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PREPARATION OF STABLE, CAMPHOR-DERIVED, OPTICALLY ACTIVE ALLYLIC SULFOXIDES

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Summary: (+)-Camphor has been stereospecifically converted in three steps into a single isoborneol allyl sulfoxide derivative, which upon heating to 145° is quantitatively converted into its sulfoxide epimer; the anions of these compounds undergo stereospecific conjugate addition to cyclopent-2-en-1-one.

The carbanions derived from allylic sulfoxides 1 and phosphine oxides 2 undergo conjugate addition to cyclic enones in THF in the absence of chelating agents to deliver the vinylic sulfoxides 3 and phosphine oxides 4 as single diastereomers.[1] The products from the corresponding cis-carbanions possess the opposite configuration at the allylic carbon atom, although in the case of the sulfoxide, configuration at sulfur is unchanged. The stereochemical features of these reactions are accounted for in the model of the TS for the trans-sulfoxide anion depicted in 5, which involves alignment of the sulfoxide oxygen with the carbonyl oxygen through chelation with the lithium cation, such that the allyl system lies over one face of the enone to constitute a "trans-fused chair-chair like" arrangement. In all cases thus far examined, the sulfoxide lone-pair assumes a pseudoaxial, and the non-allylic substituent a pseudoequatorial, disposition.[1] Quite clearly, an enantiomerically pure allylic sulfoxide will react at only one of the enantiotopic faces of the enone to deliver an enantiomerically pure conjugate addition product.

However, a general method for the preparation of optically active allylic sulfoxides is lacking.[2] Although (+)-allyl p-tolyl sulfoxide is relatively easily prepared from menthyl p-toluenesulfinate,[3] the preparation, due to the ready thermal racemization of the product, must be carried out at or below 0°, and we were uncertain that the product would have been sufficiently stable for our purposes. The method also cannot be applied to the preparation of cis- or trans-crotyl sulfoxides or higher homologues.[3] In seeking to develop an alternative method for preparation of such compounds, we were guided by the following considerations. As the rate of racemization of methyl allyl sulfoxide is lower than those of aryl allyl sulfoxides,[3] the non-allylic group attached to sulfur should preferably be alkyl. Secondly, the non-allylic group itself must be optically active and contain a group capable of selectively directing an

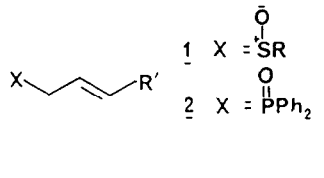
oxidizing agent to attack one of the enantiotopic lone pairs on the sulfur atom of a sulfide precursor. The non-allylic group must also be sufficiently disymmetric in order to bias any equilibration of the allylic sulfoxide, should it occur at room temperature, towards one, or predominantly, one of the two possible sulfoxide epimers. The non-allylic group should be readily available from a chiral starting compound, both enantiomers of which are readily available.

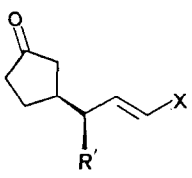
Freshly recrystallised (+)-camphor was deprotonated by LDA in THF containing HMPA (3 equiv.) at -78° and treated with allyl p-toluenethiolsulfonate[4] (2 equiv.). When the mixture was quenched at -78°, the exo-allylthiocamphor derivative 6 was formed exclusively (yellow oil, b.p. 130°/0.3 mm, 77%); if the reaction mixture was warmed to room temperature prior to quenching, a mixture of 6 and the endo-derivative 7 (yellow oil, b.p. 80°/0.1 mm) was obtained in the ratio 1:20.[6] Whereas the use of lithium aluminium hydride or other, more hindered hydride donors gave mixtures of products arising from both endo and exo carbonyl attack, sodium borohydride (10 equiv.) in ethanol at 0° cleanly converted 6 into the isoborneol 8 (pale yellow oil, b.p. 100°/0.04 mm, 86%). Next, 8 in dichloromethane or THF at -78° was treated with m-chloroperbenzoic acid (1.1 equiv.) to give solely the sulfoxide 9 (needles, from ether, m.p. 134-135°, 55%), whose absolute configuration was established by X-ray crystallography.[7] The sulfoxide 9 is a stable compound; it does not undergo detectable conversion into its sulfoxide epimer below 100°, and it can be handled without undue precautions.[8] Now, according to the model of the conjugate addition reaction, it is the configuration at sulfur which will determine the configuration of the conjugate addition product. For a sulfoxide with the opposite configuration, such as the enantiomer of 9, attack on the other enantiotopic face of the enone will take place. However, this will also be true for the sulfoxide epimer 10, which is obtained from 9 in a remarkably simple manner. If the compound is heated through its melting point (134-135°) to 145°,[10] the melt slowly solidifies to produce quantitatively this epimer, (needles, m.p. 171-174°, from ethyl acetate/light petroleum). Thus, if there is indeed any equilibration between 9 and 10 this is drawn towards the latter by deposition of solid 10 from the melt. Compound 10, like 9, can be handled without special precaution.

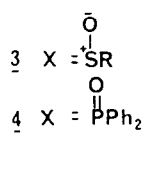
We also report that treatment of each of 9 and 10 in THF with LDA (2 equiv.), and addition of cyclopent-2-en-1-one to each of the dianion solutions so obtained at -78° gave, stereospecifically,[11] the respective adducts 11 (needles, m.p. 172-4°, from ethyl acetate light petroleum) and 12 (needles, m.p. 135-7°, from ethyl acetate light petroleum). Although the configuration at C-3 of the cyclopentanone nucleus in each of these products has not been assigned,[12] the presence of the trans-double bond implies the normal "trans-fused chair-chair like" TS 5, and the configurations as depicted derive from this consideration. The dianion of compound 9 also gave a single conjugate addition product 13 when treated with two equivalents of racemic 4-tert-butoxycyclopent-2-en-1-one; however, attempts to recover the unreacted (and in principle resolved) enone from the reaction mixture were not successful. A problem associated with the foregoing reactions has been the inability of sulfoxides 9 and 10 to react to

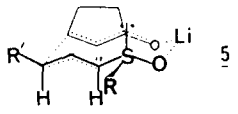
completion, which is due to a competing deprotonation of the enone by the dianion. Thus, compounds 11-13 cannot be obtained in yields greater than 50 % - 60 %. Unfortunately, attempts to mask the hydroxyl group in 9 by alkylation or silylation have not been successful. Finally, we note that (+)- allyl tolyl sulfoxide, in spite of our forebodings, has very recently been utilized in conjugate addition reactions with cyclic enones to give adducts whose absolute configurations in some cases have been established by chemical correlation.[14] The configurations are fully consistent with our model of the transition state of these reactions.

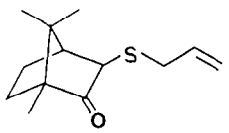
Acknowledgement: We thank the Australian Research Grants Scheme for support of this work.

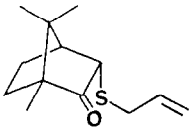


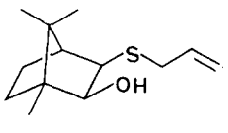


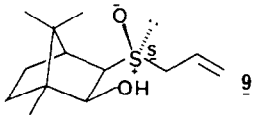


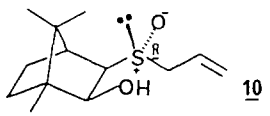


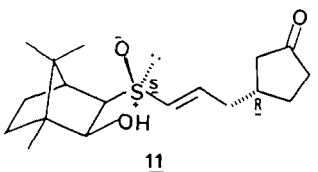


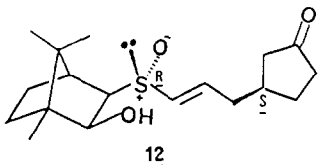


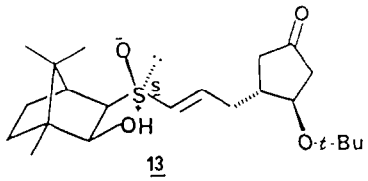












References and Notes

(1) Binns, M.R.; Haynes, R.K.; Schober, P.A.; Vonwiller, S.C. Tetrahedron Lett. 1985, 26, 1565; Binns, M.R.; Chai, O.L.; Haynes, R.K.; Katsifis, A.; Schober, P.A.; Vonwiller, S.C., Tetrahedron Lett. 1985, 26, 1569.

(2) Barbachyn, M.R.; Johnson, C.R. in "Asymmetric Synthesis", Morrison, J.D.; Scott, J.W., Eds.; Academic Press: New York, 1984, Ch. 2, and references therein.

(3) Bickart, P.; Carson, F.W.; Jacobus, J.; Miller, E.G.; Mislow, K. J.Am.Chem.Soc. 1968, 90, 4869.

(4) This was prepared from sodium p-toluenethiolsulfonate and allyl bromide in dichloromethane: water (1:1) containing $n\text{-}Bu_4N^+Cl^-$ (0.1 equiv.). Crotyl and higher homologues (Binns, M.R., Ph.D. Thesis, University of Sydney, 1985) can be prepared in this fashion: see also Yamada S., Fugita, T.; Mizoguchi, T. J.Pharm.Soc.Japan 1954, 74, 963.

(5) Sato, R.; Goto, T.; Takikawa, Y.; Takizawa, S. Synthesis, 1980, 615.

(6) All new compounds gave satisfactory microanalytical and spectral data. Selected spectral data are given below![15]

(7) Details of the determination are available from Dr. T.W. Hambley, Dept. of Inorganic Chemistry, University of Sydney. The ORTEP plot reveals that the orientation of the allyl group is as depicted in 9.

(8) We cannot yet state whether the hydroxyl group is indeed responsible for the complete asymmetric induction in the oxidation step, and if it contributes to the stability of 9. However, a number of deshydroxy steroidal allylic sulfides are oxidized by peracid in non polar solvents to mixtures of epimeric sulfoxides which undergo equilibration at 80°.[9]

(9) Jones, D.N.; Blenkinsopp, J.; Edmonds, A.C.F.; Helmy, E.; Taylor, R.J.K. J.Chem.Soc., Perkin Trans 1 1974, 937.

(10) Note that thermal syn-elimination of allylsulfenic acid from 9 cannot take place.

(11) No trace of 12 could be found in the reaction mixture by HPLC or 400 MHz ^{1}H nmr spectroscopy from the dianion of 9 and cyclopentenone. Likewise 11 was unable to be found in the reaction mixture from the dianion of 10 with the enone. The HPLC retention times on Whatman Partisil 10 M20, 60 psi 4% EtOH/EtOAc for 11 was 41 min and for 12 was 38 min.

(12) Crystals 11 and 12 are unsuitable for X-ray analysis. Attempts to degrade 11 to the known (R)-(-)-3-oxocyclopentaneacetic acid[13] were not successful. See, however, reference 14 for a solution to this problem.

(13) Hill, R.K.; Edwards, A.G. Tetrahedron 1965, 21, 1501; Kuritani, H.; Takaoka, Y.; Shingu, K. J.Org.Chem. 1979, 44, 452.

(14) Hua, D.H.; Sinai-Zingde, G.; Venkataraman, S. J.Am.Chem.Soc. 1985, 107, 4088.

(15) Selected spectral data (NMR spectra at 400 MHz in $CDCl_3$, optical rotations in CH_3COCH_3):

6. ^{1}H NMR: δ 5.82 (m, C$\underline{H}$=CH$_2$), 5.11 (m, CH=C$\underline{H}_2$), 3.45 and 3.26 (m, SC$\underline{H}_2$), 2.82 (s, SCH), 2.07-1.43 (m, aliphatics), 0.98, 0.92, 0.92 (s, 3xCH$_3$), $[\alpha]_D^{20}$=+74.9°. 7: ^{1}H NMR: δ 5.82 (m, C$\underline{H}$=CH$_2$), 5.15 (m, CH=C$\underline{H}_2$), 3.46 and 3.24 (AMX, J_{AM}=13.5, J_{AX}=7.5, J_{MX}=6.8 Hz, SC$\underline{H}_2$), 3.43 (dd, J=4.5, 2.0 Hz, SCH), 2.15-1.39 (m, aliphatics), 1.01, 0.93, 0.90 (s, 3xCH$_3$), $[\alpha]_D^{20}$=+21.9°. 8: ^{1}H NMR: δ 5.81 (m, C$\underline{H}$=CH$_2$), 5.10 (m, CH=C$\underline{H}_2$), 3.55 (d, J=7.1 Hz, C$\underline{H}$OH), 3.10 (m, SCH$_2$), 2.93 (d, J=7.1 Hz, SCH), 2.81 (s (b), OH), 1.83-1.10 (m, aliphatics), 1.00, 0.96, 0.78 (s, 3xCH$_3$), $[\alpha]_D^{20}$=+10.6°. 9: ^{1}H NMR: δ 6.01 (m, C$\underline{H}$=CH$_2$), 5.40 (m, CH=C$\underline{H}_2$), 4.09 (dd, J=7.2, 3.5 Hz, C$\underline{H}$OH), 3.72 (d, J=3.5 Hz, OH), 3.65 and 3.29 (m, C$\underline{H}_2$-CH=), 3.06 (d, J=7.2 Hz, CHSO), 1.81, 1.70, 1.54, 1.10 (m, aliphatics), 1.23, 1.00, 0.83 (s, 3xCH$_3$), $[\alpha]_D^{25}$=+31.8°. 10: ^{1}H NMR: δ 6.04 (m, C$\underline{H}$=CH$_2$), 5.42 (m, CH=C$\underline{H}_2$), 3.89 and 3.46 (AMX, J_{AM}=13.1, J_{AX}=8.5, J_{MX}=6.7 Hz, C$\underline{H}_2$-CH=), 3.84 (dd, J=7.8, 4.8 Hz, C$\underline{H}$OH), 3.02 (d, J=7.8 Hz, CHSO), 2.68 (d, J=4.8Hz, O$\underline{H}$), 2.38, 1.90, 1.57, 1.08 (m, aliphatics), 1.31, 0.94, 0.87 (s, 3xCH$_3$), $[\alpha]_D^{25}$=+92.0°. 11: ^{1}H NMR: δ 6.48 (dt, J=15.2, 6.6 Hz, =C$\underline{H}$CH$_2$), 6.39 (d, J=15.2 Hz, SOCH=), 4.10 (dd, J=7.1, 3.7 Hz, C$\underline{H}$OH), 3.31 (d, J=3.7 Hz, O$\underline{H}$), 2.95 (d, J=7.1 Hz, CHSO), 1.68-1.1 (m, aliphatics), 1.24, 1.00, 0.84 (s, 3xCH$_3$), $[\alpha]_D^{25}$=-69.2°. 12: ^{1}H NMR: δ 6.85 (d, J=15.2 Hz, SOCH=), 6.43 (dt, J=15.2, 7.2 Hz, = CH-CH$_2$), 3.89, (dd, J=7.6, 4.8 Hz, C$\underline{H}$OH), 3.28 (d, J=4.8 Hz, OH), 2.89 (d, J=7.6 Hz, C$\underline{H}$SO), 2.45-1.04 (m, aliphatics), 1.34, 0.95, 0.88 (s, 3xCH$_3$), $[\alpha]_D^{20}$=+162.8°. 13: ^{1}H NMR: δ 6.45 (dt, J=15.6, 6.8 Hz, = CHCH$_2$), 6.35 (d, J=15.6 Hz, SOC$\underline{H}$=), 4.07 (dd, J=7.0, 4.0 Hz, C$\underline{H}$OH), 3.89 (m, C$\underline{H}$OBu^t), 3.54 (d, J=4.0Hz, OH), 2.93 (d, J=7.0 Hz, CHSO), 2.74-1.09 (m, aliphatics), 1.22, 1.00, 0.82 (s, 3xCH$_3$), 1.21 (s, Bu^t), $[\alpha]_D^{20}$=-74.7°.

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