Cyclisation of Polyenic β-Keto Sulphoxides. A Novel Route to Optically Active Intermediates for Cyclic Terpenoid Synthesis

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Optically active polyenic β-keto sulphoxides **4** and **5** undergo a cyclisation mediated by $SnCl_4$ to give easily separable diastereoisomeric dihydropyran derivatives **6a,b** and **10a,b**, respectively; the crystalline stereoisomers of which can be converted into (+)-dihydroacitinidiolide **7** and (−)-norambreinolide **11**.

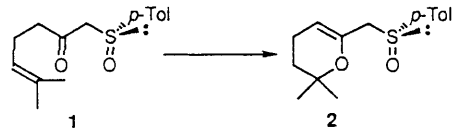
The biogenetic-like cyclisation of polyenes has proved to be an extremely useful method for ring construction in terpenoid synthesis.[1] The possibility of extending this methodology to polyenic β-keto sulphoxides is attractive for the following reasons: (*i*) the ready availability of β-keto sulphoxide precursors, (*ii*) the favourable prospect for elaboration of residual functionality after cyclisation. Moreover, to introduce a chiral sulphoxide moiety in the system might afford easy access to optically active intermediates for the synthesis of some types of cyclic terpenoids. We report herewith an efficient cyclisation of this type and the successful application to the short-step syntheses of optically pure dihydroactinidiolide and norambreinolide.

During the course of our synthetic studies on the utility of chiral sulphoxides in organic synthesis,[2] we observed that (*R*)-6-methyl-1-*p*-tolylsulphinyl-hept-5-en-2-one **1** underwent cyclisation with $SnCl_4$ in dichloromethane, giving rise to a dihydropyran derivative **2** in 85% yield (Scheme 1). This result suggested that polyenes containing a chiral β-keto sulphoxide moiety as a terminating group could serve as the precursors for the biogenetic-like cyclisation of polyenes.

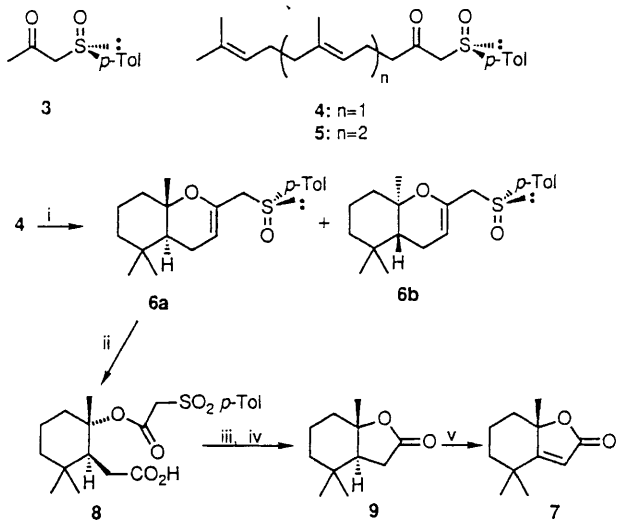
The requisite chiral alkenic β-keto sulphoxides **4** and **5** were readily prepared in high yields by alkylation of the dianion derived from (*R*)-1-*p*-tolylsulphinylpropan-2-one **3**[3,4] with geranyl bromide or farnesyl bromide, respectively.† After exploring a variety of conditions for the Lewis acid-catalysed cyclisation, it was found that treatment of **4** with 1 mol equiv. of $SnCl_4$ in dichloromethane at −25 to 10 °C for 0.5 h gave a 1 : 1 diastereoisomeric mixture of cyclic products **6a** and **6b** in 92% combined yield (Scheme 2). These products were easily separated by silica gel chromatography or recrystallisation.

† All new compounds gave satisfactory spectroscopic and analytical data. The dianion of *p*-tolylsulphinylpropan-2-one **3**, generated by using 2.2 equiv. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and warmed to −20 °C (the slightly modified method of ref. 4), was treated with geranyl bromide or farnesyl bromide, affording **4** and **5**, in 73 and 66% yield, respectively.

Selected physical data: **4**, m.p. 32–33 °C; $[\alpha]_D^{23}$ + 143° (*c* 0.227, $CHCl_3$). **5**, m.p. 25–26 °C; $[\alpha]_D^{23}$ + 112° (*c* 0.176, $CHCl_3$). **6a**, m.p. 131–133 °C; $[\alpha]_D^{23}$ + 220° (*c* 0.148, $CHCl_3$); ^{1}H NMR δ 1.22(3H, s), 3.30(2H, s), 4.74(1H, t, *J* 3.8 Hz). **6b**, oil; $[\alpha]_D^{23}$ + 104° (*c* 0.168, $CHCl_3$); ^{1}H NMR δ 1.08(3H, s), 3.31(2H, AB type q, *J* 12.6 Hz), 4.61(1H, dd, *J* 4.0 and 2.8 Hz). **10a**, m.p. 146–147 °C; $[\alpha]_D^{23}$ + 186° (*c* 0.108, $CHCl_3$); ^{1}H NMR δ 0.81(6H, s), 0.88(3H, s), 1.19(3H, s), 3.29(2H, s), 4.70(1H, t, *J* 3.8 Hz). **10b**, oil; $[\alpha]_D^{23}$ + 45.1° (*c* 0.255, $CHCl_3$); ^{1}H NMR δ 0.80(6H, s), 0.88(3H, s), 1.12(3H, s), 3.36(2H, AB type q, *J* 12.0 Hz), 4.59(1H, dd, *J* 7.4 and 4.2 Hz).



Scheme 1

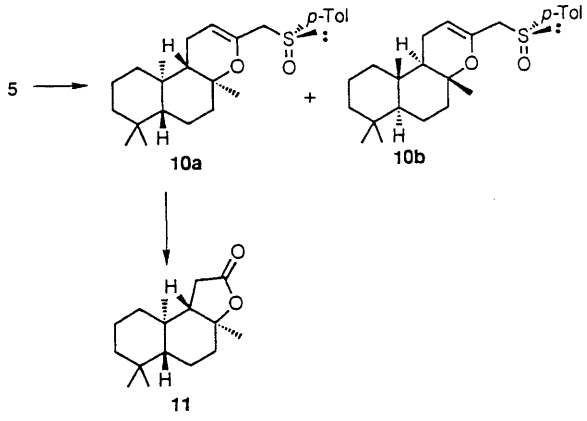


Scheme 2 *Reagents and conditions*: i, $SnCl_4$ (1 equiv.), CH_2Cl_2, room temp., 2 h; ii, RuO_2 (0.1 equiv.), $NaIO_4$ (10 equiv.), acetone–H_2O, room temp., 7 h; iii, aq. 20% NaOH, dimethyl sulphoxide, 40 °C, 2 h; iv, *p*-TsOH, benzene, reflux, 1 h; v, LDA, PhSeCl, THF, and then 30% H_2O_2, THF

The diastereoisomeric correlation between **6a** and **6b** was ascertained by removal of the chiral centre on the sulphur atom by reduction with Zn–Me_3SiCl–pyridine to produce the enantiomeric sulphides.

In order to determine the absolute configuration of the cyclised products, we undertook the conversion of **6a** to a norsesquiterpene, dihydroactinidiolide **7**, which was isolated from *Actinidia polygama*,[5] as well as from steam-volatile extracts of tobacco and black tea,[6] and was found to be physiologically active towards Felidae animals. The crystalline **6a** was subjected to oxidative cleavage of the enol double bond with RuO_2–$NaIO_4$, furnishing the acid **8** accompanied by a small amount of the lactonized product **9**. Using alkaline hydrolysis of the mixture followed by lactonization in refluxing benzene containing a catalytic amount of toluene-*p*-sulphonic acid gave (−)-*trans*-tetrahydroactinidiolide[7]‡ {m.p. 78.2–79.0 °C, $[\alpha]_D^{23}$ −70.0° (*c* 0.130, $CHCl_3$)} in 84% overall yield from **6a**. Conversion of **9** into dihydroactinidiolide **7** was accomplished *via* the reported procedure employed in the synthesis of racemic **7**.[8] Since synthetic **7** {m.p. 66–68 °C, $[\alpha]_D^{23}$ + 119° (*c* 0.141, $CHCl_3$), lit.,[9] m.p. 67–68 °C, $[\alpha]_D^{23}$ + 120.9° (*c* 1.00, $CHCl_3$)} showed a positive specific rotation value, the absolute stereochemistry of the cyclised products is established as depicted in Scheme 2.

We then examined the cyclisation of **5** (Scheme 3). The reaction proceeded smoothly under the above conditions using toluene as solvent in place of dichloromethane, at room temperature for 5 h, furnishing a *ca.* 1:1 diastereoisomeric mixture of the cyclised products **10a** and **10b**§ in 60% yield,



Scheme 3

which could be separated by silica gel chromatography or recrystallisation. The absolute stereochemistry of the products was established through the correlation to norambreinolide. The crystalline **10a** was oxidatively cleaved as described above with RuO_2–$NaIO_4$, directly providing (−)-norambreinolide **11**¶ (91%) in a single step; m.p. 121–122 °C, $[\alpha]_D^{23}$ −47.0° (*c*, 0.110, $CHCl_3$), lit., [10] m.p. 123–124 °C, $[\alpha]_D^{23}$ + 48.4° (*c*, 2.00., $CHCl_3$).

Norambreinolide, usually obtained degradatively from natural sources such as manool, ambrein, or sclareol, can be converted to Ambrox® which is the most important ambergris odourant[11] and serves as a precursor for the synthesis of di- or tri-terpenoids. Thus, the present method provides an easy access to the chiral cyclic precursors for a variety of terpenoids.

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‡ *trans*-Tetrahydroactinidiolide **9** was found in natural sources,[6] but the absolute stereochemistry had not been determined until the synthesis was accomplished.[7]

§ The enantiomeric correlation of their sulphides, derived from reduction of the diastereoisomeric sulphoxides **10a** and **10b** by the same method as described for **4**, was confirmed.

¶ Another name is sclareolide (the systematic name: dodecahydro-3a,6,6,9a-tetramethylnaphthol[2,1-*b*]furan-2-one).