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Article

Asymmetric Synthesis of Propranolol, Naftopidil and (*R*)-Monobutyrin using a Glycerol Desymmetrization Strategy

Mahendra N. Lokhande, Manojkumar U. Chopade, Dattatrya N. Bhangare and Milind D. Nikalje*

Department of Chemistry, University of Pune, Pune-411 007, India

Este trabalho descreve uma abordagem para dessimetrização de glicerol utilizando canforsulfonamida disponível como material de partida. A estratégia para síntese assimétrica de (*R*)/(*S*)-propranolol, (*R*)/(*S*)-naftopidila e (*R*)-monobutirina com formação de espirocetal por dessimetrização foi empregada e a reação de Mitsunobu foi utilizada para a formação de epóxido e éter. Esterificação de Steglich e CAN (nitrato de cério amônia) mediaram a desproteção de cetal como etapas chave na síntese. A abertura regioseletetiva do anel do epóxido forneceu a molécula desejada com bom rendimento e pureza ótica.

Herein, an approach for desymmetrization of glycerol by using a readily available camphorsulfonamide as a starting material is described. The strategy for asymmetric synthesis of (*R*)/(*S*)-propranolol, (*R*)/(*S*)-naftopidil and (*R*)-monobutyrin with spiroketal formation by desymmetrization was employed and Mitsunobu reaction was used for epoxide and ether formation. Steglich esterification and CAN (cerium ammonium nitrate) mediated ketal deprotection, were key steps in the synthesis. Regioselective ring opening of epoxide gave desired molecule with good overall yield and optical purity.

Keywords: desymmetrization, spiro-ketal, Mitsunobu etherification, Steglich esterification, camphorsulfonamide

Introduction

Glycerol is synthetically very useful as a source for the three carbon unit. The desymmetrization of glycerol is the most useful synthetic strategy for converting glycerol into a chiral synthon in the presence of (1*R*)-(–)-10-camphorsulfonamide. One of the classical ways for resolution of 1,2 and 1,3-diols is by means of formation of the ketal or acetal with a chiral ketone or aldehyde. Amino alcohols are used as β-adrenergic blocking agents for treatment of cardiovascular disorders such as cardiac arrhythmias, angina pectoris and hypertension.[1] On a similar line, Hsu *et al.*[2] demonstrated the desymmetrization of glycerol by spiroketal **5** formation with camphorsulfonamide. Thus, by entrapping the 1,2-diol functionality one can broaden the scope of glycerol to use as a chiral source in asymmetric synthesis. Marzi *et al.*[3] used this strategy for the synthesis of (*R*)-carnitine from glycerol by modified desymmetrization strategy. Our group identified that this strategy is very useful in the synthesis of the (*R*) and (*S*)-enantiomer of propranolol, naftopidil and (*R*)-monobutyrin (Figure 1).

(S)-propranolol (**1b**) is a potential β-adrenergic blocking agent and is more active than (*R*)-propranolol **1a**, whereas (*S*)-naftopidil **2b** is a α1-adrenoceptor antagonist and also possesses vasodilator activity. Several methods have been reported in the literature for the synthesis of (*R*)/(*S*)-propranolol and (*R*)/(*S*)-naftopidil. The incorporation of chirality into these was shown by Sharpless' asymmetric epoxidation,[4] asymmetric dihydroxylation,[5] nitroaldol condensation,[6] hydrolytic kinetic resolution[7] and asymmetric α-hydroxylation.[8] Further, monobutyrin is a naturally occurring lipid that stimulates angiogenesis which secreted by differentiating adipocytes. Purification from adipocytes and identification of angiogenic activity were first done by Deborah *et al.*[9] Angiogenesis refers to the growth of new blood vessels, or "neovascularization" and involves the growth of capillaries composed of endothelial cells.

The (*R*)-isomer of monobutyrin was found to be bioactive. The only useful synthetic method for obtaining both (*R*) and (*S*)-monobutyrinisomers using D- and

*e-mail: mdnik@chem.unipune.ac.in

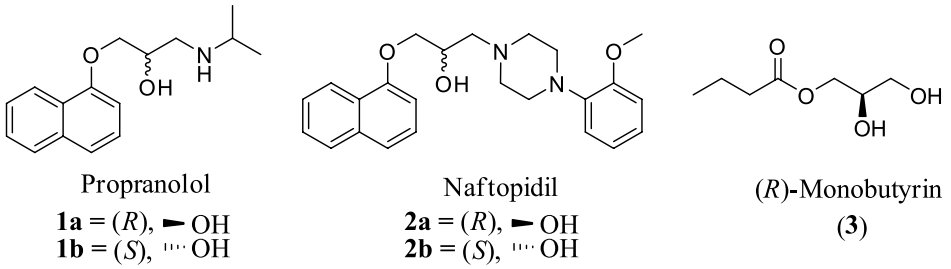


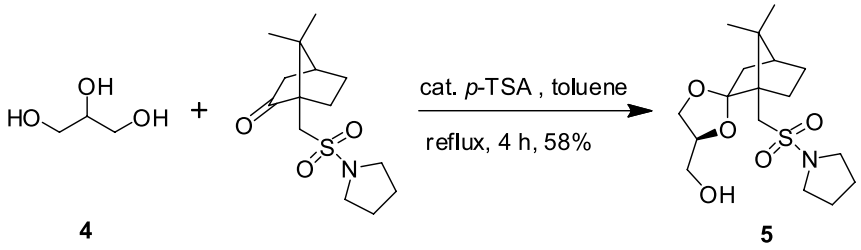
Figure 1. Chemical structure of propranolol, naftopidil and monobutyrin.

L-mannitol as chiral building blocks.[10] Although the optical purity of (*R*)-monobutyrin **3** is good, it involves multiple steps and is not very attractive. In this context, a more practical approach for the synthesis of (*R*)-monobutyrin is highly desirable. The objective of the present investigation is to provide a two-step synthesis of (*R*)-(+)-monobutyrin.

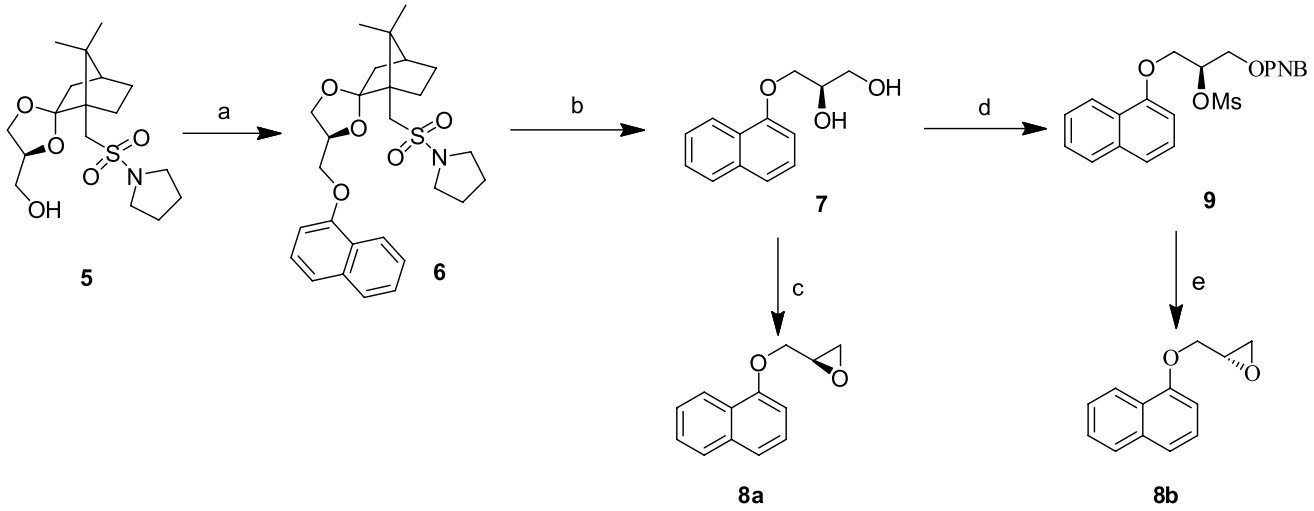
Our group identified that the introduction of the chirality by desymmetrization strategy of glycerol is not yet reported in the literature for the synthesis of **1**, **2** and **3**. It encouraged us to apply a synthetic strategy for the synthesis of both stereoisomers of propranolol, naftopidil and (*R*)-monobutyrin.

Results and Discussion

The desymmetrization of glycerol with (1*R*)-(−)-10-camphorsulfonamide as shown in Scheme 1 gave chiral spiro-ketal **5**, which was purified by column chromatography to give a white solid in 58% yield [mp 118-120 °C; $[\alpha]_D^{25}$ −18.6° (*c* 1, $CHCl_3$)] and only one diastereomer of the spiro-ketal is formed, in good agreement with the literature.[3] Enantiopure spiroketal **5** was successfully used for synthesis of both enantiomers of propranolol and naftopidil, as depicted in the Scheme 2. Our objective was to get the chiral diol **7** as a key precursor. Accordingly, it was envisioned that the chiral



Scheme 1. Desymmetrization of the glycerol with camphorsulfonamide.



Scheme 2. (a) 1-Naphthol, PPh_3, DIAD, THF, room temperature, 4 h, 71%; (b) MeOH, conc. HCl, reflux, 10 h, 96%; (c) PPh_3, DIAD, $CHCl_3$, 4 h, 78%; (d) (*i*) *p*-nitrobenzoyl chloride, pyridine, CH_2Cl_2, (*ii*) MsCl, Et_3N, CH_2Cl_2, room temperature, 10 min, over all yield 78%, (e) NaOH, dioxane, 70 °C, 18 h, 85%.

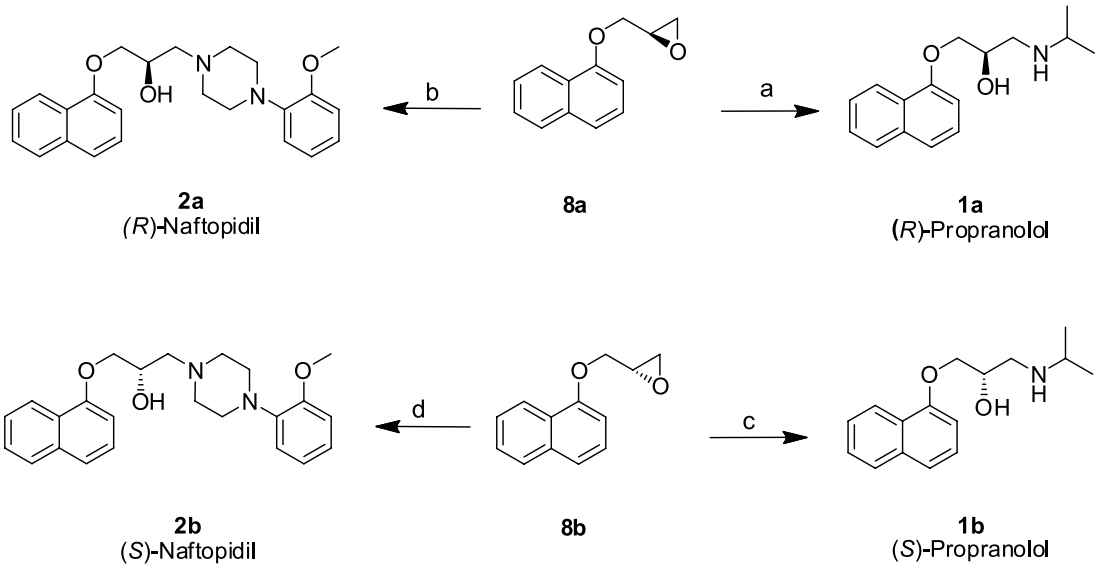
spiro-ketal **5** as an immediate precursor for diol **7**. The compound **5** was then subjected to Mitsunobu reaction with 1-naphthol to incorporate 1-naphthyloxy moiety in the form of 1-naphthylether **6** [mp 95-97 °C; $[\alpha]_D^{26}$ –13.1° (*c* 1, CH_3OH)].[11,12]

The spiroketal moiety in 1-naphthyl ether **6** was subsequently deprotected with conc. HCl to give key intermediate chiral diol **7** in 96% yield [mp 102-104 °C; $[\alpha]_D^{25}$ +6.2° (*c* 1.05, EtOH),[8] +6.69° (*c* 1.05, EtOH)].[3] The enantiomeric excess was confirmed by HPLC on chiral column and found to be 98% ee. Furthermore, the diol **7** was transformed into chiral epoxide **8a** by intramolecular Mitsunobu reaction to yield the epoxide **8a**. In order to obtain (*S*)-propranolol and (*S*)-napftopidil, diol **7** was transformed to epoxide **8b** with inversion of stereochemistry. The esterification of the primary hydroxyl with *p*-nitrobenzoyl chloride (PNB) followed by *in situ* mesylation with methanesulfonyl chloride resulted in the formation of compound **9** as a gum. Epoxide **8b** was obtained upon hydrolysis of the PNB-ester **9**, done by addition of NaOH.[13]

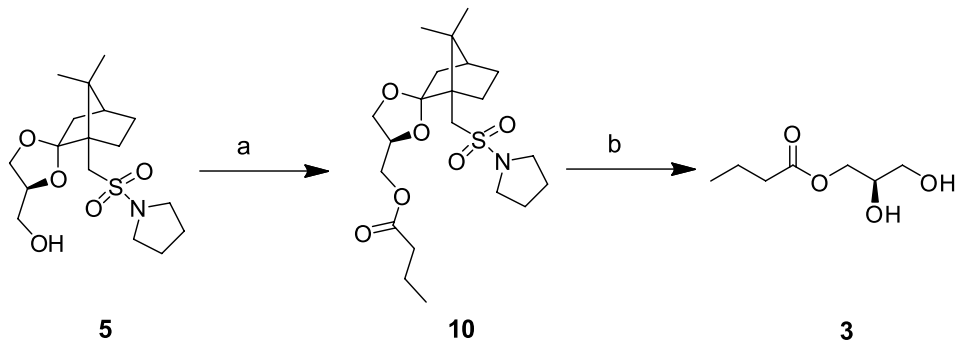
The synthesis of both stereoisomers of propranolol and naftopidil was very straightforwardand was achieved by regioselective ring opening of the epoxides **8a** and **8b** with isopropyl amine and by 1-(2-methoxyphenyl) piperazine, respectively, as shown in Scheme 3. For the asymmetric synthesis of (*R*)-monobutyrin **3**, the enantiopure spiroketal **5** was subjected to treatment of butyric acid under Steglich esterification condition to get ester **10**. It was tried ketal deprotection of compound **10** by various methods under different conditions using HCl,[3] acetic acid,[9] I_2,[14] $ZnCl_2$,[15] but none of these was useful. A number of spots and hydrolysis of the ester were observed. Finally, cerium(IV) ammonium nitrate was found suitable, selectively deprotecting **10** in 30 min.[16] This afforded (*R*)-monobutyrin in excellent yield and good optical purity.

Conclusion

In conclusion, our group demonstrated the simplicity of the synthetic desymmetrization strategy as a new



Scheme 3. (a) Isopropylamine, CH_2Cl_2, 30 h, 71%; (b) 1-(2-methoxyphenyl)piperazine, CH_2Cl_2, 30 h, room temperature, 82%; (c) isopropylamine, CH_2Cl_2, room temperature, 30 h, 72%; (d) 1-(2-methoxyphenyl)piperazine, CH_2Cl_2, 30 h, room temperature, 80%.



Scheme 4. (a) *n*-Butyric acid, DCC, DMAP, DCM, room temperature, 6 h, 90%; (b) CAN, CH_3CN, room temperature, 1 h, 80%.

approach towards the synthesis of (*S*)-propranolol, (*S*)-napftopidil and (*R*)-monobutyrin via desymmetrization of glycerol using (1*R*)-(–)-10-camphorsulfonamide as an easily available chiral auxiliary. Our synthetic strategy involved five steps, for which overall yield obtained was 32-34% and for monobutyrin 41%. The enantiomeric purity of stereoisomer of the **2**, **8** and **3** were found to be 90-95% ee in comparison with the literature value.

Supplementary Information

Experimental details and spectra of compounds synthesized in this manuscript are available free of charge at http://jbcs.sbq.org.br as a PDF file.

Acknowledgements

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