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LETTERS

A concise synthesis of homochiral *trans*-perhydroazulenes and *trans*-hydrindanes

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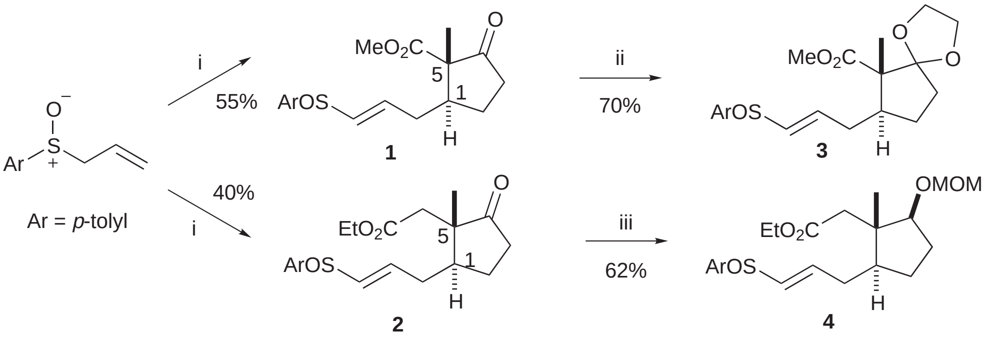
Abstract—A new approach to the synthesis of optically pure *trans*-perhydroazulenes and *trans*-hydrindanes using a homochiral sulfoxide auxiliary to control both chemical reactivity and enantioselectivity is described. © 2001 Elsevier Science Ltd. All rights reserved.

Optically active *trans*-perhydroazulene and *trans*-hydrindane ring systems are found in a variety of natural products, many of which possess biological activity. The *trans*-perhydroazulene ring system is common to many sesquiterpenes including guianolides, pseudoguaianolides and guaiazulenes. The *trans*-hydrindane ring system is also widespread, being found for example in the steroids and the D vitamins.

We have previously shown that a sulfur-based three component coupling–reductive cyclisation procedure can be effectively used to prepare racemic *trans*-hydrindane and *trans*-perhydroazulene derivatives.[1] In this communication we now report that this procedure can be efficiently adapted to produce these ring systems in excellent optical purity, using the sulfur moiety to control regio-, stereo- and enantioselectivity.

Although the use of homochiral sulfoxides as nucleophiles in asymmetric synthesis is now well established,[2] allyl substituted sulfoxides have been less frequently employed. This is probably owing to problems associated with their rapid racemisation via a facile, reversible [2,3]-sigmatropic rearrangement to give allyl sulfenates, which lack chirality at sulfur.[3] In our system, induction of chirality was best achieved at the initial 1,4-conjugate addition stage. Hua has shown previously that the lithio anion of (*R*)-(+)-allyl *p*-tolyl sulfoxide undergoes 1,4-γ addition to 2-cyclopenten-1-one in 91% yield and 96% ee.[4]



Scheme 1. *Reagents and conditions*: (i) BuLi, THF, −78–0°C; 2-methyl-2-cyclopenten-1-one, 1 min; $NCCO_2Me$, −78°C, 18 h or ICH_2CO_2Et, −78–0°C, 18 h; (ii) $HOCH_2CH_2OH$, TsOH, PhH, Δ, 12 h; (iii) a, $NaBH_4$, MeOH, 0°C, 30 min; b, $(MeO)_2CH_2$, LiBr, TsOH, THF, rt, 18 h.

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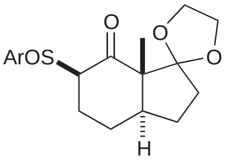
Initially we evaluated the efficiency of the tandem conjugate addition–reductive cyclisation procedure using racemic allyl aryl sulfoxide, in place of the sulfone as previously reported. The cyclopentanone derivatives **1** and **2** were obtained as single diastereoisomers, which were protected under standard conditions to give ketals **3** and **4**. The *trans* orientation about C-1–C-5 (pseudoguaianolide numbering) is a consequence of 1,2-asymmetric induction[5] (Scheme 1). The stereochemistry of the C-4 methoxymethyl ether of **4** was assigned the β-configuration by analogy with the known stereochemical consequences of sodium borohydride reduction of closely related cyclopentanone derivatives.[6]

In contrast to the comparable sulfone reactions, where the reductive cyclisation was facile, treatment of **3** with lithium butyldi-isobutylhydridoaluminate gave the desired *trans*-hydrindane **5** in only 9% yield. The major products were the hydroxy sulfoxide **6** and the ester sulfoxide **7**, obtained in approximately 50% yield in a 3:1 ratio and inseparable by flash column chromatography. Attempted cyclisation of **4** with lithium butyldi-isobutylhydridoaluminate gave the hydroxy sulfoxide **8** (46%) as the only isolable product.



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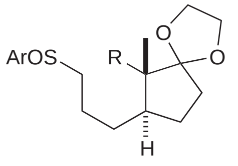
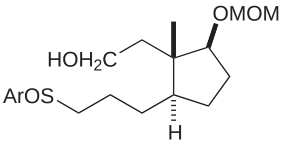


6 R=CH$_2$OH
7 R=CO$_2$Me



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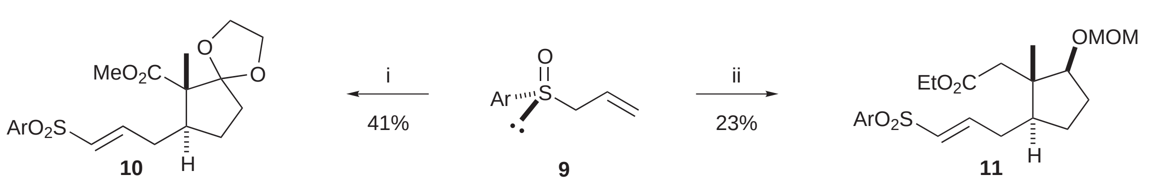
From our previous work it was apparent that this problem could be avoided by oxidising the sulfoxide to a sulfone prior to attempting the cyclisation. We therefore next addressed the homochiral system (Scheme 2). (*R*)-(+)-Allyl *p*-tolyl sulfoxide **9** was prepared in gram quantities by treatment of (*S*)-(−)-menthyl *p*-toluenesulfinate with allyl magnesium bromide.[7] Conjugate addition of the lithio anion of **9** to 2-methyl-2-cyclopenten-1-one, followed by trapping of the resultant enolate with either methyl cyanoformate or ethyl iodoacetate led to the corresponding cyclopentanone derivatives, which were subsequently converted into their sulfone derivatives **10** and **11**, respectively, as for the racemic modification.

Treatment of **10** with lithium butyldi-isobutylhydridoaluminate in hexane–THF gave an intermediate keto sulfone, which was reduced with sodium borohydride to give the hydroxy sulfone **12**; the structure of which was firmly established by X-ray crystallographic analysis of its racemic modification.† Chiral shift NMR experiments performed on this compound using the chiral shift reagent Eu(hfc)$_3$ split most signals pertaining to the racemic modification. Expansion and integration of the relevant signals revealed that the optically active hydroxy sulfone **12** was obtained in 95% enantiomeric excess.

Treatment of the vinyl sulfone **11** with lithium butyldi-isobutylhydridoaluminate gave a *trans*-perhydroazulene as a 3:1 mixture of diastereoisomers in 61% yield, together with a hydroxy sulfone (37%) which arose from reduction of both the ester and vinyl sulfone. The diastereoisomeric mixture could not be separated into its components either by chromatography or crystallisation. However, this did not prevent determination of optical purity by NMR since the signals corresponding to the bridgehead methyl group in the two diastereoisomers were distinct at δ 0.61 and 0.91, respectively. In chiral shift NMR experiments using Eu(hfc)$_3$ with the racemic modification each of these signals was split into two discrete singlets of equal intensity. However, in parallel chiral shift NMR experiments with the optically active *trans*-perhydroazulene no splitting of either



Scheme 2. *Reagents and conditions*: (i) a, BuLi, THF, −78–0°C; 2-methyl-2-cyclopenten-1-one, 1 min; NCCO$_2$Me, −78°C, 18 h; b, *m*CPBA, CH$_2$Cl$_2$, 0°C, 1 h; c, HOCH$_2$CH$_2$OH, TsOH, PhH, Δ, 12 h; (ii) a, BuLi, THF, −78–0°C; 2-methyl-2-cyclopenten-1-one, 1 min; ICH$_2$CO$_2$Et, −78–0°C, 18 h; b, *m*CPBA, CH$_2$Cl$_2$, 0°C, 1 h; c, NaBH$_4$, MeOH, 0°C, 30 min; d, (MeO)$_2$CH$_2$, LiBr, TsOH, THF, rt, 18 h.

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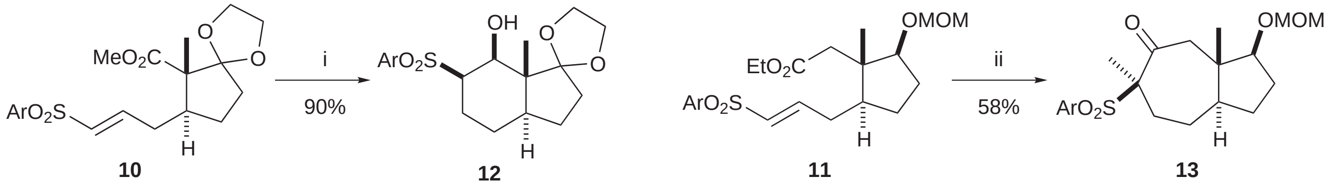
† *Crystal data* for **12**: $C_{19}H_{26}O_5S$, $M=366.48$, crystallises from ethyl acetate/petroleum ether as clear blocks; crystal dimensions: 0.45×0.2×0.125 mm. Monoclinic, $a=12.247(11)$, $b=7.343(7)$, $c=21.579(15)$ Å, $\beta=96.95(7)°$, $U=1926(3)$ Å^3, $T=293$ K, $Z=4$, $D_{\text{calcd}}=1.264$ g cm^{-3}, space group: $P2_1/n$ (a non-standard setting of $P2_1/c$ C^5_{2h}, No. 14), Mo-Kα radiation: ($\lambda=0.71069$ Å), μ(Mo-Kα)=1.84 cm^{-1}, $F(000)=783.92$. 2141 reflections, 1171 unique ($R=0.0879$) which were used in all calculations. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC).



Scheme 3. *Reagents and conditions*: (i) a, LiAl(^{i}Bu)$_2$BuH, THF, rt, 15 min; b, NaBH$_4$, MeOH, 0°C, 30 min; (ii) a, LiAl(^{i}Bu)$_2$BuH, THF, Δ, 30 min; b, NaH, MeI, THF, rt, 18 h.

signal was observed, implying an optical purity greater than 95%. To confirm this result by using chiral column chromatography it was desirable to obtain a derivative in a state of diastereoisomeric purity. This was achieved by treating the mixture of β-keto sulfones with sodium hydride, followed by alkylation of the resulting anion with methyl iodide to give the keto sulfone **13** as a single diastereoisomer in 98% yield (Scheme 3). Chromatography using a Chiralcel OD column showed separation of the racemic modification into two distinct and equally intense peaks. Repetition of this on the optically active keto sulfone **13** gave one signal only, confirming that this had an optical purity greater than 98%.

In summary, we have established methodology for the enantioselective construction of homochiral *trans*-perhydroazulenes and *trans*-hydrindanes. The tandem three component coupling procedure works well with sulfoxides, although the reductive cyclisation does not, and compounds have first to be oxidised to sulfones. The ready availability of starting materials, ease and rapidity of cyclisation, and synthetically useful functionality in the products make this an attractive procedure for synthesis.

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