

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

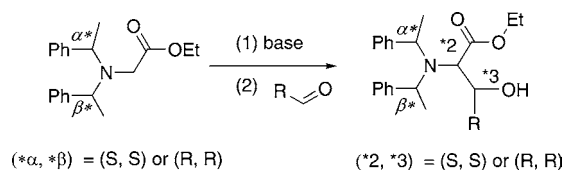
Ayako Yamashita,* Emily B. Norton, R. Thomas Williamson, Douglas M. Ho,†
Sandra Sinishtaj,‡ and Tarek S. Mansour

Chemical Sciences, Wyeth Research, Pearl River, New York 10965

yamasha@wyeth.com

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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

* Director, Small Molecule X-ray Facility, Department of Chemistry, Princeton University, Princeton, NJ 08544.

† Summer Intern, 2001.

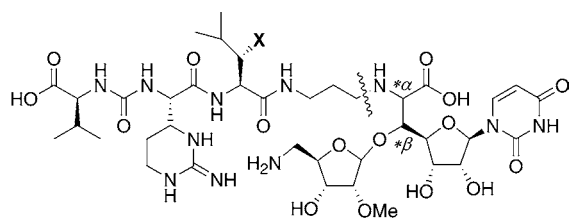
(1) Biological activity of muraymycins and their analogues: (a) Singh, G.; Yang, Y.; Rasmussen, B. A.; Petersen, P. J.; McDonald, L. A.; Yamashita, A.; Lin, Y.-I.; Norton, E.; Francisco, G. D.; Li, Z.; Barbieri, L. R. The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL; Abstract 1163; December 16–19, 2001. (b) Lin, Y.-I.; Li, Z.; Francisco, G. D.; McDonald, L. A.; Davis, R. A.; Singh, G.; Yang, Y.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2341. (c) Yamashita, A.; Norton, E.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y.; Mansour, T. S.; Ho, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, in press, and other references therein.

(2) Isolation and structure determination of muraymycins: McDonald, L. A.; Barbieri, L. R.; Carter, G. T.; Lenoy, E.; Petersen, P. P.; Siegel, M. M.; Sign, G.; Williamson, R. T. *J. Am. Chem. Soc.* **2002**, *124*, 10260.

(3) (a) Paulsen, H.; Brieden, M.; Benz, G. *Liebigs Ann. Chem.* **1987**, 565. (b) Hadrami, M. E.; Lavergne, J. P.; Viallefont, P.; Chiaroni, A.; Riche, C.; Hasnaoui, A. *Synth. Commun.* **1993**, *23*, 157. (c) Bouifraden, S.; Hadrami, M. E.; Ittobane, N.; Lavergne, J. P.; Viallefont, P. *Synth. Commun.* **1993**, *23*, 2559. (d) Borrachero, P.; Diane, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Gomez-Sanchez, A.; Lopez-Castro, A.; Perez-Garrido, S. *Carbohydr. Res.* **1995**, *279*, C9. (e) Czernecki, S.; Horms, S.; Valery, J. M. *J. Org. Chem.* **1995**, *60*, 650. (f) Czernecki, S.; Franco, S.; Valery, J. M. *Tetrahedron Lett.* **1996**, *37*, 4003. (g) Merrer, Y. L.; Gravier-Pelletier, C.; Gerrouache, M.; Depezay, J. C. *Tetrahedron Lett.* **1998**, *39*, 385.

(4) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853.

(5) Preparation of **4a** and use of **4a** for aldol and Michael reactions, etc.: (a) Scolastico, C. *Tetrahedron Lett.* **1987**, *43*, 2317. (b) Gray, B. D.; Jeffs, P. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1329. (c) Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron* **1988**, *44*, 3671. (d) Elder, T.; Gregory, L. C.; Orozco, A.; Pflug, J. L.; Wiens, P. S.; Wilkinson, T. J. *Synth. Commun.* **1989**, *19*, 763. (e) Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377.



1: Muraymycin A1 : X = $-\text{OCO}(\text{CH}_2)_{11}\text{N}(\text{OH})\text{C}(=\text{NH})\text{NH}_2$
 (* α , * β) = (R, R)

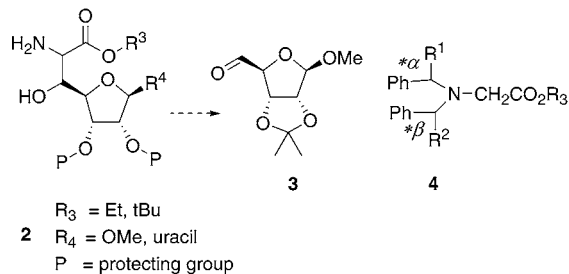
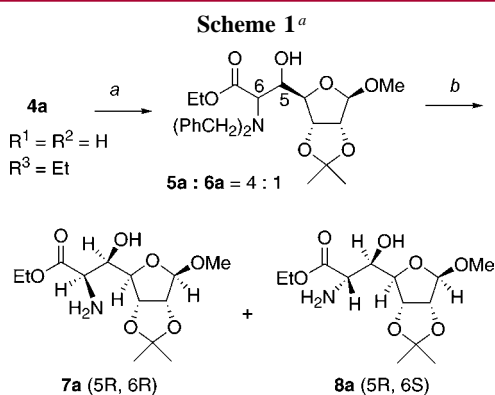


Figure 1.

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



^a Reaction conditions: (a) (i) LDA, THF, -78°C ; (ii) **3**, -30°C , 4 h, 94%. (b) H₂, 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**.

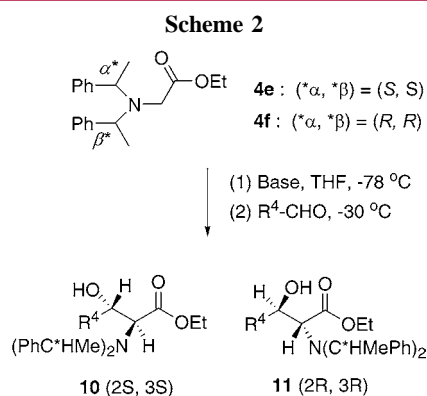
Table 1. Aldol Reactions with **3** and Glycine Esters **4**

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	<i>S</i>	Me	H	Et	76	5c/6c	2:1
4d	<i>R</i>	Me	H	Et	77	5d/6d	2.5:1
4e	<i>SS</i>	Me	Me	Et	76	5e/6e	1:199
4f	<i>RR</i>	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 ¹H 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).



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 dibenzylamine 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**

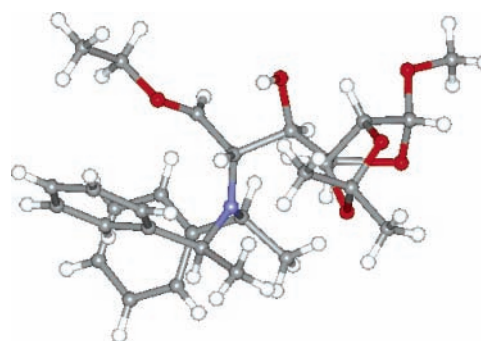
compd	* α ,* β	R ⁴	yield ^a (%)	products	ratio ^b (10 : 11)
4e	<i>SS</i>	tBu	71	10a/11a	100:"0"
4f	<i>RR</i>	tBu	88	10b/11b	"0":100
4e	<i>SS</i>	^t Pr	78	10c/11c	6:1
4f	<i>RR</i>	^t Pr	94	10d/11d	1:3
4e	<i>SS</i>	Ph	88	10e/11e	9:6 ^c

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

(*2S,3S*)-*tert*-butylserine ester¹⁰ (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 (*2R,3R*)- β -hydroxyamino ester **11b**, was reversed. Reaction of **4e** or **4f** with the less hindered isobutyraldehyde also gave good selectivities, giving the β -hydroxyamino esters¹² in ratios of 6:1 (**10c/11c**)¹³ and 1:3 (**10d/11d**), respectively. Benzaldehyde gave little control of selectivity, forming a mixture of four in a ratio¹⁴ of 9:6:1:1. Alkylations using **4e** and **4f** were also examined. In contrast to aldol reactions, however, no selectivity was observed.

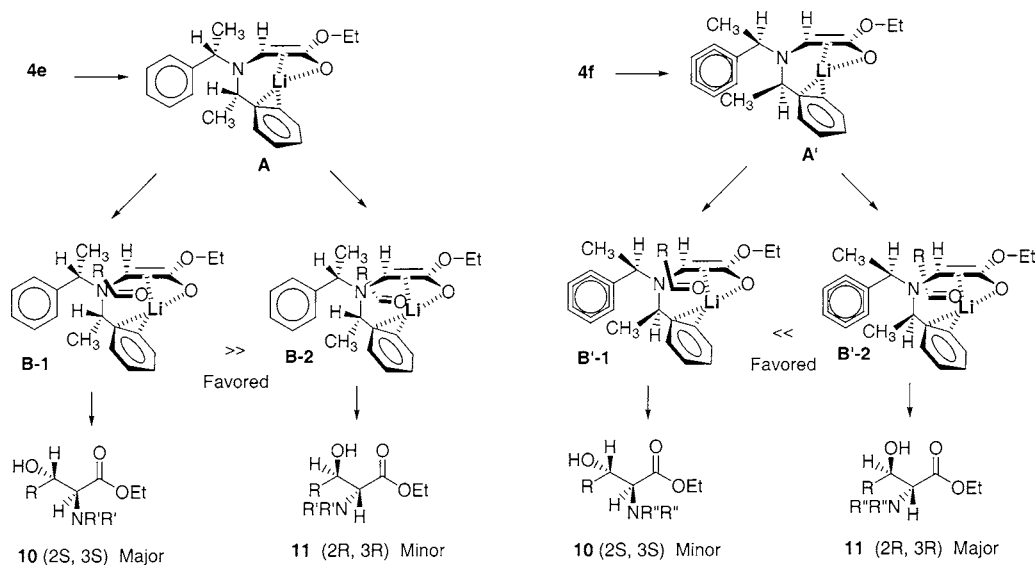
In an attempt to elucidate the transition state leading to stereoselectivity, we submitted **6e** to X-ray analysis.¹⁵ The crystal structure of **6e** reveals that the two phenyl rings in the benzyl groups are perpendicular, and they are kept fairly rigid by the two methyl groups (Figure 2).

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 (*2S,3S*)- β -hydroxyamino ester **10** should be predominately formed from **B-1**, and **B-2** would lead to the minor product, the (*2R,3R*)-isomer **11**. This would be reversed in the case of **4f**, to form the (*2R,3R*)- β -hydroxyamino ester **11** (from **B'-2**) as the favored product and the (*2S,3S*)-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

(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 ¹H NMR spectra and TLC analyses.

(10) (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1741. (b) Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481.

(11) Stereochemistry of products **10a–d** and **11a–d** listed in Table 2 was determined by ¹H NMR spectra and optical rotations. Also, the products were deprotected by hydrogenation to give the corresponding amino esters. ¹H 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.; Manaviyar, 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.

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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(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.