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Enantiospecific Synthesis of γ-Keto-α,β-diamino acid derivatives. Stereoselective Synthesis of a Precursor of Streptolidine Lactam.

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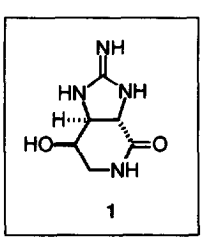
Abstract: *The reaction of dimethyl (4S,5S)-1-benzyl-2-oxo-3-(9"-phenylfluoren-9"-yl)-imidazolidine-4,5-dicarboxylate (3) with several organolithium reagents afforded the corresponding enantiomerically pure monoketones (**4a-e**) in good to excellent yields. Chloromethyl-ketone **4b** was ultimately transformed into ureido-amide **8** which incorporates the bicyclic core of streptolidine lactam (**1**), a component of the streptrothricin antibiotics.* © 1997, Elsevier Science Ltd. All rights reserved.

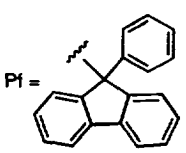
γ-Hydroxy-α,β-diamino acid derivatives are the key structural features of an interesting class of natural products isolated from microbial sources. The most significant member of this group is streptolidine lactam (**1**), which forms the core of the streptothricin antibiotics.[1-5] The high antibacterial activity of these antibiotics has drawn a great deal of synthetic attention towards them, and several syntheses of **1**, using carbohydrates as starting materials, have been reported.[6-8] These approaches are usually lengthy and non-flexible, and are, thus, of limited use for the synthesis of analogues of **1** or of other γ-hydroxy-α,β-diamino acid derivatives.

In this communication we describe an enantioespecific, stereoselective, flexible synthesis of the title compounds from aspartic acid. This approach has been used to gain access to an advanced intermediate in the preparation of streptolidine lactam.

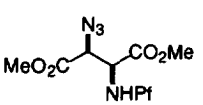
We have recently reported that dimethyl *N*-Pf-aspartate could be aminated to provide azido diester **2** (or its epimer at C-3),[9] which would be an ideal precursor to the title compounds provided that the chemoselective chain elongation of one of the ester groups to a ketone could be achieved. The ketones thus obtained would then be stereoselectively reduced to provide the desired hydroxy-diamino functionality.



1



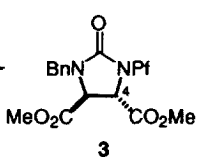
Pf =



2

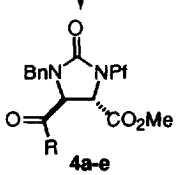
1. H_2, Pd/$BaCO_3$
2. BnBr, Na_2CO_3
3. Cl_2CO, py

83%



3

RLi
THF



4a-e

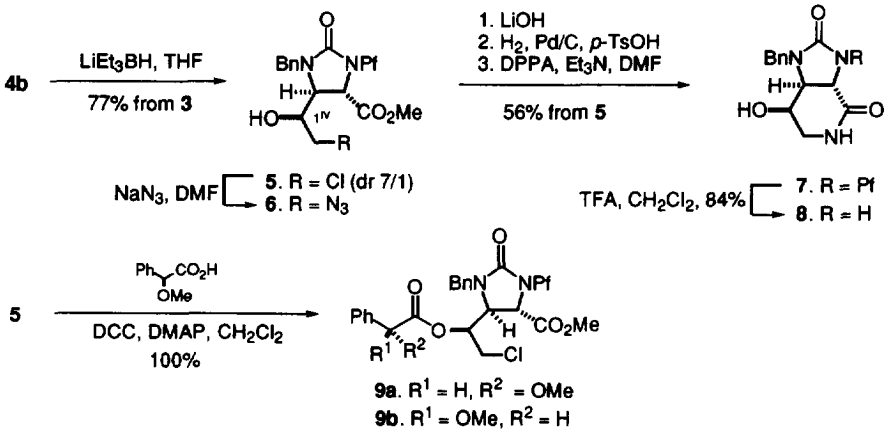
	R	mol%	t (min)	T (°C)	Yield (%)
4a	Me	105	45	-78	92
4b	CH_2Cl	200	75	-78	100
4c	*n*-Bu	125	45	-78	61[a]
4d	Ph	125	45	-78	85
4e		250	ref.14	-78 to -55	78

[a] based on recovered 3.

We decided to attempt the differentiation of the ester groups at the stage of the cyclic urea **3**, since the bulkiness of the 9-phenylfluoren-9-yl (Pf) group should hinder the approach towards the carboxyl group at C-4. Mild hydrogenation of *N*-Pf-3-azidoaspartate (**2**) [H_2 (1 atm), $Pd/BaCO_3$, MeOH], followed by *N*-monobenzylation (BnBr, Na_2CO_3, CH_2Cl_2-H_2O, reflux)[10] and cyclization of the resulting diamine with Cl_2CO (DMAP, pyridine, 70 °C)[9] provided **3**[11] in 83% overall yield.

We serendipitously found that the chemoselective chain elongation of **3** could be effected simply by treatment with several organolithium reagents (THF, -78 °C).[12-14] In this way the enantiomerically pure ketones **4a-e**[11] were obtained in good to excellent yields. This transformation is surprising since it is well known that the reactions of organolithium or organomagnesium reagents with carboxylic acid esters usually lead to tertiary alcohols.[15,16] The formation of the ketones **4a-e** is most probably due to the electron-withdrawing effect of the urea, which should stabilize the tetrahedral intermediate of the addition. In no instances were the corresponding tertiary alcohols detected in the reaction crude products.

With a method for the preparation of γ-keto-α,β-diamino acid esters in hand, we decided to proceed with the synthesis of streptolidine lactam. Thus, crude **4b** was reduced with $LiEt_3BH$ (200 mol%, 3Å molecular sieves, THF, -78°C, 2h) to give alcohol **5** (7/1 ratio of diastereoisomers, 77% yield from **3**). The configuration of the newly created stereocenter in **5** was established by reaction with both (*R*)- and (*S*)-methoxyphenylacetic acids. The diastereomeric esters **9a** and **9b** were obtained quantitatively. The application of the Trost-Mosher method for the determination of the absolute configuration of secondary alcohols to esters **9a** and **9b** led us to assign the *S* configuration to $C1^{IV}$ in **5**.[17]



Chloride displacement by azide (NaN_3, DMF, 110 °C) converted **5** into azido alcohol **6**.[11] The chemoselectivity of the formation of ketones **4** was established at this stage, since a strong NOE was observed between $H1^{IV}$ and the *N*-benzylic CH_2 group in the ^{1}H-NMR spectrum of **6**. Urea-lactam **7**,[11] which contains the bicyclic system required for the synthesis of streptolidine lactam **1**, was prepared from crude **6** by ester hydrolysis ($LiOH{\cdot}H_2O$, dioxane-H_2O) followed by azide reduction [H_2, Pd/C, *p*-$TsOH{\cdot}H_2O$ (100 mol%), MeOH] and cyclization of the resulting amino acid with diphenyl phosphoryl azide (Et_3N, DMF, 0°C to rt, 56% yield from **5**).[18] Treatment of **7** with TFA (CH_2Cl_2, rt)[19] led to the monoprotected urea-lactam **8**[11] in a 84% yield. Studies to complete the synthesis of streptolidine lactam (**1**) and analogues are in progress.

Acknowledgment. We thank the CICYT (Spain, grant SAF96-0251) and the *Xunta de Galicia* (grant XUGA 20912B96) for financial support. E.F.-M. thanks the *Xunta de Galicia* and the *Universidad de Santiago de Compostela* for fellowships. We thank Prof. Rafael Suau (Univ. de Málaga, Spain) for the elemental analyses.

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11. All new compounds showed the expected spectral properties and gave satisfactory elemental analisys. Selected physical and spectral properties: **3**: $[\alpha]^{20}_D$ -45.7° (c 1.15, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 7.6 Hz, 1H), 7.46-7.18 (m, 14H), 4.88 (d, J = 15.2 Hz, 1H, H1'), 4.08 (d, J = 15.2 Hz, 1H, H1'), 3.93 (d, J = 2.8 Hz, 1H, CH), 3.68 (d, J = 2.8 Hz, 1H, CH), 3.54 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$) δ 170.4 (CO), 169.7 (CO), 158.8 (C2), 146.9, 146.1, 141.8, 140.2, 140.0, 136.1, 129.1, 128.9, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.1, 126.6, 125.5, 119.9, 119.7, 72.9 (C9"), 58.4 (CH), 57.8 (CH), 52.5 (OCH_3), 52.0 (OCH_3), 46.5 (C1'). **4a**: $[\alpha]^{20}_D$ +93.5° (c 1.57, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.68-7.58 (m, 4H), 7.48-7.16 (m, 14H), 4.80 (d, J = 15.1 Hz, 1H, H1'), 4.03 (d, J = 15.1 Hz, 1H, H1'), 3.55 (d, J = 3.9 Hz, 1H, CH), 3.50 (d, J = 3.9 Hz, 1H, CH), 3.28 (s, 3H, OCH_3), 1.64 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 204.2 ($C1^{IV}$), 170.9 (C1'"), 159.5 (C2), 146.4, 146.2, 141.4, 140.5, 139.9, 135.9, 129.5, 129.1, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 127.3, 126.6, 125.7, 120.0, 119.9, 73.3 (C9"), 63.9 (CH), 57.3 (CH), 52.3 (OCH_3), 47.0 (C1'), 24.7 ($C2^{IV}$). **4e**: $[\alpha]^{20}_D$ -202.4° (c 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.00 (dd, J = 1.4 Hz, J = 6.3 Hz, 1H), 7.62 (t, J = 8.6 Hz, 2H), 7.42-7.16 (m, 15H), 5.23 (d, J = 2.7 Hz, 1H, CH), 5.06 (d, J = 15.6 Hz, 1H, H1'), 4.44 (d, J = 2.7 Hz, 1H, CH), 4.36 (d, J = 2.1 Hz, 1H, CH), 3.92-3.86 (m, 2H, H1' and CH), 3.66 (c, J = 7.0 Hz, 2H, OCH_2), 3.06 (s, 3H, OCH_3), 1.11 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 192.1 ($C1^{IV}$), 169.9 (C1'"), 159.1 (C2), 155.5 ($C2^{IV}$), 147.5, 145.9, 142.2, 140.3, 139.9, 136.9, 129.0, 128.8, 128.4, 128.3, 128.0, 127.3,

127.1, 126.4, 125.3, 120.0, 119.4, 93.0 ($C3^{IV}$), 72.5 (C9"), 63.9, 59.1, 58.1, 51.7 (OCH_3), 46.1 (C1'), 13.6 (CH_3). **7**: $[\alpha]^{20}_D$ -109.4° (c 1.42, Cl_3CH); ^{1}H-NMR ($CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.35-7.17 (m, 14H), 4.99 (d, J = 4.9 Hz, 1H, NH), 4.78 (d, J = 14.7 Hz, 1H, H1'), 4.09 (d, J = 12.2 Hz, 1H, H9), 3.95-3.84, m, 2H, H1' and H7), 3.45-3.34 (m, 1H, H6), 3.05 (dd, J = 3.0 Hz, J = 12.0 Hz, 1H, H8), 2.90 (d, J = 13.4 Hz, 1H, H6), 1.22 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 170.4 (C4), 163.3 (C2), 147.4, 145.9, 143.2, 141.7, 139.9, 137.1, 129.7, 129.3, 128.8, 128.6, 128.3, 128.2, 127.5, 127.4, 126.8, 126.5, 125.3, 119.7, 119.1, 74.2 (C9"), 61.8 (CH), 60.9 (CH), 54.5 (CH), 48.4 (CH_2), 47.0 (CH_2).

12. For the preparation of **4a-e** the organolithium reagent was added to a 0.1-0.18 M solution of **3** in THF at -78°C. After the specified reaction time the reaction was quenched with ethyl formate or acetone and partitioned between 1M H_3PO_4 or HCl (5%) and CH_2Cl_2. **4a** and **4c-e** were purified by column chromatography on silicagel. Crude **4b** was used directly in the next step due to its instability towards silicagel.
13. Chloromethyllithium was prepared *in situ* [$ClCH_2I$ (217 mol%, MeLi (200 mol%), LiBr (150 mol%), THF, -78 °C] in the presence of **3** and was used following a literature procedure.[16g-h]
14. 1-Ethoxy-1-lithioethene was prepared from ethyl vinyl ether (300 mol%) and tBuLi (250 mol%) (THF, -78 °C). This solution was allowed to reach 0 °C and was stirred at 0°C for 45 min, then it was cooled to -78 °C, and cannulated into a solution of **3** (THF, -78 °C). The reaction was allowed to reach -55 °C and then was stirred at this temperature for 45 min prior to quench. (a) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913-3916. (b) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830-833.
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