Enantio- and Diastereoselective Syntheses of Orthogonally Protected *anti*-2-Amino-1,3,4-butanetriols from an Achiral β-Ketoester

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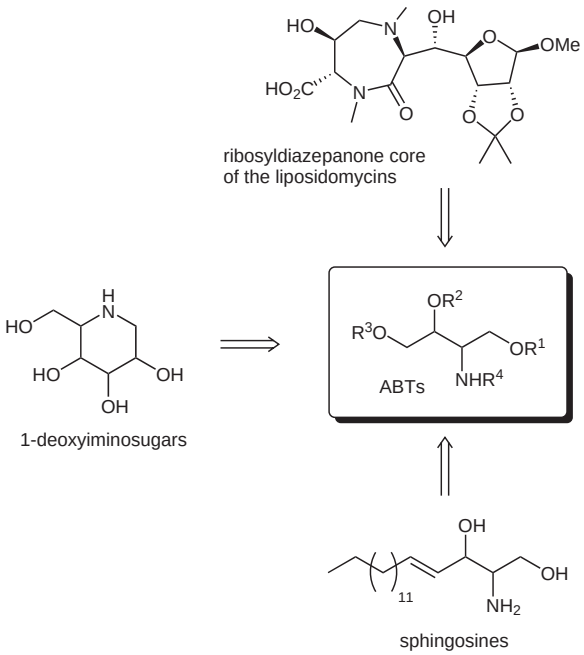
Received 15 April 2005

Abstract: An efficient enantio- and diastereoselective synthesis of orthogonally protected *anti*-2-amino-1,3,4-butanetriols from an achiral source is described. The *anti* relationship between the two adjacent aminated and hydroxylated carbons was controlled by sequential hydrogenation of a β-ketoester in the presence of a chiral ruthenium catalyst and electrophilic amination of the resulting β-hydroxyester.

Key words: aminobutanetriols, asymmetric synthesis, chiral ruthenium catalyst, electrophilic amination, orthogonal protecting groups

Enantiomerically pure 2-amino-1,3,4-butanetriols (ABTs) are highly functionalized compounds that are interesting key intermediates for the production of natural products. ABTs and ABT equivalents have been used in protected and unprotected forms for the production of biologically important compounds including sphingosines,[1] the ribosyldiazepanone core of liposidomycins[2] and glycomimetics[3] (Scheme 1).



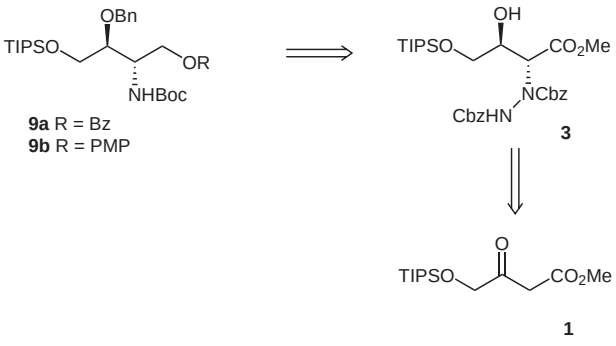
Scheme 1

SYNLETT 2005, No. 13, pp 2086–2088
Advanced online publication: 12.07.2005
DOI: 10.1055/s-2005-871954; Art ID: D10205ST

In recent years, several approaches to the synthesis of *anti*-ABTs have been developed. Most of these syntheses started from naturally occurring compounds already possessing one or two of the stereogenic centers.[1a,2a,4] To our knowledge, only a few syntheses of *anti*-ABTs using achiral sources as precursors have been described in the literature. The first relied on the asymmetric Sharpless epoxidation reaction of allylic alcohols followed by ring-opening reactions of the resulting 2,3-epoxyalcohols by nucleophilic nitrogen equivalents.[5] The second involved catalyzed hydration of chlorofumaric acid to L-*threo*-chloromalic acid by a fumarase before introducing the nitrogen atom by intramolecular nucleophilic substitution.[6] The third installed the *syn*-vicinal amino alcohol functionality by the regioselective aminohydroxylation of *trans*-ethyl 4-(4-methoxyphenoxy)crotonate before inverting the C2 hydroxy group stereochemistry.[7] In order to make possible regioselective transformations to targeted molecules, the protecting groups used should be orthogonal with one another.

In connection with our work on the asymmetric synthesis of α-amino-β-hydroxy acids,[8] we proposed a diastereoselective synthesis of orthogonally protected *anti*-2-amino-1,3,4-butanetriols **9a** and **9b** starting from a prochiral material. These compounds were derived from the α-hydrazino-β-hydroxyester **3** obtained with excellent *anti* stereoselectivity at C2-C3 from the corresponding β-ketoester **1** by catalytic hydrogenation followed by electrophilic amination of the resulting β-hydroxyester (Scheme 2).

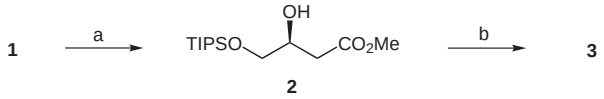
Catalytic hydrogenation of **1** conducted in methanol at 40 °C under a pressure of 10 bar of hydrogen in the presence of 2 mol% of (*R*)-BinapRuBr$_2$ afforded the β-hy-



Scheme 2 Retrosynthetic analysis.

droxyester **2** in quantitative yield. The hydrogenation was totally enantioselective as confirmed by europium NMR studies. Noyori described the catalyzed hydrogenation of ethyl 4-(triisopropyloxy)-3-oxopentanoate in the presence of previously isolated (*S*)-BinapRuBr$_2$ in similar yield and enantioselectivity.[9]

The use of 2 mol% (*S*)-BinapRuBr$_2$ yielded only the *R*-enantiomer of **2**. In our case, each catalyst was prepared in situ from commercially available Ru(Cod)(2-methylallyl)$_2$.[10]



Scheme 3 *Reagents and conditions*: (a) H_2 (10 bar), (*R*)-Binap $RuBr_2$ (2 mol%), MeOH, 40 °C, 16 h (quantitative yield, ee > 95%); (b) 1. MeZnBr (1.1 equiv) THF, 1 h, 0 °C; 2. LDA (2.2 equiv), THF, 1 h, –78 °C; 3. CbzN=NCbz (2 equiv), THF, 1.5 h, –78 °C; 4. sat. aq NH_4Cl (52%, de = 95%).

The electrophilic amination of the zinc enolate of **2** was performed at –78 °C with dibenzyl azodicarboxylate to produce the *anti* diastereoisomer **3** in 52% yield and 95% diastereomeric excess. Starting material **2** was recovered in 34% yield (Scheme 3). Our result is in contrast with that of Guanti who showed that the electrophilic amination of the lithium enolate of methyl 4-(*tert*-butyldiphenylsilyloxy)-3-oxopentanoate with di-*tert*-butylazodicarboxylate led to only a moderate selectivity of 2:1 favoring the *anti* diastereoisomer even at low temperature.[11]

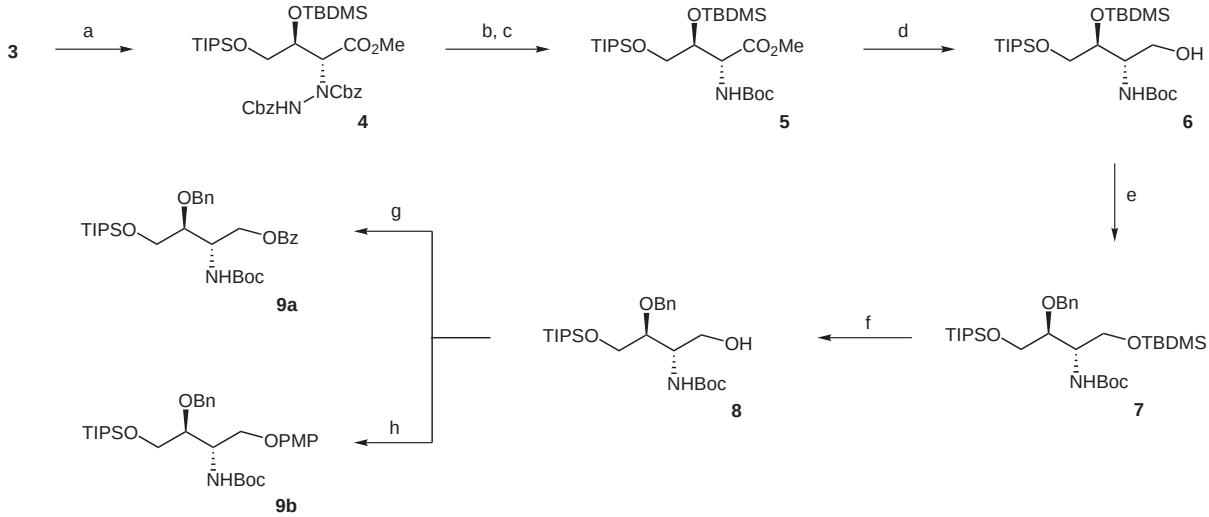
The resulting α-hydrazino-β-hydroxyester **3** was protected as a *tert*-butyldimethylsilyl ether in 93% yield. One-pot hydrogenolysis of the benzylcarbamates of **4** was accomplished and gave the resulting α-amino ester in 75% yield. The hydrazine was first deprotected using Pd/C as catalyst and the N–N bond was then cleaved by addition of Raney-Ni to the reaction mixture. Protection of the amine by the *tert*-butoxycarbonyl group afforded **5** in 93% yield. The ester function of **5** was reduced with calcium borohydride at –20 °C to room temperature and the primary alcohol **6** was obtained in 99% yield.

To obtain an orthogonally protected triol, we envisaged the introduction of a benzyl ether on the free alcohol group of **6**. Treatment of **6** with sodium hydride and benzyl bromide in DMF resulted in the migration of the *tert*-butyldimethylsilyl group to the primary alcohol and subsequent benzylation of the secondary alcohol in 80% yield. Proton NMR of the crude product showed that a small amount of **6** was benzylated on the primary alcohol. Regioselective cleavage of the *tert*-butyldimethylsilyl ether of **7** using 0.1 equivalent of PPTS in THF–EtOH afforded **8** in 86% yield.[12]

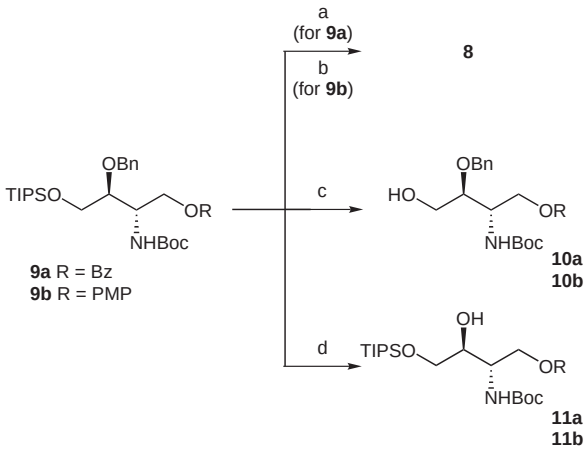
Benzoylation of **8** gave orthogonally protected ABT **9a** in 98% yield. Treatment of **8** with *para*-methoxyphenyl alcohol under Mitsunobu conditions[13] successfully furnished the desired orthogonally protected ABT **9b** in 70% yield (Scheme 4).

Finally, the orthogonality of the protection strategy employed in the synthesis was confirmed by regioselective unmasking of each O-protecting group. As expected the benzoyl, PMP, TIPS, and benzyl groups could be selectively removed by PhLi or NaOH, CAN, TBAF, and H_2 in presence of Pd/C, respectively, as shown in Scheme 5.

This synthetic route provides an efficient and general method for obtaining orthogonally protected *anti*-ABTs by coupling two sequential reactions: catalytic hydrogenation and electrophilic amination. The same key steps could be applied to prepare the enantiomers of **9a** and **9b**[14] from the same prochiral β-keto ester. The *anti*-ABTs synthesized in this work are valuable building blocks for the preparation of other types of natural products.



Scheme 4 *Reagents and conditions*: (a) TBDMSOTf (1.5 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, 2 h, –78 °C (93%); (b) 1. H_2 (1 atm), Pd/C, MeOH, 1 h; 2. H_2 (1 atm), Raney-Ni, MeOH, 1 h (75%); (c) Boc_2O (1.1 equiv), EtOAc, 2 h (93%); (d) $Ca(BH_4)_2$ (6 equiv), THF–EtOH 1:1.2, –20 °C (15 min) to r.t., 1 h (99%); (e) NaH (1.3 equiv), BnBr (2 equiv), DMF, 0 °C to r.t., 12 h (80%); (f) PPTS (0.1 equiv), THF–EtOH 2:1, 5 d (86%); (g) BzCl (1.3 equiv), pyridine, r.t., 12 h (98%); (h) PPh_3 (1.3 equiv), DEAD (1.3 equiv), PMPOH (3 equiv), THF, 80 °C, 4 h (70%).



Scheme 5 *Reagents and conditions*: (a) PhLi (9 equiv), THF, –78 °C (87%), or 1% NaOH–MeOH, r.t., 40 min, quantitative yield; (b) CAN, MeCN–H_2O 4:1, 10 min, 0 °C (94%); (c) TBAF (1.5 equiv), THF, 0 °C, 30 min (92% of **10a**; 91% of **10b**); (d) H_2 (1 atm), Pd/C, MeOH, r.t., 1 h, (95% of **11a**; 97% of **11b**).

Acknowledgment

Funding for this work was provided by the Ministère de la Recherche through a grant to Y.B.

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(14) **Characterization of Selected New Compounds:** Compound **8**: $[\alpha]_D^{25}$ –13 (*c* 0.52, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 5 H), 5.43 (d, 1 H, *J* = 6.4 Hz), 4.75 (d, 1 H, *J* = 11.7 Hz), 4.62 (d, 1 H, *J* = 11.7 Hz), 3.92–3.80 (m, 4 H), 3.71–3.63 (m, 2 H), 2.40 (s, 1 H), 1.43 (s, 9 H), 1.08, 1.07 (2 s, 21 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.1, 138.0, 128.5, 127.9, 127.8, 80.3, 79.4, 72.9, 64.2, 63.1, 52.9, 28.3, 18.0, 11.8. Anal. Calcd for $C_{25}H_{45}NO_5Si$: C, 64.20; H, 9.70; N, 2.99. Found: C, 64.43; H, 9.78; N, 2.85. Compound **9a**: $[\alpha]_D^{25}$ –12 (*c* 0.81, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (m, 2 H), 7.61–7.52 (m, 1 H), 7.44–7.41 (m, 2 H), 7.34–7.28 (m, 5 H), 5.24 (d, 1 H, *J* = 9.1 Hz), 4.78 (d, 1 H, *J* = 11.8 Hz), 4.62 (d, 1 H, *J* = 11.8 Hz), 4.49–4.37 (m, 2 H), 4.34–4.21 (m, 1 H), 3.95 (m, 2 H), 3.72–3.66 (m, 1 H), 1.40 (s, 9 H), 1.09, 1.08 (2 s, 21 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 155.5, 138.2, 133.5, 132.9, 130.1, 129.7, 128.4, 128.3, 127.9, 127.7, 79.3, 78.9, 72.8, 64.5, 64.2, 50.7, 28.3, 18.0, 11.8. Anal. Calcd for $C_{32}H_{49}NO_6Si$: C, 67.21; H, 8.64; N, 2.45. Found: C, 67.41; H, 8.89; N, 2.41. Compound **9b**: $[\alpha]_D^{25}$ –1.2 (*c* 0.50, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (s, 5 H), 6.83 (s, 4 H), 5.34 (d, 1 H, *J* = 8.1 Hz), 4.78 (d, 1 H, *J* = 11.4 Hz), 4.71 (d, 1 H, *J* = 11.4 Hz), 4.18 (dd, 1 H, *J* = 9.2, 3.5 Hz), 4.15–4.04 (m, 1 H), 4.00–3.91 (m, 3 H), 3.78 (s, 3 H), 3.76–3.71 (m, 1 H), 1.43 (s, 9 H), 1.10, 1.08 (2 s, 21 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 154.0, 152.8, 138.5, 128.3, 127.9, 127.5, 115.5, 114.7, 79.3, 78.9, 73.1, 67.5, 65.2, 55.8, 51.0, 28.4, 18.0, 11.9. Anal. Calcd for $C_{32}H_{51}NO_6Si$: C, 66.98; H, 8.96; N, 2.44. Found: C, 66.91; H, 8.84; N, 2.39.