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Use of Bis-(chiral α-methylbenzyl)glycine Esters for Synthesis of Enantiopure β-Hydroxyamino Esters

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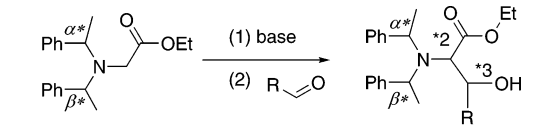
ABSTRACT



Aldol reactions using bis-(chiral α-methylbenzyl)glycine esters with aldehydes gave excellent diastereoselectivity. Thus, an enantiopure ribosylglycine was prepared for the synthesis of analogues of the natural antibiotics muraymycin. This method was extended for formation of β-hydroxyamino esters.

Muraymycins (**1**, Figure 1), isolated from *sp LL-AA896*, form a family of novel nucleoside−peptide antibiotics.[1] Their core skeleton consists of an unusual nucleotide disaccharide and a lipophilic derivative of glycine linked to a unique dipeptide urea.[2] In the course of our work[1c] on the synthesis of analogues of **1**, we studied the enantioselective preparation of intermediate **2**. Although several methods for the formation of **2** have been reported,[3] only a rather inconvenient one achieves enantioselectivity.[3c] We now report our finding that the aldol reaction of the chiral glycine ester **4** with the enantiopure ribosyl aldehyde **3**[4] produces enantiopure ribosylglycine **2**. This new method was extended to the preparation of enantiopure β-hydroxyamino esters using a number of aldehydes.

The aldol reaction of **3** was first examined with nonchiral dibenzylglycine ester **4a**.[5] The reaction conditions for aldol reactions were examined with various bases [LDA, NaH, NaHMDS, KHMDS], additives [crown ethers, HMPA], and solvents [THF, HMPA]. The best result was obtained when

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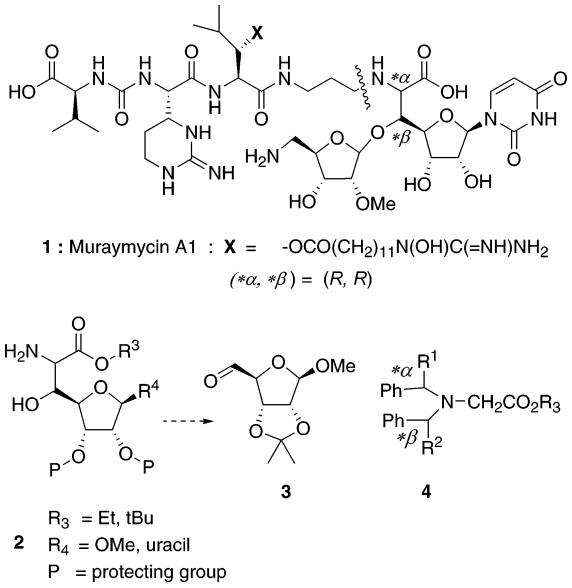
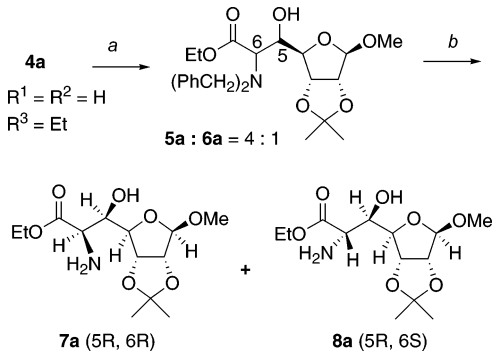


Figure 1.

LDA was used as a base in THF as the solvent. Thus, the anion of **4a** was generated by treatment with LDA [THF, −78 °C] and reacted with **3** [−78 °C, 4 h] (Scheme 1). The

Scheme 1[a]



[a] Reaction conditions: (a) (i) LDA, THF, -78 °C; (ii) **3**, −30 °C, 4 h, 94%. (b) H_2, 10% Pd/C, MeOH.

product was isolated as a 4:1 mixture of two inseparable diastereomers (**5a**, **6a**), which was directly hydrogenated, to give the deprotected amines (**7**, **8**). The absolute stereochemistry of the newly created chiral centers at C5 and C6 in **7** (a major component) was determined by X-ray analysis to be (5*R*,6*R*)-. The minor product **8** (oil) was converted to the *para*-nitrophenyl urea derivative **9a** for X-ray analysis, which revealed the stereochemistry at C5 and C6 as (5*R*,6*S*)-.[6]

(6) Crystals of **7a** suitable for X-ray were obtained as colorless prisms from ether/hexanes. Crystals of the *para*-nitrophenyl urea derivative **9a** of **8a** were obtained as yellow prisms from methylene chloride/MeOH. The supplementary publication numbers for the X-ray data are CCDC 214437 for **7a** and CCDC 214438 for **9a**.

Table 1. Aldol Reactions with **3** and Glycine Esters **4**

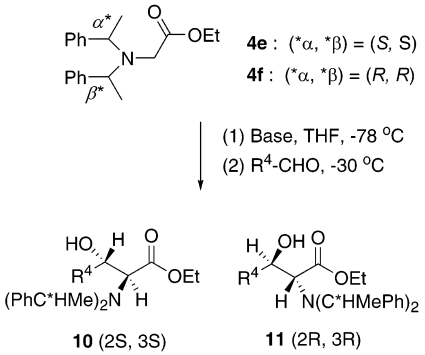
compd	*α,*β	R^1	R^2	R^3	yield[a] (%)	products	ratio[b] (**5**:**6**)
4a		H	H	Et	92	**5a/6a**	4:1
4b		H	H	tBu	80	**5b/6b**	1:1
4c	*S*	Me	H	Et	76	**5c/6c**	2:1
4d	*R*	Me	H	Et	77	**5d/6d**	2.5:1
4e	*SS*	Me	Me	Et	76	**5e/6e**	1:199
4f	*RR*	Me	Me	Et	71	**5f/6f**	5:2

[a] Isolated yield as a mixture of **5** and **6**. [b] Ratio of **5** and **6** was determined by ^{1}H NMR integration.

In a similar manner, aldol reaction of **3** using the *tert*-butyl ester of glycine **4b**[7] was examined (Table 1). In contrast to **4a**, a 1:1 mixture of two diastereomers **5b** (5*R*,6*R*) and **6b** (5*R*,6*S*) was isolated.[8] We then introduced one chiral α-methylbenzyl group with either (*S*)- or (*R*)-configuration [**4c** and **4d**, respectively]. The aldol reactions of **3** with either **4c** or **4d**, however, showed little diastereoselectivity, giving a 2:1 ratio for **5c**/**6c** and a 2.5:1 for **5d**/**6d**, respectively.[9] The new glycine ester **4e**, protected by two (*S*)-α-methylbenzyl groups, gave the remarkable result in the aldol reaction with **3** in which essentially complete double diastereoselectivity was obtained and only the (5*R*,6*S*)-diastereomer **6e** was isolated. Surprisingly, the aldol reaction of **4f**, the glycine ester protected by two (*R*)-α-methylbenzyl groups, resulted in practically no selectivity (2.5:1 = **5f**/**6f**).

The remarkable selectivity obtained from **4e** prompted us to study whether similar selectivity would be observed with simple aldehydes (Scheme 2).

Scheme 2



Aldol reaction of **4e** with sterically hindered trimethylacetaldehyde gave practically a single diastereomer **10a**, the

(7) Banfi, L.; Cardani, S.; Potenza, D.; Scolastico, C. *Tetrahedron* **1987**, *43*, 2317. Other glycine esters **4c**−**f** were prepared from ethyl bromoacetate and appropriate chiral dibeznylamine derivatives.

(8) Relative stereochemistry of **5b** and **6b** was determined by NMR spectroscopy through implementation of the J-configuration analysis method: (a) Matsumori, N.; Kaneno, D.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866. (b) Williamson, R. T.; Marquez, B. L.; Barrios Sosa, A. C.; Koehn, F. K. *Magn. Reson. Chem.* **2003**, *41*, 379. This technique was used for the structure determination of muraymycins: see ref 2.

Table 2. Aldol Reactions with **4e** and **4f**

compd	*α,*β	R[4]	yield[a] (%)	products	ratio[b] (**10**:**11**)
4e	*SS*	tBu	71	**10a/11a**	100:"0"
4f	*RR*	tBu	88	**10b/11b**	"0":100
4e	*SS*	^{i}Pr	78	**10c/11c**	6:1
4f	*RR*	^{i}Pr	94	**10d/11d**	1:3
4e	*SS*	Ph	88	**10e/11e**	9:6[c]

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR integration. [c] Two other diastereomers were also isolated; thus, the ratio was 9:6:1:1.

(2*S*,3*S*)-*tert*-butylserine ester[10] (Table 2).[11] In a similar manner, reaction of **4f** with the same aldehyde gave complete selectivity, although, as expected, the absolute stereochemistry of the product, the (2*R*,3*R*)-*β*-hydroxyamino ester **11b**, was reversed. Reaction of **4e** or **4f** with the less hindered isobutyraldehyde also gave good selectivities, giving the *β*-hydroxyleucine esters[12] in ratios of 6:1 (**10c**/**11c**[13]) and 1:3 (**10d**[13]/**11d**), respectively. Benzaldehyde gave little control of selectivity, forming a mixture of four in a ratio[14] of 9:6:1:1. Alkylations using **4e** and **4f** were also examined. In contrast to aldol reactions, however, no selectivity was observed.

In an attempt to elucidate the transition state leading to stereoselectivity, we submitted **6e** to X-ray analysis.[15] The crystal structure of **6e** reveals that the two phenyl rings in the benzyl groups are perpendicular, and they are kept fairly rigid by the two methyl groups (Figure 2).

A plausible rationale for diastereoselectivity is outlined for **4e** in Scheme 3. Treatment of the chiral glycine ester **4e** with LDA would generate the (*E*)-lithium enolate,[16] which could coordinate with one of the phenyl rings in the benzyl groups.[17] On the basis of the crystal structure of **6e**, the (*S*)-α-methyl substituent in the benzyl group would give a cup

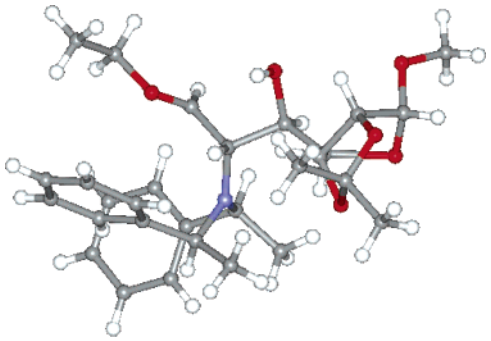
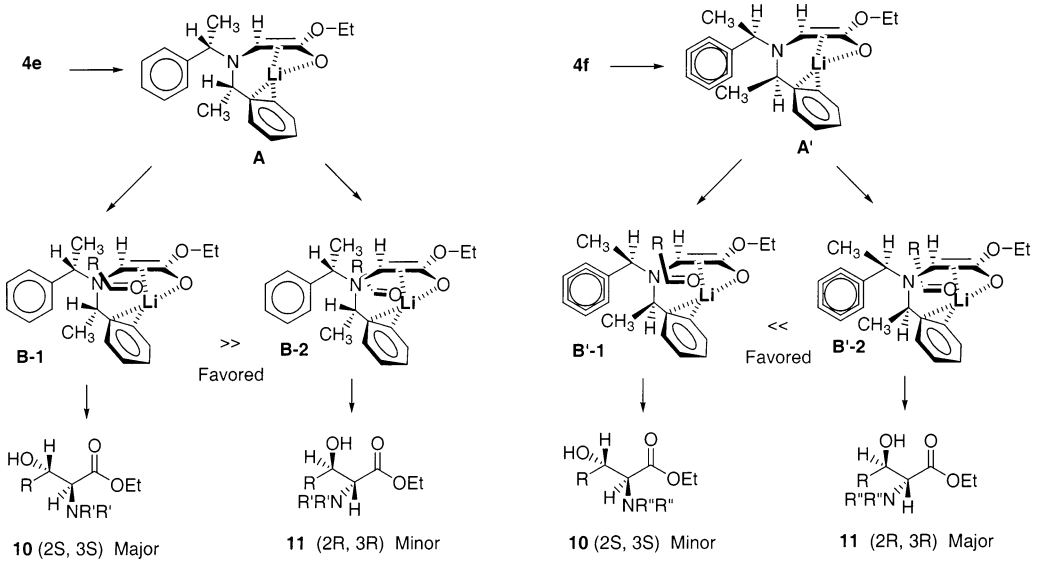


Figure 2. Crystal structure of **6e**.

shape to the resulting transition state of the enolate **A**. An aldehyde should approach from the side opposite from the (*S*)-α-methyl at the bottom of the cup (**B-1**), due to steric interaction between the methyl group and the alkyl group of the aldehyde. This makes transition state **B-1** more favorable than transition state **B-2**. Thus, the (2*S*,3*S*)-*β*-hydroxyamino ester **10** should be predominately formed from **B-1**, and **B-2** would lead to the minor product, the (2*R*,3*R*)-isomer **11**. This would be reversed in the case of **4f**, to form the (2*R*,3*R*)-*β*-hydroxyamino ester **11** (from **B′-2**) as the favored product and the (2*S*,3*S*)-isomer **10** as the minor one (from **B′-1**).

In summary, we have developed a facile method for synthesis of enantiopure *β*-hydroxyamino esters by the use of bis (chiral α-methylbenzyl)glycine esters. Considering the simplicity of preparing these glycine esters and the feasibility of removing the benzyl group by hydrogenation, this method should provide a useful tool for the synthesis of various *β*-hydroxyamino esters.

Scheme 3



Acknowledgment. The authors are thankful for the analytical support provided by Discovery Analytical Chemistry Department, Wyeth Research, Pearl River, NY, and Princeton, NJ.

Supporting Information Available: Experimental procedures for the preparation of compounds **4**−**11** with supporting analytical data; please also see ref 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Structure determination of products **5c**−**f** and **6c**−**f** from aldol reactions of **4c**−**f** was accomplished as follows: the isolated products were subjected to catalytic hydrogenation using 10% Pd/C in absolute MeOH to form the corresponding deprotected amines. Each amine was characterized with two authentic samples (**7a** and **8a**) by comparison with their ^{1}H NMR spectra and TLC analyses.

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(11) Stereochemistry of products **10a**−**d** and **11a**−**d** listed in Table 2 was determined by ^{1}H NMR spectra and optical rotations. Also, the products were deprotected by hydrogenation to give the corresponding amino esters. ^{1}H NMR spectra and optical rotations of these free amino esters were used for further confirmation of their stereochemistry.

(12) Syntheses of β-hydroxy-leucines have been reported: (a) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett*. **1989**, *30*, 6637. (b) Hale, K. J.; Manaviazar, S.; Delisser, V. M. *Tetrahedron* **1994**, *50*, 9181. (c) Yadav, J. S.; Chandrasekhar, S.; Reddy, Y. R.; Rao, A. V. R. *Tetrahedron* **1995**, *51*, 2749. (d) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc*. **1996**, *118*, 3584. (e) Kimura, T.; Vassilev, V. P.; Shen, G.-J.; Wong, C.-H. *J. Am, Chem. Soc*. **1997**, *119*, 11734. (f) Laib, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett*. **1997**, *38*, 1771. (g) Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem*. **1998**, *63*, 1709. (h) Panek, J. S.; Masse, C. E. *J. Org. Chem*. **1998**, *63*, 2382. (i) Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malley, M. F.; Gougoutas, J. Z. *Synlett* **1998**, 664. (j) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem*. **1998**, 1337. (k) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757. (l) MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883.

(13) Structures of compounds **11c** and **10d** were determined by their X-ray analyses. Crystals suitable for **11c** were obtained as colorless prisms from ether/hexanes (supplementary publication number CCDC 214440). Crystals suitable for **10d** were also obtained as colorless prisms from ether/hexanes (supplementary publication number CCDC 214439).

(14) We assumed that the (2*S*,3*S*)-diastereomer **10e** was the major component, along with the (2*R*,3*R*)-isomer **11e** as the second major component. Related references: (a) Suga, H.; Ikai, K.; Ibata, T. *J. Org. Chem.* **1999**, *64*, 7040. (b) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153. (c) Markovic, D.; Hamersak, Z.; Visnjevac, A.; Kojic-Prodic, B.; Sunjic, V. *Helv. Chem. Acta* **2000**, *83*, 603. (d) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo. P. *J. Org. Chem*. **2000**, *65*, 7663 and other references therein.

(15) Crystals of **6e** suitable for X-ray were obtained as colorless prisms from ether/hexanes. The supplementary publication number for the X-ray for **6e** is CCDC 214436.

(16) Stereochemical outcome of the lithium enolate geometry of substituted esters in various solvent systems has been reported: (a) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem*. **1974**, *74*, 373. (b) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, *16*, 1225. (c) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *16*, 3975. (d) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98*, 2868. (e) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48 and other references therein.

(17) A directing effect of neighboring aromatic groups on the regiochemistry of formation and on the stereochemistry of alkylation of lithium enolates has been suggested: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc*. **1979**, *101*, 934. Other references therein.

(18) Crystallographic data for the compounds in this manuscript, which were analyzed by X-ray, have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EW, UK. The supplementary publication number for X-ray data for each compound is individually listed in the footnote.