Pergamon

Tetrahedron Letters, Vol. 35, No. 34, pp. 6361-6364, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01285-7

Asymmetric Synthesis of Cyclopentylamine Derivatives, Intermediates for Carbocyclic Nucleoside Synthesis. Carbocyclization of 2-Amino-5-hexenyl Radicals

José Marco-Contelles* and Manuel Bernabé

Instituto de Química Orgánica (CSIC), Juan de la Cierva 3, 28006-Madrid, Spain.

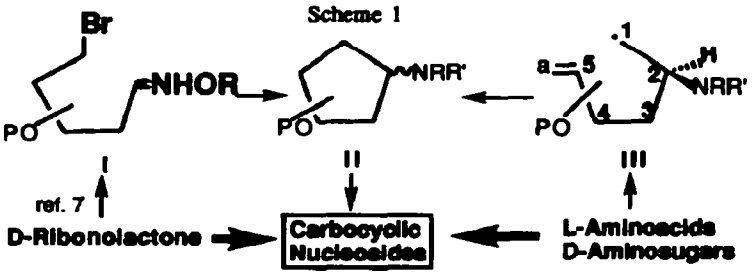
Abstract: *The carbocyclization of 2-amino-5-hexenyl radicals leading to aminocyclopentane derivatives is described for the first time. The tributyltin hydride + AIBN mediated free radical cyclization of the chiral recursors 17-19 and 24 gives compounds 25, 27 and 28, respectively, in good yield.*

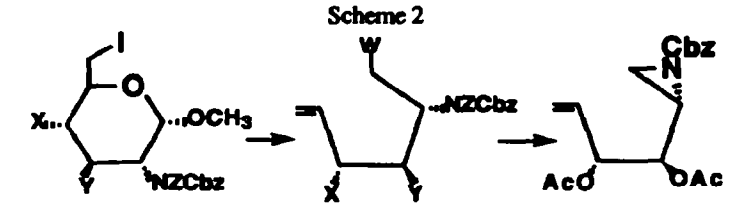
Carbocyclic nucleosides display important antitumor[1] and antiviral[2] activities. Recently, a great effort has been devoted to the chirospecific synthesis of these compounds.[3] The most elegant method[4] involves the transformation of enantiomerically pure cyclopentylamine derivatives[5] into the corresponding nucleosides following the standard methodologies.[6] In this context, we have reported the efficient, diastereoselective and enantiospecific synthesis of some cyclopentylamine derivatives II by 5-*exo* free radical cyclization of precursors of type I (PO= *O*-protecting group) prepared from D-ribonolactone[7] (Scheme 1). Now, in an alternative approach *we describe for the first time the preparation of chiral aminocyclopentane derivatives II by free radical cyclization of 2-amino-5-hexenyl radicals III*, that in turn can be obtained from precursors derived from L-aminoacids or D-aminosugars (Scheme 1). To our knowledge, although β-aminoalkyl radicals are known,[8] they have been prepared and exclusively transformed into nitracycles; their conversion into carbocycles remains until now unexplored.[9]

Preliminary experiments directed towards the synthesis of precursors **3** or **7** from compounds **1**[10a] or **5**[11] following standard protocols, gave product **4**[10b] (Scheme 2) or were unsuccessful, respectively. Then, we turned our attention to a similar, highly functionalized, more conformationally restricted precursor as **12** (Scheme 3). This product could be prepared from Garner's aldehyde **8**,[12] *via* lactone **9**,[13] after straightforward manipulations. Unfortunately, in typical free radical cyclization conditions precursor **12** proved very unstable and only extensive decomposition was observed.

In view of these results we designed the more simple and readily available radical precursors **17-19** and **24**.[14] These compounds were obtained, as shown in Scheme 4 and 5, starting from L-glutamic acid or L-serine, respectively. The carbocyclization of radical precursor **17**[16] (*E* isomer) gave the desired carbocycle **25**[17a] in 90% yield, as a mixture of isomers at C3, in 57/43 ratio, that we were unable to separate. Starting from compound **18** (*Z* isomer) we could isolate compound **25** in a similar high yield (92%), but in an improved diastereoselectivity (85:15). In both cases, the major isomer was always the same. The absolute configuration at the new stereocenter (C3) in the major cyclized isomer has been established as *S* by detailed ^{1}H NMR analysis of compound **26** (d.e.: 70%)[17b] (Scheme 4); this product has been obtained by Barbier-Wieland degradation[18] of the mixture of isomers **25**. In effect, a NOESY spectrum of compound **26** showed cross-peaks H-1/H-2b and H-3/H-2a, indicative of carboxy- and *tert*-butoxycarboxamido- groups being in a

trans orientation. The relationship between the ratios of the cyclized isomers and the double bond stereochemistry in the radical precursor is already known, the best acyclic stereoselection being observed for *Z* isomers.[19] Our results are also in accordance with this report and with the stereodirecting rules recorded for 5-*exo* free radical cyclizations.[20]

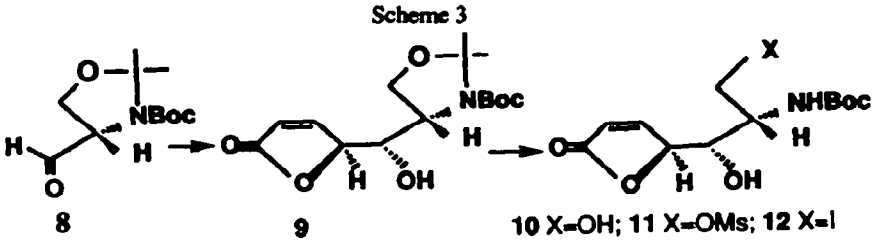




1 X,Y=OAc, Z=H
5 X=OH, Y=OBn, Z=Bn

2 X,Y=OAc, Z=H, W= OH
3 X,Y=OAc, Z=H, W=I
6 X=OH, Y=OBn, Z=Bn, W=OH
7 X=OH, Y=OBn, Z=Bn, W=I

4



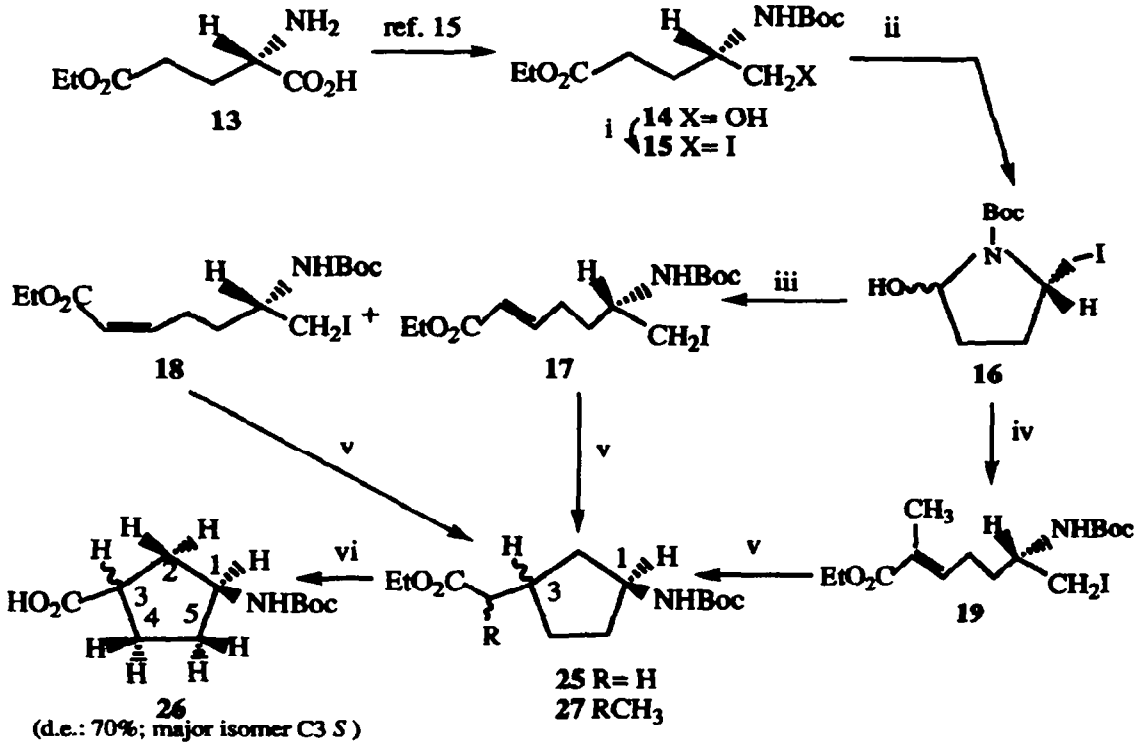
8 9 10 X=OH; 11 X=OMs; 12 X=I

The ring closure of precursor **19** (Scheme 4), obtained as the exclusive *E* isomer, as determined by ^{1}H NMR analysis and in accordance with the literature [21]) gave an unseparable mixture of the four possible isomers **27** (83% yield), in 1:1:1:1 ratio, that was not further investigated.

In the radical precursor **24** (Scheme 5) cyclization was attempted on a triple bond as radical trap.[22] Although compound **20** was obtained as a mixture of isomers at C3 (57:43),[23] during the purification by chromatography, precursor **24** was isolated in aliquots showing an improved diastereomeric ratio (70%). This same material, after cyclization,[16] gave carbocycle **28** (d.e.: 70%; the absolute configuration at C1 has been established as *S* by ^{1}H NMR analysis; in effect, in a NOESY spectrum, cross-peaks H-1/H-5b, H-2/H-3a, H-3a/H-5a and H-3b/H-5b were observed, hence a *trans*- arrangement of the benzyloxy- and *tert*-butoxycarboxamido- groups was deduced) in 89% yield, showing again the power of the present approach.

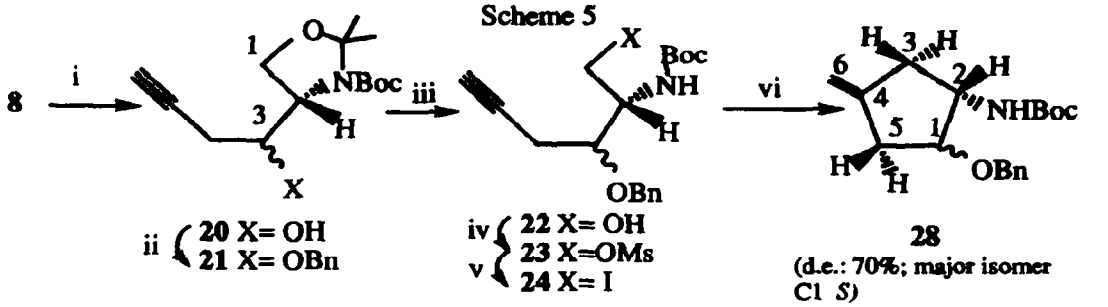
In summary, the cyclization of chiral 2-amino-5-hexenyl radicals gives the corresponding cyclopentylamines in good yield. The radical precursors can be prepared in few steps from commercial L-aminoacids. This is a new

Scheme 4



Reagents. i: Ph_3P, I_2, imidazole, toluene (66%). ii: DIBAH, -78°C, toluene (81%). iii: Ph_3PCHCO_2Et, EtOH, rt (E/Z: 2/1; 56%). iv: $Ph_3PCCH_3CO_2Et$, EtOH, rt (90%). v: $HSnBu_3$, AIBN, toluene, reflux (90%).vi: a. C_6H_5MgBr; b. Ac_2O, AcOH; c. CrO_3, AcOH.

Scheme 5



Reagents. i: HCCMgBr, -78°C → 0°C, 52%. ii: NaH, BnBr, rt (60%). iii: AcOH:H_2O, 70% (70%). iv: MsCl, Et_3N, CH_2Cl_2, -10°C (85%). v: LiI, THF,))) (74%). v: $HSnBu_3$, AIBN, toluene, reflux (89%).

strategy[5] for the preparation of enantiomerically pure carbocyclic nucleosides. The scope and applications of the present methodology is being analyzed in our laboratory and will be reported in due course

Acknowledgments. We thank Comunidad de Madrid (C195/91A), DGICYT (PB 90-0078), EEC (Human Capital and Mobility Programm; Project nº ERBCHRXCT 920027) and CICYT (SAF94-0818-C02-02) for financial support.

References and Notes

1. MacCoss, M.; Robins, M.J. *The Chemistry of Antitumor Agents*; Wilman, D.E.V.; Ed.; Blackie and Sons: U.K., 1990; pp 261, 299.

2. Robins,R.K.; Revankar, G.R.In *Antiviral Drug Development*;De Clercq, E.;Walker, R.T.; Plenum:New York,1988;p 11.

3. Borthwick, A.D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

4. Beres, J.; Sagi, G.; Tomoszi, I.; Gruber, L.; Gulacsi, E.; Otvos, L. *Tetrahedron Lett.* **1988**, *29*, 2681.

5. Chiral cyclopentylamines have been recently prepared by Dieckmann cyclization of α-aminoesteres: (a) Bergmeier, S.C.; Cobas, A.; Rapoport, H. *J.Org.Chem.* **1993**, *58*, 2369 (for other recent examples, see also reference 8 and 12 cited therein); (b) Bergmeier, S.C.; Rapoport, H. *Ibid.* **1993**, *58*, 5019; (c) Park, K.H.; Rapoport, H. *Ibid.* **1994**, *59*, 394.

6. (a) Lister, J.H. In *Fused Pyrimidines*; Brown, R.W.; Ed.; Wiley, 1971; Part II, p 31; (b) Shaw, G.; Warrener, R.W. *J.Chem.Soc.* **1958**, 153, 157.

7. (a) Marco-Contelles, J.; Ruiz, P.; Martínez, L.; Martínez-Grau, A. *Tetrahedron* **1993**, *49*, 6669. (b) Marco-Contelles, J.; Martínez, L.; Martínez-Grau, A. *Tetrahedron: Asymmetry* **1991**, *2*, 961.

8. Soucy, F.; Wernic, D.; Beaulieu, P. *J.Chem.Soc., Perkin Trans. 1* **1991**, 2885, and references cited therein.

9. The same applies for 3-amino-5-hexenyl radicals (unpublished results from this laboratory). For the formation and cyclization of 4-amino-5-hexenyl radicals, see: Simpkins, N.; Stokes, S.; Whittle, A.J. *Tetrahedron Lett.* **1992**, *33*, 793.

10. (a) Coleman, R.S.; Dong, Y.; Carpenter, A.J. *J.Org.Chem.* **1992**, *57*, 3732; (b) Coleman, R.S.; Carpenter, A.J. *Ibid.* **1992**, *57*, 5813.

11. Barton, D.H.R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumeny, J.M.; Géro, S.D.; Quiclet-Sire, B.; Stütz, P. *Tetrahedron* **1990**, *46*, 215.

12. Garner, P.; Park, J.M. *J.Org.Chem.* **1987**, *52*, 2361.

13. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J.Org.Chem.* **1991**, *56*, 6523.

14. All new compounds showed good analytical and spectroscopic data.

15. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J.Org.Chem.* **1991**, *56*, 4167.

16. In a typical experiment, to a solution of the radical precursor in toluene (0.02 M), under argon, at reflux, tributyltin hydride (1.5 equiv) + AIBN (cat.) was added in one portion and heating was continued for 30 min more (for precursor **24**, the hydride was added *via syringe pump* in 4 h). The solvent was removed and the residue dissolved in ether, treated with 20% aqueous potassium fluoride solution and stirred overnight. The organic phase was separated, dried, evaporated and submitted to chromatography eluting with hexane/ethyl acetate mixtures. The ratio of cyclized isomers was determined by GCC analysis.

17. (a) Jenny, T.F.; Horlacher, J.; Previsani, N.; Benner, S.A. *Helv.Chim.Acta* **1992**, *75*, 1944. (b) Allan, R.D.; Fong, J. *Aust.J.Chem.* **1986**, *39*, 855.

18. Riegel, B.; Moffett, R.B.; McIntosh, A.V. *Org.Synth. Coll Vol III*, **1955**, p 234.

19. Hanessian, S.; Dhanoa, D.; Beaulieu, P. *Can.J.Chem.* **1987**, *65*, 1859.

20. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds* ; Pergamon Press: Oxford 1986.

21. Hart, D.J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, *26*, 3749.

22. Rochigneux, I.; Fontanelle, M.L.; Malande, J.-C.; Douteau, A. *Tetrahedron Lett.* **1991**, *32*, 2017.

23. Jurczak, J.; Prokopowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107.

(*Received in UK* 23 *May* 1994; *revised* 28 *June* 1994; *accepted* 1 *July* 1994)