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Development of an Efficient Process for the Decomposition of the Borate Complexes Formed during the Large-Scale Synthesis of (*S*)-1,2,4-Butanetriol

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ABSTRACT: An improved multikilogram-scale process for the production of (*S*)-1,2,4-butanetriol has been developed. This process involves the efficient removal of residual boric acid and the decomposition of the borate complexes formed during the reduction of (−)-dimethyl malate with sodium borohydride by methanolysis using a circular distillation-coupled hydrolysis apparatus.

INTRODUCTION

(*S*)-1,2,4-Butanetriol (**1**) is a useful building block for the synthesis of HMG-CoA reductase inhibitors such as lovastatin (**2**), rosuvastatin (**3**), and atorvastatin (**4**) as well as the synthesis of antineoplastic natural products such as acutiphycin (**5**) and didehydroacutiphycin (**6**) (Figure 1).[1,2]

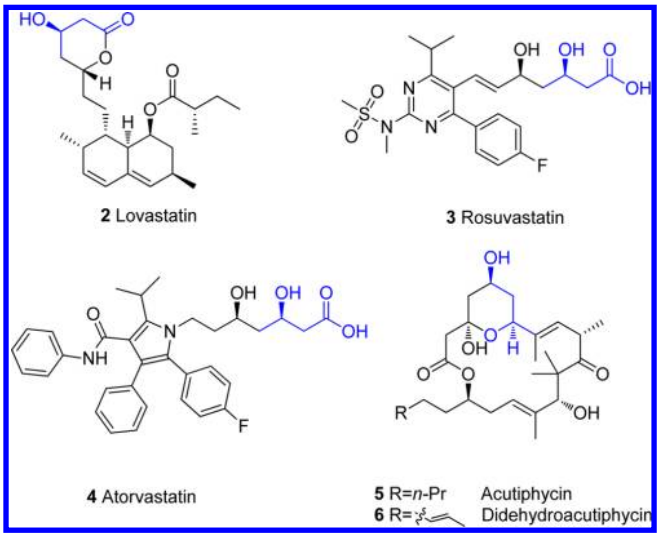
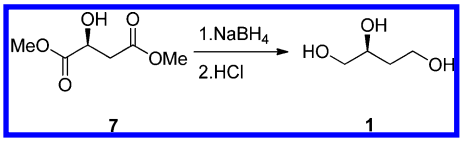


Figure 1. Structures of several HMG-CoA reductase inhibitors and antineoplastic natural products.

Although a variety of different methods for the synthesis of **1** from chiral starting materials have been reported,[3] the chiron route starting from L-malic acid is currently used as an industrial process for synthesis of **1**, with the reduction of (−)-dimethyl malate (**7**) with sodium borohydride ($NaBH_4$) being the final step in the process (Scheme 1). Izawa et al.[4] recently attempted to produce high-purity **1** via distillation of the crude product resulting from the reduction of **7**. Unfortunately, however, their efforts in this regard were unsuccessful, as only the decomposed byproduct was detected. This problem has therefore severely limited the production and subsequent application of this material. Herein we report the development of a high-yielding, convenient, and scalable method for the synthesis of **1** involving the use of circular distillation-coupled hydrolysis for the removal of residual boric acid as well as the cleavage of the borate complexes formed during the reduction of **7** with $NaBH_4$.

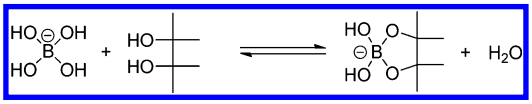
Scheme 1. Reduction of 7 with $NaBH_4$ To Give the Target Compound 1



RESULTS AND DISCUSSION

At the beginning of our own investigation, we repeated the procedure for the reduction of **7** using $NaBH_4$ and attempted to purify the crude triol product **1** by distillation in the same way as Izawa et al.[4] Not surprisingly, this procedure did not provide any of the desired product and resulted only in the formation of decomposition byproducts. The failure of this process was attributed to the formation of boric acid during the reduction of **7** with $NaBH_4$, which could readily chelate with **1** to form borate complexes[5] (Scheme 2). With this in mind, the development of a successful process for the production of high-quality **1** would require the effective removal of any residual boric acid as well as the cleavage of the borate complexes prior to the purification of the crude product by direct distillation.

Scheme 2. Complexation Reaction of Boric Acid with Multi-Hydroxylated Compounds



Several different methods of purification have been developed for the removal of borate complexes and boric

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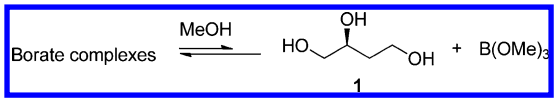
acid from the crude triol **1**, including the use of chromatography[3d] and ion-exchange resins.[3b] However, the use of chromatography on the industrial scale is impractical and expensive, whereas ion-exchange resins such as the glucosamine-specific borate adsorption resin IRA-743 or XE-583 can lose their capacity after only a few cycles. Because of these limitations, it is clear that there is an urgent need for the development of an alternative manufacturing-scale procedure for the removal of the borate-based impurities that are formed during the synthesis of **1**.

It is well-known that boric acid can undergo methanolysis to give trimethyl borate,[6] which can be readily removed from the crude product mixture by codistillation with methanol. It was envisaged that the borate complexes would undergo the reverse reaction shown in Scheme 2 following the removal of boric acid, giving the free triol **1** and boric acid; the latter of these two products would go on to react with methanol and be evaporated, leaving only triol **1**.

It was estimated that at least 160 volumes of methanol would be required to allow for the complete removal of the residual boric acid and borate complexes from the crude product, suggesting that the cleavage of the borate complexes was an equilibrium reaction that was slower than the corresponding complex-forming process (Scheme 3). On the basis of this

Scheme 3. Equilibrium between the Borate Complexes and Triol 1



requirement for a high loading of methanol in a single run, the inclusion of some process for recycling the methanol would be necessary. It is well-known that trimethyl borate is moisture- and base-sensitive, so the decision was made to quench the vaporized trimethyl borate with sodium hydroxide solution to give methanol, which could be recycled using our newly designed circular distillation-coupled hydrolysis apparatus (Figure 2).

As shown in Figure 2, the apparatus consists of two condensers, a packed column, a sample point, and two reactors. The reactors themselves are a glass-lined reactor (A) and a 316 stainless steel reactor (B). Reactor A is used to contain a methanol solution of the crude reduction mixture containing triol **1**, its borate complexes, and the residual boric acid, whereas reactor B is equipped with a packed distillation column and charged with methanol, water, and sodium hydroxide. In practice, both of the reactors are heated, and the boric acid in reactor A is converted to trimethyl borate before being codistilled with methanol into reactor B. As the concentration of boric acid in the crude product mixture is reduced, the borate complexes gradually decompose to generate the free triol and more boric acid. In reactor B, the trimethyl borate derived from the distillation in reactor A is immediately saponified by sodium hydroxide, and the resulting methanol is evaporated and transferred back to reactor A. In this way, an effective circular methanol flow is established, enabling the recycling of the solvent. In addition, the terminal point can be readily determined by checking the combustion until the green flame caused by trimethyl borate disappears. Finally, the solution in reactor A is concentrated and distilled to give high-purity (*S*)-1,2,4-butanetriol (**1**) without any of the decomposition byproduct.

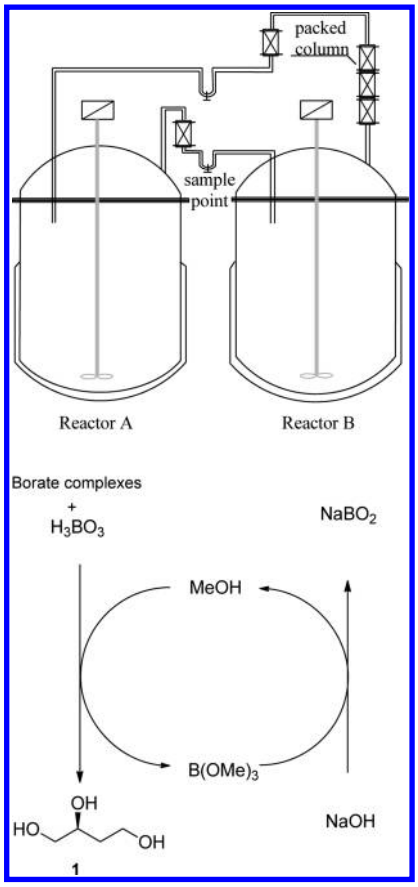


Figure 2. Apparatus for the circular distillation-coupled hydrolysis process for the decomposition of the borate complexes.

CONCLUSION

An efficient, facile, and economical circular distillation process for the purification of (*S*)-1,2,4-butanetriol (**1**) has been developed. This method allows for the cleavage of the borate complexes to afford the free triol product as well as the simultaneous removal of any residual boric acid and the recycling of the reaction solvent. Furthermore, this process could be applied universally for the removal of residual boric acid and borate complexes, especially for highly water-soluble and thermally sensitive products.

EXPERIMENTAL SECTION

General. All of the reagents used in the current study were purchased from commercial suppliers and used without further purification. the ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on Bruker instruments in D_2O, and the chemical shift values are reported as parts per million relative to TMS, which was used an internal standard. Specific rotations were determined using a PerkinElmer polarimeter (model 341-LC).

(*S*)-1,2,4-Butanetriol (1). A 200 L glass-lined reactor was charged with tetrahydrofuran (100 L) and $NaBH_4$ (7.2 kg, 180 mol), and the resulting mixture was cooled to −5 °C with stirring. (−)-Dimethyl malate (24.8 kg, 153 mol) was then added through a piston-type metering pump at a rate of 6 kg/h whilst the temperature was maintained in the range of −5 to 0 °C. Upon completion of the addition, the mixture was stirred

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for 10 h in the same temperature range. Upon completion of the reaction (as determined by TLC), 36% (w/w) hydrochloric acid (19 kg, 187 mol) was slowly charged to the stirred mixture whilst maintaining the temperature in the range of −5 to 0 °C. The resulting mixture was stirred for 1 h at same temperature before being filtered. The filter cake was then washed with tetrahydrofuran (3 × 5 L), and the combined filtrate and washings were concentrated under vacuum to give the crude product as a viscous liquid containing a small quantity of white solid. The crude product was then placed in a 200 L glass-lined reactor (A), followed by methanol (80 L). Methanol (48 L), water (30 L), and NaOH (2 kg, 50 mol) were then added sequentially to a separate reactor (B). Both reactors were heated to 85 °C, and the azeotropic mixture of methanol and trimethyl borate that was generated in reactor A was transferred to reactor B, where the trimethyl borate was hydrolyzed to give methanol, which was evaporated and condensed back into reactor A. The reaction was monitored by combustion until the green flame of trimethyl borate disappeared (ca. 10 h), at which point the solution in reactor A was sequentially concentrated and distilled (181−184 °C/20 mmHg) to give (*S*)-1,2,4-butanetriol (12.6 kg, 76% yield for two steps) as a light-yellow oil. ^{1}H NMR (D_2O): δ 1.57 (1H, m), 1.66 (1H, m), 3.40 (1H, m), 3.51 (1H, m), 3.63 (2H, m), 3.73 (1H, m). ^{13}C NMR (D_2O): δ 34.74, 58.29, 65.54, 68.85. $[\alpha]_D^{20}$ = −25.2 (*c* = 1, MeOH) (lit[3a] $[\alpha]_D^{20}$ = −25.5°).

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Notes

The authors declare no competing financial interest.

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