Pergamon

Tetrahedron Letters 42 (2001) 8955–8957

TETRAHEDRON LETTERS

A concise synthesis of α-amino acid *N*-carboxy anhydrides of (2*S*,3*S*)-β-substituted serines

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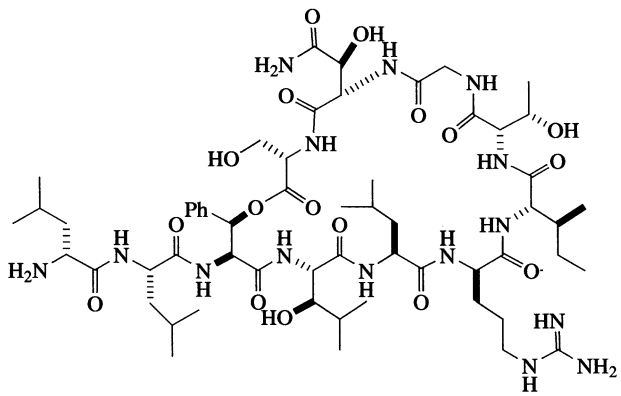
Received 3 July 2001; accepted 19 September 2001

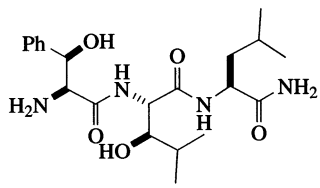
Abstract—A general access to 3-hydroxy-4-(1-hydroxyalkyl)-β-lactams with a C_4–C_1' relative configuration *unlike* is provided. The subsequent oxidative ring expansion of the corresponding 3-hydroxy β-lactam smoothly affords an α-amino acid *N*-carboxy anhydride (NCA) formally derived from (2*S*,3*S*)-β-substituted serine, which upon sequential peptide coupling furnishes the tripeptide segment **2**, present in lysobactin.

α-Amino β-hydroxy acids, also termed β-substituted serines, are frequently found in bioactive natural products,[1] as in the macrocyclic peptide lactone antibiotic lysobactin.[2] The antibacterial mode of action of lysobactin is comparable with the observed selectivity and potency of the well known, clinically useful antibiotic vancomycin.[3] In those infectious strains of vancomycin-resistant bacteria, lysobactin might be the alternative antibacterial agent of choice, in spite of its toxicity. Consequently, the development of new peptides of the lysobactin family with improved therapeutic indexes, is of considerable interest. Necessarily, synthetic or semi-synthetic approaches to lysobactin itself and to the analogs should address the construction of the α-amino β-hydroxy acid units present in their structures with a correct stereochemistry.[4]

Recently, we have reported a β-lactam approach to α-amino acid *N*-carboxyanhydrides (NCAs) formally derived from (2*S*,3*R*)-β-substituted serines, and the subsequent synthesis of tripeptide **1**.[5] According to this approach (Scheme 1) from the ring expansion of 3-hydroxy β-lactams **4**, NCAs **5** are obtained that can be directly submitted to a peptide coupling reaction. The traditionally required carboxy group activation of the intermediate α-amino acid is thus avoided.[6] The method is still slightly restricted, because NCAs **6**, showing a relative configuration *unlike*, which often



Lysobactin



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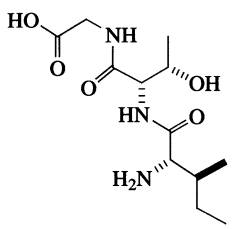

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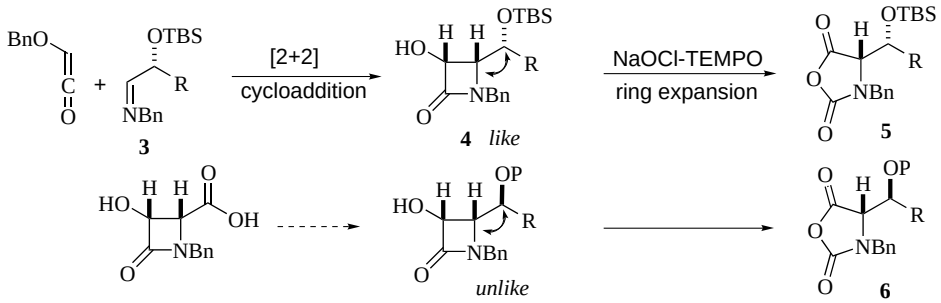


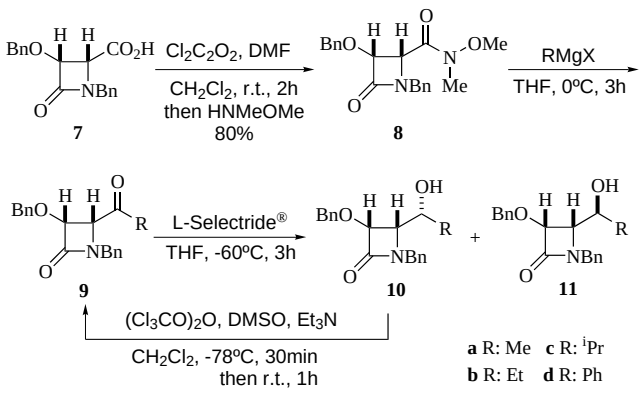
Scheme 1. General strategies for access to NCAs formally derived from β-substituted serines: previously described approach for access to the *like* series and the proposed route to the *unlike* series.

corresponds with that of the biologically active compounds, are not accessible through this route. This is so because the sense of asymmetric induction typically imparted by chiral α-oxyaldehydes-derived imines **3** during the [2+2] cycloaddition reaction[7] produces the corresponding β-lactam adducts with a α,β-*like* stereochemical relationship. With the aim of expanding the usefulness of our β-lactam approach, we herein report on the facile access to NCAs **6** and to peptides derived therefrom through a modified strategy.

In the modified strategy, the exocyclic stereocenter (carbinol) is formed in a later stage with the desired configuration. This may be achieved by diastereofacial discrimination across the two faces of the precursor carbonyl compound. The general route begins with the enantiomerically pure 3-benzyloxy-4-carboxy azetidin-2-one **7** as the key starting material that acts as a novel non-racemic α-aminomalonic acid surrogate.[8,9] The free carboxy function in **7** allows for a correlative organometallic addition–reduction process that results in the formation of the exocyclic carbinol with the right configuration. Further ring expansion and peptide coupling culminate the synthetic plan.

The carboxylic acid **7**[10] was first transformed into Weinreb's amide[11] **8**. Subsequent treatment of **8** with Grignard reagents provides ketones **9** in yields in the range 65–75%. The reduction of ketones **9** to the desired carbinols was found to be strongly sensitive to the type of reducing agent employed. For example, the reduction of **9a** with sodium borohydride in methanol as solvent provided an almost equimolecular mixture of carbinols **10a**/**11a**, while the reduction of the same compound carried out with L-Selectride in either diethyl ether or anhydrous THF furnished **10a**/**11a** in a ratio 15:85. Likewise, the reduction of **9b** with DIBAL-H in THF as solvent proceeded to give **10b**/**11b** in a ratio of 45:55. The ratio of isomers was improved up to 30:70 by using toluene as solvent, but, once again, the best result was attained when the reduction was carried out with L-Selectride. In this latter case, a mixture of **10b**/**11b** was produced in a 7:93 ratio. In every case, from the corresponding mixture of carbinols each isomer was separated by column chromatography, and the minor isomer could be reused,[12,13] as shown in Scheme 2.

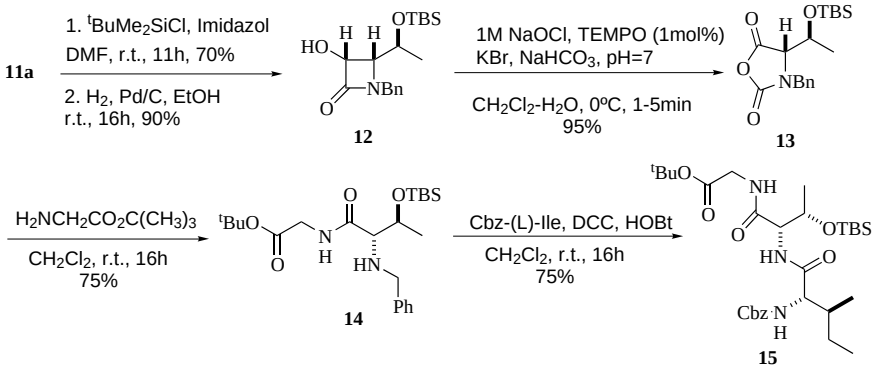
With these products in hand, the synthesis of the peptide fragment **15** of lysobactin was undertaken (Scheme 3). To this end, the hydroxyl group in **11a** was first protected as *tert*-butyldimethylsilyl ether and the resulting intermediate was subjected to *O*-debenzylation to afford **12** (oil, $[\alpha]_D^{25}=+31.0$, $c=1$, CH_2Cl_2). Compound **12**, upon treatment with a solution of commercial bleach and a catalytic amount of TEMPO, furnished the NCA **13** in 95% yield. Thus, the access to this NCA, which traditionally would require the previous synthesis of the corresponding α-amino acid, can now be obtained from a non-α-amino acid precursor in a concise fashion. Furthermore, this approach generates the required amino acid as an active species, thereby overcoming the need of additional protection and acti-



Product	Yield %[a]	10:11[b]
9a	70	
9b	65	
9c	70	
9d	75	
11a	65	15:85
11b	65	7:93
11c	70	10:90
11d	65	5:95

a) Yield of pure product.
b) Determined by HPLC analysis.

Scheme 2. Stereoselective access to β-lactams **11** from enantiomerically pure **7**.



Scheme 3. Synthesis of the tripeptide segment **15** present in lysobactin.

vation steps for peptide coupling. Accordingly, the coupling of **13** with glycine *tert*-butyl ester afforded the dipeptide product **14** in 75% yield without traces of epimerized product at $C\alpha$.[14] Subsequent *N*-debenzylation and further coupling with *N*-Cbz-Ille-OH under standard peptide coupling conditions provided **15** in 75% yield. In summary, the general route presented here, that makes use of a new non-racemic amino malonic acid surrogate, broadens the usefulness of earlier methodology for the access to α-amino acid *N*-carboxyanhydrides (NCAs) from non-amino acid precursors, and applications to the synthesis of non-trivial peptides arise.

Acknowledgements

This work was financially supported by Gobierno Vasco, Universidad del Pais Vasco and by Ministerio de Ciencia y Tecnología.

References

1. Barret, G. C. In *Amino Acids, Peptides and Proteins*: *Specialist Periodical Reports*; Davies, J. S., Ed.; The Royal Society of Chemistry: London, 1997; Vol. 28, p. 1.
2. Tymiak, A. A.; McCornick, T. J.; Unger, S. E. *J. Org. Chem.* **1989**, *54*, 1149.
3. (a) Salase, D. M.; Marino, J.; Jacobs, M. R. *Antimicrob. Agents Chemother.* **1984**, *25*, 527; (b) Horowitz, H. W.; Handwerger, S.; Van Horn, K. G.; Wormser, G. P. *Lancet* **1987**, *2*, 1329.
4. For another approach to the α-amino β-hydroxy acids of lysobactin, see: Armaroli, S.; Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2000**, *2*, 1105.
5. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Odriozola, B.; Maneiro, E.; Miranda, J. I.; Urchegui, R. *Chem. Commun.* **1996**, 161; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Pure Appl. Chem.* **2000**, *72*, 1763.
6. For a review on NCAs, see: Kricheldorf, H. R. *α-Aminoacid N-Carboxy Anhydrides and Related Heterocycles*; Springer: Berlin, 1987.
7. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.
8. For other surrogates of α-aminomalonic acid, see: (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855; (b) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511.
9. Krysan, D. J. *Tetrahedron Lett.* **1996**, *36*, 3303.
10. (a) Palomo, C.; Cabre, F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819. Also see: (b) Jayaraman, M.; Deshmukh, A. R.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 8989.
11. Weinreib, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815.
12. Representative data: **11a**: oil, $[\alpha]_D^{25}=+57.6$ ($c=1$, CH_2Cl_2); ^1H NMR (δ, ppm, $CDCl_3$): 7.36–7.20 (m, 10H), 5.00 (d, 1H, $J=11.5$ Hz), 4.78 (d, 1H, $J=15.3$ Hz), 5.74 (d, 1H, $J=11.5$ Hz), 4.73 (d, 1H, $J=4.9$ Hz), 4.10 (d, 1H, $J=15.3$ Hz), 4.00 (m, 1H), 3.43 (dd, 1H, 4.9, 5.1 Hz), 2.86 (d, 1H, $J=7.1$ Hz), 1.21 (d, 3H, $J=6.5$ Hz); ^{13}C NMR (δ, ppm, $CDCl_3$): 167.5, 136.3, 135.0, 128.7, 128.5, 128.1, 128.0, 127.9, 127.7, 81.5, 73.1, 66.0, 60.5, 44.3, 20.0; **11b**: oil, $[\alpha]_D^{25}=+12.6$ ($c=1$, CH_2Cl_2); ^1H NMR (δ, ppm, $CDCl_3$): 7.33–7.19 (m, 10H), 4.99 (d, 1H, $J=11.7$ Hz), 4.79–4.71 (m, 3H), 4.07 (d, 1H, $J=15.2$ Hz), 3.70 (m, 1H), 3.46 (m, 1H), 2.69 (d, 1H, $J=7.7$ Hz), 1.47 (m, 2H), 0.91 (t, $J=7.3$ Hz); ^{13}C NMR (δ, ppm, $CDCl_3$): 167.6, 136.3, 135.0, 128.7, 128.5, 128.1, 127.9, 127.7, 81.6, 73.2, 71.2, 59.3, 44.3, 27.0, 10.2; **11c**: oil, $[\alpha]_D^{25}=+67.6$ ($c=1$, CH_2Cl_2); ^1H NMR (δ, ppm, $CDCl_3$): 7.34–7.20 (m, 10H), 5.01 (d, 1H, $J=11.72$ Hz), 4.78 (m, 3H), 4.04 (d, 1H, $J=15.34$ Hz), 3.61 (m, 2H), 2.73 (d, 1H, $J=7.55$ Hz), 1.76 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (δ, ppm, $CDCl_3$): 167.4, 136.3, 135.0, 128.7, 128.4, 128.2, 127.9, 127.7, 81.7, 74.4, 73.1, 57.1, 44.2, 31.1, 19.7, 17.2; **11d**: oil, $[\alpha]_D^{25}=+28.6$ ($c=1$, CH_2Cl_2); ^1H NMR (δ, ppm, $CDCl_3$): 7.40–7.16 (m, 13H), 6.70 (m, 13H), 4.99 (d, 1H, $J=11.5$ Hz), 4.93 (dd, 1H, $J=7.8$, 4.4 Hz), 4.77 (d, 1H, $J=11.5$ Hz), 4.74 (d, 1H, $J=4.7$ Hz), 4.60 (d, 1H, $J=14.8$ Hz), 3.75 (dd, 1H, $J=7.8$, 4.8 Hz), 3.30 (d, 1H, $J=14.8$ Hz), 3.04 (d, 1H, $J=4.6$ Hz); ^{13}C NMR (δ, ppm, $CDCl_3$): 167.5, 140.5, 136.5, 134.7, 128.7, 128.5, 128.2, 128.1, 127.2, 81.8, 73.3, 73.0, 60.5, 44.2.
13. Prior attempts to effect carbinol inversion under the Mitsonobu reaction conditions in related substrates invariably led to yields below 50%. See: Mielgo, A., Doctoral Thesis, San Sebastián, 1996, p. 106. In the present case, direct conversion of **10** into **11** was not examined.
14. For some aspects on racemization during ring opening of NCAs, see: (a) Sim, T. B.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2532; (b) Palomo, C.; Oiarbide, M.; Landa, A.; Linden, A. *J. Org. Chem.* **2001**, *66*, 4180.