ORGANIC LETTERS

2000
Vol. 2, No. 17
2571−2573

An Asymmetric Aminohydroxylation Approach to the Azepine Core of (−)-Balanol

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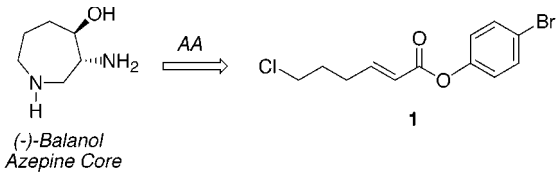
Received May 25, 2000

ABSTRACT



An efficient formal synthesis of the potent protein kinase C inhibitor (−)-balanol that relies on a modified asymmetric aminohydroxylation of the α,β-unsaturated aryl ester (1) is reported. The aryl ester functionality and the dihydroquinyl alkaloid ligand system $(DHQ)_2$−AQN are used to control the regio- and enantioselectivity of the process.

(−)-Balanol (**1**, Figure 1), an unusual metabolite first isolated from the fungus *Verticillium balanoides*[1] in 1993 and again in 1994 from another fungus, *Fusarium merismoides*,[2] is a potent inhibitor of human protein kinase C (PKC). This enzyme class plays a crucial role in signal transduction pathways that lead to a variety of cellular responses including gene expression and cellular proliferation.[3] Consequently, this family of enzymes represents a critical biological target for the development of anticancer agents and therapeutic agents for controlling inflammation, central nervous system disorders, cardiovascular disorders, and even HIV infection.

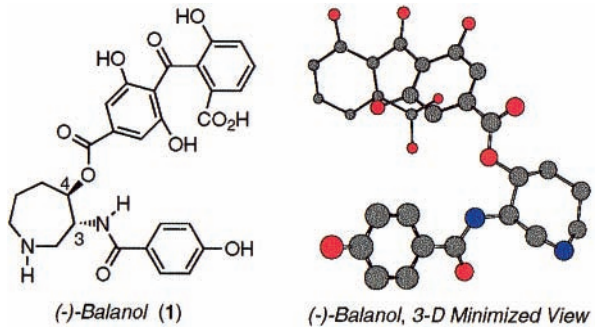


Figure 1. Energy-minimized view of (−)-balanol.[4]

Despite the fact that the selectivity of **1** for the known PKC isoenzymes is low, it has displayed potent activity with IC_{50} values in the 5−9 nM range[5] for the α, β-I, β-II, γ, δ, ϵ, and η PKCs, making (−)-balanol an ideal lead structure. The structure and absolute configuration of the natural product were determined by NMR and X-ray crystallographic analysis.[1] These results showed an *anti* orientation of the substituents at C3 and C4 and established the absolute configuration as 3*R*,4*R*. A stereoview of an energy-minimized (−)-balanol conformation illustrating its associated structural elements is shown in Figure 1. Because of its potent inhibitory properties, (−)-balanol has been the focus of numerous synthetic efforts. Recently, Naito and co-workers reported an approach to the azepine core which centered

(1) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452−6453.

(2) Ohshima, S.; Yanagisawa, M. Katoh, A.; Fujii, T.; Sano, T.; Matsukama, S.; Furumai, T.; Fujiu, M.; Watanabe, K.; Yokose, K.; Arisawa, M.; Okuda, T. *J. Antibiot.* **1994**, *47*, 639−641.

(3) Nishizuka, Y. *Science* **1992**, *258*, 607−614. (b) Nishizuka, Y. *Nature* **1988**, *334*, 661−665.

(4) Three-dimensional modeling was carried out with Chem 3D Pro using MM2 minimization techniques.

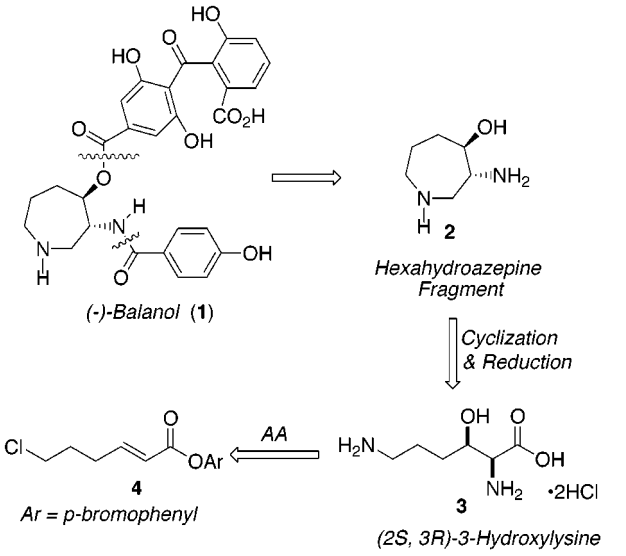
(5) Boros, C.; Hamilton, S. M.; Katz, B.; Kulanthaivel, P. *J. Antibiot.* **1994**, *47*, 1010−1016.

10.1021/ol0061034 CCC: $19.00
Published on Web 07/26/2000

around a SmI_2-mediated intramolecular radical cyclization of oxime ethers.[6] This methodology afforded the azepine core as a 6.6:1 mixture of diastereomers; however, the major isomer required a lipase resolution at a later stage in the synthesis. A racemic total synthesis of balanol was achieved by Adams and co-workers in 1995 utilizing a ring expansion of 3-bromopiperidin-4-ones to access the azepine core.[7] The Tanner group utilized a regio- and stereoselective opening of a chiral epoxide to control the C3−C4 stereogenic centers of the heterocycle.[8] An asymmetric synthesis of balanol was reported by Nicolaou and co-workers using D-serine and an asymmetric allylation with $[Ipc]_2$B-allyl to install the vicinal amino alcohol functionality as a 12:1 mixture of diastereomers.[9] Hughes and Lampe utilized (2*S*,3*R*)-hydroxylysine as a key synthon in their total synthesis of balanol.[10] However, the preparation of the hydroxylysine synthon required eight steps, which resulted in a somewhat lengthy synthesis. Additionally, a number of formal syntheses of the hexahydroazepine core **2** have been reported.[11] It was our intention to develop a streamlined approach to enantiomerically pure **2** which would make use of a modified aminohydroxylation methodology to construct the (2*R*,3*S*)-hydroxylysine needed for the rapid assembly of the azepine core.

Our synthetic plans for the construction of the azepine core of (−)-balanol centered around the use of the modified asymmetric aminohydroxylation (AA) methodology developed in our laboratories and recently applied in our synthesis of (+)-lactacystin.[12] This AA methodology is capable of installing the C3−C4 stereocenters in an efficient one-step procedure provided the proper regiochemical outcome could be achieved in the AA process. Our retrosynthetic analysis is illustrated in Scheme 1. Disconnection of the ester linkage

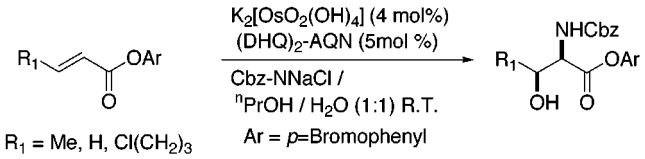
Scheme 1



of (−)-balanol affords the azepine and aromatic fragments. The hexahydroazepine core of (−)-balanol (**2**) can be further disconnected to the hydroxylysine synthon (**3**). Cyclization of **3** to the ϵ-caprolactam and reduction of the amide would afford the hexahydroazepine core.

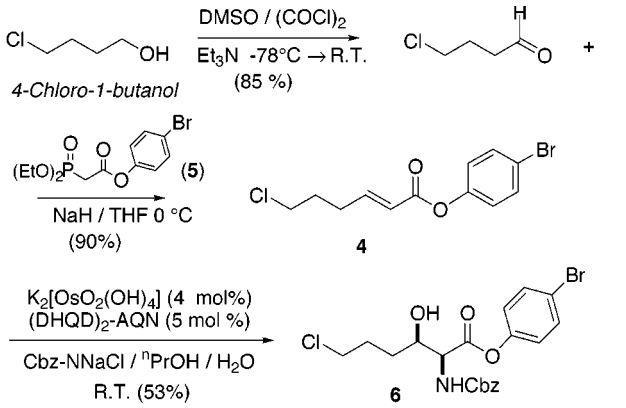
We have previously demonstrated that the asymmetric aminohydroxylation of *p*-bromo-substituted aryl esters of various β-substituted acrylate systems provides access to unnatural amino acid derivatives including the desired hydroxylysine derivative for use in the synthesis of the hexahydroazepine core of (−)-balanol (Scheme 2).[12a]

Scheme 2



The preparation of substrate **4** and its conversion to the hydroxylysine synthon starting from commercially available 4-chloro-1-butanol are shown in Scheme 3. Swern oxidation

Scheme 3



of 4-chloro-1-butanol provided 4-chlorobutanal which was subjected to a Horner−Emmons olefination with diethyl (*p*-bromophenyl)phosphonate **5** to give the requisite olefin **4** in

(6) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397−4407.
(7) Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem Soc., Perkin Trans. 1* **1995**, 2335−2362.
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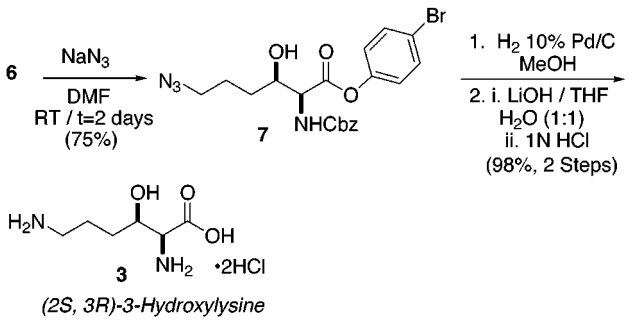
77% overall yield. The asymmetric aminohydroxylation of **4** proceeded as expected to afford the α-amino-β-hydroxy ester **6** with good levels of enantioselection (82% ee). The ratio of regioisomers was >20:1 as determined by ^{1}H NMR analysis of the crude product, and it was expected that the initial ee of 82%[13] could be enhanced at a later stage by recrystallization of the hydroxylysine bis-hydrochloride salt. This AA reaction resulted in the installation of the C3−C4 stereogenic centers in a single step with high levels of regioselectivity and useful levels of enantioselectivity. The high levels of enantioselection with these aryl ester substrates offset their susceptibility to saponification under the standard conditions of the AA reaction.[14] The degree of saponification can be attenuated by careful monitoring of the reaction by TLC; however, yields could be significantly improved by limiting the competing hydrolytic pathway. Attempts to reduce saponification by using the analogous *p*-bromobenzyl esters were less successful as these substrates proved less reactive in terms of the rate of the reaction and afforded generally lower levels of regio- and enantioselection.

Transformation of **6** to the hydroxylysine synthon is illustrated in Scheme 4 and commenced with a displacement

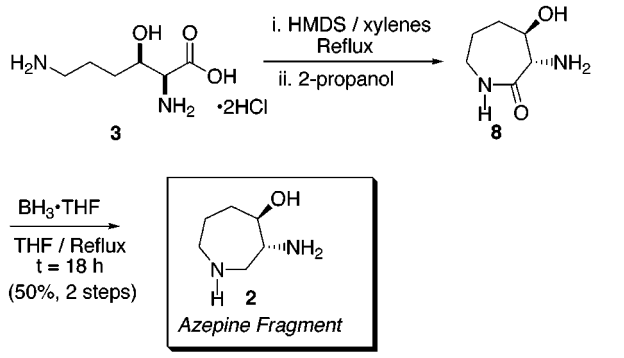
Scheme 4



of the primary chloride with an azide (NaN_3/DMF) to afford **7**. The terminal azido group served as the masked amino functionality of the hydroxylysine derivative. Hydrogenation of azide **7** resulted in deprotection of the Cbz group with simultaneous reduction of the azide moiety to give hydroxylysine *p*-bromophenyl ester which was immediately saponified to afford, after an acidic workup, (2*S*,3*R*)-hydroxylysine as its bis-hydrochloride salt (**3**).

Completion of the synthesis of the azepine core involved cyclization of **3** using a procedure from a recent patent.[15] The choice of these conditions stemmed from their successful application in the Hughes and Lampe synthesis.[10] As such, addition of **3** to hexamethyldisilazane in refluxing xylenes followed by treatment of the persilylated material with 2-propanol, to effect desilylation, afforded the ϵ-caprolactam (Scheme 5). Reduction of lactam **8** with excess borane (5.5

Scheme 5



equiv) furnished the hexahydroazepine core **2** in eight steps (from 4-chloro-1-butanol) with an overall yield of 16%. Azepine **2** proved identical in all respects to the corresponding compound obtained by Lampe and co-workers[10] (^{1}H and ^{13}C NMR, IR, HRMS, and optical rotation). The virtues of this approach are apparent from the concise nature of the synthetic route leading to the critical hydroxylysine synthon (**2**), the availability of starting materials, the mild reaction conditions employed, and the fact that either enantiomer of **2** can be accessed by proper choice of the alkaloid ligand in the AA reaction. Additionally, structural modifications to the azepine core can be addressed by selection of the olefinic substrate utilized in the AA protocol, allowing for the preparation of substituted azepine rings for SAR studies.

A formal total synthesis of (−)-balanol has been accomplished in a highly concise manner. The synthesis of the azpeine ring of (−)-balanol has been achieved in eight steps in an overall yield of 16%. In this synthesis, the target's two stereogenic centers are established using a Sharpless AA protocol with modified olefin substrates. The synthetic strategy should provide access to sufficient quantities of the azepine ring system for further biological evaluation and use as probes of protein kinase C activity.

Acknowledgment. This work has been financially supported by the National Institutes of Health (RO1GM55740). Support by a Pfizer PREPARE summer fellowship for A.J.M. is gratefully acknowledged.

Supporting Information Available: General experimental procedures and full characterization of compunds **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0061034

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