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Diastereotopic group selective intramolecular cycloadditions of sulfenic acids to 1,4-dienes †

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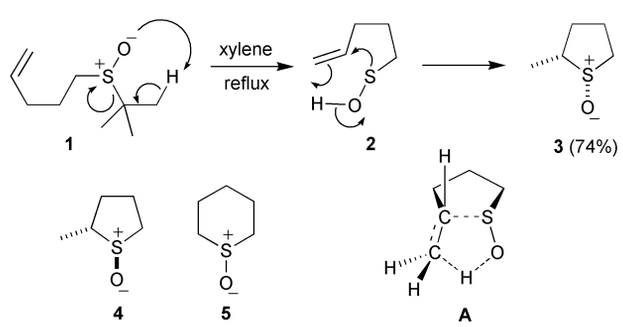
The ratio of diastereomeric *cis*-fused perhydrobenzothiophene *S*-oxides formed *via* the intramolecular addition of a sulfenic acid to a 1,4-diene is controlled by the nature of the protecting group on a chiral alcohol in the connecting chain.

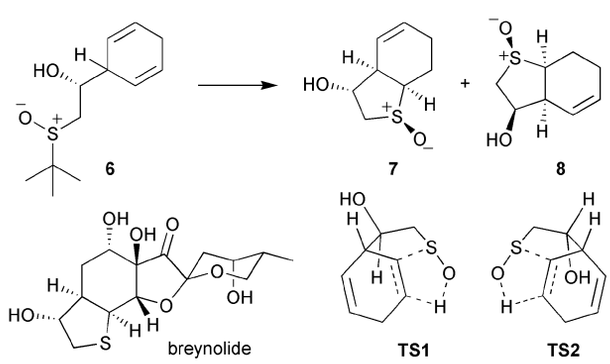
Employment of a group selective reaction can be a powerful strategy for asymmetric synthesis.[1] While a large body of work has concentrated on enantioselective desymmetrisation,[2] an important class of diastereoselective transformations involves the differentiation of diastereotopic groups through the influence of a pre-existing stereocentre covalently attached to the substrate.[3] In this communication we outline a new diastereotopic group selective reaction based on the intramolecular addition of a sulfenic acid to an alkene.

The thermally induced elimination of sulfoxides to give sulfenic acids and alkenes is an important reaction in organic chemistry.[4] Whereas the alkene is frequently the desired product, the reverse reaction – the addition of a sulfenic acid to an alkene to form a sulfoxide – also finds application in synthesis, and is subject to the same concerted *syn*-intramolecular mechanism.[5] Jones exploited the reversibility of this reaction in an elegant tandem sulfoxide elimination–intramolecular sulfenic acid addition to form cyclic sulfoxides with high levels of regio- and diastereocontrol (Scheme 1).[6] The exclusive formation of *cis*-sulfoxide **3** from thermolysis of *tert*-butyl sulfoxide **1** is a consequence of the geometric requirement of the transition state **A** for a concerted addition, in particular the need for the five participating atoms to achieve co-planarity. Cyclic transition states for the cyclisation of sulfenic acid **2** into the *trans*-sulfoxide **4** or the thiane oxide **5** are sterically impossible.



Scheme 1 Jones' tandem sulfoxide elimination–sulfenic acid addition.

We envisioned that this reaction would be ideal for the synthesis of the highly oxygenated, *cis*-fused perhydrobenzothiophene ring system found in breynolide. Breynolide is the aglycon hydrolysis product of breynin A, a naturally occurring glycoside isolated from a Taiwanese plant, which shows oral hypocholesterolemic activity.[7] Our group selective strategy is outlined in Scheme 2. Thermolysis of *tert*-butyl sulfoxide **6** should give rise to a sulfenic acid intermediate which can cyclise onto one of the two diastereotopic alkenes in the diene moiety *via* cyclic transition states **TS1** or **TS2** to provide cyclic sulfoxides **7** and/or **8** respectively, which differ only in the relative stereochemistry between the hydroxyl group and the three newly formed stereocentres. These three stereocentres in turn are set by the geometrical contraints of the transition state for sulfenic acid addition by analogy with the Jones system, with that leading to a *trans* ring junction also being sterically impossible. Our intention therefore is for the hydroxyl group in the connecting chain to act as both a stereochemical control element – controlling the relative amount of diastereomers **7** and **8** – and a source of the requisite oxygen functionality in the natural product.[8]



Scheme 2 Group selective sulfenic acid addition strategy.

We have tested this hypothesis on the readily synthesized methyl substituted diene **11a** (Scheme 3). Birch reduction of ethyl benzoate and quenching with methyl iodide[9] gave the 1,4-diene **9** in 93% yield. Ester **9** was coupled with two eq. of the anion of *tert*-butyl methyl sulfoxide to provide β-keto-sulfoxide **10**.[10,11] Stereoselective reduction of the ketone group furnished alcohol **11a** as a single diastereomer.[10,12] § Gratifyingly, thermolysis of sulfoxide **11a** in refluxing xylene provided a mixture of just two perhydrobenzothiophene *S*-oxides **12a** and **13a**, but in a 1 : 1 ratio (Table 1, entry 1). The structures of the two sulfoxides **12a** and **13a** were unambiguously determined by X-ray crystallography. ¶ Both **12a** and **13a** crystallise in a conformation in which the sulfoxide oxygen and bridgehead methyl groups occupy pseudo-equatorial positions on the thiolane ring, with the alcohol pseudo-axial in **12a** and pseudo-equatorial in **13a**. †

Although the 1 : 1 ratio of sulfoxides **12a** and **13a** was disappointing, we felt this ratio might be influenced by the nature of the substituent on oxygen. To this end, alcohol **11a** was protected under standard conditions with a variety of groups of varying steric and electronic demands (Scheme 3).[13] Results of the thermolyses of **11b–g** are presented in Table 1. In each

† Electronic supplementary information (ESI) available: Ball and stick representations of the X-ray crystal structures of **12a** and **13a**. See http://www.rsc.org/suppdata/ob/b3/b314176d/

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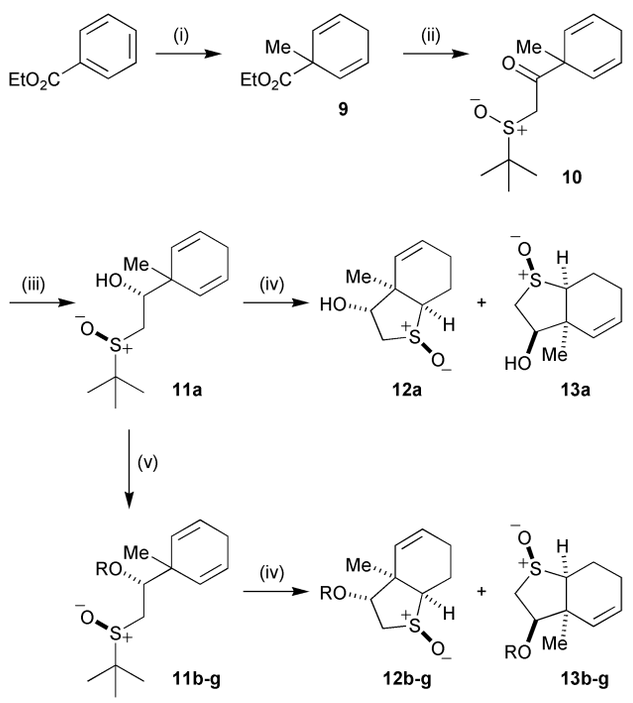
Table 1 Group selective cyclisation of **11** to **12** and **13**

Entry	R	Time/h	Yield (%)[a]	Ratio **12** : **13**
1	H	3.5	41[b]	1 : 1[c]
2	Me	3	65	4 : 1[d]
3	Bn	1	83	3.6 : 1[d]
4	Ac	4	80	2 : 1[c]
5	Bz	2.5	74	2 : 1[d]
6	TIPS	2	45	4.3 : 1[d]
7	TBDMS	2.5	59	4.9 : 1[c]

[a] Combined isolated yield of **12** and **13**. [b] 14% recovered starting material **11a**. [c] Ratio of separated cycloadducts. [d] Ratio determined by integration in ^{1}H NMR of combined cycloadducts.



b R=Me, **c** R=Bn, **d** R=Ac, **e** R=Bz, **f** R=TIPS, **g** R=TBDMS

Scheme 3 *Reagents and conditions:* (i) Na, NH_3, THF, *t*-BuOH then piperylene, MeI, 93%; (ii) *t*-BuS(O)Me, LDA, THF, −78 °C, 76%; (iii) DIBAL-H, THF, −78 °C, 96% (> 95% de); (iv) xylene, reflux; (v) **b**: NaH, MeI, THF, 66%; **c**: NaH, BnBr, THF, 74%; **d**: Ac_2O, cat. DMAP, 65 °C, 80%; **e**: BuLi, BzCl, THF, −78 °C, 54%; **f**: TIPSOTf, 2,6-lutidine, CH_2Cl_2, 56%; **g**: TBDMSCl, imidazole, DMF, 49%.

case the stereochemistry of the major and minor products was determined by comparison with alcohols **12a** and **13a** of known configuration, either by *O*-alkylation of **12a** and **13a** (in the case of R = Me and Bn), or deprotection of **12d**–**g** and **13d**–**g** (TBAF in the case of silyl protecting groups, basic hydrolysis in the case of ester protecting groups) to yield **12a** and **13a**.

In all cases the reaction gave rise to a major isomer **12b**–**g** with the bridgehead methyl and adjacent substituted oxygen *cis* to one another. However, the diastereomeric ratio is apparently not simply a reflection of the relative size of the group attached to oxygen.[14] Alkyl substituents gave rise to similar levels of selectivity (entries 2 and 3). Lower and identical selectivity is observed in the case of ester groups (entries 4 and 5). The best selectivity is seen in the case of a silyl ether (entries 6 and 7), with the TBDMS group proving optimum in terms of diastereomeric ratio, product stability, and ease of separation.

The origin of the selectivity presented in Table 1 has yet to be determined, but we believe it represents a thermodynamic rather than kinetic preference. A number of separated sulfoxides **12** and **13** (R = H, Me, Ac, Bz, TBDMS) have been independently resubjected to the reaction conditions (refluxing xylene), and found to give a mixture of sulfoxides **12** and **13** in an identical ratio to that derived from thermolysis of **11**. The reversible nature of the sulfoxide elimination–sulfenic acid addition reaction means that the product sulfoxides **12** and **13** can also eliminate to reform the sulfenic acid intermediate under the reaction conditions – presumably the temperature required for elimination of a sulfenic acid from **12** or **13** is similar or less than that from *tert*-butyl sulfoxide **11**.[15]

In conclusion the stereoselective synthesis of *cis*-fused perhydrobenzothiophenes related to the breynolide ring system can be controlled by a combination of the stereoelectronic requirements for the addition of sulfenic acids to alkenes, and the preference of an oxygen substituent other than hydroxyl to occupy a position on the newly formed thiolane ring *cis* to the adjacent bridgehead methyl and the lone pair on sulfur. The overall process generates four contiguous stereocentres starting from a simple sulfoxide starting material.

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Notes and references

§ Although the relative stereochemistry between the alcohol and the sulfoxide in **11** is unimportant in determining the ratio of diastereomers **12 : 13** (since the sulfoxide stereocentre is destroyed in the process of elimination to the sulfenic acid intermediate), the fact that the sulfoxide stereocentre can be used to set the alcohol stereochemistry means that this approach can be used to access enantiomerically pure compounds *via* a chiral relay starting from enantiomerically pure *tert*-butyl methyl sulfoxide.

¶ *Crystal data* for **12a**: $C_9H_{15}O_{2.50}S$, M = 195.27, colourless prism, 0.80 × 0.25 × 0.20 mm^3, triclinic, space group *P*-1 (No. 2), a = 7.1304(3), b = 10.9979(4), c = 13.4699(6) Å, α = 109.079(2), β = 92.0540(10), γ = 100.681(2)°, V = 975.68(7) Å^3, Z = 4, D_c = 1.329 g cm^{-3}, F_{000} = 420, Nonius KappaCCD diffractometer, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 3808 reflections collected, 2637 unique (R_{int} = 0.0534). Final *GooF* = 1.047, *R1* = 0.0347, *wR2* = 0.0832, *R* indices based on 2203 reflections with $I > 2\sigma(I)$ (refinement on F^2), 239 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.298 mm^{-1}. CCDC reference number 218530. See http://www.rsc.org/suppdata/ob/b3/b314176d/ for crystallographic data in.cif or other electronic format.

Crystal data for **13a**: C_9 H_{14} O_2 S, M = 186.26, 0.20 × 0.15 × 0.10 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 7.5780(3), b = 9.7836(4), c = 12.0885(5) Å, β = 92.028(2)°, V = 895.68(6) Å^3, Z = 4, D_c = 1.381 g cm^{-3}, F_{000} = 400, Nonius KappaCCD diffractometer, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 2782 reflections collected, 1640 unique (R_{int} = 0.0388). Final *GooF* = 1.069, *R1* = 0.0361, *wR2* = 0.0779, *R* indices based on 1265 reflections with $I > 2\sigma(I)$ (refinement on F^2), 115 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.317 mm^{-1}. CCDC reference number 218529. See http://www.rsc.org/suppdata/ob/b3/b314176d/ for crystallographic data in.cif or other electronic format.

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