Synthesis of 2,9,10-Trioxatricyclo[4.3.1.0^{3,8}]decane Analogues of Resiniferatoxin[1]

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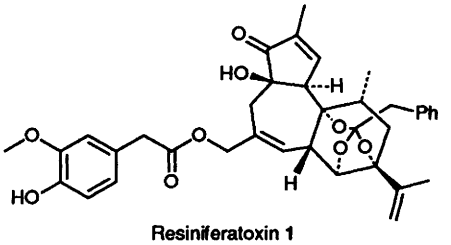
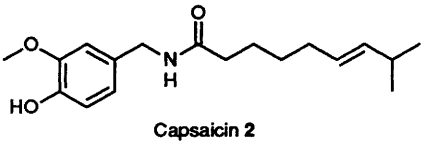
Structurally simplified analogues of the daphnane diterpene resiniferatoxin (RTX) **1**, possessing the unusual 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane system have been synthesised stereoselectively from cyclohexa-1,3-diene: functionalisation of the diene afforded the *anti*-epoxide, 1,4-di-*O*-benzyl-*t*-2,*t*-3-epoxycyclohexane-*r*-1,*c*-4-diol **4**, the ring-opening of which was examined using various organometallic reagents; organoaluminium species were found to be the most efficient to effect this reaction. When trimethylsilyl (in place of benzyl) ethers were used to protect the diol, selective deprotection of 1,4-di-*O*-trimethylsilyl-2-*O*-(*p*-tolylsulfonyl)-*c*-3-[3-(*tert*-butyldiphenylsilyloxy)-prop-1-ynyl]cyclohexane-*r*-1,*t*-2,*c*-4-triol **16** was achieved using citric acid in methanol—the equatorially disposed trimethylsilyl ether was found to be more easily cleaved than the axially orientated one. Formation of the tricyclic orthoester was achieved by the generation of a dioxolenium ion from 1-*O*-phenylacetyl-2-*O*-(*p*-tolylsulfonyl)-*c*-3-[3-(*tert*-butyldiphenylsilyloxy)-prop-1-ynyl]cyclohexane-*r*-1,*t*-2,*c*-4-triol **19**, by heating in 2,4,6-trimethylpyridine, with *in situ* intramolecular trapping by the suitably orientated hydroxy group to give 1-benzyl-7-(3-*tert*-butyldiphenylsilyloxyprop-1-ynyl)-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **20**.

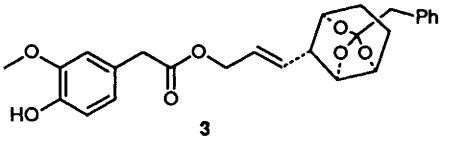
Resiniferatoxin (RTX) **1**[2] is a Daphnane-type diterpene isolated from the latex of certain species of the Genus *Euphorbia*. RTX has been found to be extremely irritant, but does not exhibit biological effects typical of the structurally related phorbol esters. It has also been found[3] that RTX acts as an ultrapotent analogue of capsaicin **2**, the pungent principle from *Capsicum* species, in that both these substances possess the ability to excite and subsequently desensitize sensory nociceptor neurons, leading to analgesia. As part of a project aimed at understanding the structure–activity relationships which are present in resiniferatoxin and are responsible for its action on nociceptive neurons, the synthesis of a partial RTX structure, namely **3**, was required.



Resiniferatoxin 1



Capsaicin 2



3

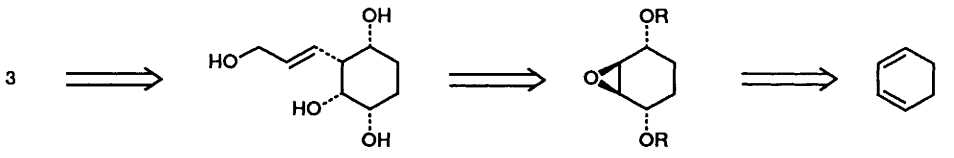
Results and Discussion

The obvious synthetic challenge in the preparation of **3** is the presence of the tricyclic phenyl orthoacetate (trioxatricyclo-[4.3.1.0^{3,8}]decane) system. Disconnection of this ortho ester gives rise to a 3-alkenylcyclohexane-1,2,4-triol, with all the substituents *cis*, as the key synthetic intermediate. It was envisaged that such a system could be prepared from a suitable oxirane precursor which should be readily available by the stereocontrolled functionalisation of cyclohexa-1,3-diene. This retrosynthetic plan is shown in Scheme 1.

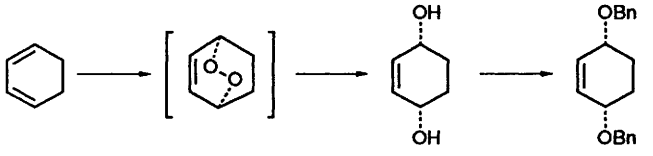
Cyclohexa-1,3-diene has been transformed into *cis*-cyclohex-2-ene-1,4-diol by reaction with singlet oxygen with *in situ* reduction of the resulting endoperoxide.[4] In our hands, it was found that it was not necessary to utilise a high-pressure mercury UV lamp, irradiation being conveniently carried out using a sodium lamp or indeed by simply placing the reaction vessel in direct sunlight. After all the diene had reacted, the endoperoxide was reduced *in situ* by the addition of thiourea, and the resulting *cis*-cyclohex-2-ene-1,4-diol purified chromatographically (Scheme 2).† Benzylation of the diol afforded a derivative, the ^{1}H NMR spectrum of which was consistent with the published[5] data for *trans*- rather than *cis*-di-*O*-benzylcyclohex-2-ene-1,4-diol. In order to clarify the situation, commercially available *trans*-cyclohex-2-ene-1,4-diol (Aldrich Chemical Company Ltd.) was benzylated in a similar way to give a derivative whose melting point and ^{1}H NMR spectrum was in agreement with the published data for the corresponding *cis*-rather than *trans*-di-*O*-benzylcyclohex-2-ene-1,4-diol. It therefore appears that the published physical and spectroscopic characteristics of the *cis* and *trans* derivatives have been reported incorrectly and should be interchanged.

Epoxidation of the *cis*-di-*O*-benzylcyclohex-2-ene-1,4-diol with *m*-chloroperbenzoic acid proceeded slowly and afforded mainly the *anti*-epoxide **4** as expected, the oxygen atom being delivered to the less hindered face of the alkene. In order to introduce the required 3-carbon 'side chain' unit, as required for the eventual synthesis of **3**, ring opening of the epoxide with propynyllithium species was investigated, with the aim of generating the alcohol **8**; in all cases the epoxide was recovered unchanged from these reactions, even when activity-enhancing co-reactants such as boron trifluoride–diethylether, hexamethylphosphoramide or ethylenediamine were used. The corresponding propynylmagnesium halides, with or without the addition of copper salts, were similarly unreactive, although cleavage of the epoxide did take place in some cases by

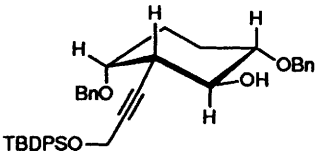
† Throughout Bn = $PhCH_2$, TBDPS = Bu^tPh_2Si, TMS = Me_3Si, and Ts = *p*-$MeC_6H_4SO_2$.



Scheme 1

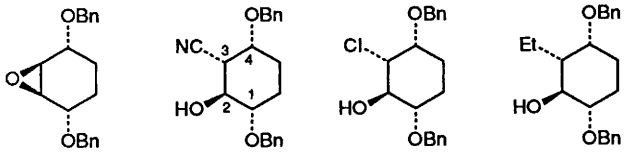


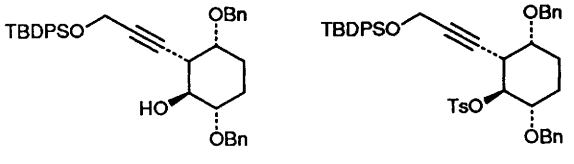
Scheme 2



8a

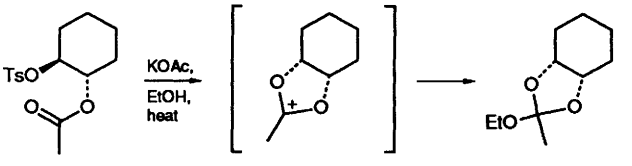
competitive attack by halide giving rise to the corresponding halohydrins. Consequently, the reactivity of the epoxide towards organoaluminium reagents was studied and proved to be much more fruitful: treatment of the epoxide with commercial diethylaluminium cyanide smoothly formed the desired 1,2-cyanohydrin **5** in good yield (80%). Further experiments were carried out using alkynylalanes, generated from the corresponding alkynyllithium species by treatment with diethylaluminium chloride; it was found that success with these reagents depended very much on reaction time and temperature, and solvent used, to minimise side reactions from the lithium chloride generated *in situ* (giving rise to the chlorohydrin **6**), and from attack by the ethylalane (to afford the corresponding ethyl derivative **7**). The best method was found to be a procedure based on the published[6] work of Nicolaou, which gave good yields of the desired propynyl alcohol **8**, with little or no side products. Recently Liverton and co-workers[7] at Merck, have employed diethylalkynylalanes to ring-open a related cyclohexane epoxide in this way. Thus, the alcohol **8** was now accessible, possessing three of the required





ring substituents in the correct orientation, and it was hoped that the remaining stereocentre could be inverted to give the desired all-*cis* arrangement. The ^{1}H NMR spectrum of **8** suggested that this molecule exists in the chair form shown in structure **8a** with three of the four substituents equatorial; the proton attached to the carbon bearing the hydroxy moiety (2-H) exhibited two large vicinal coupling constants (*J ca.* 10 Hz) in agreement with two axial–axial interactions. The alcohol was found to be unstable upon storage, even at low temperature, and attempts to oxidise this derivative to the corresponding ketone (which could then be hopefully reduced stereoselectively to the epimeric alcohol) using a variety of methods failed. Tosylation of the freshly purified alcohol with toluene-*p*-sulfonic anhydride proceeded quantitatively to give the stable tosylate **9**, however subsequent attempts to carry out S_N2 displacement reactions on this substrate using several oxygen nucelophiles also proved fruitless. The inability to carry out similar transformations on an oxygenated cyclopentane alcohol has recently been reported by Pattenden *et al.*[8]

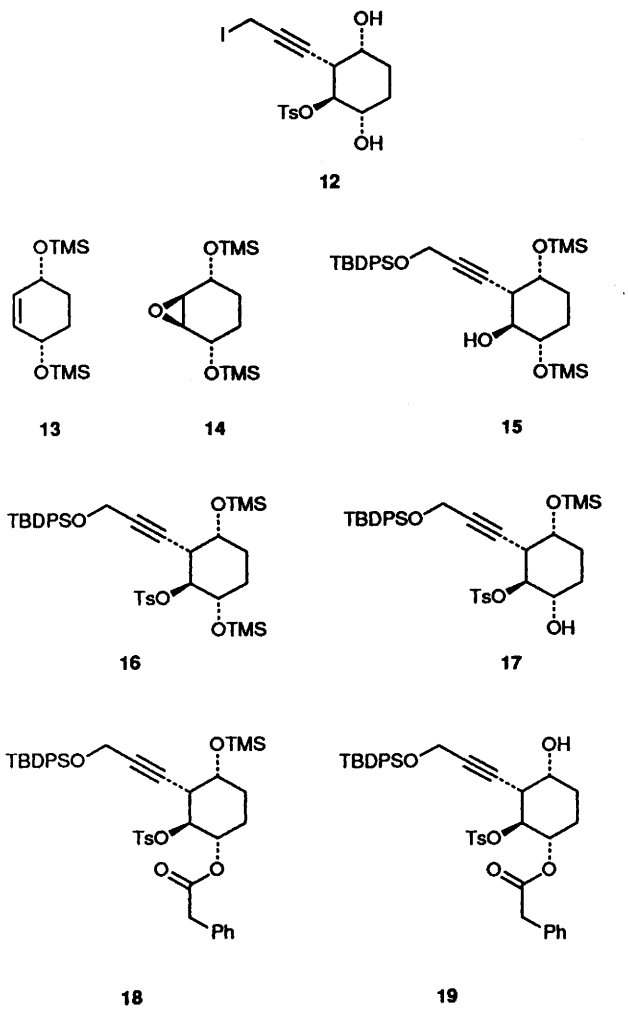
It was clear that the approach of any nucleophile towards the ring carbon bearing the tosyloxy function would be severely restricted by the adjacent groups attached to the neighbouring carbons. It was, therefore, decided that a suitable nucleophilic moiety attached to an adjacent carbon atom in the same molecule would be more likely to displace the tosyloxy leaving group by neighbouring-group participation. A relevant example of this type of reaction was found in the literature; Winstein and Buckles generated[9] the corresponding dioxolenium ion **10a** from *trans*-2-acetoxycyclohexyl toluene-*p*-sulfonate **10**, which underwent a variety of reactions under differing conditions; the most interesting reaction, in the context of our research, was the solvolysis of **10**, in absolute ethanol with 1 equiv. of potassium acetate which afforded the bicyclic ortho ester **11** (Scheme 3). This observation suggested to us that,

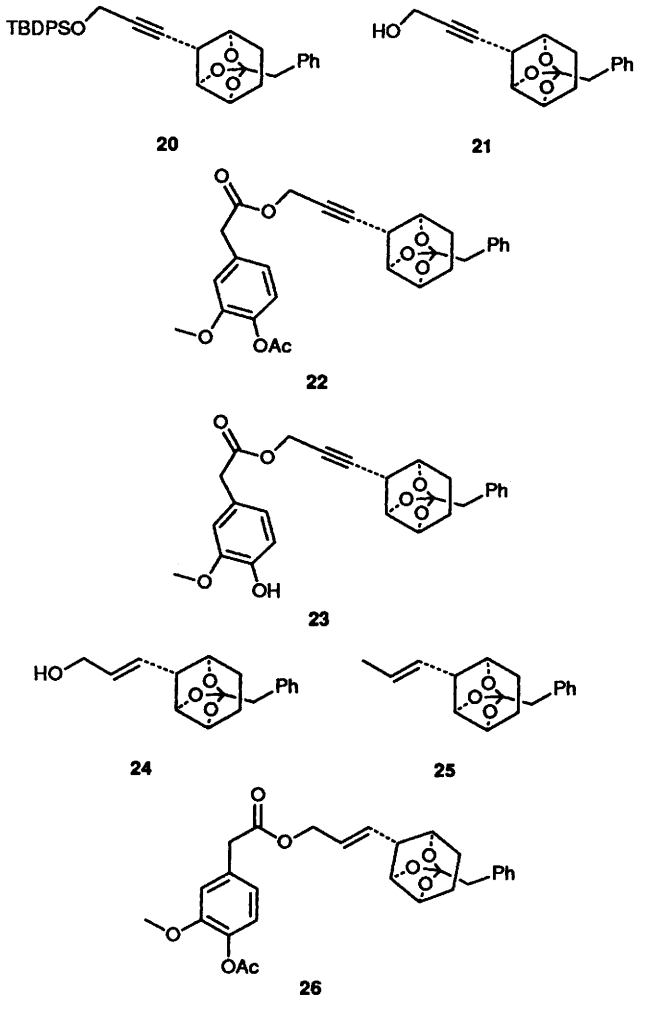


10 10a 11

Scheme 3

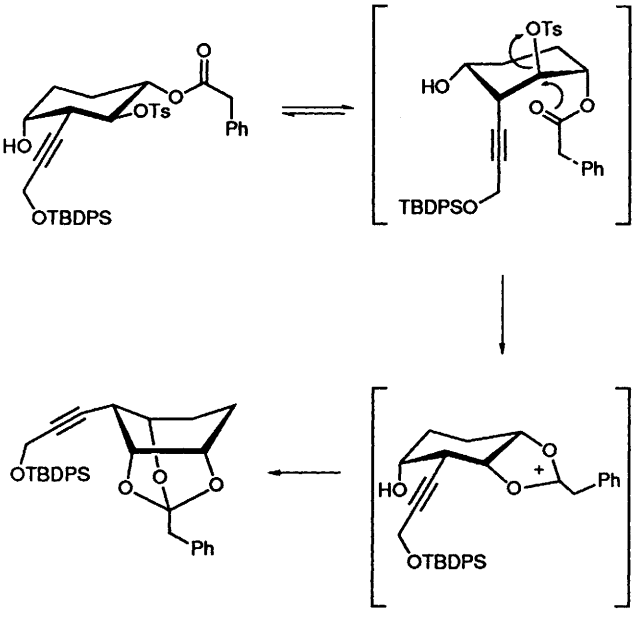
in our system, the tosylate **19** would be a substrate for an analogous reaction where the dioxolenium ion could be trapped not by solvent but in an intramolecular sense, by the free hydroxy group present in the same molecule, generating precisely the ortho ester required. In order to access **19** from tosylate **9**, removal of the benzyl ethers, and acylation of the alcohol adjacent to the tosyloxy moiety was required. Since hydrogenolysis of the benzyl ethers would almost certainly reduce the alkyne moiety, an alternative cleavage method was required. Unfortunately, treatment with sodium in liquid ammonia afforded a mixture of products; the ^{1}H NMR spectrum of the major component suggested that ether cleavage and reduction of the alkyne to the *E*-alkene had occurred, but with concomitant reductive fission of the side chain C–O bond to give an unwanted deoxy derivative. Treatment of **9** with trimethylsilyl iodide yielded the deprotected diol where the *tert*-butyldiphenylsilyloxy moiety had been lost to give the somewhat unstable propynyl iodide **12**. Since the removal of the benzyl ethers in this system was problematic, and bearing in mind the apparent lability of the *tert*-butyldiphenylsilyl propynyl ether, an alternative ether for protection of the diol, which could subsequently be removed under mild conditions, was chosen.





Thus, *cis*-cyclohex-2-ene-1,4-diol was silylated with chlorotrimethylsilane–triethylamine to give the bis-trimethylsilyl ether **13**; this was found to be sufficiently pure (>90%) after work-up that it could be used without further purification. Epoxidation of **13**, as with *cis*-di-*O*-benzylcyclohex-2-ene-1,4-diol, proceeded slowly but gave the desired *anti*-epoxide **14** which could also be used without purification. None of the *syn*-epoxide appeared to be formed in this reaction, presumably due to the increased steric bulk of the trimethylsilyl group relative to the benzyl group. In an analogous manner to that outlined above, **14** was treated with the alkynylalane to give the alcohol **15** which also appeared to be unstable upon storage; subsequent tosylation as above gave the tosylate **16**. Citric acid in methanol has been used[10] as a mild procedure for the removal of trimethylsilyl ethers; when **16** was treated with a catalytic amount (10 mol%) of citric acid monohydrate in methanol solution at room temperature for 5 h, a single product was formed in 82% yield which was identified by ^{1}H NMR spectroscopy as alcohol **17**, where only the equatorially disposed trimethylsilyl ether had been cleaved. Fortunately, the revealed alcohol was the hydroxy group that required acylation, in order to access **19**. This was carried out using phenylacetic acid, with *N*,*N*′-dicyclohexylcarbodiimide as the dehydrating agent to afford the crystalline ester **18**. The remaining trimethylsilyl ether was removed using slightly more vigorous conditions (5 mol% citric acid, methanol–water, 40 min reflux) to afford **19**. With this in hand, attempts to generate the corresponding dioxolenium ion were carried out. After 100 h at reflux in pyridine (b.p. 115 °C), **19** was largely unchanged; however a small amount of product, which appeared to be the desired ortho ester **20**, could be isolated from this reaction; after 100 h reflux in 2,6-dimethylpyridine (b.p. 143–145 °C) **19** was completely transformed into **20**, and the reaction time could be reduced to 10 h when 2,4,6-trimethylpyridine was used as solvent (b.p. 171–172 °C); in this way the ortho ester **20** could be prepared in 73% isolated yield from **19**. The necessity for very high temperatures for this reaction to take place is presumably due to conformational restraints: as mentioned above, **19** probably exists in a chair form with three equatorial substituents; in order to bring the tosyloxy and phenylacetoxy moieties into a diaxial arrangement to allow displacement of the leaving group by the ester, an alternative, and presumably high-energy conformation must be formed to some extent (the alternative chair conformation for the cyclohexane ring is shown in Scheme 4 as a possible intermediate). Subsequent formation of the dioxolenium ion and intramolecular trapping by the alcohol function would then occur rapidly. The presence of the phenyl orthoacetate was confirmed by NMR spectroscopy: the ^{13}C NMR spectrum contained a characteristic ortho ester resonance at δ 119, and in the ^{1}H NMR spectrum, the methylene protons adjacent to the ortho ester carbon resonated as a singlet at δ 3.20, in good agreement with the resonance of the corresponding protons in resiniferatoxin.

With the formation of the required tricyclic ortho ester completed, the *tert*-butyldiphenylsilyl ether was cleaved using tetrabutylammonium fluoride to afford the propynylic alcohol **21** which was acylated with 4-acetoxy-3-methoxyphenylacetic acid to give the ester **22**. Selective removal of the aromatic acetate using an excess of pyrrolidine yielded **23**, the alkynyl analogue of the target molecule **3**, in 86% overall yield from **21**.



Scheme 4

In order to obtain **3**, the propynylic alcohol **21** was treated with Red-Al in tetrahydrofuran to afford the corresponding *trans*-propenylic alcohol **24** in 50% yield. As found previously with **9**, the alcohol **21** suffered reductive C–O bond fission when treated with sodium in ammonia to give the unwanted deoxy analogue **25**. The alcohol **24** was subsequently coupled with 4-acetoxy-3-methoxyphenylacetic acid to give the ester **26** which was deprotected in a similar manner to give **3** in 61% overall yield from **24**.

Experimental

M.p.s are uncorrected and were determined using a Reichert Thermovar hot-stage microscope apparatus. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR spectra were obtained using either a Perkin-Elmer Hitachi T60 (60 MHz), Varian Gemini-200 (200 MHz) or Varian VXR400 (400 MHz) instrument. ^{13}C NMR spectra were obtained using the Gemini-200 or the VXR400 instruments at 50 and 100 MHz respectively. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard. Coupling constant values (J) are given in Hz. Mass spectra were recorded using either a MAT 212 or a VG 70-SE instrument. Solvents were HPLC-grade and dried using standard techniques. Ether refers to diethyl ether and hexane refers to n-hexane. Thin layer chromatography was carried out using polyester-backed silica gel sheets (Aldrich Cat. No. Z12,278-5) and developed with phosphomolybdic acid (5% in IMS) or vanillin (5% in IMS containing 0.5% concentrated sulfuric acid). Preparative column chromatography was carried out using Merck 9385 silica gel (230–400 mesh ASTM).

cis-*Cyclohex*-2-*ene*-1,4-*diol*.—A stirred solution of cyclohexa-1,3-diene (5.00 g, 62.4 mmol) in tetrachloromethane (120 cm^3) containing 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (20 mg) at −10 °C was placed in direct sunlight whilst a slow stream of oxygen gas was bubbled through the mixture. After 5.5 h, the solvent was evaporated under reduced pressure and the residue dissolved in methanol (120 cm^3). Thiourea (4.75 g, 62.4 mmol) was added in one portion and the mixture stirred at room temperature overnight. The reaction mixture was filtered and the filtrate evaporated. Chromatography of the residue on silica gel using ether–methanol (40:1) as eluent yielded *cis*-cyclohex-2-ene-1,4-diol (3.81 g, 54%), m.p. 58–60 °C (lit.,[4] 59–60 °C).

cis-*Di*-O-*benzylcyclohex*-2-*ene*-1,4-*diol*.—A stirred solution of *cis*-cyclohex-2-ene-1,4-diol (2.00 g, 17.52 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (25 cm^3) at 0 °C under argon was treated with 80% sodium hydride (1.31 g, 43.81 mmol, 2.5 equiv.) in one portion. After 1 h, benzyl chloride (5.04 cm^3, 43.81 mmol, 2.5 equiv.) was added dropwise over 7 min. After a further 3 h, the reaction mixture was poured into ice–water and extracted with ether (3 × 100 cm^3). The combined extracts were washed with water (2 × 50 cm^3) and then brine (50 cm^3), dried ($MgSO_4$), filtered under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (1:6) as eluent yielded the title compound as a colourless syrup (4.25 g, 82%), δ_H(60 MHz; $CDCl_3$) 1.6–2.1 (4 H, m, 5-H, 6-H), 3.7–4.0 (2 H, m, 1-H, 4-H) (4 H, s, OCH_2Ph), 5.95 (2 H, s, 2-H, 3-H) and 7.1–7.5 (10 H, m, aromatic H) (lit.,[5] for *trans* derivative, 1.5–2.0 (4 H, ring methylene), 3.7–4.0 (2 H, 1-H, 4-H), 4.55 (4 H, OCH_2Ph) and 5.90–5.95 (2 H, olefinic).

trans-*Di*-O-*benzylcyclohex*-2-*ene*-1,4-*diol*.—80% Sodium hydride (0.059 g, 1.971 mmol, 2.5 equiv.) was added to stirred dimethyl sulfoxide (DMSO) (2 cm^3) at room temperature under argon. After 15 min, *trans*-cyclohex-2-ene, 1,4-diol (0.090 g, 0.789 mmol) was added and after a further 30 min benzyl chloride was added dropwise over 5 min. After a further 4 h, the mixture was poured into ice–water and extracted with ether (2 × 30 cm^3). The combined extracts were washed with water (2 × 15 cm^3) and then brine (15 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a pale yellow oil (0.224 g) which was dissolved in hexane (5 cm^3) and stored in the refrigerator. The crystalline precipitate which formed was collected by vacuum filtration, washed with hexane and dried *in vacuo* to afford the title compound (0.098 g, 42%), m.p. 52–54 °C (lit.,[5] for *cis* derivative, 53–54 °C); δ_H(60 MHz, $CDCl_3$) 1.3–2.4 (4 H, m, 5-H, 6-H), 3.85–4.15 (2 H, m, 1-H, 4-H), 4.52 (4 H, s, OCH_2Ph), 5.92 (2 H, s, 2-H, 3-H) and 7.2–7.5 (10 H, m, aromatic H) (lit.,[5] for *cis* derivative, 1.3–2.4 (4 H, ring methylene), 3.85–4.2 (2 H, 1-H, 4-H), 4.55 (4 H, OCH_2Ph), 5.95 (2 H, olefinic) and 7.33 (10 H, phenyl).

Epoxidation of cis-*Di*-O-*benzylcyclohex*-2-*ene*-1,4-*diol*.—A stirred solution of *cis*-di-*O*-benzylcyclohex-2-ene-1,4-diol (2.00 g, 6.79 mmol) in dichloromethane (25 cm^3) at 0 °C was treated with *m*-chloroperoxybenzoic acid (1.655 g, 8.15 mmol, 1.2 equiv.) portionwise over 10 min and the mixture allowed to warm to room temperature. After 4 d, the reaction mixture was diluted with dichloromethane (150 cm^3) and washed with 1 mol dm^{-3} aqueous sodium hydroxide (2 × 30 cm^3), water (2 × 30 cm^3); and brine (30 cm^3), dried ($CaCl_2$), filtered through Celite and evaporated under reduced pressure. Chromatography of the syrupy residue on silica gel with ethyl acetate–hexane (1:6) as eluent yielded 1,4-*di*-O-*benzyl*-t-2,t-3-*epoxycyclohexane*-r-1,c-4-*diol* **4** (1.574 g, 75%), m.p. 59–60 °C (from ether–hexane) (Found: C, 77.3; H, 7.2. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%); δ_H(400 MHz, $CDCl_3$) 1.51–1.57 (2 H, m, 3-H, 4-H), 1.67–1.73 (2 H, m, 3-H, 4-H), 3.25 (2 H, s, 1-H, 6-H), 3.79 (2 H, m, 2-H, 5-H), 4.63 (4 H, m, OCH_2Ph) and 7.28–7.38 (10 H, m, aromatic H); m/z (FAB) 311 (MH$^+$, 70%), 181 (100%) and 167 (23%). Further elution afforded the *syn*-isomer 1,4-*di*-O-*benzyl*-c-2,c-3-*epoxycyclohexane*-r-1,c-4-*diol* (0.201 g, 10%), m.p. 57–59 °C (from ether–hexane) (Found: C, 77.0; H, 7.25. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%); δ_H(400 MHz, $CDCl_3$) 1.48–1.52 (2 H, m, 3-H, 4-H), 1.84–1.90 (2 H, m, 3-H, 4-H), 3.41 (2 H, s, 1-H, 6-H), 3.82 (2 H, m, 2-H), 5-H), 4.70 (4 H, m, OCH_2Ph) and 7.28–7.41 (10 H, m, aromatic H); m/z (FAB) 311 (MH$^+$, 20%), 197 (15) and 181 (100).

1,4-*Di*-O-*benzyl*-c-3-*cyanocyclohexane*-r-1,t-2,c-4-*triol* **5**.—A stirred solution of the anti-epoxide **4** (0.500 g, 1.611 mmol) in anhydrous toluene (5 cm^3) at 0 °C under argon was treated with

a 1.0 mol dm^3 solution of diethylaluminium cyanide (3.22 cm^3, 3.22 mmol, 2.0 equiv.) dropwise over 5 min, and the mixture stored in the refrigerator. After 17 h, the reaction was poured into 1 mol dm^{-3} sodium hydroxide solution (250 cm^3) and extracted with ether (2 × 100 cm^3). The combined extracts were washed with water (25 cm^3) and then brine (25 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the yellow syrupy residue on silica gel with ether–hexane (3:2) as eluent yielded the *title compound* **5** as a colourless gum (0.435 g, 80%) (Found: C, 74.3; H, 6.9; N, 4.05. $C_{21}H_{23}NO_3$ requires C, 74.7; H, 6.9; N, 4.15%); ν_{max}(neat)/cm^{-1} 3440, 3035, 2940, 2875, 2250, 1608, 1499, 1360, 1209, 1090, 1030, 914, 843, 741 and 700; δ_H(400 MHz, $CDCl_3$) 1.24–1.33 (1 H, m), 1.63–1.75 (1 H, m), 1.89–1.96 (1 H, m), 2.02–2.08 (1 H, m), 2.60 (1 H, dd, *J* 10.9 and 2.7, 3-H), 2.95 (1 H, d, *J* 2.6, OH), 3.17–3.23 (1 H, m, 1-H), 3.95 (1 H, m, 4-H), 4.04–4.10 (1 H, m, 2-H), 4.52–4.71 (4 H, m, OCH_2Ph) and 7.27–7.41 (10 H, m, aromatic H); δ_C(50 MHz, $CDCl_3$) 23.10, 25.87, 40.64, 70.39, 71.32, 71.45, 73.11, 81.14, 118.85, 127.65, 127.69, 127.81, 127.89, 128.39, 128.53, 137.46 and 137.96; *m/z* (FAB) 338 (MH^+, 100%), 336 (38) and 181 (82).

1,4-*Di*-O-*benzyl*-c-3-*chlorocyclohexane*-r-1,t-2,c-4-*triol* **6**.—To stirred anhydrous toluene (1 cm^3) at room temperature under argon, was added a solution of 0.5 mol dm^{-3} lithium (trimethylsilyl)acetylide in tetrahydrofuran (2.58 cm^3, 1.29 mmol, 2.0 equiv.) and then a solution of 1 mol dm^{-3} diethylaluminium chloride in hexane (1.29 cm^3, 1.29 mmol, 2.0 equiv.). After 35 min, the mixture was added to a stirred solution of the *anti*-epoxide **4** (0.200 g, 0.644 mmol) in toluene (3 cm^3) at room temperature under argon. After 24 h, the reaction mixture was poured into 1 mol dm^{-3} aqueous sodium hydroxide and extracted with ether (2 × 70 cm^3). The combined extracts were washed with water (25 cm^3) and then brine (25 cm^3) and dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the residual syrup on silica gel with ether–hexane (1:2.5) as eluent afforded starting material (0.043 g, 20%); further elution yielded the title compound **6** as a white crystalline solid (0.136 g, 61%), m.p. 73–74 °C (from ether–hexane) (Found: C, 69.2; H, 6.75; Cl, 10.5. $C_{20}H_{23}ClO_3$ requires C, 69.3; H, 6.7; Cl, 10.2%); ν_{max}(CH_2Cl_2)/cm^{-1} 3580, 3039, 2955, 2875, 1604, 1497, 1453, 1365, 1138, 1084, 1030 and 861; δ_H(400 MHz, $CDCl_3$) 1.26–1.34 (1 H, m), 1.72–1.83 (1 H, m), 1.85–1.92 (1 H, m), 2.01–2.06 (1 H, m), 2.72 (1 H, d, *J* 2.0, OH), 3.25–3.31 (1 H, m, 1-H), 3.77 (1 H, dd, *J* 10.4 and 2.8, 3-H), 3.83 (1 H, m, 4-H), 3.97–4.02 (1 H, m, 2-H), 4.60–4.71 (4 H, m, OCH_2Ph) and 7.24–7.39 (10 H, m, aromatic H); δ_C(50 MHz, $CDCl_3$) 23.59, 25.84, 65.67, 71.74, 72.13, 74.63, 76.82, 81.19, 127.47, 127.57, 127.69, 127.72, 128.28, 128.45, 138.18 and 138.34; *m/z* (FAB) 347 (MH^+, 38%) and 181 (100).

1,4-*Di*-O-*benzyl*-c-3-*ethylcyclohexane*-r-1,t-2,c-4-*triol* **7** *and* 1,4-*Di*-O-*benzyl*-c-3-[3-(tert-*butyldiphenylsilyloxy*)*prop*-1-*ynyl*]*cyclohexane*-r-1,t-2,c-4-*triol* **8**.—To a stirred suspension of 3-(*tert*-butyldiphenylsilyloxy)prop-1-yne[6] (2.372 g, 8.05 mmol, 2.5 equiv.) in anhydrous hexane (20 cm^3) at −70 °C under argon, was added 1.6 mol dm^{-3} solution of butyllithium in hexane (5.03 cm^3, 8.05 mmol, 2.5 equiv.) dropwise over 3 min. After a further 20 min, a solution of 1 mol dm^{-3} diethylaluminium chloride in hexane (8.05 cm^3, 8.05 mmol, 2.5 equiv.) was added dropwise over 5 min and the resulting cloudy mixture warmed to −40 °C; after a further 30 min, a solution of the *anti*-epoxide **4** (1.00 g, 3.22 mmol) in anhydrous toluene (5 cm^3) was added over 5 min. After a further 4 h, saturated aqueous sodium hydrogencarbonate (2 cm^3) was added to the reaction mixture, which was then diluted with ether (150 cm^3), washed with 1 mol dm^{-3} aqueous sodium hydroxide (2 × 20 ml), water (20 cm^3) and then brine (20 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the syrupy residue on silica gel with ether–hexane (2:5) as eluent afforded the *title compound* **7** as a white solid (0.07 g, 6%), m.p. 72–74 °C; ν_{max}(KBr)/cm^{-1} 3350, 2948, 2929, 1500, 1453, 1132, 1121, 1090, 1065, 1046, 731 and 702; δ_H(200 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 7.5, CH_2CH_3), 1.15–2.00 (6 H, m), 2.16 (1 H, br dd, *J* 13 and 5, 3-H), 2.61 (1 H, d, *J* 2, OH), 3.24 (1 H, m, 1-H), 3.57–3.76 (2 H, m, 2-H, 4-H), 4.27–4.78 (4 H, m, OCH_2Ph) and 7.20–7.40 (10 H, m, aromatic H); *m/z* (FAB) 341 (MH^+, 100%), 233 (32), 197 (30) and 181 (77); further elution yielded the title compound **8** as a colourless syrup (1.24 g, 64%); ν_{max}(neat)/cm^{-1} 3590, 3042, 2950, 2870, 2255, 1600, 1375, 1084 and 865; δ_H(200 MHz, $CDCl_3$) 1.07 [9 H, s, $C(CH_3)_3$], 1.19–1.38 (1 H m), 1.65–2.03 (3 H, m), 2.47 (1 H, dd, *J* 10.5 and 2.7, 3-H), 2.55 (1 H, d, *J* 2, OH), 3.25 (1 H, m, 1-H), 3.79 (1 H, m, 4-H), 3.95 (1 H, m, 2-H), 4.39 (2 H, d, *J* 2, CCH_2O), 4.59–4.76 (4 H, m, OCH_2Ph), 7.20–7.48 (16 H, m, aromatic H) and 7.75 (4 H, m, aromatic H); δ_C(50 MHz, $CDCl_3$) 19.41, 24.29, 26.99, 27.32, 42.04, 53.34, 71.84, 72.28, 73.20, 76.06, 81.38, 81.97, 84.32, 127.88, 128.03, 128.14, 128.22, 128.75, 128.97, 130.30, 133.78, 133.86, 136.21 and 139.33; *m/z* (FAB) 603 ([M − H]$^+$, 10%), 548 ([M − Bu]$^+$, 18), 457, 421, 241, 199 (82) and 197 (100).

1,4-*Di*-O-*benzyl*-c-3-[3-tert-*butyldiphenylsilyloxy*)-2-O-(p-*tolylsulfonyl*)*prop*-1-*ynyl*]*cyclohexane*-r-1,t-2,c-4-*triol* **9**.—A stirred solution of the alcohol **8** (0.527 g, 0.871 mmmol) in anhydrous pyridine (5 cm^3) at 0 °C was treated with toluene-*p*-sulfonic anhydride (0.569 g, 1.743 mmol, 2.0 equiv.) in one portion. After 2 h, the reaction mixture was poured into ice-cold mol dm^{-3} hydrochloric acid solution (200 cm^3) and extracted with ether (3 × 50 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (20 cm^3), water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to afford the crude title compound **9** as a pale yellow gum (0.631 g, 96%); δ_H(200 MHz, $CDCl_3$) 1.04 [9 H, s, $C(CH_3)_3$], 1.20–1.35 (1 H, m), 1.74–1.98 (3 H, m), 2.02 (3 H, s, $ArCH_3$), 2.70–2.80 (1 H, br dd, *J* 10 and 2.5, 3-H), 3.26–3.39 (1 H, br m, 1-H), 3.72–3.80 (1 H, m, 4-H), 4.12 (2 H, d, *J* 2, CCH_2O), 4.36–4.69 (4 H, m, OCH_2Ph), 5.07 (1 H, dd, *J* 10.5 and 10, 2-H), 7.09 (2 H, d, *J* 9, aromatic H), 7.20–7.48 (16 H, m, aromatic H) and 7.69–7.80 (6 H, m, aromatic H); *m/z* (FAB) 760 (MH^+, 12%), 702 ([M − Bu]$^+$, 21), 457 (35) and 197 (100).

c-3-(3-*Iodoprop*-1-*ynyl*)-2-O-(p-*tolylcyclohexane*-r-1,t-2,c-4-*triol* **12**.—A stirred solution of the tosylate **9** (0.316 g, 0.416 mmol) in anhydrous dichloromethane (2 cm^3) containing powdered molecular sieves (50 mg) at 0 °C under argon, was treated with iodotrimethylsilane (0.196 cm^3, 1.374 mmol, 3.3 equiv.) dropwise over 2 min and the mixture allowed to slowly warm to room temperature. After 5 h, the reaction mixture was evaporated under reduced pressure; chromatography of the residue on silica gel with ethyl acetate–hexane (1:1) as eluent afforded the unstable *iodide* **12** (0.079 g, 42%); δ_H(200 MHz, $CDCl_3$) 1.40–1.60 (1 H, m), 1.76–2.01 (3 H, m), 2.28 (1 H, br s, OH), 2.48 (3 H, s, $ArCH_3$), 2.69 (1 H, dd, *J* 10 and 3, 3-H), 3.10 (1 H, br d, *J* 3, OH), 3.56 (2 H, d, *J* 2, CCH_2I), 3.54–3.70 (1 H, m, 1-H), 4.05–4.14 (1 H, m, 4-H), 4.79 (1 H, dd, *J* 11 and 10, 2-H), 7.40 (2 H, m, *J* 8, aromatic H) and 7.92 (2 H, d, *J* 8, aromatic H); *m/z* (FAB) 451 (MH^+, 30%), 149 (76), 133 (86) and 105 (100).

cis-*Bis*-O-*trimethylsilylcyclohex*-2-*ene*-1,4-*diol* **13**.—A stirred solution of *cis*-cyclohex-2-ene-1,4-diol (1.11 g, 9.725 mmol) in dry DMF (50 cm^3) at 0 °C under argon was treated with triethylamine (4.07 cm^3, 29.175 mmol, 3.0 equiv.) dropwise and then with chlorotrimethylsilane (3.09 cm^3, 24.312 mmol, 2.5 equiv.) dropwise; the reaction mixture was allowed to slowly

warm to room temperature. After 24 h, the mixture was poured into ice–water (200 cm^3) and extracted with ether (3 × 80 cm^3). The combined extracts were washed with water (2 × 50 cm^3) and the combined washings were re-extracted with ether (80 cm^3). The combined ethereal extracts were washed with brine (2 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. High vacuum distillation of the residual oil yielded the *title compound* **13** (1.810 g, 72%) as a colourless oil, b.p. 75 °C/0.02 Torr (Found: C, 55.8; H, 10.0. $C_{12}H_{26}O_2Si_2$ requires C, 55.8; H, 10.1%); ν_{max}(neat)/cm^{-1} 3035, 2959, 2908, 2870, 1439, 1392, 1252, 1090, 1054, 1022, 980, 840 and 750; δ_H(200 MHz, $CDCl_3$) 0.11 [18 H, s, $Si(CH_3)_3$], 1.61–1.85 (4 H, m, 5-H, 6-H), 4.10 (2 H, m, 1-H, 4-H) and 5.69 (2 H, m, 2-H, 3-H); δ_C(50 MHz; $CDCl_3$) 0.38, 28.80, 65.91 and 132.64; *m/z* (EI) 259 (MH^+, 8%), 243 ($[M - CH_3]^+$, 10), 230 (13), 168 (63), 147 (100), 142 (83), 127 (64) and 73 (89).

Epoxidation of cis-*Bis*-O-*trimethylsilylcyclohex*-2-*ene*-1,4-*diol* **13**.—Sodium hydrogen carbonate (1.09 g, 12.94 mmol, 1.5 equiv.) was added to a stirred solution of cis-bis-*O*-trimethylsilylcyclohex-2-ene-1,4-diol **13** (2.23 g, 8.63 mmol) in anhydrous dichloromethane (120 cm^3) at 0 °C, followed by 85% *m*-chloroperoxybenzoic acid (2.79 g, 12.94 mmol, 1.5 equiv.) portionwise over 5 min; the reaction mixture was then allowed to warm slowly to room temperature. After 4 d, the mixture was rapidly washed with 1 mol dm^{-3} aqueous sodium hydroxide (25 cm^3) and then brine (25 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 1,4-*di*-O-*trimethylsilyl*-t-2,t-3-*epoxycyclohexane*-r-1,c-4-*diol* **14** as a colourless oil (2.18 g, 92%) (Found: C, 52.5; H, 9.4. $C_{12}H_{26}O_3Si_3$ requires C, 52.5; H, 9.55%); ν_{max}(CH_2Cl_2)/cm^{-1} 2960, 2880, 1445, 1381, 1073, 1011, 963 and 846; δ_H(200 MHz; $CDCl_3$) 0.15 [18 H, s, $Si(CH_3)_3$], 1.41–1.59 (4 H, m, 5-H, 6-H), 3.06 (2 H, s, 2-H, 3-H) and 3.94–4.05 (2 H, m, 1-H, 4-H); δ_C(50 MHz; $CDCl_3$) 0.16, 24.77, 57.01 and 65.85; *m/z* (FAB) 273 (MH^+, 1%), 259 ($[M - CH_3]^+$, 4), 169 (88), 147 (100), 129 (40), 95 (55) and 73 (100).

c-3-[3-(tert-*Butyldiphenylsilyloxy*)*prop*-1-*ynyl*]-1,4-*Bis*-O-*trimethylsilylcyclohexane*-r-1,t-2,c-4-*triol* **15**.—A stirred suspension of 3-(*tert*-butyldiphenylsilyloxy)prop-1-yne (1.743 g, 5.920 mmol, 2.5 equiv.) in anhydrous toluene (3 cm^3) at −40 °C under argon was treated with a 1.6 mol dm^{-3} solution of butyllithium in hexane (3.70 cm^3, 5.920 mmol, 2.5 equiv.) dropwise over 4 min. After a further 15 min, a solution of 1 mol dm^{-3} diethylaluminium chloride in hexane (5.92 cm^3, 5.920 mmol, 2.5 equiv.) was added dropwise over 3 min. After a further 30 min, a solution of the epoxide **14** (0.650 g, 2.368 mmol) in anhydrous toluene (1 cm^3) was added dropwise; after a further 3.5 h, the reaction mixture was quenched by the addition of saturated aqueous sodium hydrogen carbonate (2 cm^3) and allowed to warm to room temperature. The mixture was diluted with ether (100 cm^3), washed with 1 mol dm^{-3} aqueous sodium hydroxide (2 × 20 cm^3) and then water (20 cm^3). The combined washings were re-extracted with ether (20 cm^3) and the combined ethereal extracts washed with brine (25 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the syrupy residue on silica gel with ethyl acetate–hexane (1:15) as eluent afforded the *title compound* **15** as a colourless syrup (0.943 g, 70%); ν_{max}(neat)/cm^{-1} 3590, 3470, 2958, 2860, 2240, 1590, 1429, 1373, 1250, 1112, 1084, 946, 843, 742 and 701; δ_H(200 MHz; $CDCl_3$) 0.09 [9 H, s, $Si(CH_3)_3$], 0.12 [9 H, s, $Si(CH_3)_3$], 1.09 [9 H, s, $SiC(CH_3)_3$], 1.30–1.51 (1 H, m), 1.54–1.73 (2 H, m), 1.77–1.99 (1 H, m), 2.30 (1 H, s, OH), 2.34 (1 H, dd, *J* 10 and 2, 3-H), 3.29–3.44 (1 H, m, 1-H), 3.62–3.76 (1 H, m, 2-H), 4.04–4.14 (1 H, m, 4-H), 4.35 (2 H, d, *J* 2, CCH_2O), 7.32–7.50 (6 H, m, aromatic H) and 7.67–7.81 (4 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 0.41, 0.57, 19.33, 26.91, 27.85, 31.53, 42.75, 53.18, 70.01, 73.58, 76.74, 80.92, 84.97, 128.18, 130.21 and 136.18; *m/z* (FAB) 569 (MH^+, 10%), 511 $\{[M - C(CH_3)_3]^+$, 5}, 401 (25), 313 (27), 295 (33), 223 (51) and 197 (100).

c-3-[3-(tert-*Butyldiphenylsilyloxy*)-2-O-p-*tolylsulfonyl*)-1,4-*bis*-O-*trimethylsilylprop*-1-*ynyl*]*cyclohexane*-r-1,t-2,c-4-*triol* **16**.—A stirred solution of the alcohol **15** (0.940 g, 1.652 mmol) in anhydrous pyridine (6 cm^3) at 0 °C under argon was treated with toluene-*p*-sulfonic anhydride (1.079 g, 3.304 mmol, 2.0 equiv.) in one portion. After 1.33 h, the reaction was diluted with dichloromethane (160 cm^3), washed with water (2 × 25 cm^3), 2 mol dm^3 hydrochloric acid (2 × 25 cm^3), water (25 cm^3) and then brine (25 cm^3), dried ($CaCl_2$), filtered and evaporated under reduced pressure. Chromatography of the syrupy residue on silica gel with dichloromethane–hexane (3:2) as eluent yielded the *title compound* **16** as a colourless gum (0.783 g, 66%) (Found: C, 63.0; H, 7.8. $C_{38}H_{54}O_6SSi_3$ requires C, 63.1; H, 7.5%); ν_{max}(CH_2Cl_2)/cm^{-1} 3039, 2960, 2860, 2250, 1600, 1361, 1190, 1179, 1105, 1100, 1058, 992, 911 and 849; δ_H(200 MHz; $CDCl_3$) 0.09 [9 H, s, $Si(CH_3)_3$], 0.11 [9 H, s, $Si(CH_3)_3$], 1.00 [9 H, s, $SiC(CH_3)_3$], 1.30–1.49 (1 H, m), 1.61–1.79 (2 H, m), 1.87–2.05 (1 H, m), 2.10 (3 H, s, $ArCH_3$), 2.52 (1 H, br d, *J* 10, 3-H), 3.46–3.62 (1 H, m, 1-H), 3.90 (2 H, d, *J* 2, CCH_2O), 4.04–4.10 (1 H, m, 4-H), 4.88 (1 H, dd, *J* 10 and 9, 2-H), 7.03 (2 H, d, *J* 8, aromatic H), 7.33–7.49 (6 H, m, aromatic H) and 7.63–7.78 (6 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 0.01, 0.13, 0.18, 19.05, 21.21, 26.62, 28.09, 30.42, 41.17, 52.67, 70.29, 72.81, 80.76, 83.23, 84.90, 128.01, 128.06, 128.56, 129.36, 129.71, 130.03, 133.40, 135.84, 135.88 and 143.79; *m/z* (FAB) 723 (MH^+, 75%), 651 (99), 569 (62), 423 (95), 401 (80), 331 (70), 313 (97), 273 (73) and 257 (86).

c-3-[3-(tert-*Butyldiphenylsilyloxy*)*prop*-1-*ynyl*]-2-O-(p-*tolylsulfonyl*)-4-O-*trimethylsilylcyclohexane*-r-1,t-2,c-4-*triol* **17**.—A stirred solution of the tosylate **16** (0.752 g, 1.040 mmol) in anhydrous methanol (10 cm^3) at 18 °C was treated with citric acid monohydrate (0.022 g, 0.104 mmol, 0.1 equiv.) in one portion. After 4.33 h, the methanol was evaporated under reduced pressure and the residue dissolved in ether (100 cm^3). After being washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) followed by brine (10 cm^3), the solution was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (2:3) as eluent afforded the *title compound* **17** as a colourless glass (0.557 g, 82%) (Found: C, 64.3; H, 7.0. $C_{35}H_{46}O_6SSi_2$ requires C, 64.6; H, 7.1%); ν_{max}(CH_2Cl_2)/cm^{-1} 3575, 2961, 2863, 1600, 1475, 1361, 1191, 1179, 1115, 1077, 1000, 981, 900, 850 and 828; δ_H(200 MHz; $CDCl_3$) 0.08 [9 H, s, $Si(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.30–1.51 (1 H, m), 1.61–1.76 (1 H, m), 1.80–1.97 (2 H, m), 2.23 (3 H, s, $ArCH_3$), 2.53 (1 H, dd, *J* 10 and 2, 3-H), 3.30 (1 H, d, *J* 3, OH), 3.53–3.72 (1 H, m, 1-H), 4.02–4.12 (3 H, m, 4-H and CCH_2O), 4.77 (1 H, dd, *J* 10.5 and 8.5, 2-H), 7.11 (2 H, d, *J* 8, aromatic H), 7.36–7.50 (6 H, m, aromatic H), 7.62–7.76 (4 H, m, aromatic H), and 7.80 (2 H, d, *J* 8, aromatic H); δ_C(50 MHz; $CDCl_3$) 0.36, 21.65, 26.63, 26.89, 30.52, 41.18, 52.98, 70.49, 72.47, 85.99, 128.28, 128.79, 129.95, 130.33 and 136.12; *m/z* (FAB) 651 (MH^+, 27%), 579 (12), 423 (19), 293 (24), 273 (32) and 199 (100).

c-3-[3-(tert-*Butyldiphenylsilyloxy*)*prop*-1-*ynyl*]-1-O-*phenylacetyl*-2-O-(p-*tolylsulfonyl*)-4-O-*trimethylsilylcyclohexane*-r-1,t-2,c-4-*triol* **18**.—A stirred solution of phenylacetic acid (0.143 g, 1.049 mmol, 1.2 equiv.) in anhydrous dichloromethane (7 cm^3) at 0 °C was treated successively with dicyclohexylcarbodiimide (0.217 g, 1.049 mmol, 1.2 equiv.), 4-*N*,*N*-dimethylaminopyridine (0.021 g, 0.175 mmol, 0.2 equiv.) and a solution of the alcohol **17** (0.569 g, 0.874 mmol) in dichloro-

methane (2 cm^3) and the resulting mixture allowed to slowly warm to room temperature. After 18 h, the reaction mixture was diluted with dichloromethane (50 cm^3) and washed successively with saturated aqueous sodium hydrogen carbonate (20 cm^3); 2 mol dm^{-3} hydrochloric acid (15 cm^3), water (20 cm^3) and brine (20 cm^3). The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was dissolved in hot methanol (25 cm^3) and upon slow cooling, a white crystalline precipitate appeared. The crystals were collected by vacuum filtration, washed with cold methanol and dried *in vacuo* to afford the *title compound* **18** (0.510 g, 76%), m.p. 125–126.5 °C (Found: C, 67.3; H, 6.9; S, 4.2. $C_{43}H_{52}O_7SSi_2$ requires C, 67.2; H, 6.8; S, 4.2%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2960, 2859, 1741, 1599, 1497, 1360, 1349, 1190, 1178, 1111, 1074, 1041, 996, 940, 918 and 844; δ_H(200 MHz; $CDCl_3$) 0.15 [9 H, s, $Si(CH_3)_3$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.36–1.56 (1 H, m), 1.60–2.05 (3 H, m), 2.18 (3 H, s, $ArCH_3$), 2.58 (1 H, dd, *J* 10 and 2, 3-H), 3.66 (2 H, d, *J* 2, $OCOCH_2Ph$), 4.05 (2 H, d, *J* 2, CCH_2O), 4.09–4.16 (1 H, m, 4-H), 4.77–4.93 (1 H, m, 1-H), 5.11 (1 H, dd, *J* 10 and 9.5, 2-H), 7.05 (2 H, d, *J* 8.5, aromatic H), 7.20–7.52 (11 H, m, aromatic H) and 7.62–7.80 (6 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 0.42, 21.57, 24.43, 26.87, 30.53, 41.19, 41.70, 49.38, 52.97, 70.19, 73.63, 81.64, 82.99, 127.43, 127.57, 128.24, 128.28, 128.94, 129.24, 129.77, 130.02, 130.07, 130.32, 133.58, 136.14 and 171.92; *m/z* (FAB) 769 (MH^+, 2%), 579 (63), 473 (50), 355 (100), 336 (72) and 211 (81).

c-3-[3-(tert-*Butyldiphenylsilyloxy*)*propyn*-1-*yl*]-1-O-*phenylacetyl*-2-O-(p-*tolylsulfonyl*)*cyclohexane*-r-1,t-2,c-4-*triol* **19**.—A stirred suspension of the silyl ether **18** (0.45 g, 0.585 mmol) in methanol (20 cm^3) and water (1 cm^3) was treated with citric acid monohydrate (0.006 g, 0.029 mmol, 0.05 equiv.) and the mixture heated to reflux. After 40 min, the reaction mixture was allowed to cool to room temperature and the solvent evaporated under reduced pressure. The residue was dissolved in ether (100 cm^3) and washed successively with saturated aqueous sodium hydrogen carbonate (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (1:1) as eluent yielded the *title compound* **19** as an amorphous white solid (0.339 g, 83%) (Found: C, 69.1; H, 6.3. $C_{40}H_{44}O_7SSi$ requires C, 68.9; H, 6.4%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3535, 2960, 2932, 2859, 1741, 1599, 1496, 1350, 1218, 1190, 1178, 1158, 1111, 1074, 989 and 823; δ_H(200 MHz; $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 1.35–1.57 (1 H, m), 1.77–1.95 (3 H, m), 1.98 (1 H, s, OH), 2.30 (3 H, s, $ArCH_3$), 2.64 (1 H, dd, *J* 10 and 2, 3-H), 3.59 (2 H, s, $OCOCH_2Ph$), 3.85–3.93 (1 H, m, 4-H), 4.17 (2 H, d, *J* 2, CCH_2O), 4.82 (1 H, 1-H), 5.03 (1 H, dd, *J* 10 and 9.5, 2-H), 7.18 (2 H, d, *J* 8.5, aromatic H), 7.20–7.35 (5 H, m, aromatic H), 7.35–7.52 (6 H, m, aromatic H) and 7.66–7.83 (6 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 21.70, 24.38, 26.88, 28.18, 41.15, 41.70, 52.87, 68.96, 73.12, 81.06, 82.08, 83.46, 127.46, 128.27, 128.32, 128.38, 128.95, 129.91, 130.02, 130.49, 130.54 and 136.11; *m/z* (FAB) 697 (MH^+, 17%) and 199 (100).

1-*Benzyl*-7-(3-tert-*butyldiphenylsilyloxyprop*-1-*ynyl*)-2,9,10-*trioxatricyclo*[4.3.1.0^{3,8}]*decane* **20**.—A stirred solution of the cyclohexanetriol **19** (0.31 g, 0.44 mmol) in anhydrous 2,4,6-trimethylpyridine (15 cm^3) containing powdered 4 Å molecular sieves (0.2 g) was heated to reflux under argon. After 10 h the reaction mixture was allowed to cool to room temperature, filtered through Celite and evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (1:3) as eluent yielded the title compound **20** as a white amorphous solid (0.17 g, 73%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3040, 2960, 2940, 2860, 2240, 1605, 1590, 1500, 1470, 1450, 1370, 1240, 1210, 1170, 1110, 1090, 1065, 1020, 1000, 950, 930, 910, 880, 860, 840, 820 and 610; δ_H(200 MHz; $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 1.36–1.55 (1 H, m), 1.66–1.88 (1 H, m), 2.00–2.21 (2 H, m), 2.26–2.39 (1 H, m, 7-H), 3.20 (2 H, s, CCH_2Ph), 4.16 (1 H, d, *J* 5, 6-H), 4.40 (2 H, d, *J* 2, CCH_2O), 4.41–4.54 (2 H, m, 3-H, 8-H), 7.10–7.50 (11 H, m, aromatic H) and 7.61–7.82 (4 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 19.39, 21.71, 26.76, 26.98, 27.96, 30.22, 40.69, 53.39, 73.68, 74.23, 80.91, 84.11, 119.15, 126.97, 128.15, 128.35, 130.19, 130.82, 133.89, 135.51 and 136.24; *m/z* (FAB) 525 (MH^+, 37%) and 199 (100).

1-*Benzyl*-7-(3-*hydroxyprop*-1-*ynyl*)-2,9,10-*trioxatricyclo*-[4.3.1.0^{3,8}]*decane* **21**.—A stirred solution of the silyl ether **20** (0.17 g, 0.32 mmol) in anhydrous tetrahydrofuran (10 cm^3) at room temperature was treated with a 1.0 mol dm^{-3} solution of tetrabutylammonium fluoride in tetrahydrofuran (0.52 cm^3, 0.52 mmol, 1.6 equiv.). After 10 min the solvent was evaporated. Chromatography of the residue on silica gel with ether as eluent yielded the title compound **21** as a white solid (0.09 g, 96%) [Found (for acetate derivative): C, 69.3; H, 6.1; O, 24.4. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1; O, 24.4%]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3680, 3600, 3040, 2960, 2940, 2870, 2240, 1605, 1500, 1450, 1375, 1355, 1325, 1300, 1240, 1210, 1170, 1155, 1090, 1065, 1050, 1020, 1005, 980, 960, 950, 930, 910, 880, 860 and 840; δ_H(200 MHz; $CDCl_3$) 1.36–1.91 (3 H, m), 2.05–2.26 (2 H, m), 2.39–2.48 (1 H, m, 7-H), 3.22 (2 H, s, CH_2Ph), 4.24 (1 H, d, *J* 6, 6-H), 4.30 (2 H, br s, CCH_2OH), 4.48–4.62 (2 H, m, 3-H, 8-H) and 7.19–7.44 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 21.66 (4-C), 27.90 (5-C), 30.21 (7-C), 40.77 (CCH_2Ph), 51.69 (CCH_2OH), 73.83 (6-C), 74.28 (3-C; 8-C), 81.02, 84.61, 119.24 (1-C), 127.04, 128.38, 130.81 and 135.52; *m/z* (FAB) 287 (MH^+, 100%).

7-[3-(4-*Acetoxy*-3-*methoxyphenyl*)*acetoxyprop*-1-*ynyl*]-1-*benzyl*-2,9,10-*trioxatricyclo*[4.3.1.0^{3,8}]*decane* **22**.—A stirred solution of 4-acetoxy-3-methoxyphenylacetic acid (0.07 g, 0.32 mmol, 1.5 equiv.) in anhydrous dichloromethane (10 cm^3) at room temperature was treated with dicyclohexylcarbodiimide (0.07 g, 0.32 mmol, 1.5 equiv.) and 4-*N*,*N*-(dimethylamino)pyridine (0.004 g, 0.032 mmol, 0.15 equiv.) followed by a solution of the alcohol **21** (0.06 g, 0.21 mmol) in anhydrous dichloromethane (5 cm^3). After 2 h the reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (2.5:1) as eluent yielded the *title compound* **22** (0.10 g, 97%); δ_H(200 MHz; $CDCl_3$) 1.38–1.56 (1 H, m), 1.71–1.90 (1 H, m), 2.03–2.24 (2 H, m), 2.30 (3 H, s, $OCOCH_3$), 2.45 (1 H, br s, 7-H), 3.22 (2 H, s, CH_2Ph), 3.64 (2 H, s, $OCOCH_2Ar$), 3.81 (3 H, s, $ArOCH_3$), 4.24 (1 H, d, *J* 5, 6-H), 4.46–4.62 (2 H, m, 3-H, 8-H), 4.78 (2 H, d, *J* 1.5, CCH_2OCO), 6.82–7.02 (3 H, m, aromatic H) and 7.18–7.44 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 20.86, 21.67, 27.89, 30.26, 40.70, 41.12, 53.59, 56.20, 73.59, 74.17, 74.22, 72.26, 86.01, 113.97, 119.26, 122.08, 123.26, 127.03, 128.39, 130.76, 132.80, 135.50, 151.60, 169.50 and 171.19; *m/z* (FAB) 493 (MH^+, 100%), 409 (34), 351 (30), 334 (32), 305 (36), 291 (30) and 255 (60).

1-*Benzyl*-7-[3-(4-*hydroxy*-3-*methoxyphenyl*)*acetoxyprop*-1-*ynyl*]-1,2,9-*trioxatricylo*[4.3.1.0^{3,8}]*decane* **23**.—A stirred solution of the acetate **22** (0.1 g, 0.20 mmol) in dichloromethane (5 cm^3) at room temperature was treated with pyrrolidine (0.17 cm^3, 2.0 mmol, 10 equiv.). Two further additions of pyrrolidine (0.09 cm^3, 1.0 mmol, 5 equiv.) were made at 30 min intervals and, 15 min after the final addition, the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with dichloromethane–methanol (99:1) as eluent yielded the *title compound* **23** as a white amorphous solid (0.08 g, 89%) (Found: C, 69.2; H, 6.0; O, 24.7. $C_{26}H_{26}O_7$ requires C, 69.3; H, 5.8; 24.9%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3680, 3540, 2960, 2940, 2840, 2240, 1740, 1610, 1515, 1500, 1465, 1455, 1370, 1240,

1210, 1170, 1150, 1085, 1065, 1035, 1020, 1005, 995, 980, 955, 935, 910, 880, 840 and 800; δ_H(200 MHz; $CDCl_3$) 1.37–1.59 (1 H, m), 1.70–1.90 (1 H, m), 2.02–2.24 (2 H, m), 2.39–2.49 (1 H, m, 7-H), 3.22 (2 H, s, CCH_2Ph), 3.60 (2 H, s, $OCOCH_2Ar$), 3.88 (3 H, s, $ArOCH_3$), 4.24 (1 H, br d, *J* 5, 6-H), 4.45–4.62 (2 H, m, 3-H, 8-H- 4.76 (2 H, d, *J* 1.5, CCH_2OCO), 5.60 (1 H, s, ArO*H*), 6.75–6.90 (3 H, m, aromatic H) and 7.15–7.43 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 21.67, 27.90, 30.27, 40.70, 40.90, 53.48, 56.22, 73.60, 74.18, 76.38. 85.86, 112.27, 114.85, 119.26, 122.70, 125.83, 127.04, 128.40, 130.76, 135.43 and 172.11; *m/z* (FAB) 451 (MH^+, 14%), 287 (10), 164 (42) and 137 (100).

(E)-1-*Benzyl*-7-(3-*hydroxyprop*-1-*enyl*)-2,9,10-*trioxatricyclo*-[4.3.1.0^{3,8}]*decane* **24**.—A stirred solution of Red-Al (0.13 cm^3, 0.45 mmol, 2.0 equiv.) in anhydrous ether (2 cm^3) at 0 °C under argon was treated with a solution of the propynyl alcohol **21** (0.07 g, 0.23 mmol) in anhydrous ether (3 cm^3) dropwise. After 3.5 h further Red-Al (0.13 cm^3, 0.45 mmol, 2.0 equiv.) was added. After a further 2 h the reaction mixture was poured into water (10 cm^3) and extracted with ethyl acetate (3 × 20 cm^3). The combined organic layers were washed successively with water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel with ethyl acetate–hexane (1.5:1) as eluent yielded the *title compound* **24** (0.032 g, 49%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3690, 3600, 3040, 2950, 2880, 1605, 1500, 1455, 1375, 1330, 1215, 1170, 1095, 1085, 1065, 1020, 1010, 985, 950, 930, 910, 840 and 685; δ_H(200 MHz; $CDCl_3$) 1.37 (1 H, br s, OH), 1.45–1.69 (1 H, m), 1.73–1.91 (1 H, m), 2.02–2.28 (3 H, m), 3.20 (2 H, s, CCH_2Ph), 4.05 (1 H, d, *J* 6, 6-H), 4.14 (2 H, d, *J* 6, $CHCH_2OH$), 4.36–4.47 (1 H, m, 3-H), 4.49–4.59 (1 H, m, 8-H), 5.76 (1 H, dt, *J* 15 and 6, $CH{=}CHCH_2OH$), 6.09 (1 H, dd, *J* 15 and 8 Hz, $CH{=}CHCH_2OH$) and 7.19–7.42 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 21.99, 28.22, 39.34, 40.99, 63.97, 74.30, 74.71, 75.72, 119.04, 127.02, 128.40, 130.78, 131.39, 131.52 and 135.70; *m/z* (FAB) 289 (MH^+, 100%).

(E)-1-*Benzyl*-7-[3-(4-*acetoxy*-3-*methoxyphenyl*)*acetoxyprop*-1-*enyl*]-2,9,10-*trioxatricyclo*[4.3.1.0^{3,8}]*decane* **26**.—A stirred solution of 4-acetoxy-3-methoxyphenylacetic acid (0.03 g, 0.13 mmol, 1.5 equiv.) in anhydrous dichloromethane (3 cm^3) was treated with dicyclohexylcarbodiimide (0.02 g, 0.13 mmol, 1.5 equiv.) and then 4-*N*,*N*-(dimethylamino)pyridine (0.002 g, 0.017 mmol, 0.2 equiv.) followed by a solution of the propenyl alcohol **24** (0.025 g, 0.087 mmol) in anhydrous dichloromethane (3 cm^3). After 1 h, the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (2:1) as eluent yielded the *title compound* **26** (0.036 g, 83%); $\nu_{max}(CDCl_3)$/cm^{-1} 2960, 2940, 1760, 1735, 1610, 1510, 1500, 1470, 1460, 1425, 1370, 1285, 1275, 1220, 1200, 1155, 1130, 1080, 1065, 1040, 1020, 1010, 985 and 840; δ_H(200 MHz; $CDCl_3$) 1.47–1.66 (1 H, m), 1.71–1.90 (1 H, m), 2.00–2.23 (3 H, m), 2.10 (3 H, s, $OCOCH_3$), 3.17 (2 H, s, CH_2Ph), 3.59 (2 H, s, $OCOCH_2Ar$), 3.80 (3 H, s, $ArOCH_3$), 4.03 (1 H, d, *J* 6, 6-H), 4.30–4.45 (1 H, m, 3-H), 4.47–4.63 (3 H, m, 8-H, $CHCH_2OCO$), 5.67 (1 H, dt, *J* 16 and 7, $CHCHCH_2OCO$), 6.14 (1 H, dd, *J* 16 and 9, $CHCHCH_2O$), 6.76–7.01 (3 H, m, aromatic H) and 7.18–7.40 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$) 20.89, 21.96, 28.16, 39.51, 40.96, 41.44, 56.19, 65.74, 74.17, 74.67, 75.57, 112.79, 113.92, 119.08, 122.06, 123.22, 126.19, 127.05, 128.43, 130.75, 134.56 and 176.47; *m/z* (FAB) 495 (MH^+, 100%) and 327 (16).

(E)-1-*Benzyl*-7-[3-(4-*hydroxy*-3-*methoxyphenyl*)*acetoxyprop*-1-*enyl*]-2,9,10-*trioxatricyclo*[4.3.1.0^{3,8}]*decane* **3**.—A stirred solution of the acetate **26** (0.036 g, 0.07 mmol) in dry dichloromethane (8 cm^3) at room temperature was treated with pyrrolidine (0.12 cm^3, 1.45 mmol, 20 equiv.). Two further additions of pyrrolidine (0.12 cm^3, 1.45 mmol, 20 equiv.) were made at 30 min intervals and 1 h after the final addition, the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with dichloromethane–methanol (99:1) as eluent afforded the title compound **3** (0.017 g, 53%) (Found: C, 68.6; H, 6.5. $C_{28}H_{28}O_7$ requires C, 69.0; H, 6.2%): $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3690, 3540, 2970, 1735, 1610, 1520, 1500, 1470, 1455, 1375, 1240, 1210, 1175, 1150, 1080, 1065, 1040, 1020, 1005 and 985; δ_H(200 MHz; $CDCl_3$) 1.43–1.66 (1 H, m), 1.70–1.89 (1 H, m), 2.01–2.26 (3 H, m), 3.19 (2 H, s, CH_2Ph), 3.55 (2 H, s, $OCOCH_2Ar$), 3.88 (3 H, s, $ArOCH_2$), 4.02 (1 H, d, *J* 5, 6-H), 4.36–4.44 (1 H, m, 3-H), 4.47–4.55 (1 H, m, 8-H), 4.58 (2 H, d, *J* 6, $CHCH_2OCO$), 5.57 (1 H, s, ArOH), 5.68 (1 H, dt, *J* 15 and 6, $CHCH_2OCO$), 6.14 (1 H, dd, *J* 15 and 8, $CHCHCH_2O$), 6.73–6.90 (3 H, m, aromatic H) and 7.17–7.41 (5 H, m, aromatic H); δ_C(50 MHz; $CDCl_3$); 21.96, 28.17, 29.13, 39.53, 40.96, 41.17, 56.21, 65.61, 74.18, 74.67, 75.58, 112.22, 114.82, 119.10, 122.66, 126.22, 126.31, 127.04, 128.42, 130.75, 134.42, 135.65, 145.33 and 172.20; *m/z* (FAB) 453 (MH^+, 100%), 271 (4), 182 (10) and 164 (7).

(E)-1-*Benzyl*-7-(*prop*-1-*enyl*)-2,9,10-*trioxatricyclo*-[4.3.1.0^{3,8}]-*decane* **25**.—A stirred solution of the trioxatricyclodecane **21** (0.01 g, 0.03 mmol) in dry ether (2 cm^3) and liquid ammonia (3 cm^3) at −40 °C was treated with sodium metal until a persistent blue colour was obtained. After 1 h the reaction mixture was treated with ethanol (1 cm^3), allowed to warm to room temperature, poured into water (20 cm^3) and extracted with ethyl acetate (3 × 20 cm^3). The combined extracts were washed successively with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude title compound **25** (0.008 g, 98%); δ_H(200 MHz; $CDCl_3$) 1.46–1.89 (2 H, m), 1.70 (3 H, dd, *J* 6 and 1.5, $CHCH_3$), 1.96–2.24 (3 H, m), 3.19 (2 H, s, CH_2Ph), 4.00 (1 H, d, *J* 5, 6-H), 4.34–4.43 (1 H, m, 3-H), 4.45–4.56 (1 H, m, 8-H), 5.54 (1 H, dq, *J* 15 and 6, $CH{=}CHCH_3$), 5.87 (1 H, dd, *J* 15 and 8, $CH{=}CHCH_3$) and 7.18–7.47 (5 H, m, aromatic H); *m/z* (FAB) 273 (MH^+, 100%), 137 (53) and 109 (40).

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