Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4926

www.rsc.org/obc

**PAPER**

# Synthesis of the *trans*-hydrindane core of dictyoxetane†

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***Received 22nd February 2012, Accepted 26th April 2012***
**DOI: 10.1039/c2ob25384d**

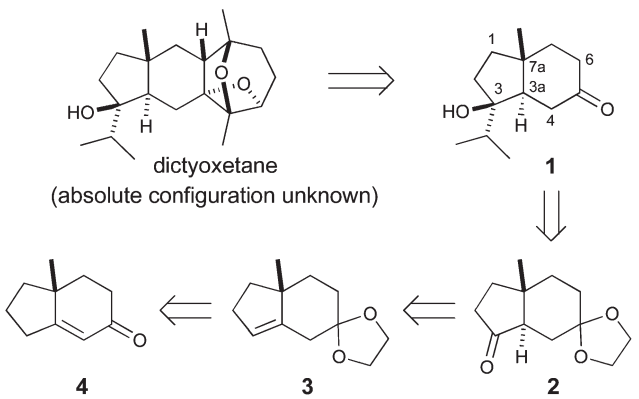


A concise, stereoselective synthesis of the *trans*-hydrindane core of the marine natural product dictyoxetane is reported, starting from a Robinson annelation derived bicyclic enone. A phosphorane-mediated, pinacol-like rearrangement of a *cis*-diol, *via* a formal 1,2-hydride shift, is used to establish the requisite *trans* ring junction. $^{31}$P NMR supports the formation of the intermediate phosphorane, generated *in situ* from the reaction of a diol with $Ph_3PCl_2$.

## Introduction

Dictyoxetane is a marine diterpene isolated from the brown alga *Dictyota dichotoma* (Hudson) Lamouroux, and is structurally related to the dollabolanes.[1] X-ray analysis established the relative configuration of dictyoxetane and revealed a densely functionalised pentacyclic ring system, so far unique in Nature. The structure of dictyoxetane presents a considerable synthetic challenge, and a total synthesis has yet to be reported. Preparation of the dioxatricyclic ring system has been described by both Heathcock[2] and Hoffmann,[3] with the latter reporting promising biological data for model compounds. However there have been no reports to date on the preparation of the *trans*-hydrindane core of dictyoxetane. In this paper, we report a novel approach to a fully functionalised *trans*-hydrindanone **1** suitable for further elaboration towards the natural product (Scheme 1).

A number of elegant approaches have been developed for the preparation of *trans*-hydrindanes, particularly in the context of steroid and vitamin D synthesis,[4] and more recently in the cortistatin field.[5,6] However a survey of the literature suggested a lack of methods directly applicable to the substitution pattern required for dictyoxetane, particularly oxygenation at C-3.[7] A novel approach to **1** was therefore devised, based on the retrosynthetic analysis shown in Scheme 1. Tertiary alcohol **1** should be accessible from stereoselective addition of a suitable organometallic reagent to *trans*-hydrindanone **2** followed by acetal deprotection.




**Scheme 1** Retrosynthetic analysis of dictyoxetane.

Ketone **2** was envisaged to be formed from regio- and stereoselective manipulation of the known alkene **3**,[8] available in one step, *via* acetal formation with concomitant alkene migration, from a Robinson annelation derived enone **4**.[9]

## Results and discussion

Hydroboration of **3**[8] with 9-BBN gave alcohol **5** as a single diastereomer (Scheme 2). The stereochemistry of **5** was assigned through nOe measurements (see ESI† for details). Oxidation of **5** with IBX[10] gave the *cis*-hydrindanone **6**, the structure of which was confirmed by X-ray crystallography.[11] Hence hydroboration of **3** occurs from the presumably less hindered top face of **3**, *cis* to the methyl group at the ring junction. Attempts to epimerize **6** to the *trans*-hydrindanone **2** under basic conditions (NaOMe–MeOH or DBU–MeCN, reflux) met with failure, with starting material recovered unchanged, unsurprisingly given the general trend for angularly-substituted *trans*-hydrindanes to be thermodynamically less stable than *cis*.[6b,12]

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†Electronic supplementary information (ESI) available: Copies of $^1$H and $^{13}$C NMR for all new compounds, including nOe analyses of **5**, **7**, **8** and **1**. Copies of $^{31}$P NMR for rearrangement experiment. X-ray crystal structures of **6** and **10**: CCDC 855564 and 855565. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25384d

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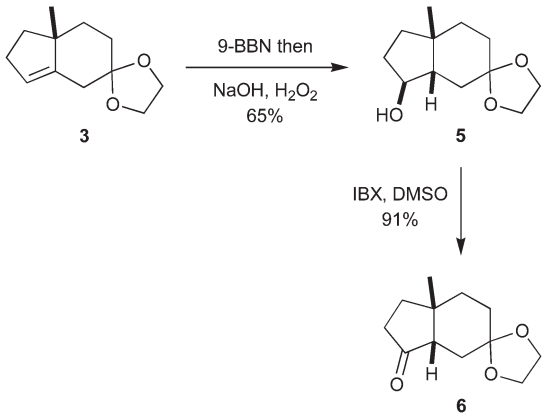
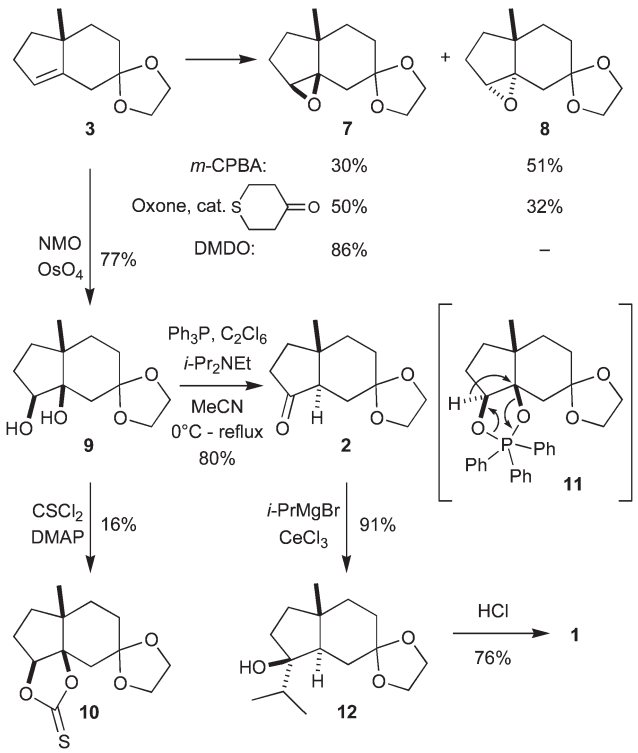



**Scheme 2** Stereoselective synthesis of *cis*-hydrindanone **6**.




**Scheme 3** Tandem stereoselective oxidation-rearrangement approach to *trans*-hydrindanes.

With knowledge of the facial preference for reactions of alkene **3** in hand, an alternative approach to ketone **2** was devised. A stereoselective Meinwald rearrangement of *cis*-epoxide **7** would be expected to occur through a formal 1,2-hydride migration, and hence deliver the requisite *trans* ring junction (Scheme 3).[13] Epoxidation of **3** with *m*-CPBA gave a separable mixture of two epoxides **7** and **8**, the structures of which were determined by nOe studies (see ESI† for details). A reversal of selectivity was observed using Oxone® and catalytic 4-tetrahydrothiopyran (oxidised to the dioxirane-sulfone *in situ*).[14] The formation of *trans*-epoxide **8** as the major diastereoisomer in the *m*-CPBA oxidation may therefore be due to a directing effect from an acetal oxygen, hydrogen-bonding with *m*-CPBA, a situation which is not possible with the dioxirane.[15] Complete selectivity for the desired *cis*-epoxide **7** was achieved using dimethyldioxirane (DMDO) as oxidant.

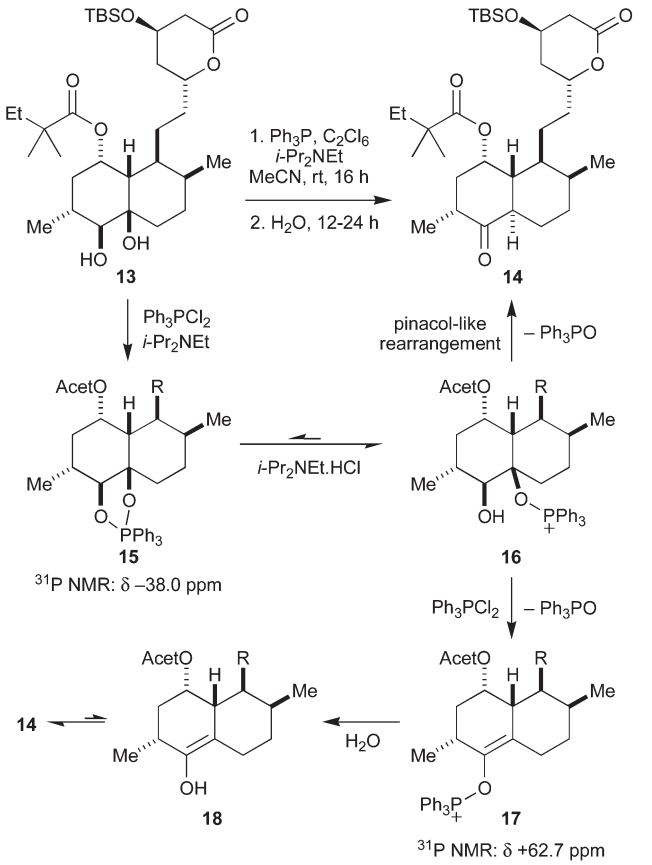
Treatment of epoxide **7** with a range of Lewis and Brønsted acids under a variety of conditions unfortunately gave complex mixtures of products from which the desired hydrindanone **2** could not be isolated in any significant quantities (<5%), with the *cis*-hydrindanone **6** and compounds resulting from cleavage of the acetal group also present. However an alternative to the Meinwald rearrangement employed diol **9**, obtained through dihydroxylation of **3** under Upjohn conditions. The dihydroxylation was completely diastereoselective, with the stereochemistry of **9** confirmed through single crystal X-ray structure determination of the corresponding cyclic thionocarbonate **10**.[16] Treatment of **9** with dichlorotriphenylphosphine, generated *in situ* from triphenylphosphine and hexachloroethane,[17] gave a clean and rapid transformation to a new species, presumed to be the cyclic phosphorane **11** (observable by t.l.c. analysis and supported by mass spectroscopy and $^{31}$P NMR, *vide infra*). Subsequent heating gave the requisite *trans*-hydrindanone **2** in good yield, through formal hydride migration with the expulsion of $Ph_3P{=}O$, along with small amounts of *cis*-hydrindanone **6**, separable by column chromatography.[18] Comparable yields of **2** and **6** were obtained in both THF and MeCN as solvent. The use of $Ph_3PCl_2$ has rarely been employed for a diol to ketone (pinacol-like) rearrangement,[17,19] but in the present case notably avoids the need to selectively functionalise the more hindered tertiary alcohol in **9**.[20–22]

With diastereomerically pure **2** in hand, transformation into the dictyoxetane core required just two additional steps. Cerium trichloride-mediated addition of *iso*-propylmagnesium chloride[23] gave the tertiary alcohol **12**, which upon acetal hydrolysis gave the target hydrindanone **1** (Scheme 3). The stereochemistry of **1** was elucidated through nOe analysis, confirming that addition to ketone **2** occurred from the less hindered face, opposite to the methyl group at the ring junction (see ESI† for details). Hydrindanones related to **1** have been selectively functionalized at C-6,[7] thus paving the way for further C–C bond formation as required for application of **1** in dictyoxetane synthesis.

## Discussion

We are aware of only two previous reports describing the pinacol-like rearrangement of a 1,2-diol to a ketone *via* a cyclic phosphorane analogous to **11**.[17,19] The Merck process group reported a detailed study of the conversion of *cis*-diol **13** to the *trans*-decalone **14**, observing intermediates by phosphorus NMR (Scheme 4).[17] The putative hydroxy oxyphosphonium salt **16** (not observed) was proposed as a common intermediate in the formation of **14** and a major byproduct, the enol phosphonium salt **17**. Both **14** and **17** were observed to form at room temperature from the phosphorane **15**, generated *in situ* from diol **13**. Addition of water converted the undesired enol phosphonium salt **17** to an enol **18**, which subsequently tautomerised to the *trans*-decalone **14**, thus increasing the overall yield.

The rearrangement of phosphorane **11** may also proceed *via* amine hydrochloride-catalysed ring-opening to give a hydroxy oxyphosphonium salt, analogous to the conversion of **15** to **16**, or through the concerted mechanism shown in parentheses in




**Scheme 4** Formation of a *trans*-decalin through a pinacol-like rearrangement as proposed by Decamp *et al.*[17]

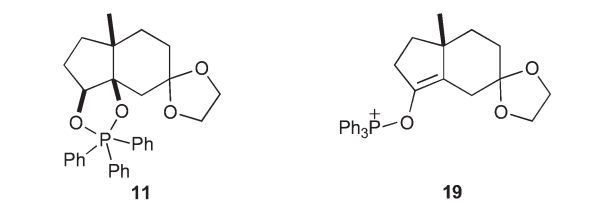



**Fig. 1** Phosphorane **11** and putative enol phosphonium **19**.

Scheme 3. In order to gain further insight into potential reaction pathways, a $^{31}$P NMR study was undertaken. Addition of diol **9** to a solution of $Ph_3P$, $C_2Cl_6$ and Hünig's base in $CD_3CN$ clearly showed rapid conversion of $Ph_3PCl_2$ ($\delta$ 55.7 ppm) to cyclic phosphorane **11** ($\delta$ −36.3 ppm, Fig. 1). Although **11** cannot be isolated, its structure in solution is also supported by mass spectroscopy. Warming to 60 °C resulted in slow disappearance of the signal for **11** and appearance of a signal for $Ph_3P{=}O$ ($\delta$ 28.2 ppm), with reaction complete after 3 h.

The formation of an enol phosphonium **19** would not be expected to result in formation of *trans*-**2** in the same manner as formation of **14** from **17**: hydrolysis to the corresponding enol and tautomerisation would result in the thermodynamically more favourable *cis*-hydrindanone **6**. The small quantities of **6** obtained may be the result of this minor pathway, or due to epimerisation of **2**. A small peak at $\delta$ 64.8 ppm is visible in the $^{31}$P NMR of the reaction mixture after addition of diol to $Ph_3PCl_2$ which can be tentatively assigned to an enol phosphonium **19**. This peak is still evident after heating but disappears upon addition of water, further supporting this assignment and mechanism.

Minimal epimerisation of *trans*-**2** to *cis*-**6** occurs on treatment with Hünig's base in refluxing MeCN over 3 h, or upon re-exposure of **2** to the reaction conditions. In contrast, significant epimerisation to **6** occurs when **2** is treated with 1 M HCl (1.4 : 1 *trans* : *cis* after 10 min in $CDCl_3$/MeCN at room temperature then evaporation).

## Conclusions

In conclusion, enone **4** can be selectively converted in three steps to either the *cis*- or *trans*-hydrindanone, **6** and **2** respectively, with the latter used in the first synthesis of the hydrindane core of dictyoxetane. Although this study has been carried out in the racemic series, the approach is amenable to the preparation of either enantiomer of **2** *via* an asymmetric synthesis of **4**,[24] an important consideration since the absolute configuration of dictyoxetane remains unknown. The use of a pinacol-like, 1,2-diol to ketone rearrangement represents a novel strategy for the more general and long-standing problem of stereoselective *trans*-hydrindane synthesis.

## Experimental

### General experimental

Chemicals were used as purchased from commercial suppliers and used as received unless otherwise indicated. Petrol refers 60–80 petroleum ether. Purification of *m*-CPBA and preparation of DMDO solutions were carried out according to our previous report.[25] Full NMR assignment including details of stereochemistry in the case of **5**, **7**, **8** and **1** were made using COSY, HSQC, HMBC and nOe data as appropriate (see ESI†). Compound numbering is shown on the $^1$H NMR in the ESI.†

**(±)-(*R**)-7a′-Methyl-1′,2′,4′,6′,7′,7a′-hexahydrospiro[[1,3]dioxolane-2,5′-indene] (3).**[8] Ethylene glycol (6.90 g, 0.11 mmol) and *p*-TSA (0.38 g, 2.00 mmol) were added to a solution of enone **4**[9] (3.00 g, 0.02 mol) in toluene (50 mL) and the reaction mixture refluxed for 3 h under a Dean–Stark apparatus. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was dissolved in diethyl ether (30 mL), water (20 mL) was added and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with sodium hydrogen carbonate (20 mL of a saturated aq soln.) and water (20 mL), dried ($Na_2SO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 10 : 1) to afford **3** (2.72 g, 70%) as a yellow oil, $R_f$ 0.54 (petrol–diethyl ether, 4 : 1); $\nu_{max}$ (neat) 1727 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$), 1.04 (3H, s, $CH_3$), 1.52 (1H, td, *J* 4.3 Hz, *J* 13.8 Hz, H-7′), 1.63–1.69 (3H, m, H-1′, H-6′, H-7′), 1.75–1.88 (2H, m, H-1′, H-6′), 2.23–2.37 (3H, m, 2 × H-2′, H-4′), 2.40 (1H, dd, *J* 2.5 Hz, *J* 13.5 Hz, H-4′), 3.88–3.95 (4H, m, 2 × H-4, 2 × H-5), 5.26 (1H, d, *J* 1.9 Hz, H-3′); $\delta_C$ (125 MHz, $CDCl_3$), 21.1 (q, $CH_3$), 29.3 (t, C-2′),

30.6 (t, C-6′), 35.0 (t, C-4′), 36.5 (t, C-7′), 39.1 (t, C-1′), 43.9 (s, C-7a′), 63.3 (t, C-4), 63.4 (t, C-5), 108.6 (s, C-5′), 121.3 (d, C-3′), 145.2 (d, C-3a′); *m/z* (EI$^+$) 194 (M$^+$, 3%); HRMS (EI$^+$) calculated for $C_{12}H_{18}O_2$ (M$^+$) 194.1307, found 194.1312.

**(±)-(3′*S**,3a′*S**,7a′*R**)-7a′-Methyloctahydrospiro[[1,3]dioxolane-2,5′-inden]-3′-ol (5).** A solution of 9-BBN (2 mL of a 0.5 M soln. in THF, 1.10 mmol) was added to alkene **3** (0.101 g, 0.52 mmol) and the reaction mixture was stirred at rt under an atmosphere of argon for 30 min. After this time the reaction mixture was treated with NaOH (0.27 mL of a 3 M aq soln., 0.81 mmol) and $H_2O_2$ (0.22 mL of a 27% aq soln.). The reaction mixture was stirred at rt for 1 h, quenched with water (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organics were washed with sodium hydrogen carbonate (10 mL of a saturated aq soln.) and brine (10 mL), dried ($Na_2SO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 1 : 1) to afford **5** (71 mg, 65%) as a clear oil, $R_f$ 0.21 (petrol–diethyl ether, 1 : 1); $\nu_{max}$ (neat) 3416 cm$^{-1}$; $\delta_H$ (500 MHz, $CD_3CN$), 1.06 (3H, s, $CH_3$), 1.24–1.30 (1H, m, H-7′), 1.37–1.56 (7H, m, 2 × H-1′, H-2′, H-3a′, 2 × H-6′, H-7′), 1.63 (2H, d, *J* 5.4 Hz, 2 × H-4′), 1.99–2.06 (1H, m, H-2′), 2.68 (1H, d, *J* 4.8 Hz, OH), 3.78–3.91 (4H, m, 2 × H-4, 2 × H-5), 4.21–4.23 (1H, m, H-3′); $\delta_C$ (125 MHz, $CD_3CN$), 26.7 (q, $CH_3$), 31.5 (t, C-6′), 32.4 (t, C-4′), 32.6 (t, C-2′), 33.6 (t, C-7′), 37.8 (t, C-1′), 39.3 (s, C-7a′), 54.5 (d, C-3a′), 64.3 (t, C-4), 64.8 (t, C-5), 76.6 (d, C-3′), 109.6 (s, C-5′); *m/z* (EI$^+$) 212 (M$^+$, 3%); (ES$^+$) 235 (M.Na$^+$, 100%); HRMS (EI$^+$) calculated for $C_{12}H_{20}O_3$ (M$^+$) 212.1412, found 212.1424.

**(±)-(3a′*S**,7a′*R**)-7a′-Methylhexahydrospiro[[1,3]dioxolane-2,5′-inden]-3′(2′*H*)-one (6).** A solution of alcohol **5** (0.144 g, 0.678 mmol) and IBX (0.380 g, 1.36 mmol) in DMSO (3.4 mL) was stirred for 12 h at rt under an atmosphere of argon. After this time the mixture was quenched with water (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (3 × 5 mL) and brine (2 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 4 : 1) to afford **6** (0.130 g, 91%) as a white solid, $R_f$ 0.25 (petrol–diethyl ether, 1 : 1); m.p. 49–51 °C; $\nu_{max}$ (neat) 1737 cm$^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$), 1.21 (3H, s, $CH_3$), 1.46–1.48 (1H, m, H-6′/7′), 1.49–1.67 (3H, m, H-1′, H-4′, H-6′/7′), 1.68–1.81 (2H, m, H-6′, H-7′), 1.86 (1H, dt, *J* 2.6 Hz, *J* 9.1 Hz, H-1′), 1.91 (1H, ddd, *J* 1.7 Hz, *J* 3.5 Hz, *J* 6.9 Hz, H-3a′), 2.15 (1H, dt, *J* 2.9 Hz, *J* 13.8 Hz, H-4′), 2.28 (1H, dddd, *J* 1.4 Hz, *J* 2.6 Hz, *J* 8.8 Hz, *J* 19.3 Hz, H-2′), 2.42 (1H, ddd, *J* 9.0 Hz, *J* 10.4 Hz, *J* 19.3 Hz, H-2′), 3.84–4.02 (4H, m, 2 × H-4, 2 × H-5); $\delta_H$ (300 MHz, $C_6D_6$), 0.79 (3H, s, $CH_3$), 0.98–1.18 (2H, m), 1.29–1.38 (2H, m), 1.45–1.57 (3H, m), 1.60–1.74 (2H, m), 1.95 (1H, dddd, *J* 1.1 Hz, *J* 2.3 Hz, *J* 8.8 Hz, *J* 18.9 Hz, H-2′), 2.15 (1H, dd, *J* 9.1 Hz, *J* 10.8 Hz), 2.21–2.34 (1H, m), 3.42–3.51 (2H, m, 2 × H-4/5), 3.53–3.59 (1H, m, H-4/5), 3.61–3.71 (1H, m, H-4/5); $\delta_C$ (100 MHz, $CDCl_3$), 26.3 (q, $CH_3$), 29.1 (t, C-4′), 30.9 (t, C-6′/7′), 31.8 (t, C-6′/7′), 34.1 (t, C-1′), 35.4 (t, C-2′), 37.4 (s, C-7a′), 55.5 (d, C-3a′), 63.6 (t, C-4), 64.4 (t, C-5), 107.8 (s, C-5′), 219.0 (s, C-3′); *m/z* (EI$^+$) 210 (M$^+$, 11%); HRMS (EI$^+$) calculated for $C_{12}H_{18}O_3$§ (M$^+$) 210.1256, found 210.1259.

**(±)-(1a′*S**,3a′*R**,7a′*R**)-3a′-Methylhexahydro-1a′*H*-spiro[[1,3]-dioxolane-2,6′-indeno[1,7*a*–*b*]oxirene] (7) and (±)-(1a′*R**,3a′*R**,-7a′*S**)-3a′-methylhexahydro-1a′*H*-spiro[[1,3]dioxolane-2,6′-indeno-[1,7*a*–*b*]oxirene] (8)**

*Method 1.* *m*-CPBA[25] (0.400 g, 2.32 mmol) was added to a solution of alkene **3** (0.200 g, 1.03 mmol) in DCM (10 mL) and the reaction mixture stirred for 10 min at rt. The mixture was quenched with NaOH (5 mL of a 5% aq soln.) and extracted with diethyl ether (2 × 10 mL). The combined organic fractions were dried ($Na_2SO_4$), the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (petrol–diethyl ether, 2 : 1) to afford epoxide **7** (65 mg, 30%) and epoxide **8** (110 mg, 51%).

*Method 2.* Tetrahydrothiopyran-4-one (8 mg, 0.069 mmol) was added to a solution of alkene **3** (0.101 g, 0.520 mmol) in MeCN (2.5 mL), followed by $Na_2$·EDTA (1.5 mL of a 4.10 M soln.). The mixture was stirred at rt. A mixture of oxone® monopersulfate (0.480 g, 0.781 mmol) and sodium hydrogen carbonate (0.200 g, 2.38 mmol) was added portionwise over a period of 3 h and the reaction mixture stirred for a further 3 h. After this time the mixture was extracted with ethyl acetate (2 × 5 mL), the combined organic layers were washed with brine (5 mL), dried ($Na_2SO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 8 : 1) to afford epoxide **7** (55 mg, 50%), followed by epoxide **8** (35 mg, 32%).

*Method 3.* A solution of DMDO in acetone[25] was added to a solution of **3** (0.501 g, 2.58 mmol) in acetone (10 mL) with stirring at rt until complete consumption of starting material was observed by t.l.c. analysis. The solution was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (petrol–diethyl ether, 4 : 1) to afford **7** (0.47 g, 86%).

Epoxide **7** was obtained as a pale yellow oil, $R_f$ 0.28 (petrol–diethyl ether, 4 : 1); $\nu_{max}$ (neat) 2937, 1266 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$), 1.06 (3H, s, $CH_3$), 1.29–1.32 (2H, m, 2 × H-3′), 1.36 (1H, ddd, *J* 2.9 Hz, *J* 4.2 Hz, *J* 13.5 Hz, H-4′), 1.49–1.55 (2H, m, H-4′, H-7′), 1.63 (1H, ddd, *J* 2.8 Hz, *J* 6.5 Hz, *J* 13.6 Hz, H-5′), 1.70–1.80 (2H, m, H-2′, H-5′), 1.89 (1H, dt, *J* 4.6 Hz, *J* 13.9 Hz, H-2′), 2.18 (1H, d, *J* 13.1 Hz, H-7′), 2.28 (1H, br s, H-1a′), 3.90–3.95 (4H, m, 2 × H-4, 2 × H-5); $\delta_C$ (125 MHz, $CDCl_3$), 18.2 (q, $CH_3$), 25.0 (t, C-2′), 31.2 (t, C-5′), 31.8 (t, C-4′), 34.6 (t, C-3′), 35.6 (t, C-7′), 39.3 (s, C-3a′), 64.3 (t, C-4), 64.3 (t, C-5), 64.4 (d, C-1a′), 68.7 (s, C-7a′), 109.7 (s, C-6′); *m/z* (ES$^+$) 233 (M.Na$^+$, 100%); HRMS (ES$^+$) calculated for $C_{12}H_{18}O_3Na$ (M.Na$^+$) 233.1256, found 233.1254.

§ **6**: $C_{12}H_{18}O_3$, *M* = 210.26, Monoclinic, *a* = 7.11(3), *b* = 14.86(6), *c* = 11.69(4) Å, *β* = 101.6(2)°, *U* = 1210(8) Å3, *T* = 296(2) K, space group $P2_1/n$, *Z* = 4, 5422 reflections measured, 1641 unique ($R_{int}$ = 0.0426) which were used in all calculations. The final $R_1$ was 0.0502 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.1445 (all data). CCDC 855564.

**10**: $C_{13}H_{18}O_4S$, *M* = 270.33, Monoclinic, *a* = 10.0589(1), *b* = 10.5323(1), *c* = 12.3056(1) Å, *β* = 100.646(1)°, *U* = 1281.26(2) Å3, *T* = 120(2) K, space group $P2_1/n$, *Z* = 4, 10 547 reflections measured, 2390 unique ($R_{int}$ = 0.0207) which were used in all calculations. The final $R_1$ was 0.0306 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.0857 (all data). CCDC 855565.

Epoxide **8** was obtained as a pale yellow oil, $R_f$ 0.11 (petrol–diethyl ether, 4 : 1); $\nu_{max}$ (neat) 2957, 1265 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$), 1.00 (3H, s, $CH_3$), 1.16 (1H, dd, *J* 7.8 Hz, *J* 12.0 Hz, H-3′), 1.22–1.28 (1H, m, H-3′), 1.56–1.61 (2H, m, H-4′, H-7′), 1.66–1.73 (1H, m, H-2′), 1.73–1.89 (3H, m, H-4′, 2 × H-5′), 1.94 (1H, dd, *J* 7.7 Hz, *J* 13.9 Hz, H-2′), 2.37 (1H, d, *J* 13.8 Hz, H-7′), 3.33 (1H, br s, H-1a′), 3.87–4.05 (4H, m, 2 × H-4, 2 × H-5); $\delta_C$ (125 MHz, $CDCl_3$), 20.5 (q, $CH_3$), 26.3 (t, C-2′), 31.1 (t, C-4′), 31.3 (t, C-5′), 32.7 (t, C-3′), 34.3 (t, C-7′), 38.6 (s, C-3a′), 59.1 (d, C-1a′), 64.3 (t, C-4), 64.6 (t, C-5), 69.5 (s, C-7a′), 109.7 (s, C-6′); *m*/*z* ($EI^+$) 210 ($M^+$, 2%); ($ES^+$) 233 (M. $Na^+$, 100%); HRMS ($EI^+$) calculated for $C_{12}H_{18}O_3$ ($M^+$) 210.1256, found 210.1243.

**(±)-(3′*S**,3a′*R**,7a′*R**)-7a′-Methyloctahydrospiro[[1,3]dioxolane-2,5′-indene]-3′,3a′-diol (9).** A crystal of $OsO_4$ was added to a solution of NMO (67 mg, 0.570 mmol) and alkene **3** (0.100 g, 0.515 mmol) in THF (0.5 mL), *t*-BuOH (1.8 mL) and water (0.2 mL). The reaction mixture was stirred for 2 days at rt and then quenched by addition of sodium metabisulfite (0.160 g, 0.842 mmol). The mixture was stirred for a further 1 h and then extracted with ethyl acetate (5 mL). The combined organic layers were washed with HCl (5 mL of a 1 M aq soln.) and brine (2 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 1 : 5) to afford diol **9** (90 mg, 77%) as a white solid, $R_f$ 0.11 (petrol–diethyl ether, 1 : 4); m.p. 70–72 °C; $\nu_{max}$ (neat) 3438, 3362 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$), 1.00 (3H, s, $CH_3$), 1.46–1.75 (9H, m, 2 × H-1′, H-2′, 2 × H-4′, 2 × H-6′, 2 × H-7′), 2.04–2.12 (1H, m, H-2′), 2.42 (1H, s, OH), 2.94 (1H, s, OH), 3.90–3.99 (4H, m, 2 × H-4, 2 × H-5), 4.17–4.18 (1H, m, H-3′); $\delta_C$ (100 MHz, $CDCl_3$), 21.5 (q, $CH_3$), 28.7 (t, C-2′), 30.3 (t, C-6′/7′), 32.4 (t, C-6′/7′), 33.9 (t, C-1′), 40.2 (t, C-4′), 42.3 (s, C-7a′), 64.1 (t, C-4), 64.4 (t, C-5), 76.6 (d, C-3′), 80.1 (s, C-3a′), 109.1 (s, C-5′); *m*/*z* ($EI^+$) 228 ($M^+$, 13), 210 ($[M - H_2O]^+$, 10%); HRMS ($EI^+$) calculated for $C_{12}H_{20}O_4$ ($M^+$) 228.1362, found 228.1354.

**(±)-(3a′*S**,5a′*R**,9a′*R**)-5a′-Methylhexahydro-3a′*H*-spiro[[1,3]-dioxolane-2,8′-indeno[1,7*a*–*d*][1,3]dioxole]-2′-thione (10).** A solution of thiophosgene (0.107 mL, 1.39 mmol) in DCM (3 mL) was added to a solution of diol **9** (0.160 g, 0.701 mmol) and DMAP (0.425 g, 3.48 mmol) in DCM (12 mL). The reaction mixture was stirred at rt under an atmosphere of argon for 6 h, after which time silica was added and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petrol–diethyl ether, 1 : 1) to afford **10** (30 mg, 16%) as a white crystalline solid, $R_f$ 0.35 (petrol–diethyl ether, 2 : 1); m.p. 127–129 °C; $\nu_{max}$ (neat) 1167 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$), 1.19 (3H, s, $CH_3$), 1.41–1.48 (1H, m, $CH_2$), 1.55–1.61 (3H, m, 3 × $CH_2$), 1.64–1.75 (1H, m, $CH_2$), 1.78–1.87 (1H, m, $CH_2$), 1.95 (1H, dd, *J* 7.9 Hz, *J* 15.5 Hz, $CH_2$), 2.04–2.12 (2H, m, 2 × $CH_2$), 2.13–2.24 (1H, m, $CH_2$), 3.88–3.97 (4H, m, 4 × $CH_2$), 5.29 (1H, d, *J* 7.4 Hz, CH); $\delta_C$ (100 MHz, $CDCl_3$), 19.1 (q, $CH_3$), 29.4 (t, $CH_2$), 30.0 (t, $CH_2$), 31.4 (t, $CH_2$), 36.4 (t, $CH_2$), 37.2 (t, $CH_2$), 44.4 (s, C), 64.3 (t, $CH_2$), 64.6 (t, $CH_2$), 90.6 (d, CH), 101.3 (s, C), 108.1 (s, C), 191.0 (s, C); *m*/*z* ($EI^+$) 270 ($M^+$, 14); HRMS ($EI^+$) calculated for $C_{13}H_{18}O_4S$ ($M^+$) 270.0926, found 270.0920.

**(±)-(3a′*R**,7a′*R**)-7a′-Methylhexahydrospiro[[1,3]dioxolane-2,5′-inden]-3′(2′*H*)-one (2).** Triphenylphosphine (144 mg, 0.549 mmol) was dissolved in MeCN (2 mL) under an atmosphere of argon. Hexachloroethane (130 mg, 0.549 mmol) was added in one portion and the mixture stirred for 20 min, after which time di-*iso*-propylethylamine (191 μL, 1.10 mmol) was added. The mixture was cooled to 0 °C and a solution of diol **9** (57 mg, 0.250 mmol) in MeCN (2 mL) was added dropwise over 5 min. After 50 min t.l.c. analysis (petrol–diethyl ether, 1 : 1) indicated complete consumption of **9** ($R_f$ 0.0) and formation of a single product ($R_f$ 0.38). The reaction mixture was then heated to reflux for 2 h, after which time t.l.c. analysis (petrol–diethyl ether, 1 : 1) indicated complete consumption of phosphorane intermediate ($R_f$ 0.38) and formation of a single product ($R_f$ 0.25). The reaction mixture was cooled, diluted with diethyl ether (20 mL) and washed with water (2 × 5 mL). The aq fractions were combined and extracted with diethyl ether (2 × 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (petrol–diethyl ether, 1 : 1) to afford ketone **2** (42 mg, 80%) as a clear oil, which solidified on standing to give a white solid, m.p. 62–64 °C; $\nu_{max}$ (neat) 1728 $cm^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$), 0.50 (3H, s, $CH_3$), 1.15 (1H, br t, *J* 10.0 Hz, H-1′), 1.32 (1H, dt, *J* 5.1 Hz, *J* 12.2 Hz, H-1′), 1.37 (1H, dt, *J* 2.5 Hz, *J* 12.3 Hz, H-7′), 1.49 (1H, td, *J* 4.2 Hz, *J* 13.2 Hz, H-7′), 1.56 (1H, ap t, *J* 13.1 Hz, $H\text{-}4_{ax}'$), 1.55–1.61 (1H, m, H-6′), 1.75 (1H, td, *J* 4.9 Hz, *J* 13.8 Hz, H-6′), 1.90 (2H, dd, *J* 5.2 Hz, *J* 9.8 Hz, 2 × H-2′), 2.13 (1H, dt, *J* 2.7 Hz, *J* 13.2 Hz, $H\text{-}4_{eq}'$), 2.19 (1H, dd, *J* 3.1 Hz, *J* 12.5 Hz, H-3a′), 3.40–3.51 (4H, m, 2 × H-4, 2 × H-5); $\delta_H$ (300 MHz, $CDCl_3$), 0.85 (3H, s, $CH_3$), 1.43 (1H, br t, *J* 12.9 Hz), 1.55–1.88 (6H, m), 1.92 (1H, dt, *J* 2.6 Hz, *J* 13.3 Hz), 2.17–2.39 (3H, m), 3.85–3.99 (4H, m, 2 × H-4, 2 × H-5); $\delta_C$ (100 MHz, $C_6D_6$), 16.6 (q, $CH_3$), 30.5 (t, C-4′), 32.1 (t, C-6′), 35.3 (t, C-1′), 35.5 (t, C-2′), 36.0 (t, C-7′), 38.3 (s, C-7a′), 56.9 (d, C-3a′), 64.1 (t, C-4), 64.4 (t, C-5), 109.6 (s, C-5′), 213.4 (s, C-3′); *m*/*z* ($EI^+$) 210 ($M^+$, 19%); HRMS ($EI^+$) calculated for $C_{12}H_{18}O_3$ ($M^+$) 210.1256, found 210.1254.

Further elution afforded a mixture of **2** and **6** (4 mg, 8%, 3 : 1 respectively).

**(±)-(3′*R**,3a′*R**,7a′*R**)-3′-*iso*-Propyl-7a′-methyloctahydrospiro-[[1,3]dioxolane-2,5′-inden]-3′-ol (12).** A solution of ketone **2** (59 mg, 0.281 mmol) in THF (5 mL) was added, under an atmosphere of argon, to a flask containing anhydrous cerium trichloride (138 mg, 0.561 mmol). The suspension was stirred at rt for 90 min and a yellow gel-like solution formed. *iso*-Propylmagnesium chloride (0.421 mL of a 2 M soln., 0.842 mmol) was added dropwise over 5 min. After 90 min t.l.c. analysis (hexane–ethyl acetate, 3 : 1) indicated complete consumption of ketone **2** ($R_f$ 0.24) and formation of a single product ($R_f$ 0.28). The reaction mixture was diluted with diethyl ether (10 mL) and quenched with water (2 mL). The aq fraction was extracted with diethyl ether (2 × 2 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexane–ethyl acetate, 3 : 1) to afford alcohol **12** (65 mg, 91%) as a clear oil; $\nu_{max}$ (neat) 2927 $cm^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$), 0.61 (1H, br s, OH), 0.83 (3H, d, *J* 6.8 Hz, $CH_3$), 0.90 (3H, d, *J* 6.8 Hz, $CH_3$),

1.03 (1H, br q, $J$ 10.6 Hz, H-1$_{ax}$′), 1.12 (3H, s, $CH_3$), 1.47–1.54 (4H, m, H-1′, 2 × H-7′, H-9′), 1.64–1.72 (3H, m, H-2′, H-4′, H-6′), 1.77–1.95 (4H, m, H-2′, H-3a′, H-4′, H-6′), 3.50–3.61 (4H, m, 2 × H-4, 2 × H-5); $\delta_C$ (100 MHz, $C_6D_6$), 17.6 (q, C-10′/11′), 18.4 (q, C-8′), 18.4 (q, C-10′/11′), 32.0 (t, C-6′), 32.2 (t, C-4′), 36.7 (t, C-2′), 37.5 (d, C-9′), 37.6 (t, C-7′), 39.8 (t, C-1′), 41.7 (s, C-7a′), 51.2 (d, C-3a′), 64.1 (t, C-4), 64.4 (t, C-5), 82.8 (s, C-3′), 110.9 (s, C-5′); $m/z$ (EI$^+$) 254 ($M^+$, 5), 236 ([M – $H_2O$]$^+$, 13%); HRMS (EI$^+$) calculated for $C_{15}H_{26}O_3$ ($M^+$) 254.1882, found 254.1885.

**(±)-(3*R**,3a*R**,7a*R**)-3-Hydroxy-3-*iso*-propyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (1).** A solution of acetal **12** (40 mg, 0.157 mmol) in THF (3 mL) was treated with HCl (1.3 mL of a 1 M aq soln.). The solution was stirred at rt for 4 h after which time t.l.c. analysis (hexane–ethyl acetate, 7 : 3) indicated complete consumption of **12** ($R_f$ 0.46) and formation of a single product ($R_f$ 0.36). The reaction mixture was quenched with sodium hydrogen carbonate (5 mL of a saturated aq soln.) and extracted with diethyl ether (5 × 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexane–ethyl acetate, 4 : 1) to afford ketone **1** (25 mg, 76%) as a clear oil; $\nu_{max}$ (neat) 3477, 1699 cm$^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$), 0.60 (1H, br s, OH), 0.62 (3H, d, $J$ 6.8 Hz, $CH_3$), 0.70 (3H, d, $J$ 6.8 Hz, $CH_3$), 0.80 (1H, br q, $J$ 11.4 Hz, H-1$_{ax}$), 1.02 (3H, s, $CH_3$), 1.10 (1H, td, $J$ 6.0 Hz, $J$ 12.7 Hz, H-7$_{ax}$), 1.25 (1H, septet, $J$ 6.8 Hz, H-9), 1.36 (1H, dd, $J$ 5.9 Hz, $J$ 12.5 Hz, H-3a), 1.40–1.46 (2H, m, H-1, H-7$_{eq}$), 1.62 (1H, ddd, $J$ 8.2 Hz, $J$ 11.2 Hz, $J$ 14.2 Hz, H-2), 1.75 (1H, ddd, $J$ 1.1 Hz, $J$ 9.6 Hz, $J$ 14.2 Hz, H-2), 2.10 (1H, ddd, $J$ 6.9 Hz, $J$ 12.7 Hz, $J$ 16.3 Hz, H-6$_{ax}$), 2.20 (1H, ddt, $J$ 1.5 Hz, $J$ 6.0 Hz, $J$ 16.3 Hz, H-6$_{eq}$), 2.27–2.34 (2H, m, 2 × H-4); $\delta_C$ (100 MHz, $C_6D_6$), 17.4 (q, C-10/11), 18.0 (q, C-8), 18.1 (q, C-10/11), 37.2 (t, C-2), 37.3 (d, C-9), 37.6 (t, C-6), 38.0 (t, C-7), 39.2 (t, C-1), 39.3 (t, C-4), 41.1 (s, C-7a), 52.8 (d, C-3a), 82.7 (s, C-3), 209.5 (s, C-5); $m/z$ (EI$^+$) 210 ($M^+$, 18), 192 ([M – $H_2O$]$^+$, 43), 167 ([M – $^i$Pr]$^+$, 88%); HRMS (EI$^+$) calculated for $C_{13}H_{22}O_2$ ($M^+$) 210.1620, found 210.1630.

**$^{31}$P NMR experiment: phosphorane 11.** Triphenylphosphine (35 mg, 0.133 mmol) was dissolved in $CD_3CN$ (0.75 mL) under an atmosphere of argon. Hexachloroethane (32 mg, 0.133 mmol) was added in one portion and the mixture stirred for 20 min, after which time di-*iso*-propylethylamine (46 μL, 0.266 mmol) was added. The mixture was cooled to 0 °C and a solution of diol **9** (14 mg, 60.5 μmol) in $CD_3CN$ (0.75 mL) was added dropwise over 2 min. After 30 min t.l.c. analysis (petrol–diethyl ether, 1 : 1) indicated complete consumption of **9** ($R_f$ 0.0) and formation of a single product ($R_f$ 0.38), characterised in solution as follows: $\delta_P$ (162 MHz, $CD_3CN$), −36.3; $m/z$ (ES$^+$) 490 (M.H$^+$, 100%); HRMS (ES$^+$) calculated for $C_{30}H_{34}O_4P$ (M.H$^+$) 489.2187, found 489.2195. The reaction mixture was heated to 60 °C and monitored by $^{31}$P NMR (acquired at 20 min intervals) for 4 h. During this time the intensity of the resonance at −36.3 ppm (phosphorane **11**) gradually decreased, and the resonance at 28.2 ppm ($Ph_3P{=}O$) increased, in intensity. A third peak at 64.8 ppm remained largely unchanged throughout.



## Acknowledgements

We thank the EPSRC and University of Birmingham for financial support. The NMR spectrometers used in this research were obtained through Birmingham Science City: Innovative Uses for Advanced Materials in the Modern World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and part funded by the European Regional Development Fund (ERDF). We thank Nick May and Peter Ashton (University of Birmingham) for assistance with mass spectrometry.

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