ASYMMETRIC SYNTHESIS VIA HETEROCYCLIC INTERMEDIATES. ASYMMETRIC SYNTHESIS OF (-)-(1S, 2R)-ALLOCORONAMIC ACID

José L. Marco

Instituto de Química Orgánica General, CSIC, 3, Juan de la Cierva,

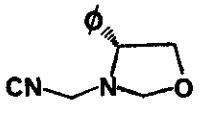
28006-Madrid, Spain

Abstract- The first total asymmetric synthesis of (-)-(1S, 2R)-allocoronamic acid is described.

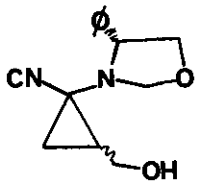
In connection with our current work on asymmetric synthesis via heterocyclic intermediates [1], we report here the first total asymmetric synthesis of (-)-(1S, 2R)-allocoronamic acid [2], (11), a simple member of the α-aminocyclopropanecarboxylic acids [3], an interesting group of substances which in some cases are or form part of natural products [4].

Our synthetic plan started with the readily available heterocyclic chiron (1) [5], as an useful " chiral glycine equivalent ", by metallation [initiated by inverse addition of LDA/HMPA (1:1), (2.5 eq), in dry THF, at -78°C, under argon, to (1) (1 eq)] and double *in situ* dialkylation with epibromohydrin [6] (1.1 eq). Whithout isolation of intermediates (2), the crude reaction mixture was hydrolyzed (NaOH, 2.2 eq, H_2O, reflux, 27 h), acidified (HCl 20%, overnight, r.t.), evaporated to dryness and submitted to reaction with thionyl chloride in dry methanol (reflux, 4 h). After conventional work-up and flash-chromatography, we obtained a mixture of (3) [7] and (4) that we could not unfortunately separate. Following with hydrogenolysis (Pd/C 10%, AcOEt, r.t., 1 atm, 48 h) and tosylation of (5) + (6) for 24 h at 6°C, we obtained finally a mixture cleanly resoluble by flash-chromatography of (7) [8] [mp 101-103°C, $[\alpha]_D^{25}$ + 64.8° (c 2.51, $CHCl_3$)], (8) [mp 127-129°C, $[\alpha]_D^{25}$ + 1.5° (c 2.10, $CHCl_3$)] and (9) [mp 184-187°C, $[\alpha]_D^{25}$ + 15.7° (c 0.91, pyridine)], in 4% overall yield respectively from (1). Reaction of (7) or (8) with $(CH_3)_2LiCu$ (5 eq, THF, 5°C, 8 h) gave (10) [mp 110-112°C, $[\alpha]_D^{25}$ + 2.0° (c 0.49, $CHCl_3$)], in 68% yield, which after Na/NH_3 reaction [9], afforded (11) [amorphous, $[\alpha]_D^{25}$ -19.6° (c 1.81, H_2O); lit. [2] $[\alpha]_D^{25}$ -65.8° (c 1.83, H_2O)] in 1% overall yield from (1) and 30% e.e. [10]

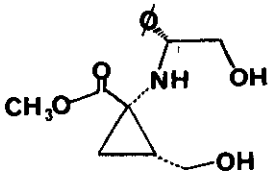
Efforts are now in progress to improve the stereochemical results, using the very well known chiral epibromohydrins [11], and apply some of the intermediates here described to the synthesis of related natural products.



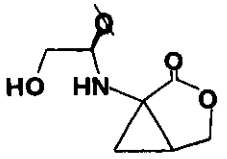
1



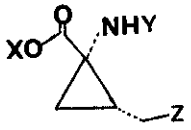
2

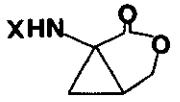


3



4





5, X = CH_3, Y = H, Z = OH
7, X = CH_3, Y = Ts, Z = Cl
8, X = CH_3, Y = Ts, Z = OTs
10, X = H, Y = Ts, Z = CH_3
11, X = Y = H, Z = CH_3

6, X = H
9; X = Ts

ACKNOWLEDGMENTS

The author is deeply grateful to Dr. Husson for his continous support during the course of this work.

REFERENCES AND NOTES

1. J.L. Marco, J. Heterocyclic Chem., 1986, 23, 287, 1059.
2. K. Shiraishi, A. Ichihara, and S. Sakamura, Agric. Biol. Chem., 1977, 41, 2497.
3. Enantiomerically pure compounds in this group have been obtained by resolution : E.J. Baldwin, R.M. Adlington, and B.J. Rawlings, Tetrahedron Lett., 1985, 26, 485; T. Wakamiya, Y. Oda, H. Fujita, and T. Shiba, Tetrahedron Lett., 1986, 27, 2143 , or asymmetric synthesis : U. Schöllkopf, M. Hauptreif, J. Dippel, and E. Egert, Angew. Chem. Int. Ed., 1986, 192; M.C. Pirrung and G.M. McGeehan, J. Org. Chem., 1986, 51, 2103.
4. T. Wakamiya, H. Nakamoto, and T. Shiba, Tetrahedron Lett., 1984, 25, 4411; A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, and T. Matsumoto, J. Am. Chem. Soc., 1977, 99, 636.
5. J.L. Marco, J. Royer, and H.P. Husson, Tetrahedron Lett., 1985, 26, 3567.
6. G. Mouzin, H. Cousse, and B. Bonnand, Synthesis, 1978, 304.
7. In this and subsequent figures only the major diastereomer or enantiomer is shown for simplicity. For (4), (6) and (9) the absolute configuration in the major one has not been resolved.
8. All new compounds showed analytical and spectroscopic data in full agreement with the structures.
9. V. du Vigneaud and O.K. Behrens, J. Biol. Chem., 1937, 27, 117.
10. Determined by chiroptical analysis. It is interesting to note that after crystallization (7), (8) and (10) were obtained as pure compounds showing sharp melting points, but in low optical yield; this is probably due to co-crystallization and to the moderate diastereoselectivity shown by (1) in its reaction with epibromohydrin yielding (3) and (4) in poor diastereomeric excess; in fact, in the case of (3) we could not separate the diastereomers.
11. J.J. Baldwin, A.W. Raab, K. Mensler, H.H. Arisson, and D.E. McClure, J. Org. Chem., 1978, 43, 4876.

Received, 13th May, 1987