HIGH SPECIFIC ACTIVITY TRITIATED PROSTAGLANDIN ANALOGS I: SYNTHESIS OF ENPROSTIL-[13, 14-^{3}H]*

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SUMMARY

Partial reduction of the acetylenic precursor 1 with carrier-free tritium gas in the presence of Lindlar catalyst gave the highly labelled *cis*-allylic alcohol 2. Tritium was thus contained in the metabolically stable 13,14-position of the lower side chain. Elaboration of 2 via a fourteen step, microscale sequence gave enprostil-[13,14-^{3}H] **19** having a specific activity of 41 Ci/mmol.

Key Words: Prostaglandins-[^{3}H], Enprostil-[^{3}H].

INTRODUCTION

Enprostil (1) is a highly active antisecretory prostaglandin (PG) analog. The development of this substance for the treatment of gastrointestinal ulcers in man required labelled material for use in absorption, distribution, metabolism, and excretion studies. High specific activity was essential because of the drug's potency, i.e., low administered dose, as well as for use in RIA analysis.

Although several thousand PG analogs have been synthesized (2), only a few of these have been prepared in isotopically labelled form. The specific activities of these labelled compounds have been uniformly low, generally being below 1 Ci/mmol (3). In fact, a survey of the literature did not reveal any products having a specific activity higher than 15 Ci/mmol (4,5), a very marginal value for use in RIA. The probable reason for the lack of high specific activity products is the complexity and multistep nature of PG chemistry. The present work describes a fifteen step,

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micro-scale synthesis (using carrier-free intermediates) in which Enprostil-[13,14-^{3}H] was obtained at 41 Ci/mmol.

DISCUSSION

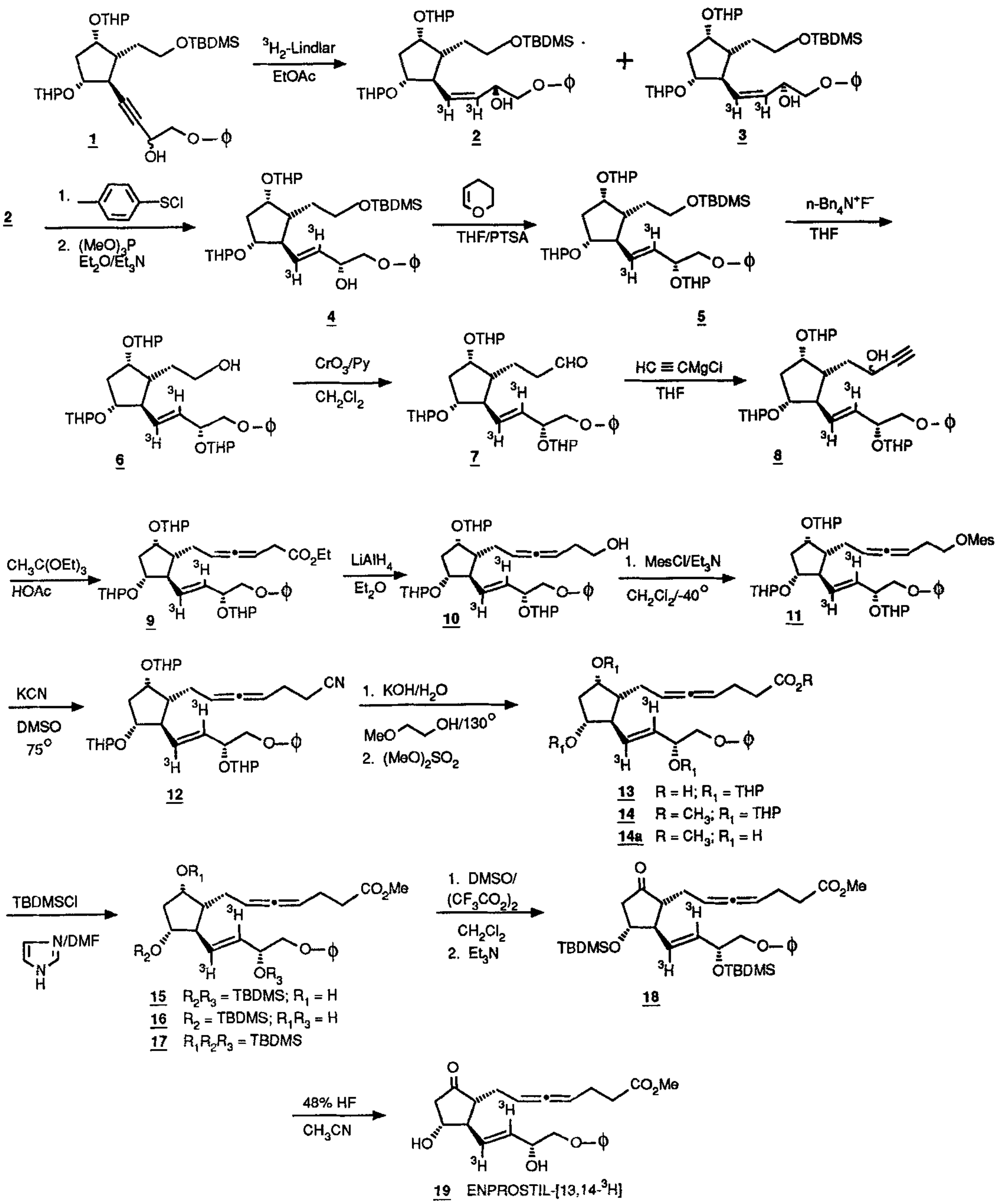
Our approach to the synthesis of **19** was based on the availability of the lower side chain acetylenic precursor **1** (6) which could be partially reduced to the 13,14-labelled olefin with high incorporation of tritium. The upper side chain could then be elaborated to produce **19**. Since the triple bond could not be selectively reduced in the presence of the upper side chain allene, it was necessary to introduce tritium in an early step in the reaction sequence. This did not prove to be a serious disadvantage since tritium gas is very inexpensive and rather large radiochemical quantities of reduction products can be generated for use in subsequent steps.

The entire reaction sequence is depicted in Scheme 1.

Reduction of **1** with carrier-free tritium gas in the presence of Lindlar catalyst gave a mixture consisting of starting material, and approximately equal amounts of the *cis*-15α-alcohol **3**, and the desired *cis*-15β-alcohol **2**. A total of 2.5 Ci of pure **2** was isolated by preparative HPLC.

The sulfenate-sulfoxide rearrangement, so elegantly developed by Evans (7), had been previously applied to the construction of PG lower side chains (8). We utilized this approach in the current synthesis to transform **2** to the required 13,14-*trans*-15α-alcohol **4**. Thus, treatment of **2** with p-tolylsulfenyl chloride followed by addition of trimethylphosphite as the thiophile, gave **4** as the exclusive product of rearrangement in 74% yield after purification. Protection of the 15-hydroxyl as the THP ether **5** was effected in 94% yield using dihydropyran/pTSA in THF. Since the final product and all the intermediates have only a weak chromophore in the phenyl group, it was decided to determine the specific activity of the tris-THP ether **5** by weight and radioassay. This intermediate was ideal for such a determination because of its high molecular weight and the fact that at this early stage of the synthesis a large amount of radiolabelled **5** was available. Thus, a solution of pure **5** was assayed and found to contain 1,480 mCi. Evaporation of the solvent left a residue weighing 24.3 mg (0.036 mmol). In this way the specific activity of this intermediate was determined to be 41.1 Ci/mmol. Since the lower side chain was not involved in any subsequent synthetic steps, it was assumed that the specific activity determined at this point would correspond

SCHEME 1: Synthesis of Tritiated Enprostil



to the specific activity of the final product. This assumption was actually verified (9) by comparison of a solution of **19** to a calibration curve developed by gas chromatography of a series of standard solutions of unlabelled **19**.

Having completed the construction of this suitably protected lower side chain intermediate we proceeded to elaborate the upper side chain according to methodology developed at Syntex (10).

Removal of the silyl protecting group with tetra-n-butylammonium fluoride followed by Collins oxidation (11) gave the upper side chain aldehyde 7 in 89% overall yield. Subsequent addition of acetylene magnesium chloride furnished the propargyl alcohol 8 in 91% yield. The specific activity was confirmed at this point when 910 mCi of 8 was found to weigh 12.6 mg (0.0222 mmol) again giving a calculated specific activity of 41 Ci/mmol.

Reaction of 8 with triethylorthoacetate and acetic acid at 120° effected the orthoester Claisen rearrangement (12,13), thereby homologating the upper side chain by two carbons and introducing the allene functionality to give the allenic ester 9. In order to prevent rearrangement of 9 to the corresponding conjugated diene ester it was necessary to promptly reduce crude 9 with $LiAlH_4$ to the stable allenic alcohol **10**. Conversion of 8 to **10** was accomplished in 84% yield. The alcohol **10** was homologated by mesylation followed by displacement with KCN to give the nitrile **12** having the correct number of upper side chain carbons. Aqueous workup followed by chromatographic purification afforded pure 12 in only 68% yield (from 10) although radiochromatography of the reaction mixture showed at least 90% conversion to the desired product. In subsequent work with a similar nitrile it was found that a modified workup, in which the crude reaction mixture was applied directly to a silica gel column and diluted with 50% ethyl acetate/hexane, furnished pure nitrile in 85% yield. Base hydrolysis of the nitrile in methoxyethanol followed by careful aqueous workup with dilute HCl at <5° gave a quantitative yield of the tris-THP protected 9, 11, 15-trihydroxycarboxylic acid 13. Attempts to prepare the corresponding methyl ester 14 by simple methylation with diazomethane failed although the same procedure was successfully implemented in cold trial reactions at the 20-50 mg level. No satisfactory explanation could be found for the failure of acid **13** to react with diazomethane on the microscale level in the hot reaction. Esterification attempts with a variety of reagents under different conditions gave unsatisfactory yields of **14**.

The problem was finally resolved by treatment of the crude nitrile hydrolysis mixture at 0° directly with an excess of dimethylsulfate. Stirring overnight at ambient temperature effected the desired esterification. Furthermore, the methylhydrogen sulfate produced as the by-product of esterification, caused the concomitant removal of the THP protecting groups to give the [13,14-^{3}H]trihydroxy ester 14 in 83% yield from 12 after purification.

Selective protection of the 11 and 15-hydroxyl groups was accomplished by treatment of 14a with t-butyldimethylsilyl chloride/imidazole in dichlomethane(14). The somewhat more hindered steric environment of the 9-hydroxyl group allowed for selective silylation of the 11 and 15-hydroxyls. The mixture of starting material 14a, mono 16, di 15 and tri 17 protected products obtained was easily separated chromatographically to furnish the desired product 15 in 65% yield. Recycling of isolated triol and mono protected products increased the yield of 15 to 86%.

Swern oxidation (15) of 15 gave the corresponding 9-ketone 18 in 82% yield. Removal of the TBDMS groups with aqueous HF in acetonitrile afforded Enprostil-[13,14-^{3}H] at 41 Ci/mmol in 83% yield and >99% purity after chromatographic purification. The overall yield for the fourteen step sequence from 2 was 15.6% which translates to an average yield of nearly 88% per step. Enprostil-[13,14-^{3}H] was stored in ethyl acetate solution at 5° and was stable for at least four months. The product could be readily repurified by Chromatotron chromatography as described in the experimental section.

The synthesis described herein demonstrates that a multistep process involving complex reactions and sensitive intermediates can be effectively implemented on a microscale level to afford high specific activity prostaglandins. Continued work in this area has led to the development of a general strategy for the synthesis of lower side chain labelled prostaglandins which can be obtained at specific activities in excess of 100 Ci/mmol. This latter approach will be described in a subsequent publication.

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EXPERIMENTAL

Carrier-free tritium gas was purchased in break-seal ampouls from New England Nuclear Corp., Boston, Mass. All standard reagents and solvents were used without purification. "Chromatotron" is a radial chromatography apparatus manufactured by Harrison Research, Palo Alto, CA. Radiochromatography was performed on either a Berthold Model or Bioscan Model 200 scanner. Radioassays were obtained using a Packard Model 4000 Liquid Scintillation Counter. Products were identified by chromatographic mobility compared to authentic standards. All intermediates which were purified by chromatography were >98% radiochemically pure. In the interest of consistency, the prostaglandin numbering system is used throughout to describe intermediates. Optimized reaction results are reported for each step.

6,9α,11α,15β-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,4,5-pentanor-13(c)-ene-[13,14-^{3}-H]-9,11-bis-tetrahydropyranyl ether-6-t-butyldimethylsilyl ether 2.

A side-arm septum flask was charged with Lindlar catalyst (60 mg), connected to a high vacuum line and evacuated overnight. The acetylenic precursor 1 (55 mg; 0.094 mmol) in 1.5 ml of EtOAc was injected through the rubber septum and the system was degassed. The reaction flask was immersed in liquid nitrogen and carrier-free tritium gas (15 Ci; 0.25 mmol) was transferred in by means of a Toepler pump. The nitrogen bath was removed and the reduction mixture was stirred overnight at ambient temperature. Excess gas and solvent were removed into a waste bulb by vacuum transfer. Methanol was added to the residue and the catalyst was filtered through a disposable teflon filter connected to the end of a 30 cc. plastic syringe. The filtrate was evaporated to dryness three times from methanol to remove labile radioactivity. The non-volatile residue contained 3,000 mCi. Purification by HPLC (10mm x 50cm column, 10μ SiO_2 eluted with 15% EtOAc-hexane, R.I. detection) afforded 825 mCi of pure 2.

p-Toluenesulfenyl Chloride.

Anhydrous pyridine (480 mg, 6.07 mmol) was added to p-tolyldisulfide (4.93 g, 20 mmol) in 10 ml of methylene chloride. After cooling to -5° a solution of sulfuryl chloride (1.59 ml, 2.67 g, 19.75 mmol) in 4 ml of methylene chloride was added slowly over 15 min. The reaction was stirred for 1.5 hrs. at ambient temperature and then was distilled. The fraction boiling at 75° was collected and used in the following step.

6,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,4,5-pentanor-13-(t)-ene-[13,14-^{3}H]-9,11-bis-tetrahydropyranyl-6-t-butyldimethylsilyl ether **4.**

A solution of 2 (820 mCi) was evaporated to dryness two times with toluene. The residue was dissolved in 15 ml of anhydrous ether containing 0.5 ml of triethylamine. After cooling to <5°, an excess of freshly prepared p-toluenesulfenyl chloride (333 μl) was added. The reaction was stirred at ambient temperature for 3 hrs. at which time TLC analysis (25% ETOAc-hexane) showed no remaining starting material. Trimethylphosphite(333 μl) was added and stirring was continued for 30 min. The solvent was evaporated and the residue was dissolved in 1 ml of EtOAc. Preparative TLC (25% EtOAc-hexane) afforded 610 mCi (74% yield) of pure 13-*trans*-15α-alcohol 4.

6,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,4,5-pentanor-13(t)-ene-[13,14-^{3}H]-9,11,15-tris-tetrahydropyranyl-6-t-butyldimethylsilyl ether **5.**

To a solution of 4 (1,570 mCi) in 10 ml THF was added 1 ml of freshly distilled dihydropyran and a trace of p-TSA. The reaction was stirred at ambient temperature overnight. Neutralization with 15 μl of triethylamine followed by preparative TLC (16% EtOAc-hexane) gave 5 (1,480 mCi) in 94% yield. The solvent was evaporated to leave 24.3 mg (0.036 mmol) of 5. The specific activity was thus determined to be 41.1 Ci/mmol.

6,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,4,5-pentanor-13(t)-ene-[13,14-^{3}H]-9,11,15-tris-tetrahydropyranyl ether **6.**

To a solution of 5 (1,400 mCi) in 10 ml THF was added 2 ml of a 1 M solution of tetra-n-butylammonium fluoride in THF. The reaction was stirred under nitrogen for 8 hrs. Aqueous workup afforded a quantitative yield of pure 6 (radio-TLC: 50% EtOAc-hexane).

9α,11α,15α-Trihydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,4,5-pentanor-13(t)-ene-[13,14-^{3}H]-6-carboxaldehyde-9,11,15-tris-tetrahydropyranyl ether 7.

Dry CrO_3 (200 mg) was ground to a powder under 10 ml of dry methylene chloride. After cooling the resulting suspension in an ice bath, pyridine (250 μl) was added and the reaction was stirred for

30-60 min. At this point 100 mg of celite (dried at 160° in a vacuum oven overnight) was added followed by a methylene chloride solution of 6 (1,400 mCi). After 5 min. the reaction mixture was poured directly onto a small SiO_2 column (a 10 ml disposable pipet filled to 5 ml mark with silica gel). Elution with 25 ml of methylene chloride gave pure aldehyde 7 (1, 010 mCi). Further elution with 10 ml of EtOAc furnished an additional 230 mCi of pure aldehyde (radio-TLC: 50% EtOAc-hexane). In this manner 7 was isolated in 89% yield.

4-Ethynyl-6,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1,2,3,-trinor-13(t)-ene-[13,14-^{3}H]-9,11,15-tris-tetrahydropyranyl ether **8.**

To 10 ml THF (freshly distilled from $LiAlH_4$) was added 4 ml of 2.86 M methylmagnesium chloride in THF. Acetylene was bubbled (via a sulfuric acid gas washing trap) into the reaction vessel for 3 hrs. No methylmagnesium chloride remained when an aliquat of the reaction solution was analyzed by gas chromatography as the cyclopentanone adduct.

A solution of 7 (1,000 mCi) in 10 ml of methylene chloride was cooled to <5° and treated with 2 ml of the acetylenemagnesium chloride solution prepared above. After 30 min. the reaction was quenched with aqueous ammonium chloride and the product was extracted with methylene chloride. Purification on the Chromatotron (1 mm rotor eluted with 30% EtOAc-hexane) afforded 910 mCi (91%) of pure propargyl alcohol **8**. The solvent was evaporated to leave a residue weighing 12.6 mg (0.022 mmol). The specific activity was thus determined to be 41 Ci/mmol.

9α,11α,15α-Trihydroxy-16-phenoxy-17,18,19,20-tetra-norprosta-1-nor-4,5,13(t)-triene--[13,14-^{3}H]-carboxylic acid ethyl ester 9,11,15-tris-tetrahydropyranyl ether **9**.

The propargyl alcohol **8** (910 mCi) was dissolved in 10 ml of triethylorthoacetate under a nitrogen atmosphere. Acetic acid (100 μl) was added and the reaction mixture was heated at 120° for 2 hrs. while a very gentle stream of nitrogen was bubbled under the surface to remove ethanol formed in the reaction. The reaction solution was evaporated to dryness two times from toluene and the crude residue (820 mCi; 90%) was used directly in the next step. The product was identified by radio-TLC (50% EtOAc-hexane).

2,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1-nor-4,5,13-(t)-triene-[13,14^{3}H]-9,11,15-tris-tetrahydropyranyl ether **10.**

A solution of the crude allene ester **9** (410 mCi) in ether was treated with $LiAlH_4$ (100 mg). Radio-TLC (50% EtOAc-hexane) showed complete reaction after 15 min. Excess $LiAlH_4$ was quenched by slow addition of 1 ml of acetone. Addition of aqueous sodium potassium tartrate gave a grey/white suspension of filterable aluminum salts. Aqueous workup of the filtrate gave the primary alcohol **10** (380 mCi; 93%).

2,9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-1-nor-4,5,13-(t)-triene-[13,14^{3}H]-2-methanesulfonyl acid ester 9,11,15-tris-tetrahydropyranyl ether **11.**

The crude alcohol **10** (310 mCi) was dissolved in 5 ml methylene chloride containing 100 μl of triethylamine, cooled to -40° in a bath of liquid nitrogen and methanesulfonyl chloride (25 μl) was added. After 1 hr. the reaction was judged to be complete by radio-TLC (50% EtOAc-hexane). Aqueous workup with cold saturated $NaHCO_3$ afforded a quantitative yield of **11**.

1-Cyano-9α,11α,15α-Tetrahydroxy-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13-(t)-triene-[13,14-^{3}H]-9,11,15-tris-tetrahydropyranyl ether **12.**

The crude mesylate **11** (280 mCi) was dissolved in DMSO (3.5 ml). Following addition of KCN (76 mg; 1 mmol), the reaction was flushed with nitrogen, and stirred for 1 hr. at 75°. Aqueous workup, including two back extractions of the aqueous phase, followed by preparative TLC (40% EtOAc-hexane) afforded 235 mCi (68%) of pure nitrile **12**.

9α,11α,15α-Trihydroxy-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13(t)-triene-[13,14^{3}H]-carboxylic acid methyl ester **14a.**

The nitrile **12** (165mCi) was dissolved in methoxyethanol (4 ml) and 20% aqueous KOH (200 μl) was added under nitrogen. The reaction was stirred for 64 hrs. at 130°. Radio-TLC (toluene-THF-methanol-acetic acid, 60:30:5:1) indicated that all of the radioactivity was associated with a single more polar spot. The reaction mixture was cooled to ambient temperature and stirred overnight with dimethylsulfate (250 µl; 2.6 mmol). The reaction was diluted with 10 ml of 1:1 EtOAc-hexane and stirred for 10 min. with 1:1 satd. $NaHCO_3$-water. The crude product was isolated by means of an aqueous workup, including two back extractions of the aqueous phase. Purification on a short SiO_2 column (10 ml disposable pipet filled to 8 ml with silica gel, 66% EtOAc-hexane) afforded the unprotected triol methylester **14a** (137 mCi) in 83% yield.

9α,11α,15α-Trihydroxy-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13(t)-triene-[13,14-^{3}H]-11,15-bis-t-butyldimethylsilyl ether carboxylic acid methyl ester **15**.

A silylating solution was prepared by mixing t-butyldimethylchlorosilane (90 mg; 0.59 mmol) in 1 ml of methylene chloride with a solution of imidazole (102 mg; 1.5 mmol) in 1.25 ml of the same solvent. After stirring at ambient temperature for 1 hr., 7.5 ml of hexane was added and stirring was continued for an additional hour. The precipitate which formed was allowed to settle and 5 ml of the supernatant was added to triol **14a** (166 mCi). The reaction was stirred at ambient temperature for 64 hrs. then applied directly to the Chromatotron (1 mm rotor; 10% EtOAc-hexane). A total of 94 mCi of pure 11,15-bis-TBDMS ether **15** was isolated along with 66 mCi of mixed fractions consisting of starting material and the 11-monosilyl derivative **16**. The mixed fractions were recycled with fresh silylating solution as described above to yield an additional 49 mCi **15**. Thus, a total of 143 mCi (86%) of pure **15** was isolated. In addition, 9,11,15-tris TBDMS ether **17**, isolated in the above reactions, was treated with 48% aqueous HF/acetonitrile) to yield 16 mCi of pure triol **14a**.

11α,15α-Dihydroxy-16-phenoxy-17,18,19,20-tetranor-9-oxoprosta-4,5,13(t)-triene-[13,14-^{3}H]-11,15-bis-t-butyldimethylsilyl ether carboxylic acid methyl ester **18**.

A solution of trifluoroacetic anhydride (1.06 ml; 7.5 mmol) in 3 ml of methylene chloride was added to a solution of DMSO (700 µl; 10 mmol) in 5 ml of the same solvent at -78°. A solution of the 9-alcohol **15** (45 mCi) in 2 ml of methylene chloride was added. After stirring for 1.5 hrs., 2 ml of triethylamine was added and the reaction was warmed to ambient temperature. Aqueous workup followed by purification on the Chromatotron (1 mm rotor, 5% EtOAc-hexane) gave 37 mCi of the pure 9-ketone **18** (82%).

<u>11α,15α-Dihydroxy-16-phenoxy-17,18,19,20-tetranor-9-oxoprosta-4,5,13,(t)-triene-[13,14-^{3}H]-carboxylic acid methyl ester (Enprostil-[13,14-^{3}H] **19**.</u>

A solution of **<u>18</u>** (84.4 mCi) in 7 ml of acetonitrile was treated with a solution of 48% aqueous HF (750 μl) in 3 ml of acetonitrile. The reaction was stirred for 20 hrs. at ambient temperature and diluted with EtOAc. Aqueous workup with $NaHCO_3$ to pH 7 followed by purification on the Chromatotron (1 mm rotor; 40-100% EtOAc-hexane gradient) afforded 69 mCi (83%) of pure Enprostil **<u>19</u>** having a specific activity of 41.1 Ci/mmol.

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