Application of Tellurium Chemistry and Sharpless Asymmetric Epoxidation to the Synthesis of Optically Active Boivinose

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Received March 3, 1994

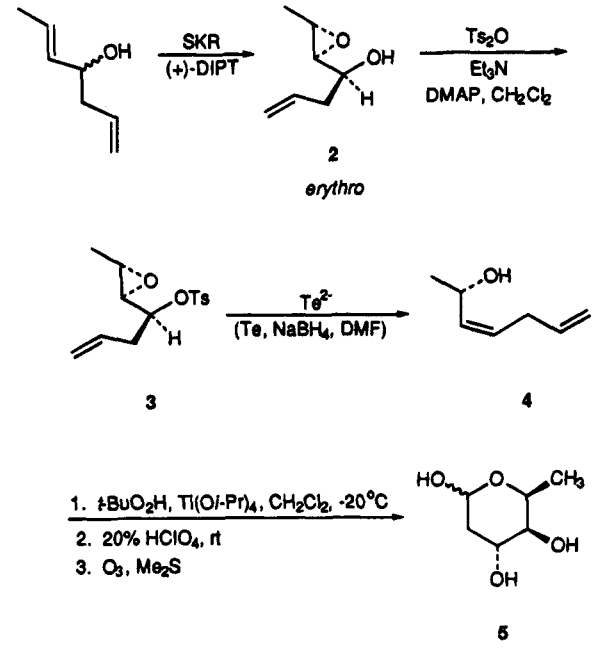
Introduction

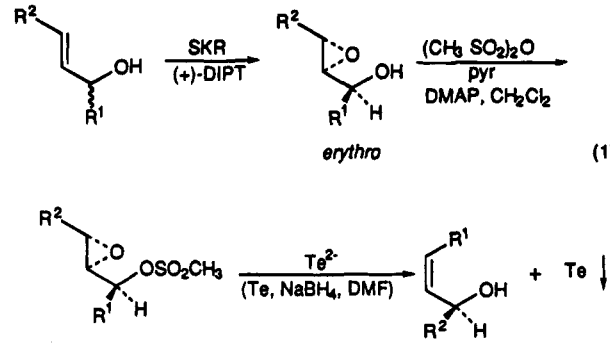
The D-isomer of the rare sugar boivinose (2,6-dideoxy-*xylo*-hexose) is a constituent of the steroidal glycoside stroboside, from which it was obtained by hydrolysis.[1a–c] It is also a constituent of corchoroside A,[1c,d] the jute glycoside, deglucocoroloside,[1e] and several other cardiac glycosides.[1f,g] Boivinose has been prepared in optically active form from natural sugar derivatives,[1b] and L-boivinose has been obtained as a product of a reaction sequence starting with the addition of allylmagnesium bromide to (4*R*,5*S*)-4-formyl-2,2,5-trimethyl-1,3-dioxolane and concluding with hydrolysis and ozonolysis.[2] D,L-Boivinose is formed by treatment of butyl (*E*)-2,3,4-trideoxy-*aldehydo*-D,L-hex-2-enuroate with methylmagnesium bromide followed by dihydroxylation (OsO_4) and Ruff degradation.[3] The syntheses of four 2,6-dideoxyhexoses [(+)-digitoxose, (+)-olivose, (+)-oliose, (+)-cymarose] were achieved by application of the Sharpless–Katsuki kinetic resolution (SKR) in a key step to install the appropriate chirality.[4] The synthesis of optically active boivinose by this SKR route was not attempted because the secondary allylic alcohol, (*Z*)-3,6-heptadien-2-ol, required as starting material, was deemed to be unsuitable for a kinetic resolution since the procedure frequently gives a low enantiomeric excess (ee) with (*Z*)-substrates.[5]

Results and Discussion

We reported recently a tellurium-based method for obtaining scalemic (*Z*)-allylic alcohols from scalemic epoxy tosylates of (*E*)-allylic alcohols (eq 1).[6] Application of this process to the synthesis of the above-mentioned key intermediate, (*Z*)-3,6-heptadien-2-ol, in optically active form **4** and its subsequent conversion to boivinose would demonstrate the usefulness of the tellurium method. Since (−)-boivinose (**5**) had been reported recently,[2] this unnatural isomer was targeted for synthesis *via* the steps shown in Scheme 1, starting with the known (*E*)-1,5-heptadien-4-ol prepared from crotonaldehyde and allylmagnesium bromide.[4,7] (+)-Diisopropyl tartrate (DIPT) was used in the SKR of this (*E*)-alcohol to provide the correct stereochemistry for (−)-boivinose.

Scheme 1





The tellurium transposition reaction exemplified by the conversion **3** → **4** involves the reduction of the relatively nontoxic element[8] *in situ* to telluride ion which accomplishes the transformation, possibly *via* an epitelluride intermediate, during which Te^{2-} is oxidized back to Te^0 which is recovered and reused if desired.[9] The diastereomeric purity of **4** depends somewhat on the method of reduction of tellurium. The (*Z*)/(*E*) ratio for **4** is 99:1 by GC and NMR analysis when Te is reduced by $NaBH_4$ in DMF but falls to 6:1 when $LiEt_3BH$ in THF is the reducing agent. Overall yields in both cases are good. The greater proportion of (*E*)-**4** obtained with $LiEt_3BH$

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(9) We recently have modified conditions for some reactions such that only catalytic amounts (0.1–0.2 equiv) of tellurium are required, the element being continuously reduced as it is formed in the reaction. Kumar, A.; Dittmer, D. C. *Tetrahedron Lett.* **1994**, in press. In the conversion of **3** to **4**, a stoichiometric or excess amount of Te^0 was used. This ensures a rapid reaction and avoids the possible isomerization of the substrate that may occur on prolonged treatment with the tellurium reagent.

0022-3263/94/1959-4311$04.50/0

may be the result of a Lewis-acid catalyzed conversion of some *erythro* tosylate **3** to the *threo* isomer, the latter giving the (*E*) diastereomer as shown previously.[6] Lewis acid species present are Et_3B (formed in the reduction of Te) and Li^+. With $NaBH_4$ as the reducing agent, lithium ion is absent and some of the Lewis acid BH_3 formed in the reduction is removed by reaction with DMF to yield the BH_3–Me_3N complex[10] which would be expected to show weaker Lewis acid characteristics than uncomplexed BH_3. Borane byproducts in the reduction of Te by $NaBH_4$ and $LiEt_3BH$ are implicated in the stereospecific deoxygenation and deacetylation of glycidyl acetates by Te^{2-}, since non-Lewis acid forming reducing agents for Te, e.g. rongalite ($HOCH_2SO_2Na{\cdot}2H_2O$), are not very active.[11] The remaining steps in the synthesis of (−)-boivinose have been described previously.[4]

Experimental Section

^{13}C and ^1H NMR spectra were taken at 75 and 300 MHz, respectively, in $CDCl_3$ unless otherwise specified. *J* values are given in hertz. Other procedures (determination of %ee, solvent and reagent purification, Sharpless asymmetric epoxidations (SAE), workup of reactions, tellurium reductions and transposition reactions) have been described previously.[5,6,11,12] Stereochemical assignments follow the rules for SAE and SKR.[5] Silica gel was used for column chromatography.

(2*S*,3*R*,4*S*)-(−)-2,3-Epoxy-6-hepten-4-ol [(α*S*,2*R*,3*S*)-(−)-3-Methyl-α-(2-propenyl)oxiranemethanol] (2). The SKR of (*E*)-1,5-heptadien-4-ol (**1**) (8.33 g, 74.3 mmol) was done as described previously.[4] The reaction gave (−)-**2** as a clear oil (3.46 g, 30.8 mmol, 41%) after distillation (30–35 °C, 0.60 mmHg, kugelrohr): $[\alpha]^{25}_D$ −3.07° (*c* 5.1, CH_2Cl_2); 94% de by GC and ^1H NMR analysis [lit.[4] $[\alpha]^{20}_D$ −2.8° (*c* 4.9, CH_2Cl_2) for (−)-**2** of >95%ee]. The ^1H and ^{13}C NMR data were as previously reported.[4]

***p*-Toluenesulfonate [4-Methylbenzenesulfonate] of (−)-2 (3).** The *p*-toluenesulfonate was prepared by treatment of (−)-**2** (0.62 g, 4.83 mmol) in CH_2Cl_2 (10 mL) with *p*-toluenesulfonic anhydride (1.83 g, 5.43 mmol) in CH_2Cl_2 (10 mL) in the presence of DMAP (0.0128 g, 0.100 mmol) and Et_3N (0.85 mL, 6.0 mmol) at 0 °C under N_2. The reaction mixture was cooled to −10 °C and worked up in the usual way[6b] after 37 h to yield an oil that was purified by chromatography (1:4 ether/hexanes) to yield **3** (0.99 g, 3.5 mmol, 73%): $[\alpha]^{23}_D$ −9.69° (*c* 0.96, $CHCl_3$); ^1H NMR δ 1.19–1.20 (d, 3, *J* = 5.2), 2.45 (s, 3), 2.42–2.51 (m, 1), 2.72–2.75 (dd, 1, *J* = 6.8, 1.9), 2.81–2.89 (dq, 1, *J* = 5.2, 2.0), 4.15–4.21 (m, 1), 5.04–5.12 (m, 2), 5.58–5.72 (m, 1), 7.32–7.35 (d, 2, *J* = 8.2), 7.76–7.79 (d, 2, *J* = 8.2). ^{13}C NMR δ 16.92, 21.64, 36.60, 54.68, 58.28, 80.93, 119.1, 127.9, 129.7, 131.3, 145.0.

(2*S*)-(+)-(*Z*)-3,6-Heptadien-2-ol (4). Tosylate (−)-**3** (0.38 g, 1.35 mmol) in DMF (5 mL) was treated with a solution of telluride ion [prepared at 80 °C from Te (0.35 g, 2.72 mmol) and $NaBH_4$ (0.27 g, 6.89 mmol) in DMF (10 mL) and cooled to rt]. Purification of the product by chromatography (1:4 ether/hexanes) gave **4** as a colorless oil (0.14 g, 1.2 mmol, 91%): $[\alpha]^{22}_D$ +7.70° (*c* 1.45, $CHCl_3$); ^1H NMR and GC analysis indicate a 99:1 ratio of *Z* to *E* isomers. ^1H and ^{13}C NMR spectra were as previously reported for (±)-**4**.[4]

The Te transposition reaction applied to (−)-**3** (0.94 g, 3.34 mmol) was also effective with telluride ion produced by reduction of Te (0.86 g, 6.68 mmol) with $LiEt_3BH$ (13.4 mL, 1 M in THF), but a 6:1 ratio of *Z* to *E* isomers was obtained. Purification by chromatography (1:2 ether/hexanes) gave (+)-**4** (0.084 g, 0.75 mmol, 23%) whose ester with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[13] was analyzed by ^1H and ^{19}F NMR spectroscopy to show an ee > 95%. The low yield in this case was attributed to inadvertent loss caused by the volatility of the product.

(−)-2,6-Dideoxy-*xylo*-hexose (Boivinose) (5). Previously described procedures were followed.[4] A solution of (+)-**4** (0.128 g, 1.40 mmol) in dry CH_2Cl_2 (10 mL) at −20 °C under Ar was treated with $Ti(O\text{-}i\text{-}Pr)_4$ (0.340 mL, 1.14 mmol) and *t*-BuOOH (0.25 mL, 5.5 M in isooctane, 1.38 mmol). Purification by distillation (35–40 °C, 0.60 mmHg, kugelrohr) gave the epoxide of **4** [(α*S*,2*R*,3*R*)-α-methyl-3-(2-propenyl)oxiranemethanol] (0.0362 g, 0.280 mmol, 25%[14]): $[\alpha]^{22}_D$ −12.0° (*c* 0.72, CH_2Cl_2). Analysis by capillary GC indicates only one diastereomer is present. ^1H and ^{13}C NMR spectra are essentially the same as those reported for the optically inactive epoxide.[4] The epoxide (0.0263 g, 0.200 mmol) in THF (0.50 mL) was treated with aqueous perchloric acid (20%, 0.15 mL) at room temperature. Purification of the product by chromatography (4:1 EtOAc/hexanes) gave the triol [(2*S*,3*R*,4*R*)-6-hepten-2,3,4-triol] (0.0212 g, 0.140 mmol, 73%): $[\alpha]^{23}_D$ +9.7° (*c* 0.42, acetone). The ^1H and ^{13}C NMR spectra were as previously reported.[4] The triol (0.0208 g, 0.140 mmol) in MeOH (2 mL) was treated with ozone at −20 °C (*ca* 1.5 min). Workup with Me_2S (rt, 22 h) followed by removal of volatile compounds *in vacuo* and chromatography (4:1 CH_2Cl_2/EtOH) gave (−)-boivinose (**5**) (0.0166 g, 0.110 mmol, 79%): $[\alpha]^{22.5}_D$ −15.9° (*c* 0.96, acetone) [lit.[2] $[\alpha]^{20}_D$ −13.5° (*c* 1.0, acetone)]. ^1H and ^{13}C NMR spectra are as previously reported for racemic boivinose[3,4] and (−)-boivinose (^1H NMR only).[2]

Acknowledgment. We thank the donors of the Petroleum Research Fund administered by the American Chemical Society, the National Science Foundation (CHE-9102998), and Syracuse University for support of this research. We are indebted to Professor John Baldwin for the use of a polarimeter.

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