Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 22, pp. 3715–3716, 1997

Printed in Great Britain
PII: S0957-4166(97)00537-5 0957-4166/97 $17.00 + 0.00

Solid phase synthesis of (*R*)- and (*S*)-[^{13}C]-butadiene monoxide

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Abstract: A stereospecific route to (*R*)- and (*S*)-[^{13}C]-butadiene monoxide was developed using (*R*)- or (*S*)- glycidaldehyde and a polymer-supported Wittig reagent. © 1997 Elsevier Science Ltd

Butadiene monoxide (BMO) is a carcinogenic metabolite of butadiene, a monomer employed in the production of synthetic rubber. Several epidemiological studies[1,2] have suggested an excess mortality from lymphatic and hematopoetic neoplasms in the 65,000 workers potentially exposed to butadiene in the United States. Recent studies have demonstrated a stereoselective course for the metabolic activation of butadiene to (*R*)- and (*S*)-BMO.[3] Since the observed dramatic species differences in sensitivity to butadiene toxicity may involve differences in the stereochemical course of metabolism, the elucidation of the stereochemical fate of butadiene is essential. Enantiomerically pure [^{13}C]- and [^{14}C]-labeled enantiomers of butadiene monoxide were required for metabolic studies. The [^{13}C]-procedure described was designed to be applicable to the synthesis of [^{14}C]-BMO enantiomers.

We planned to produce the individual BMO enantiomers by treatment of the respective glycidaldehyde enantiomers with the methylenetriphenylphosphonium ylide derived from either [^{13}C]- or [^{14}C]-iodomethane. This route has proved facile for olefination of chiral aldehydes.[4] (*R*)- and (*S*)-Glycidal could be produced starting with D- and L-mannitol, respectively. A major consideration in the route was the volatility and instability of glycidal and radiolabeled BMO.

Treatment of D-mannitol (**1**) with 2.2 equivalents of tosyl chloride at 0°C gave 1,6-di-*O*-tosyl-D-mannitol (**2**) (Scheme 1). This was titrated with sodium hydroxide to afford 1,2-5,6-dianhydro-D-mannitol (**3**). Oxidative cleavage of **3** with sodium periodate[5] gave (*R*)-glycidaldehyde (**4**) in 60% yield. Treatment of **4** with [^{13}C]-methylenetriphenylphosphonium ylide gave [^{13}C]-butadiene monoxide (**5**) in 81% yield with the concomitant presence of appreciable amounts of inseparable volatiles such as benzene and DMSO. Fractional distillation of BMO from the reaction mixture proved cumbersome and low yielding. An insoluble polymer-supported Wittig reagent[6] proved much more successful. The Wittig reagent was formed by treating triphenylphosphine bound on a polystyrene support with [^{13}C]-iodomethane to give the methyl triphenylphosphonium iodide salt.[7] This was treated[8] with the sodium salt of DMSO to give the ylide which was then washed thoroughly with tetrahydrofuran and diethyl ether. Treatment of an ether solution of the glycidaldehyde with the polymer-supported ylide gave butadiene monoxide in 75–85% yield. The total yield of BMO in ether was determined by GC–MS employing a standard calibration curve. For the formation of neat BMO, the Wittig reaction was conducted in di(ethylene glycol) diethyl ether as solvent after removing the solvents used in ylide formation. The BMO was isolated in 70–80% yield by fractional distillation of the reaction mixture by cold trapping in a side-arm short-path micro-distillation apparatus constructed for this purpose. Reduction of L-mannose with lithium borohydride in water gave L-mannitol in high yield which can be similarly converted to (*S*)-[^{13}C]-BMO.

Acknowledgements

The authors are indebted to the National Institutes of Health (ES06448) for support of this work.

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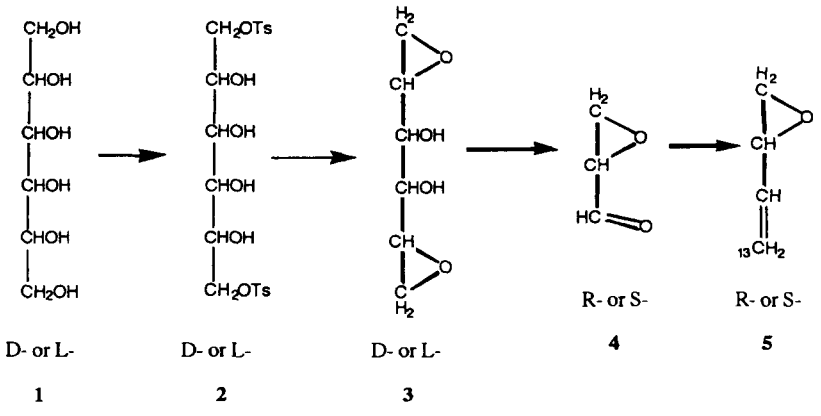

Scheme 1.

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7. [^{13}C]-Methyl iodide (0.20 mL, 0.47 g, 3.3 mmol) was added dropwise with stirring to a suspension of polymer-supported triphenylphosphine (1.0 g) (polystyrene, cross-linked with 2% DVB, ca. 3 mmol P/g) in N,N-dimethylformamide. The mixture was sealed and stirred at 70°C for 48 hours, cooled, filtered, washed several times with methylene chloride and diethyl ether over the course of several hours. Drying under vacuum for several hours gave yellow beads (1.3 g).
8. To 200 mg of 2% cross-linked polystyrene-supported [^{13}C]-methyltriphenylphosphonium iodide in 2 ml of a 2:1 (v/v) mixture of THF in DMSO was added with stirring under nitrogen 1 mL (10 molar equiv.) of the sodium salt of DMSO in DMSO. After several minutes the yellow beads turned brown, and after 2 hours a black color was observed. The suspension was filtered and washed with dried THF (2×5mL) and dried diethyl ether (4×5ml), and cooled to −5°C. Diethyl ether (0.5 ml) was added to the polymer, followed by the dropwise addition of (*R*)-glycidaldehyde (22 mg, 0.3 mmol) in ether (0.2 mL) with stirring. The mixture was allowed to stir for 2 hours, after which the suspension was filtered and washed with diethyl ether to give [^{13}C]-BMO (17 mg, 81% yield) in diethyl ether (1 mL). Chemical purity and identity were confirmed by ^{13}C-NMR and GC–MS. The compound exhibited a single peak (enantiomeric purity >98%) by GC on a chiral nickel camphorate column (procedure detailed in Ref. 3).

(Received in USA 24 September 1997)