ORGANIC LETTERS

2006
Vol. 8, No. 7
1359−1362

A Practical Chiral Bicyclic Thioglycolate Lactam Auxiliary for Stereoselective Quaternary Carbon Formation

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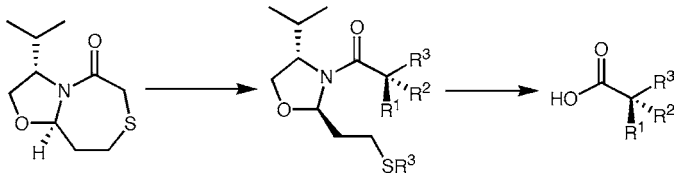
Received January 13, 2006

ABSTRACT



Chiral bicyclic thioglycolate lactams may be prepared in three steps from inexpensive commercial materials. The resulting lactams may be alkylated three times, twice using basic enolization and once using reductive enolization, to form α-quaternary carboxylic acid derivatives in high yield and with high diastereoselectivity. The alkylation products may be cleaved under either acidic or reductive conditions to furnish either carboxylic acids or primary alcohols, respectively.

The formation of all-carbon quaternary stereocenters is a significant challenge in asymmetric synthesis.[1] One approach to this problem is by the alkylation of α,α-disubstituted enolates. Although some progress has been made in achieving this goal using catalytic asymmetric methods,[2] most methods have involved chiral auxiliaries,[3] particularly in reactions with unactivated alkyl halides.[4] As enolate stereocontrol, a key requirement in most methods, is difficult to achieve in the formation of simple acyclic α,α-disubstituted enolates, most enolates that have been employed in quaternary stereocenter formation have either been cyclic or possessed chelating functionality, thus limiting the generality of these methods.

Recently, we reported the stereoselective preparation of acyclic α,α-disubstituted enolates by reduction of bicyclic

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(2) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8830. (c) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62−63. For examples of catalytic asymmetric alkylations to form α,α-dialkylated-α-amino acids, see: (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028. (e) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506−517.

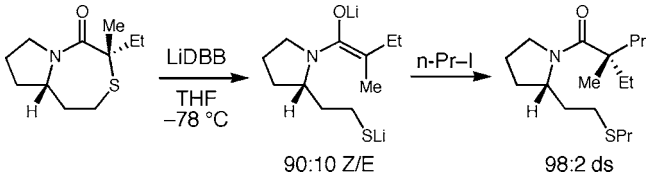
(3) For chiral auxiliary based methods for quaternary centers formation, see: (a) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463−2464. (b) Davies, S. G.; Walker, J. C. *J. Chem. Soc., Chem. Commun.* **1986**, 495−496. (c) Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, *J. Org. Chem.* **1989**, *54*, 5413−5414. (d) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207−213. (e) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843−9873. (f) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825−2528. (g) Enders, D.; Zamponi, A.; Raabe, G.; Runsink, J. *Synthesis* **1993**, 725−728. (g) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429−6433. (h) Boeckman, R. K., Jr.; Boehmler, D. J.; Musselman, R. A. *Org. Lett.* **2001**, *3*, 3777−3780. (i) Enders, D.; Teschner, P.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2001**, 4463−4466.

(4) For selected examples of quaternary carbon formation from enolates via activation of allylic, aryl, and vinyl halides, see: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760. (b) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500−3501. (c) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897−1900. For recent organocatalytic aldol and imine additions, see: (d) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007. (e) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420−2423. For examples of enolate Michael additions, see reviews in ref 1 and (e) Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688−1690.

10.1021/ol060106k CCC: $33.50
Published on Web 03/03/2006

thioglycolate lactams and subsequently demonstrated their alkylation to form quaternary carbon centers with excellent levels of stereocontrol (Scheme 1).[5] The method can also

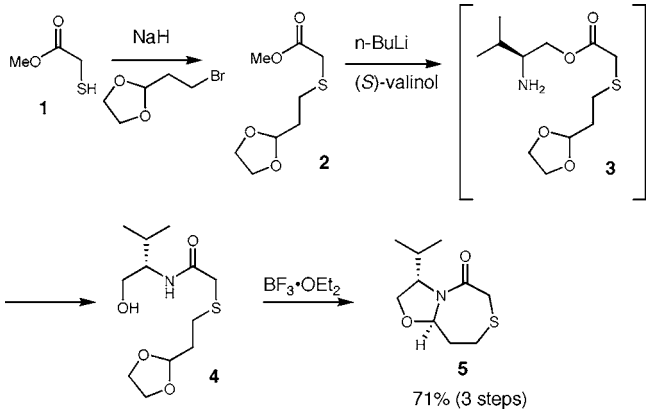
Scheme 1. Quaternary Carbon Formation via Bicyclic Thioglycolate Lactams



be extended to aldol reactions if the lithium enolate is first transmetalated to boron.[6] The removal of the need for a cyclic enolate held the potential for this to be a highly general method. However, there were several limitations including low selectivity in the alkylations of (*E*)-enolates, the inability to directly hydrolyze the products to carboxylic acids, and most importantly, a lengthy 10-step synthesis of the starting lactam. Herein we report a significantly improved second-generation bicyclic lactam that removes these shortcomings resulting in a general purpose auxiliary with wide scope.

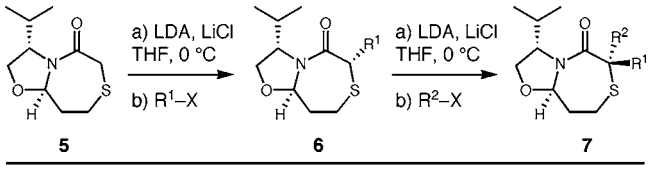
Our prior studies showed that a 5,7-bicylic thioglycolate lactam was required to maintain the optimum *O*−*C*−*C*−*S* dihedral angle necessary for high enolate stereocontrol.[5a] To prepare such an auxiliary from proline, a one-carbon extension was required, resulting in a lengthy auxiliary synthesis. We reasoned that the auxiliary preparation could be significantly shortened by incorporating an oxygen in the five-membered ring (e.g., **5**).[7] This was expected to enable a modular synthesis from readily available starting materials as well as to facilitate hydrolysis (and synthesis) of the auxiliary through *N* ↔ *O* acyl transfer chemistry. One concern was that low yields and poor stereoselectivity have been reported in closing related 5,7-bicyclic lactam acetals.[8] In practice, however, we found that the desired acetals could be formed efficiently and in high yield. *S*-Alkylation of methyl thioglycolate with 2-(2-bromoethyl)-1,3-dioxolane followed by transesterification/O → N acyl transfer with the alkoxide of valinol produced lactam precursor **4** cleanly. Transacetalization in **4** with $BF_3{\cdot}OEt_2$ afforded bicyclic lactam **5** in excellent yield as a single stereoisomer (Scheme 2). The overall process could be carried out on large scale without chromatographic purification of the intermediates; the final product was isolated directly as a crystalline solid (mp 138−139 °C).[9]

Scheme 2. Synthesis of Bicyclic Lactams



Incorporation of the first two alkyl groups of the α-quaternary center could easily be achieved by sequential alkylation of **5** using LDA and an alkyl halide in the presence of LiCl.[10] Both alkylation steps proceeded in high yield and with excellent stereoselectivity (Table 1). In both cases, the

Table 1. Alkylation of Bicyclic Lactams



5 6 7

R^1-X	product	yield [%]	dr	R^2-X	product	yield [%]	dr[a]
Et-I	**6a**	95	98:1	Me-I	**7a**	90	99:1
				Pr-I	**7b**	92	98:2
Me-I	**6b**	90	99:1	Et-I	**7c**	86	99:1
Pr−I	**6c**	89	99:1	Et-I	**7d**	89	97:3
Bn-Br	**6d**	88	98:2	Me-I	**7e**	95	98:2
				Et-I	**7f**	92	99:1

[a] Determined by GC using a Chirasil Dex column.

alkyl halide approaches the convex face of the bicyclic lactam enolate; as expected the isopropyl group plays no significant role in facial discrimination. This result is consistent with that observed in our first-generation auxiliary.

The reduction of the dialkylated bicyclic lactams to form α,α-disubstituted enolates was easily carried out under standard Birch conditions (Li/NH_3, THF, −78 °C). Although lithium di-*tert*-butylbiphenylide could also be used as a reducing agent, reactions were generally cleaner, afforded higher yields in the subsequent alkylations, and could be run on larger scales using Li/NH_3. In general, alkylations of the

(5) (a) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091−2092. (b) Manthorpe, J. M.; Gleason J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2338−2341.

(6) Burke, E. D.; Gleason, J. L. *Org. Lett.* **2004**, *6*, 405−407.

(7) The derived bicyclic system bears a close resemblance to the bicyclic lactams reported by Meyers that give excellent selectivity for quaternary carbon formation via cyclic enolates. See ref 3e.

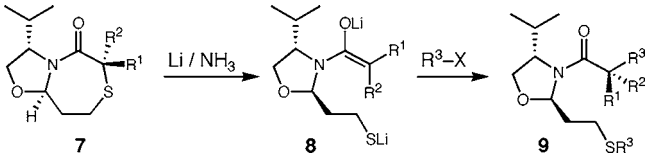
(8) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413−1419.

(9) Lactam **5** is the kinetic transacetalization product; extended treatment with an excess of $BF_3{\cdot}OEt_2$ over 5 days affords the stereoisomeric aminal as the major product (2:1 ratio).

(10) For the use of LiCl in alkylations of amides enolates, see: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. G.; Gleason J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

resulting α,α-disubstituted enolates were complete within a few hours at −78 °C, and the products could be isolated in high yield (Table 2). The reaction proved to be highly

Table 2. Reduction and Alkylation to Form Quaternary Carbon Stereocenters



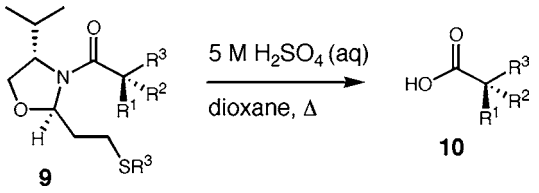
entry	lactam	R^1	R^2	R^3-X	product	yield [%]	dr[a]
				(*Z*)-Enolates			
1	**7a**	Et	Me	Bn-Br	**9a**	92	93:7
2	**7a**	Et	Me	Pr-I	**9b**	88	99:1
3	**7a**	Et	Me	$TBSO(CH_2)_3I$	**9c**	86	96:4
4	**7a**	Et	Me	$Cl(CH_2)_4I$	**9d**	79	95:5
5	**7d**	Pr	Et	allyl-Br	**9e**	91	95:5
6	**7e**	Bn	Me	Et-I	**9f**	87	97:3
				(*E*)-Enolates			
7	**7c**	Me	Et	Bn-Br	**9g**	85	93:7
8	**7c**	Me	Et	Pr−I	**9h**	91	99:1
9	**7c**	Me	Et	$Cl(CH_2)_4I$	**9i**	81	95:5
10	**7c**	Me	Et	$TBSO(CH_2)_3I$	**9j**	84	95:5
11	**7b**	Et	Pr	allyl-Br	**9k**	89	96:4

[a] Diastereoselectivities were determined by chiral HPLC and/or GC analysis of products after auxiliary removal. See Supporting Information for details.

stereoselective for both (*Z*)- and (*E*)-enolates.[11,12] The increased selectivity in the latter case, relative to the first-generation auxiliary, presumably results from the pseudo-C_2-symmetric nature of the enolate, which compensates for rotational isomerism about the *N*−*C* enolate bond.[13] The absolute configuration of the alkylation products is consistent with that observed with true C_2-symmetric enolates.[14,15] The reaction worked well with a variety of functionalized and unfunctionalized alkyl halides. Significantly, the method is not limited to products that contain methyl groups at the quaternary carbon stereocenter, and the method can produce a stereocenter with three groups of nearly identical size: ethyl, propyl, and allyl (entries 5 and 11). Finally, in some cases, altering the order of alkylation improved the diastereoselectivity in the formation of stereorelated products (compare entry 1 vs entry 6).[16]

Auxiliary cleavage was carried out under two sets of conditions. First, direct hydrolysis to the carboxylic acid occurs in excellent yield under acidic conditions (5 M H_2SO_4, H_2O, dioxane; Table 3). Monitoring this hydrolysis by NMR

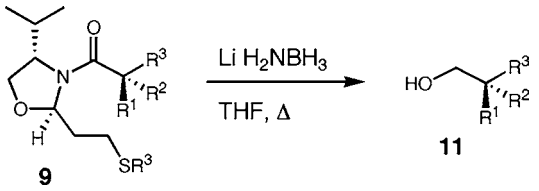
Table 3. Direct Hydrolysis to Carboxylic Acids



entry	series	R^1	R^2	R^3	yield [%]
1	a	Et	Me	Bn	81
2	b	Et	Me	Pr	79
4	d	Et	Me	$Cl(CH_2)_4$	80
4	g	Me	Et	Bn	60
5	h	Me	Et	Pr	82
6	j	Me	Et	$Cl(CH_2)_4$	81

revealed, as expected, that the reaction occurs by acetal cleavage to form a *β*-amido alcohol followed by *N* → *O* acyl transfer to form a *β*-aminoester, which finally undergoes acid hydrolysis to the carboxylic acid.[17] Alternatively, reductive cleavage to the primary alcohol could also be carried out in excellent yield using lithium amidoborohydride (Table 4) in THF.[18]

Table 4. Reductive Cleavage to Primary Alcohols



entry	series	R^1	R^2	R^3	yield [%]
1	a	Et	Me	Bn	85
2	e	Pr	Et	allyl	84
2	f	Bn	Me	Et	87
3	g	Me	Et	Bn	85
4	k	Et	Pr	allyl	84

In conclusion, we have developed a bicyclic lactam auxiliary that may be readily prepared in a short sequence

(11) Enolate selectivities were estimated at >90:10 by reduction of **7a** (*Z*-enolate) and **7c** (*E*-enolate) with LiDBB followed by trapping with TMSCl.

(12) Because of rotational isomerism about the amide bond, it was not possible to determine the stereoselectivity of the alkylation reactions directly by NMR. Thermal instability prevented heating to coalesce rotational isomers. Separation by GC and/or HPLC was also not possible. Thus diastereoselectivity was inferred from the stereoisomer ratio of the auxiliary cleavage products.

(13) Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* **1999**, *1*, 2069−2071.

(14) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857−860.

(15) The absolute configuration was determined by comparison of the optical rotation of the hydrolysis products of **9b** and **9h** with literature values. See Supporting Information for details.

(16) Products **9a** and **9f** are not true stereoisomers, as alkylation on sulfur produces molecules with different molecular formulas. However, upon cleavage of the auxiliary, the products are identical.

(17) For examples of N → O acyl transfer in the acceleration of amide hydrolysis, see: Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233−4236 and ref 10.

(18) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623−3626.

from inexpensive starting materials. The auxiliary produces all-carbon quaternary stereocenters with excellent stereoselectivity via alkylation of α,α-disubstituted enolates, and the products may be readily cleaved to afford α-quaternary carboxylic acids and primary alcohols. Application of this method to other types of enolate functionalizations as well as to natural product synthesis is currently under study.

Acknowledgment. The authors thank NSERC and Merck Frosst Inc. for funding of this research. A.A. acknowledges support from NSERC and FQRNT in the form of postgraduate scholarships, and J.M.M. acknowledges support from FCAR/FQRNT in the form of a postgraduate scholarship.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060106K