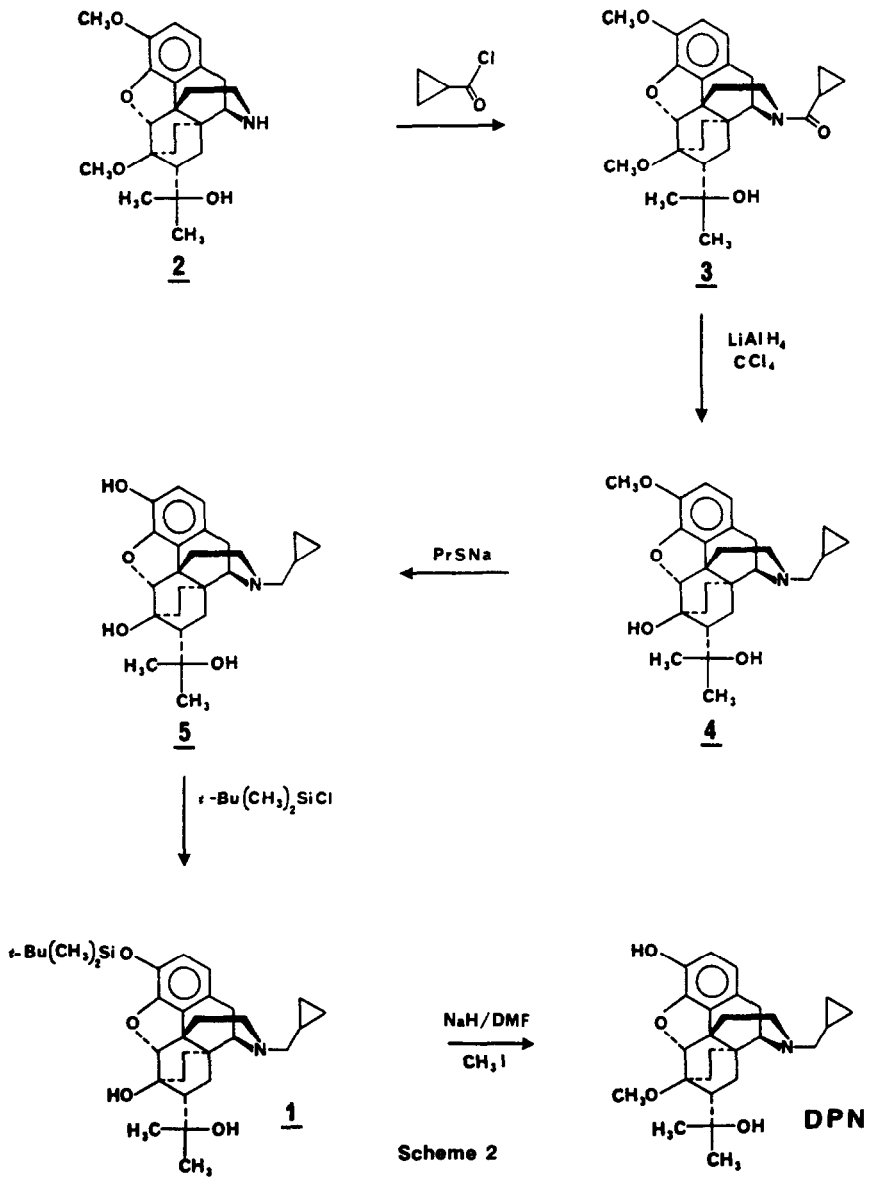
Scheme 1

The required precursor 1 was obtained as follows (Scheme 2).[7] Amine 2 was synthesized from thebaine[8] in five steps, 52% over-all yield, as described by Bentley and Hardy[9] and converted to amide 3 in 80% yield by treatment with cyclopropanecarbonyl chloride and K_2CO_3 in ether for 12 hours. The key 6-O-demethylation of 3 as well as reduction of the amide moiety were effected by $LiAlH_4$ in THF containing CCl_4 at reflux for 20 hours to give 4 in 79% yield. These unusual demethylation conditions, specific for the 6-methoxy position, recently were described by Kopcho and Schaeffer[10] for several morphinans which have an electron-rich group on the 7α-substituent and are similar to 3. Demethylation of the aryl ether of 4 by standard conditions, sodium propanethiolate in DMF at reflux for 3 hours,[11] gave triol 5 in 88% yield.

At this juncture, the synthesis of DPN demanded appropriate differentiation of these three hydroxyl groups. Therefore, the phenolic hydroxyl was blocked by O-silylation of 5 with t-Bu(Me)$_2$SiCl in DMF containing imidazole at ambient temperature for 3 hours which afforded diol 1 in 93% yield. Although the 6-hydroxy and 19-hydroxy positions are both tertiary, examination of Dreiding molecular models indicated that the 6-hydroxy position should be more sterically accessible to approach by electrophiles. In practice, addition of a solution of 1 (60 mg) in DMF (5 mL) containing methyl iodide (0.5 equivalents) to dry NaH (50 equivalents) followed by heating at 80°C for two minutes and quenching with aqueous methanolic HCl provided DPN in nearly quantitative isolated yield based on methyl iodide as limiting reagent (Scheme 2). The product was identical to an authentic sample of DPN[12] by [^{1}H]-NMR (400 MHz), [^{13}C]-NMR (100 MHz), and high resolution mass spectroscopy as well as by reverse-phase HPLC and normal-phase TLC.[13] Triol 6, resulting from simple desilylation of 1, completed the mass balance. Desilylation occurs under the initial reaction conditions and is not dependent upon the quenching step; however, the protecting group is sufficiently stable to allow the facile methylation of the 6-hydroxy position.

This method proved amenable to the preparation of [^{11}C]-DPN from [^{11}C]-methyl iodide (Scheme 1). [^{11}C]-Carbon dioxide was produced *via* the $^{14}N(p,\alpha)^{11}C$ reaction in a biomedical cyclotron by 16 MeV proton irradiation of a nitrogen target and converted to [^{11}C]-methanol by $LiAlH_4$ reduction. Treatment of the [^{11}C]-methanol with HI at reflux generated [^{11}C]-methyl iodide[14] which, carried by a stream of nitrogen, was trapped in a solution of 1 (*ca.* 1 mg) in DMF (0.2 mL) at -78°C. The solution was transferred by cannula to dry NaH (*ca.* 3 mg), heated at 80°C for 2 minutes, and the excess base was quenched with aqueous HCl. The radioactive product corresponding to [^{11}C]-DPN was isolated by reverse-phase HPLC in excellent chemical and radiochemical purity. The synthesis, purification, and formulation of the radioligand for intravenous injection were accomplished within 30 minutes from end of bombardment of the target. At end of synthesis, the average radiochemical yield was 10% based on [^{11}C]-methyl iodide while the average specific activity was 1740 mCi/μMol as determined by analytical HPLC (n=7). All preparations tested were sterile and pyrogen-free.

The position of the label can be inferred from the method of synthesis (*vide infra*); however,additional evidence which validates the structural identity of the radiolabeled substance as [^{11}C]-DPN was obtained from a radiosynthesis which utilized [^{11}C]-methyl iodide doped with [^{13}C]-methyl iodide (0.5 equivalents; 99 atom %). The isolated product, rendered by HPLC purification, displayed a single resonance at 52.6 ppm in the proton-decoupled [^{13}C]-NMR (100 MHz) spectrum which matched that observed for the 6-methoxy carbon of an authentic sample of DPN.



Scheme 2

This procedure for [^{11}C]-DPN synthesis is compatible with the short half-life (20.4 minutes) of carbon-11 and will facilitate tomographic studies of opiate receptors in normal and disease states. In addition, the selectivity observed for alkylation of 1 with methyl iodide suggests that the method also will allow convenient entry to a variety of previously inaccessible 6-alkyloxy analogs of DPN. Recently, Knipmeyer and Rapoport[15] found that methyl or methoxy substitutents at the 6-position increased the analgesic potency of agonists which are structural congeners of DPN; thus, higher homologs of the related antagonists may prove of interest as probes of opiate receptor-ligand interactions.

Acknowledgment

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