Palladium-catalysed Spirocyclisation of 3-Acetoxy-1-(4-aminoalkyl)-cyclohexenes

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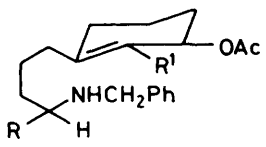
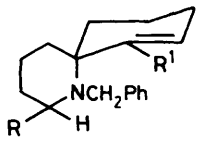
The 2,7-disubstituted 1-azaspiro[5.5]undecene (**2**; R = pentyl, R^1 = Bu) cannot be obtained by Pd^0-catalysed cyclisation of the cyclohexenyl acetate (**1**; R = pentyl, R^1 = Bu), but the monosubstituted derivative (**2**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$) is readily obtained from (**1**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$).

In earlier work[1] Pd^0-catalysed cyclisation of 3-acetoxy-1-(4-aminoalkyl)cyclohexenes [*e.g.* (**1**; R = H, R^1 = Bu)] was shown to provide a convenient route to 1-azaspiro[5.5]-undecenes [*e.g.* (**2**; R = H, R^1 = Bu)] and this reaction formed the basis of a synthesis of depentylperhydrohistrionicotoxin (**3**; R = H, R^1 = Bu).[2] It seemed of interest to determine whether the same sequence could be used to prepare perhydro-histrionicotoxin itself (**3**; R = pentyl, R^1 = Bu) from the appropriate precursor (**1**; R = pentyl, R^1 = Bu), thus circumventing the troublesome introduction of the pentyl substituent into the preformed spirocyclic nucleus in some syntheses of the alkaloid.[3] In the event we have been unable to effect the cyclisation of (**1**; R = pentyl, R^1 = Bu).



(**1**)



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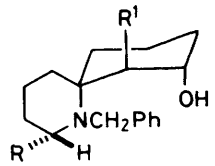

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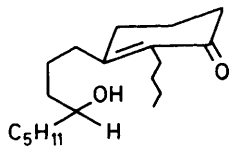

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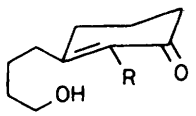

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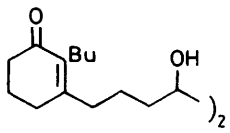


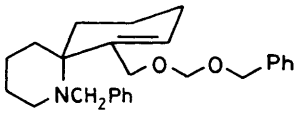
(**6**)

The amine (**1**; R = pentyl, R^1 = Bu) was obtained from the alcohol (**4**) by the sequence of reactions employed in the synthesis of depentylperhydrohistrionicotoxin,[2] namely, conversion into the toluene-*p*-sulphonate, reduction of the carbonyl group with sodium borohydride and cerium chloride,[4] acetylation of the resulting alcohol, and final displacement of the sulphonyloxy group by reaction with benzylamine in the presence of sodium iodide. Preparation of the alcohol (**4**) caused some problems. It was initially attempted by reaction of the Normant–Grignard reagent[5] from 1-chlorononan-4-ol with 2-butyl-3-ethoxycyclohex-2-enone, but this reaction was very capricious and frequently failed completely. The difficulty appears to lie in the formation of the Grignard reagent; 2-pentyltetrahydrofuran was isolated from the reaction mixtures in considerable amounts, formed presumably by intramolecular cyclisation of the alkoxide before formation of the Grignard reagent could take place. Attempts to overcome this difficulty by using tetrahydropyranyl or trimethylsilyl derivatives of the chlorononanol instead of the alcohol itself were frustrated by our inability to obtain a Grignard reagent from either derivative under a wide variety of conditions.[6]

The required alcohol (**4**) was eventually obtained from our previously prepared[2] alcohol (**5**; R = Bu) by Swern oxidation and reaction of the resulting aldehyde with tri-isopropoxy-(pentyl)titanium.[7] Reaction took place selectively at the aldehyde group to give the desired alcohol (**4**) in 59% yield. An unexpected by-product of this reaction, when conducted at temperatures above *ca.* −78 °C, was the pinacol (**6**) formed possibly by the action of low-valent titanium species in the reaction mixture.[8] Its structure is supported by its ^1H and ^{13}C n.m.r. and mass spectra and by cleavage with periodate to regenerate the keto aldehyde.

Attempted Pd^0-catalysed cyclisation of the amine (**1**; R = pentyl, R^1 = Bu) under conditions which were successful with the depentyl compound gave virtually no reaction. More forcing conditions (150 °C, methyl cyanide, sealed tube) led to a complex mixture of alkenic products from which no pure constituent could be isolated. No acetate-methyl or -carbonyl signals were present in the ^1H or ^{13}C n.m.r. spectra of the product, suggesting that the π-allylpalladium complex might have been formed to some extent; presumably subsequent attack by the amine leading to cyclisation was hindered by the steric effect of the butyl and pentyl substituents, allowing other faster reactions to intervene. It seems clear from this result that Pd^0-catalysed cyclisation of 3-acetoxy-1-(4-aminoalkyl)cyclohexenes is not suitable for the preparation of disubstituted 1-azaspiro[5.5]undecenes bearing alkyl substituents at C-2 and C-7.

However, we have successfully used the reaction to prepare the monosubstituted spirocycle (**7**), which we envisaged might be a useful intermediate for the synthesis of the histrionicotoxin analogue (**8**) by way of the free alcohol (**2**; R = H, R^1 = CH_2OH)[9] or the derived aldehyde.[10] The required 4-amino-alkylcyclohexenyl acetate (**1**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$) was prepared from the cyclohexenone (**10**), which was itself obtained from 2,6-dimethoxy-1,4-dihydrobenzoic acid, prepared by Birch reduction of 2,6-dimethoxybenzoic acid by modification of the published procedure.[11] Reduction of the carboxy group with lithium aluminium hydride and alkylation of the primary alcohol with benzyloxymethyl chloride gave the ether (**9**; R = $CH_2OCH_2OCH_2Ph$) which was converted into the enone (**10**) by treatment with toluene-*p*-sulphonic acid in ethanol.[12] The corresponding benzyl and dimethyl-t-butylsilyl



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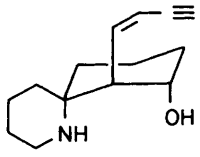

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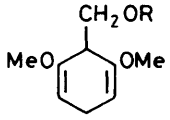
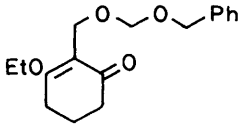


(9)



(10)

ethers (**9**; R = CH_2Ph and Bu^tMe_2Si) were both unsuitable; the benzyl ether gave an inseparable mixture on treatment with toluene-*p*-sulphonic acid in ethanol and the dimethyl-t-butylsilyl ether did not give the desired product.

Reaction of the cyclohexenone (**10**) with the Grignard reagent prepared from 1-chloro-4-(dimethyl-t-butylsilyloxy)butane afforded the dimethyl-t-butylsilyl ether of the alcohol (**5**; R = $CH_2OCH_2OCH_2Ph$) in 44% yield. Reduction of the carbonyl group with sodium borohydride and cerium chloride,[4] acetylation, cleavage of the silyl protecting group with tetrabutylammonium fluoride, and reaction of the derived toluene-*p*-sulphonate with benzylamine in the presence of sodium iodide led in good yield to the amine (**1**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$). This compound cyclised smoothly when heated with tetrakis(triphenylphosphine)palladium in acetonitrile to give the spirocycle (**2**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$) in 46% yield. Its structure is fully supported by the ^1H and ^{13}C n.m.r. spectra and the high resolution mass spectrum. As in the ^1H n.m.r. spectrum of (**2**; R = H, R^1 = Bu)[2] the signals due to the *N*-benzylic methylene group appear as a well-resolved quartet.

Preliminary attempts to hydroborate the spirocycle (**2**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$) with a view to preparing the alcohol (**3**; R = H, R^1 = $CH_2OCH_2OCH_2Ph$) have been unsuccessful. No reaction occurred with borane in tetrahydrofuran at room temperature, and at the boiling point an intractable mixture of products was obtained.

Experimental

^1H N.m.r. spectra (100 MHz) were determined using a JEOL JNM-MH 100 CW instrument, and 250 MHz ^1H and 62.9 MHz ^{13}C n.m.r. spectra with a Bruker AM250 instrument. Short column chromatography[13] and 'dry column flash' chromatography[14] used Merck Kieselgel 60H (Merck No. 7736) and flash chromatography[15] used Camlab Kieselgel 60, 230—400 mesh. Unless otherwise stated high resolution accurate mass spectra were determined at the Physico-Chemical Measurements Unit, Harwell or the S.E.R.C. Mass Spectroscopy Centre, University College, Swansea.

2-Butyl-3-(4-oxobutyl)cyclohex-2-enone.—Dimethyl sulphoxide (392 μl, 5.57 mmol) was added to a stirred solution of oxalyl chloride (445 μl, 5.12 mmol) in tetrahydrofuran (13 ml) under nitrogen at −78 °C. The resulting solution was warmed to −50 °C for 30 min, cooled again to −78 °C, and a solution of 2-butyl-3-(4-hydroxybutyl)cyclohex-2-enone[2] (1.04 g, 4.64 mmol) in tetrahydrofuran (6 ml) was added. After 2 h at −50 to 60 °C, triethylamine (3.22 ml, 23.2 mmol) was added and the reaction mixture allowed to rise to room temperature and stirred for 1 h more. The recovered product was purified by flash chromatography [eluant: ethyl acetate–light petroleum (1:3)] and gave the aldehyde as a pale yellow oil (0.86 g, 83.5%); δ_H(250 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 6.77 Hz, $MeCH_2$), 1.26—1.31 (4 H, m, 2-CH_2), 1.78—1.95 (4 H, m, 2-CH_2), 2.23—2.40 (8 H, m, 4-CH_2), 2.52 (2 H, dt, J_t 7.1 J_d 1.3 Hz, CH_2CH_2CHO), and 9.05 (1 H, t, *J* 1.3 Hz, CH_2CHO); δ_C(62.9 MHz; $CDCl_3$), 13.97 (Me), 20.27, 22.59, 22.98, 24.97, 30.46, 31.99, 34.05, 38.13, 43.55 (9-CH_2), 136.48, 156.88 (2-CH), 198.91 (C=O), and 201.33 (CHO); $\nu_{max.}$(film) 1 719, 1 658, and 1 616 cm^{-1} (Found: M^+, 222.1624. $C_{14}H_{22}O_2$ requires *M*, 222.1618).

2-Butyl-3-(4-hydroxynonyl)cyclohex-2-enone (**4**).—A solution of pentylmagnesium bromide in tetrahydrofuran (0.811 mol l^{-1}; 25 ml, 20.3 mmol) was added to a stirred solution of chlorotriisopropoxytitanium (4.85 ml, 20.3 mmol) in tetrahydrofuran,[9] (40 ml) at −30 °C under nitrogen. After 1 h at −10 °C the orange solution was cooled to −78 °C and a solution of the above aldehyde (3.76 g, 16.9 mmol) in tetrahydrofuran (10 ml), was added. The reaction mixture was maintained at −78 °C for 5 h and at room temperature for 13 h, poured into ice-cold saturated aqueous ammonium chloride (100 ml) and the product was recovered with ether. Purification by flash chromatography (eluant: chloroform) afforded the title compound as a pale yellow oil (2.92 g, 58.7%) with spectroscopic properties in excellent agreement with those of material prepared in poorer yield by reaction of the Normant-Grignard reagent from 1-chlorononan-4-ol with 2-butyl-3-ethoxycyclohex-2-enone by Dr. V. C. M. Garvin in this Department and by another published route,[16] δ_H(250 MHz; $CDCl_3$) 0.90 (6 H, 2 overlapping t, 2-$MeCH_2$), 1.23—1.58 (17 H, m, 8-CH_2 + OH), 1.88—1.96 (2 H, 2 overlapping t, CH_2), 2.24—2.39 (8 H, m, 4-CH_2), and 3.62 (1 H, br m, $CHOH$); $\nu_{max.}$(film) 3 421, 1 653, and 1 617 cm^{-1} (Found: M^+, 294.8. $C_{19}H_{34}O_2$ requires *M*, 294.5).

In some experiments carried out at −10 or −30 °C the pinacol (**6**) was isolated in variable amounts by further elution of the flash chromatography column with chloroform. It formed a glass [Found: (M^+ + 1), 447.6. $C_{28}H_{16}O_4$ requires *M*, 446.7]; $\nu_{max.}$(film) 3 412, 1 656, and 1 612 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 0.89 (6 H, t, *J* 6.8 Hz, 2-$MeCH_2$), 1.21—1.96 (21 H, m, 10-CH_2 + OH), 2.22—2.39 (16 H, m, 8-CH_2), 2.54 (1 H, br s, OH), 3.44 (1 H, br s, $CHOH$), and 3.63 (br s, 1 H, $CHOH$). Signals at δ 3.44 and 3.63 sharpened on addition of D_2O and appear to be unresolved triplets; δ_C(62.9 MHz; $CDCl_3$), 14.02 (Me), 22.60, 22.97, 24.19, 24.58, 24.92, 30.58, 30.61, 31.65, 31.96, 33.84, 34.87, 34.94, 38.12 (13-CH_2), 74.19, 74.52 (2-CH), 135.92, 135.94, 158.56, 158.61 (4 alkenic C), and 199.37 (C=O).

3-Acetoxy-2-butyl-1-(4-p-tolylsulphonyloxynonyl)cyclohex-1-ene.—Sodium borohydride (0.124 g, 3.26 mmol) was added in small portions to a stirred solution of the toluene-*p*-sulphonate of the above alcohol (1.01 g, 2.25 mmol) in methanol (6 ml) containing cerium(III) chloride[4] (0.4 mol l^{-1}) so that the temperature of the solution was maintained below 35 °C. After the addition was complete, the reaction mixture was kept at room temperature for 0.5 h and was then diluted with ether (50 ml) and filtered. The cyclohexenol was recovered as an oil (0.98 g, 97%).

This unstable alcohol (2.57 g, 5.7 mmol) was converted directly into the acetate with acetic anhydride (1.74 g, 17.1 mmol) and 4-dimethylaminopyridine (0.26 g, 2.11 mmol) at room temperature during 18 h. The recovered acetate was purified by flash chromatography [eluant: ethyl acetate–light petroleum (1:9)] and was obtained as an oil (2.16 g, 76.9%); $\nu_{max.}$(film) 1 736 and 1 652 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 0.86 (6 H, 2 overlapping t, 2-$MeCH_2$), 1.17—2.05 (29 H, m, with s at δ 2.05, 13-CH_2 + $MeCO_2$), 2.44 (3 H, s, ArMe), 4.57 [1 H, m,

$CH_2CH(OTs)CH_2$], 5.26 (1 H, br s, CHOCOMe), 7.30—7.81 (4 H, q, ArH); δ_C(62.9 MHz; $CDCl_3$) 13.89, 14.01 (2-Me), 18.5 (CH_2), 21.47, 21.61 (2-Me), 22.44, 23.00, 23.41, 23.44, 24.44, 29.22, 29.32, 29.67, 31.32, 31.34, 31.50, 32.99 (2 signals), 34.17, 34.22, 34.35 (16-CH_2), 70.23 ($MeCO_2CH$), 84.32, 84.37 (2-CH), 127.84 (CH), 129.56 (C, C=C), 129.75 (CH), 135.10, 137.50, 144.44 (3-C), and 171.15 (C=O) [Found: (M^+ − $MeCO_2H$), 432.71. $C_{28}H_{44}O_5S$ requires M, 492.71; $C_{26}H_{40}O_3S$ requires M, 432.66]. (We thank Dr. R. A. W. Johnstone, University of Liverpool, for this and the following determination).

3-*Acetoxy*-1-(4-*benzylaminononyl*)-2-*butylcyclohexene* (**1**; R = pentyl, R = Bu).—To a stirred solution of the above toluene-*p*-sulphonate (0.48 g, 0.97 mmol) in dimethyl sulphoxide (6 ml) under nitrogen, was added benzylamine (0.52 g, 4.72 mmol) and sodium iodide (0.24 g, 1.60 mmol). The mixture was stored in the dark for 7 days, then diluted with ether, and washed with brine. The recovered product was purified by flash chromatography (eluant: chloroform) to give the required amine as a pale yellow oil (0.27 g, 65%); δ_H(250 MHz; $CDCl_3$) 0.89 (6 H, 2 overlapping t, 2-$MeCH_2$), 1.28—2.09 (30 H, m, 13-CH_2, N*H*, and $MeCO_2$ at 2.05), 2.58 (1 H, m), 3.78 (2 H, s, NCH_2Ph), 5.30 (1 H, br s, C*H*OAc), and 7.24—7.34 (5 H, m); δ_C(62.9 MHz; $CDCl_3$), 14.01, 14.05 (2-Me), 18.53 (CH_2), 21.47 ($MeCO_2$), 22.68, 23.01, 24.29, 24.34, 25.34, 25.38, 29.25, 29.51, 29.70, 31.35, 32.15, 33.57, 33.78 (2 signals), 33.87 (14-CH_2), 51.07 (NCH_2Ph), 56.76 [$CH_2CH(NCH_2Ph)CH_2$] 70.30 (*C*HOAc), 127.02, 128.33, 128.44 (3-CH), 129.08, 138.10 (2-C, alkene), and 171.07 (C=O) [Found: (M^+ + 1), 428.27 (f.a.b.). $C_{28}H_{45}NO_2$ requires M, 427.34; $C_{28}H_{46}NO_2$ requires M, 428.35].

1,4-*Dihydro*-2,6-*dimethoxybenzoic Acid*.—Small freshly cut pieces of sodium were added to a stirred solution of 2,6-dimethoxybenzoic acid (1 g, 5.48 mmol) in methanol (10 ml) and liquid ammonia (30 ml) at −78 °C until the solid dissolved and the blue colour of the solution persisted for 10 min between additions. Solid ammonium chloride (2.9 g) was then added at 78 °C with vigorous stirring. After the ammonia had evaporated the residue was dissolved in water (5 ml), and the cooled (0 °C) solution was acidified to pH 3, the temperature being kept below 5 °C. The suspension was extracted into dichloromethane and the recovered product was crystallised from ethanol–light petroleum (b.p. 40—60 °C), to give the acid as colourless crystals (0.41 g, 41%), m.p. 126—128 °C (lit.,[17] m.p. 129.5 °C); $\nu_{max.}$(Nujol) 3 600—2 200, 1 704, 1 689, and 1 661 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 2.95 (2 H, m), 3.60 (6 H, s), 3.90 (1 H, t, J 3.3 Hz), 4.90 (2 H, t, J 3.5 Hz), and 8.65 (1 H, br s, exchangeable with D_2O) (Found: M^+, 184. $C_9H_{12}O_4$ requires M, 184).

1-*Benzyloxymethoxymethyl*-1,4-*dihydro*-2,6-*dimethoxybenzene* (**9**; R = CH_2OCH_2Ph).—A solution of the above 1,4-dihydro-2,6-dimethoxybenzoic acid (86.3 mg, 0.47 mmol) in tetrahydrofuran (5 ml) was added dropwise to a slurry of lithium aluminium hydride (60.5 mg, 1.59 mmol) in tetrahydrofuran (7 ml) at room temperature under nitrogen. After 30 min the reaction was quenched with ethyl acetate (10 ml) and water (2 ml) and the product was recovered as an oil (71.5 mg, 89%); $\nu_{max.}$(film) 3 691, 3 438, 1 686, and 1 657 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.03 (1 H, br s, OH), 2.80—2.88 (2 H, m), 3.58 (6 H, s), 3.55—3.62 (1 H, t), 3.83 (2 H, d, J 3.9 Hz), and 4.82 (2 H, t, J 3.6 Hz) (Found: M^+, 170.2. $C_9H_{14}O_3$ requires M, 170.2).

This alcohol was converted directly into the benzyloxymethyl derivative by addition of ethyl(di-isopropyl)amine (7.61 g, 58.90 mmol) and benzyloxymethyl chloride (7.38 g, 47.12 mmol) to a solution of the alcohol (4.01 g, 23.56 mmol) in dichloromethane (50 ml) at room temperature under nitrogen. After 4 h the title compound was obtained as an oil (6.24 g, 91%) after flash chromatography [eluant: light petroleum–ethyl acetate (9:1)]; δ_H(250 MHz; $CDCl_3$) 2.80—2.99 (3 H, m, 4-H_2 and 1-H), 3.56 (6 H, s, 2-MeO), 3.94 (2 H, d, J 2.6 Hz, OCH_2CH), 4.53 (2 H, s, $PhCH_2O$), 4.71 (2 H, s, OCH_2O), 4.75—4.88 (2 H, m, 3- and 5-H), and 7.25—7.39 (5 H, m) [Found: (M^+ − $PhCH_2OH$) 182. $C_{17}H_{22}O_4$ (M − C_7H_8) requires 182]. The compound decomposed rapidly at room temperature and a satisfactory elemental analysis could not be obtained.

The corresponding diphenyl-t-butylsilyl ether was obtained from the alcohol (2.0 g, 11.75 mmol), diphenyl-t-butylsilyl chloride (3.37 ml, 12.92 mmol) and imidazole (1.75 g, 25.8 mmol) in dichloromethane (30 ml) at reflux under nitrogen. It formed colourless platelets from aqueous ethanol, m.p. 83—84 °C (Found: C, 73.55; H, 7.9. $C_{25}H_{32}O_3Si$ requires C, 73.49; H, 7.89%).

2-*Benzyloxymethoxymethyl*-3-*ethoxycyclohex*-2-*enone* (**10**).—To a stirred solution of the above benzyloxymethyl ether (0.31 g, 1.06 mmol) in ethanol at room temperature (3 ml) was added toluene-*p*-sulphonic acid (2 mg). After 1 h the reaction mixture was diluted with ether and washed with saturated aqueous sodium hydrogen carbonate. Dry column flash chromatography of the recovered product [eluant: chloroform–methanol (9:1)] gave the cyclohexenone as a pale yellow oil (0.28 g, 91%); $\nu_{max.}$(film) 1 640 and 1 601 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.34 (3 H, t, J 7.0 Hz, $MeCH_2O$), 2.01 (2 H, m, 5-H_2), 2.37 (2 H, unresolved t), 2.60 (2 H, t, J 6.2 Hz), 4.11 (2 H, q, J 7.0 Hz, OCH_2Me), 4.42 (2 H, s, $PhCH_2OCH_2OCH_2$), 4.65 (2 H, s, $PhCH_2O$), 4.81 (2 H, s, OCH_2O), and 7.26—7.42 (5 H m); δ_C(62.9 MHz; $CDCl_3$) 15.20 (Me), 20.68, 25.92, 36.25 (3-CH_2), 57.78 ($CH_2OCH_2OCH_2Ph$), 64.15 (OCH_2Me), 68.90 ($PhCH_2O$), 94.62 (OCH_2O), 116.20 (C), 127.5, 127.99, 128.33 (3 phenyl, CH), 138.33 (phenyl C), 175.33 (C-3), and 197.38 (C=O) (Found: M^+, 290.1527. $C_{17}H_{22}O_4$ requires M, 290.1516).

2-*Benzyloxymethoxymethyl*-3-(4-*dimethyl*-t-*butylsilyloxybutyl*)*cyclohex*-2-*enone*.—A solution of the preceding cyclohexenone (1.69 g, 5.81 mmol) in tetrahydrofuran (5 ml) was added dropwise to a solution of the Grignard reagent at −78 °C, prepared from magnesium powder (0.19 g, 7.75 mmol) and 1-chloro-4-dimethyl-t-butylsilyloxybutane (1.44 g, 6.46 mmol) in tetrahydrofuran (16 ml) at reflux for 15 h. The solution was kept at −78 °C for 3 h and at room temperature overnight. Saturated aqueous ammonium chloride was added and the recovered product purified by short column chromatography [eluant: light petroleum–ethyl acetate (17:3)] furnished the title compound as an oil (1.14 g, 45%); $\nu_{max.}$(film) 3 090, 2 860, 1 673, and 1 640 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 0.04 (6 H, s, 2-SiMe), 0.89 (s, 3-Me, Bu^t), 1.55—1.65 (4 H, m, 2-CH_2), 1.91—2.02 (2 H, 2 overlapping t,), 2.37—2.46 (6 H, m, 3-CH_2), 3.61 (2 H, t, J 5.7 Hz, $SiOCH_2CH_2$), 4.37 (2 H, s, $PhCH_2OCH_2OCH_2$), 4.64 (2 H, s, $PhCH_2O$), 4.79 (2 H, s, $PhCH_2OCH_2O$), and 7.26—7.42 (5 H, m); δ_C(62.9 MHz; $CDCl_3$) 5.28 (Me), 18.32 (Bu^t), 22.27, 24.60 (2-CH_2), 25.97 (Me), 30.73, 32.87, 34.76, 37.72 (4-CH_2), 59.72 ($PhCH_2OCH_2OCH_2$), 62.63 ($SiOCH_2$), 69.39 ($PhCH_2O$), 94.66 ($PhCH_2OCH_2O$), 127.60, 127.93, 128.38 (phenyl 3-CH), 131.95 (C-2), 138.12 (phenyl C), 164.99 (C-3), and 198.01 (C=O) [Found: (M^+ + 1), 433.2779. $C_{25}H_{40}O_4Si$ requires M, 432.2696].

3-*Acetoxy*-1-(4-*dimethyl*-t-*butylsilyloxybutyl*)-2-(*benzyloxymethoxymethyl*)*cyclohex*-1-*ene*.—The foregoing cyclohexenone (1.92 g) was reduced to the cyclohexenol with sodium borohydride and cerium(III) chloride as described above for another case, and was obtained as an oil (1.87 g, 97%). It was converted directly into the title compound by reaction with acetic anhydride and pyridine in the presence of 4-dimethylaminopyridine as in the experiment described previously. The acetate was obtained as an oil (1.58 g, 74% for the two steps);

$\nu_{max.}$(film) 2 930, 2 854, and 1 729 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 0.04 (6 H, s, 2-MeSi), 0.89 (9 H, s, 3-Me), 1.43—1.86 (8 H, m, 4-CH_2), 2.02 (3 H, s, $MeCO_2$), 2.04—2.19 (4 H, m, 2-CH_2), 3.60 (2 H, t, *J* 6.0 Hz, $SiOCH_2$), 3.93, 3.97, 4.21, 4.26 (2 H, AB system, *J* 11.0 Hz, $PhCH_2OCH_2OCH_2$), 4.55, 4.60, 4.61, and 4.66 (2 H, AB system, *J* 11.8 Hz, $PhCH_2O$), 4.71, 4.73, 4.74, and 4.77 (2 H, AB system, *J* 6.8 Hz, $PhCH_2OCH_2O$), 5.50 (1 H, br s), and 7.26—7.36 (5 H, m); δ_C(62.9 MHz; $CDCl_3$) −5.25 (MeSi), 18.13 (CH_2), 18.35 (CMe_3), 21.40 ($MeCO_2$), 24.94 (CH_2), 26.01 (3-CMe_3), 28.82, 29.90, 32.93, and 33.25 (4-CH_2), 62.98 ($SiOCH_2$), 64.48 (CH_2), 68.74 (CH), 69.37 ($PhCH_2O$), 94.20 (CH_2), 125.89 (C), 127.71, 127.91, and 128.49 (3-CH), 138.15 (C), 144.71 (C), and 170.92 ($MeCO_2$) [Found: ($M^+ + NH_4$), 494.3306. $C_{27}H_{44}O_5Si$ requires *M*, 476.2958; $C_{27}H_{48}O_5NSi$ ($M^+ + NH_4$) requires *M*, 494.3302].

3-*Acetoxy*-1-(*benzyloxymethoxymethyl*)-2-(4-*hydroxybutyl*)*cyclohex*-1-*ene*.—The above dimethyl-t-butylsilyl ether (1.55 g, 3.26 mmol) in THF (10 ml) was converted into the free alcohol with tetrabutylammonium fluoride in THF (1.0 mol l^{-1}; 9.77 ml) at room temperature for 30 min. After having been purified by short column chromatography [eluant: light petroleum–ethyl acetate (3:2)] it was obtained as an oil (1.05 g, 89%); $\nu_{max.}$(film) 3 439, 2 935, 2 867, and 1 733 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.43—1.87 (9 H, m, 4-CH_2 + OH), 2.02 (3 H, s, $MeCO_2$), 2.04—2.18 (4 H, m, 2-CH_2), 3.59 (2 H, t, *J* 6.1 Hz, CH_2CH_2OH), 3.93, 3.98, 4.22, and 4.26 (2 H, AB system, *J* 11.1 Hz, $PhCH_2OCH_2OCH_2$), 4.55, 4.60, 4.61, and 4.66 (2 H, AB system, *J* 11.8 Hz, $PhCH_2O$), 4.70, 4.73, 4.73, 4.76 (2 H, AB system, *J* 6.8 Hz, $PhCH_2OCH_2O$), 5.49 (1 H, br s, CH at C-3), and 7.27—7.35 (5 H, m) [Found: M^+, 362.2337 ($M^+ + NH_4 - H_2O$) requires 362.2331].

The corresponding toluene-*p*-sulphonate was prepared from the alcohol (1.0 g, 2.75 mmol) and toluene-*p*-sulphonyl chloride (0.79 g, 5.5 mmol) and pyridine (445 μl, 5.5 mmol) in chloroform (2.7 ml) at 0 °C for 3 h. It was purified by short column chromatography [eluant: light petroleum–ethyl acetate (3:1)] and was obtained as an oil (1.23 g, 87%); δ_H(250 MHz; $CDCl_3$) 1.43—2.00 (8 H, m, 4-CH_2), 2.02 (3 H, s, $MeCO_2$), 2.04—2.12 (4 H, m, 2-CH_2), 2.43 (3 H, s), 3.89, 3.93, 4.14, and 4.19 (2 H, AB system, *J* 11.1 Hz, $PhCH_2OCH_2OCH_2$), 4.01 (2 H, t, *J* 6.2 Hz, CH_2CH_2OTs), 4.53, 4.57, 4.59, and 4.64 (2 H, AB system, *J* 11.9 Hz, $PhCH_2O$), 4.68, 4.70, 4.71, and 4.74 (2 H, AB system, *J* 6.8 Hz, $PhCH_2OCH_2O$), 5.47 (1 H, br s, 3-H), and 7.26—7.79 (9 H, m, ArH); δ_C(62.9 MHz; $CDCl_3$), 18.05 (CH_2), 21.39 ($MeCO_2$), 21.62 (Ar*Me*), 24.44, 28.74, 28.89, 29.70, and 32.74 (5-CH_2), 64.32 ($PhCH_2OCH_2OCH_2$), 68.58 (C-3), 69.39 ($PhCH_2O$), 70.31 (CH_2OTs), 94.15 ($PhCH_2OCH_2O$), 126.45 (C), 127.74, 127.86, 127.98, 128.51, and 129.93 (5-CH), 133.51, 138.11, 143.82, and 144.79 (4-C), and 170.90 ($MeCO_2$) [Found: M^+, 534.2528. $C_{28}H_{40}NO_7S$ requires ($M^+ + NH_4$) 534.2525].

3-*Acetoxy*-1-(4-*benzylaminobutyl*)-2-(*benzyloxymethoxymethyl*)*cyclohex*-1-*ene* (**1**; R = H, $R^1 = CH_2OCH_2OCH_2Ph$).—Benzylamine (0.61 g, 5.71 mmol) and sodium iodide (10 mg) were added to a solution of the above toluene-*p*-sulphonate (1.18 g, 2.28 mmol) in dimethyl sulphoxide (7 ml) under nitrogen. After 14 h the mixture was diluted with ether and the recovered product purified by flash chromatography [eluant: chloroform–methanol (19:1)], to give the amine as a pale yellow oil (0.83 g, 81%); δ_H(250 MHz; $CDCl_3$) 1.42—1.86 (8 H, m, 4-CH_2), 2.01 (3 H, s, $MeCO_2$), 2.03—2.17 (4 H, m, 2-CH_2), 2.61 (2 H, t, *J* 6.7 Hz, CH_2CH_2N), 3.76 (2 H, s, $PhCH_2N$), 3.92, 3.96, 4.20, and 4.24 (2 H, AB system, *J* 11.1 Hz, $PhCH_2OCH_2OCH_2$), 4.54, 4.59, 4.60, 4.64 (2 H, AB system, *J* 11.9 Hz, $PhCH_2O$), 4.69, 4.72, 4.73, and 4.75 (2 H, AB system, *J* 6.8 Hz, $PhCH_2OCH_2O$), 5.49 (1 H, br s, 3-H), and 7.21—7.34 (10 H, m); δ_C(62.9 MHz; $CDCl_3$), 18.09 (CH_2), 21.40 ($MeCO_2$), 26.48, 28.76, 29.84, 30.07, and 33.40 (5-CH_2), 49.26 (CH_2NHCH_2Ph), 54.06 ($PhCH_2N$), 64.39, $PhCH_2OCH_2OCH_2$), 68.64 (CH, C-3), 69.30 ($PhCH_2O$), 94.09 ($PhCH_2OCH_2O$), 125.79 (C), 126.93, 127.63, 127.80, 128.12, and 128.40 (6-CH), 138.03, 140.44, and 144.55 (3-C), and 170.82 ($MeCO_2$) [Found: ($M^+ + 1$), 452.2804. $C_{28}H_{37}NO_4$ requires *M*, 451.2800].

1-*Benzyl*-7-(*benzyloxymethoxymethyl*)-1-*azaspiro*[5.5]*undec*-7-*ene* (**2**; R = H, $R^1 = CH_2OCH_2OCH_2Ph$).—A stirred solution of the foregoing benzylamine (0.25 g, 0.55 mmol), triethylamine (153 μl, 1.10 mmol) and tetrakis(triphenylphosphine)palladium(0) (74 mg) in acetonitrile (10 ml) was refluxed under argon for 48 h. The cherry red solution was evaporated under reduced pressure, and the residue was dissolved in chloroform (50 ml) and filtered through silica gel 60H to remove salts. Short-column chromatography of the concentrated filtrate [eluant: light petroleum–chloroform (1:1)] afforded the spiro compound as a pale yellow oil (99 mg, 46%); δ_H(250 MHz; $CDCl_3$) 1.51—1.76 (9 H, m, 4-CH_2 and 1 H of CH_2), 2.02—2.06 (3 H, m, CH_2 and 1 H of CH_2), 2.27—2.29 (m, 1 H of CH_2), 2.52—2.57 (1 H, of CH_2), 3.14, 3.19, 3.79, and 3.85 (2 H, AB system, *J* 14.8 Hz, $PhCH_2N$), 4.07—4.13 and 4.46—4.51 (2 H, AB system, OCH_2C=), 4.51, 4.56, 4.58, and 4.63 (2 H, AB system, *J* 11.8 Hz, $PhCH_2O$), 4.73, 4.75, 4.76, and 4.78 (2 H, AB system, *J* 6.7 Hz, $PhCH_2OCH_2O$), 5.99 (1 H, unresolved t, 8-H), and 7.15—7.32 (10 H, m); δ_C(62.9 MHz; $CDCl_3$) 20.04, 20.33, 21.57, 25.37, and 26.23 (5-CH_2), 33.56 (C-9), 45.67 (C-2), 55.02 ($PhCH_2N$), 59.12 (C-6), 66.51 ($PhCH_2OCH_2OCH_2$), 69.39 ($PhCH_2O$), 94.34 ($PhCH_2OCH_2O$), 126.25, 127.51, 127.68, 127.82, 128.16, 128.21, 128.34 (7-CH), and 138.22, 140.31, and 140.66 (3-C) (Found: M^+, 391.2519. $C_{26}H_{33}NO$ requires *M*, 391.2511).

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