Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 3

A CONVENIENT SYNTHESIS OF CARBON-13 LABELED 1-KETO-7-METHOXYOCTAHYDROPHENANTHRENE

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SUMMARY

Carbon-13 labeled 1-keto-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (III) and 1-keto-7-methoxy-2-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (IV) were prepared in good yields via the cyanidation of an organoborane.

KEY WORDS: Carbon-13, Organoborane, Steroid, Labeled Steroids

INTRODUCTION

In connection with our ongoing program directed toward the synthesis of carbon-11 labeled 17β-estradiol and related hormones using organoborane chemistry,[1-3] we required isomerically pure trans-1-keto-7-methoxy-1,2,3,4,-9,10,11,12-octahydrophenanthrene (III) and 1-keto-7-methoxy-2-methyl-1,2,3,-4,9,10,11,12-octahydrophenanthrene (IV). Although the preparations of III and IV have been reported,[4-8] the syntheses are not stereospecific (cis and trans isomers are formed), numerous reactions are involved, and the required starting materials are not readily available. In addition, the reactions are not suitable for the regiospecific incorporation of carbon isotopes.

We now wish to report an improved procedure for the synthesis of trans-tricyclic ketone III. The syntheses of carbon-13 labeled trans-tricyclic ketones, III and IV , were carried out via the reaction of

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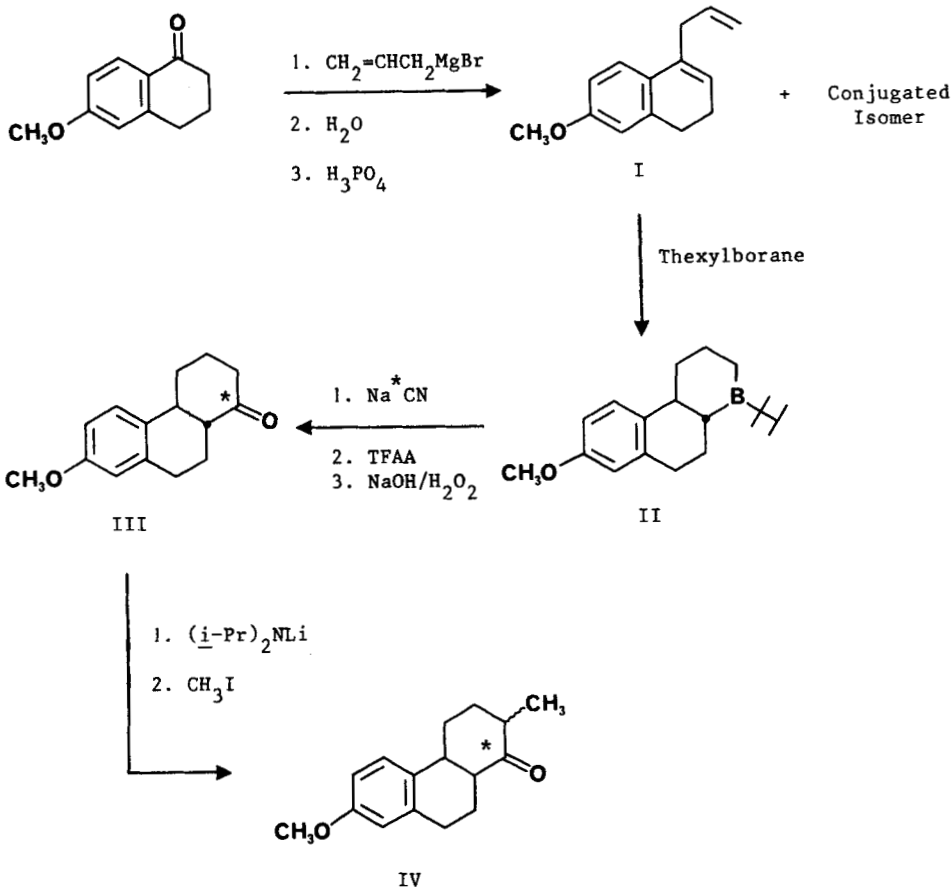
0362-4803/87/030317-06$05.00

Received April 4, 1986

B-thexyl-7-methoxy-2,3,4,9,10,11,12-octahydro-1-boraphenanthrene, II , with carbon-13 labeled sodium cyanide. The synthetic sequences are summarized below:



The formation of diene I via dehydration of the 1-allyl-6-methoxytetralol is complicated by the formaion of the corresponding conjugated diene. However the hydroboration of diene I can be achieved in the presence of the conjugated diene to yield the desired cyclic borane, II,[10,11] which is then converted to the desired trans-tricyclic ketone, III.

EXPERIMENTAL

The reaction flasks were dried in an oven at 130° and then assembled while flushing with dry nitrogen. Commercially available samples of 6-methoxy-1-tetralone, allyl magnesium bromide, 2,3-dimethylbutene, methyl-

lithium, trifluoroacetic anhydride (Aldrich), methyl iodide, phosphoric acid and hydrogen peroxide (Fisher) were used as received. Diisopropylamine (Aldrich) was distilled prior to use from $LiAlH_4$ and stored under nitrogen. ^{13}C-Enriched sodium cyanide (10%, MSD Isotopes) was oven-dried and powdered prior to use. Tetrahydrofuran was dried over CaH_2 and distilled prior to use from Na/benzophenone and stored under dry nitrogen. ^{1}H and ^{13}C-NMR spectra were obtained on a Jeol FX-90Q Fourier Transform NMR spectrometer. Chemical shifts expressed in parts per million (δ) downfield from TMS. All reagents were added via nitrogen-flushed, dry syringes or double-ended needles.

B-Thexyl-7-methoxy-2,3,4,9,10,11,12-octahydro-1-boraphenanthrene (II).

Allylmagnesium bromide in Et_2O (100 mmol, 100 mL of a 1 M soln.) was transferred via a double-ended needle into a three-necked, 500 mL round-bottomed flask equipped with a magnetic stirrer, addition funnel, condenser, a septum inlet, and which was cooled to 0°. 7-Methoxy-1-tetralone (99 mmol, 17.68 g) was placed in a 250 mL flask and deoxygenated by repeated evacuation and readmission of nitrogen; dry THF was added to the flask, the solution transferred to the addition funnel, and then added dropwise to the cold allylmagnesium bromide solution. After the addition, the ice bath was removed and the solution was refluxed gently for 1.5 h (bath temp. 55-65°). After cooling to 0°, aqueous NH_4Cl [5.0 g in 100 mL of chilled water] was added to the cold mixture and stirred at room temperature for 30 min. The mixture was extracted into ether (400 mL), the ether layer cooled to 0°, and then ice-cold phosphoric acid (100 mL, 85%) was added gradually while maintaining the reaction temperature ~5°. The mixture was stirred for 1 h at 0°. The resultant yellow-colored suspension was poured into 100 mL of cold water. Ether (400 mL) was added and then the ether extract was washed sequentially with 5% aqueous Na_2CO_3 (2 x 25 mL) and water (3 x 25 mL). [All solvent and reagents were cooled to 0° before use.] After drying ($MgSO_4$), removal of the solvent under reduced pressure (at room temperature) yielded the crude product (21.5 g of a light brown oil) which was purified by chromatography on a silica gel column using petroleum ether. The diene was collected in the

first two fractions. Removal of the solvent under reduced pressure yielded 12.58 g (78 mmol, 78%) of a mixture of two dienes. The dienes were deoxygenated by repeated evacuation and readmission of nitrogen and then dissolved in THF (100 mL.) The solution was transferred, using a double-ended needle, to a flask containing 80 mmol of thexylborane[12] in THF, at 0°. The solution was allowed to stir overnight at room temperature. The product, B-thexyl-7-methoxy-2,3,4,9,10,11,12-octahydro-1-boraphenanthrene (II), was transferred to a flask containing sodium cyanide via a double-ended needle without exposure to atmospheric oxygen.

Synthesis of trans-1-keto-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-^{13}C (III).

Carbon-13 labeled sodium cyanide (78 mmol, 3.76 g) was placed in a 500 mL round-bottom flask equipped with a septum inlet, magnetic stirring bar and a gas outlet tube connected to a Hg bubbler. The flask was deoxygenated by repeated evacuation and readmission of nitrogen. The B-thexyl-7-methoxy-2,3,4,9,10,11,12-octahydro-1-boraphenanthrene (II) was added to the flask with a double-ended needle. The mixture was stirred for 1 h at 25°. The flask was then cooled to -78° and trifluoroacetic anhydride (TFAA) (78 mmol, 12.1 mL) was added with stirring. The cooling bath was removed and the mixture allowed to come to room temperature (1 h). The mixture was cooled to 0°, 3N NaOH (78 mL) was then added followed by the slow addition of 50% H_2O_2 (56 mL). The cooling bath was removed and the oxidation continued for 3 h at 25° and then for 15 min. at 50°. The product was extracted into ether (400 mL), washed sequentially with 2N NaOH (2 x 25 mL), 2N HCl (2 x 25 mL), and water (4 x 50 mL). The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield 18.9 g of the crude product. The product was purified by chromatography on a silica gel column (100 g) by elution (successively) with pet.ether (300 mL), 5% EtOAc-pet.ether (400 mL), and 10% EtOAc-pet.ether, to yield 7.5 g (32.5 mmol, 41.7%), of ketone III. Recrystallization from ethanol gave white needles, m.p. 107-108° (lit. trans:[4,6] 107-108°, 109°; cis.[5,6] 67-68°, 68-71°). ^{1}H-NMR ($CDCl_3$); δ 1.5-2.64 (methylene envelope integrating to 10 H), 2.7-2.9 (m, 2H, -C-H), 3.78

(s,3H,OCH_3), 6.64-6.76 (m, 2H, Ar), 7.17-7.26 (m, 1H, Ar); ^{13}C-NMR ($CDCl_3$): δ 211.8 ($\overset{*}{\underline{C}}$=O), 157.8 (Ar $\underline{C}$-OMe),137.8, 131.5 (fused Ar C), 126.89, 113.7, 111.9 (Ar $\underline{C}$-H), 55.1 ($\underline{CH_3}$O), 52.6 (-$\underline{C}$-C=O), 44.3 (-$\underline{CH}$-CH-C=O), 41.4 ($\underline{CH_2}$-CO), 30.5 (Ar$\underline{CH_2}$), 29.2, 26.2, 21.6 ($\underline{CH_2}$).

1-Keto-7-methoxy-2-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-^{13}C (IV).

Diisopropylamine (0.4 mL, 2.85 mmol) was added to a catalytic amount of triphenylmethane in dry THF (10 mL) contained in a nitrogen flushed 50 mL flask. The solution was cooled to -78° and MeLi (1.85 mmol, 1.9 mL of a 1.5 M soln) was added dropwise to the stirred solution. The temperature of the solution was increased (by removing the dry ice acetone trap) until a pink color was observed. Tricyclic ketone, III , (2 mmol, 0.47 g) in 10 mL of dry THF was added to the stirred solution which was cooled once again to -78°. The temperature of the reaction mixture was raised to room temperature and the solution stirred for 10 min. Methyl iodide (16 mmol, 1 mL) was then added and the solution stirred for 0.5 h. The resultant yellow solution was extracted into ether (50 mL), the extract washed sequentially with 5% HCl (2 x 15 mL) and H_2O (4 x 15 mL), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a white solid (0.55 g). The solid was recrystallized from ethanol to yield the epimeric product ketones, IV, (0.4 g, 88%). ^{1}H-NMR showed two doublets at δ1.03-1.26 for the methanol group α to the carbonyl. The m.p. of the epimeric mixture was 106-110°C (lit.[7,8] 118-119°). The epimeric compounds were chromatographed on a silica gel (100 g) column [eluted sequentially with petroleum ether, 5%, 10%, and 20% EtOAc-petroleum ether (150-300 mL each)] to yield 0.30 g (66%) of the α-product, m.p. 119-120°. ^{1}H-NMR ($CDCl_3$): δ 1.197-1.27 (d, 3H, $\underline{CH_3}$-CH), 1.5-3.0 (m, 11H, CH_2 and -C-H), 3.7 (s, 3H, OCH_3), 6.6-7.3 (m, 3H, Ar); ^{13}C-NMR ($CDCl_3$): δ 213.18 ($\overset{*}{\underline{C}}$=O), 157.92 ($\underline{C}$-$OCH_3$), 137.99, 131.59 (fused Ar), 126.99, 113.77, 112.12 (Ar $\underline{C}$), 55.30 (CH_3O), 47.87, 43.81, 43.51, 31.62, 29.43, 25.74, 21.90, 17.37 ($\underline{CH_3}$-C-H).

ACKNOWLEDGEMENT

This research was supported by PHS Grant Number CA 33591 awarded by the National Cancer Institute, DHHS and DOE Grant Number DE-FG05-86ER-60434.

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