Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 22, pp. 3717–3718, 1997

Printed in Great Britain
PII: S0957-4166(97)00530-2
0957-4166/97 $17.00 + 0.00

An efficient synthesis of the cyclic form of scalemic 2,4-di-*epi*-polyoxamic acid exploiting the hetero Diels–Alder approach

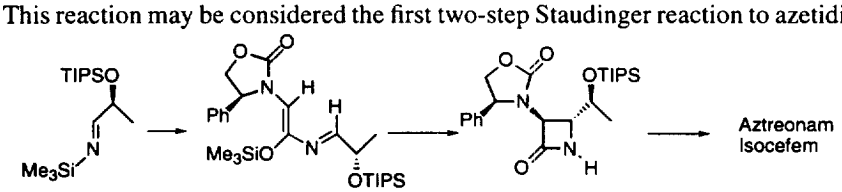
Elisa Bandini,[a] Giorgio Martelli,[a] Giuseppe Spunta,[a] Alessandro Bongini,[b] Mauro Panunzio[b,*] and Giovanni Piersanti[b]

[a] I.Co.C.E.A.-C.N.R. Via Gobetti 101, 40129 Bologna, Italy
[b] Dipartimento di Chimica 'G. Ciamician', Via Selmi 2, 40126 Bologna, Italy

Abstract: An efficient synthesis of the lactonic derivative of 2,4-di-*epi*- polyoxamic acid, in high enantiomeric purity, through a hetero Diels–Alder approach, is reported. © 1997 Elsevier Science Ltd

Optically active amino polyols are valuable building blocks for the syntheses of polyhydroxy amino acids, peptide isosters, amino sugars, polyhydroxy pyrrolidines and piperidines, etc.[1] Most commonly, they can be synthesised from carbohydrates or amino acids, depending on the stereogenic centre(s). Since their chemical conversion and asymmetric induction have sometimes been inefficient, it is evidently desirable to develop more facile and stereoselective synthetic routes. In this context we planned to investigate the possibility of using an asymmetric hetero Diels–Alder approach as the key step. It is known, in fact, that this reaction is one of the most useful tools for achieving C–C bond formation with a high degree of asymmetric control.[2–7]

Recently in our laboratory we have developed a new, stable, highly functionalyzed class of azadienes starting from *N*-trimethylsilyl imines. Such compounds have been cyclized, by simple reflux, to give β-lactams. This reaction may be considered the first two-step Staudinger reaction to azetidinones rings.



1

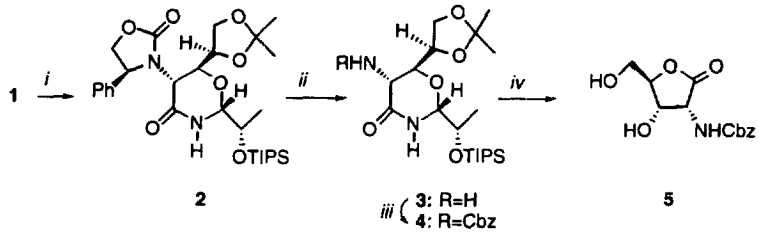
In conjunction with a program on a *de novo* asymmetric synthesis of antibiotics, including antifungal agents, polyoxins and nikkomycin,[8] we targeted polyoxamic acid, the novel amino acid substituent of antifungal agents.[9–16] We wish to report on preliminary results on the synthesis of polyhydroxylated amino acids using our homochiral glycine-derived azadienes.

The azadiene **1** was prepared from (S)-triisopropylsilyloxy lactic imine and the acid chloride of (S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid according to a reported procedure,[17] in a one pot, two step synthesis in almost quantitative yields and high purity as evaluated by ^1H and ^{13}C NMR. Treatment of crude **1** with (D)-glyceraldehyde acetonide[18] gave rise to dihydrooxazinone **2** $[\alpha]_D^{20}=+52.2$ (*c* 0.94, $CHCl_3$), contaminated by 8% of its diastereoisomer, in 64% overall yields (calculated on the starting lactaldehyde).

After purification by column chromatography (SiO_2, methylene chloride:acetone=95:5) and removal of the oxazolidine protecting group by Li/NH_3[19] the stable amino derivative **3** $[\alpha]_D^{20}=-8$ (*c* 0.65, $CHCl_3$) was obtained in quantitative yields. Protection of the amino group by CbzCl ($NaHCO_{3aq}$/acetone/pH 8) gave rise to compound **4** $[\alpha]_D^{20}=-10.38$ (*c* 1.06, $CHCl_3$) in 64% yield.

* Corresponding author. Email: panunzio@ciam.unibo.it

Treatment of this compound with methanolic HCl (1 hr, rt) furnished the lactone **5** $[\alpha]_D^{20}$=+11.9 (*c* 2.3, CH_3OH) in 54% yield (Scheme 1).[20]



Reagents and Conditions: *i*, (D) Glyceraldehyde acetonie, BF_3, CH_2Cl_2, -78°C; *ii*, LI/NH_3; *iii*: CbzC $NaHCO_{3aq}$, acetone, pH 8; *iv*: HCl /MeOH.

Scheme 1.

The facile conversion of azadiene **1** into oxazinone **3**, and in turn into lactone **5** provides a particularly flexible asymmetric synthesis of high functionalized polyhydroxy amino acid intermediates and may be extended to other numerous targets. Access to *epi*-polyoxamic acid in this way realises just one such potential. Further work exploring such routes is underway.

Acknowledgements

This work was partially supported by 'Progetto Strategico Tecnologie Chimiche Innovative, CNR, Rome'. MP thanks GlaxoWellcome Research Laboratories, Verona for financial support.

References

1. For recent reviews, see: (a) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241. (b) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360. (c) Reetz, M. T. *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 1531. (d) Cintas, P. *Tetrahedron* **1991**, *47*, 6079.
2. Barluenga, J.; Joglar, J.; Gonzales, F. J.; Fustero, S. *Synlett* **1990**, 129.
3. Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Eds.; Pergamon Press: Oxford, 1991; Vol. 2; pp. 661.
4. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Vol. 47.
5. Boger, D. L. *Chemtracts — Org. Chem.* **1996**, *9*, 149.
6. Enders, D.; Meyer, O. *Liebigs Ann. Chem.* **1996**, 1023.
7. Weinreb, S. M. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Eds.; Pergamon Press: Oxford, 1991; Vol. 2; pp. 401.
8. Isono, K. *J. Antibiotics* **1988**, *41*, 1711.
9. Trost, B. M.; Krueger, C. A.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
10. Kang, S. H.; Choi, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1521.
11. Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431.
12. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733.
13. Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111.
14. Dondoni, A.; Franco, S.; Merchan, F. L.; Merlino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479.
15. Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979.
16. Rassu, G.; Zanardi, F.; Cornia, M.; Casiraghi, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2431.
17. Bandini, E.; Martelli, G.; Spunta, G.; Panunzio, M. *Synlett* **1996**, 1017.
18. Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6.
19. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.
20. All products gave spectral and analytical data consistent with the assigned structures.

(Received in UK 10 September 1997)