Direct Conversion of (*S*)-3-Hydroxy-γ-butyrolactone to Chiral Three-Carbon Building Blocks

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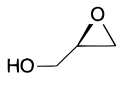
Received September 8, 1998

Many pharmaceutical compounds contain three-carbon chiral substructures, the development of routes to which is often the most difficult aspect of the large scale synthesis of such compounds. Because of this, there is a constant ongoing effort to identify synthetic routes to these three-carbon chiral building blocks. Another strategy, the so-called "chiral pool" approach, is to identify natural sources containing these substructures and carve them out to provide the substructures in a form that could be integrated easily into a drug synthesis scheme. Such building blocks include chiral glycidols, halo diols, and aminodiols. Three key three-carbon building blocks are (*R*)-glycidol (**1**), (*R*)-1-bromo-2,3-dihydroxypropane (**2**), and (*S*)-3-amino-1,2-dihydroxypropane (**3**). Current



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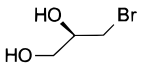

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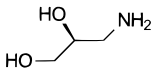

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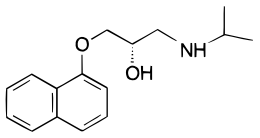
routes to (*R*)-glycidol (**1**) and its (*S*)-isomer utilize strategies such as catalytic oxidations with peroxides and chiral transition metal complexes,[1,2] enzymatic resolutions of racemic esters using lipases to selectively deacylate one enantiomer,[3−5] or using glycerol kinase to selectively phosphorylate one isomer.[6] Another common method is to treat a chiral 1,2-propanediol with a leaving group such as a halide or tosylate ester in the 3-position with base.[7] The chemistries of compound **1** and **2** are interconnected.[8] The availability of an easy route to **2** constitutes a straightforward route to **1** since this transformation is easily effected by treatment of **2** with a mild base such as silver oxide or potassium carbonate.[9,10] The amino diol **3** is a substructure that appears in a large number of classes of important drugs. These include the β-blockers[11−13] such as Propanalol (**4**) and Atenolol (**5**) and antiviralagents[14] such as (**6**) and the thromboxane synthase inhibitor[15] (**7**). Despite the existence of these



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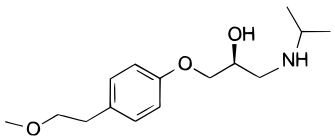

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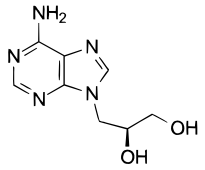

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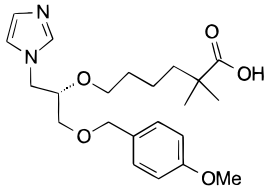

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methods, there is a need for others that might have certain advantages. For instance, they might have the potential to yield some compounds more directly, give better results at larger scale, not require the use of high pressures or hydrogen, give superior optical purity, offer some potential price advantages, or not produce certain waste materials especially those containing heavy metals.

Because of the high degree of oxygenation in the desired three-carbon fragments, carbohydrates are a logical choice when the strategy is to carve out the desired chiral substructure from some readily available, naturally occurring, chiral raw materials. They have the highest density of chiral functional groups of all naturally occurring materials. Many of them, such as starch and lactose, are readily available and are very cheap, renewable feedstock. It is, however, extremely difficult to convert carbohydrate raw materials into chiral small molecules in good yield by a simple process. This is because several steps of protection and functionalization typically have to be followed. In addition to this, carbohydrates are appreciably soluble only in water. This has proven to be a serious limitation to the chemical transformations they can be subjected to. They are also very sensitive both to acids and bases, and pH conditions are also a major constraint. Despite these difficulties, there are some applications where carbohydrates have been used as a source of small chiral building blocks. One of these methods with some practical value is outlined in Scheme 1. In this process, fructose or mannose is reduced to mannitol by catalytic hydrogenation.[16] This is then converted to a di-*O*-isopropylidene acetal which can be oxidized to yield two molecules of D-isopropylideneglyceraldehyde, a valuable three-carbon synthon, by treatment with sodium periodate[17] or lead tetraacetate.[18] The drawback of this approach is that the carbohydrate

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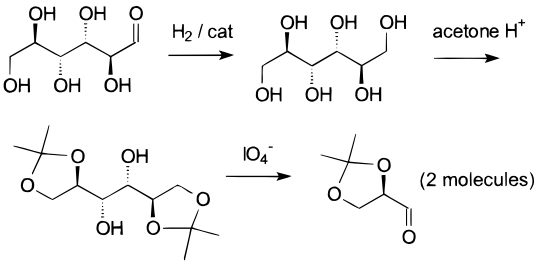
10.1021/jo9818226 CCC: $18.00
Published on Web 01/15/1999

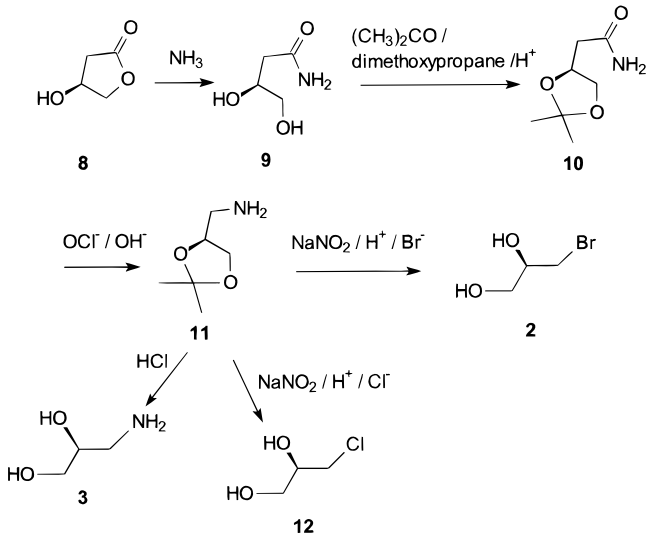
Scheme 1



has to be modified and protected before the actual reaction to generate the building block is applied. In addition to this, lead is toxic, periodate is relatively expensive, and large quantities are required because of its high molecular weight. An alternative set of reagents for carrying out this oxidation is sodium hypochlorite and ruthenium(III) chloride. In this case, the protected glyceric acid is the product.[19]

There is one significant advance in the use of an unprotected carbohydrate as a raw material for producing a chiral building block that could be used to gain access to compounds such as **1**−**3**. This is the development of a route to (*S*)-3-hydroxy-γ-butyrolactone (**8**), a very valuable four-carbon chiral synthon for which a simple, one-step, high-yield route starting from starch, maltose, lactose, maltodextrins, and other 4-linked D-pyranoses has only recently been introduced into the literature.[20−22] (*S*)-3-Hydroxy-γ-butyrolactone readily undergoes a variety of chemical transformations to yield chiral substituted tetrahydrofurans, amides, lactams, nitriles, and epoxides. This high degree of flexibility as a chiral intermediate makes it a very valuable synthon for the pharmaceutical industry. A simple one-carbon degradation method should provide the desired transformation of this intermediate to a three-carbon structure, thus providing routes for obtaining the building blocks of interest. In principle, this chain degradation is possible from (*S*)-3-hydroxy-γ-butyrolactone by any one of the classical routes such as the Hoffman, Curtius, Lossen, or Schmidt reactions which involve rearrangement of acyl species with migration to an electron-deficient nitrogen and loss of the acyl carbon. Of these, the Hoffman reaction[23] seemed the most attractive because the starting compound is a primary amide. This primary amide can easily be obtained by treating the lactone with ammonia. There are potential complications, however. Some of these are peculiar to this starting material and include β-elimination and the participation of the γ-hydroxy group instead of migration to re-form the lactone. There are also a myriad of side reactions, such as dialkyl urea formation, that normally attend the Hoffmann reaction. Protection of the hydroxy groups was necessary, and the use of an isopropylidene function was explored because of the ease of installation and removal. In addition, confining the β-alkoxy fragment

Scheme 2



to a dioxolane ring could also restrict the group sufficiently to limit access to the conformation required for elimination. The reaction sequence is shown in Scheme 2.

The lactone[20] was first converted to the protected amide **10**. The first product of the Hoffmann reaction on the protected amide was the protected aminodiol (**11**). This was formed with virtually quantitative conversion as judged by NMR spectroscopic analysis of the crude reaction mixture although some product was lost on extraction and concentration. The isopropylidene acetal **11** is a very useful form of **3** since it allows modification of the amino group without interference from the hydroxyl functions. It also has a much lower boiling point than **3**, and this makes purification by distillation possible even with very modest vacuums. The acetal group was readily removed by treatment of **11** with slightly more than an equivalent of acid to give **3** as a salt. The protected aminodiol (**11**) could be easily converted to the bromodiol **2** by treating it with nitrous acid in the presence of bromide ion. The corresponding chloro compound (**12**) was prepared in good yield by using hydrochloric acid and sodium chloride instead.

In summary, we have developed a general route for converting the (*S*)-3-hydroxy-γ-butyrolactone to other useful chiral three-carbon building blocks including (*S*)-3-amino-1,2-dihydroxypropane as its isopropylidene acetal, (*R*)-1-bromo-2,3-dihydroxypropane, and the corresponding chloro compound. The latter two compounds are glycidol equivalents. The chemical yields are high, and the enantiomeric purities are extremely high. The propensity for the γ-hydroxyl group to participate has been removed by tying it up in a cyclic acetal. No β-elimination was observed. The same reaction schemes can be used to obtain the other enantiomers of the above three-carbon building blocks by using (*R*)-3-hydroxy-γ-butyrolactone as starting material.

Experimental Section

(*S*)-4-(2,2-Dimethyl)-1,3-dioxolane Acetamide (10). (*S*)-3-Hydroxy-γ-butyrolactone (204 g, 2 mol) was converted to the amide by treatment at room temperature for 14 h with 440 mL of 30% ammonium hydroxide (3.4 mol). The solution was then concentrated to a syrup at ~50° C under reduced pressure until no more water could be removed. Acetone (2 L) and 2,2-

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dimethoxypropane (420 g, 2 mol) were added. Sulfuric acid (6 mL) was then added, and the mixture was protected from moisture with a calcium chloride drying tube, heated at 60 °C for 30 min, and stirred at room temperature for 12 h. Sodium carbonate (50 g) was added and the mixture stirred for 1 h. Methanol (400 mL) was then added and the mixture filtered and concentrated to dryness. The amide (**10**) crystallized on concentrating. The crystals were washed with hexane and then acetone and were used without further purification. Conversion was essentially quantitative. A small amount when recrystallized from acetone gave white crystals, mp 106−108 °C. **10**: $[\alpha]^{23}_{589} = -15.4$ ($CHCl_3$, $c = 1$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 6.10 (s, 1H), 5.65 (s, 1H), 4.43 (m, 1H), 4.14 (dd, 1H, $J = 8.1$, 6.3 Hz), 3.63 (dd, 1H, $J = 8.1$, 6.8 Hz), 2.55 (dd, 1H, $J = 15.3$, 7.5 Hz), 2.46 (dd, 1H, $J = 15.3$, 4.8 Hz), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 172.9, 109.5, 72.2, 69.0, 40.1, 26.9, 25.5; IR ($CHCl_3$, NaCl window) cm^{-1} 3361, 3190, 2994, 2898, 1661, 1633, 1431, 1419, 1372; MS (EI, MH^+) calcd 160.0974, found 160.0968.

(*S*)-4-(2,2-Dimethyl)-1,3-dioxolan-4-ylmethylamine (11) The amide (**10**) (79.5 g, 0.5mol) was treated with a 10−12% sodium hypochlorite solution (500 mL) and the mixture stirred until all of the solid had dissolved (∼5 min). Sodium hydroxide (80 g dissolved in 500 mL of water) was added to the mixture, and the solution was warmed to 50−60 °C and kept at this temperature for 24 h by which time conversion to amine **11** was completed. ^{1}H NMR spectroscopy indicated 100% conversion of **10** to **11**. The amine **11** was isolated as a light yellow liquid by extraction of the mixture with ether which upon standing gave colorless crystals. This was reported[24] to be a liquid, probably because it was not isolated in as pure a state as we have here. The yield was 56.5 g (86%). **11**: mp 54−56 °C, bp 61 ± 2 °C, 15 Torr; 98−100 °C, 100 Torr (lit.[24] bp 62−65 °C, 15 Torr); $[\alpha]^{23}_{589} = +0.9$ ($CHCl_3$, $c = 1$) (lit.[24] $[\alpha]^{20}_D = +15.0$, neat); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 4.13 (m, 1 H), 4.00 (dd, 1 H, $J = 8.1$, 6.6 Hz), 3.67 (dd, 1H, $J = 8.1$, 6.3 Hz), 2.85 (dd, 1H, $J = 13.2$, 4.2 Hz), 2.78 (dd, 1H, $J = 13.2$, 6.0 Hz), 1.40 (s, 3H), 1.34 (s, 3H), 1.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 109.1, 77.4, 66.9, 44.7, 26.8, 25.3 (lit.[24] $CDCl_3$, 109.1, 77.5, 67.0, 44.8, 26.8, 25.4).

(*S*)-3-Amino-1,2-propanediol (3). Compound **11** (1 g) was treated with 2 mL of concentrated hydrochloric acid and 2 mL of water. The solution was heated on a steam bath for 30 min. The solvent was removed by rotatory evaporation to yield a light yellow syrup, which upon cooling to room temperature gave white crystals of the hydrochloride salt. The conversion was quantitative. **3**: $[\alpha]^{23}_{589} = -23.3$ (H_2O, $c = 1$) (lit.[24] $[\alpha]^{20}_D = -28.8$, $c = 2.0$, 5 N HCl); ^{1}H NMR (D_2O, 300 MHz) δ ppm 3.76 (m, 1 H), 3.47 (dd, 1 H, $J = 12$, 4.8 Hz), 3.41 (dd, 1H, $J = 12$, 5.7 Hz), 3.00 (dd, 1H, $J = 13.2$, 3.0 Hz), 2.78 (dd, 1H, $J = 13.2$, 9.3 Hz; ^{13}C NMR (D_2O, 75 MHz) δ ppm 63.3, 58.6, 37.2.

(*R*)-3-Bromo-1,2-propanediol (2). The amine **11** (10 g) was dissolved in 400 mL of water. HBr solution (50 mL, 47% aqueous solution) and 52 g of sodium bromide were added to the solution which was then cooled to 10 °C. Sodium nitrite (70 g) was added to the mixture, and it was stirred at room temperature for 20 h after which time NMR spectroscopy indicated complete conversion of the aminodiol to the bromodiol. The mixture was neutralized by sodium bicarbonate, then most of the water was removed by rotary evaporation, and the residue was taken up in chloroform. The chloroform solution was dried over sodium sulfate, and removal of the solvent gave the bromodiol **2** as a yellow liquid. The yield was 10.3 g (87%). **2**: $[\alpha]^{23}_{589} = -4.00$ ($CHCl_3$, $c = 1$) (lit.[17b] $[\alpha]^{25}_{589} = -3.94$, $c = 5.07$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 3.91 (m, 1H), 3.75 (dd, 1H, $J = 11.4$, 3.6 Hz), 3.64 (dd, 1H, $J = 11.4$, 6.0 Hz), 3.44 (m, 2H) (lit.[2], ^{1}H NMR, $CDCl_3$, 400 MHz, 3.98−3.89, 3.78, 3.69, 3.51, 3.46 ppm); ^{13}C NMR ($CDCl_3$,75 MHz) δ ppm 71.4, 64.3, 34.6 (lit.[2], $CDCl_3$, 100 MHz, 71.4, 64.3, 34.9 ppm).

(*R*)-3-Chloro-1,2-propanediol (12). The procedure was similar to that used in the preparation of the bromodiol. The amine **11** (2.62 g, 0.02 mol) was dissolved in 10 mL of water. Sodium chloride (8.78 g, 0.15 mol) and concentrated hydrochloric acid (20 mL, 0.2 mol) diluted with 10 mL of water were added to the mixture. Sodium nitrite (10.4 g, 0.15mol) was then added over a period of 10 min. The mixture was then stirred for 24 h, after which time an analysis of the reaction by NMR spectroscopy indicated complete conversion to the chlorodiol. The mixture was then concentrated to dryness, and the product was extracted with chloroform 3 or 4 times. The extracts were combined and dried with sodium sulfate. Removal of solvent gave chlorodiol **12** as a light yellow liquid (1.81 g, 82%): $[\alpha]^{23}_{589} = -7.2$ (H_2O, $c = 5$) (lit.[25] $[\alpha]^{20}_D = -6.8$, $c = 5$, H_2O; lit.[26] $[\alpha]^{25}_{589} = -7.4$, $c = 1$, H_2O); ^{1}H NMR (D_2O, 300 MHz) δ ppm 3.86 (m, 1H), 3.68−3.48 (m, 4H) (lit.[25] ^{1}H NMR, D_2O, δ (DSS), 3.85−4.0, 3.6−3.5 ppm); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 71.7, 63.6, 45.8. All products were >99.5% optically pure by chiral GC.

Acknowledgment. This work was supported by Synthon Corporation and the Michigan State University Research Excellence Fund.

JO9818226

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