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Efficient synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-2-amino-1,3,4-butanetriols through stereodivergent hydroxymethylation of D-glyceraldehyde nitrones

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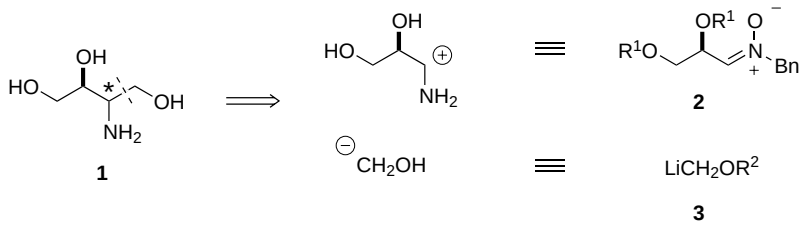
Abstract—The nucleophilic addition of two alkoxymethyllithium derivatives to three D-glyceraldehyde derived nitrones has been investigated. The diastereofacial selectivity of the reaction could be controlled by the appropriate use of Lewis acids as precomplexing agents of the nitrones. The obtained *syn* and *anti* adducts were further converted into C-4 building blocks and β-hydroxy-α-aminoacids. © 2002 Elsevier Science Ltd. All rights reserved.

Optically active 2-amino-1,3,4-butanetriols (ABTs) **1** find application as C-4 building blocks for the synthesis of a variety of biologically interesting compounds, as Inaba and co-workers have recently pointed out.[1] Several studies have been aimed at preparing differentially protected ABTs in chiral non-racemic forms.[1,2] However, to the best of our knowledge, no approaches have addressed the stereodivergent synthesis of *syn* and *anti* compounds.

Recent work from our laboratory has demonstrated the utility of Lewis acid controlled nucleophilic addition to nitrones for the stereocontrolled formation of nitrogenated compounds.[3] In continuation of these studies, we envisaged that addition of a hydroxymethylanion to D-glyceraldehyde derived nitrones **2** will provide a direct route to compounds **1** (Scheme 1). As suitable synthetic equivalents of the hydroxymethylanion we chose (methoxymethoxy)methyllithium **3a** and (benzyloxy)methyllithium **3b**, easily available from the corresponding alkoxymethyl tributylstannanes.[4]

Nitrones **2** were prepared by condensation of the corresponding protected D-glyceraldehyde with *N*-benzylhydroxylamine, following our previously described procedure for nitrone **2a**.[5] This nitrone was chosen as the reference substrate for our investigation. The following standard reaction conditions were employed to screen the efficiency of the Lewis acids as stereocontrolling agents: in situ formation of an excess (2.5 equiv.) of the alkoxymethyllithium derivative at low temperature (−80°C), following the reported procedures,[4] and addition of a THF solution of nitrone (1.0 equiv.), in the presence or absence of additives. The reaction mixture was maintained at −80°C for 15 min and then stopped by adding saturated aqueous ammonium chloride. After extractive work-up the hydroxylamines **4**–**9** (Scheme 2) were obtained. The results from these experiments are given in Table 1.



Scheme 1.

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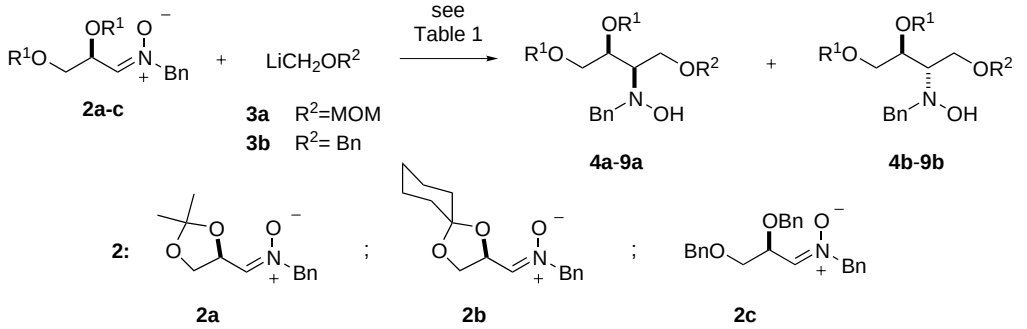


Scheme 2.

Table 1. Diastereoselective addition of α-alkoxymethyllithium derivatives **3** to nitrones **2**[a]

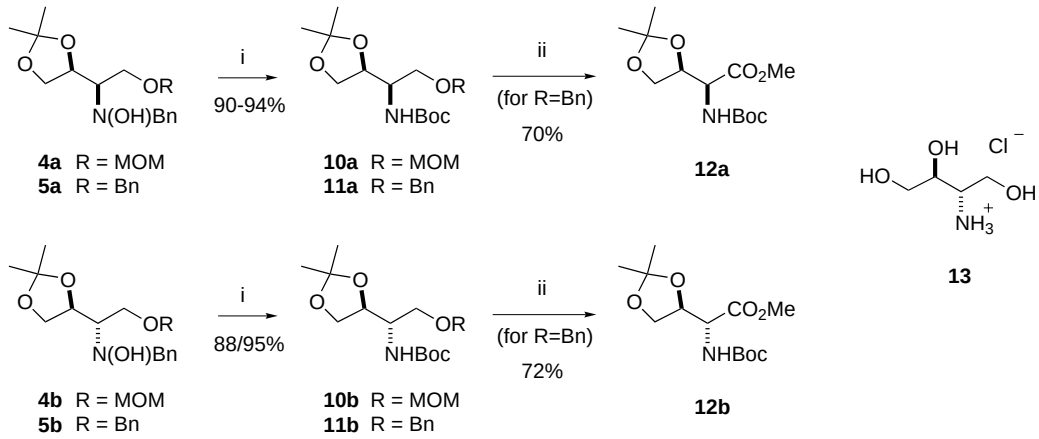
Entry	Nitrone	α-Alkoxy methyllithium	Additive[b]	Hydroxylamine[c]	*Syn*:*anti*[d]	Yield %[e]
1	**2a**	**3a**	None	**4**	90:10	72
2	**2a**	**3a**	TMSOTf	**4**	88:12	58
3	**2a**	**3a**	$ZnBr_2$	**4**	80:20	77
4	**2a**	**3a**	Et_2AlCl	**4**	5:95	80
5	**2a**	**3b**	None	**5**	86:14	70
6	**2a**	**3b**	TMSOTf	**5**	88:11	61
7	**2a**	**3b**	$ZnBr_2$	**5**	80:20	75
8	**2a**	**3b**	Et_2AlCl	**5**	5:95	81
9	**2b**	**3a**	None	**6**	90:10	64
10	**2b**	**3a**	Et_2AlCl	**6**	30:70	73
11	**2b**	**3b**	None	**7**	85:15	66
12	**2b**	**3b**	Et_2AlCl	**7**	32:68	70
13	**2c**	**3a**	None	**8**	58:42	64
14	**2c**	**3a**	Et_2AlCl	**8**	45:55	72
15	**2c**	**3b**	None	**9**	60:40	65
16	**2c**	**3b**	Et_2AlCl	**9**	45:55	70

[a] All reactions were carried out at –80°C using an excess (2.5 equiv.) of **3**.
[b] The nitrone was previously treated with the additive (1.0 equiv.) at ambient temperature for 5 min.
[c] **a** and **b** series refer to *syn* and *anti* compounds, respectively.
[d] Determined by NMR analysis of the crude reaction mixture.
[e] Isolated yields of diastereomeric mixtures after radial-centrifugally accelerated chromatography.

Addition of α-alkoxymethyllithium **3a** to nitrone **2a** resulted in an acceptable degree of *syn* selectivity (entry 1) which was slightly decreased when the nitrone was previously treated with either TMSOTf (entry 2) or $ZnBr_2$ (entry 3). A complete reversal of diastereoselectivity was achieved precomplexing the nitrone with Et_2AlCl (entry 4). The same behavior was observed for the organolithium **3b** (entries 5–8), thus revealing that the sense of the diastereofacial selectivity is strictly dependent on the nature of the precomplexing agent (and on its presence). In fact, similar results were obtained with nitrone **2b** (entries 9–12), although a remarkable decrease of the *anti* isomer was observed in the reaction carried out in the presence of Et_2AlCl. In contrast, nitrone **2c** displayed unsatisfactory diastereoselectivities (entries 13–16). The relative configuration assignement of the obtained hydroxylamines was carried out with pure compounds,[6] with the only exception of hydroxylamines **8** and **9**, which were not separated, due to the poor selectivity observed. Thus, configuration of hydroxylamines **4** and **5** was established by chemical correlation as discussed below. Hydroxylamines **6** and **7** were converted into **4** and **5**, respectively, by transketalization.[7] The experimental findings listed in Table 1 are in good agreement with previous data reported by us[5] and by others,[8] which showed that a reversal of stereoselectivity occurred when Et_2AlCl was used as a precomplexing agent in nucleophilic additions to D-glyceraldehyde nitrones.

With respect to their synthetic utility, *syn* and *anti* hydroxylamines **4** and **5** may be considered immediate precursors of *syn* and *anti* ABTs **1**. Catalytic hydrogenation, in the presence of Boc_2O, of **4a**,**b** and **5a**,**b** gave the orthogonally protected ABTs **10a**,**b** and **11a**,**b**, respectively (Scheme 3).[9]

In order to prove the configuration of the hydroxylamines and to illustrate further useful transformations, compounds **11** were debenzylated and in situ oxidized with ruthenium(IV) oxide to afford, after esterification, methyl esters **12** which had been previously prepared.[10] The overall yields for compounds **12a** and **12b**, from the nitrone **2a**, were 39.5 and 41%, respectively. The stereochemistry of compounds **10** was confirmed by the



Scheme 3. *Reagents and conditions*: (i) H_2, $Pd(OH)_2$-C, MeOH, Boc_2O, rt, 1500 psi, 24 h; (ii) (1) Na, NH_3(l); (2) RuO_2, $NaIO_4$, CH_3CN:CCl_4:H_2O, then CH_2N_2, Et_2O.

complete deprotection (10% HCl–MeOH, 10°C, 6 h) of **10b** into the hydrochloride **13**. This compound showed the same physical and spectroscopic properties (except for the sign of the optical rotation) that those described for its enantiomer,[11] thus also confirming the assigned stereochemistry to hydroxylamines **4**.

The present method provides a convenient asymmetric synthesis of either diastereoisomer of differentially protected ABTs desired by choosing the appropriate Lewis acid. Throughout this study, we also showed that ABTs are also an effective entry to β-hydroxy-α-aminoacids. Applications of this methodology for the synthesis of biologically interesting nitrogenated compounds are under investigation.

Acknowledgements

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References

1. For a complete list of references concerning preparation and synthetic applications of ABTs see: Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem.* **2000**, *65*, 1623–1628 and references cited therein. During the preparation of this manuscript Kwon and Ko reported the stereoselective preparation of (2*S*,3*S*)-2-amino-1,3,4-butanetriol, see: Kwon, S. J.; Ko, S. Y. *J. Org. Chem.* **2001**, *66*, 6833–6835.
2. (a) Delle Monache, G.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2961–2973; (b) Fadnavis, N. W.; Sharfuddin, M.; Vadivel, S. K. *Tetrahedron: Asymmetry* **2001**, *11*, 691–693.
3. For an account, see: Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454.
4. R^2 = MOM: (a) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. *Org. Synth.* **1992**, *71*, 133–139; (b) Johnson, C. R.; Medich, J. R.; Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K. *Org. Synth.* **1992**, *71*, 140–145. R^2 = Bn: Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1486.
5. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489–3496.
6. Selected data (solvent for optical rotations: $CHCl_3$) for **4a**: $[\alpha]_D^{20}$ = +6 (*c* 0.40); **4b**: $[\alpha]_D^{20}$ = −24 (*c* 0.31); **5a**: $[\alpha]_D^{20}$ = +2 (*c* 0.33); **5b**: $[\alpha]_D^{20}$ = −8 (*c* 0.29); **6a**: $[\alpha]_D^{20}$ = −14 (*c* 0.76); **6b**: $[\alpha]_D^{20}$ = −16 (*c* 0.52); **7a**: $[\alpha]_D^{20}$ = −7 (*c* 0.34); **7b**: $[\alpha]_D^{20}$ = −4 (*c* 0.20).
7. Treatment of acetone solutions of hydroxylamines **6** and **7** with catalytic amounts of *p*-toluensulfonic acid afforded, after 8 h, the corresponding hydroxylamines **4** and **5**, in ca. 80% yield.
8. (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632–634; (b) Fiumana, A.; Lombardo, M.; Trombini, C. *Tetrahedron* **1997**, *53*, 11721–11730.
9. Data for **10a**: $[\alpha]_D^{20}$ = +7 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 328 K) δ 1.32 (s, 3H), 1.41 (s, 3H), 1.43 (s, 9H), 3.34 (s, 3H), 3.54 (dd, 1H, *J* = 7.3, 9.8 Hz), 3.58 (dd, 1H, *J* = 5.4, 9.8 Hz), 3.72 (dd, 1H, *J* = 6.8, 8.0 Hz), 3.81 (m, 1H), 4.00 (dd, 1H, *J* = 6.5, 8.0 Hz), 4.32 (dt, 1H, *J* = 2.4, 6.5 Hz), 4.60 (s, 2H), 4.74 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, 328 K) δ 25.0, 26.3, 28.3, 50.3, 55.3, 66.1, 67.5, 74.1, 79.7, 96.5, 109.4, 154.8. Compound **10b**: $[\alpha]_D^{20}$ = +3 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 328 K) δ 1.30 (s, 3H), 1.37 (s, 3H), 1.41 (s, 9H), 3.33 (s, 3H), 3.58 (m, 1H), 3.76 (m, 2H), 3.88 (dd, 1H, *J* = 6.4, 8.5 Hz), 3.99 (dd, 1H, *J* = 5.3, 8.5 Hz), 4.08 (dt, 1H, *J* = 5.9, 7.3 Hz), 4.58 (s, 2H), 4.82 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, 328 K) δ 25.4, 26.6, 28.3, 52.9, 55.2, 67.1 (2C), 75.4, 79.5, 96.8, 109.3, 155.5. Compound **11a**: $[\alpha]_D^{20}$ = +2 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 328 K) δ 1.33 (s, 3H), 1.40 (s, 3H), 1.42 (s, 9H), 3.49 (t, 1H, *J* = 9.1 Hz), 3.54 (dd, 1H, *J* = 5.9, 9.3 Hz), 3.72 (dd, 1H, *J* = 7.3, 8.1 Hz), 3.88 (m, 1H), 3.99 (dd, 1H, *J* = 6.4, 8.1 Hz), 4.36 (dt, 1H, *J* = 2.4, 6.8 Hz), 4.50 (d, 1H, *J* = 11.7 Hz), 4.54 (d, 1H, *J* = 11.7 Hz), 4.80 (bd, 1H, *J* = 8.8 Hz), 7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, 328 K) δ 25.0, 26.3, 28.3, 50.3, 66.2, 70.0, 73.1, 74.2, 79.6,

109.2, 127.5, 127.6, 128.4, 138.0, 155.9. Compound **11b**: $[\alpha]_D^{20}=+7$ (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, 328 K) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.42 (s, 9H), 3.55 (dd, 1H, $J=3.4$, 9.3 Hz), 3.73 (dd, 1H, $J=2.9$, 9.3 Hz), 3.80 (m, 1H), 3.90 (dd, 1H, $J=5.9$, 8.8 Hz), 4.00 (dd, 1H, $J=6.4$, 8.8 Hz), 4.14 (dt, 1H, $J=5.9$, 7.3 Hz), 4.49 (d, 1H, $J=11.7$ Hz), 4.52 (d, 1H, $J=11.7$ Hz), 4.94 (bd, 1H, $J=8.3$ Hz), 7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, 328 K) δ 25.6, 26.8, 28.4, 52.6, 67.1, 69.5, 73.4, 75.5, 79.7, 109.4, 127.7, 127.8, 128.5, 138.2, 155.7.

10. Selected data (solvent for optical rotations: $CHCl_3$) for **12a**: $[\alpha]_D^{20}=-64$ (*c* 0.50); **12b**: $[\alpha]_D^{20}=-34$ (*c* 0.22). For a previous preparation and full data of **12a** and **12b** see Ref. 5. Compound **12b** had been previously described: Kirschbaum, B.; Stahl, U.; Jager, V. *Bull. Soc. Chim. Belg*. **1994**, *103*, 425–432.
11. Selected data for **13**: $[\alpha]_D^{20}=-15$ (*c* 0.32, MeOH); lit. for the enantiomer:[12] $[\alpha]_D^{20}=+14$ (*c* 0.32, MeOH).
12. Dequeker, E.; Compernolle, F.; Toppet, S.; Hoornaert, G. *Tetrahedron* **1995**, *51*, 5877–5890.