Tetrahedron Letters,Vol.30,No.23,pp 3101-3104,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF ASYMMETRIC 1-AMINO-2-PHENYLCYCLOPROPANECARBOXYLIC ACIDS BY DIASTEREOSELECTIVE CYCLOPROPANATION OF HIGHLY FUNCTIONALIZED HOMOCHIRAL OLEFINES

Mª Dolores Fernández, Mª Pilar de Frutos, José L. Marco,
Eldiberto Fernández-Alvarez, and Manuel Bernabé*

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

Abstract *- Homochiral benzylidenediketopiperazine and α-benzoylamino-cinnamic esters react with diazomethane giving high to good diastereomeric ratios of spiropyrazoline derivatives which, on photolysis and acid hydrolysis of the resulting spirocyclopropyl compounds gave, respectively, (+)- and (-)-1-amino-2-phenylcyclopropanecarboxylic acids.*

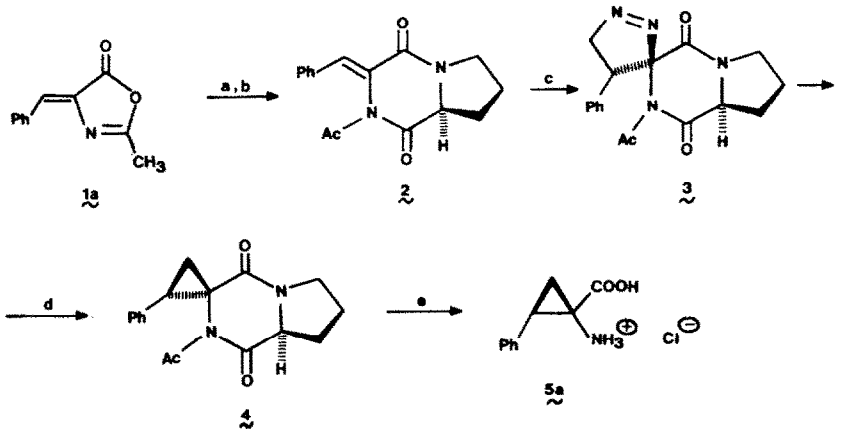
During the last years, 1-amino-1-cyclopropanecarboxylic acids have attracted special interest because of their documented biological activity.[1-9] Although several procedures for the preparation of this class of aminoacids have been described,[6-16] an inexpensive and general synthetic method for producing enantiomeric pure forms of these compounds is still lacking.

We have reported a simple method to produce racemic (Z)- and (E)-1-amino-2-arylcyclopropanecarboxylic acids,[11] starting from inexpensive 4-arylidene-oxazolones. This still appeared as a convenient approach for asymmetric synthesis, provided pertinent modifications of the starting syntons were made in order to include homochiral substituents which could induce asymmetric cyclopropanation, the key step in the process.

Thus, treatment of (Z)-2-methyl-4-benzylideneoxazolone (**1a**) with L-proline, and cyclisation of the resulting N-acetyl-phenyldehydroalanyl-L-proline gave diketopiperazine **2**[17] in an overall yield of 72%, (Scheme I). This was reacted with diazomethane to give 70% of an almost single diastereoisomer (>95%) of the corresponding pyrazoline **3**[19] which on photolysis in the usual way produced 90% of the spirocyclopropane **4**. Acid hydrolysis of **4** yielded 70% of (+)-1-amino-2-phenyl-cyclopropanecarboxylic acid (**5a**), easily isolated from the mixture with the starting L-proline by precipitation at pH = 8 and recrystallization of the resulting solid.

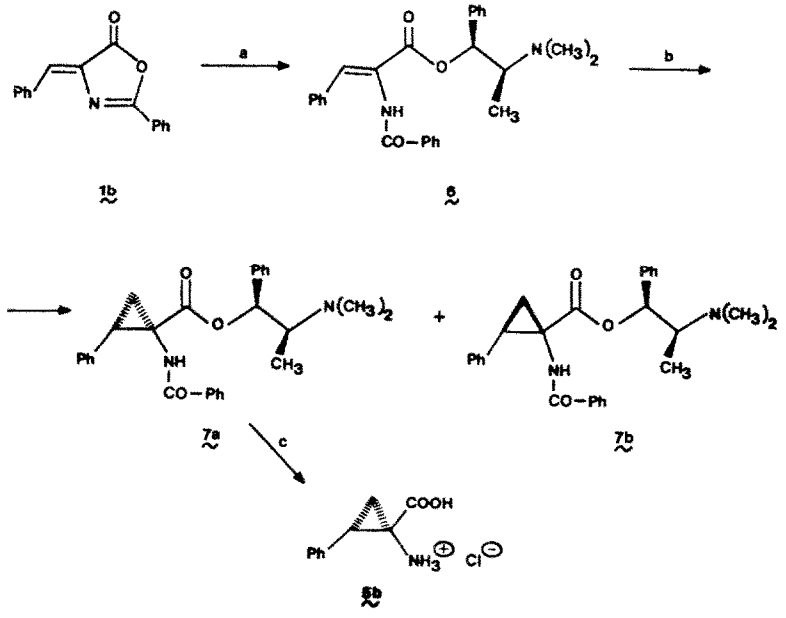
On the other hand, similar cleavage of the (Z)-oxazolone **1b** with (-)-N-methylephedrine gave 91% of the homochiral ester **6** (Scheme II). Cycloaddition of diazomethane and subsequent photolytic treatment of the resulting pyrazoline mixture gave 57% of a mixture of both possible cyclopropyl diastereoisomers, which were separated by medium pressure column chromatography on silica gel (3% MeOH/CH_2Cl_2). Acid hydrolysis of the major ester 7a (66%) produced 65% of (-)-1-amino-2-phenylcyclopropanecarboxylic acid (**5b**).

SCHEME I[a, 18,20]



[a] (a) NaOH; S-Proline, H_2O-acetone, r.t. 12 h.; (b) Ac_2O, r.t. 48 h.; (c) CH_2N_2/benzene, 3 days, r.t.; [19] (d) hν, benzene, 7 h.; (e) 6N HCl-HOAc, 100°C, 24 h.

SCHEME II[b, 18,20]



[b] (a) (-)-N-Methylephedrine, HNa, THF, r.t. 2 h.; (b) (1) CH_2N_2/Cl_3CH, -20°, 3.5 days. (2) hν, benzene 6 h.; (c) 6N HCl-dioxane, 100°C, 17 h.

The depicted absolute configuration of compounds **3 - 7** were estimated from ^{1}H-NMR chemical shifts of the diastereoisomers of compound **4**, and later corroborated by X-ray crystallographic analysis of deacetylated **4**.[21]

Further studies on the scope and limitations of the method are under way.

Acknowledgments

The authors wish to express their appreciation to Prof. C. Cativiela, Departamento de Química Orgánica, Universidad de Zaragoza, Spain, for helpful discussions; to Ministerio de Educación y Ciencia for scholarships (M.D.F. and M.P.F.) and DGICYT (Grant PR 84-0089) for financial support.

References and notes

1. (a) R. J. Breckenridge, C. J. Suckling, *Tetrahedron* 1986, **42**, 5665.
   (b) C. J. Suckling, *Angew. Chem. Int. Ed. Engl.* 1988, **27**, 537 and references therein.
2. K. Shiraishi, K. Konoma, H. Sato, A. Ichibara, K. Sakamura, N. Nishiyama, P. Sakai, *Agric. Biol. Chem.* 1979, **43**, 1753.
3. C. Walsh, R. A. Pascal, M. Johnston, R. Raines, D. Dikskit, A. Krantz, M. Homma, *Biochemistry* 1981, **20**, 7509.
4. (a) M. Bernabé, O. Cuevas, E. Fernández-Alvarez, *An. Quím.* 1979, **75**, 977.
   (b) I. Arenal, M. Bernabé, E. Fernández-Alvarez, A. M. Gibello, *ibid.* 1983, **79C**, 65.
5. (a) M. C. Pirrung, *J. Am. Chem. Soc.* 1983, **105**, 7207.
   (b) M. C. Pirrung, G. M. McGeehan, *Angew. Chem. Int. Ed. Engl.* 1985, **24**, 1044.
6. N. Kurokawa, Y. Ohfune, *Tetrahedron Lett.* 1985, **26**, 83.
7. J. E. Baldwin, R. M. Adlington, B. J. Rawlings, *Tetrahedron Lett.* 1985, **26**, 481.
8. K. Yamanoi, Y. Ohfune, *Tetrahedron Lett.* 1988, **27**, 537.
9. M. Bernabé, O. Cuevas, E. Fernández-Alvarez, *Eur. J. Med. Chem.* 1979, **14**, 35.
10. (a) S. W. King, J. M. Riordan, E. M. Holt, C. H. Stammer, *J. Org. Chem.* 1982, **47**, 3270.
    (b) J. M. Bland, C. H. Stammer, K. I. Varughese, *ibid.* 1984, **49**, 1634.
    (c) A. Bartolussi, C. H. Stammer, *ibid.* 1988, **53**, 992.
    (d) L. F. Elrod, E. M. Holt, C. Mapelli, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* 1988, 252.
11. (a) I. Arenal, M. Bernabé, E. Fernández-Alvarez, M. L. Izquierdo, S. Penadés, *J. Heterocycl. Chem.* 1983, **20**, 607.
    (b) I. Arenal, M. Bernabé, E. Fernández-Alvarez, S. Penadés, *Synthesis* 1985, 773.
12. M. L. Izquierdo, I. Arenal, M. Bernabé, E. Fernández-Alvarez, *Tetrahedron* 1985, **40**, 215.
13. C. Cativiela, M. D. Díaz de Villegas, E. Meléndez, *Tetrahedron* 1986, **42**, 583.
14. T. Wakamiya, Y. Oda, H. Fujita, T. Shiba, *Tetrahedron Lett.* 1986, **27**, 2143.
15. U. Schöllkopf, M. Hauptreif, J. Dippel, M. Nieger, E. Egert, *Angew. Chem. Int. Ed. Engl.* 1986, **25**, 192.

16. U. Schöllkopf, B. Hupfeld, R. Gull, *Angew. Chem. Int. Ed. Engl.* 1986, **25**, 1754.

17. H. Poisel, U. Schmidt, *Chem. Ber.* 1973, **106**, 3408.

18. All new compounds gave satisfactory IR and elementary or HRMS analytical data. Relevant ^{1}H-NMR parameters of selected derivatives were as follows: compound **3**: δ (Cl_3CD): *ca.* 2.0 (m, 3H, proline); 2.30 (s, 3H, CH_3); *ca.* 2.3 (m, 1H, proline); 3.66 (dd, 1H, CH-Ph, J = 7.8, J = 8.0 Hz); *ca.* 3.68 (m, 1H, proline); *ca.* 3.82 (m, 2H, proline); 5.10 (dd, 1H, pyrazoline, J = 7.8, J = 18.0 Hz); 5.28 (dd, 1H, pyrazoline, J = 9.0, J = 18.0 Hz); *ca.* 7.2 (m, 5H, arom.). Compound **4**: δ (Cl_3CD); *ca.* 2.0 (m, 2H, proline); *ca.* 2.2 (m, 2H, proline); 2.31 (dd, 1H, cyclopropane, J = 6.5; J = 7.0 Hz); 2.33 (s, 3H, CH_3); 2.60 (dd, 1H, cyclopropane, J = 6.5, J = 9.8 Hz); 2.67 (dd, 1H, cyclopropane , J = 7.0, J = 9.8 Hz); *ca.* 3.56 (m, 2H, proline); 4.11 (dd, 1H, proline, J = 7.9, J = 7.7 Hz); *ca.* 7.2 (m, 5H, arom.). Compound **5a**: δ (D_2O) 1.66 (dd, 1H, cyclopropane, J = 7.0, J = 8.3 Hz); 1.80 (dd, 1H, cyclopropane, J = 7.0, J = 9.6 Hz); 3.03 (dd, 1H, cyclopropane, J = 8.3, J = 9.6 Hz); *ca.* 7.25 (m, 5H, arom.). Compound **7a**: δ (Cl_3CD); 0.98 (d, 3H, CH_3, J = 6.7 Hz); 1.90 (dd, 1H, cyclopropane, J = 6.0, J = 8.1 Hz); 2.30 (dd, 1H, cyclopropane); 2.32 (s, 6H $(CH_3)_2N$); *ca.* 2.82 (m, 1H, C*H*-CH_3); 3.08 (dd, 1H, cyclopropane, J = 9.3, J = 8.1 Hz); 6.00 (d, 1H, OC*H*-Ph, J = 4.2 Hz); 6.19 (s, broad, NH); *ca.* 7.3 (m, 15H, arom.). Compound **7b**: δ (Cl_3CD); 1.01 (d, 3H, CH_3, J = 6.8 Hz); 1.88 (dd, 1H, cyclopropane, J = 6.0, J = 8.0 Hz); 2.29 (s, 6H, $(CH_3)_2N$); 2.30 (dd, 1H, cyclopropane, J = 6.0, J = 9.6 Hz); *ca.* 2.83 (m, 1H, C*H*-CH_3); 3.05 (dd, 1H, cyclopropane, J = 9.6, J = 8.0 Hz); 6.00 (d, 1H, C*H*-Ph, J = 4.8 Hz); 6.17 (s, broad, NH); *ca.* 7.3 (m, 15H, arom.). Compound **5b**: δ (D_2O); 1.80 (dd, 1H, cyclopropane, J = 7.0, J = 8.4 Hz); 1.94 (dd, cyclopropane, J = 7.0, J = 9.8 Hz); 3.15 (dd, 1H, cyclopropane, J = 9.8, J = 8.4 Hz); *ca.* 7.3 (m, 5H, arom.).

19. Diastereomeric ratios were determined by ^{1}H-NMR analysis of the crude reaction mixtures.

20. Melting points and $[\alpha]_D$ values of relevant compounds were as follows: compound **2**: mp 163-5°C; $[\alpha]_D^{25}$ +57° (c 0.28, Cl_3CH). Compound **3**: mp 171-3°C; $[\alpha]_D^{25}$ -266° (c 0.22, Cl_3CH). Compound **4**: mp 144°C; $[\alpha]_D^{25}$ -270° (c 1.1, Cl_3CH). Compound **5a**: mp 201°C (dec.); $[\alpha]_D^{25}$ +105° (c 0.69, H_2O). Compound **6**: 63-5°C; $[\alpha]_D^{25}$ +95° (c 1.1, Cl_3CH). Compound **7a**: mp 119-22°C (dec.); $[\alpha]_D^{25}$ -12.5° (c 4.3, Cl_3CH). Compound **7b**: syrup; not further purified. Compound 5b: mp 199°C (dec.); $[\alpha]_D^{25}$ -103° (c 0.76, H_2O).

21. Details will be reported soon elsewhere.

(Received in UK 6 March 1989)