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Synthesis of enantiopure isoprene epoxides from (*S*)-lactic acid *via* 'dispoke' intermediates

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'Dispoke protected lactate' derived from (*S*)-lactic acid was converted into the enantiopure isoprene epoxides (*S*)-2-ethenyl-2-methyloxirane and (2*R*,2′*S*)-2-methylbioxirane.

The mechanistic toxicology of isoprene is a subject of considerable current importance.[1] In this context, samples of single enantiomers of isoprene epoxides are required for the preparation of reference standards of DNA adducts. We describe efficient syntheses of enantiomerically pure (*S*)-2-ethenyl-2-methyloxirane **1** and (2*R*,2′*S*)-2-methylbioxirane **2**, using as starting material the 'dispoke protected lactate' **3** derived from (*S*)-lactic acid.[2] An eight-step synthesis of (*S*)-2-(1-methylethenyl)oxirane (88% ee) from D-mannitol has been reported.[3] This was oxidised with MCPBA to a mixture of (2*S*,2′*R*)- and (2*R*,2′*R*)-2-methylbioxirane.

There is concern about the toxicology of isoprene because of its structural similarity to buta-1,3-diene, which is a multi-organ carcinogen in rodents.[4,5] This has raised the question of the effect of the methyl group in isoprene on its toxicity and carcinogenic potential. Studies with isoprene have shown that its carcinogenicity towards rodents is much lower than buta-1,3-diene.[6] It is therefore important to determine the significance of these findings for the cancer risk from human exposures to isoprene, which are unavoidable because isoprene is produced during normal metabolism.[7,8] Human exposures can also occur due to the presence of isoprene in tobacco smoke,[9] automobile exhaust gases,[9] emissions from plants and trees[10] and industrial sources.[11]

In vitro studies have shown that the mammalian metabolism of isoprene is similar to that of buta-1,3-diene and involves cytochrome P450 oxidation to mono- and then di-epoxides, which may be metabolites responsible for toxicity. It is important to clarify the influence of the stereochemistry of these epoxides on isoprene's toxicology, as well as determining the effect of the methyl group. We have previously shown stereochemical differences between rat, mouse and human in the formation of the mono-epoxides of isoprene by liver preparations *in vitro*.[13]

A key intermediate for the preparation of (*S*)-2-ethenyl-2-methyloxirane **1** is (*S*)-2-hydroxy-2-methylbutenoic acid **4**. Several approaches to prepare **4** in enantiopure form were tried using Evans' chiral oxazolidinone chemistry,[14] but none were successful. Furthermore, we were unable to resolve racemic 2-hydroxy-2-methylbutenoic acid, either *via* diastereoisomeric salts with optically active amines, or by lipase-catalysed hydrolysis of its esters. The failure of these approaches may be due to the similarity of the methyl and vinyl groups, which leads to diastereoisomers derived from 2-hydroxy-2-methylbutenoic acid having similar physical and chemical properties. However, (*S*)-2-hydroxy-2-methylbutenoic acid **4** could be readily prepared from the 'dispoke protected lactate' **3** (Scheme 1).‡ Ley and his coworkers[2] have shown that condensation with acetaldehyde of the carbanion derived by deprotonation of **3** with LDA gives predominately diastereoisomer **5**. We converted **5** into its triflate **6**, which underwent smooth DBU-induced elimination to **7**. Deprotection of **7** by treatment with 95% TFA gave (*S*)-2-hydroxy-2-methylbutenoic acid **4**. The synthesis of **1** was completed by reduction of **4** to (*S*)-2-methylbut-3-ene-1,2-diol **8**, tosylation of **8** to **9**, treatment of **9** with base and direct distillation of **1** from the reaction mixture in the manner described.[15] The high enantiomeric purity of **1** {$[\alpha]_D$ + 17.6 (*c* 6.2 g/100 ml in ethyl acetate at 19 °C)} was confirmed using ^{1}H NMR spectroscopy in conjunction with the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorate] in deuterioacetonitrile.

(2*R*,2′*S*)-2-Methylbioxirane **2**, was also readily prepared from the 'dispoke protected lactate' **3**. Condensation of the carbanion derived by deprotonation of **3** with LDA with 2-(4-methoxybenzyloxy)acetaldehyde[16] gave predominately diastereoisomer **10**, which was converted into lactone **11** by treatment with 95% TFA. Reduction of **11** to tetraol **12** was

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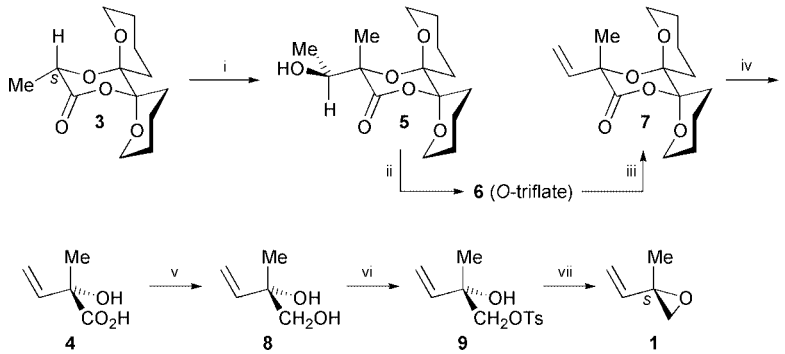

Scheme 1 Synthesis of (*S*)-2-ethenyl-2-methyloxirane **1**. *Reagents and conditions*: i, LDA + DMPU/Bu^{n}Li in THF; MeCHO, 93% (*cf.* ref. 2); ii, triflic anhydride/pyridine in CH_2Cl_2, 100%; iii, DBU in CH_2Cl_2 71%; iv, 95% TFA, 88%; v, $LiAlH_4$ in diethyl ether, 100%; vi, TsCl/pyridine in toluene, 51%; vii, $NaOCH_2CH_2OH$ in $HOCH_2CH_2OH$, 80%.

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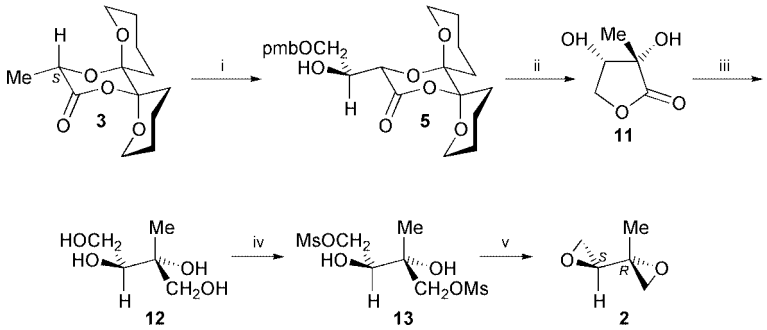

Scheme 2 Synthesis of (2*R*,2′*S*)-2-methylbioxirane **2**. *Reagents and conditions*: i, LDA + DMPU/Bu^{n}Li in THF; pmbOCH$_2$CHO, 73%; ii, 95% TFA, 78%; iii, NaBH$_4$ in MeOH, 100%; iv, MsCl in pyridine, 37%; v, NaOCH$_2$CH$_2$OH in HOCH$_2$CH$_2$OH, 49% (pmb = *p*-methoxybenzyl).

followed by selective mesylation of the primary hydroxy groups to give **13** and finally base-induced ring closures to diepoxide **2**. The resulting **2** {[α]$_D$ −0.4 (*c* 5.8 g/100 ml ethyl acetate at 19 °C)} was shown to be enantiomerically and diastereomerically pure using ^{1}H NMR spectroscopy with the same chiral shift reagent as above. A racemic reference sample of both diastereoisomers of 2-methylbioxirane was prepared from *rac*-2-ethenyl-2-methyloxirane by oxidation with MCPBA in dichloromethane.[3]

The work described herein makes the isoprene epoxides **1** and **2** available in sufficient amounts for the preparation of adduct standards from proteins and DNA. The kinetics and mechanisms of biologically relevant reactions of isoprene epoxides are currently under study in our laboratory.

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Notes and references

‡ All new compounds gave analytical and spectroscopic data in accord with their assigned structure.

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