

Efficient Synthesis of An Epoxy Alcohol, A Key Intermediate for LTA₄ Synthesis

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An efficient and very short synthesis of epoxy alcohol **5**, a key intermediate for leukotriene synthesis, was described. The key reaction involves the regioselective benzylidene acetal formation from methyl 5,6,7-trihydroxyheptanoate **1**.

Introduction

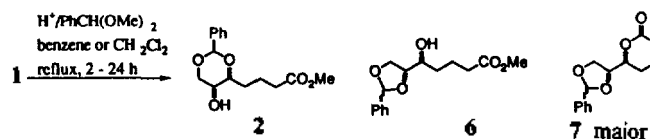
Slow reacting substances, the family of peptido-leukotrienes known as LTC₄, LTD₄ and LTE₄, were postulated to be major mediator of inflammation and allergy.¹ For the unique structure and biological importances, many researchers have devoted to the synthesis of these leukotrienes.

As with the first stereospecific total synthesis of LTC₄,² epoxy alcohol **5** has been considered to be an important intermediate for the synthesis of leukotrienes. Therefore, the effective synthesis of **5** has been the major concern on recent reports.³ The compound **5** has usually been obtained from various sugars, which have the required chirality within. But, several chemical manipulations were required to reach to the epoxy alcohol **5** since sugars have several hydroxy groups.

Although a number of regioselective acetal and ketal formation of 1,2,4-trihydroxy compounds have been reported in many reports,^{4,5} the regioselective acetal formation from 1,2,3-trihydroxy compounds were unexpectedly little known except for glycerol.⁶ Furthermore, synthetic efforts for the construction of epoxy alcohol **5** using regioselective 6-ring acetal formation from acyclic 1,2,3-trihydroxy ester compound **1** were scarcely known.

We now wish to report herein a very short and efficient synthesis of epoxy alcohol **5** by regioselective 6-ring benzylidene acetal **2** formation from methyl 5,6,7-trihydroxyheptanoate **1** (Scheme 1).

In the reaction of **1** with benzaldehyde dimethyl acetal or *p*-nitrobenzaldehyde dimethyl acetal in the presence of several acid catalysts,^{4,5} the major product was unhappily the



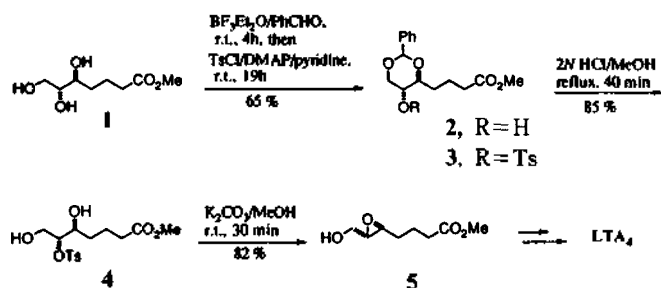
Scheme 2.

lactone **7** due to the presence of methyl ester functionality in trihydroxy compound **1** (Scheme 2). After examining several experimental conditions, we found that Lewis acids such as ferric chloride, zinc chloride and boron trifluoride etherate were good catalysts for the regioselective formation of 6-ring benzylidene acetal **2** in benzaldehyde as a solvent (**2/6** ≥ 85 : 15). But, the 6-ring benzylidene acetal **2** was isolated in moderate yield (60%) owing to the competing formation of **2** with 5-ring benzylidene acetal **6** during the isolation process. Benzylidene acetal **2** was tosylated in the presence of catalytic amount of 4-dimethylaminopyridine (TsCl/pyridine) to give **3** in only 64% yield with a considerable amount of side products. The moderate yields of 6-ring acetal and tosylate forming reactions can be improved by the one-pot process: the benzylidene acetal formation followed by the successive addition of pyridine, *p*-toluenesulfonyl chloride, and catalytic amount of 4-dimethylaminopyridine (65% yield). The compound **3** was hydrolysed with 2 N HCl in methanol to give the dihydroxytosylate **4** in 85% yield. This deprotection of benzylidene acetal group of **3** should be noted in that **4** was obtained in only 13% yield with the starting material **2** (65% recovered) when the compound **3** was subjected to anhydrous methanol solution saturated with dry HCl (0°C to reflux, 4 h). The diol **4** was smoothly converted to epoxy alcohol **5** by treating with K₂CO₃ in methanol. A careful ¹H-NMR (300 MHz) spectrum analysis of the epoxy alcohol **5** proved the absence of other isomers.

In conclusion, we obtained epoxy alcohol **5** efficiently starting from methyl 5,6,7-trihydroxyheptanoate in very short route (overall 43% yield) comprising of benzylidene acetal formation, tosylation, deprotection of benzylidene acetal, and epoxide formation.

Experimental

All reagents and solvents were of commercial quality. Ben-



Scheme 1.

zaldehyde was purchased from Kanto Chemical Co. and used without purification. $\text{BF}_3\text{Et}_2\text{O}$, TsCl , DMAP were purchased from Aldrich Chemical Co. Analytical TLC were performed with E. Merck precoated TLC plates (silica gel 60F-254, layer thickness 0.25 mm). Flash column chromatographical separation was performed using E. Merck Kieselgel 60 (230-400 mesh) silica gel. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were obtained using either a Gemini Varian-300 (300 MHz), a Bruker AM-200 (200 MHz), or JEOL JNM-60 (60 MHz) spectrometer. Infrared (IR) spectra were obtained on a analect FX-6160 FT-IR spectrometer using potassium bromide pellet and sodium chloride cell. Mass spectra were recored on a HP 5988 A GC-Mass by chemical ionization method (CI) using ammonia. Microanalyses were performed by Perkin-Elmer 240DS analyser. Melting point were determined on a Thomas-Hoover capillary melting apparatus and were uncorrected. Optical rotations were measured using a Perkin-Elmer 241 Polarimeter at room temperature using the sodium D line. Methyl 5,6,7-trihydroxyheptanoate was prepared by using known procedure.^{3d}

Methyl 4-(2-Phenyl-5*R*-*p*-toluenesulfonyloxy-1,3-dioxan-6*S*-yl)butanoate (3). To a solution of triol **1** (2.5 g, 15 mmol) in benzaldehyde (20 ml) was added boron trifluoride etherate (69 mg, 0.48 mmol) at room temperature and the solution was stirred for 4 h. If necessary, 1,3-dioxane **2** and 1,3-dioxolane (**6**, **7**) can be isolated by usual work up and flash column chromatography ($\text{MeOH}/\text{CHCl}_3 = 1 : 60$). **2**: $^1\text{H-NMR}$ (CDCl_3) δ 7.33-7.53 (5H, m), 5.47 (1H, s, benzyldiene), 4.22 (1H, m), 3.67 (3H, s), 3.48-3.62 (3H, m), 2.43 (2H, t, $J=7$ Hz), 1.60-1.98 (4H, m); $^{13}\text{C-NMR}$ (CDCl_3) δ 174, 138, 129, 128, 126, 101, 82, 71, 65, 52, 34, 31, 21; M.S (CI) 298 ($\text{M}^+ + \text{NH}_4$, base), 281 ($\text{M}^+ + 1$), 217, 210. **6**: $^1\text{H-NMR}$ (CDCl_3) δ 7.36 (5H, m), 5.63 and 5.80 (1H, two s, benzyldiene), 3.40 (3H, s). **7**: $^1\text{H-NMR}$ (CDCl_3) δ 7.20 (5H, m), 5.58 and 5.75 (1H, two s, benzyldiene), 3.96 (4H, m), 2.60 (2H, m), 1.4-1.9 (4H, m).

To the above reaction mixture were added pyridine (40 ml), *p*-toluenesulfonyl chloride (9.88 g, 52 mmol), and 4-dimethylaminopyridine (0.3 g, 2.45 mmol) and the solution was stirred for 12 h. Further addition of *p*-toluenesulfonyl chloride (9.88 g) is required and the reaction was nearly completed in 19 h. The reaction mixture was treated at 0°C with saturated aqueous NaHCO_3 solution and stirred vigorously for 2 h at room temperature. The mixture was extracted with methylene chloride (3×20 ml). The organic layer was washed successively with ice-cold 2 N H_2SO_4 solution (3×40 ml), saturated aqueous NaHCO_3 solution, and brine. The organic layer was dried (MgSO_4) and distilled under reduced pressure to remove benzaldehyde. The residue was purified by flash column chromatography ($\text{EtOAc}/\text{Hexane} = 1 : 4$) to give the tosylated 1,3-dioxane **3** (3.59 g, 65%) as a white solid. mp. $101\text{--}103^\circ$; $[\alpha]_D -40^\circ$ (c 0.05, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 7.21-7.74 (9H, m), 5.34 (1H, s), 4.16 (2H, m), 3.62 (2H, s), 3.52 (3H, s), 2.32 (3H, s), 2.09 (2H, t, $J=7.2$ Hz), 1.16-1.60 (4H, m); $^{13}\text{C-NMR}$ (CDCl_3) δ 173, 145, 137, 133, 130, 129, 128.49, 128.31, 126.41, 101, 75, 72, 68, 51, 33, 30, 21, 20; IR (neat) 2962, 1726, 1456, 1363, 1289, 1252, 1229, 1182, 1130, 1094, 1033, 993 cm^{-1} ; anal. calcd. for $\text{C}_{22}\text{H}_{26}\text{O}_7\text{S}$: C, 60.81; H, 6.03; S, 7.38; found: C, 60.69; H, 6.03; S, 7.60.

Methyl 5*S*,6*R*-5,7-dihydroxy-6-*p*-toluenesulfonylox-

heptanoate (4). To a solution of tosylated 1,3-dioxane **3** (200 mg, 0.46 mmol) in methanol (4 ml) was added 2 N HCl (0.2 ml) and heated at reflux for 40 min. The reaction mixture was cooled to room temperature and diluted with brine (15 ml), the mixture was extracted with methylene chloride (3×10 ml). The combined organic layers were washed with saturated aqueous NaHCO_3 solution and brine. The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography ($\text{EtOAc}/\text{Hexane} = 1 : 2$ to $4 : 1$) to afford tosylated diol **4** (136 mg, 85.3%) as a white solid with recovered starting material **3** (16 mg, 8%). **4**: mp. $65\text{--}67^\circ$; $[\alpha]_D -1.5^\circ$ (c 0.05, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 7.34-7.83 (4H, m), 4.41 (1H, bs), 3.77-3.85 (3H, m), 3.66 (3H, s), 2.50-3.00 (2H, bs), 2.45 (3H, s), 2.29 (2H, t, $J=7$ Hz), 1.36-1.77 (4H, m); $^{13}\text{C-NMR}$ (CDCl_3) δ 174, 145, 133, 130, 128, 84, 71, 61, 51, 33.5, 32.1, 21.7, 20.7; IR (neat) 3308, 2948, 1733, 1370, 1216, 1166, 1069, 928 cm^{-1} ; anal. calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_7\text{S}$: C, 52.01; H, 6.40; S, 9.25; found: C, 52.37; H, 6.40; S, 9.11.

Methyl 7-hydroxy-trans-5*S*,6*R*-oxidoheptanoate (5).

To a solution of tosylated 1,3-diol **4** (144 mg, 0.41 mmol) in absolute methanol (25 ml) was added anhydrous potassium carbonate (57 mg, 0.41 mmol). After 30 min, the mixture was diluted with methylene chloride (40 ml) and washed with water (20 ml) and brine. The combined aqueous layer was reextracted with methylene chloride (2×10 ml). The combined organic layers were washed again with brine, dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by short column chromatography ($\text{EtOAc}/\text{Hexane} = 1 : 2$) to give the (5*S*,6*R*)-*trans*-epoxy alcohol **5** (56 mg, 78%); $[\alpha]_D -34.9^\circ$ (c 0.05, CHCl_3 , lit.^{3c} -34.6°); $^1\text{H-NMR}$ (CDCl_3) δ 3.85 (1H, dd, $J=12$ Hz, 2 Hz), 3.60 (1H, dd, $J=12$ Hz, 4 Hz), 3.64 (3H, s), 2.87-2.95 (2H, m), 2.35 (2H, t, $J=8$ Hz), 1.53-1.82 (4H, m).

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CO₂ Laser Absorption Measurement of CH₃CH₂Br using Photoacoustic Method

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The CO₂ laser absorption measurement of CH₃CH₂Br utilizing photoacoustic (PA) technique was performed using a cw and a pulsed CO₂ lasers. The absorption profile in the CO₂ laser wavelength region (9-10 μm) and the macroscopic small signal absorption cross section at 10P(20) (10.59 μm, 944 cm⁻¹) laser line were measured using a cw CO₂ laser. The laser fluence dependence on infrared multiphoton absorption (IRMPA) was also studied with a pulsed TEA CO₂ laser at 10P(20) laser line. In view of monotonic increase of PA signal with the rise of laser fluence, it was suggested that the anharmonicity in pumped vibration mode did not restrict ir multiphoton absorption in CH₃CH₂Br system as found in large molecular system.

Introduction

Number of reports on the infrared multiphoton absorption/dissociation (IRMPA/D) of molecules have been continuously increased recent years in accordance with the development of high power infrared lasers. These studies have been focused not only to develop an effective laser isotope separation technique¹⁻⁴ but also to investigate pure scientific features, such as mechanisms or dynamics of multiphoton absorption and dissociation.⁵⁻⁹

The vibrational bottleneck due to anharmonicity in pumped vibration mode or the rotational hole-filling phenomena has been found to exert significant effects on IRMPA processes.⁷⁻⁹ These effects are dependent on the molecular size of substrate, the kinds of buffer gases and the pressure of reaction system. An example of such effects has been reported on a small size molecule system, CDF₃.³ In the system it has shown several variation points of PA signal intensity with laser fluence change. These variation have been interpreted in terms of energy barriers caused by anharmonicities of the vibrational ladders.¹⁰ On the other hand, the MPA signal has shown monotonic increase with the rise of laser fluence for larger molecule system than CF₃CH₂Cl.^{11,12} This phenomenon in the larger molecule system has suggested that the quasicontinuum state is started at very low molecular energy levels, so an anharmonicity in pumped vibrational mode does not restrict energy randomization. Therefore, the mismatch of laser frequency due to anharmonicity in pumped mode at high energy levels or the rotational hole-filling effect plays insignificant roles in IRMPA process.

In this study we measured the ir absorption profile of CH₃CH₂Br in the CO₂ laser wavelength region and the macroscopic small signal absorption cross section at 10P(20) (10.59 μm, 944 cm⁻¹) laser line. The laser fluence dependence on IRMPA was also studied at the line using a pulsed TEA CO₂ laser. The present system was chosen for the study with two objectives in mind: First, CH₃CH₂Br, a prototype molecule of BHC (bromohydrocarbon), is a suitable molecule for the comparative study of photochemical behaviors between BHC and HFC (hydrofluorocarbon) groups, and easy to handle due to its strong absorption around 10 μm CO₂ laser wavelength region. Secondly, the PA technique was adopted for the measurement of photoabsorption because of its broad dynamic range.

Experimentals

Laser Systems

A home-made cw CO₂ laser was used to measure the ir absorption profile and the small signal absorption cross section of CH₃CH₂Br. The details of construction scheme have been described elsewhere.¹⁰ In brief, the laser gas mixed with CO₂:N₂:He=1:1.2:8 was flown fast into the laser cavity using a pump and maintaining ca. 10 Torr in the cavity. The output coupler mount was used as a cathode and the brewster window mount as an anode. The applied voltage between two electrodes was 20 kVDC. Laser cavity was constructed using a 1" dia ZnSe output coupler (80% reflection at 9-11 μm) and a ML-501 grating (PTR Co., 150 lines/mm, blazed at 10.6 μm). The laser was able to operate through 9R to 10P laser lines. The measured output power at 10P(20) laser line was ca. 5 W.

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