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SOB as an alternate to BOB: findings from the preparation of injectable antifungal Sch 59884

P. Renton, D. Gala* and G. M. Lee

Chemical Process Research & Development, Schering-Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083, USA

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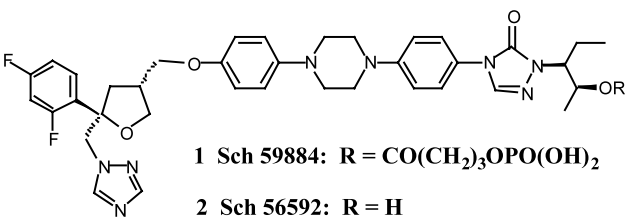
Abstract—A facile preparation of 4-silyloxybutyrates (SOB) and their potential use as an alternate to 4-benzyloxybutyrate (BOB) are described.

Recently, Professor Ganem has described the development of BOB as a synthetically useful protecting group towards the synthesis of glycolipids such as keruffarides and crasserides.[1] The use of BOB via Jacobson asymmetric epoxide opening[2] allowed for the preparation of synthetically useful diol monoesters. After appropriate manipulation of the free hydroxy group, BOB can be removed in a stepwise fashion to free the protected hydroxy group. This report prompts us to describe our findings towards the preparation of BOB and SOB and their synthetic utility. The latter can be an attractive alternate to BOB for larger scale synthesis.



1 Sch 59884: R = $CO(CH_2)_3OPO(OH)_2$

2 Sch 56592: R = H

Our synthesis of the injectable antifungal Sch 59884, **1**, from Posaconazole (Sch 56592), **2**, via the *p*-nitrobenzyl ester of 4-hydroxybutyric acid is being published.[3] Although this synthesis was scaled up to prepare several kilos of the antifugal, the *p*-nitrobenzyl was far from a desirable protecting group. Not only did it involve the use of irritant *p*-nitrobenzyl halide, its deprotection with either Na_2S or Zn/HCl was problematic. The sulfide method required rigorous emission controls and led to decomposition of intermediates, whereas the zinc method formed polymeric byproducts which entrained the intermediates making their isolation difficult with lowered yields upon scale-up.

To overcome the above difficulties, alternate synthetic strategies were considered. In one of our strategies we reevaluated the use of BOB, i.e. 4-benzyloxybutyric acid, **5**.[4] Compound **5** can be reacted with **2** to generate ester **6** (Scheme 1). This after debenzylation to alcohol **7** can be directly phosphorylated with a pentavalent phosphorylating reagent such as dibenzylchlorophosphate (DBCP) to the known precursor of **1**.[3] The literature conditions,[5] described in Scheme 1, allowed for the preparation of **5** from commercially available γ-lactone **3**. The reaction between **3** and excess benzylbromide generated few byproducts and **5** along with compound **4**. This mixture was then hydrolyzed to **5** which was isolated via acid/base work-up. Our previously described mixed anhydride procedure,[2,6] depicted below Scheme 1, worked well for the coupling of **5** with **2** to form the benzylether **6**. The debenzylation of **6** with hydrogen in a variety of solvents, with or without acid, required long reaction times (1–3 days) even in the presence of a large ($\geq$50 wt%) amount of 5% Pd/C. Furthermore, debenzylation generated several impurities which could only be removed via chromatography. This difficulty in deprotection of **6** does not appear to be specific to **6** as most of the BOB protected alcohols reported by Ganem also required large amounts (50–100 wt%) of Pd/C catalyst. Transfer hydrogenation with formic acid contaminated **7** with the formate ester of **7** also requiring chromatographic purification. The reactions with an excess of ammonium formate were very slow (incomplete after 7 days, 75 wt% 5% Pd/C). For a large-scale synthesis of **1**, the long reaction times for the preparation of **5** as well as **7**, excesses of BnBr

* Corresponding author.

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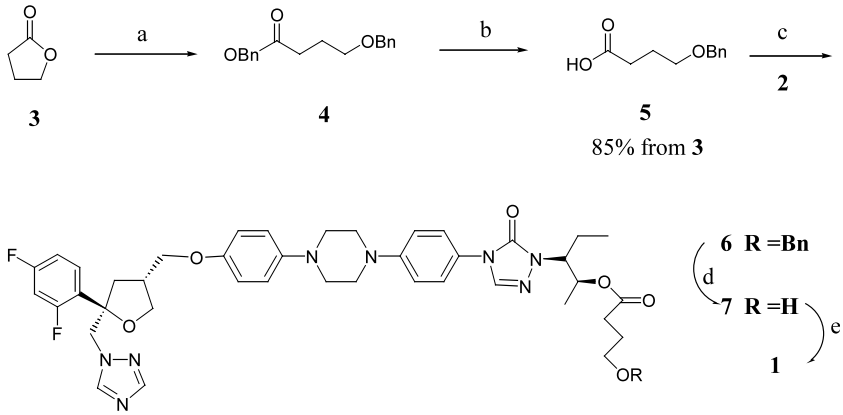


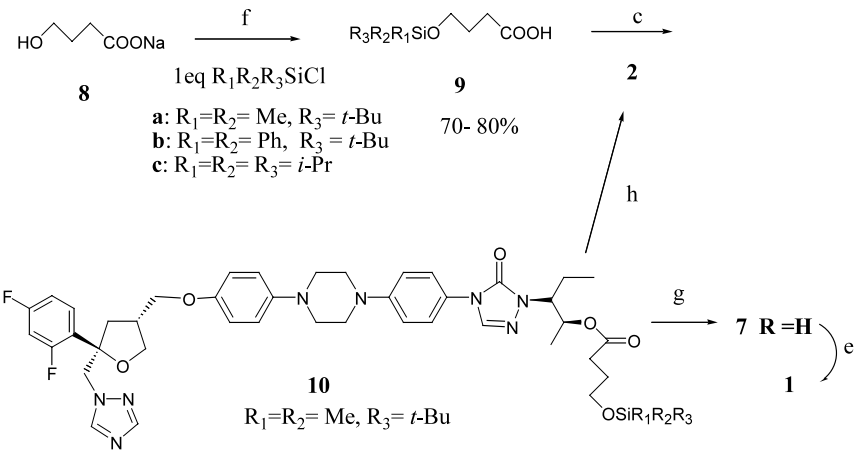
Scheme 1. Preparation of **1** via the use of BOB (**5**): (a) 4 equiv. BnBr, KOH, tol. reflux, 3 days; (b) tol., aq. NaOH, reflux, 1 day; 85% from **3**; (c) TsCl, DMAP, THF, 0°C as in Refs. 3 and 6; 90%; (d) 100 wt% 5% Pd/C, H_2 100 psi, THF, 24 h 100 psi, 75% soln; 60% isolated after chromatography;[7] (e) Refs. 3 and 10.

and Pd/C, and chromatographic purifications for the removal of impurities formed in theses reactions were undesirable.

The above difficulties were overcome by the use of SOB **9**, in place of BOB, **5**, as described in Scheme 2. It was observed in our laboratory that under very mild conditions the reaction of commercially available 4-hydroxy sodium butyrate **8** with a variety of silylchlorides led directly to the formation of 4-silyloxybutyric acids (SOB, **9**) in good to excellent isolated yield (70–90%). To the best of our knowledge the formation of **9** proceeds via an intramolecular carboxy to a hydroxy silyl transfer reaction which is novel. This new finding was then applied to the synthesis of **1**. For the purpose of synthesizing **1**, we chose TBDMS as the protecting group of choice.[8] Once again, the mixed anhydride coupling procedure[3,6] was well suited for the conversion of **9** to **10**, and in fact it led to an excellent isolated yield of **10**, as shown in Scheme 2. The conversion of **7** from **10** with fluorides generated a minimum amount of the desired product and its implications are listed later. This forced evaluation of several alternate conditions for the conversion of **10** to **7**, of which the preferred one entailing the use of dil. aq. HCl leading to good isolated yield (85%) is depicted in Scheme 2.

The removal of the silyl group from **10** with TBAF (tetrabutylammoniumfluoride) was investigated first for the conversion of **10** to **7**. Even under mild conditions (−10 to 0°C) and with limited amount of this reagent, the formation **7** was immediately followed by the formation of **2** and γ-lactone. Interestingly, this facile desilylation and elimination overcomes difficulties associated with the removal of BOB. Thus, a facile preparation, subsequent easy deprotection, and apparent compatibility of SOB to mild Jacobsen asymmetric epoxide opening conditions should allow for the use of SOB in epoxide opening leading to an alternate to BOB for synthetic purposes.

A detailed description of the intramolecular carboxyl to hydroxyl group transfer in **8**, identification of the inter-



Scheme 2. Preparation of **1** via use of SOB (**9**): (c) **2**, TsCl, DMAP, THF, 0°C to rt, 24 h; 98%; (e) Refs. 3 and 10; (f) DMF, rt, 8–20 h, 70–90% yield; (g) 5% aq. HCl, THF, 0–22°C, 85%; (h) 1.1 equiv. TBAF, THF, rt, 75% unoptimized;[9] (e) as in Scheme 1.

mediates involved in this transfer via modern spectral techniques, preparation of **9**, as well as development of an efficient alternative (to DBCP) phosphorylation method for the conversion of **7** to **1** is the subject of a separate publication.[10]

In summary, the preparation of SOB via a novel silyl transfer reaction is described. The preparation and removal of SOB is accomplished under mild conditions. SOB may provide an attractive alternate to the use of BOB for synthetic purposes.

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7. A number of byproducts were seen via HPLC. The large excess of catalyst adsorbed product as well as starting materials. The use of methylenechloride was necessary for sampling as well as obtaining good mass balance from the catalyst.
8. Of the three silyl groups evaluated, TBDMS was commercially less expensive than the others, and had all the desirable properties for the synthesis of **1**, hence it was the group of choice. Although TMS-Cl is readily available and less expensive than TBDMS-Cl, the former was expected to be unstable as a carboxylic acid protecting group. Hence, TMS was not considered as a suitable silyl protecting reagent for a large scale preparation of **1**.
9. Compound **7** accounted for the rest of the mass balance. In theory, extended reaction time or slight excess of TBAF could lead to complete conversion to **2**, which was not our interest.
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