Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 9

SYNTHESIS OF [6-^{2}H] and [6-^{3}H]FECAPENTAENE-12

Mohamad Z. Kassaee and David G. I. Kingston

Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061, U.S.A.

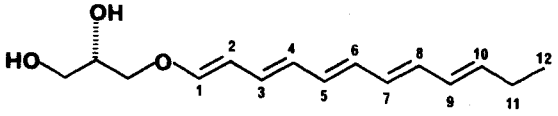
SUMMARY

The title compounds (**6** and **9**) were prepared by exchange of the α-protons of (E,E)-2,4,-heptadienyldiphenylphosphine oxide (**2**) with either ^2H_2O or ^3H_2O, followed by condensations with (E,E)-5-[2,3-bis(t-butyldimethylsilyl) oxy]-propoxy)-2,4-pentadienal (**4**) and deprotection.

Key Words: Fecapentaene-12, mutagen.

INTRODUCTION

The potent mutagen fecapentaene-12 was first isolated from human feces, and has been shown to have the structure **1** (1-3). It is a potential inducer of colon



1

cancer, and its occurrence has been correlated with populations at risk for this desease (4). Because of its possible biological importance, we have initiated a study of its interactions with DNA. As a part of this study we required a supply of radiolabeled fecapentaene-12; this paper describes the synthesis of both deuterium and tritium-labeled material.

0362-4803/87/091071-06$05.00

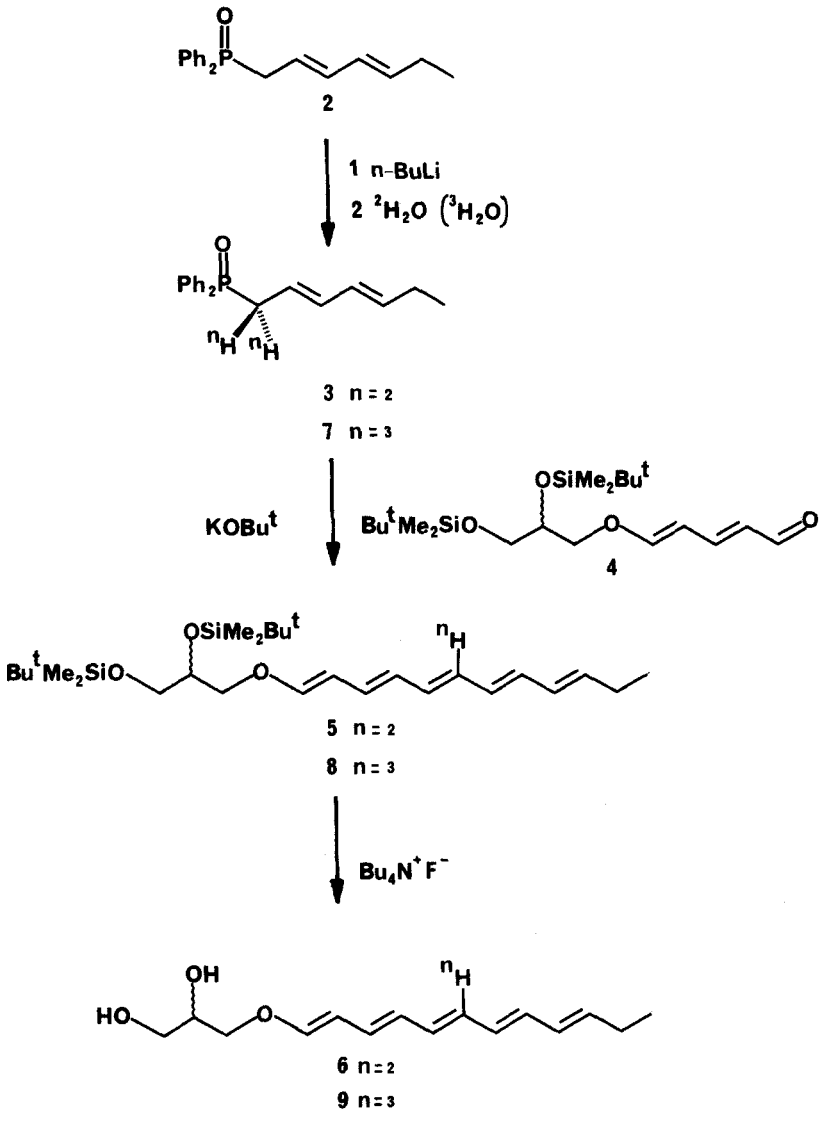
Received September 18, 1986

RESULTS AND DISCUSSION

[6-^{2}H]Fecapentaene-12 (**6**) was synthesized as shown in Scheme 1. (E,E)-2,4-heptadienyldiphenylphosphine oxide (**2**) was prepared as previously described (5,6), and was then converted into its [1-^{2}H] derivative (**3**) by treatment with slightly less than one equivalent of n-butyllithium followed by quenching with ^2H_2O. A ^{1}H-NMR spectrum of the isolated product showed that exchange had taken place exclusively at the 1-position, since only the resonance at 3.15 ppm decreased in area, and that slightly more than one equivalent of deuterium had been incorporated. The additional incorporation over the one equivalent of base used was presumably due to exchange promoted by $^2HO^-$ formed on quenching with ^2H_2O. Analysis by mass spectrometry was complicated by the presence of a moderate $(MH)^+$ ion in the spectrum of the unlabeled compound, but a comparison of the spectra of the labeled and unlabeled compounds suggested a composition of $^2H_0$:$^2H_1$:$^2H_2$ of 20: 51: 29, indicating an average ^{2}H content of 1.09 atoms/molecule. This result is consistent with the ^{1}H-NMR spectrum, which indicated an average ^{2}H content of 1.14 atoms/molecule.

Treatment of the labeled phosphine oxide **3** with the aldehyde **4** (7) in the presence of potassium t-butoxide resulted in both Horner-Wittig coupling and elimination of diphenylphosphinic acid to yield the ^{2}H-labeled protected fecapentaene-12 **5**, identical with unlabeled material as prepared previously by a slightly different route (8) except for slight differences in the intensity of the ^{1}H-NMR resonances around 6.2 ppm. We have found this direct coupling and elimination to be more convenient than carrying out the reaction in two separate steps as previously described (5,6).

Deprotection of the silylated compound **5** with fluoride ion yielded [6-^{2}H]-fecapentaene-12 (**6**) as the product in reasonable yield. The compound was obtained free of contaminating Z-isomers by careful washing with hexane and ether, and its ^{1}H-NMR spectrum was identical with that of pure all-E fecapentaene-12 (9,10), except for the intensity of the resonance at 6.2 ppm. Mass spectral analysis indicated a $^1H_1$: $^2H_1$ ratio of 65:35; this ratio is different from that in the precursor **3**, presumably due to hydrogen exchange



Scheme I

during the coupling step to produce 5.

Preparation of ^{3}H-labeled fecapentaene-12 was carried out by an analogous pathway. Exchange of phosphine oxide **2** with excess ^3H_2O yielded [1-$^3H_2$]-2,4-heptadienyldiphenylphosphine oxide **7**, with a specific activity of 0.41 mCi/mmole. Condensation of **7** with the aldehyde **4** gave the silylated derivative **8**, which was treated with fluoride ion to give [6-^{3}H]fecapentaene-12 (**9**), specific activity 0.24 mCi/mmole. The isolated material was identical by ^{1}H-NMR and UV spectroscopy

with unlabeled material (9, 10); the higher relative retention of ^{3}H in the coupling step may be attributed to the larger isotope effect associated with breaking C-^{3}H bonds.

EXPERIMENTAL

General experimental conditions were as previously described (7). $^{3}H_2O$ was purchased from New England Nuclear and had a nominal specific activity of 0.45 mCi/mole.

[1-^{2}H]-2,4-Heptadienyldiphenylphosphine oxide (3). 2,4-Heptadienyldiphenylphosphine oxide (5,6) (1.67g, 5.64 mmol) in dry THF (40 ml) was treated with n-butyllithium (2.03 ml of a 2.5M solution, 5.08 mmol) under argon at -78° over a period of 3 min, followed by stirring for 15 min. To the resulting deep red solution of the anion was added $^{2}H_2O$ (0.10 ml, 5.0 mmol) in one batch. The solution was then allowed to warm to room temperature, the THF evaporated, and the product treated with H_2O and CH_2Cl_2. The organic layer was separated, washed, and dried, and then filtered through a short column of silica gel to yield a pale yellow solution. Evaporation of this solution and washing with hexane yielded a white solid, m.p. 106-107°. ^{1}H-NMR ($C^{2}HCl_3$): δ 7.72 (4H,m), 7.47 (6H,m), 6.12-5.88 (2H,m), 5.66-5.42 (2H,m), 3.15 (0.8H, m, $\underline{CH_2}P$), 2.05 (2H, quintet, $\underline{CH_2}CH_3$), 0.98 (3H,t, $CH_2\underline{CH_3}$). MS(EI): m/z 298 (4), 297 (5), 296 (2), 202 (15), 201 (45), 147 (20), 131 (25), 86 (60), 84 (100), 77 (15).

3[[6-^{2}H]-1,3,5,7,9-Dodecapentaenyloxy]-1,2-propane diol di(t-butyldimethylsilyl) ether (5). The phosphine oxide 2 (1.1g, 3.7 mmol) was dissolved in dry THF (15 ml) and the solution added to potassium t-butoxide (1.25g, 10.2 mmol) in a flame-dried flask under an argon atomosphere at -15°. A solution of (E,E)-5-[2,3-bis[(t-butyldimethylsilyl)oxy] propoxy]-2,4-pentadienal (4) (7) (1.1g, 2.75 mmol) in THF (5 ml) was then added, and the mixture was stirred and allowed to warm to room temperature. A further 10 ml portion of THF was added to dissolve some precipitated solid. The reaction mixture was quenched after 40 min with H_2O (60

ml) and Et_2O (300 ml), and then transferred to a separatory funnel with the aid of a further 600 ml of Et_2O. The organic layer was separated after a thorough shaking, washed with brine (100 ml) and dried (K_2CO_3). Evaporation followed by flash chromatography (0.5% Et_2O in petroleum ether) yielded the product 5 as a pale yellow oil, yield 1.08g (2.25 mmol, 82% based on 4). ^{1}H-NMR (C^2HCl_3): δ 6.58 (^{1}H, two overlapping doublets with intensities approximately 1:3, J=12Hz, -OCH=) 6.29-6.01 (6-7H,m,-CH=), 5.79-5.54 (2H,m,-CH=), 3.88 (2H,m,-CH_2OC=), 3.68 (1H,m,-CHO-), 3.55 (2H,m,-CH_2O), 2.12 (2H, quintet,-$\underline{CH_2}$CH=), 0.90 (9H,s,$(CH_3)_3C$), 0.88 (9H,s,$(CH_3)_3C$), 0.02 (6H,s) 0.04 (6H,s). MS (FAB in glycerol): m/z 480 (33), 479 (80), 478 (100), 321 (52), 303 (100), 277 (90), 185 (20), 93 (48), 73 (100).

[6-^{2}H]Fecapentaene-12 (6). The silyl ether 5 (0.5g, 1.21 mmol) in 50 ml dry THF was treated under argon with tetrabutylammonium fluoride (Aldrich, 3.03 ml of 1M solution in THF, 3.03 mmol). The resulting mixture was stirred for 6hr at room temperature, and then treated with Et_2O (1000 ml) and H_2O (50 ml). The ether layer was separated, washed with brine (50 ml) and dried (K_2CO_3). Evaporation of the solvent yielded a brown solid which was washed with hexane (2 x 50 ml) and Et_2O (2 x 10 ml) to give a pale yellow solid. Yield 0.2g (0.8 mmol, 66%). ^{1}H-NMR ($C^2H_3SOC^2H_3$): δ 6.78 (1H,d,J=12Hz,-OCH=), 6.28-6.04 (6-7 H, m, -CH=), 5.74 (1H, dt,=$\underline{CH}CH_2CH_3$), 5.66 (1H,dd,$\underline{CH}$=CHO), 4.98 (1H,bd s,CHO$\underline{H}$), 4.72 (1H,bd s, $CH_2O\underline{H}$), 3.88-3.80 (1H,m,$\underline{H}$CHOC), 3.73-3.64 (2H,m,C$\underline{H}$OH, HC$\underline{H}$OC), 3.3 (H_2O peak and $\underline{CH_2}$OH), 2.12 (2H,dq, $\underline{CH_2}CH_3$), 0.96 (3H,t,CH_3). MS(EI): m/z 252 (18), 251 (75), 250 (100).

[1-^{3}H]-2,4-Heptadienyldiphenylphosphine oxide (7). The title compound was prepared from 2 (3g), by a method similar to that of its ^{2}H analog 3, but with excess ^3H_2O. The product was obtained in 95% chemical yield, m.p. 106-107°, and had a ^{1}H-NMR spectrum identical to that of unlabeled material. Specific activity = 0.415 mCi/mmol.

[6-^{3}H]-Fecapentaene-12 (9). Compound 9 was prepared by Horner-Wittig coupling of

the phosphine oxide **7** with the aldehyde **4** to give the pentaene **8**, followed by deprotection by fluoride ion to give the product **9**. These reactions were carried out exactly as described for the ^{2}H analogs. The isolated product **9** (0.52g) had a ^{1}H-NMR spectrum and UV-spectrum identical to that of unlabeled material. Specific activity = 0.244 mCi/mmol.

Acknowledgments Financial support of this work by the National Cancer Institute (Grant Number CA-23857) is gratefully acknowledged. We thank Dr. A. van der Gen for a ^{1}H-NMR spectrum of synthetic fecapentaene-12, and Mr. Clare Zaronsky for assistance in the preparation of compound **4**.

REFERENCES

1) Hirai, N., Kingston, D.G.I., Van Tassell, R.L. and Wilkins T.D. - J. Am. Chem. Soc. **104**: 6149 (1982).

2) Gupta, I., Baptista, J., Bruce, W.R., Che, C.T., Ferrer, R., Gingerich, J.S., Grey, A.A., Marai, L. and Yates, P. - Biochemistry **22**: 241 (1983).

3) Hirai, N., Kingston, D.G.I., Van Tassell, R. L. and Wilkins, T. D. - J. Nat. Prod. **48**: 622 (1985).

4) Ehrich, M.F., Aswell, J.E., Van Tassell, R.L., Wilkins, T.D., Walker, A.R.P. and Richardson, N.J. - Mutat.Res. **64**: 231 (1979).

5) Nicolaou, K.C., Zipkin, R. and Tanner, D. - J. Chem. Soc. Chem. Commun.: 349 (1984).

6) Zipkin, R. - Synthesis of Several Highly Unsaturated Natural Products, Ph.D. Thesis, Philadelphia, PA: University of Pennsylvania, 1984.

7) Govindan, S.V., Kingston, D.G.I., Gunatilaka, A.A.L., Van Tassell, R.L., Wilkins, T.D., de Wit, P.P., Van der Steeg, M. and Van der Gen, A. - J. Nat. Prod., submitted for publication.

8) Gunatilaka, A.A.L., Hirai, N. and Kingston, D.G.I. - Tetrahedron Lett. **24**: 5457 (1983).

9) de Wit, P.P., van der Steeg, M. and van der Gen, A. - Recl. Trav. Chim. Pays-Bas **104**: 307 (1985).

10) Pfaendler, H.R., Maier, F.K. and Klar, S. - J. Am. Chem. Soc. **108**: 1338 (1986).