Silenes in organic synthesis: a concise synthesis of (±)-*epi*-picropodophyllin†

Robert D. C. Pullin, Jonathan D. Sellars and Patrick G. Steel*

Received 9th July 2007, Accepted 13th August 2007
First published as an Advance Article on the web 31st August 2007
DOI: 10.1039/b710370k

A concise, seven step synthesis of the aryl tetralin lignan lactone *epi*-picropodophyllin from piperonal is described. The key steps are a silene diene Diels–Alder reaction and the Hosomi–Sakurai reaction of the resultant silacyclohexene.

Introduction

Podophyllotoxin **1** is a naturally occurring aryltetralin lignan lactone, first isolated from the resin mixture of the plant toxin podophyllin by Podwyssotzki in 1880.[1] The resin podophyllin is obtained from the roots of the American Mayapple tree (*Podophyllum peltatum*), and the Indian (*Podophyllum emodi*) and Taiwanese (*Podophyllum pleianthum*) plant derivatives.[2,3] Whilst podophyllotoxin has important antitumour properties, clinical application has been limited by serious toxicity and its major role has been as the precursor for semi-synthetic analogues with better therapeutic profiles. Consequently, whilst podophyllotoxin has proved only to be an effective and comparatively safe drug for the treatment of genital warts,[4] the semi-synthetic derivatives etoposide, **7**, etopophos **8**, tenoposide **9** and GL-331 **10** have all been successfully utilised as antitumour agents in clinical trials against a variety of malignant conditions.[4,5]

Reflecting both the significant clinical roles and intriguing structures, podophyllotoxin **1** and related analogues **2–6**, Fig. 1, have received considerable attention from synthetic chemists over the years.[6–8] As a component of a project exploring the application of silenes (compounds containing a silicon–carbon double bond) in organic synthesis,[9–15] we have recently demonstrated that the silacyclohexene cycloadducts obtained from a silene diene Diels–Alder reaction function as a silacyclic allyl silane in the Hosomi–Sakurai reaction with various acetals, Scheme 1.[16] When electron rich aryl acetals are employed a second cationic cyclisation occurs to give a one-pot synthesis of aryl tetralols with moderate to complete diastereoselectivity.[17]

Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham, UK DH1 3LE. E-mail: p.g.steel@durham.ac.uk

† Electronic supplementary information (ESI) available: Experimental and analytical details for compounds **21a**, **24–26**, **28** and **29**. See DOI: 10.1039/b710370k

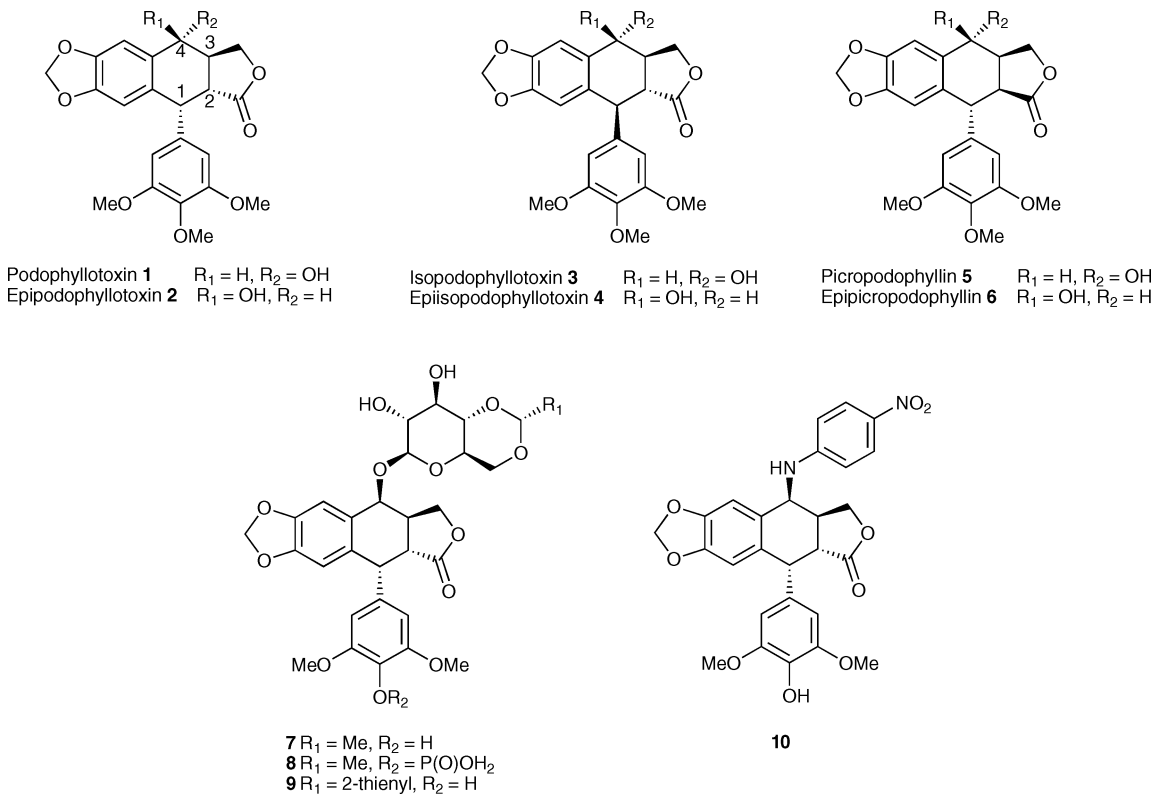
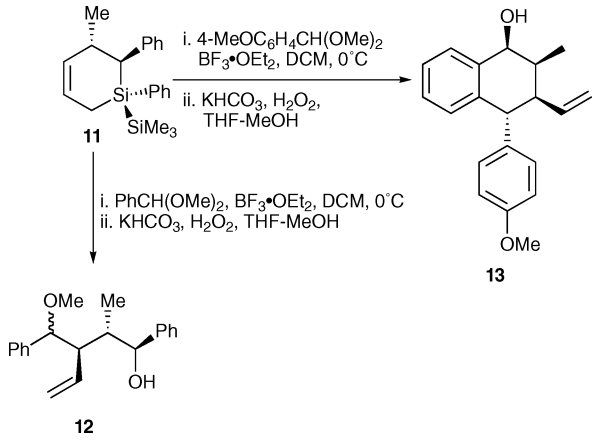
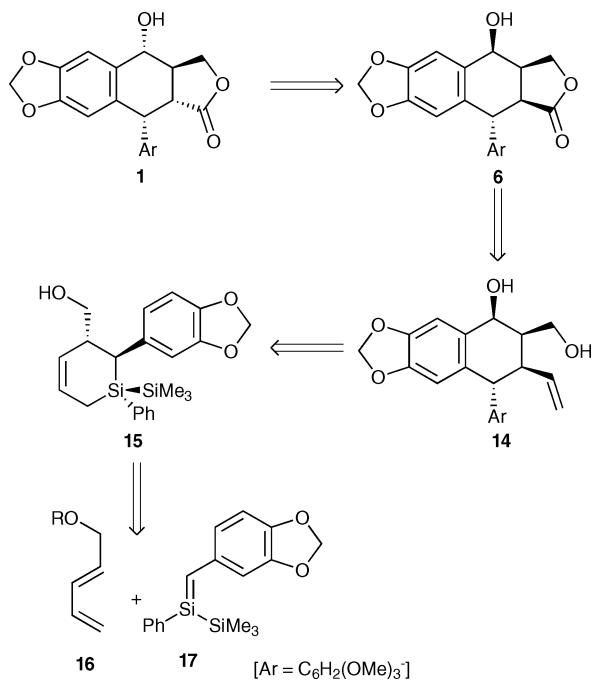


Fig. 1 Podophyllotoxin and selected analogues.



Scheme 1

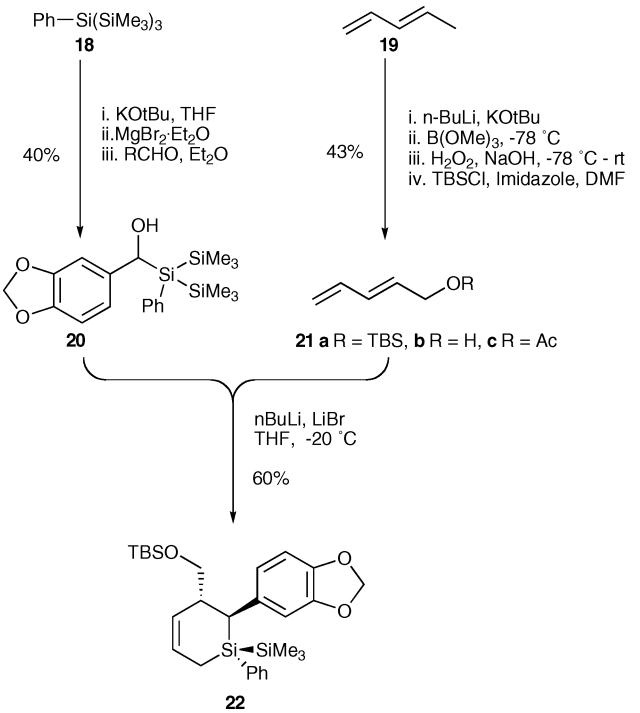
Recognising the similarity between these products and the aryl tetralin lignan lactones we sought to apply this methodology to a synthesis of this class of natural product. The basic retrosynthetic analysis is shown in Scheme 2. Given that late stage epimerisation of the *cis* lactone found in picropodophyllin **5** to the *trans* lactone found in podophyllotoxin was demonstrated in the first reported synthesis of podophyllotoxin,[18,19] the initial target was the *cis* lactone establishing the *trans* arrangement between the aryl substituent at C-1 and the hydroxymethyl group at C-3. This requires access to the silacycle **15** and subsequent elaboration to the tetralol **14**. In this paper we describe our efforts which lead to a realisation of this goal and provide a concise synthesis of (±)-*epi*-picropodophyllin **6**, and hence a formal synthesis of podophyllotoxin **1**.



Scheme 2

Results and discussion

As described in Scheme 2, our approach to *epi*-picropodophyllin **6** relied on the efficient access to the silacyclohex-4-ene **15**. Accordingly, this became the first objective of the synthesis. Silyl alcohol **20** was synthesised in good yield following procedures previously described, Scheme 3.[12] This involved generation of the silyl potassium reagent by reaction of phenylpolysilane **18** with KO^{t}Bu followed by transmetallation to the silyl Grignard and addition of piperonal to provide silyl alcohol **20** in 40% yield. Similarly, the desired diene **21a** could be prepared following protocols established by Schlosser.[20] This involved metallation of piperylene **19** with KO^{t}Bu–^{n}BuLi, reaction of the ensuing pentadienyl potassium with trimethyl borate followed by an oxidative workup and final protection of the resulting alcohol to afford the TBS ether **21a** as a 9 : 1 *E* : *Z* mixture of isomers.



Scheme 3

Silene generation from silyl alcohol **20** *via* the LiBr promoted sila-Peterson reaction and *in situ* Diels–Alder reaction followed the precedents established in our earlier reports to afford the desired silacyclohexene **22** as an inseparable mixture of diastereoisomers in the ratio 80 : 13 : 3 : 4, as determined by integration of the GCMS trace (integration of peaks with $m/z = 510$ (M^+), $R_t = 28.8$–29.3 min). The stereochemistry of the major silacycle stereoisomer was determined by NMR studies with all data being consistent with those previously reported for such reactions.[12] The coupling constant between 2-H and 3-H was of a magnitude consistent with coupling between two axially oriented protons ($J = 9.0$ Hz). Moreover, NOESY correlations were observed between 2-H and 3-CH_2OTBS and for transannular interactions between 2-H and 6-H and the TMS group and 3-H, Fig. 2. Interestingly, the yield of this process is higher than that previously obtained

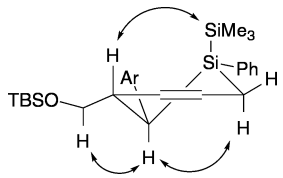


Fig. 2 Selected NOESY correlations for **22**.

with simple phenyl and alkyl substituted silenes. We speculate that this corresponds to the fact that the sesamyl silene is stabilised by some degree of reversed polarisation and therefore is less prone to dimerisation.[21,22]

With a robust, high yielding procedure established to gain access to the desired sesamyl substituted silacyclohex-4-ene **22**, subsequent studies focused on its application in the Hosomi–Sakurai reaction. Initial reaction of silacyclohex-4-ene **22**, under the standard conditions with 3,4,5-trimethoxybenzaldehyde dimethylacetal, was disappointing, generating only minor amounts (7%) of the unprotected aryl tetralin diol **14**. Importantly however, the aryl tetralin diol **14** was generated as a single diastereoisomer with all data, particularly NOESY correlations, Fig. 3, for the tetrahydronaphthalene **14** being consistent with those observed previously for related substrates. Suspecting that the formation of a diol product indicated instability of the TBS group to the acidic nature of the reaction conditions, alternative protecting group strategies were then explored.

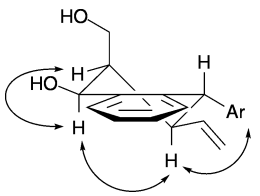
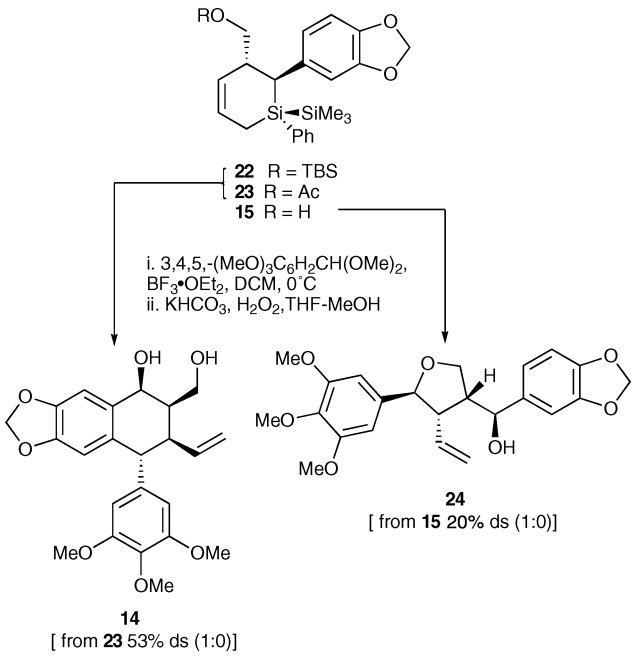


Fig. 3 Selected NOESY correlations for **14** (methylenedioxy group omitted for clarity).

Simple deprotection of the silacyclohexene **22** using *p*-TsOH and reaction with acetyl chloride afforded the corresponding acetate **23**. Satisifyingly, this proved stable to the Sakurai reaction conditions and permitted the isolation of the desired tetralol **14** in 53% yield. Presumably, the acetate is cleaved during the basic Tamao oxidation. Attempts to shorten the synthesis through either using dienyl acetate **21c** in the Diels–Alder reaction or hydroxymethyl silacyclohexene **15** in the Sakurai reaction were not successful. Acetate **21c** proved unstable with respect to the basic/nucleophilic nature of the silene generation conditions whilst alcohol **15** underwent an alternative cyclisation to afford, following oxidation of the intermediate silyl fluoride, furan **24** in modest yield but excellent diastereoselectivity, Scheme 4.

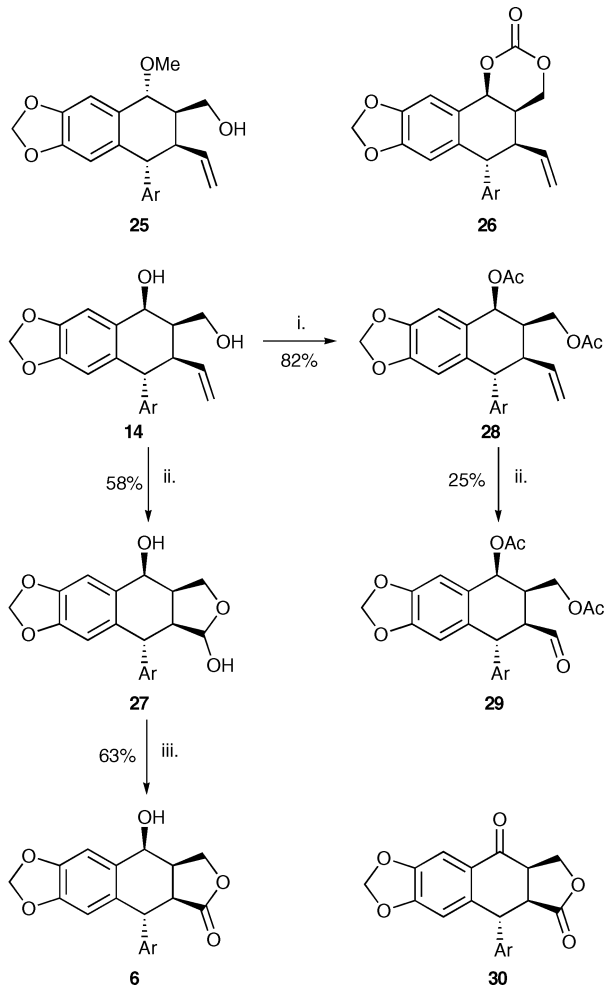
Having established the tetrol skeleton with the correct *trans* arrangement between the hydroxymethyl substituent at C-3 and the aryl group at C-1, all that remained was to convert the ethenyl side chain to a carboxylate and form the lactone. Initially, believing that protection of the diol functionality would be beneficial, various protecting groups were explored. However, attempts to introduce either a silyl or benzylidene acetal were unsuccessful, leading to recovered starting material, whilst reaction with 2,2-dimethoxypropane afforded the corresponding methyl ether **25**. Interestingly, this had the alternative C-4 stereochemistry indicating the facile interconversion between the two series. In contrast to these difficulties, formation of either the diacetate **28** or cyclic carbonate **26** proved to be straightforward. Whilst the latter proved not to be stable to the oxidation conditions explored, the diacetate could be converted to the aldehyde **29** on treatment with OsO_4–$NaIO_4$ albeit in only modest yield. Moreover, subsequent oxidation to the acid proved problematic with extensive decomposition occurring. Given these difficulties, it was decided to circumvent protecting group issues and explore direct oxidation of the diol **14**. Whilst oxidation with ozone was unsuccessful, reaction with OsO_4–$NaIO_4$ afforded the lactol **27** in 58% yield as a 3 : 1 mixture of anomers, Scheme 5.



Scheme 4

Delighted with this result, attention turned to the selective oxidation of the lactol **27** in the presence of the C-4 alcohol. Nicolaou *et al.* have recently described such a transformation using excess NIS (5 eq.) and TBAI (2 eq.).[23] However, reaction of lactol **27** following these precedents afforded equimolar amounts of *epi*-picropodophyllin **6** and the corresponding ketone, picropodophyllone **30**, identified by comparison of the spectral data with those reported in the literature.[24] Fortunately, simply reducing the stoichiometry of the oxidant to 1 eq. NIS and 0.4 eq. TBAI afforded *epi*-picropodophyllin **6** in 63% yield with only trace amounts of the over-oxidation product.

In conclusion, the strategy of silene Diels–Alder reaction followed by a Hosomi–Sakurai reaction provides a very concise entry to the aryl tetralin lignan lactones of the picropodophyllin series, requiring only seven steps from piperonal for the synthesis of *epi*-picropodophyllin. Moreover, the chemistry is modular allowing both aryl components to be easily varied. Finally, given that methods for epimerisation at both C-2 and C-4 are well established,[19,25,26] this work also represents a formal approach



Scheme 5 *Reagents*: i. Ac_2O, DIPEA, DCM; ii. OsO_4 (cat.), $NaIO_4$, 2,6-lutidine, THF, H_2O; iii. NIS, Bu_4NI (0.4 eq.), DCM.

to the other lignan lactone series including that of podophyllotoxin **1**.

Experimental

All air and/or moisture sensitive reactions were carried out under an argon atmosphere. Solvents were purified and dried following established protocols. Petrol refers to petroleum spirit boiling in the 40–60 °C range. Ether refers to diethyl ether. Aldehydes and dienes were distilled, immediately prior to use, from anhydrous calcium sulfate and sodium borohydride, respectively. All other commercially available reagents were used as received unless otherwise stated. Flash column chromatography was performed according to the method of Still *et al.* using 200–400 mesh silica gel.[27] Yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H and ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory).

Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded using a Diamond ATR (attenuated total reflection) accessory (Golden Gate) or as a solution in chloroform *via* transmission IR cells on a Perkin-Elmer FT-IR 1600 spectrometer. Unless otherwise stated, ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Mercury 200, Varian Unity-300, Varian VXR-400 or Varian Inova-500 spectrometers and are reported as follows; chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). Residual protic solvent $CHCl_3$ (δ_H = 7.26) was used as the internal reference. ^{13}C NMR spectra were recorded at 63 MHz or 126 MHz, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. ^{29}Si NMR spectra were recorded at 99 MHz on a Varian Inova-500. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants are given in Hertz. All ^{13}C spectra were proton decoupled. Assignment of spectra was carried out using DEPT, COSY, HSQC, HMBC and NOESY experiments.

Gas chromatography-mass spectra (GCMS, EI or CI) were obtained using a Thermo TRACE mass spectrometer. Electrospray mass spectra (ES) were obtained on a Micromass LCT mass spectrometer. High resolution mass spectra were obtained using a Thermo LTQ mass spectrometer (ES) at the University of Durham, or performed by the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Methods for the preparation of and associated characterisation data for **20**, **21b** and **21c** have previously been reported.[17,20] Characterisation data for compounds **21a**, **24–26**, **28** and **29** can be found in the ESI.†

(1*SR*,2*SR*,3*RS*)-2-(3′,4′-Methylenedioxyphenyl)-1-phenyl-3-*tert*-butyldimethylsilyloxymethyl-1-trimethylsilylsilacyclohex-4-ene 22

^{n}Butyllithium (1.10 ml, 1.6 M, 1.75 mmol) was added to a stirred solution of silyl alcohol **20** (0.67 g, 1.67 mmol) and diene **21a** (0.99 g, 5.01 mmol) in diethyl ether (20 ml). The mixture was stirred for 2 h and then cooled to −20 °C. An anhydrous suspension of LiBr in diethyl ether (0.31 ml, 0.31 M, 0.096 mmol) was added and the reaction mixture was stirred for 18 h. The reaction was quenched with saturated ammonium chloride (20 ml) and the aqueous layer was separated and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an orange oil. Flash column chromatography [petroleum ether, petroleum ether–diethyl ether (99 : 1)] afforded a mixture of **22** and diene **21a**. The latter was separated *via* Kugelrohr distillation (bp 95–100 °C, 1.5 mbar) to afford **22** as a viscous colourless oil as a mixture of diastereoisomers in the ratio 80 : 13 : 3 : 4 by GCMS (513 mg, 60%). R_f: 0.45 [petroleum ether–diethyl ether (95 : 5)]; spectroscopic data for major isomer **22**: ν_{max} (ATR) 3080, 3020, 2952, 2894, 2854, 1484, 1440, 1244, 1184, 1099, 1040, 938, 909, 832, 775, 733, 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$); 7.54–7.53 (5H, m, Ar-*H*), 6.69 (1H, d, *J* 8.0, 6′-*H*), 6.62 (1H, s, 2′-*H*), 6.55 (1H, d, *J* 8.0, 5′-*H*), 6.03 (1H, m, 5-*H*), 5.91 (2H, s, –OCH_2O–), 5.81 (1H, d, *J* 10.6, 4-*H*), 3.42 (1H, dd, *J* 9.7, 5.0, 3-C*H*HOTBS), 3.25 (1H, dd, *J* 9.7, 5.0, 3-CH*H*OTBS), 2.73 (1H, m, 3-*H*), 2.54 (1H, d, *J* 9.0, 2-*H*), 1.80 (1H, m, 6-*H*H), 1.64 (1H, m, 6-H*H*), 0.82 (9H, s, –OSiC(CH_3)$_3$), −0.05 (9H, s, –Si(CH_3)$_3$), −0.10 (6H, s, –OSi(CH_3)$_2$); δ_C (126 MHz) 147.6 (*C*-5′), 144.7 (*C*-4′), 138.4 (*C*-1′), 137.0 (Ar-*C*), 134.4 (Ar-*C*), 132.4 (*C*-4), 128.6 (Ar-*C*), 127.6 (Ar-*C*), 125.7 (*C*-5), 120.7 (*C*-2′), 108.6 (*C*-6′), 108.2 (*C*-3′), 100.6 (–OCH_2O–), 65.6 (–CH_2OTBS), 44.9

(*C*-3), 33.2 (*C*-2), 25.9 (–OSiC(CH_3)$_3$), 18.2 (–OSi*C*(CH_3)$_3$), 9.2 (6-*C*), −1.3 (–Si(CH_3)$_3$), −5.4 (–Si(CH_3)$_2$); *m/z* (EI) 510 (M^+, 1%), 438 (M^+ − ^{t}Bu − Me, 4), 437 (M^+ − TMS, 10), 135 (57), 73 (TMS, 100); HRMS (CI, NH_3): found M^+, 510.2432, $C_{28}H_{42}O_3Si_3$ requires 510.2436.

(1*SR*,2*SR*,3*RS*)-3-Hydroxymethyl-2-(3′,4′-methylenedioxyphenyl)-1-phenyl-1-trimethylsilylsilacyclohex-4-ene 15

To a solution of silacycle **22** (0.2 g, 0.4 mmol) in THF–MeOH (1 : 1, 2 ml) was added a catalytic amount of *p*-toluene sulfonic acid and 0.5 M aq. HCl. The solution was stirred for 1 h at room temperature then diluted with Et_2O and washed with water (5 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography [pet. ether–ether (9 : 1, 4 : 1, 7 : 3)] gave the title compound **15** as a colourless oil (0.1 g, 64%); R_f 0.3 (pet. ether–ether 7 : 3); ν_{max} (thin film) 3508–3192 (broad, OH), 3016, 2950, 2882, 1606, 1502, 1484, 1246, 1041, 835 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29–7.28 (5H, m, Ar-*H*), 6.72 (1H, d, *J* 8, Ar-*H*), 6.65 (1H, s, Ar-*H*), 6.57 (1H, d, *J* 8, Ar-*H*), 6.15 (1H, m, 5-*H*), 5.95 (2H, s, –OCH_2O–), 5.76 (1H, m, 4-*H*), 3.55 (1H, dd, *J* 10, 5, 3-C*H*HOH), 3.45 (1H, dd, *J* 10, 5, 3-CH*H*OH), 2.82 (1H, m, 3-*H*), 2.63 (1H, d, *J* 9, 2-*H*), 1.87 (1H, m, 6-*H*H), 1.68 (1H, m, 6-H*H*), −0.02 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 148.0 (Ar-*C*), 145.2 (Ar-*C*), 137.9 (*ipso*-Ar-*C*), 134.6 (Ar-*C*), 134.2 (Ar-*C*), 131.6 (*C*-4), 128.9 (Ar-*C*), 128.1 (Ar-*C*), 127.9 (*C*-5), 121.1 (Ar-*C*), 108.8 (Ar-*C*), 108.6 (Ar-*C*), 101.0 (–OCH_2O–), 65.6 (3-CH_2OH), 45.4 (*C*-3), 38.8 (*C*-2), 9.8 (*C*-6), −0.9 (Si(CH_3)$_3$); δ_{Si} (100 MHz, $CDCl_3$) −18.96, −22.60; *m/z* (ES^+) 419 (MNa^+); HRMS (ES^+): found MNa^+, 419.1473, $C_{22}H_{28}O_3NaSi_2$ requires 419.1469.

(1*SR*,2*SR*,3*RS*)-3-Acetoxymethyl-2-(3′,4′-methylenedioxyphenyl)-1-phenyl-1-trimethylsilylsilacyclohex-4-ene 23

A solution of hydroxysilacycle **15** (100 mg, 0.3 mmol) in dichloromethane (3 ml) was treated consecutively with diisopropylethylamine (DIPEA, 0.18 ml, 1.0 mmol), acetic anhydride (0.05 ml, 0.5 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction was stirred at room temperature for 45 min after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography [pet. ether; pet. ether–ether (9 : 1, 4 : 1)] afforded the title compound **23** as a colourless oil (80 mg, 70%); R_f 0.5 (pet. ether–ether 7 : 3); ν_{max} (thin film) 2955, 2884, 1720 (C=O), 1502, 1484, 1439, 1285, 1246, 1160, 1041, 896, 835 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.30–7.25 (5H, m, Ar-*H*), 6.71 (1H, d, *J* 8, Ar-*H*), 6.62 (1H, s, Ar-*H*), 6.55 (1H, d, *J* 8, Ar-*H*), 6.11 (1H, m, 5-*H*), 5.94 (2H, s, –OCH_2O–), 5.71 (1H, m, 4-*H*), 4.00 (1H, dd, *J* 10, 5, 3-C*H*H), 3.81 (1H, dd, *J* 10, 5, 3-CH*H*), 2.93 (1H, m, 3-*H*), 2.48 (1H, d, *J* 9, 2-*H*), 1.99 (3H, s, CH_3CO), 1.87 (1H, m, 6-*H*H), 1.69 (1H, m, 6-H*H*), −0.01 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 171.1 (*C*=O), 147.8 (Ar-*C*), 145.0 (Ar-*C*), 137.1 (*ipso*-Ar-*C*), 136.4 (Ar-*C*), 134.3 (Ar-*C*), 133.9 (Ar-*C*), 130.8 (4-*C*), 129.8 (Ar-*C*), 127.8 (Ar-*C*), 127.2 (*C*-5), 120.7 (Ar-*C*), 108.4 (Ar-*C*), 100.8 (–OCH_2O–), 67.1 (3-CH_2), 41.2 (*C*-3), 34.4 (*C*-2), 20.9 (*C*H_3CO), 9.5 (*C*-6), −1.3 (Si(CH_3)$_3$); *m/z* (ES^+) 461 (MNa^+); HRMS (ES^+): found MH^+, 439.1758, $C_{24}H_{31}Si_2O_4$ requires 439.1755.

(1*RS*,2*SR*,3*RS*,4*SR*)-2-Ethenyl-4-hydroxy-3-hydroxymethyl-6,7-methylenedioxy-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene 14

A solution of silacycle **23** (2.0 g, 4.6 mmol) in dichloromethane (75 ml) was treated with 3,4,5-trimethoxybenzaldehyde dimethylacetal (9.2 mmol) and cooled to 0 °C. The solution was then treated with $BF_3{\cdot}Et_2O$ (0.5 M in DCM, 4.6 mmol) and stirred at 0 °C for 6 h. The reaction mixture was then poured into aq. NH_4Cl and extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude organic material was dissolved in methanol–THF (5 ml, 1 : 1) and treated with $KHCO_3$ (1.0 mmol) and a 35% w/w solution of H_2O_2 (4.0 mmol) at room temperature. The reaction mixture was then heated under reflux for 5 h and then poured into saturated aq. $Na_2S_2O_3$ and extracted with EtOAc (3 × 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a colourless oil. Flash column chromatography [pet. ether–ethyl acetate (6 : 4, 4 : 6), ethyl acetate] afforded tetralol **14**, which crystallised as a white solid (1.0 g, 53%); R_f: 0.52 (ethyl acetate); mp 178–182 °C (from ethyl acetate); ν_{max} (ATR) 3411–3318, 2950, 2890, 2850, 1592, 1503, 1485, 1456, 1421, 1331, 1236, 1129, 1022, 930, 879, 796, 668 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.09 (1H, s, 5-*H*), 6.38 (1H, s, 8-*H*), 6.15 (2H, s, 2′-*H*, 6′-*H*), 5.98 (1H, m, 2-C*H*=C), 5.95 (1H, d, *J* 1.4, –OC*H*HO–), 5.94 (1H, d, *J* 1.4, –OCH*H*O–), 5.07 (1H, bd, *J* 18.5, C=C*H*H), 5.06 (1H, bd, *J* 7.7, C=CH*H*), 4.99 (1H, m, 4-*H*), 3.95 (1H, m, C*H*HOH), 3.88 (2H, m, CH*H*OH, 1-*H*), 3.82 (3H, s, 4′-OCH_3), 3.76 (6H, s, 3′-OCH_3, 5′-OCH_3), 2.94 (1H, d, *J* 5.8, 4-O*H*), 2.68 (1H, m, 2-*H*), 2.42 (1H, m, 3-*H*), 1.14 (1H, d, *J* 6.4, –CH_2O*H*); δ_C (126 MHz, $CDCl_3$) 153.0 (*C*-3′, *C*-5′), 147.3 (Ar-*C*), 146.8 (Ar-*C*), 140.7 (*C*-1′), 139.4 (2-*C*H=C), 136.5 (*C*-4′), 132.0 (Ar-*C*), 130.2 (Ar-*C*), 116.3 (C=*C*H_2), 109.4 (*C*-8), 107.7 (*C*-5), 106.0 (*C*-2′, *C*-6′), 101.0 (–OCH_2O–), 70.4 (*C*-4), 62.0 (3-*C*H_2), 60.8 (4′-O*C*H_3), 56.1 (3′-O*C*H_3, 5′-O*C*H_3), 49.5 (*C*-1), 47.02 (*C*-2), 42.03 (*C*-3); *m/z* (ES^+) 437 (MNa^+); HRMS (ES^+): found MNa^+, 437.1571, $C_{23}H_{26}O_7Na$ requires 437.1571.

(1*SR*,2*SR*,3*RS*,4*SR*)-6,7-(Methylenedioxy)-4-(3,4,5-trimethoxyphenyl)-1,2,2′,3,3′,4-hexahydronaptho[2,2′-c]furan-1,3′-diol 27

A solution of tetralol **14** (30 mg, 0.06 mmol) in THF–H_2O (1 : 1, 3 ml) was treated with 2,6-lutidine (0.01 ml, 0.1 mmol), osmium tetroxide (2 mg, 0.006 mmol) and sodium periodate (50 mg, 0.2 mmol) at room temperature. The solution was stirred for 1 h then poured into H_2O and extracted with DCM (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography (ether) afforded the title compound **27** as a light brown oil (14 mg, 58%) as a mixture of diastereoisomers in the ratio 3 : 1 by NMR; R_f 0.3 (ether); ν_{max} (thin film) 3155 (broad, OH), 2982, 2901, 1793, 1591, 1482, 1382, 1238, 1130, 913, 731 cm^{-1}; NMR data given for major isomer: δ_H (500 MHz, $CDCl_3$) 6.74 (1H, s, Ar-*H*), 6.48 (2H, s, Ar-*H*), 6.31 (1H, s, Ar-*H*), 5.91 (1H, s, –OC*H*HO–), 5.89 (1H, s, –OC*H*HO–), 5.19 (1H, m, 2-C*H*HO), 4.97 (1H, m, 2-CH*H*O), 4.70 (1H, s, 3-C*H*OH), 4.24–4.15 (2H, m, 1-*H*,

4-*H*), 3.88 (3H, s, Ar–OCH_3), 3.83 (6H, s, Ar–OCH_3), 3.03 (1H, s, 3-CHO*H*), 2.87 (1H, m, 2-*H*), 2.73 (1H, m, 3-*H*); δ_C (126 MHz, $CDCl_3$) 153.8 (Ar-*C*), 148.1 (Ar-*C*), 145.8 (Ar-*C*), 140.0 (Ar-*C*), 135.6 (Ar-*C*), 132.0 (Ar-*C*), 109.3 (Ar-*C*), 108.6 (Ar-*C*), 106.3 (Ar-*C*), 106.1 (Ar-*C*), 101.4 (OCH_2O), 97.4 (2-CH_2), 70.3 (3-*C*H), 67.2 (*C*-1), 61.2 (Ar–OCH_3), 56.4 (Ar–OCH_3), 50.1 (*C*-2), 43.7 (*C*-4), 42.0 (*C*-3); *m*/*z* (ES^+) 855 (M_2Na^+); HRMS (ES^+): found M_2Na^+, 855.2845, $C_{44}H_{48}O_{16}Na$ requires 855.2835.

(±)-*epi*-Picropodophyllin 6[28]

A solution of lactol **27** (10 mg, 0.04 mmol) in DCM (2 ml) was treated with *N*-iodosuccinimide (NIS, 20 mg, 0.08 mmol) and *tert*-butyl ammonium iodide (TBAI, 10 mg, 0.02 mmol) at room temperature. The solution was stirred for 1 h then poured into saturated aq. $Na_2S_2O_3$ and extracted with DCM (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography [pet. ether–ether (2 : 3, 3 : 7, 1 : 4, 1 : 9, ether] afforded the title compound as a semi solid (9 mg, 63%); R_f 0.3 (ether); mp 185–188 °C (lit.[28] mp 190–192 °C); ν_{max} (thin film) 3155 (broad, OH), 2903, 1765 (C=O), 1483, 1383, 1246, 1130, 1095, 927, 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.01 (1H, s, Ar-*H*), 6.60 (1H, s, Ar-*H*), 6.35 (2H, s, Ar-*H*), 5.98 (1H, d, *J* 1.0, –OCH*H*O–), 5.95 (1H, d, *J* 1.0, –OC*H*HO–), 4.82 (1H, m, 1-*H*), 4.45 (1H, d, *J* 4, 4-*H*), 4.35 (2H, m, 2-CH_2O), 3.82 (3H, s, Ar–OCH_3), 3.78 (6H, s, Ar–OCH_3), 3.44 (1H, dd, *J* 10, 4, 3-*H*), 3.16 (1H, m, 2-*H*), 2.08 (1H, d, *J* 5, 1-O*H*); δ_C (126 MHz, $CDCl_3$) 178.8 (*C*=O), 153.3 (Ar-*C*), 147.5 (Ar-*C*), 147.1 (Ar-*C*), 137.6 (Ar-*C*), 136.8 (Ar-*C*), 131.1 (Ar-*C*), 130.1 (Ar-*C*), 109.8 (Ar-*C*), 106.3 (Ar-*C*), 104.9 (Ar-*C*), 101.2 (OCH_2O), 68.1 (2-CH_2), 67.9 (*C*-1), 60.9 (Ar–OCH_3), 56.2 (Ar–OCH_3), 45.2 (*C*-4), 44.4 (*C*-3), 39.5 (*C*-2); *m*/*z* (ES^+) 415 (MH^+).

(±)-Picropodophyllone 30[24]

Obtained from oxidation of lactol **27** using excess oxidant (5 eq. NIS) following the same procedure as described for *epi*-picropodophyllin **6** yielded after chromatography picropodophyllone as a white solid (26%); R_f 0.5 (ether); mp 146–148 °C (lit.[26] mp 152–158 °C); ν_{max} (thin film) 2982, 1780 (C=O), 1722 (C=O), 1479, 1383, 1343, 1257, 1161, 1130, 1097, 899, 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.50 (1H, s, Ar-*H*), 6.70 (1H, s, Ar-*H*), 6.23 (2H, s, Ar-*H*), 6.06 (1H, d, *J* 1.2, –OCH*H*O–), 6.04 (1H, d, *J* 1.2, –OC*H*HO–), 4.76 (1H, d, *J* 9, 4-*H*), 4.69 (1H, s, 3-*H*), 4.35 (1H, m, 2-*H*), 3.79 (3H, s, Ar–OCH_3), 3.75 (6H, s, Ar–OCH_3), 3.31 (2H, m, 2-CH_2O); δ_C (126 MHz, $CDCl_3$) 177.5 (*C*=O), 175.9 (*C*=O), 154.0 (Ar-*C*), 153.9 (Ar-*C*), 148.7 (Ar-*C*), 139.8 (Ar-*C*), 138.2 (Ar-*C*), 137.4 (Ar-*C*), 127.4 (Ar-*C*), 109.7 (Ar-*C*), 106.3 (Ar-*C*), 104.8 (Ar-*C*), 102.5 (OCH_2O), 70.8 (*C*-3), 66.1 (2-CH_2), 61.1 (Ar–OCH_3), 56.4 (Ar–OCH_3), 46.9 (*C*-4), 43.6 (*C*-2); *m*/*z* (ES^+) 413 (MH^+), 454 ($MMeCN^+$).

Acknowledgements

We thank the EPSRC (DTA studentships to JDS) and Durham University for financial support of this work; The EPSRC Mass Spectrometry Service for accurate mass determinations, Dr A. M. Kenwright for assistance with NMR experiments and Dr M. Jones for mass spectra.

References

1 V. Podwyssotzki, *Arch. Exp. Pathol. Pharmakol.*, 1880, **13**, 29.
2 C. Canel, R. M. Moraes, F. E. Dayan and D. Ferreira, *Phytochemistry*, 2000, **54**, 115.
3 S. Desbene and S. Giorgi-Renault, *Curr. Med. Chem.*, 2002, **2**, 71.
4 M. Gordaliza, M. A. Castro, J. M. M. del Corral and A. San Feliciano, *Curr. Pharm. Des.*, 2000, **6**, 1811.
5 K. H. Lee and Z. Xiao, *Phytochem. Rev.*, 2003, **13**, 341.
6 R. S. Ward, *Synthesis*, 1992, 719.
7 R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75; R. S. Ward, *Nat. Prod. Rep.*, 1997, **14**, 43; R. S. Ward, *Nat. Prod. Rep.*, 1995, **12**, 183; R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1.
8 J. D. Sellars and P. G. Steel, *Eur. J. Org. Chem.*, 2007, 3815.
9 H. Ottosson and P. G. Steel, *Chem.–Eur. J.*, 2006, **12**, 1576.
10 J. D. Sellars and P. G. Steel, *Org. Biomol. Chem.*, 2006, **4**, 3223.
11 M. J. Sanganee, P. G. Steel and D. K. Whelligan, *Org. Biomol. Chem.*, 2004, **2**, 2393.
12 M. B. Berry, R. J. Griffiths, M. J. Sanganee, P. G. Steel and D. K. Whelligan, *Org. Biomol. Chem.*, 2004, **2**, 2381.
13 M. B. Berry, R. J. Griffiths, M. J. Sanganee, P. G. Steel and D. K. Whelligan, *Tetrahedron Lett.*, 2003, **44**, 9135.
14 M. B. Berry, R. J. Griffiths, J. A. K. Howard, M. A. Leech, P. G. Steel and D. S. Yufit, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3645.
15 A. S. Batsanov, I. M. Clarkson, J. A. K. Howard and P. G. Steel, *Tetrahedron Lett.*, 1996, **37**, 2491.
16 J. D. Sellars, P. G. Steel and M. J. Turner, *Chem. Commun.*, 2006, 2385.
17 N. J. Hughes, R. D. C. Pullin, M. J. Sanganee, J. D. Sellars and P. G. Steel, *Org. Biomol. Chem.*, 2007, **5**, 2841.
18 W. J. Gensler and C. D. Gatsonis, *J. Am. Chem. Soc.*, 1962, **84**, 1748.
19 W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, 1966, **31**, 3224.
20 M. Schlosser, in *Organoalkali Reagents*, ed. M. Schlosser, J. Wiley, Chichester, 1994, pp. 119–120.
21 Y. Apeloig and M. Karni, *J. Am. Chem. Soc.*, 1984, **106**, 6676.
22 H. Ottosson, *Chem.–Eur. J.*, 2003, **9**, 4144.
23 K. C. Nicolaou, P. M. Pihko, F. Bernal, M. O. Frederick, W. Y. Qian, N. Uesaka, N. Diedrichs, J. Hinrichs, T. V. Koftis, E. Loizidou, G. Petrovic, M. Rodriquez, D. Sarlah and N. Zou, *J. Am. Chem. Soc.*, 2006, **128**, 2244.
24 S. Yoshida, T. Yamanaka, T. Miyake, Y. Moritani, H. Ohmizu and T. Iwasaki, *Tetrahedron*, 1997, **53**, 9585; M. Pohmakotr, T. Komutkul, P. Tuchinda, S. Prabpai, P. Kongsaeree and V. Reutrakul, *Tetrahedron*, 2005, **61**, 5311.
25 E. J. Bush and D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1993, 1200.
26 R. C. Andrews, S. J. Teague and A. I. Meyers, *J. Am. Chem. Soc.*, 1988, **110**, 7854.
27 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
28 S. P. Forsey, D. Rajapaksa, N. J. Taylor and R. Rodrigo, *J. Org. Chem.*, 1989, **54**, 4280.

