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Highly Efficient Approach to Orthogonally Protected (2*S*,4*R*)- and (2*S*,4*S*)-4-Hydroxyornithine

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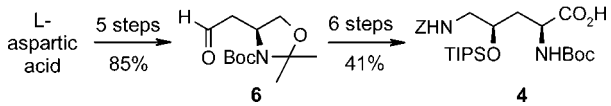
ABSTRACT



A concise stereoselective approach to both orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine, key constituents of the biphenomycin- and clavalanine-type antibiotics, respectively, has been developed. The approach is based on bis(oxazoline) copper(II)-complex-catalyzed diastereoselective Henry reactions of nitromethane with the homoserine-derived aldehyde 6. The synthesis of this versatile chiral building block has been markedly improved.

4-Hydroxyornithine is a rare amino acid found in lentils[1] (e.g., *Lens culinaris* Medik.) and some members of the genus *Vicia*[2] (e.g., *V. unijuga* A. Br.). Moreover, it is a key constituent of the β-lactam antibiotic clavalanine[3] and the cyclopeptide antibiotics biphenomycin A and B **1**.[4] The latter have received considerable attention in recent years due to their high in vitro and in vivo antibacterial activity against multiresistant gram-positive pathogens.[5]

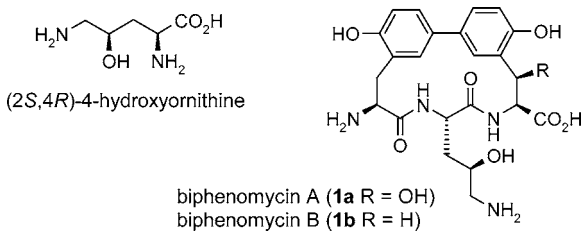


Figure 1.

As part of our program directed toward a convergent total synthesis of these antibiotics[6] and analogues thereof with a modified biaryl moiety, we sought an efficient access to an appropriate N^{α},N^{δ},O^{γ}-protected (2*S*,4*R*)-4-hydroxyornithine building block. While a number of synthetic pathways, including stereoselective approaches, have been developed for the synthesis of 4-hydroxyornithine,[7] only two approaches dealt with the synthesis of a derivative bearing N^{α},N^{δ},O^{γ}-protection suitable for peptide synthesis. Schmidt et al. reported a 13 step synthesis starting from (*R*)-isopropylidene glyceraldehyde to form the *N*,*O*-acetal **2**, albeit in low overall yield.[8] More recently, Rudolph et al. described a very concise

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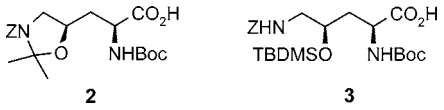
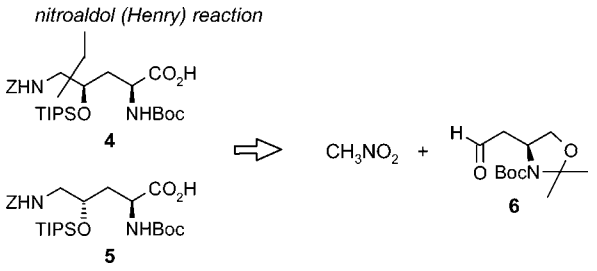
access to the TBDMS-protected 4-hydroxyornithine **3** starting from (*S*)-*N*-Boc aspartic acid *tert*-butyl ester. This approach, which is based on an initial homologization of the acid side chain to form an α-nitroketone and its subsequent diastereoselective reduction to the corresponding *β*-nitro alcohol, however, also suffers from a low overall yield.[5,9]



2 **3**

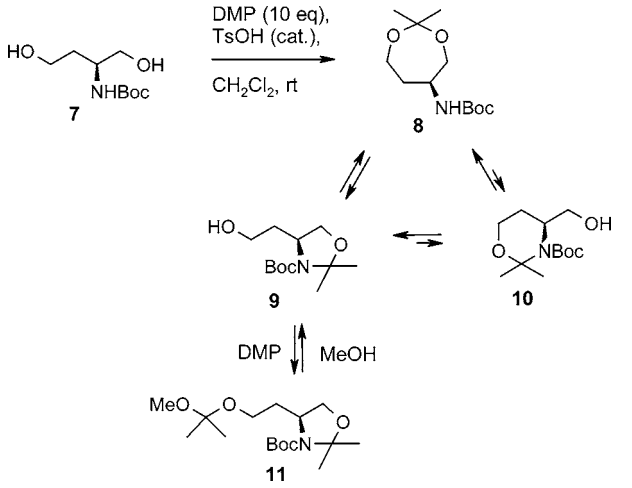
In this paper, we disclose a short and efficient stereoselective approach to both orthogonally N^{α},N^{δ},O^{γ}-protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine based on an asymmetric nitroaldol (Henry) reaction of nitromethane with the homoserine-derived aldehyde **6**[10] (Scheme 1).[11]

Scheme 1. Retrosynthetic Analysis



A simple two-step preparation of building block **6** starting from readily available N-Boc-protected (*S*)-2-amino-1,4-butandiol **7**[12] was previously reported by Ksander and coworkers.[13,14] This commonly used approach, however, suffers from low regioselectivity in the formation of the five-membered cyclic *N*,*O*-acetal **9** (Scheme 2). Thus, this crucial step was reported to proceed in only 42−48% yield by reacting **7** with excess 2,2-dimethoxypropane (DMP) (10 equiv, CH_2Cl_2, rt) in the presence of a catalytic amount of TsOH due to concurrent formation of the corresponding six-membered cyclic *N*,*O*-acetal **10**.[13,15]

Scheme 2. Acid-Catalyzed *N*,*O*-Acetal Formation of N-Boc-Protected (*S*)-2-Amino-1,4-butandiol **7** with DMP



In the course of our studies, however, the structure of this byproduct was revised on the basis of $^{1}H-^{13}C$ HMBC and $^{1}H-^{15}N$ HMQC NMR experiments to be the corresponding seven-membered cyclic *O*,*O*-acetal **8**. Indeed, this isomer was shown to be the product of kinetic control, which slowly equilibrates with **9** under the reported reaction conditions. No evidence has been found for the occurrence of the six-membered cyclic *N*,*O*-acetal **10**.[16] Furthermore *N*,*O*-acetal **9** was shown to exist also in an equilibrium with its 1-methyl-1-methoxyethyl (MIP) ether derivative **11**, a fact not mentioned in the previous papers.[17] In the end, trapping **9** to form **11** allows the overall equilibrium to shift to the desired five-membered ring system. Accordingly, slight modification of the reported reaction conditions, i.e., using 2,2-dimethoxypropane as the solvent and addition of 2-methoxypropene (3.0 equiv) to trap liberated methanol, led to **9** in high overall yield (92%) after mild hydrolysis (wet silica gel, CH_2Cl_2, rt) of the intermediate MIP ether **11**. Finally, Swern oxidation provided the desired aldehyde **6** in 97% yield (Scheme 3).[14]

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(11) An analogous Henry reaction-based strategy for the synthesis of 4-hydroxyornithine was previously reported by Rudolph et al. (ref 9). This approach, however, suffers both from an unfavorable stereoselectivity and from a very low yield in the key nitroaldol reaction step and therefore was not pursued further.

(12) Although N-Boc-protected (*S*)-2-amino-1,4-butandiol **7** is commercially available (Aldrich), its relatively high price leads us to recommend its preparation on a multigram scale from inexpensive L-aspartic acid (see Supporting Information).

(13) Ksander, G.; de Jesus, R.; Yuan, A.; Ghai, R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495−505.

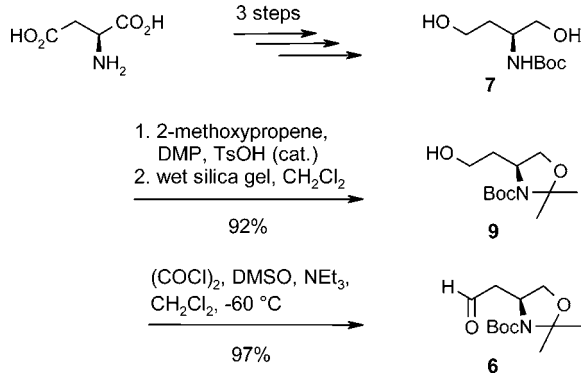
(14) For an alternative approach to **6** starting from *N*-*tert*-butoxycarbonyl-L-aspartic acid *γ*-benzyl ester, see: Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Synlett* **1993**, 409−410.

(15) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206−215.

(16) Ab initio MO calculations (DFT/B3LYP/6-311G+) showed an energy difference of about 7.8 kcal/mol between **9** and the six-membered cyclic *N*,*O*-acetal **10**, indicating that only traces of this regioisomer are to be expected.

(17) Products **8**, **9**, and **11** were obtained in a ratio of 30:45:25 (as determined by ^{1}H NMR analysis of the crude reaction product) by treatment of **7** with DMP (10 equiv) and TsOH (0.1 equiv, CH_2Cl_2, rt, 36 h) according to ref 15.

Scheme 3. Improved Synthesis of Aldehyde **6**



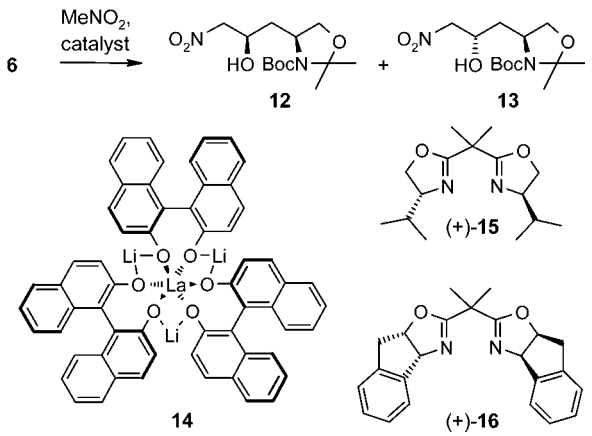
With key building block **6** in hand, its nitroaldol (Henry) reaction with nitromethane was examined (Table 1). $LiAlH_4$-,[18] TBAF-,[19] as well as *t*-BuOK-catalyzed[20] Henry reactions led to nitro alcohols **12** and **13** with low diastereoselectivity, reflecting that the existing stereogenic center is too far away from the newly created one to exert appreciable asymmetric induction (Table 1, entries 1−3).[21] An obvious way of resolving this problem was the introduction of additional chiral information, i.e., application of a chiral catalyst. In fact, double stereodifferentiation using Shibasaki's well-established heterobimetallic (*S*)-BINOL catalyst **14**[22] (5 mol %, THF, −40 °C, 3 days) led to **12** with high diastereoselectivity, albeit in low yield (Table 1, entry 4).

Recently, other highly efficient chiral catalysts for asymmetric Henry reactions have been developed. Thus, Corey[23] and Maruoka[24] have utilized chiral quaternary ammonium fluorides as catalysts, while Trost[25] has presented a dinuclear zinc catalyst. Salen−cobalt(II) complexes have been used by Yamada,[26] whereas Jørgensen[27] and Evans[28] have introduced bis(oxazoline)−copper(II) complexes. The latter seemed to be the catalysts of choice, at least for aliphatic aldehydes, with respect to attainable yields and degree of stereoselectivity.

Indeed, application of Evans' bis(oxazoline) copper(II) acetate-based catalysts {Cu[(+)-**15**]}$(OAc)_2$ and in particular {Cu[(+)-**16**]}$(OAc)_2$ (5 mol %, EtOH, rt, 5 days) gave the desired nitro alcohol **12** both with high diastereoselectivity and in high yield (Table 1, entries 5 and 7). Finally, to selectively obtain diastereomer **13**, aldehyde **6** was reacted with nitromethane in the presence of the enantiomeric catalysts {Cu[(−)-**15**]}$(OAc)_2$ and {Cu[(−)-**16**]}$(OAc)_2$, respectively. In these cases, slightly lower stereoselectivities and yields were observed, reflecting a mismatched pairing (Table 1, entries 6 and 8).

We next turned our attention to the transformation of *β*-nitro alcohol **12** into the desired amino acid building block **4** (Scheme 4).[29] Protection of the hydroxyl group as a TIPS ether proceeded smoothly under standard conditions (TIPSOTf/2,6-lutidine). Reduction of the nitro group was accomplished using ammonium formate as a hydrogen source and palladium on carbon as the catalyst to afford the

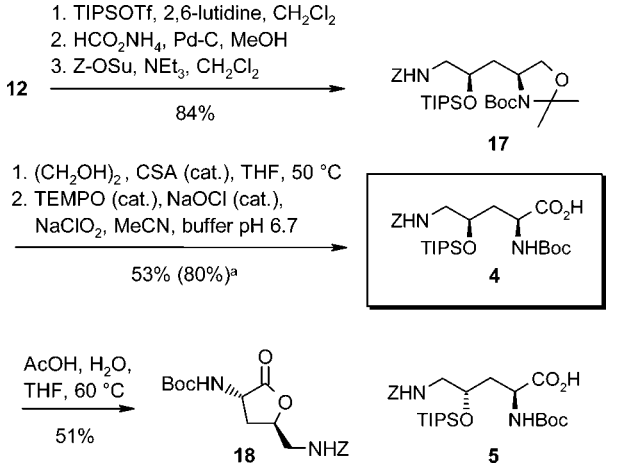
Table 1. Diastereoselective Henry Reaction of Aldehyde **6** with Nitromethane



entry	catalyst	conditions	yield (%)[a]	ratio[b] **12**:**13**
1	$LiAlH_4$	THF, rt	53	56:44
2	TBAF	THF, rt	33	43:57
3	*t*-BuOK	*t*-BuOH/THF, 0 °C	72	23:77
4	**14**	THF, −40 °C	45	98:2
5	{Cu[(+)-**15**]}$(OAc)_2$	EtOH, rt	87	92:8
6	{Cu[(−)-**15**]}$(OAc)_2$	EtOH, rt	85	9:91
7	{Cu[(+)-**16**]}$(OAc)_2$	EtOH, rt	94	97:3
8	{Cu[(−)-**16**]}$(OAc)_2$	EtOH, rt	91	8:92

[a] Isolated yield. [b] Determined by HPLC analysis of crude reaction mixtures.

Scheme 4. Synthesis of Orthogonally Protected (2*S*,4*R*)-4-Hydroxyornithine **4**



[a] Based on recovered starting material.

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(19) Öhrlein, R.; Jäger, V. *Tetrahedron Lett.* **1988**, *29*, 6083−6086.
(20) Hanessian, S.; Brassard, M. *Tetrahedron* **2004**, *60*, 7621−7628.
(21) Low stereoselectivity in nitroaldol reactions with aldehydes bearing a stereogenic center at the *β*-position has been observed previously. See ref 9 and references therein.

corresponding amine, which was transformed (Z)-OSu/NEt_3) to the N^{δ}-Z-protected 4-hydroxyornithine derivative **17** in 84% overall yield (three steps). Selective hydrolysis of the *N*,*O*-acetal using several methods (e.g., pyridinium tosylate, MeOH, 60 °C; I_2, MeOH, rt or $CeCl_3 \cdot 7H_2O$/oxalic acid, rt) proved to be difficult due to concomitant partial cleavage of the TIPS ether. Fortunately, we were able to effect this transformation cleanly and in good yield (64%, 96% based on recovered starting material) using ethylene glycol/CSA (THF, 50 °C, 2 days).[30] The final oxidation of the amino alcohol was best accomplished with TEMPO/NaOCl/$NaClO_2$[31] to give the desired carboxylic acid **4** {mp 45−47 °C, $[\alpha]^{22}_D$ +67.6 (*c* 1.64, CH_2Cl_2)} in 83% yield without epimerization. The absolute configuration of product **4** was established to be 2*S*,4*R* by subsequent transformation into the known γ-lactone **18**[32] {mp 148−149 °C, lit. mp 143−145 °C; $[\alpha]^{23}_D$ −25.2 (*c* 0.85, $CHCl_3$), lit. $[\alpha]^{23}_D$ −22.4 (*c* 0.5, $CHCl_3$)}.

According to this reaction sequence, **13** was converted to **5** {mp 53−55 °C, $[\alpha]^{20}_D$ −28.5 (*c* 1.00, CH_2Cl_2)} in 57% overall yield (66% based on recovered starting materials) in five steps.

In conclusion, we have developed a short and highly efficient approach to orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine building blocks **4** and **5**, respectively, based on bis(oxazoline) copper(II)-complex-catalyzed diastereoselective Henry reactions of nitromethane with aldehyde **6**. In addition, a greatly improved procedure for a multigram synthesis of this valuable chiral building block and its precursor **9** has been developed.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Since β-nitro alcohols **12** and **13** were difficult to separate, **12** was used as a mixture of diastereomers (97:3). The minor diastereomer could be easily removed by flash chromatography on silica gel at the stage of the N^{δ}-Z-protected β-amino alcohol **17**.

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