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Highly stereoselective oxy-Michael additions to α,β-disubstituted nitro olefins: asymmetric synthesis of pseudo-norephedrine derivatives and THP* protected α-hydroxy ketones†

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Received 5th May 2004, Accepted 30th July 2004
First published as an Advance Article on the web 22nd September 2004

The "naked" anion of (*S*)-6-methyl delta lactol undergoes efficient oxy-Michael addition to α,β-disubstituted nitro olefins to give the THP* protected Henry products with excellent (95→98% de) stereocontrol at the β-position and moderate (up to 3 : 1) stereocontrol at the α-position in favour of the *syn*-diastereoisomer. Nitro group reduction with *in situ N*-Boc protection and THP* removal provides α,β-disubstituted ethanolamine derivatives, while treatment with tetrapropylammonium perruthenate gives THP* protected α-hydroxy ketone derivatives in high diasteromeric excess.

Introduction

The stereoselective oxy-Michael addition to nitro olefin acceptors provides a direct route to *O*-protected Henry products.[1–3] When the chiral water equivalent is readily available in both enantiomeric forms, it imparts high levels of stereocontrol on addition, and becomes a desirable protecting group, this approach can be considered as complementary in many respects to the enantioselective nitro aldol reaction.[4]

We have recently reported the highly diastereoselective oxy-Michael addition of the "naked" anion of (*S*)-6-methyl delta lactol to β-substituted nitro olefins. This work provided the basis of an efficient method for the synthesis of enantiomerically enriched amino alcohol products after nitro group reduction and removal of the THP* ether protecting group.

Encouraged by these results we were keen to investigate whether the high levels of control and reaction efficiency could be maintained in additions to α-substituted nitro olefin acceptors as the products of these reactions would have considerable utility in synthesis. Here we wish to report our findings on the addition of the naked lactol anion to α,β-disubstituted nitro olefins and the application of these additions to the synthesis of α,β-disubstituted ethanolamine derivatives[5] and to protected α-hydroxy ketones *via* Nef-type oxidation.

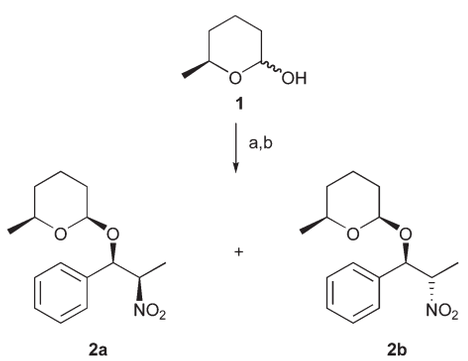
Results and discussion

Preliminary studies using the "naked" alkoxide of (*S*)-6-methyl delta lactol **1** [formed by deprotonation with KHMDS (1.0 eq) and subsequent addition of 18-crown-6 (1.0 eq)] were performed on *E*-β-methyl-β-nitro styrene[6] at −78 °C in THF to ascertain reactivity and diastereocontrol at the three newly formed stereocentres on quenching with a range of proton sources. The screened acids included, acetic acid, trichloroacetic acid, trifluoroacetic acid, methanol, 2,4-dinitrophenol and ammonium chloride and were added neat *via* syringe or as solutions in THF or water as appropriate. In all cases *only two*, of the possible eight diastereomeric products were observed in the reaction mixtures post aqueous work-up. In all-but-one case, **2a** and **2b** were formed in ~1 : 1 ratio. The optimal conditions used neat acetic acid (2.0 eq) injected directly into the −78 °C reaction mixture and gave rise to **2a** and **2b** in the ratio of 3 : 1, respectively (Scheme 1, Table 1). These two products, **2a** and **2b**, epimeric at the α-centre were consistent with the lactol anion reacting predominantly *cis* across the (*S*)-6-methyl tetrahydropyranyl (THP*) ring and to the *Re*-face of the nitro olefin acceptor in agreement with our previous work.[2] Unambiguous proof of the relative *syn*-stereochemistry of **2a** was established by single crystal X-ray diffraction.‡

Table 1 Dependence of alpha stereocontrol on nature of the acid quench

Entry	HA	**2a** : **2b**[a]
1	MeOH	1 : 1.4
2	NH_4Cl	1.2 : 1
3	2,4-dinitrophenol	1 : 1
4	CF_3COOH	1.1 : 1
5	CCl_3COOH	1 : 1.2
6	CH_3COOH	3.0 : 1

[a] Measured by analysis of the 400 or 600 MHz ^{1}H nmr spectra of the crude reaction product.



Scheme 1 Reagents and conditions: (a) KHMDS (1.0 eq), THF, −78 °C then 18-crown-6 (1.0 eq) then (*E*)-PhCHC(Me)NO_2 (0.67 eq), 1 h. (b) HA, −78 °C.

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all new compounds. See http://www.rsc.org/suppdata/ob/b4/b406804c/

‡ Crystal data for **2a**. $C_{15}H_{21}N_1O_4$, M = 279.33, monoclinic, *a* = 19.5297(6), *b* = 5.7494(2), *c* = 13.7124(6) Å, *U* = 1485.65(9) Å^3, *T* = 180(2) K, space group *C*2, *Z* = 4, μ(Mo–Ka) = 0.090 mm^{-1}, 3197 reflections measured. The final *R*1(*F*^{2}) was 0.0708 (all data). The Flack parameter was 0.9(12); Crystal data for **5a**. $C_{14}H_{21}N_1O_4S_1$, *M* = 299.38, monoclinic, *a* = 21.0458(9), *b* = 5.9725(2), *c* = 13.3797(7) Å, *U* = 1578.12(12) Å^3, *T* = 180(2) K, space group *C*2, *Z* = 4, μ(Mo–Ka) = 0.217 mm^{-1}, 3195 reflections measured. The final *R*1(*F*^{2}) was 0.0836 (all data). The Flack parameter was 0.06(13). CCDC reference numbers 238145 for **5a** and 238146 for **2a**. See http://www.rsc.org/suppdata/ob/b4/b406804c/ for crystallographic data in .CIF or other electronic format.

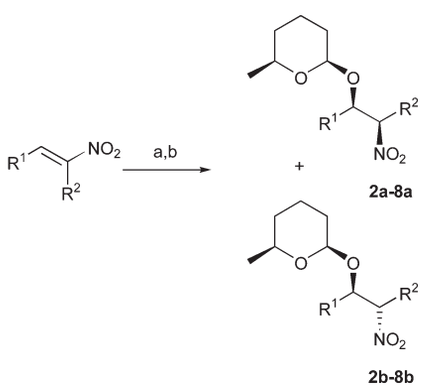
DOI: 10.1039/b406804c

Table 2 Yields and selectivities for the addition of the "naked" lactol alkoxide to α,β-unsaturated nitro olefins

Entry	R^1, R^2	de (β)[a]	dr (α)[a]	Adduct	Yield[b]
1	 , Me	>98%	3.0 : 1	**2**	99%
2	 , Me	>98%	2.8 : 1	**3**	89%
3	 , Me	96%	2.0 : 1	**4**	66%
4	 , Et	>98%	2.8 : 1	**5**	84%
5	 , Et	97%	2.6 : 1	**6**	78%
6	 , Et	96%	2.3 : 1	**7**	89%
7	 , Et	95%	1 : 1	**8**	78%

[a] Measured by analysis of the 400, 500 or 600 MHz ^{1}H nmr spectra of the crude reaction product. [b] Reaction yield after purification.

The optimal conditions were applied to a range of α,β-disubstituted nitro olefins and the results are presented in Scheme 2, Table 2. The diastereoselectivity at the β-centre was uniformly good to excellent for branched alkyl, aryl and heteroaryl groups with the best control arising in the aryl and heteroaryl cases [95→98% de (β)]. The selectivity at the α-centre ranged from absent in one case (entry 7, dr (α) = 1 : 1) to moderate (entries 1–6, dr (α) = 2.0–3.1 : 1) in favour of the *syn*-diastereoisomer.§ The reaction yields were uniformly good to excellent.¶



Scheme 2 Reagents and conditions: (a) **1**, KHMDS (1.0 eq), THF, −78 °C, then 18-crown-6 (1.0 eq) then (*E*)-nitro olefin (0.67 eq), 1 h. (b) AcOH (2 eq), −78 °C.

Single crystal X-ray diffraction allowed unambiguous determination of the stereochemistry of product **5a**.‡ Taken with the known stereochemistry of **2a** and through analysis of the ^{1}H nmr spectra of both relative to their minor *anti*-diastereoisomeric products, it was possible by comparison to assign the stereochemistry of all the products in Table 2 (Fig. 1).

Subjection of single diastereoisomers **2a**, **5a** and **5b** to simulated post-quench end-of-reaction conditions followed by the usual reaction work up resulted in little (<5%) or no epimerisation at the α-centre, indicating the observed α-selectivity is a result of kinetic control.

§ In related work, a predominance for the *anti*-diastereoisomers was noted when *O*-benzyl protected Henry products were treated with potassium *tert*-butoxide in THF at −78 °C followed by quenching with AcOH; see ref. 5.

¶ Interestingly, in the cases of adducts **2** and **3** *only*, purification by filtration through silica gel and evaporation facilitated a dynamic epimerisation—crystallisation process resulting in the isolation of **2a** and **3a** as essentially single diastereoisomeric products in high yield.

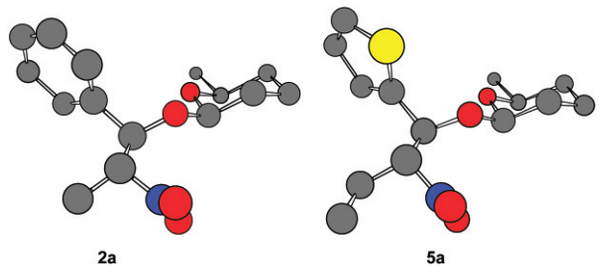
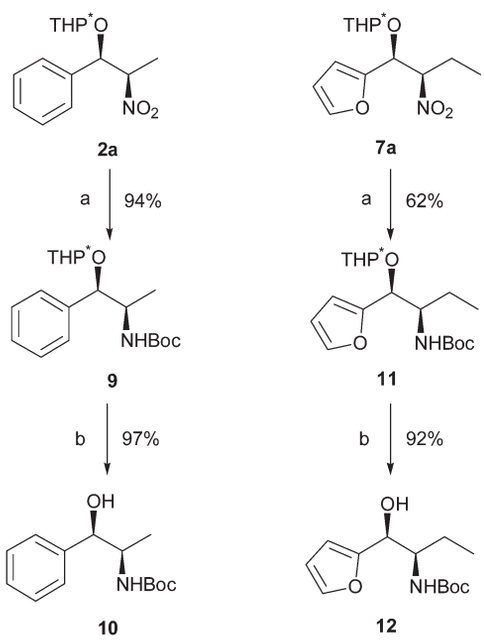


Fig. 1 X-ray crystal structures of compounds **2a** and **5a**.

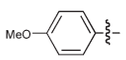
As well as demonstrating that the "naked" delta lactol anion is capable of addition to α,β-disubstituted nitro olefins with high stereocontrol, these reactions provide access to important products in only a few steps. Thus, nickel boride reduction[7] and *in situ* *N*-Boc protection of isomerically pure **2a** gave **9** in good yield. Removal of the THP* using polymer supported sulfonic acid resin and methanol occurred smoothly and afforded *N*-Boc–pseudo-norephedrine **10**. The relative and absolute stereochemistry of **10** was confirmed by comparison of the ^{1}H nmr[8] and the specific rotation $[\alpha]^{25}_D$ −35.1 (*c* 1.0, $CHCl_3$) [Lit.;[9] $[\alpha]^{20}_D$ −35.2 (*c* 0.47, $CHCl_3$)] with the literature and was consistent with the stereochemistry of the oxy-Michael adduct. The same sequence, when applied to diastereoisomerically pure **7a**, afforded *N*-Boc protected α-ethyl, β-furanyl ethanolamine product **12** in good yield over the three step transformation.[10] Gratifyingly, no loss of stereochemical integrity was observed in either of the nickel boride reduction reactions (Scheme 3).



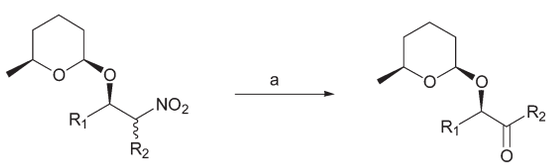
Scheme 3 Reagents and conditions: (a) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, THF, 0 °C then Boc_2O, 0 °C to rt. (b) MP–TsOH II, MeOH, rt.

The Nef oxidation of nitro alkanes to ketones is frequently performed under either strongly basic or strongly acidic (or Lewis acidic) conditions.[11] Both extremes of conditions are incompatible with the oxy-Michael adducts listed in Table 2. Under acidic conditions, the THP* is labile to deprotection, whereas under basic conditions at high temperatures, the adducts are prone to degradative retro-Michael addition. However, oxidation of *O*-THP* protected Henry products **2**, **3**, **5**, **6** was possible under near-neutral conditions. Thus treatment with excess tetrapropylammonium perruthenate[12] (TPAP) in DCM at room temperature overnight furnished the THP* protected α-hydroxy ketones in good to excellent yields and with little or no compromise to the stereochemical

Table 3 Results of TPAP mediated Nef-type oxidation

Entry	R^1	R^2	Product	de[a]	Yield
1		Me	**13**	>98%	66%
2[b]		Me	**14**	>98%	50%
3		Et	**15**	98%	48%
4		Et	**16**	98%	83%

[a] Measured by analysis of the 400, 500 or 600 MHz ^{1}H nmr spectra of the purified reaction product. [b] Reaction performed for 3 h at rt in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (1.0 eq).



2,3,5,6 **13-16**

Scheme 4 Reagents and conditions: (a) TPAP (xs), CH_2Cl_2, RT, o/n.

integrity of the β-stereocentre formed in the oxy-Michael reaction (Scheme 4, Table 3).

This method worked well, albeit slowly, for the β-aryl and β-heteroaryl oxy-Michael adducts, but interestingly no reaction was observed when the β-alkyl adduct **8** was subjected to the same reaction conditions.

In summary, the naked alkoxide of (*S*)-6-methyl delta lactol adds efficiently and with excellent β-selectivity to α,β-disubstituted nitro olefins. Diastereofacial protonation of the generated nitronate anions with acetic acid allows moderate control of the α-stereocentre (1 : 1→3 : 1 favouring the *syn*-products). These materials can be reduced with nickel boride to give the amino alcohol products, or oxidized *via* the Nef-type reaction to give the protected α-hydroxy ketones in high diastereoisomeric excess. The origins of stereocontrol at both the α- and β-centres, as well as various applications of this work will be reported in due course.

Acknowledgements

We gratefully acknowledge GlaxoSmithKline (to djb), EPSRC (to fah-j), Dr J. E. Davies for X-ray crystallography, EPSRC National Mass Spectrometry Service Centre, Swansea and Prof. S. V. Ley.

References and notes

1 (*a*) D. Enders, A. Haertwig, G. Raabe and J. Runsink, *Angew. Chem., Int. Ed.*, 1996, **35**, 2388–2390; (*b*) D. Enders, A. Haertwig, G. Raabe and J. Runsink, *Eur. J. Org. Chem.*, 1998, 1771–1792; (*c*) D. Enders, A. Haertwig and J. Runsink, *Eur. J. Org. Chem.*, 1998, 1793–1802.
2 (*a*) N. J. Adderley, D. J. Buchanan, D. J. Dixon and D. I. Lainé, *Angew. Chem., Int. Ed.*, 2003, **42**, 4241–4244; (*b*) D. J. Buchanan, D. J. Dixon, M. S. Scott and D. I. Lainé, *Tetrahedron: Asymmetry*, 2004, **15**, 195–197.
3 For early studies into the oxy-Michael (racemic, unstereoselective) see J. L. Duffy, J. A. Kurth and M. J. Kurth, *Tetrahedron Lett.*, 1993, **34**, 1259–1260 and references cited therein.
4 (*a*) H. Sasai, N. Itoh, T. Suzuki and M. Shibasaki, *Tetrahedron Lett.*, 1993, **34**, 855–858; (*b*) H. Sasai, N. Itoh, T. Suzuki, S. Arai and M. Shibasaki, *Tetrahedron Lett.*, 1993, **34**, 2657–2660; (*c*) R. Chinchilla, C. Najera and P. Sanchez-Agullo, *Tetrahedron: Asymmetry*, 1994, **5**, 1393–1402; (*d*) M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem., Int. Ed.*, 1997, **36**, 1236–1256; (*e*) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 7388–7389; (*f*) B. M. Trost, V. S. C. Yeh, H. Ito and N. Bremeyer, *Org. Lett.*, 2002, **4**, 2621–2623.
5 A. Kamimura and N. Ono, *Tetrahedron Lett.*, 1989, **30**, 731–734.
6 α,β-Disubstituted nitro olefins are readily prepared by the condensation of nitroalkanes with aldehydes. See for example: Y. Kawai, Y. Inaba and N. Tokitoh, *Tetrahedron: Asymmetry*, 2001, **12**, 309–318.
7 (*a*) A. Nose and T. Kudo, *Chem. Pharm. Bull.*, 1981, **29**, 1159–1161; (*b*) A. Nose and T. Kudo, *Chem. Pharm. Bull.*, 1988, **36**, 1529–1533; (*c*) A. Nose and T. Kudo, *Chem. Pharm. Bull.*, 1989, **37**, 816–818; (*d*) J. O. Osby and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 6413–6416.
8 P. Besse, H. Veschambre, M. Dickman and R. Chênevert, *J. Org. Chem.*, 1994, **59**, 8288–8291.
9 C. Agami, F. Couty, L. Hamon and O. Venier, *Bull. Soc. Chim. Fr.*, 1995, **132**, 808–814.
10 The stereochemistry of **12** was predicted by analogy with that of **10**.
11 R. C. Larock, *Comprehensive Organic Transformations*; VCH Publishers, Inc., 1989, pp. 603–604.
12 Y. Tokunaga, M. Ihara and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1997, 207–209.