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What about BOB? A synthetically useful protecting group†

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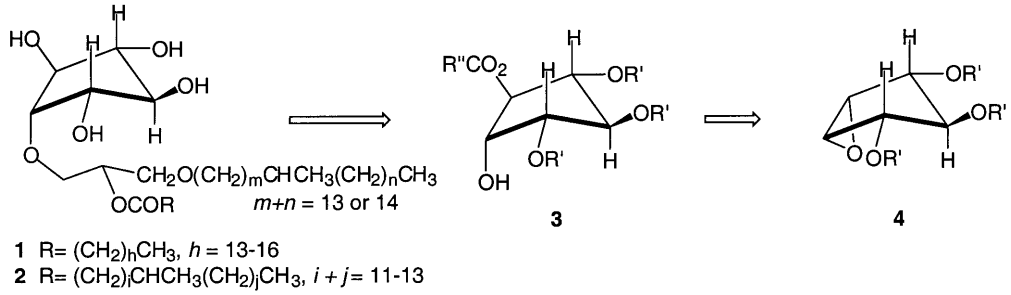
Abstract

Benzyloxybutyryl (BOB) esters of alcohols can be prepared from commercially available 4-benzyloxybutyric acid by standard acylation techniques, by the Mitsunobu reaction (with inversion of configuration), or by the Jacobsen asymmetric nucleophilic ring opening of epoxides. BOB esters can be removed selectively in the presence of other esters under conditions that are compatible with a variety of sensitive functional groups.

As part of a program in our laboratory aimed at the synthesis of novel monosaccharide mimics, we have been interested in the keruffarides[1] **1** and crasserides[2] **2**, a family of naturally-occurring glycolipid mimics produced by marine sponges. We envisioned a retrosynthetic strategy (Scheme 1) whereby **1** might arise from a suitably tetraprotected pentaol **3** by *O*-alkylation. Intermediate **3** might come from protected epoxycyclopentanetriol **4** by an asymmetric Jacobsen epoxide opening.[3]



Scheme 1.

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The Jacobsen reaction creates one of the two new hydroxyl groups in **3** as a carboxylate ester, and it seemed attractive to use such an ester as a temporary blocking group while attaching the glyceryl side chain. However, the final deprotection step must be compatible with the fatty acyl ester in **1** and **2**.

Removal of esters by lactonization is a common strategy, and has already been reported for the 2-(2-benzyloxyethyl)benzoates.[4,5] However, the starting material for this protecting group is not readily available. Here we describe the synthesis and chemistry of 4-benzyloxybutyryl (BOB) esters of alcohols. BOB esters, which do not appear to have been used as protecting groups in synthesis, can be prepared in three ways from commercial 4-benzyloxybutyric acid (BOBOH): (1) by direct esterification; (2) by the Mitsunobu reaction; or (3) by nucleophilic opening of epoxides (the Jacobsen reaction). We further show that BOB esters undergo selective removal by hydrogenolysis and lactonization in the presence of other esters and reducible functional groups.

Using standard dehydration conditions (EDC, DMAP, CH_2Cl_2), commercially available alcohols **5**, **7**, **8**, **11**, **12** and **13** (Fig. 1) were condensed with BOBOH to furnish BOB esters **14**, **16**, **17**, **20**, **21** and **22** in good to excellent yields.[6] Although the shelf life of these BOB esters was not extensively studied, several representative examples showed no detectable change in NMR, TLC or color after standing several months at rt. One notable exception was **22**, which underwent elimination of BOBOH upon standing at rt for several days to afford the corresponding tropanol 2′-phenylacrylate ester (not shown). To investigate the formation of BOB esters by the Mitsunobu reaction, alcohols **6** and **11** were reacted with diisopropylazodicarboxylate (DIAD) and PPh_3 in Et_2O or THF as solvent. The desired BOB esters **15** and **20** were obtained in moderate to good yields. In the case of **15**, some product was lost as a result of additional chromatography needed to remove unreacted DIAD.

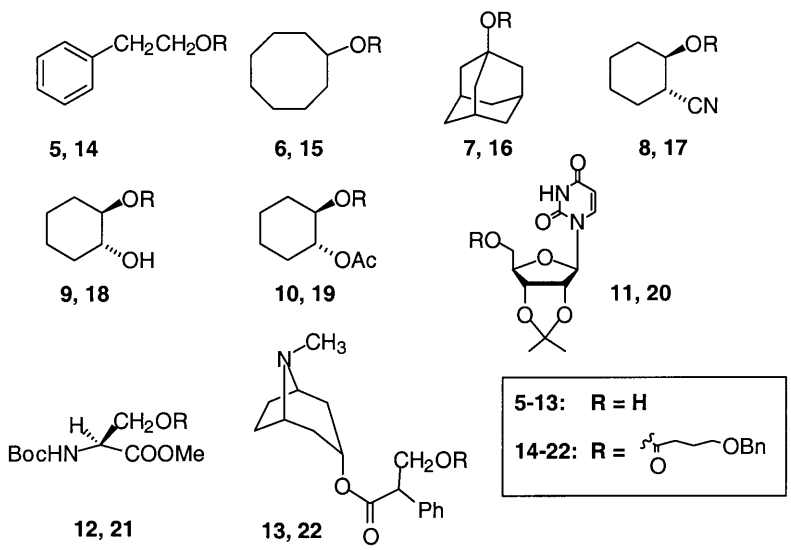

Figure 1. Representative alcohols and their BOB esters

The synthetic plan we envisioned for **1** and **2** required that one BOB ester be installed by a Jacobsen asymmetric epoxide opening. To test that strategy, BOBOH was reacted with cyclohexene oxide following published conditions.[3] Diol monoester **18** was isolated in 89% yield as a pale yellow oil.[7] Upon acetylation (Ac_2O, pyr, CH_2Cl_2), **18** afforded the diester **19**.

Using **14** as a representative BOB ester, debenzylation proceeded smoothly using 10% Pd/C as catalyst (1 atm H_2, EtOAc). Hydrogenolysis was complete in 12–48 h, depending on the quantities of Pd/C used, with optimal results achieved using 0.5–1.0 weight equiv. catalyst. Release of butyrolactone from the resulting 4-hydroxybutyrate ester was tested using a variety of bases. Very little butyrolactone was released using Et_3N or DBU. However, addition of 10 mol% KOBu^t, which is known to promote lactonization,[4] to a dry THF solution of **14** immediately generated **5**.

Using the above described hydrogenolysis/cyclization conditions, BOB-derivatives **14**, **15**, **16**, **18**, **19** and **21** were successfully deprotected in high yield (Table 1). It is noteworthy that the free alcohol in **18** did not significantly interfere with deprotection. Both the acetate moiety of **19** and the methyl ester in **21** were stable to the deprotection conditions, confirming the hoped-for utility of BOB esters in our synthetic approach to **1** and **2**.

Table 1
Formation and deprotection of BOB esters

Entry	Starting material	Formation method[a]	BOB ester (% yield)	Deprotection method[b]	Alcohol (% yield)
1	**5**	A	**14** (96)	D	**5** (90)
2	**6**	B	**15** (58)	D	**6** (90)
3	**7**	A	**16** (60)	D	**7** (93)
4	**8**	A	**17** (99)	E	**8** (91)
5	Epoxy-cyclohexane	C	**18** (89)	D	**9** (94)
6	**18**	Ac_2O	**19** (>95)	D	**18** (91)
7	**11**	A, B	**20** (90)	E[c]	**11** (84)
8	**12**	A	**21** (89)	D	**12** (92)
9	**13**	A	**22** (87)	–	–

[a] A = EDC, DMAP, CH_2Cl_2; B = DIAD, Ph_3P, Et_2O; C = Jacobsen's catalyst, $(i\text{Pr})_2\text{NEt}$, CH_3OBu^t.

[b] D = (I) H_2, 10% Pd/C, EtOAc or THF; (ii) 10 mol% KOBu^t, THF; E = (I) 1,4-cyclohexadiene, Pd, EtOH; (ii) 0.1 equiv. KOBu^t, THF.

[c] 1.1 equiv. of KOBu^t used in step (ii) of Method E.

In the case of BOB-derivatives **17** and **20**, hydrogenolysis was accompanied by reduction of the nitrile and alkene groups, respectively. However, by adopting catalytic transfer hydrogenation conditions[8] (Pd^0, cyclohexadiene, EtOH), BOB ester **17** could be debenzylated without affecting the cyano group. Base-catalyzed lactonization proceeded smoothly to give **8** in good yield. In similar fashion, ester **20** was cleanly debenzylated without reduction of the heterocyclic ring. Although the acidity of the imide N–H on the uracil ring necessitated the use of 1.1 equiv. KOBu^t, unprotected nucleoside **11** was obtained in 84% yield.

Besides representing a practical implementation of the synthetic approach to keruffarides and crasserides outlined earlier, the BOB group now provides a convenient method for deprotecting an ester using a relatively non-nucleophilic base, through the agency of hydrogenolysis. In addition, BOB esters may prove useful in designing new traceless linkers for solid-phase chemistry.

Representative deprotection procedure: A solution of **16** (66 mg, 0.2 mmol) in THF (2 mL) was added to 10% Pd/C (33 mg) and stirred for 24 h under 1 atm of H_2 in a balloon. After filtering the catalyst, the THF solution was dried (Na_2SO_4) and concentrated. The residue was dissolved

in dry THF (1 mL) and treated with KOBu^t (1.0 M THF solution, 20 μL). After 10 min, the reaction mixture was acidified with glacial acetic acid (40 μL), diluted with EtOAc (2 mL) and washed with aqueous $NaHCO_3$. After drying and concentrating, the residue was chromatographed (SiO_2, 4:1 hexanes:EtOAc) to afford 1-adamantanol **7** (28 mg, 93%).

Acknowledgements

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6. For **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.16 (m, 10H), 4.47 (s, 2H), 4.27 (t, 2H, $J=7$ Hz), 3.47 (t, 2H $J=7$ Hz), 2.91 (t, 2H, $J=7$ Hz), 2.41 (t, 2H, $J=7$ Hz), 1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.7, 129.2, 128.7, 128.6, 128.5, 127.9, 127.8, 126.8, 73.1, 69.4, 65.1, 35.4, 31.4, 25.3; IR (λ_{max} film) 2870, 1735 cm^{-1}; FIMS m/z 298 (M$^+$, 100%). For **17**: ^{1}H NMR 7.34–7.25 (m, 5H), 4.87 (m, 1H), 4.49 (s, 2H), 3.51 (t, 2H, $J=6$ Hz), 2.62 (m, 1H), 2.47 (t, 2H, $J=6$ Hz), 2.16–1.90 (m, 4H), 1.80–1.20 (m, 6H); ^{13}C NMR 173.4, 139.4, 129.4, 128.8, 128.7, 121.0, 74.0, 72.3, 70.1, 34.7, 32.3, 31.3, 28.9, 26.2, 24.6, 23.8; IR 2940, 2240, 1745 cm^{-1}; FIMS m/z 301 (M$^+$, 100%). For **21**: ^{1}H NMR 7.37–7.29 (m, 5H), 5.33 (br. d, 1H), 4.54 (m, 1H), 4.48 (s, 2H), 4.45–4.27 (m, 2H), 3.73 (s, 3H), 3.47 (t, 2H, $J=6$ Hz), 2.42 (t, 2H, $J=6$ Hz), 1.90 (m, 2H), 1.43 (s, 9H); ^{13}C NMR 174.0, 171.4, 156.2, 139.3, 129.4, 128.7, 81.3, 74.0, 70.1, 65.2, 53.9, 53.8, 32.0, 29.3, 26.0; IR 3365, 1746, 1715 cm^{-1}; EIMS m/z 396 (M+1, 15%), 42 (100%).
7. For **18**: ^{1}H NMR 7.36–7.25 (m, 5H), 4.55 (m, 1H), 4.48 (s, 2H), 3.51 (m, 3H), 2.80 (br. s, 1H), 2.45 (m, 2H), 1.99 (m, 4H), 1.67 (m, 2H), 1.26 (m, 4H); ^{13}C NMR 173.9, 138.4, 128.6, 128.0, 127.9, 78.3, 73.2, 72.8, 69.5, 33.1, 32.2, 30.2, 25.5, 24.2, 24.0; IR 3450, 1725 cm^{-1}; ESI-MS m/z 293 (M+1, 20%), 41 (100%).
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