ORGANIC LETTERS

2003
Vol. 5, No. 13
2331−2334

Stereocontrolled Synthesis of 3-(*trans*-2-Aminocyclopropyl)alanine, a Key Component of Belactosin A

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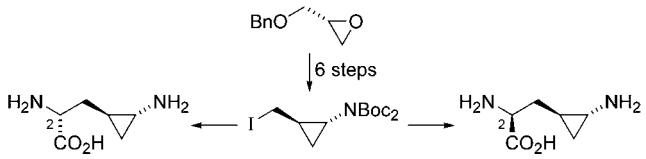
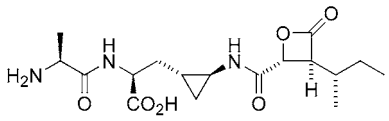
Received April 24, 2003

ABSTRACT



Herein we report a concise synthesis of 3-(*trans*-2-aminocyclopropyl)alanine, a component of belactosin A, using asymmetric alkylation of a glycine enolate in the presence of chiral phase-transfer catalysts to control the configuration at C2. Reaction of protected glycidol with triethyl phosphonoacetate (Wadsworth–Emmons cyclopropanation) is used for enantiospecific preparation of an intermediate cyclopropanecarboxylate that is converted to a cyclopropylamine via Curtius rearrangement.

Belactosin A **1** is a recently isolated *Streptomyces* metabolite that mediates cell-cycle progression via inhibition of cyclin−cdk complexes and is therefore of interest as a potential antitumor agent.[1] Reports in the patent literature also suggest that this compound and analogues effect proteasome inhibition.[1b]



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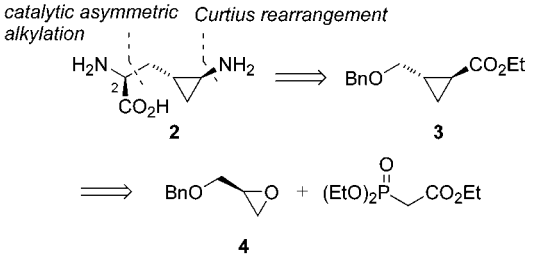
A particularly interesting feature of **1** is the presence of the unique central (2*S*,1′*R*,2′*S*)-3-(*trans*-2-aminocyclopropyl)-alanine amino acid **2**. An efficient stereocontrolled route to **2** with the flexibility to provide other stereoisomers in a controlled fashion would provide access to an expanded range of important compounds for screening and be applicable to a total synthesis of **1**. The only synthesis of **2** reported to date has come from the de Meijere group[2a] as part of their significant contributions to the synthesis of functionalized cyclopropanes.[2] However, their route to **2** required resolution by recrystallization to give enantiomerically pure material and prepared the compound as an inseparable mixture of diastereomers at the C2-stereocenter. We envisaged that reagent-controlled catalytic asymmetric alkylation of a glycine enolate equivalent would allow separate preparation of either C2-diastereomer, as well as provide a test of the methodology in a highly demanding molecular environment. Among several routes evaluated for the synthesis of the aminocyclopropane unit, the most concise appeared to proceed via Curtius rearrangement of the ester **3**, which we hoped could be accessed by reaction of the enantiomerically pure protected glycidol **4** with a phosphonate carbanion (Scheme 1). This reaction, which we term

(1) (a) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 81−83. (b) Asai, A.; Mizukami, T.; Yamashita, Y.; Akinaga, S.; Ikeda, S.; Kanda, Y. Eur. Patent 1166781, 2002; *Chem. Abstr.* **2002**, *133*, 120677.

(2) (a) Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O. V.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Synlett* **2000**, 1741−1744. (b) Wiedemann, S.; Frank, D.; Winsel, H.; de Meijere, A. *Org. Lett.* **2003**, *5*, 753−755. (c) Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869−877. (d) Zindel, A.; de Meijere, A. *J. Org. Chem.* **1995**, *60*, 2968−2073. (e) Zindel, J.; Zeeck, A.; König, W. A.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 1917−1920.

10.1021/ol0346887 CCC: $25.00
Published on Web 05/22/2003

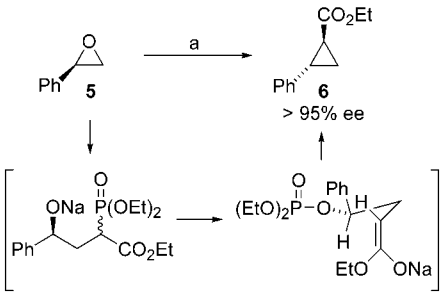
Scheme 1



the Wadsworth−Emmons cyclopropanation, has rarely been exploited in synthesis.[3] Here we report successful implementation of this strategy, leading to enantioselective synthesis of either C2-epimer of *ent*-**2**.

At the outset of our studies, the degree of stereospecificity of the Wadsworth−Emmons cyclopropanation reaction (and hence its applicability to complex total synthesis of this type) had not been determined, although optical rotation measurements suggested that the transformation proceeds with some degree of inversion at the epoxide stereocenter.[3b,c] We addressed this issue by demonstrating that enantiomerically pure (*R*)-styrene oxide **5** could be converted to the (*S*, *S*)-*trans*-2-phenylcyclopropanecarboxylate **6** of >95% ee, thus demonstrating essentially complete inversion of the epoxide configuration. This is in accord with the proposed mechanism (Scheme 2), which involves epoxide opening followed by

Scheme 2[a]



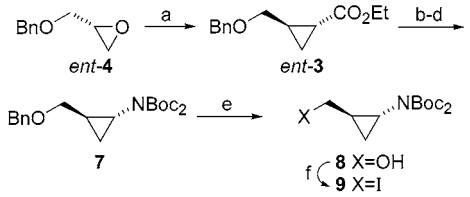
[a] Conditions: (a) triethyl phosphonoacetate, NaH, xylenes, 135 °C, 51%.

migration of the phosphonate group from carbon to oxygen and subsequent S_N2 ring closure. Recently, workers at Bristol-Myers Squibb have reported similar cyclopropanation of an aryl epoxide, confirming clean stereochemical inversion.[4]

(3) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. (b) Tomoskozi, I. *Tetrahedron* **1966**, *22*, 179−182. (c) Izydore, R. A.; Ghirardelli, R. D. *J. Org. Chem.* **1973**, *38*, 1790−1793. (d) Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279−1287. (e) Clive, D. L. J.; Daigneault, S. *J. Chem. Soc., Chem. Commun*. **1989**, 332−335. (f) Petter, R. C. *Tetrahedron Lett.* **1989**, *30*, 399−402. (g) Petter, R. C.; Banerjee, S.; Englard, S. *J. Org. Chem.* **1990**, *55*, 3088−3097. (h) Jacks, T. E.; Nibbe, H.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584−4588. (i) Robl, J. A.; Sieber-McMaster, E.; Sulsky, R. *Tetrahedron Lett.* **1996**, *37*, 8985−8988. (j) Meul, T.; Kampfen, U. U.S. Pat. 5149869, 1992; *Chem. Abstr*. **1992**, *118*, 38500. (k) Padmavathi, V.; Sharmila, K.; Reddy, A. S.; Reddy, D. B. *Ind. J. Chem. B.* **2001**, *40*, 11−14.

Encouraged by this result, we proceeded with the synthesis of **2** by applying the reaction to commercially available (*S*)-glycidol benzyl ether, *ent*-**4** (Scheme 3). Screening of a range

Scheme 3[a]



[a] Conditions: (a) triethyl phosphonoacetate, NaH, toluene, 110 °C, 14 h, 63%; (b) NaOH (aq), EtOH, 96%; (c) DPPA, ^{t}BuOH, NEt_3, 53%; (d) Boc_2O, MeCN, DMAP, 95%; (e) Pd/C, H_2, cat. AcOH, THF, 98%; (f) Bu_4NI, DDQ, PPh_3, $CHCl_3$, rt.

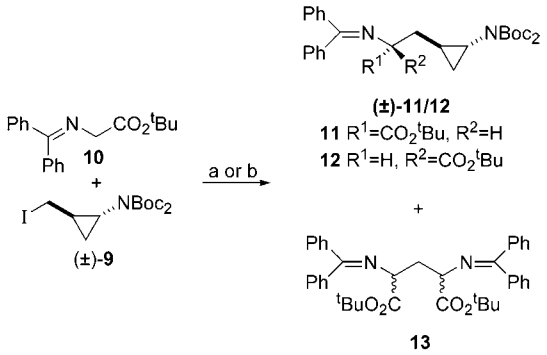
of solvents, bases, and temperatures (see Supporting Information) revealed that the highest yields were obtained using 2 equiv of phosphonate and NaH in toluene at 110 °C, providing the desired *ent*-**3** in 63% yield and >95% ee (analysis by ^{1}H NMR in the presence of Eu(hfc)$_3$ as chiral shift reagent). NOE studies confirmed the trans relative configuration of the cyclopropane. This reaction was performed equally successfully on (*R*)-glycidol benzyl ether **4**, providing **3** (>95% ee), which possesses the same absolute configuration as the natural product. With the aim of preparation of novel material for biological testing, we proceeded in the synthesis with the unnatural enantiomer *ent*-**3**. Pleasingly, hydrolysis of *ent*-**3** followed by Curtius rearrangement of the derived azide and Boc-protection afforded the cyclopropylamine **7**. Removal of the benzyl ether protecting group furnished (1′*R*,2′*R*)-(aminocyclopropyl)methanol **8**.

Exploratory work on the glycine enolate alkylation reaction established a need for iodide **9** as the electrophile, since other leaving groups (e.g., OMs, OTs) did not provide the necessary reactivity. However, preparation of **9** from **8** using several methods proved to be problematic due to the instability of **9**. Pleasingly, we were able to effect this transformation cleanly and in high yield using Ph_3P/DDQ/Bu_4NI,[5] with **9** being used directly due to its sensitivity upon chromatography and storage, as noted for its dideutero analogue.[2a] We next studied the alkylation of iodide **9** with the O'Donnell glycine equivalent **10** under phase-transfer conditions, with a view to eventually using chiral catalysts. We initially employed racemic **9** in order to ascertain the level of any intrinsic 1,3-asymmetric induction in the alkylation. However, attempts to perform the reaction under liquid−liquid PTC conditions (50% aqueous KOH, toluene) failed. Better results were obtained under solid−liquid-phase transfer conditions (Bu_4NBr catalyst). In CH_2Cl_2 as a solvent, however, the inseparable protected (aminocyclopropyl)-

(4) Singh, A. K.; Rao, M. N.; Simpson, J. H.; Li, W.; Thornton, J. E.; Kuehner, D. E.; Kacsur, D. J. *Org. Proc. Res. Dev.* **2002**, *6*, 618−620.

(5) Iranpoor, N.; Firouzabadi, H.; Aghapour, Gh; Vaez zadeh, A. R. *Tetrahedron* **2002**, *58*, 8689−8693.

Scheme 4[a]



[a] Conditions: (a) 2 equiv of **10**, KOH (s), 10 mol % Bu_4NBr, CH_2Cl_2, rt, 14 h, 30% **11/12** (from **8**), 51% **13** (*meso*:C_2 87:13); (b) 1 equiv of **10**, KOH (s), 10 mol % Bu_4NBr, toluene, rt, 14 h, 55% **11/12** (from **8**).

alanines **11** and **12** were obtained in only 30% yield in a 53:47 ratio, confirming a lack of 1,3-induction. Interestingly, a major side product was the 1,3-diamino acid derivative **13**, which formally arises from double alkylation of dichloromethane. While side-products of this type have been observed in phase-transfer-catalyzed alkylations using other nucleophiles,[6] to the best of our knowledge, it has not been reported previously in alkylations of **10** and serves as a warning of the potential reactivity of CH_2Cl_2 solvent when relatively unreactive electrophiles are employed. Switching to toluene solvent afforded a yield of 55% (44:56 dr) of (±)-**11/12** over two steps from alcohol **8** (Scheme 4).

With success in the racemic alkylation, we now turned our attention to asymmetric catalysis using quaternary ammonium salts derived from cinchona alkaloids. Following the pioneering work of O'Donnell et al.,[7] important structural modifications made independently by Corey and Lygo[8] have led to exceptional enantioselectivities using third-generation catalysts such as the *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium (**14**) and cinchonium (**15**)[9] bromides. We began by using **14**, which precedent suggested should provide the (2*S*)-stereoisomer. However, extensive optimization was required in order to accomplish efficient reaction with the demanding electrophile **9** (Table 1). Toluene was selected initially as a solvent in order to avoid the bis-alkylation of CH_2Cl_2 observed in the racemic series. With 10 mol % catalyst **14** (with respect to glycine) and 10 equiv of solid $CsOH\cdot H_2O$ at −20 °C in toluene, only 29% de was observed (entry 1), but this was improved to 38% de through the addition of 4 Å molecular sieves (entry 2). This effect has previously been attributed to a closer contact cation−anion pair being generated in the absence of water.[10] Through further lowering of the temperature to −40 °C, a dramatic increase in selectivity was observed (>95% de, entry 3). However, the reaction was prohibitively slow, with only ca. 53% conversion after 7 days. Increasing the concentration of reactants increased the conversion but only to ca. 70% after 6 days (entry 4). We reasoned that the reduced reaction rate was due to the limited solubility of catalyst **14** in the toluene solvent. As a consequence, a 1:1 toluene/CH_2Cl_2 solvent mixture was utilized in the hope of improving catalyst solubility. In addition, a high iodide concentration was utilized to minimize any CH_2Cl_2 bis-alkylation. Gratifyingly, the desired iodide alkylation was complete in 40 h at −40 °C to give protected (aminocyclopropyl)alanine **12** in 66% yield and 97:3 dr (entry 5 and Scheme 5). In addition, the diastereoisomer with the natural relative configuration at C2, **11**, was successfully synthesized in 52% yield and 6:94 dr utilizing the pseudoenantiomeric catalyst **15** under the same conditions (Scheme 5). In this case, a single recrystallization provided diastereomerically pure material, and crystallographic analysis of **11** (Figure 1) also confirmed that the relative stereochemical outcome of asymmetric alkylation was in line with precedent. At this stage, correlation with

Table 1. Alkylation of **10** with **9** Catalyzed by **14**[a]

entry	temp/°C	[**9**] /M	equiv of **10**	time	de[d]	yield[e]/%
1[b]	−20	0.09	1.0	3 days	29	27
2	−20	0.09	1.0	3 days	38	40
3	−40	0.07	2.0	7 days	>95	28
4	−40	0.33	2.0	6 days	>95	50
5[c]	−40	0.22	2.0	40 h	>95	66

[a] **14** (10 mol % with respect to **10**), $PhCH_3$, 4 Å molecular sieves. [b] Molecular sieves omitted. [c] $PhCH_3/CH_2Cl_2$ (1:1) was used as a solvent. [d] Estimated by integration of the ^1H NMR spectrum. [e] Yield from **8**.

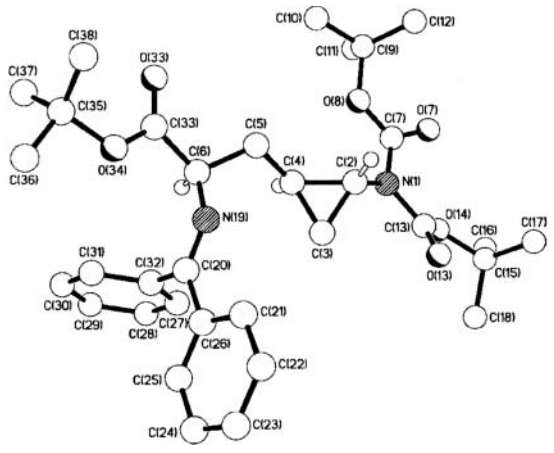


Figure 1. X-ray crystal structure of **11**.

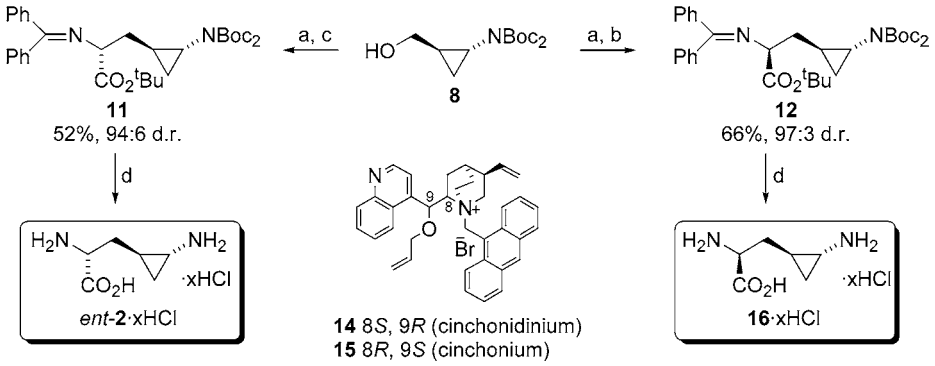
(6) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; VCH: Weinheim, Germany, 1993; p 72. Dalgaard, L.; Jensen, L.; Lawesson, S.-O. *Tetrahedron* **1974**, *30*, 93−104. Vinogradova, N. M.; Artyushin, O. I.; Kalyanova, R. M.; Lyssenko, K. A.; Petrovskii, P. V.; Mastryukova, T. A.; Kabachnik, M. I. *Russ. Chem. Bull.* **1998**, *47*, 960−966.

(7) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355. O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507−4518.

(8) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598.

(9) O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347−6362.

Scheme 5[a]



[a] Conditions: (a) Bu_4NI, DDQ, PPh_3, $CHCl_3$, rt; (b) 2 equiv of **10**, 20 mol % **14**, 10 equiv of $CsOH \cdot H_2O$ (s), 1:1 toluene/CH_2Cl_2, −40 °C, 40 h; (c) 2 equiv of **10**, 20 mol % **15**, 10 equiv of $CsOH \cdot H_2O$ (s), 1:1 toluene/CH_2Cl_2, −40 °C, 40 h; (d) 1.2 M HCl (aq)/THF, rt, 48 h.

the reported data for the natural product was possible via global deprotection of **11** and **12** and comparison with ^{1}H NMR data for 3-(2-aminocyclopropyl)alanine·HCl obtained by degradation of the natural product. Gratifyingly, the ^{1}H NMR spectrum of *ent*-**2** was in very good agreement with that of the genuine sample,[1b] confirming the reported stereochemical assignment.

In conclusion, we have developed a concise synthesis of either C2-epimer of the unusual cyclopropylamine amino acid *ent*-**2**. The synthesis highlights the under-exploited Wadsworth−Emmons procedure for the enantiospecific formation of cyclopropanes, as well as the extension of catalytic asymmetric alkylation of glycine enolate equivalents to highly functionalized, relatively unreactive electrophiles. We anticipate that selective removal of the imine functionality in **11** and *mono*-Boc-deprotection will allow *ent*-**2** to be incorporated into biologically significant analogues of belactosin A. The total synthesis of the natural product will require the synthesis of **2** and will thus proceed via cyclopropanation of (*R*)-glycidol benzyl ether, which we have already shown to be feasible. Further studies in this area will be reported in due course.

Acknowledgment. We thank the EPSRC (studentship to J.N.S.) for support of this work. We are grateful to Pfizer, Merck Sharp and Dohme, AstraZeneca, and Bristol-Myers Squibb for unrestricted support of our research programs. We thank Dr. A. Asai of Kyowa Hakko Kogyo Co., Ltd., for supplying ^{1}H NMR data for **2** and Dr. A. J. P. White for the X-ray structure determination.

Supporting Information Available: Experimental procedures and spectroscopic characterization information; details of optimization of reaction conditions for formation of *ent*-**3** and ee determination; ^{1}H NMR spectrum and NOE data for *ent*-**3**; NOE data for **7**; ^{1}H NMR spectra of **11**, **12**, *ent*-**2**·*x*HCl, **16**·*x*HCl; and X-ray structural data of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0346887

(10) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567−1571.