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Synthesis of β,γ-Dihydroxyhomotyrosines by a Tandem Petasis–Asymmetric Dihydroxylation Approach

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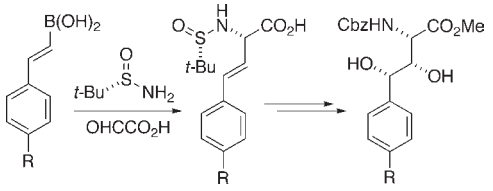
ABSTRACT



Petasis reactions of substituted styrenylboronic acids and glyoxylic acid, employing *tert*-butylsulfinamide as the 'amine' component, proceed with high stereoselectivity to produce β,γ-dehydrohomoarylalanine derivatives. Subsequent asymmetric dihydroxylation under neutral conditions gives the corresponding protected β,γ-dihydroxyhomoarylalanines with up to 15:1 dr. The method has been exploited in the efficient, stereoselective synthesis of protected β,γ-dihydroxyhomotyrosine, a component of the antifungal cyclic peptide echinocandin B.

The echinocandins (Figure 1) are a family of cyclic peptide natural products isolated from *Aspergillus ruglosus* and *Aspergillus nidulan* that constitute a novel class of potent antifungal agents with low mammalian toxicity.[1] Several semisynthetic members of the echinocandin family have recently been approved for clinical use in the treatment of invasive fungal infections.[2]

The total synthesis of echinocandin D,[3] the simplest member of the family, has been reported while echinocandin B has not succumbed to total synthesis, in part due to the limited procedures for preparation of highly hydroxylated amino acids. The only synthesis to date of a dihydroxyhomotyrosine derivative was reported by Palomo et al.,[4] which incorporates an early asymmetric dihydroxylation and subsequent imine-ketene [2 + 2] cycloaddition and Baeyer–Villiger oxidation as key steps in the multistep synthesis.

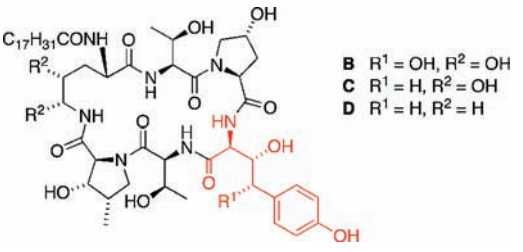


Figure 1. Echinocandins.

We envisaged a concise, stereoselective preparation of dihydroxyhomotyrosine derivatives in which the three contiguous stereocenters would be generated in two key

(1) Denning, D. W. *J. Antimicrob. Chemother.* **2002**, *49*, 889.
(2) Morris, M. I.; Villmann, M. *Am. J. Health Syst. Pharm.* **2006**, *63*, 1693.
(3) (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron* **1993**, *49*, 6195. (c) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041. (d) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6043.
(4) Palomo, C.; Oiarbide, M.; Landa, A. *J. Org. Chem.* **2000**, *65*, 41.

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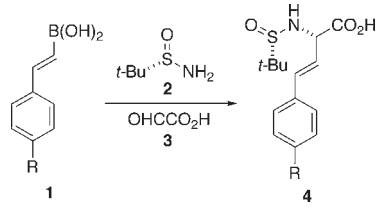
asymmetric steps. The diol functionality would be introduced through a late-stage asymmetric dihydroxylation,[5] with the requisite β,γ-unsaturated amino acid directly accessible through a Petasis reaction of a styrenylboronic acid.[6]

Table 1. Petasis Reactions with *tert*-Butylsulfinamide



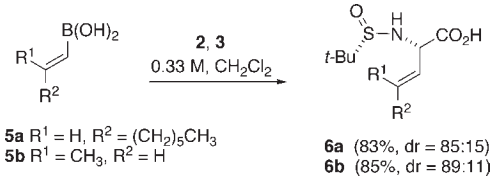
entry	R	yield %[a]	yield %[b]	dr
a	H	55 (65[c])	94	10:1
b	Me	55 (65[c])	99	20:1
c	Ph		90	20:1
d	OAc		99	18:1
e	OMe		99	>20:1
f	Cl		95	13:1
g	F		90	>20:1

[a] 0.2 M in CH_2Cl_2, rt, 48 h. [b] 0.33 M in CH_2Cl_2, rt, 12 h. [c] 0.2 M in 9:1 CH_2Cl_2/HFIP, rt, 2 h.

We have previously reported the preparation of β, γ-unsaturated homoarylalanine derivatives through Petasis reactions employing *N*-benzylphenylglycinol as the chiral amine.[7] However, these reactions proceeded with poor diastereoselectivity. Further, *N*-benzylic groups are typically removed by hydrogenolysis, which also reduces the olefin, and we therefore wished to discover a chiral amine-type auxiliary that was removable under non-hydrogenolytic conditions. Naskar and co-workers reported the use of *tert*-butylsulfinamide in Petasis reactions with arylboronic acids to generate arylglycines, but with no diastereoselectivity.[8] We were intrigued to further explore the use of *tert*-butylsulfinamide in Petasis reactions, both as a chiral amine equivalent and due to the fact that the *tert*-butylsulfinyl group can be removed under mildly acidic conditions.[9]

Accordingly, the Petasis reactions of glyoxylic acid **3** and *tert*-butylsulfinamide **2** with a range of substituted styrenylboronic acids **1a**–**g** were investigated. Initial results were encouraging, with the Petasis adducts produced in reasonable yield and, surprisingly, with significant diastereoselectivity (entries a–b, Table 1). Nevertheless, reactions only proceeded to ~70% conversion after 48 h (55% isolated yield) and longer reaction times did not improve the yield. Increasing the temperature, use of additives such as molecular sieves or magnesium sulfate, and use of excess reactants all failed to improve the yield. Addition of hexafluoroisopropanol (HFIP) increased the reaction rate[10] such that yields of 65% were obtained after just 2 h, yet complete conversion was still elusive. Following extensive optimization it was found that conducting reactions at a higher concentration (0.33 vs 0.2 M) resulted in the reactions proceeding to complete conversion, with products isolated in >90% yield. The marked increase in yield and rate at a higher concentration is possibly due to a combination of second-order kinetic effects and a solubility effect where precipitation of the product drives the reaction to completion.[11]

Scheme 1



To further probe the scope of the use of *tert*-butylsulfinamide **2** in the Petasis reaction, *trans*-octenyl boronic acid **5a** and *cis*-propenyl boronic acid **5b** were employed under the newly developed conditions (Scheme 1), providing the corresponding unsaturated amino acid derivatives **6a** and **6b**, respectively, in good yield and stereoselectivity.

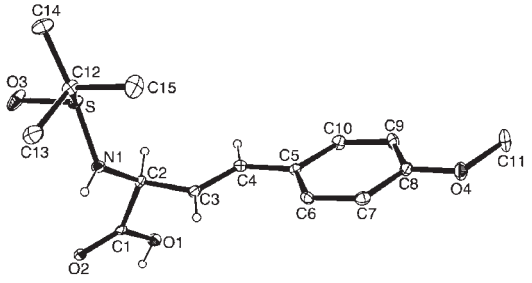


Figure 2. ORTEP of *N*-sulfinylamino acid **4e**.

The relative stereochemistry of the unsaturated amino acid derivatives was determined by X-ray crystallographic

(5) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(6) (a) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. (b) Kaiser, P. F.; Churches, Q. I.; Hutton, C. A. *Aust. J. Chem.* **2007**, *60*, 799. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.

(7) (a) Churches, Q. I.; Johnson, J. K.; Fifer, N. L.; Hutton, C. A. *Aust. J. Chem.* **2011**, *64*, 62. (b) Churches, Q. I.; Stewart, H. E.; Cohen, S. B.; Schröder, A.; Turner, P.; Hutton, C. A. *Pure Appl. Chem.* **2008**, *80*, 687.

(8) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865.

(9) (a) Buesking, A. W.; Baguley, T. D.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 964. (b) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (c) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.

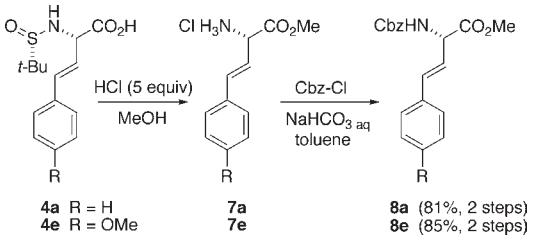
(10) Nanda, K. K.; Trotter, W. B. *Tetrahedron Lett.* **2005**, *46*, 2025.

(11) (a) Li, L.; Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 11648. (b) Zhang, W.; Brombosz, S. M.; Mendoza, J. L.; Moore, J. S. *J. Org. Chem.* **2005**, *70*, 10198. (c) Ulijn, R. V.; De Martin, L.; Gardossi, L.; Janssen, A. E. M.; Moore, B. D.; Halling, P. J. *Biotechnol. Bioeng.* **2002**, *80*, 509.

analysis of the *p*-methoxy-substituted product **4e**, which indicated that the (*S*,*S*)-isomer was formed as the major product (Figure 2).

The *N*-sulfinyl amino acids **4** were sparingly soluble in organic solvents. Accordingly, we sought to switch the *N*-sulfinyl group to a more commonly used amino acid protecting group. Treatment of the *N*-sulfinyl amino acids **4a** and **4e** with hydrochloric acid in methanol resulted in cleavage of the sulfinamide group and concomitant esterification to the corresponding methyl esters **7a** and **7e**, respectively (Scheme 2). Subsequent protection of the amine as the Cbz-carbamate gave protected dehydrohomoarylalanine derivatives **8a**,**e**. Use of biphasic reaction conditions in conjunction with an inorganic base was found to be essential to achieving good yields of the Cbz-protected products **8**. Employing homogeneous conditions with triethylamine as base led to rapid base-catalyzed isomerization to the conjugated α,β-unsaturated ester.

Scheme 2



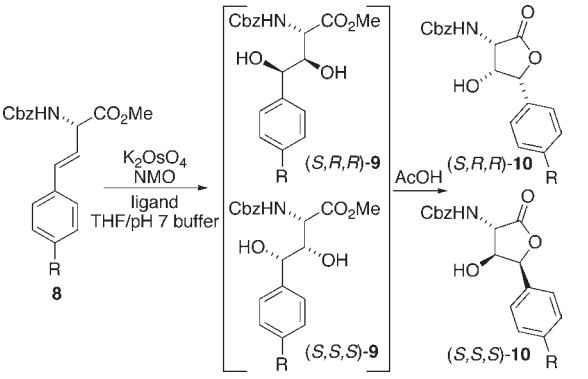
A 'one pot' process was ultimately developed for the combined *N*-sulfinyl deprotection, esterification, and carbamylation process, giving high isolated yields of dehydrohomophenylalanine and dehydrohomotyrosine derivatives, **8a** and **8e**, respectively (Scheme 2).

With Petasis reactions employing *tert*-butylsulfinamide providing rapid access to β,γ-unsaturated amino acid derivatives in high yield and diastereoselectivity, asymmetric dihydroxylation to furnish the dihydroxyhomotyrosine target was investigated.

Treatment of dehydrohomophenylalanine **8a** with either of the commercially available AD-mixes under standard conditions[12] did not result in dihydroxylation; instead base-catalyzed isomerization to the α,β-dehydrohomophenylalanine was observed.

Bicarbonate-buffered conditions were employed in an attempt to reduce isomerization,[13] but starting materials were recovered. Use of THF/pH 7 aqueous buffer was ultimately found to facilitate dihydroxylation.[14] Under ligand-free conditions, a good yield of the dihydroxylated product resulted, however, as a mixture of methyl ester **9a** and lactone **10a**. Presumably, subsequent lactonization of the diol-ester **9a** occurs at a similar rate to the dihydroxylation to provide a mixture of **9a** and **10a**. To facilitate analysis of the diastereoselectivity of the reaction, complete conversion to the lactone **10a** was effected by treatment during workup with acetic acid at 40 °C for 30 min. The lactone **10a** was isolated in 57% yield as a 1.5:1 ratio of diastereomers, indicating weak substrate-induced stereoselectivity (Table 2, entry 1).

Table 2. Ligand Screen for Asymmetric Dihydroxylation of **8**



entry	R	ligand	yield % of **10**	dr[a]
1	H	none	57	1.5:1
2	H	$(DHQD)_2$-PHAL	79	14:1
3	H	$(DHQ)_2$-PHAL	86	6:1
4	H	$(DHQD)_2$-AQN	74	1:1.4
5	H	$(DHQ)_2$-AQN	77	5:1
6	H	$(DHQD)_2$-PYR	89	2.2:1
7	H	$(DHQ)_2$-PYR	64	2:1
8	OMe	$(DHQD)_2$-PHAL	97	15:1
9	**OMe**	**$(DHQ)_2$-PHAL**	**74**	**1:5**
10	OMe	$(DHQD)_2$-AQN	84	9:1
11	OMe	$(DHQ)_2$-AQN	81	8:1
12	OMe	$(DHQD)_2$-PYR	99	1.2:1
13	OMe	$(DHQ)_2$-PYR	67	1.2:1

[a] (*S*,*R*,*R*):(*S*,*S*,*S*).

With conditions enabling efficient dihydroxylation in hand, the addition of chiral ligands was investigated toward developing highly stereoselective AD reaction conditions. Use of $(DHQD)_2$-PHAL gave the lactone

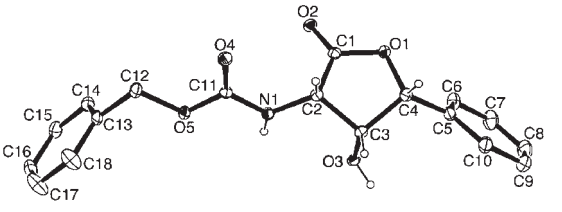


Figure 3. ORTEP of lactone (*S*,*R*,*R*)-**10a**.

(12) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(13) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Tetrahedron Lett.* **2003**, *44*, 2869.

(14) Anderson, E. A.; Holmes, A. B.; Collins, I. *Tetrahedron Lett.* **2000**, *41*, 117.

10a in 79% yield and in an excellent diastereomeric ratio of 14:1. X-ray crystallographic analysis of the major product established the configuration of the major isomer as the undesired (*S*,*R*,*R*)-isomer (Figure 3).

It was envisaged that use of the pseudoenantiomeric ligand $(DHQ)_2$-PHAL would furnish the desired (*S*,*S*,*S*)-isomer. However, replacing $(DHQD)_2$-PHAL with $(DHQ)_2$-PHAL gave a 6:1 d.r. of lactone **10a** again favoring the (*S*,*R*,*R*)-isomer (Table 2, entry 3).

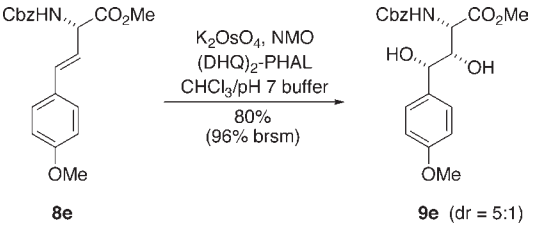
The failure of pseudoenantiomeric ligands to direct opposite facial selectivity in the dihydroxylation of allylic *N*- and *O*-substituted olefins is a reasonably common occurrence.[15−17] Screening a range of cinchona-derived ligands has been shown to overcome such issues,[17] and accordingly a variety of chiral ligands were employed in AD reactions of the dehydrohomophenylalanine derivative **8a** (Table 2, entries 2−7). The $(DHQD)_2$-AQN ligand was the only one to provide even low selectivity in favor of the (*S*,*S*,*S*)-isomer (dr 1:1.4, entry 4).

With no discernible trend in the stereoselectivity of the dihydroxylation reactions of **8a** (R = H), it was decided to examine the corresponding reactions of the dehydrohomotyrosine derivative **8e** (R = OMe) with a range of chiral ligands (entries 8−13). To our surprise, use of $(DHQD)_2$-AQN—the only ligand to direct selectivity toward the desired (*S*,*S*,*S*)-isomer of **10a**—resulted in selectivity for the undesired (*S*,*R*,*R*)-diastereomer of the methoxy-substituted derivative **10e** (dr 9:1, entry 10). Fortunately, $(DHQ)_2$-PHAL was found to yield the desired (*S*,*S*,*S*)-configured dihydroxy-homotyrosine lactone **10e** with good selectivity (dr 1:5, entry 9).

It is apparent that several factors are affecting the stereoselectivity of the dihydroxylation reactions of **8a** and **8e**. There are not only different binding interactions with the different ligands, and matched/mismatched effects of the ligands with the chiral substrates, but also the inherent facial bias directed by the allylic stereocenter.[18] In addition, there is the effect of the different substituents (H vs OMe) on the electronic nature of the olefins. The subtle interplay of these multiple factors makes it difficult to interpret the seemingly random nature of the stereoselectivities observed under different conditions.

Next, given that Edagwa and Taylor recently reported that γ-lactones arising from β,γ-dihydroxy amino acids are unsuitable for incorporation into peptide synthesis,[19] conditions were sought that minimized lactonization of the diol. The homogeneous aqueous THF solvent mixture was therefore changed to a biphasic system. Conducting the dihydroxylation reaction of **8e** in chloroform/pH 7 aqueous buffer provided the desired diol ester **9e** in 80% yield (96% based on recovered starting material), with no lactonization evident (Scheme 3). The diastereoselectivity was the same as that observed in the homogeneous reaction.

Scheme 3



8e **9e** (dr = 5:1)

In conclusion, an efficient and stereoselective route to β,γ-dihydroxyamino acid derivatives has been developed through a Petasis reaction−AD approach that generates the three contiguous stereocenters in two key steps. The route was exemplified through synthesis of the β,γ-dihydroxyhomotyrosine component of echinocandin B. Importantly, the use of *tert*-butylsulfinamide as the 'amine' component in Petasis reactions with vinylboronic acids was shown to proceed in excellent yield and stereoselectivity. Further, the *tert*-butylsulfinyl group is removed under mild, acidic conditions that do not affect the olefin, such that it is available for further elaboration. The judicious choice of AD reaction conditions to suppress ester hydrolysis, epimerization and lactonization enables synthesis of all isomers of the corresponding *syn*-β,γ-dihydroxyamino acid derivatives.

Acknowledgment. The Australian Research Council is acknowledged for support.

Supporting Information Available. Full experimental details, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.
(16) Thoen, J. C.; Morales-Ramos, A. I.; Lipton, M. A. *Org. Lett.* **2002**, *4*, 4455.
(17) Iwashima, M.; Kinsho, T.; Smith, A. B., III. *Tetrahedron Lett.* **1995**, *36*, 2199.
(18) (a) Krysan, D. J.; Rockway, T. W.; Haight, A. R. *Tetrahedron: Asymmetry* **1994**, *5*, 625. (b) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094. (c) Houk, K. N.; Moses, l. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (d) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.
(19) Edagwa, B. J.; Taylor, C. M. *J. Org. Chem.* **2009**, *74*, 4132.