ORGANIC LETTERS

2004
Vol. 6, No. 24
4427−4429

Highly Stereoselective Michael Addition Reactions of CamTHP*-Desymmetrized Glycinamide for the Synthesis of Functionally Dense Amino Acid Derivatives

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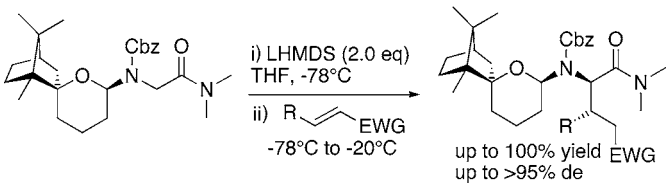
Received July 23, 2004 *(Revised Manuscript Received October 2, 2004)*

ABSTRACT



The camphor-derived tetrahydropyran (camTHP*)-desymmetrized glycinamide 1 undergoes efficient and highly diastereoselective lithium enolate Michael additions to nitro olefins, α,β-unsaturated ketones, esters, and lactones. Straightforward manipulation of these products affords 3-substituted pyroglutamides and β-aryl-α,γ-diamino acid derivatives, highlighting the ease of synthesis of enantiomerically enriched, functionally dense molecules using this novel building block.

The biological importance of α-amino acid derivatives has been clearly demonstrated over the past few years.[1] Equally, glutamic acid derivatives, pyroglutamic acid derivatives, and related structures are important as both chiral building blocks[2] and bioactive substances.[3]

An attractive approach to such derivatives involves the stereocontrolled Michael addition of a chiral glycine-derived enolate to the corresponding electron-poor olefin.[3a,b,4,7a] This process leads to the generation of up to three new stereogenic centers in the product, and clearly, when high levels of control are observed, these reactions are of considerable importance.

In the preceding paper, we introduced the camTHP*-desymmetrized glycinamide **1** (Figure 1) for the enantioselective synthesis of α-amino carbonyl compounds **2** through highly diastereoselective enolate alkylation reactions and subsequent deprotection and manipulation of the dimethyl amide.[5] Here, we report the use of this building block in highly diastereoselective Michael addition reactions.

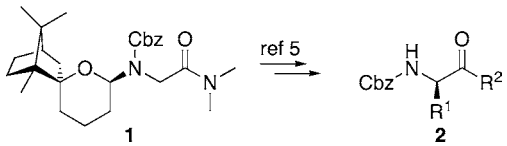


Figure 1. CamTHP*-desymmetrized glycinamide **1** as a building block for α-amino carbonyl derivatives **2**.

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(1) Jung, M. J. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 227.
(2) For a recent review, see: Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245.

10.1021/ol048568q CCC: $27.50
Published on Web 10/26/2004

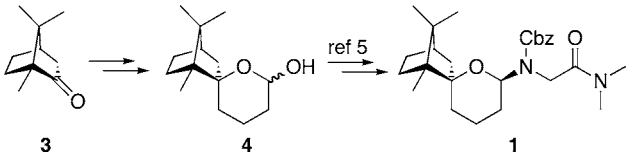
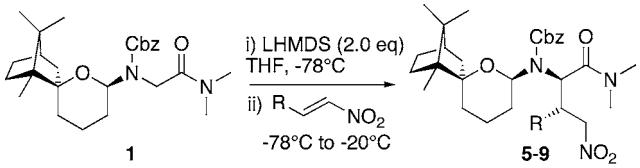


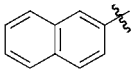
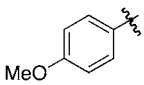
Figure 2. Synthesis of camTHP*-desymmetrized glycinamide **1** from (+)-camphor **3**.

Multigram quantities of camTHP*-desymmetrized glycinamide **1** are readily prepared in four high-yielding steps from commercially available (+)-camphor **3**. The stereogenic tertiary alcohol center is created in a facially selective allylation reaction, and the stereogenic aminol center is established via a chiral relay effect during the condensation of glycinamide with the lactol **4** (Figure 2).

Our preliminary studies focused on the Michael addition of camTHP*-desymmetrized glycinamide **1** to reactive nitro olefin Michael acceptors. The optimal reaction conditions were established quickly and comprised treatment of a −78 °C THF solution of the building block **1** (1.0 equiv) with 2.0 equiv of lithium hexamethyldisilazide (LHMDS) for 1 h followed by the nitro olefin acceptor (1.1 equiv). After being stirred for 1 h at this temperature and 1 h at −20 °C, the reaction mixture was quenched by the addition of 4.0 equiv of acetic acid. On warming to room temperature, diethyl ether was added, and the mixture was filtered through a short (1−2 cm) plug of silica eluting with diethyl ether. Evaporation of solvents gave the corresponding crude products **5**−**9**, which were purified by silica gel column chromatography (Table 1).

Table 1. Diastereoselective Michael Addition of **1** to Nitro Olefin Acceptors



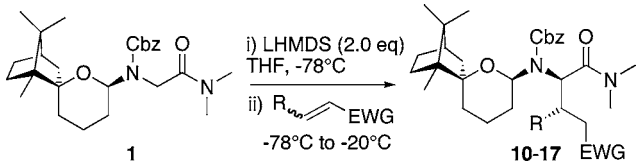
entry	R	product	yield/%[a]	de/%[b]
1		**5**	85	>95
2		**6**	78	>95
3		**7**	100	>95
4		**8**	97	>95
5		**9**	98	>95

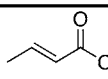
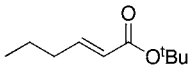
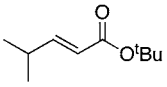
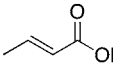
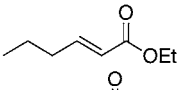
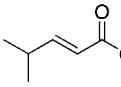
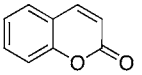
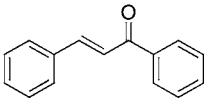
[a] Yield of purified material. [b] Measured by analysis of the 500 MHz ^{1}H NMR spectra of the crude reaction product.

In all cases, the reaction yields were good (78−100%) and the observed diastereoselectivities were uniformly excellent (>95% de). Notable is entry 3, where a quantitative yield of only one of the possible four diastereoisomers was obtained. The structures of compounds **5**, **6**, **8**, and **9** were assigned by analogy to compound **7**, the stereochemistry of which was unambiguously established by single-crystal X-ray diffraction.

Having established the utility in the addition to reactive nitro olefin acceptors, we next turned our attention to less reactive Michael acceptors (Table 2).

Table 2. Diastereoselective Michael Addition of **1** to α,β-Unsaturated Esters, Lactones, and Ketones



entry	Michael acceptor	product	yield/%[a]	de/%[b]
1		**10**	100	>95
2		**11**	100	>95
3		**12**	76	>95
4		**13**	100	>95
5		**14**	100	>95
6		**15**	94	>95
7		**16**	85	>95
8		**17**	100	78

[a] Yield of purified material. [b] Measured by analysis of the 500 MHz ^{1}H NMR spectra of the crude reaction product.

Using the previously described conditions, good to excellent isolated yields were obtained with α,β-unsaturated *tert*-butyl and ethyl esters, lactones, and ketones. Reaction diastereoselectivities ranged from good to excellent in all cases.

(3) (a) Wehbe, J.; Rolland, V.; Roumestant, M. L.; Martinez, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1123 and references therein. (b) Hartzoulakis, B.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525 and references therein. (c) Hruby, V. J.; Sharma, S. D.; Collins, N.; Matsunaga, T. O.; Russell, K. C In *Synthetic Peptides: A User's Guide*; Grant, G. A., Ed.; W. H. Freeman and Co.: New York, 1992; p 259. (d) Hruby, V. J.; Qian, X. In *Methods in Molecular Biology, Vol. 35, Peptide Synthesis and Purification Protocols*; Pennington, M. W., Dunn, B. M., Eds.; Humana Press: Clifton, NJ, 1994; p 201.

The stereochemistry of the products was assigned by analogy to **7** and **13** in which the relative stereochemistry was determined by chemical correlation (vide infra).

The product stereochemistry is consistent with the Michael acceptor attacking the *Re* face of the lithium enolate and is in agreement with the stereochemical outcome of the enolate alkylation reactions of **1**.[5] Moreover, the configurational assignment of the products is compatible with a synclinal approach model[6] (Figure 3).[7]

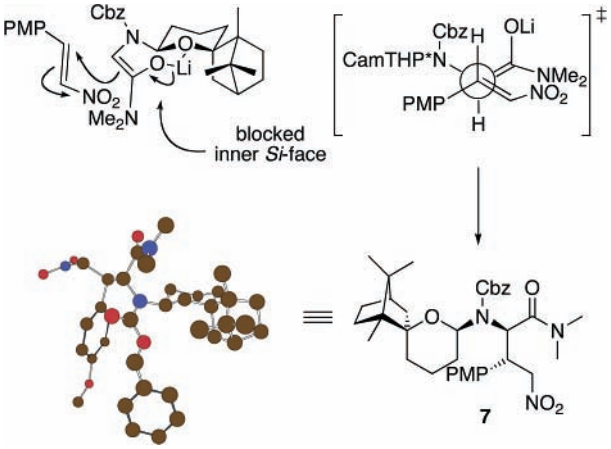
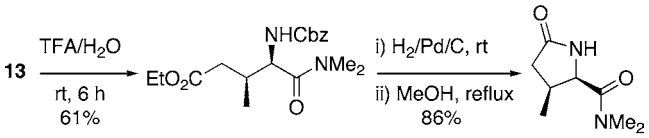


Figure 3. Stereochemical model to rationalize the outcome in the Michael addition reactions and single-crystal X-ray structure of **7**.

To confirm the relative stereochemistry of the adducts **10**−**17** it was necessary to convert a representative example to a cyclic product for NMR analysis. Hence, removal of the camTHP* protecting group was achieved by dissolution of the Michael adduct **13** in aqueous TFA for 6 h to give the corresponding Cbz-protected β-substituted glutamic acid derivative **18** in 61% yield. Subjection of this product to standard hydrogenolysis conditions afforded the open form glutamide which cyclized on heating to the pyroglutamic acid derivative **19** (Scheme 1).[8]

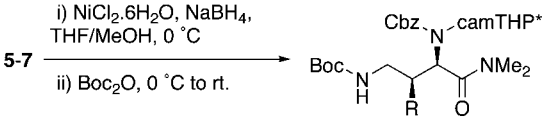
Scheme 1. Manipulation of **13** to Pyroglutamide **19**



18 **19**

Reductive *N*-Boc protection of the nitro group following our previous conditions[9] allowed access to the differentially protected β-aryl-α,γ-diamino acid derivatives **20**−**22** (Scheme 2).

Scheme 2. Reductive Manipulation of Michael Adducts **5**−**7**



20	R = Ph	82%
21	R = 2-Nap	77%
22	R = PMP	80%

In summary, camTHP*-desymmetrized glycinamide building block **1** undergoes efficient and highly diastereoselective lithium enolate Michael additions to nitro olefins, α,β-unsaturated ketones, esters, and lactones. Subsequent manipulation of these Michael adducts gives stereochemically defined polyfunctional α-amino acid derivatives in high yields. Further utility and synthetic applications of this chemistry will be reported in due course.

Acknowledgment. We thank Vernalis plc for a studentship (to R.A.J.H.), Pfizer Global Research and Development (UK) for a summer scholarship (to P.B.), the National Mass Spectrometry Service at Swansea for HRMS, Dr. John E. Davies for the X-ray structure determination, and Prof. Steven V. Ley for continued and valued support.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra, and high-resolution mass spectra for compounds **5**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) (a) For a highly diastereoselective but racemic synthesis, see: Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688. For asymmetric examples, see: (b) Busch, K.; Groth, U. M.; Kühnle, W.; Schöllkopf, U. *Tetrahedron* **1992**, *48*, 5607. (c) Schöllkopf, U.; Kühnle, W.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 480. (d) Pettig, D.; Schöllkopf, U.; *Synthesis* **1988**, 173. For an example using an achiral glycine anion and chiral electrophiles, see: (e) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984 and references therein.

(5) Dixon, D. J.; Horan, R. A. J.; Monck, N. J. T. *Org. Lett.* **2004**, *6*, 4423.

(6) Although an open transition-state model cannot be ruled out: Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903.

(7) For some excellent works on the steric course of enolate Michael addition reactions, see: (a) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51. (b) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (c) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

(8) The relative stereochemistry of **19** is supported by NOE (see the Supporting Information).

(9) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241.