ORGANIC LETTERS

2007
Vol. 9, No. 23
4833−4836

Stereocontrolled Synthesis of 2,4-Diamino-3-hydroxyacids Starting from Diketopiperazines: A New Route for the Preparation of Statine Analogues

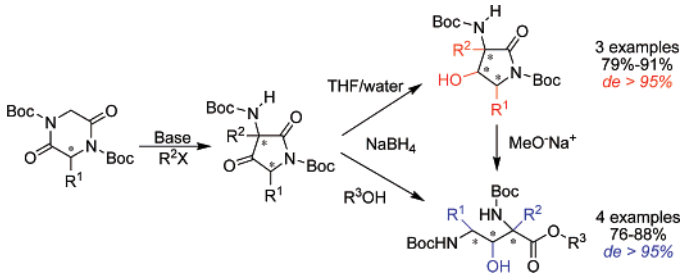
Daniel Farran,[†] Loïc Toupet,[‡] Jean Martinez,[†] and Georges Dewynter*,[†]

Institut des Biomolécules Max Mousseron, UMR 5247, Université Montpellier 2, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France, and Groupe Matière Condensée et Matériaux, UMR 6626, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France

dewynter@univ-montp2.fr

Received September 3, 2007

ABSTRACT



Chiral 3-aminopyrrolidine-2,4-diones, obtained by transannular rearrangement of activated diketopiperazines, could be a springboard toward an exceptional stereoselective synthesis of original 2-disubstituted statines. After a selective reduction of the pyrrolidine-2,4-diones, the access to opened 2,4-diamino-3-hydroxyacid esters was carried out by a subsequent alkaline treatment or directly through a tandem reduction-solvolysis.

Statines, β-hydroxy-γ-aminoacids, are potent transition state analogue inhibitors of aspartic proteases,[1] therapeutic targets in many diseases such as AIDS (HIV proteases),[2−4] malaria (plasmepsins),[5] cancer and Alzheimer's disease (cathepsin D, BACE, β-secretase),[5] hypertension (renin),[6−7] and congestive heart failure or bacterial infections (pepsin).[1,2,8,9] The 3,4-*syn* relative configuration of the amino and the hydroxyl groups of statines was demonstrated to be crucial to mimic the topography of the enzyme-bound peptide conformations (Figure 1).[8]

Furthermore, a subsequential C2 substitution proved to be also an important key structural element for biological activities. Janolusimide,[10] a tripeptide marine toxin, or bleomycin,[11,12] a glyco peptide-derived antitumor agent, have

[†] Institut des Biomolécules Max Mousseron.
[‡] Groupe Matière Condensée et Matériaux.

(1) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.
(2) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.
(3) Richards, A. D.; Roberts, R.; Dunn, B. M.; Graves, M. C.; Kay, J. *FEBS Lett.* **1989**, *247*, 113 and references therein.
(4) Richards, A. D.; Broadhurst, A. V.; Ritchie, A. J.; Dunn, B. M.; Kay, J. *FEBS Lett.* **1989**, *253*, 214 and references therein.
(5) Maly, D. J.; Huang, L.; Ellman, J. A. *ChemBioChem* **2002**, *3*, 16.
(6) Boger, J.; Lohr, N. S.; Ulm, E. H.; Poe, M.; Blaine, E. H.; Fanelli, G. M.; Lin, T.-H.; Payne, L. S.; Schorn, T. W.; LaMont, B. I.; Vassil, T. C.; Stabilito, I. I.; Veber, D.; Rich, D. H.; Bopari, A. S. *Nature* **1983**, *303*, 81.
(7) Guégan, R.; Diaz, J.; Cazaubon, J.; Beaumont, M.; Carlet, C.; Clément, J.; Demarne, H.; Mellet, M.; Richaud, J. P.; Segondy, D.; Vedel, M.; Gagnol, J.-P.; Roncucci, R.; Castro, B.; Corvol, P.; Evin, G.; Roques, P. B. *J. Med. Chem.* **1986**, *29*, 1152.
(8) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263.
(9) Kratzel, M.; Schlichtner, B.; Kirchmayer, R.; Bernkop-Schnürk, A. *J. Med. Chem.* **1999**, *42*, 2041.
(10) Giordano, A.; Della Monica, C.; Landi, F.; Spinella, A.; Sodano, G. *Tetrahedron Lett.* **2000**, *41*, 3979.

10.1021/ol7021593 CCC: $37.00
Published on Web 10/16/2007

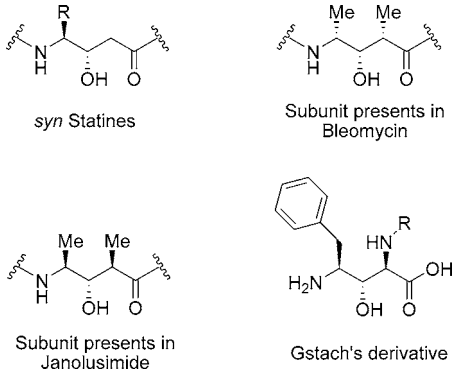


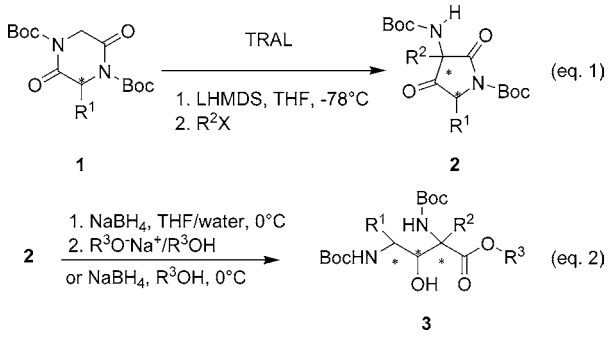
Figure 1. Statines derivatives.

been clinically introduced for the treatment of various malignancies, including those of the testes and lymph nodes (Figure 1). Relevant 2-amino statine compounds developed by Gstach et al.[13,14] were revealed to be more effective inhibitors of HIV-1 protease than related initial statine-containing compounds.

Owing to the importance of statine derivatives, several approaches for their synthesis have already been developed,[15] among which is the stereoselective reduction of tetramic acids.[16−22] It is remarkable, however, that only few examples of syntheses of 2-substituted statines are described in the literature, mainly taking advantage of ring opening of an α,*β*-epoxy ester,[23] aldol-type reactions,[24,25] or allylation reactions of protected α-amino aldehydes, followed by oxidative transformation of the olefinic moiety.[26] To date, to the best of our knowledge, no reports on the synthesis of 2-alkyl-2-amino-statine derivatives have been published.

We present here the first stereocontrolled synthesis of 2,4-dialkyl-2,4-diamino-3-hydroxyacid derivatives **3** (Scheme 1, eq 2). Our strategy was based on the recent observation that

Scheme 1. Synthesis of Statines Analogues

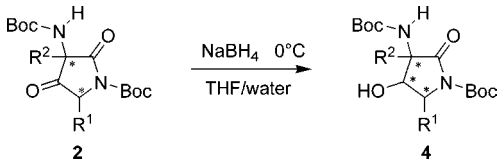


a transannular rearrangement of activated lactams (TRAL) leads to an exceptional stereocontrolled synthesis of pyrrolidine-2,4-diones **2** starting from 2,5-diketopiperazines **1** (Scheme 1, eq 1).[27,28]

We anticipated that a selective reduction and a suitable opening reaction of **2** would be expected to give the desired statine derivatives, allowing us to access to an important set of α,*γ*-diamino-*β*-hydroxyacid esters **3** by changing the nature of the DKP and/or the electrophilic agent R^2X (Scheme 1).

We first examined the reduction of pyrrolidine-2,4-diones **2** by the experimental procedure in the presence of $NaBH_4$ described by Leban.[29] The results are summarized in Table 1.

Table 1. Stereocontrolled Reduction of Pyrrolidine-2,4-diones



entry	2	R^1	R^2	product yield[a] (%)	de[b] (%)
1	**2a**	Me (*S*)	Me (*S*)	**4a** (80)	>95
2	**2b**	*i*Pr (*R*)	Bn (*R*)	**4b** (91)	>95
3	**2c**	*i*Pr (*R*)	CH_2=$CHCH_2$ (*R*)	**4c** (79)	>95

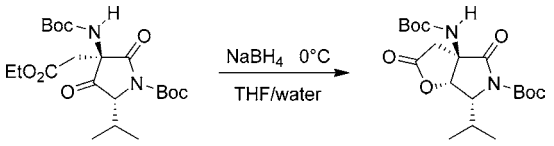
[a] Yield of isolated products after purification by flash chromatography. [b] The ^{13}C NMR spectrum of the crude material gave only one set of peaks. ^1H NMR spectrum ($^3J_{H4-H5} = 8-9$ Hz) was not sufficient to fully establish the configuration of C4. The confirmation will be brought afterward by X-ray diffraction analysis of a compound coming later in the synthesis (Scheme 4).

Unexpectedly, the reducing conditions proved to be highly chemoselective and diastereoselective, providing only the diastereoisomer **4** in good yield. This unprecedented stereo-

(11) Burger, R. M. *Chem. Rev.* **1998**, *98*, 1153.
(12) Boger, D. L.; Cai, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 448.
(13) Scholz, D.; Billich, A.; Charpiot, B.; Ettmayer, P.; Lehr, P.; Rosenwirth, B.; Schreiner, E.; Gstach, H. *J. Med. Chem.* **1994**, *37*, 3079.
(14) Lehr, P.; Billich, A.; Charpiot, B.; Ettmayer, P.; Scholz, D.; Rosenwirth, B.; Gstach, H. *J. Med. Chem.* **1996**, *39*, 2060.
(15) Castejon, P.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 7063 and references therein.
(16) Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3287.
(17) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177.
(18) Klutchko, S.; O'Brien, P.; Hodges, J. C. *Synth. Comm.* **1989**, *19*, 2573.
(19) Poncet, J.; Jouin, P.; Castro, B.; Nicolas, L.; Boutard, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 611.
(20) Bänziger, M.; McGarrity, J. F.; Meul, T. *J. Org. Chem.* **1993**, *58*, 4010.
(21) Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S. *Synthesis* **1993**, 216.
(22) Fehrentz, J. A.; Bourdel, E.; Califano, J.-C.; Chaloin, O.; Devin, C.; Garrouste, P.; Lima-Leite, A.-C.; Llinares, M.; Rieunier, F.; Vizavonna, J.; Winternitz, F.; Loffet, A.; Martinez, J. *Tetrahedron Lett.* **1994**, *35*, 1557.
(23) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477.
(24) Travins, J. M.; Bursavich, M. G.; Veber, D. F.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2725.
(25) Piveteau, N.; Audin, P.; Paris, J. *Synlett* **1997**, 1269.
(26) Le Carrer-Le Golf, N.; Audin, P.; Paris, J.; Cazes, B. *Tetrahedron Lett.* **2002**, *43*, 6325.
(27) Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 7488.
(28) Dewynter, G.; Farran, D.; Martinez, J. International Patent 0753973, deposited 03/21/2007.
(29) Leban, J. J.; Colson, K. L. *J. Org. Chem.* **1996**, *61*, 228.

chemistry could be correlated to steric factors, leaving the 4-hydroxyl and the 3-amino groups in a *trans* configuration in compound **4**. When R^2 is an alkyl chain substituted by an ester group (**2d**, Scheme 2), the reduction led interestingly

Scheme 2. Synthesis of Bicyclo Lactam-lactone with Garcinia Junction

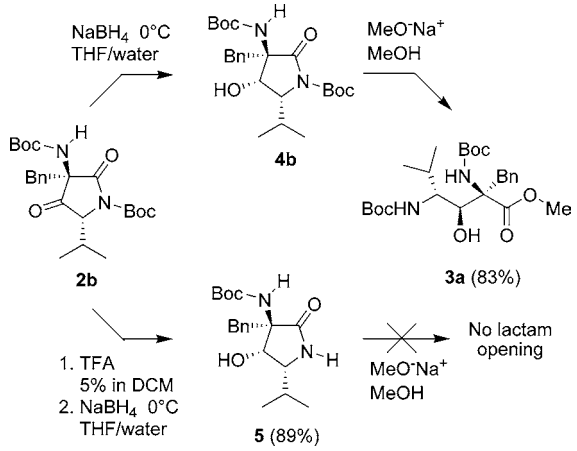


to the corresponding bicyclo compound **4d** by intramolecular cyclization between the hydroxyl and the ester groups present on the neighboring chain.

This spontaneous lactonization was an additional chemical proof for the stereochemistry of the reduction. For example, this type of *cis* junction (garcinia junction) could be found in the mescaline isocitrimide lactone, a psychotic bioprinciple isolated from mescal (*Lophophora williamsii*).[30]

Given our interest in the synthesis of statines, we have then concentrated on the transformation of 3-aminopyrrolidine-2-ones **4** into corresponding α,γ-diamino-β-hydroxyacid esters **3**. The reaction was carried out on the substrate **4b** in the presence of sodium methanolate, allowing the synthesis of the diastereoisomer **3a** in good yield, as a proof of concept (Scheme 3). However, the opening reaction was unsuccessful

Scheme 3. Opening of Activated Lactam

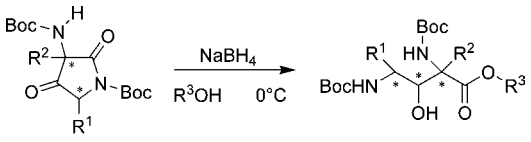


using other nucleophiles such as primary amines or thiolates. At this stage, it is important to notice that, when a chemoselective cleavage of the Boc group linked to the heterocycle was realized, the electrophilic reactivity of the related lactam **5** and consequently its opening ability were then lost, keeping the same alkaline conditions as for the opening of **4b** (Scheme 3).

(30) Ibnusaud, I.; Thomas, G. *Tetrahedron Lett.* **2003**, *44*, 1247.

We were next able to access α,γ-diamino-β-hydroxyacid esters **3** in a one-step reductive-opening strategy starting from pyrrolidine-2,4-diones **2** (Table 2).

Table 2. Tandem Reduction−Opening of Pyrrolidine-2,4-diones



2 **3**

entry	2	R^1	R^2	R^3	product yield[a] (%)	de[b] (%)
1	**2b**	*i*Pr (*R*)	Bn (*R*)	Me	**3a** (83)	>95
2	**2c**	*i*Pr (*R*)	CH_2=$CHCH_2$ (*R*)	Me	**3b** (88)	>95
3	**2e**	*i*Pr (*R*)	Me (*R*)	Me	**3c** (85)	>95
4	**2f**	*s*Bu (*S*)	CH_2=$CHCH_2$ (*S*)	Et	**3d** (76)	>95

[a] Yield of isolated product after purification by flash chromatography. [b] The ^{13}C NMR spectrum of the crude material gave only one set of peaks.

By using methanol (or ethanol) during the reduction step, we highlighted a highly chemo- and stereoselective pathway allowing the synthesis of various 2-disubstituted statines in good yields. The diastereoselectivity of this tandem reduction-opening reaction was established by X-ray diffraction crystal analysis of the linear compound (2*R*,3*S*,4*R*)-**3b** (Figure 2 and Supporting Information).[31]

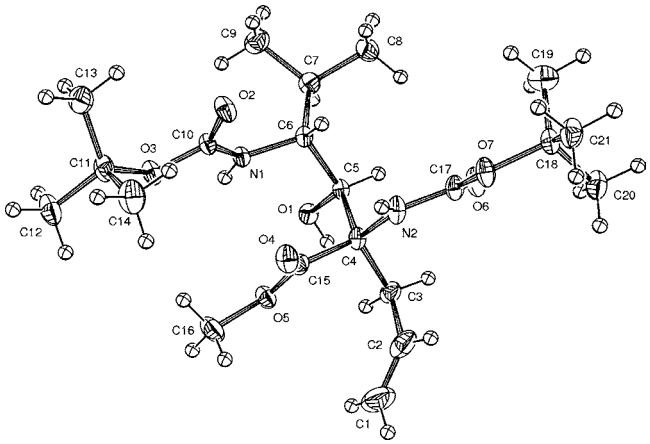
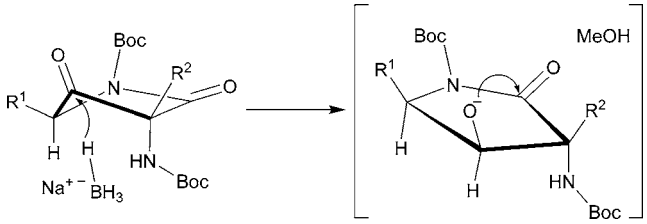


Figure 2. ORTEP representation of (2*R*,3*S*,4*R*)-**3b**.

The total stereoselectivity observed during the reduction could be explained by the fact that the initial cyclic substrate

(31) Crystal data for **3b**: $C_{21}H_{38}N_2O_7$, M = 430.53, orthorhombic, space group $P2_12_12_1$, a = 11.4775(3) Å, b = 11.7018(3) Å, c = 18.3794(5) Å, V = 2468.5(1) Å^3, Z = 4, D_x = 1.158 Mg·m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 0.86 cm^{-1}, F(000) = 936, T = 100 K. CCDC 274799. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif.

Scheme 4. Possible Intermediates Proposed To Explain the Observed Stereoselectivity of the Tandem Reduction−Opening Reaction



is a constrained molecule. In the most favored envelope conformation, R^1 and R^2 are located in pseudo-equatorial positions, allowing a Bürgi−Dunitz attack of the hydride entity with low sterical constraints (Scheme 4). This stereocontrolled approach could be moreover improved by a potential H-bonding association between the hydride reagent and the N*H* carbamate group, as demonstrated for the borohydride reduction of α-hydroxycyclopentanones.[32] The resulting alcoholate group could then participate in the methanolysis of activated lactam through anchimeric assistance, to produce the desired compounds **3**.

(32) Gatling, S. C.; Jackson, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 8655.

In conclusion, we have developed here the first successful application of the TRAL reaction leading to an unprecedented highly selective pathway, essential for the synthesis of various novel 2-disubstituted statines. Pyrrolidine-2,4-diones obtained by TRAL reaction were reduced, in good yields with excellent diastereoselectivity, into 4-hydroxypyrrolidine-2-ones or into α,γ-diamino-β-hydroxyacids esters, according to the reaction conditions. These linear compounds were synthesized taking advantage of the electrophile activation of the lactam by a Boc protecting group. Regarding the structural analogy of the original analogues we have synthesized with subunits occurring in biologically active compounds such as statines and bleomycine, further work will be devoted to pharmacological studies and incorporation into peptidic sequences.

Acknowledgment. The authors thank Dr. Isabelle Parrot for help during preparation of manuscript.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and X-ray structural information of **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7021593