An Enantiodivergent Synthesis of Fused Bicyclo[2.2.1]heptane Lactones *via* an Asymmetric Diels–Alder Reaction

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An enantiodivergent synthesis of the bicyclo[2.2.1]heptane lactone (**2**) is described, by regioselective reduction of the Diels–Alder adducts (**3**) and (**4**) with di-isobutylaluminium hydride followed by reductive elimination of the chiral auxiliary, 10-mercaptoisoborneol (**9**) through reaction with samarium(II) iodide.

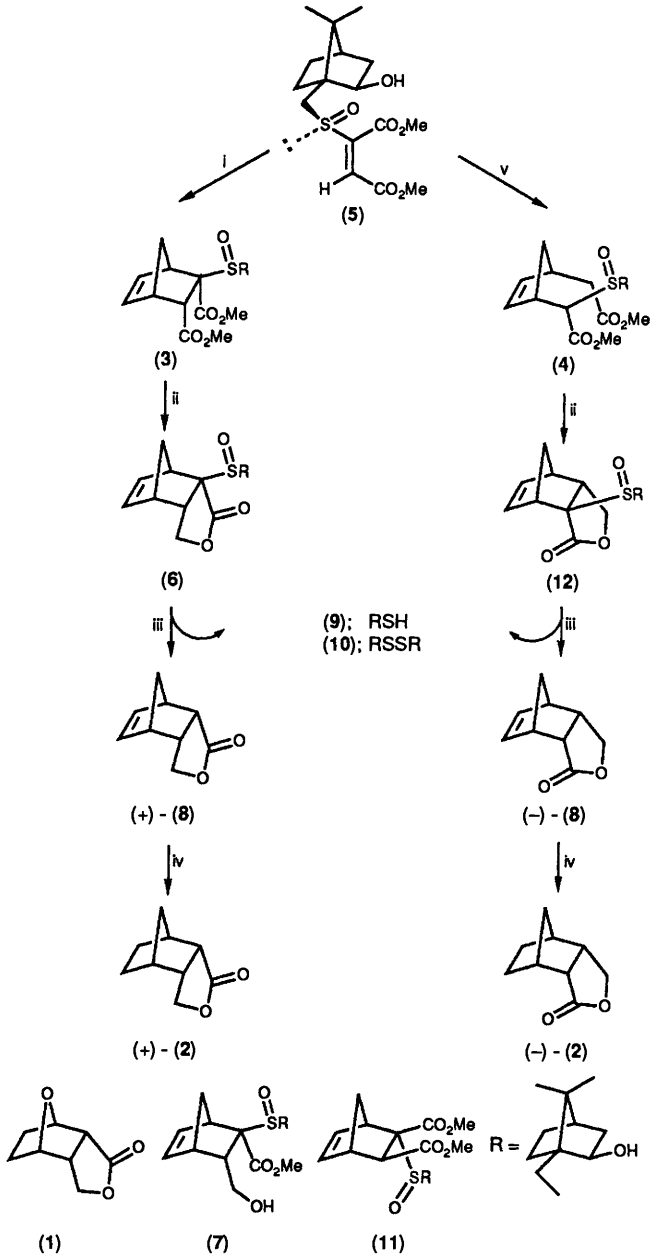
The synthesis of chiral 7-oxa- and bicyclo[2.2.1]heptane derivatives is attracting much attention because of their biological properties, *e.g.* inhibitory effects such as prostaglandin/thromboxane receptor antagonist properties.[1] For the preparation of chiral 7-oxabicyclo[2.2.1]heptane derivatives, the chiral lactone (**1**) has been widely employed as a useful intermediate for their syntheses because of its availability through chemical[2] or enzymatic[3–5] resolution. In contrast, despite its promise as a building block for synthesis,[6] there are few reports of the preparation of the chiral bicyclo[2.2.1]heptane lactone (**2**). The first successful route to the (+)-lactone (**2**) reported was by enzymatic oxidation of a racemic diol.[7] Recently both enantiomers of (**2**) were synthesized starting with D-mannitol.[8] Herein, we disclose a short, enantiodivergent route to the lactone (**2**), which makes use of the adducts (**3**) and (**4**) derived from cyclopentadiene and the sulphoxide (**5**)[9] (see Scheme). We have also devised an efficient method for reductive elimination of the chiral auxiliary, 10-mercaptoisoborneol (**9**) by the use of samarium(II) iodide.

The adduct (**3**), m.p. 126–127 °C, $[\alpha]_D$ +36.8°, prepared by the previously described method [C_5H_6, (**5**), $ZnCl_2$, −40→ −20 °C, 3 h],[9] was converted into the lactone (**6**),† m.p. 224–225 °C, $[\alpha]_D$ +44.2°, by regioselective reduction with di-isobutylaluminium hydride [DIBAL (4 equiv.), −78 °C→ room temp., 48 h] in 61% yield as the sole product.‡ Deoxygenation of the sulphinyl group in (**6**) using either phosphorus tribromide or zinc–acetic acid proceeded smoothly, but was accompanied by concomitant skeletal rearrangement of the isobornyl residue. Fortunately samarium(II)-induced reduction[10] of (**6**) [SmI_2 (5 equiv.), tetrahydrofuran, HOBu^t, room temp., 10 min] proceeded smoothly to give the (+)-lactone (**8**), m.p. 122–124 °C, $[\alpha]_D$ +143.9° [lit.,[7] m.p. 120–122 °C, $[\alpha]_D$ +143.2° (*c* 5.2, $CHCl_3$)] in 98% yield. At this stage the chiral auxiliary, (−)-10-mercaptoisoborneol (**9**) was recovered in high yield.§ Hydrogenation of the (+)-lactone (**8**) (5% Pd–C, EtOH, room temp., 2 h) furnished the (+)-lactone (**2**), m.p. 146–147 °C, $[\alpha]_D$ +150.4° [lit.,[8] $[\alpha]_D^{25}$ +153.28° (*c* 1.01, $CHCl_3$)] in quantitative yield. To our knowledge, no reports of a one-step procedure involving treatment with SmI_2 to

† All new compounds reported here gave satisfactory spectral and analytical data. Optical rotations were taken in $CHCl_3$ (*c* 1.0) at 25 °C unless otherwise indicated.

‡ In this reduction the amount of DIBAL used and the reaction temperature was critical. Under the different conditions [DIBAL (2.2–4 equiv.), −78 °C, 3–22 h)], the alcohol (**7**) was produced, along with variable amounts of (**6**).

§ The disulphide (**10**) was also recovered [ratio (**9**):(**10**) ~4:1]. The reaction was carried out with Bu^{t}OH as a proton source. However, when SmI_2 was allowed to react in the absence of Bu^{t}OH, only traces of (**9**) were isolated: under these conditions (**10**) was produced exclusively.



Scheme. *Reagents:* i, $ZnCl_2$, CH_2Cl_2 then C_5H_6; ii, Bu^i_2AlH, toluene; iii, SmI_2, tetrahydrofuran, $HOBu^t$; iv, H_2, 5% Pd–C, HOEt; v, C_5H_6, CH_2Cl_2.

eliminate the sulphinyl group attached to the quaternary carbon atom have appeared.*

Alternatively, the reaction of (**5**) with cyclopentadiene (30 equiv., CH_2Cl_2, room temp., 19 h) without Lewis acid gave the adduct (**4**), m.p. 124–125 °C, $[\alpha]_D$ +106.2°, in 68% yield, accompanied by small amounts of minor diastereoisomers (**3**) and (**11**) [19%, ratio (**3**):(**11**) 1:1.2]. The diastereoisomeric excess of the *exo* sulphoxides (**4**) and (**3**) was 84%. Reduction of (**4**) with DIBAL produced the lactone (**12**), m.p. 179–180 °C, $[\alpha]_D$ −47.6°, in 88% yield. Treatment of the sulphoxide (**12**) with samarium(II) iodide (tetrahydrofuran, $HOBu^t$, room temp., 10 min) gave the (−)-lactone (**8**), m.p. 121–123 °C, $[\alpha]_D$ −135.9°, in quantitative yield. Hydrogenation of (−)-(**8**) yielded the (−)-lactone (**2**), m.p. 149–150 °C, $[\alpha]_D$ −151.0° (*c* 0.95) {lit.,[8] $[\alpha]_D^{26}$ −156.21° (*c* 0.81, $CHCl_3$)}.

Thus, an enantiodivergent synthesis of the useful chiral lactones (**2**) and (**8**) has been achieved starting from the sulphoxide (**5**) in a few steps. The method using samarium(II) iodide allows a great versatility in the elimination of a sulphiny group attached to the α-carbonyl quarternary carbon atom. In addition, the reduction has the advantage that the chiral thiol can be recovered. Further transformation of (**2**) and (**8**) into biologically active compounds is in progress.

Experimental

(+)-(2S,3R)-cis-endo-3-(*Hydroxymethyl*)*bicyclo*[2.2.1]*hept*-5-*ene*-2-*carboxylic Acid Lactone* (**8**).—SmI_2 in tetrahydrofuran (0.08M; 18 ml) was added to compound (**6**) (100 mg) and Bu^tOH (0.11 ml) at room temperature under argon. After 10 min cold 1M hydrochloric acid (30 ml) was added to the mixture. The aqueous layer was extracted with chloroform (3 × 20 ml). The organic phase was washed with brine, dried, and evaporated under reduced pressure to leave a white solid, which was purified by column chromatography on silica gel (8 g). The fraction eluted with 25% AcOEt in hexane (v/v) afforded compounds (**9**) and (**10**) [50 mg; ratio (**9**):(**10**) 81:19] and (+)-(**8**) (42 mg, 98%) as a white powder (hexane–AcOEt), m.p. 122–124 °C.

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* Molander reported that 2-methyl-2-phenylsulphinylcyclohexanone was unsuitable for reduction with SmI_2 and gave a complex product mixture: see ref. 10.

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