Tetrahedron Vol. 42, No. 21, pp. 5849 to 5856, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

ALKYLATION REACTIONS OF PROPARGYL ALCOHOL; IMPROVED ROUTES TO PROSTAGLANDIN α-SIDE CHAIN PRECURSORS

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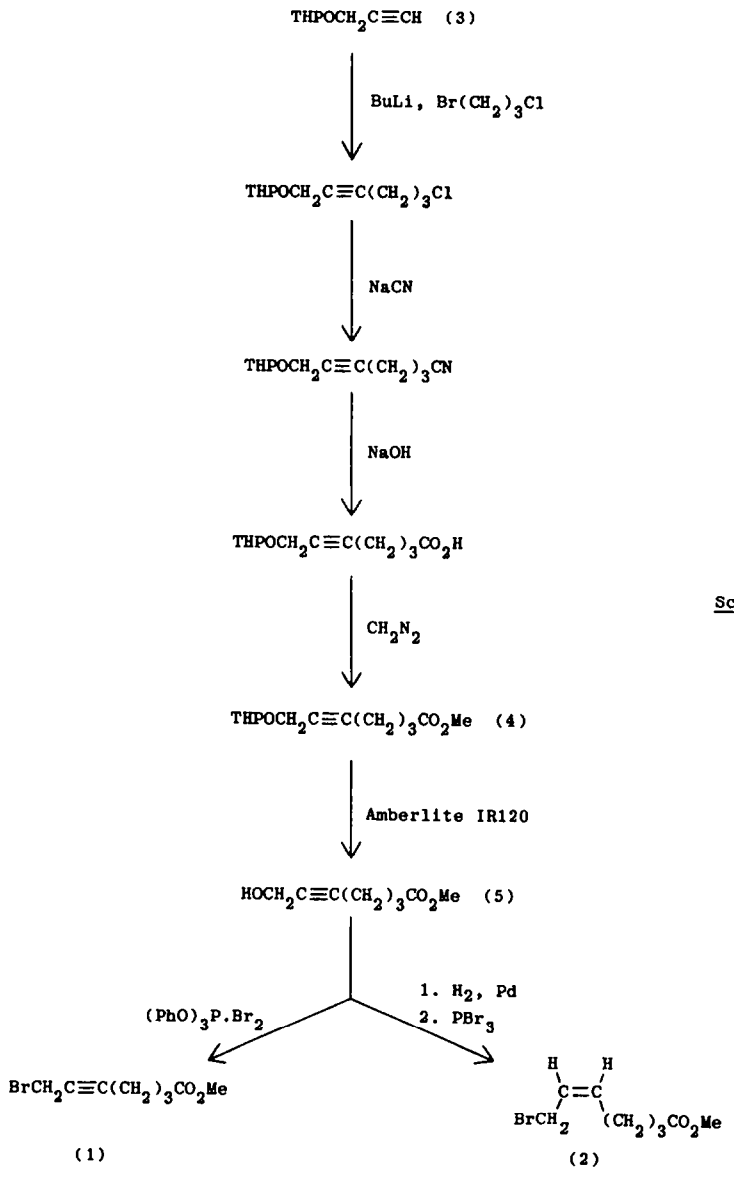
(*Received in USA* 17 *June* 1986)

Abstract - Alkylation reactions of the dilithio derivative of propargyl alcohol and the lithio derivative of tetrahydropyranyl protected propargyl alcohol have been explored in order to develop improved synthetic routes to the key prostaglandin α-side chain precursor methyl 7-hydroxyhept-5-ynoate (5). The use of methyl 4-bromobutanoate or the lithium salt of 4-bromobutanoic acid in these reactions did not produce the required products whereas alkylation using trimethyl ortho-4-bromobutanoate (15) gave methyl 7-hydroxyhept-5-ynoate (5) or the corresponding THP ether (4) in good yield after orthoester hydrolysis. Procedures are also described for the transformation of alcohol (5) and THP (4) into methyl 7-bromohept-5-ynoate (1). Alcohol (5) can also be converted into methyl (Z)-7-bromohept-5-enoate (2) using literature procedures.

A large number of different synthetic approaches to prostaglandins and prostaglandin analogues have now been developed.[1] In many of these approaches, particularly those based on three component coupling reactions,[2] the "top" (α-) prostaglandin side chain is introduced in its entirety via regiospecific cyclopentanone enolate alkylation using methyl 7-bromohept-5-ynoate (1),[2-7] methyl (Z)-7-bromohept-5-enoate (2)[2,8-11] or the corresponding iodides/ethyl esters. The first synthesis of alkyne (1) was reported in outline form by Corey and Sachdev (Scheme 1)[4] and subsequently the intermediate acetylenic alcohol (5) was employed to prepare the corresponding alkene (2).[8] Martel *et al* later used the same general approach to prepare alkene (2) as its ethyl ester and published full experimental details.[9]

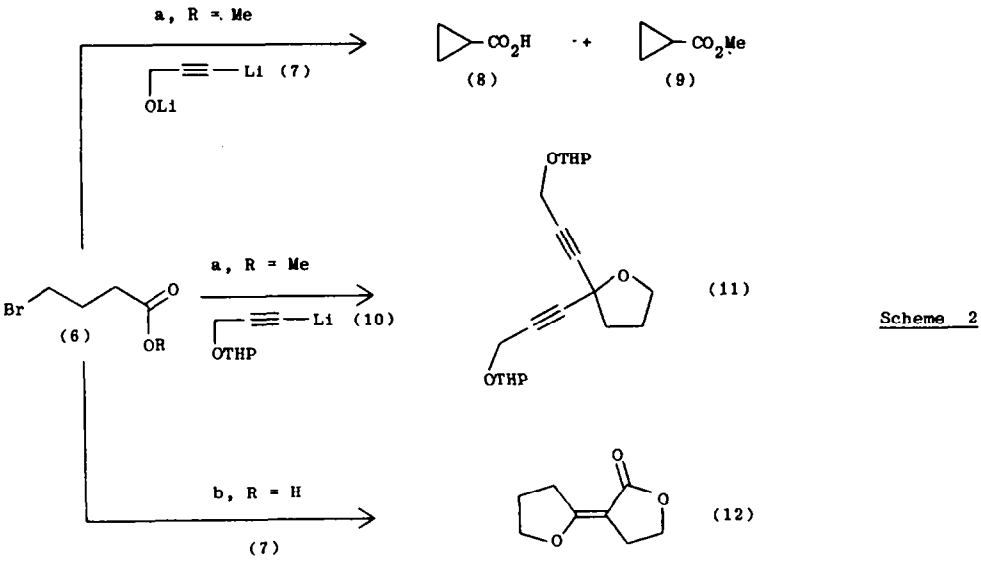
We required relatively large quantities of alkyne (1) and alkene (2) for the synthesis of prostacyclin[12] and thromboxane[13] analogues, respectively. We repeated the synthesis shown in Scheme 1[4] but found it to be time-consuming and relatively inefficient, even using recently introduced modifications.[7,9,10] We therefore turned our attention to the development of a new and improved synthesis of alkylating agents (1) and (2). The major drawback of the route in Scheme 1 is that the 4-carbon homologation of the protected propargyl alcohol (3) is achieved in two steps. Homologation by alkylating the anion of (3) with a 4-halobutanoic ester, for example, would produce the key intermediate (4) directly. Alternatively, the same alkylation using the dianion derived from propargyl alcohol[6] would give the corresponding alcohol (5) in one step. Other groups have also investigated the use of 4-carbon electrophiles in such reactions,[6,7] but have not been successful with 4-halobutanoates.



Scheme 1 [4,8,9]

We first examined the direct reaction between the dilithio derivative (7) of propargyl alcohol and bromoester (6a) as shown in Scheme 2. When this alkylation was attempted in liquid ammonia, the bromoester was consumed but the propargyl alcohol was recovered unchanged. Cyclopropane carboxylic acid (8) and the corresponding ester (9) were also isolated from this reaction. The use of a less polar solvent (THF) for the alkylation reaction still failed to produce the expected product (5) although in this case bromoester (6a) was recovered unchanged. The corresponding reaction of lithium acetylide (10) in THF produced an adduct which proved to be the double addition product (11). Clearly, selective halide displacement from bromoester (6a), as opposed to enolisation or addition to the ester, is not straightforward. Unsatisfactory results have also been obtained from similar alkylation reactions using 4-iodobutanoate esters.[7]

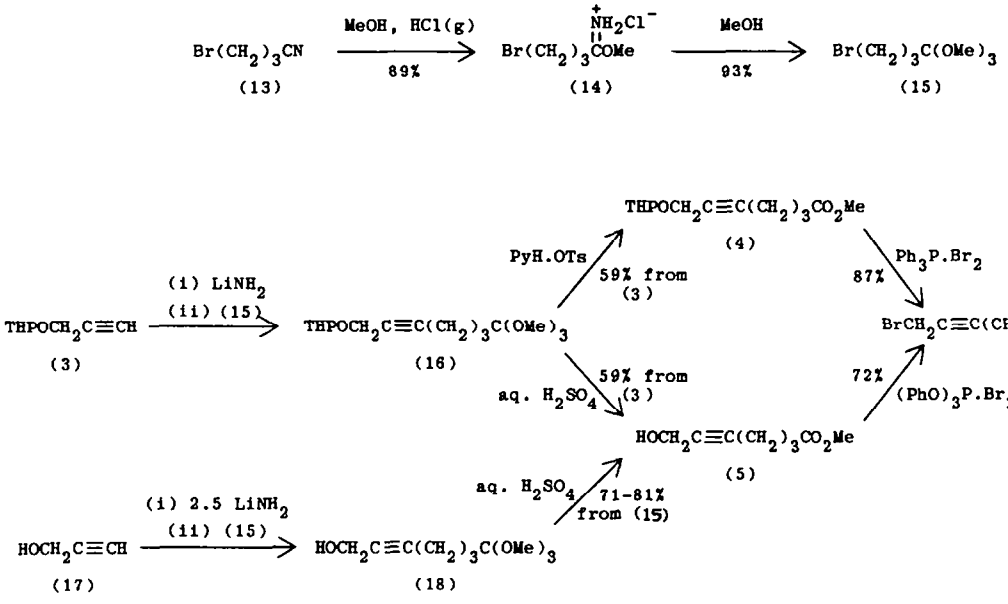
The alkylation of metal acetylides using ω-bromocarboxylic acids has been successful for the preparation of long chain acetylenic carboxylic acids.[14] The alkylation of dilithio derivative (7) with the lithium salt of 4-bromobutanoic acid (formed in situ) was therefore attempted (Scheme 2), although the feasibility of carrying out such a reaction has been questioned.[15] In the event a



Scheme 2

product was isolated with an empirical formula $C_8H_{10}O_3$ showing eight distinct resonances in its ^{13}C-n.m.r. spectrum. This compound proved to be the known[16] butyrolactone dimer (12).

These difficulties have now been overcome by the use of a protected 4-bromobutanoate in the alkylation reaction. Trimethyl ortho-4-bromobutanoate (15) was chosen and was prepared from 4-bromobutanenitrile (13) in 83% overall yield using the Pinner reaction (Scheme 3).[17] After this work had commenced, a related reaction involving the corresponding triethyl orthoester was reported.[18]



Scheme 3

Treatment of THP protected propargyl alcohol (3) with lithium amide in liquid ammonia, to generate acetylide (10), followed by alkylation with orthoester (15) and mild acid hydrolysis gave the required protected hydroxy-alkyne (4) in 59% overall yield. Alternatively, the use of aqueous sulphuric acid in the hydrolysis produced the hydroxy-alkyne (5) directly in 59% overall, distilled yield. A more efficient procedure involved the alkylation of the dilithio derivative (7) of propargyl alcohol and hydrolysis of the orthoester (18) in situ. Hydroxy alkyne (5) was produced in 81% overall yield by this route as a coloured, analytically pure oil. After Kugelrohr distillation, hydroxyalkyne (5) was obtained as a colourless oil in 71% overall yield. Treatment of alcohol (5) with bromine/triphenylphosphite[4] gave methyl 7-bromohept-5-ynoate (1) in good yield. Alternatively, the THP derivative (4) could be converted directly into bromide (1) using triphenylphosphine dibromide.[19]

Partial hydrogenation of alkyne (5) under standard conditions[8,9,10] followed by bromide formation using published[8-11] procedures gives bromoalkene (2) in good yield.

In summary, the use of ortho ester alkylating agent (15) provides an extremely efficient means of converting propargyl alcohol into methyl 7-hydroxyhept-5-ynoate (5). Alcohol (5) is easily transformed into the acetylenic bromide (1) and alkenyl bromide (2). Compounds (1), (2) and (5) can also be employed to prepare the corresponding iodides using literature [2,7,9,10,11] procedures.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Jeol PMX 60 spectrometer in $CDCl_3$ as solvent unless otherwise stated. I.r. spectra were obtained on a Perkin-Elmer 297 spectrophotometer. Petrol is the fraction b.p. 40-60°C, ether is diethyl ether. Ether and hexane were dried by distillation from sodium/benzoquinone, methanol by distillation from magnesium/iodine. Column chromatography was carried out using silica gel (Merck 7734).

Methyl 4-bromo-1-butanimidate hydrochloride (14)

Hydrogen chloride gas was bubbled through a solution of 4-bromobutanenitrile (ex Lancaster synthesis, 29.6 g, 0.20 mol) in dry ether (200 ml) containing dry methanol (7.69 g, 0.24 mol) at 5°C until 2.5 equivalents of HCl (18.2 g, 0.50 mol) had been absorbed. The reaction vessel was sealed, and left at -5°C (refrigerator) for 4 days. The precipitated salt was separated by filtration, washed thoroughly with dry ether (500 ml), and dried over solid potassium hydroxide in an evacuated dessicator to give the title hydrochloride (14) as fine white crystals (38.5 g, 89%), m.p. 96-7°C; $\nu_{max.}$ (nujol) 1650, 1405, 1215, 875 cm^{-1}; δ (TFA-d) 9.52 (2H, br.s), 4.32 (3H, s); 3.48 (2H, t, J 6Hz); 3.04 (2H, t, J 7Hz), 2.64-2.08 (2H, m); δ_C (TFA-d) 183.65, 60.77, 33.41, 30.82, 28.53. Found: C, 27.3; H, 5.2; N, 6.8. $C_5H_{11}BrNO$ requires C, 27.7; H, 5.1; N, 6.5%.

Trimethyl ortho-4-bromobutanoate (15)

A suspension of methyl 4-bromo-1-butanimidate hydrochloride (14) (37.9 g, 0.175 mol) in dry methanol (16.8 g, 0.525 mol) and dry hexane (450 ml) was stirred at room temperature for 48 h under nitrogen, then filtered to remove precipated ammonium chloride. The filtrate was evaporated to leave a colourless liquid to which was added anhydrous potassium carbonate (0.25 g); distillation under reduced pressure afforded the title orthoester (15) as a colourless oil (36.9 g,

93%), b.p. 70°C/0.7 mm Hg, $\nu_{max.}$ (thin film) 2840, 1740, 1070 cm^{-1}; δ 3.60-3.33 (2H, m), 3.23 (9H, s), 2.03-1.77 (4H, m); δ_C 115.31, 49.38, 33.88, 29.00, 26.54; m/z 195, 197 (M^+-MeOH). Found: C, 37.4; H, 6.7; Br, 35.1. $C_7H_{15}O_3Br$ requires C, 37.0; H, 6.7; Br 35.2%.

Methyl 7-hydroxyhept-5-ynoate (5)

(a) From Propargyl alcohol (preferred procedure)

Anhydrous ammonia (500 ml) was condensed into a 1L 3-necked flask fitted with a dry-ice condenser, at -33°C under nitrogen. Lithium wire (ca. 0.1 g) was added in small portions until a permanent blue colour was observed. Ferric nitrate (ca. 0.05 g) was added to discharge the blue colour, and after stirring for 5 min, further lithium metal (2.85 g, 0.409 mol) was added portionwise. Stirring was continued for 20 min to obtain a grey suspension of lithium amide (0.409 mol) to which was added dropwise a solution of redistilled propargyl alcohol (9.17 g, 0.1635 mol) in dry ether (10 ml). After stirring for 20 min, a solution of trimethyl ortho-4-bromobutanoate (15) (24.8 g, 0.109 mol) in dry ether (25 ml) was added dropwise. Stirring was continued at -33°C for 3 h and then the mixture was allowed to warm to room temperature overnight (ca 16 h). The mixture was heated at 50°C under a stream of nitrogen for 2 h to remove any remaining ammonia. The resultant grey solid was cooled to 0°C, and dilute sulphuric acid (5%; 400 ml) added portionwise until pH1 was obtained. The mixture was stirred at room temperature for 30 min and then extracted with ether (3 x 200 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (200 ml), dried ($MgSO_4$), and concentrated in vacuo to leave an amber oil (pure by microanalysis, TLC and ^1H NMR; 13.8 g, 81%). Bulb-to-bulb distillation gave methyl 7-hydroxyhept-5-ynoate (5) as a colourless, analytically pure oil (12.05 g, 71%), b.p. 150°C/0.05 mm Hg; R_f 0.15 (CH_2Cl_2); $\nu_{max.}$ (thin film) 3420, 1735, 1015 cm^{-1}; δ 4.30-4.12 (2H, m); 3.67 (3H, s); 3.24 (1H,s); 2.63-1.63 (6H, m). Found: C, 61.5; H, 7.9. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%.

(b) via Tetrahydropyranyloxyprop-2-yne (3)

A solution of the title compound (3) (10.2 g, 0.0727 mol) in ether (10 ml) was added in one portion to a stirred suspension of lithium amide (0.0727 mol) in liquid ammonia (200 ml), prepared as described in (a), at -33°C. After stirring for a further 1 h, a solution of orthoester (15) (15 g, 0.0661 mol) in ether (10 ml) was added and the mixture was stirred at -33°C overnight (ca. 15 h). The remaining ammonia was removed on a water bath at 60°C, distilled water (200 ml) added and the mixture extracted with ether (2 x 300 ml). The combined extracts were washed with brine, dried (K_2CO_3) and concentrated in vacuo to give alkylated orthoester (18) as a yellow oil (19.7 g). The crude orthoester (18) (8 g) was dissolved in a mixture of methanol (150 ml) and water (10 ml) and conc. sulphuric acid (3 ml) added. After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo and water (100 ml) added. Ether extraction (2 x 100 ml), drying ($MgSO_4$) followed by removal of the solvent in vacuo and Kugelrohr distillation gave methyl 7-hydroxyhept-5-ynoate (5) [2.705 g, 59% based on THP (3)] identical to the product from procedure (a).

Methyl 7-tetrahydropyranyloxyhept-5-ynoate (4)

Crude ortho ester (18) (3 g), prepared as described in the preceding section (procedure (b)), was dissolved in a mixture of methanol (60 ml) and water (5 ml) containing pyridinium tosylate (0.2 g) and the mixture stirrred at 60°C for 5 h and then at room temperature overnight. The methanol was removed in vacuo, water added and the product extracted into ether (2 x 100 ml). The combined extracts

were dried ($MgSO_4$), concentrated in vacuo, and the resulting oil chromatographed on silica gel (CH_2Cl_2). Kugelrohr distillation of the product gave the title compound (4) as a colourless oil (1.59 g, 59% based on THP (3)), b.p. 165°C/0.3 mm Hg; $\nu_{max.}$ (thin film) 2300, 2250, 1730 cm^{-1}; δ 4.90-4.75 (1H, m), 4.25 (2H, m), 3.67 (3H, s), 4.00-3.40 (2H, m), 2.60-2.10 (4H, m), 2.05-1.40 (8H, m). This compound was identical to an authentic[4] sample.

Methyl 7-bromohept-5-ynoate (1)

(a) From alcohol (5)[4]

Bromine (15.50 g, 0.098 mol) and then pyridine (7.25 g; 0.09 mol) were added to a stirred solution of triphenylphosphite (30.68 g, 0.10 mol) in dry THF (170 ml) under nitrogen at 0°C. Methyl 7-hydroxyhept-5-ynoate (5) (15.00 g, 0.10 mol) was then added slowly over 1h at 0°C.The reaction was then stirred at room temperature for 2 h, filtered and the solvent removed from the filtrate in vacuo. Water (50 ml) was added and the mixture extracted with ether (2 x 100 ml). The combined extracts were dried ($MgSO_4$), the solvent removed in vacuo and the residue distilled to give methyl 7-bromohept-5-ynoate (1) as a colourless oil (15.33 g, 72%) b.p. 90-94°C/1.0 mm Hg; R_f 0.6 (petrol-ether, 2:1) $\nu_{max.}$ (thin film) 2300, 2240, 1740 cm^{-1}; δ 3.85 (2H, t, J 2Hz), 3.60 (3H, s), 2.60-2.10 (4H, m), 2.00-1.50 (2H, m) which was identical to an authentic[4] sample.

(b) From THP derivative (4)

A stirred solution of triphenylphosphine (16.80 g, 0.064 mol) in dichloromethane (50 ml) was cooled to 0°C and treated with a solution of bromine (11.23 g, 0.07 mol) in dichloromethane (20 ml). After 30 min, a solution of methyl 7-tetrahydropyranyloxyhept-5-ynoate (4) (10.00 g, 0.042 mol) in dichloromethane (20 ml) was added to the triphenylphosphine dibromide and the reaction was stirred at room temperature for 12 h. Petrol (50 ml) was added to the mixture and the solvent reduced to a third of its volume in vacuo. The residue was diluted with petrol (50 ml) and filtered through a silica gel pad which was then washed with ether. Removal of the solvent from the filtrate under reduced pressure followed by chromatography on silica using petrol-ether (20:1) as eluant gave bromide (1) as a colourless oil (8.0 g, 87%) identical to the compound obtained in procedure (a).

Attempted alkylation of propargyl alcohol dianion (7) with methyl 4-bromobutanoate (6a)

Ammonia (125 ml) was distilled from sodium/ferric nitrate into a flask fitted with a dry-ice condenser and charged with lithium amide (2.7 g, 0.118 mol). Propargyl alcohol (2.8 g, 0.05 mol) was added in ether (12 ml). After stirring for 1 h, methyl 4-bromobutanoate (6a) (9.05 g, 0.05 mol) was added in ether (24 ml). After 4 h under reflux, the ammonia was allowed to evaporate overnight to leave a brick-red solid. Addition of ice and water gave a red solution which was extracted with ether (4 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to leave a red oil (1.07 g) which was distilled (80-90°C, 60 mm Hg, Kugelrohr) to afford a 2:1 mixture of propargyl alcohol and cyclopropanecarboxylic acid methyl ester (9); δ_C 176.1, 52.0, 12.9, 8.6 [lit.[20] 175.2, 51.5, 12.7, 8.3 ppm]. The aqueous fraction was acidified (Congo red) by addition of hydrochloric acid and then extracted with ethyl acetate (4 x 30 ml). Cyclopropanecarboxylic acid (b.p. 60°C, 3 x 10^{-2} mm Hg, Kugelrohr) was obtained from this fraction (0.88 g, 20%); δ 11.75 (1H, m), 1.60 (1H, m), 1.06 (2H, m), 0.95 (2H, m) ppm [lit.[21] (CCl_4, 11.85 (1H, m), 1.58 (1H, m), 1.06 (2H, m), 0.97 (2H, m)].

The attempted alkylation was repeated using THF as solvent. Butyl lithium in hexane (1.62 M, 18 ml, 0.03 mol) was added to a solution of triphenylmethane (indicator) in THF (20 ml). The dark red solution was cooled to 0°C and propargyl alcohol (0.9 ml, 0.016 mol) was added from a syringe until the colour was discharged. The resulting solution was transferred into a solution of methyl 4-bromobutanoate (6a) (2.75 g , 0.015 mol) in THF (50 ml) at 0°C. After 1 h, iced water was added and the solution was extracted with ether. Methyl 4-bromobutanoate (6a) (1.7 g, 61% recovery), identical with starting material, was obtained by distillation (40°C, 10^{-3} mm Hg, Kugelrohr).

Alkylation of 3-tetrahydropyranyloxyprop-1-yne (3) with methyl 4-bromobutanoate (6a)

A solution of butyl lithium in hexane (1.62 M, 5 ml, 8.1 mmol) was added to a solution of 3-tetrahydropyranyloxyprop-1-yne (3) (1.13 g, 8.1 mmol) in THF (50 ml). After 10 min, methyl 4-bromobutanoate (1.47 g, 8.1 mmol) was added in THF (5 ml). The solution was stirred at room temperature for 2 h and then heated a reflux for 20 h. Addition of water and extraction with petrol gave an oil that was distilled (150°C, 10^{-3} mm Hg, Kugelrohr) to afford 2,2-bis(3'-tetrahydropyanyloxyprop-1'-ynyl)tetrahydrofuran (11), [0.9 g, 64% based on (3)]; m/z (chemical ionisation using ammonia) 366 ($M^+ + NH_4$, 19%); m/z 209 (209.1180; $M^+ - C_8H_{11}O_2$ requires 209.1178, 3%); $\nu_{max.}$ (liquid film) 2940, 2870, 1202, 1120, 1025, cm^{-1}; δ 4.80 (2H, m), 4.29 (4H, s), 3.98 (2H, t, J 6.5 Hz), 3.84 (2H, m), 3.45 (2H, m), 2.32 (2H, m), 2.08 (2H, m) 1.90-1.40 (12H, m) ppm; δ_C 96.7 (d, J 164 Hz), 84.7 (s), 79.5 (s), 69.8 (s), 68.9 (t, J 146 Hz), 61.7 (t, J 143 Hz), 54.1 (t, J 148 Hz C3'), 42.2 (t, J 138 Hz), 30.1 (t, J 129 Hz) 25.3 (t, J 126 Hz and t, J 129 Hz), 19.0 (t, J 130 Hz) ppm.

Attempted alkylation of propargyl alcohol dianion (7) with 4-bromobutanoate (6b)

Ammonia (125 ml) was distilled from sodium/ferric nitrate into a flask fitted with a dry-ice condenser and charged with lithium amide (4 g, 0.174 mol). Propargyl alcohol (2.8 g, 0.05 mol) was added in ether (12 ml). After stirring for 2 h, 4-bromobutanoate (6b) (8.35 g, 0.05 mol) was added in ether (24 ml). After stirring for a further 4 h the solution became pale green. The ammonia was allowed to evaporate over night to leave a yellow solid. Ice and water were added and the resulting solution was acidified (Congo red) and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and evaporated to afford the crude product (5.22 g) as a golden oil. Distillation (140°C/10^{-3} mm Hg, Kugelrohr) gave a white solid which was identified as dibutyrolactone (12)[16] (2.65 g, 34%), m.p. 82-84°C [lit.[16] m.p. 86.5°C] which gave spectroscopic/analytical data entirely consistent with the assigned structure.

Acknowledgements

G.R.S. thanks the Royal Society for a 1983 University Research Fellowship and Prof. L.N. Mander for provision of laboratory facilities at the Research School of Chemistry, Australian National University, where part of this work was performed. We are grateful to the S.E.R.C. for studentships (G.C., M.F. and K.A.R.), to Fisons Pharmaceutical Divison and Searle Research and Development for C.A.S.E. support. We would also like to thank Dr. S.C. Burford (Fisons) and Dr. J. Saunders (Searle) for their interest and support and Dr. J.W. Patterson (Syntex Research, California) for helpful experimental advice.

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