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CamTHP*OH: A Camphor-Derived δ-Lactol Auxiliary for the Effective Desymmetrization of Attached Glycinamide Residues. Asymmetric Synthesis of α-Amino Carbonyl Compounds

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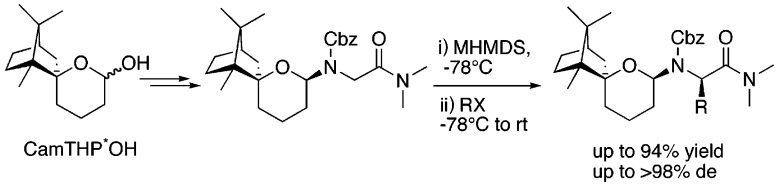
ABSTRACT



Stereoselective allylation of camphor and subsequent terminal hydroformylation affords a new δ-lactol auxiliary (camTHP*OH) on multigram scale. Stereoselective condensation with glycine dimethylamide and Cbz protection affords a camTHP*-desymmetrized glycinamide building block which undergoes efficient and highly diastereoselective metal enolate alkylation reactions. Acid-mediated deprotection affords the *N*-Cbz-protected α-amino amide products which may be converted directly to α-amino ketones on treatment with Grignard or organolithium reagents without loss of stereochemical integrity.

Enantiopure δ-lactols and their derivatives provide many opportunities for the asymmetric synthesis of a range of desirable product materials. As nucleophiles in the oxy-Michael[1] reaction, they serve as effective chiral water equivalents leading to the production of protected Henry products, amino alcohols, and β-hydroxy esters. In alkylations and acylations, they lead to THP- protected ethers[2] and esters[3] which have been employed as starting materials in anomeric oxygen-to-carbon rearrangement reactions. On treatment with amines they efficiently and stereoselectively condense to provide the THP*-protected amine[4] which may be further manipulated in an asymmetric fashion. In all events, the lability of the anomeric ether or amine products to acid hydrolysis is an attractive feature, allowing mild and controlled cleavage of the desired products from the auxiliary/protecting group at the end of the sequence.

As chiral water equivalents in the oxy-Michael reaction, enantiopure 6-methyl δ-lactols **1** function optimally. However, for the asymmetric alkylation of tethered glycinamide

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(1) (a) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241. (b) Buchanan, D. J.; Dixon, D. J.; Scott, M. S.; Lainé, D. I. *Tetrahedron: Asymmetry* **2004**, *15*, 195. (c) Buchanan, D. J.; Dixon, D. J.; Hernandez-Juan, F. A. *Org. Lett.* **2004**, *6*, 1357.

(2) (a) Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1091. (b) Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1093.

(3) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2665.

(4) Dixon, D. J.; Horan, R. A. J.; Monck, N. J. T. *Tetrahedron: Asymmetry* **2004**, *15*, 913.

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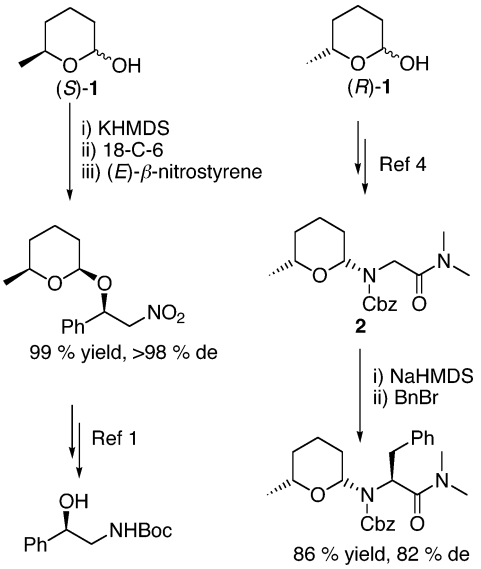
Scheme 1. Enantiopure δ-Lactols as Tools in Asymmetric Synthesis



2 only moderate to good diastereocontrol was observed and the facial bias was electrophile dependent (Scheme 1). Despite its ease of preparation, the use of **2** in the asymmetric synthesis of α-amino carbonyl compounds could lead to problems because of the selectivity issues. With this in mind, we began investigating the potential utility of the camTHP* glycinamide **3** for this purpose (Figure 1).

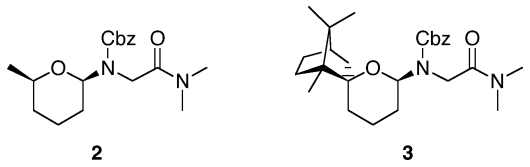


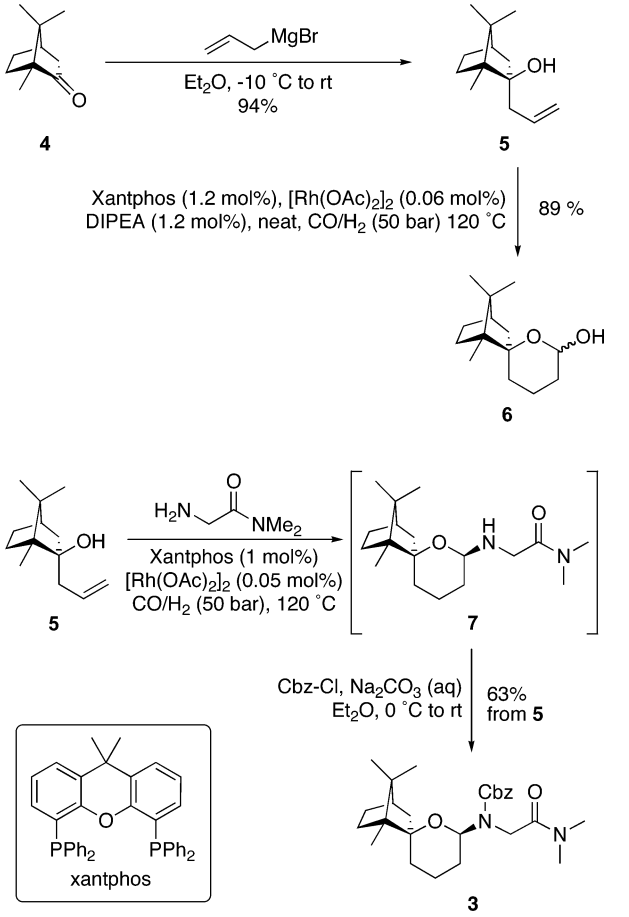
Figure 1. MeTHP*-desymmetrized glycinamide building block **2** and a sterically augmented analogue, camTHP* glycinamide **3**, for improved improved facial selection in metal enolate chemistry.

In this paper, we describe the large-scale synthesis of the camphor-derived δ-lactol (camTHP*OH) **6**, its function as a stereodirecting group in enolate alkylation reactions of an attached glycinamide residue, and the utility of the novel building block **3** for the highly stereoselective synthesis of α-amino carbonyl compounds.

The α-amino carbonyl unit is an ideal synthon for the stereoselective synthesis of alkaloids,[5] 1,2-amino alcohols,[6] and other amine-containing natural products,[5] as well as exhibiting interesting biological properties in its own right.[7]

As a consequence, simple synthetic procedures for their synthesis are important,[8] especially when the parent amino acid is non-proteinogenic.

Scheme 2. Stereoselective Construction of CamTHP*-Desymmetrized Glycinamide Building Block **3**



The camphor-derived δ-lactol **6** was readily prepared on multigram scale in two high-yielding and scalable steps. First, a diastereoselective allylation of commercially available (+)-camphor **4** using allylmagnesium bromide[9] afforded homoallylic alcohol **5** in nearly quantitative (94%) yield. Treatment of this material with $[Rh(OAc)_2]_2$ and Xantphos (4,5-bis-(diphenylphosphino)-9,9-dimethylxanthine) under an atmo-

(5) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis—Construction of Chiral Molecules Using Amino Acids*; Wiley-Interscience: New York, 1987.

(6) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415.

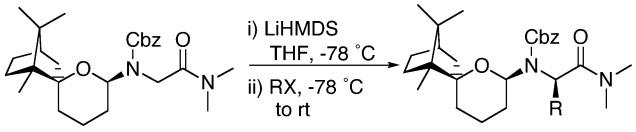
(7) Jung, M. J. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 227.

(8) (a) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798. (b) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173. (c) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (d) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075. (e) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (f) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (g) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (h) Seebach, D.; Gees, T.; Schuler, F. *Liebigs Ann. Chem.* **1993**, 785. (i) Studer, A.; Seebach, D. *Liebigs Ann. Chem.* **1995**, 217. (j) Myers, A. G.; Gleason, J. L. *Org. Synth.* **1999**, *76*, 57. (k) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321. For reviews, see: (l) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (m) Hegedus, L. *Acc. Chem. Res.* **1995**, *28*, 299. (n) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (o) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215. (p) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290.

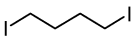
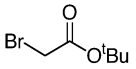
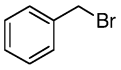
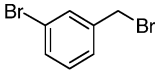
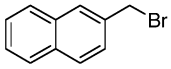
(9) Dimitrov, V.; Simova, S.; Kostova, K. *Tetrahedron* **1996**, *52*, 1699.

sphere of CO/H_2 at 50 bar, 120 °C with Hünig's base in the absence of solvent afforded lactol **6** in 89% yield. However, in the presence of glycine dimethylamide,[10] hydroformylation of **5** afforded the crude camTHP*-amine **7** in one pot. This compound was subsequently *N*-protected with the Cbz group under standard conditions to furnish **3** in 63% yield from **5** (Scheme 2). The relative stereochemistry across the THP ring, with the amino group occupying an equatorial site, was in agreement with our previous results[4] and was unambiguously established by single-crystal X-ray diffraction of a related compound.[11]

Table 1. Diastereoselective Metal Enolate Alkylations of CamTHP*-Desymmetrized Glycinamide **3**



3 **8-17**

entry	RX	product	yield/%	de/%[a]
1		**8**	80	>98
2		**9**	60	>98
3		**10**	88	>98
4		**11**	50	>98
5		**12**	62	>98
6		**13**	77	>98
7		**14**	46	90
8[b]		**15**	94	95
9[b]		**16**	77	>98
10[b]		**17**	75	>98

[a] Measured by analysis of the 500 MHz ^{1}H NMR spectra of the crude reaction product in DMSO-d_6 at 120 °C. [b]Using NaHMDS as the base and toluene as solvent.

With multigram quantities of the building block **3** in hand, its performance in enolate alkylation reactions, using a wide range of commercially available alkyl halide reagents, was tested (Table 1). With aliphatic alkyl iodide reagents (linear and branched, entries 1−5) the observed diastereoselectivities in the lithium enolate alkylations were excellent in each case, and good to very good reaction yields were obtained. Similarly, with multifunctional alkyl halide electrophiles (entries 5−7), good to excellent stereoselectivities were observed in the reactions with the lithium enolate. With bromomethyl arenes it was found that that the standard conditions gave lower diastereoselectivities. However, reaction of the sodium enolate in toluene yielded the desired products in excellent diastereoselectivities and good to excellent yields (entries 8−10). The stereochemistry of the reaction products was proven in two cases (**8** and **15**) by chemical correlation methods (vide infra) and was consistent with the electrophile attacking the *Re*-face of the *Z*-enolate ion.

To explain the stereochemical outcome we propose the following model (Figure 2). Deprotonation affords the *Z*-enolate[12] which undergoes alkylation via a 7-membered ring chelate with the oxygen of the THP ring. The favored approach of the electrophile avoids steric clash with the bulk of the camphor skeleton, and alkylation occurs on the *Re*-face of the enolate ion.

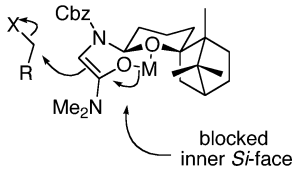
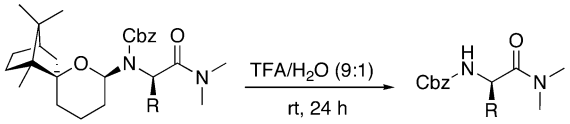


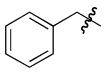
Figure 2. Proposed stereochemical model for metal enolate alkylation reactions of camTHP*-desymmetrized glycinamide **3**.

Removal of the camTHP* auxiliary is readily achieved using standard TFA/water hydrolysis conditions and affords the *N*-Cbz-protected amino amides **18**−**21** in good to excellent yields without loss of stereochemical purity (Table 2). The absolute stereochemistry of products **18** and **21** was

Table 2. Acid-Mediated Hydrolysis of CamTHP* Auxiliary from Alkylated Glycinamide Derivatives



8, **10**, **11**, **15** **18-21**

entry	R	product	yield/%	ee/%[a]
1		**18**	73	>97
3		**19**	91	>97
3		**20**	70	>97
4		**21**	94	94

[a] ee determined by HPLC using a Chiralcel OD column.

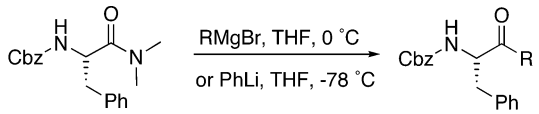
(10) For an example of the tandem hydroformylation−enamine formation sequence, see: Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M., *Angew. Chem., Int. Ed.* **2003**, *42*, 5615.

(11) Dixon, D. J.; Horan, R. A. J.; Monck, N. J. T.; Berg, P. *Org. Lett.* **2004**, *6*, 4427.

unambiguously determined by comparison of their specific rotations with those of authentic samples.[13] The enantiomeric excess of products **18**−**21** was determined by HPLC using a chiral stationary phase.

These compounds are good substrates for the direct synthesis of α-amino ketones.[6,14] To demonstrate this, **22**[15] was treated with excess Grignard or organolithium reagent in THF to afford the desired carbonyl compounds in good yield and without racemization (Table 3).

Table 3. Synthesis of Enantiomerically Pure α-Amino Ketones from **22**



22 **23** or **24**

entry	RM	product	yield/%	ee/%[a]
1	MeMgBr	**2 3**	74	>99
2	PhMgBr	**2 4**	94	>99
3	PhLi	**2 4**	63	>99

[a] ee determined by chiral HPLC using a Chiralcel OD column.

In summary, a new δ-lactol auxiliary derived from camphor has been designed, synthesized, and tested as a stereocontrolling element in the enolate chemistry of attached glycinamide residues. Good to excellent diastereocontrol was observed with a wide range of alkyl halide electrophiles. Acid hydrolysis affords the enantioenriched *N*-Cbz-protected amino acid dimethyl amides which may be converted without loss of stereochemical integrity to the ketone products by addition of Grignard or organolithium reagents.

Application of the building block **3** to the synthesis of bioactive natural products is currently underway and will be reported in due course.

Acknowledgment. We thank Vernalis plc for a studentship (to R.A.J.H.), the National Mass Spectrometry Service at Swansea for HRMS, and Prof Steven V. Ley for continued and valued support.

Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for compounds **3**, **5**, **6**, **8**−**21**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048569I

(12) Oare D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock C. H. *J. Org. Chem.* **1990**, *55*, 132

(13) **18** $[\alpha]^{25}_{D} = -17.0$ (c 0.365, $CHCl_3$). **21** (94% ee) $[\alpha]^{25}_{D} = -34.4$ (*c* 0.948, $CHCl_3$). Authentic samples: *ent*-**18** $[\alpha]^{25}_{D} = +17.8$ (*c* 1.164, $CHCl_3$), *ent*-**21** $[\alpha]^{25}_{D} = +35.4$ (*c* 1.326, $CHCl_3$).

(14) For related examples using other *N*-carbamate-protected α-amino amides, see: (a) Nájera, C.; Abellán, T.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2809. (b) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107.

(15) Compound **22** was available in one step from commercial *N*-Cbz-L-phenylalanine.