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ASYMMETRIC SYNTHESIS XVI[1]. ENANTIOMERICALLY PURE SUBSTITUTED CYCLOPROPANE AMINO ACID PRECURSORS VIA THE CN(R,S) METHOD

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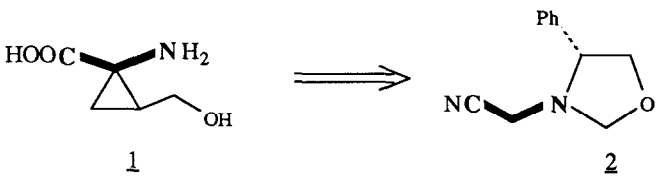
Abstract : The synthesis of tractable derivatives of 2-hydroxymethyl-1-amino-1-cyclopropanecarboxylic acid (+)- 6 and (-)- 7 in optically pure form has been achieved from the (-)-N-cyanomethyl-4-phenyl-oxazolidine synthon 2.

There is at present considerable interest in cyclopropane amino acids, or derivatives of 1-amino-1-cyclopropanecarboxylic acid (ACC), on account of their significance in ethylene biosynthesis,[2] in naturally occurring products,[3] and in the synthesis of conformationally restricted peptides[4]. Despite the obvious importance of chirality in biological studies, most of the reported synthetic routes to 2-substituted ACC's yield racemates[5]. Enantiomerically pure compounds have usually been obtained through resolution[6,7].

In continuation of our programme dealing with the diastereoselective substitutions of α-aminonitriles according to the CN(R,S) method,[8] we describe in this paper an efficient procedure for the enantioselective synthesis of derivatives of 2-hydroxymethyl-ACC 1 from the chiral synthon 2 (Scheme 1).



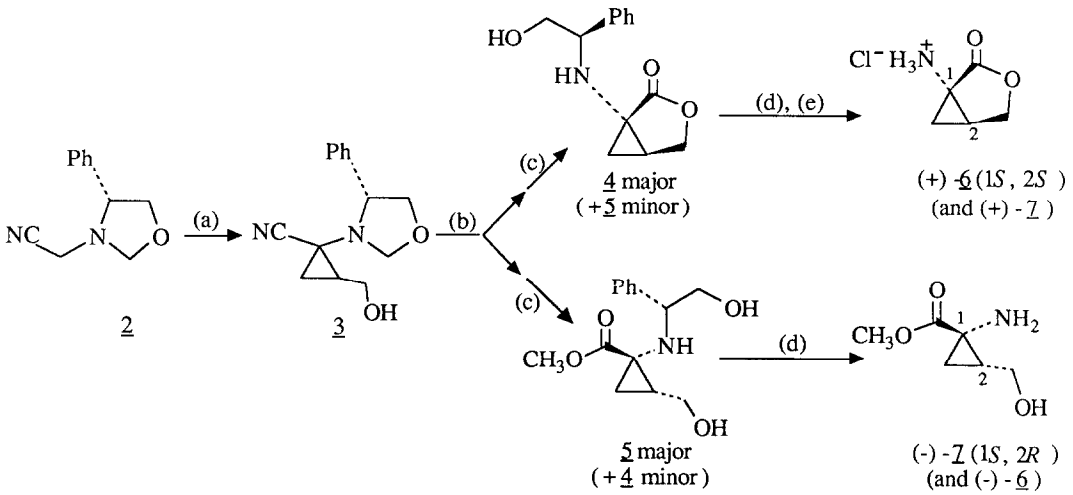
1 2

Scheme 1

Sequential dialkylations of 2 have been found in this laboratory to proceed with good yields and reasonable diastereoselectivity[9]. We employed the same strategy (generation of the aminonitrile anion with a strong base) to effect the double in situ alkylation of 2 with racemic epibromohydrin,[10] and obtained four diastereomeric cyclopropanes 3 (Y 45-50% and recovered unreacted 2 : conversion c. 90%). ^{13}C Nmr analysis of crude

3 showed two major diastereomeric components and two minor ones. Careful chromatography of samples of 3 allowed the separation of approximately equal quantities of two pairs of components, each of which contained one major and one minor product (in a ratio of approximately 85:15 for both pairs[11]). It transpired that in the first pair the major component had a cis- relative configuration of the nitrile and hydroxymethyl substituents, while in the second pair the major component has a trans- configuration.

The difference in substituent geometry within each 3-pair was exploited in the subsequent chemical transformations towards 1 to allow further separation of the major and minor components (Scheme 2).



(a) : i) LDA/HMPT 2.1 eq., THF, -70°,45 min, ii) epibromohydrin, THF, -70°, 1h;
(b) : Chromatography (silica, 40 : 60 EtOAc : hexane);
(c) : i) NaOH, Δ, 20 h, ii) H_3O^+ , pH 2-3, r.t. , iii) $SOCl_2$/MeOH, Δ, 3h;
(d) : i) 3 atm. H_2, 10% Pd/C, MeOH, 20h , ii) chromatography (silica, 10:90 MeOH:EtOAc);
(e) : HCl/EtOH.

Scheme 2

In a one-pot procedure, each sample of the 3-pairs was treated sequentially with aqueous base, acid, and a thionyl chloride/methanol mixture to effect esterification. In this last step, cyclopropanes with the cis- configuration undergo exclusive γ-lactone formation giving compounds 4, while those with the trans- configuration yield the monocyclic methyl esters 5. Thus we obtained two pairs of derivatives 4 and 5, having as the major component a single diastereomeric lactone 4 in the first case, and a single diastereomeric ester 5 in the second. Separation of the cis- and trans- derivatives at this stage was not convenient,[12] but was achieved after hydrogenolysis of the chiral appendage to give the primary amino compounds 6 and 7.[13]

In this way, the first 3-pair led to a single stereomer of lactone (+)-6 (28% overall yield),[14] while the second pair afforded a single stereomer of ester (-)-7 (46% overall yield).[15] The enantiomeric purity of compounds (+)-6 and (-)-7 is a consequence of, and is guaranteed by, their separation as diastereomers before cleavage of the chiral auxiliary.

A tentative assignment of the absolute configurations of (+)-6 and (-)-7 is based upon our previous observations[9] that the *S* configuration is formed preferentially during dialkylations of 2 with alkyl halides. The higher diastereomeric excess observed in the case of epibromohydrin (d.e. 70%) is probably the result of the intramolecular nature of the second substitution reaction. X-ray analysis of an appropriate crystalline derivative is currently in progress to check unambiguously this postulate.

In summary, a simple five-step reaction sequence starting from the chiral synthon 2 and incorporating two chromatographic separations has facilitated the convenient preparation and isolation of useful derivatives of two out of the four isomers of 2-hydroxymethyl-ACC in optically pure form. Although the other two stereomers were also produced in the sequence, the high degree of asymmetric induction during formation of the C-1 cyclopropane centre resulted in a very low yield of the two minor isomers. Recourse to the (+)- isomer of synthon 2 represents a more practical means of procuring these isomers.[16]

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REFERENCES AND NOTES

1. For Part XV, see J.C. Quirion, D.S. Grierson, J. Royer and H.-P. Husson, Tetrahedron Lett., preceding paper.

2. M.C. Pirrung, J. Org. Chem., 1987, 52, 4179.

3. (a) T. Wakamiya, H. Nakamoto and T. Shiba, Tetrahedron Lett., 1984, 25, 4411 ; (b) A. Ichihara, K. Shiraishi and S. Sakamura, Tetrahedron Lett., 1979, 365.

4. C. Mapelli, H. Kimura and C.H. Stammer, Int. J. Peptide Protein Res., 1986, 28, 347.

5. (a) L.F. Elrod, E.M. Holt, C. Mapelli and C.H. Stammer, J. Chem. Soc. Chem. Commun., 1988, 252 ; (b) U. Schöllkopf, B. Hupfeld and R. Gull, Angew. Chem., Int. Ed. Engl., 1986, 25, 754 ; (c) J.E. Baldwin, R.M. Adlington and B.J. Rawlings, Tetrahedron Lett., 1985, 26, 481 ; (d) I. Arenal, M. Bernabé, E. Fernandez Alvarez, M.L. Izquierdo and S. Penadés, J. Heterocyclic Chem., 1983, 20, 607 ; (e) U. Schöllkopf, R. Harms and D. Hoppe, Justus Liebigs Ann. Chem., 1973, 611.

6. (a) T. Wakamiya, Y. Oda, H. Fujita and T. Shiba, Tetrahedron Lett., 1986, 27, 2143 ; (b) J.E. Baldwin, R.M. Adlington, B.J. Rawlings and R.H. Jones, Tetrahedron Lett., 1985, 26, 485 ; (c) H. Kimura and C.H. Stammer, J. Org. Chem., 1983, 48, 2440 ; (d) K. Shiraishi, A. Ichihara and S. Sakamura, Agric. Biol. Chem., 1977, 41, 2497.

7. Two asymmetric syntheses of substituted ACC's have been reported : (a) U. Schöllkopf, M. Hauptreif, J. Dippel, M. Nieger and E. Egert, Angew. Chem., Int. Ed. Engl., 1986, 25, 192 ; (b) M.C. Pirrung and G.M. McGeehan, J. Org. Chem., 1986, 51, 2103.

8. S. Arseniyadis, P.Q. Huang and H.-P. Husson, Tetrahedron Lett., 1988, 29, 1391.

9. J.L. Marco, J. Royer and H.-P. Husson, Tetrahedron Lett., 1985, 26, 3567.

10. G. Mouzin, H. Cousse and B. Bonnaud, Synthesis, 1978, 304.

11. Assessments of diastereomeric ratios in 3 were made by examination of the peak heights of the ^{13}C nmr signals for the hydroxymethyl groups (at 59.1, 59.5, 61.2 and 61.6ppm) and for C-3 of the cyclopropane rings (at 17.2, 17.4, 18.8 and 19.2ppm).

12. Nevertheless, each sample of 4/5 mixture was examined by ^{13}C nmr spectroscopy to confirm the presence of only one isomer each of lactone and ester.

13. All new compounds (as mixtures or single isomers) gave satisfactory analytical and spectroscopic data.

14. Lactone (+)-6 hydrochloride : white crystals ; m.p. 164-166°C (dec.) (EtOH) ; $[\alpha]_D^{21}$ + 49.7° (c 0.94, MeOH) ; ν_{max} (mull) 3060w and 1770cm^{-1} ; δ_b (D_2O) 1.28 (1H, t, J 5.0Hz), 1.63 (1H, dd, J 5.0 and 8.0Hz), 2.72 (1H, m), 4.10 (1H, d, J 8.5Hz), 4.33 (1H, dd, J 8.5 and 4.5Hz) ; δ_c (D_2O), 17.0 (CH_2), 23.3 (CH), 38.8 (C_q), 71.4 (CH_2), 174.9 (C_q).

15. Ester (-)-7 : oil ; b.p. 110-115°C/0.5mm ; $[\alpha]_D^{21}$ - 38.4° (c 1.01, MeOH) ; ν_{max} (film) 3350br and 1710cm^{-1} ; δ_b ($CDCl_3$) 1.28 (1H, dd, J 4.7 and 7.3Hz), 1.47 (1H, dd, J 4.7 and 9.7Hz), 1.75 (1H, m), 2.75 (3H, br s), 3.75 (3H, s), 3.86 (1H, dd, J 12.0 and 5.2Hz), 4.09 (1H, dd, J 12.0 and 2.5Hz) ; δ_c ($CDCl_3$) 18.8 (CH_2), 28.7 (CH), 38.6 (C_q), 52.1 (CH_3), 59.5 (CH_2), 175.9 (C_q).

16. The same sequence has been followed in this laboratory without separation of the intermediates to obtain (-)-allocoronamic acid (1% overall yield and 30% e.e.) by J.L. Marco and published on his own initiative (Heterocycles, 1987, 26, 2579).

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