The Stereoselective Synthesis of 2,9,10-Trioxatricyclo[4.3.1.$0^{3,8}$]decane Analogues of Resiniferatoxin

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Structurally simplified analogues of the diterpene resiniferatoxin possessing a 2,9,10-trioxatricyclo[4.3.1.$0^{3,8}$]decane system are synthesised stereoselectively from cyclohexa-1,3-diene.

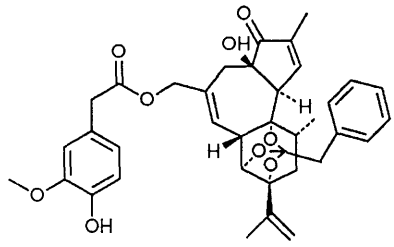
Resiniferatoxin **1**[1], a diterpene component isolated from the resin of *Euphorbia resinifera*, has attracted recent attention due to its potent irritant and antinociceptive activity, and its similarity in pharmacological properties to capsaicin[2] **2**, the active principle from *Capsicum* species, which also possesses analgesic properties.

As part of a project to determine the structure–activity relationships responsible for analgesia that are present in resiniferatoxin, the synthesis of a simplified fragment, namely **3**, was required. The key structural feature present in such a molecule is the unusual tricyclic phenylorthoacetate moiety. This trioxatricyclo[4.3.1.$0^{3,8}$]decane skeleton occurs in a number of natural products but to our knowledge the total synthesis of such a structure has not been reported in the literature. We report here the successful stereoselective synthesis of the orthoester **3** and the corresponding propynyl analogue **4**, starting from cyclohexa-1,3-diene.

Cyclohexa-1,3-diene was converted in two steps into *cis*-cyclohex-2-ene-1,4-diol using literature procedures.[3] Silylation with chlorotrimethylsilane–triethylamine in dimethylformamide afforded the bis-trimethylsilyl ether **5**,† which was oxidised with *m*-chloroperoxybenzoic acid in dichloromethane in the presence of sodium hydrogen carbonate to give the expected *anti*-epoxide **6** by approach of the reagent from the least hindered side of the alkene. The reactions to form **5** and **6** were sufficiently high-yielding (>90%) to allow the crude products, obtained after work-up, to be used without further purification.

Attempts to effect ring-opening of the epoxide to introduce the 3-carbon side chain using organolithium, organomagnesium or organocopper reagents failed. However, the alkynylalane system ($Bu^tPh_2SiOCH_2C{\equiv}CAlEt_2$) described[4] by Nicolaou smoothly converted epoxide **6** into the desired racemic alcohol **7** in good yield (−40 °C, 3 h, 56–70%), which was then converted to the *p*-toluenesulphonate **8** with *p*-toluenesul-

† New compounds exhibited spectroscopic (IR, ^1H NMR, ^{13}C NMR and MS) data in agreement with their structures and satisfactory elemental analyses.



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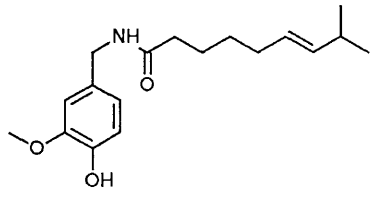

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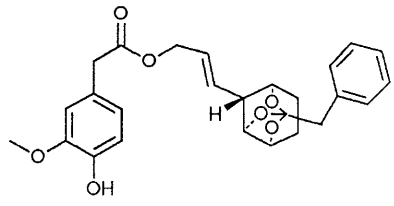

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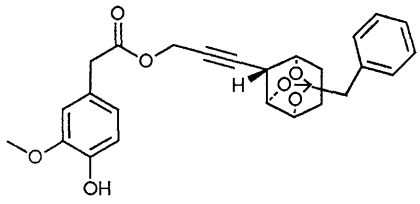

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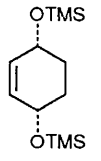

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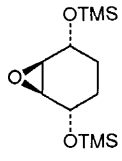

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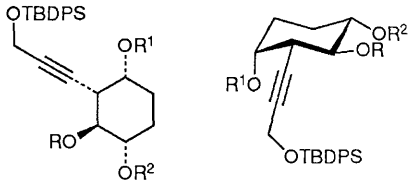
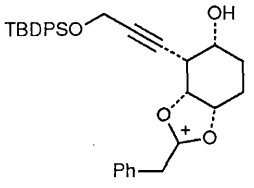
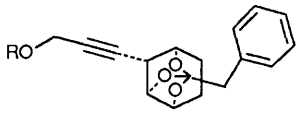


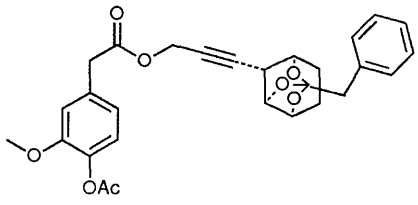
7 R = H, $R^1 = R^2$ = TMS
8 R = Ts, $R^1 = R^2$ = TMS
9 R = Ts, R^1 = TMS, R^2 = H
10 R = Ts, R^1 = TMS, $R^2 = COCH_2Ph$
11 R = Ts, R^1 = H, $R^2 = COCH_2Ph$



11a



12 R = TBDPS
13 R = H



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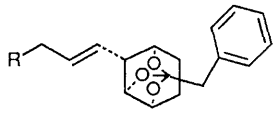

15 R = OH
16 R = H

TMS = trimethylsilyl;
TBDPS = *tert*-butyldiphenylsilyl;
Ts = *p*-$MeC_6H_4SO_2$

phonic anhydride in pyridine (0–25 °C, 1.3 h, 66%). ^{1}H NMR spectroscopy suggested that **7** and **8** existed in the chair conformation as shown with three of the four substituents equatorial; the proton attached to the carbon bearing the tosyloxy function exhibited two large vicinal coupling constants (*J ca.* 10 Hz) in agreement with two axial–axial interactions.

Treatment of **8** with catalytic (10 mol%) citric acid monohydrate in methanol at room temperature for 5 h selectively hydrolysed the equatorially disposed trimethylsilyl ether to give the alcohol **9** in 82% yield, which was acylated with phenylacetic acid–dicyclohexylcarbodiimide (DCC)–4-dimethylaminopyridine (DMAP) in dichloromethane to afford the crystalline phenylacetate **10** (0–25 °C, 4 h, 76%, m.p. 125–126.5 °C). More vigorous conditions (10 mol% citric acid–methanol–water, reflux, 30 min) cleaved the other trimethylsilyl ether (TMS) to give the alcohol **11**‡ in 83% yield. Alternatively, simple treatment of crude **10**, obtained after acylation and work-up, with methanol at room temperature immediately gave **11**, in 75% overall yield from **9**.

‡ *Spectroscopic data* for **11**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (9H, s, $-CMe_3$); 1.45 (1H, m, ring CH); 1.84 (3H, m, ring CH); 1.98 (1H, br s, –OH); 2.30 (3H, s, $ArCH_3$); 2.64 (1H, dd, *J* 2.2, 10.2 Hz, $-CHC{\equiv}C-$); 3.59 (2H, s, $OCOCH_2Ph$); 3.89 (1H, m, $-CHOH$); 4.17 (2H, d, *J* 1.8 Hz, $-OCH_2C{\equiv}C-$); 4.82 (1H, m, $-CHOCOCH_2Ph$); 5.03 (1H, dd, *J* 10.2, 10.2 Hz, $-CHOTs$); 7.14–7.34 (7H, m, Ar*H*); 7.36–7.51 (6H, m, Ar*H*); 7.65–7.80 (6H, m, Ar*H*).

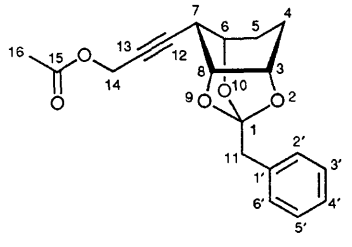

Fig. 1

It has been reported[5] previously that the solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulphonate in absolute ethanol containing potassium acetate affords the bicyclic 2-ethoxy-1,3-dioxolane orthoester *via* the corresponding dioxolenium ion intermediate. In the case of **11**, it was envisaged that if such a dioxolenium ion (*i.e.* **11a**) could be generated, intramolecular trapping by the hydroxy function would lead directly to the phenylorthoacetate **12**. This was indeed found to be the case; **11** was converted smoothly to **12** in 73% yield, after 10 h at reflux in 2,4,6-collidine under argon. Heating at lower temperatures, *e.g.* in pyridine or 2,6-lutidine at reflux, resulted in prolonged reaction times and/or incomplete conversion of **11**. Confirmation of the presence of the required phenylorthoacetate was obtained by NMR spectroscopy; the ^{13}C NMR spectrum contained a characteristic orthoester

resonance at δ 119 and in the ^{1}H NMR spectrum, the methylene protons adjacent to the orthoester carbon resonated as a singlet at δ 3.20, in good agreement with the resonance of the corresponding protons in resiniferatoxin.

Removal of the *tert*-butyldiphenylsilyl ether (TBDPS) with tetra-n-butylammonium fluoride in tetrahydrofuran (THF) gave an essentially quantitative yield of the propynylic alcohol **13** (room temperature, 20 min., 97%), which was coupled with 4-*O*-acetylhomovanillic acid (DCC, DMAP, CH_2Cl_2, room temperature, 3 h) to give **14**. Subsequent cleavage of the phenolic acetate with excess pyrrolidine at room temperature for 1 h afforded **4** in 86% overall yield from **13**.§

§ *Spectroscopic data* for the acetate derivative of **13**: (see Fig. 1) ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50 (1H, m, H-4$_{ax}$); 1.82 (1H, m, H-5$_{ax}$); 2.11 (3H, s, H-16); 2.14 (2H, m, H-4$_{eq}$, H-5$_{eq}$); 2.46 (1H, m, H-7); 3.22 (2H, s, H-11); 4.25 (1H, m, H-6); 4.51 (1H, m, H-3); 4.59 (1H, m, H-8); 4.74 (2H, d, H-14); 7.28 (3H, m, H-3′, H-4′, H-5′); 7.38 (2H, m, H-2′, H-6′).

^{13}C NMR (90 MHz, $CDCl_3$) δ 21.0 (C-16); 21.6 (C-4); 27.8 (C-5); 30.2 (C-7); 40.7 (C-11); 52.9 (C-14); 73.3 (C-6); 74.0 (C-3, C-8); 76.2 (C-12); 85.4 (C-13); 118.9 (C-1); 126.7 (C-4′); 128.0 (C-3′, C-5′); 130.2 (C-2′, C-6′); 135.0 (C-1′); 170.3 (C-15).

In order to obtain the corresponding *trans*-alkenyl derivative **3**, the propynylic alcohol **13** was treated with Red-Al in THF to give stereoselectively the desired *E*-isomer **15** in 50% yield. Treatment of **13** with sodium in liquid ammonia also reduced the alkyne to the *E*-alkene but concomitant reductive fission occurred giving rise to the unwanted deoxy-analogue **16**. Coupling of **15** with the protected homovanillic acid and final deprotection as above afforded **3** in 61% yield.

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