A Simple Route to (*R*)-(+)-4-t-Butoxycyclopent-2-enone†

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(−)-10-Mercaptoisoborneol undergoes conjugate addition to racemic 4-t-butoxycyclopent-2-enone in methanol in the presence of a catalytic amount of *N,N,N′,N′*-tetramethylethylenediamine to give a 1 : 1 mixture of the sulphide adducts, which with *m*-chloroperbenzoic acid in ether at −70 °C is converted into a mixture of the corresponding sulphoxides; a single diastereoisomer of one of the sulphoxides is easily obtained by crystallization, and the diastereoisomer is converted by silica gel into (*R*)-(+)-4-t-butoxycyclopent-2-enone (**1**).

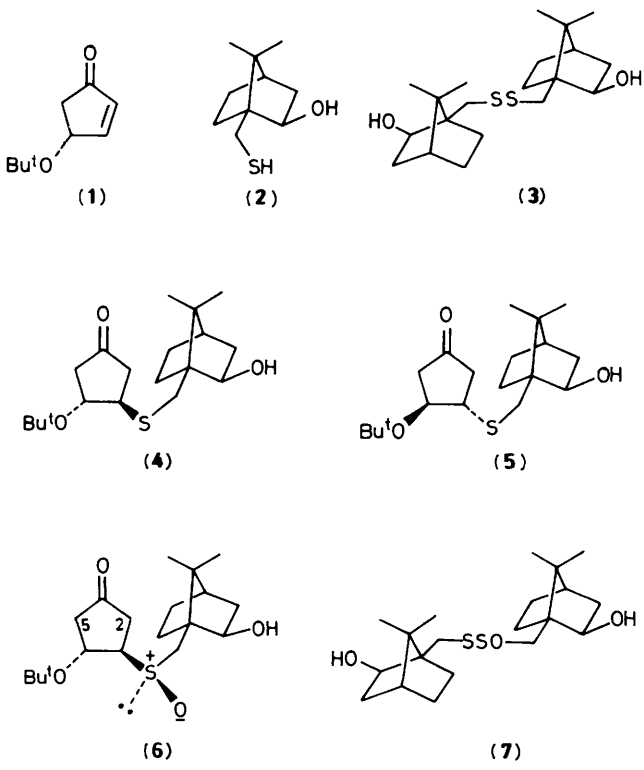
We have recently assembled an advanced prostaglandin precursor in one step from racemic 4-t-butoxycyclopentenone,[1] an enone which is far more easily and cheaply prepared than any other protected 4-hydroxycyclopentenone.[2] In connection both with this synthesis and also with a kinetic resolution experiment,[3] we required both the (*R*)- and (*S*)-enantiomers of this compound. As none of the methods[4] reported for the preparation of optically-active protected 4-hydroxycyclopent-2-enones can be adapted to fulfil our requirements, we have devised a conceptually new approach to such compounds which involves a novel resolution of the racemic enone.

Racemic 4-t-butoxycyclopent-2-enone (16—32 mmol), purified by low temperature (−30 °C) crystallisation of the neat liquid, and (−)-10-mercaptoisoborneol (**2**) (16—32 mmol) [prepared from commercially available (+)-10-camphorsulphonyl chloride[5]] in dry methanol (75—100 ml) containing *N,N,N′,N′*-tetramethylethylenediamine (200 mg) under nitrogen during 24 h at room temperature gave the sulphides (**4**) and (**5**) as a 1 : 1 mixture (55—93%) after flash chromatography (silica gel, ethyl acetate–light petroleum, 1 : 9) to remove small and variable amounts of the disulphide (**3**) and unchanged starting materials. The mixture (12 mmol) in dry dichloromethane (100 ml) at −70 °C upon treatment with *m*-chloroperbenzoic acid (13 mmol) in dichloromethane (50 ml) and then quenching after 30 min with aqueous sodium sulphite (10%; 100 ml) gave a semi-crystalline thermally unstable residue. Analysis of the mixture by h.p.l.c. indicated the presence of *two* sulphoxides in an approximate ratio of 1 : 1; other uncharacterized products were also present in minor amounts. A solution of the mixture in light petroleum–ether (9 : 1) at −12 °C slowly deposited needles, m.p. 109—110 °C, of a single sulphoxide (26—33%), whose absolute configuration, as revealed by an *X*-ray crystallographic study,‡ is as depicted in (**6**). As only the (4*R*)-enantiomer within the starting racemate can give this compound, the overall yield of (**6**) is thus 52—66%. The purity of (**6**), as assessed by analysis of the signals in the high field ^{1}H n.m.r. spectrum due to the 8- and 9-methyl groups in the bornyl residue, was 99.5%.§ The other sulphoxide could not be obtained in a pure state from the mother liquors; it is non-crystalline, and appears to be less stable than the sulphoxide (**6**).

Next, a solution of the sulphoxide (**6**) (5—10 mmol) in light petroleum (30 ml) was stirred with flash silica gel (15—20 g) during 24 h at room temperature. The mixture was applied to a chromatography column and eluted with ethyl acetate–light petroleum (1 : 5) to give 4-t-butoxycyclopentenone (**1**) (85—92%), $[\alpha]_D$ +33.8° (*c* 10.8, acetone, 20 °C), and the thiolsulphinate (**7**) (54—58%).

As the enantiomeric purity of the enone (**1**) could not be reliably assessed by ^{1}H n.m.r. methods based upon the use of chiral lanthanide shift reagents, it was treated with (−)-10-mercaptoisoborneol (**2**) according to the original conditions to give in high yield a product estimated from its ^{1}H n.m.r. spectrum to contain 99.5% of the adduct (**4**).¶ The enantiomeric purity of the enone (**1**) thus corresponds to this value.

Several factors are crucial to the success of this resolution. Firstly, the conjugate addition of the thiol to the racemic enone proceeds *trans* to the t-butoxy group; that is, it proceeds in stereospecific fashion so that each enantiomer of the enone delivers a single diastereoisomer. Secondly, the oxidation of each of the sulphides to the sulphoxides must be essentially stereoselective so that a proliferation in the number of diastereoisomers does not occur. It was partly for this reason



(**1**) (**2**) (**3**) (**4**) (**5**) (**6**) (**7**)

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‡ Details are available from Dr. T. W. Hambley, Department of Inorganic Chemistry, The University of Sydney, NSW 2006.

§ For (**6**), the signals appear at δ 0.829 (9-Me) and at 1.087 (8-Me); the corresponding signals from the second sulphoxide in the original mixture are at δ 0.848 and 1.136.

¶ This analysis is based on the signal due to the 9-methyl group; in the adduct (**4**) this appears at δ 0.852 (9-Me) and in adduct (**5**) at δ 0.841. The signal due to the 8-methyl appears at δ 1.065 for both compounds.

that the thiol (**2**) bearing a hydroxy group adjacent to the sulphur was chosen; the stereoselective oxidation of hydroxysulphides to sulphoxides wherein the stereochemical outcome of the oxidation is controlled by the hydroxy group is now well documented.[3,6] Thirdly, and fortuitously, it turns out that only one of the two diastereoisomeric sulphoxides is crystalline. Fourthly, the silica-gel induced formation of the enone, first encountered during attempts to separate the sulphoxide diasteroisomers by chromatography, is rapid and high-yielding, and is completely selective with respect to elimination of sulfenate.** Products resulting from a competing elimination of t-butoxide are not observed.††

Although the reaction of thiols with enones is well known,[8] the use of chiral thiols in the reaction appears not to have been previously recorded. Through judicious choice of the chiral thiol, it should now be generally posible to resolve racemic enones; this could in principle be carried out by separation of the diastereoisomers produced in the initial addition at any of the sulphide, sulphoxide, or sulphone levels. The method also has the advantage that the chiral thiol can be recovered, either directly as such or by reduction of its oxidized derivatives obtained at the end of the resolution experiment. The use of 10-mercaptoisoborneol as the chiral thiol, however, does have the further advantage that both enantiomers are easily obtained from the corresponding sulphonyl chlorides.

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** Two examples of related reactions involving adducts of simple enones have been reported previously (ref. 7).

†† Our original intention was to effect elimination of bornylsulphenate from the sulphoxide under base catalysis, wherein the hydroxy group would play the important role of ensuring that deprotonation at C-2, rather than at C-5, of the cyclopentanone would take place. Whether the group plays a significant role in causing the elimination of sulphenate on the silica remains to be established.

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