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Enantioselective Synthesis of (+)-(1R,2S)-Allocoronamic Acid

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Abstract: The asymmetric synthesis of (+)-(1R,2S)-allocoronamic acid is reported. Diazomethane addition to (Z)-N-(*tert*-butoxycarbonyl)ethyldehydroalanyl-L-prolin-anhydride, easily prepared from (Z)-2-phenyl-4-propylidene-5(4H)-oxazolone and L-proline, gave in high diastereomeric excess the corresponding spiropyrazoline, which was transformed, on photolysis and acid hydrolysis of the resulting spirocyclopropane, into (+)-(1R,2S)-1-amino-2-ethyl-cyclopropanecarboxylic acid.

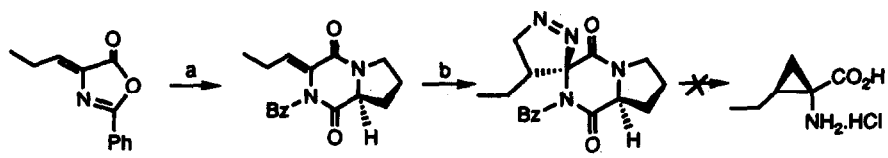
Since the first report on the isolation[1] and identification of 1-amino-1-cyclopropanecarboxylic acid (ACC) as an intermediate in the biosynthesis of ethylene in higher plants,[2] the synthesis of this compound and its derivatives have attracted special interest,[3] because of their biological activity[3,4] and potencial use in conformationally restricted peptides.[5]

Although several approaches to the preparation of this class of amino acids have been described,[3] only a few asymmetric synthesis have been published.[6] We have previously reported the preparation of (+)-(1S,2S) and (-)-(1R,2R)-2-phenyl ACC by reaction of diazomethane with chirally derived 4-benzylidene-oxazolones.[6e] Very recently we have also described the synthesis of rac-allocoronamic acid (2-ethyl ACC)[7] starting from 2-phenyl-4-propylidene-5(4H)-oxazolone (**1**).[8]

The recent report about the first enantiomerically pure synthesis of (1S,2S)-2-alkyl-1-amino-cyclopropanecarboxylic acids[6h] prompted us to describe here our current work in this area, which has culminated in the synthesis of (1R,2S)-1-amino-2-ethyl-cyclopropanecarboxylic acid [(+)-allocoronamic acid], the preferred of the four possible stereoisomers of 2-ethyl ACC which is processed to 1-butene by plant tissues.[9]

Applying Schmidt's procedure[10] we have synthesized diketopiperazine **2a** [50% yield from (Z)-2-phenyl-4-propylidene-5(4H)-oxazolone (**1**)[8]] (Scheme 1). Problems arose in the photolytic reaction of the corresponding N-benzoyl pyrazoline **5a**, which led to complex mixtures of compounds, not further investigated. As we had also observed extensive decomposition in the photolysis of N-benzoyl substituted arylpyrazolines analogous to **5a**,[11] the change of the N-protecting group seemed advisable. The

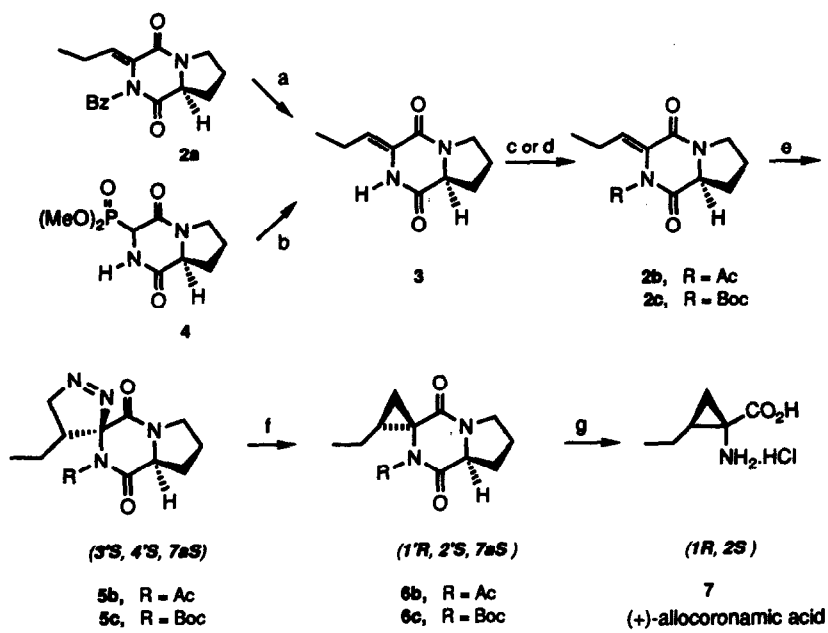
Scheme 1



1 2a 5a 7

(a) 1. NaOH, S-Proline, H_2O-acetone, r.t., 24 h; 2. Ac_2O, r.t., 12 h (b) CH_2N_2, benzene, 0-5°C, 24 h

Scheme 2



2a 4 3 2b, R = Ac; 2c, R = Boc

(3'S, 4'S, 7aS) *(1'R, 2'S, 7aS)* *(1R, 2S)*

5b, R = Ac; 5c, R = Boc 6b, R = Ac; 6c, R = Boc 7 (+)-allocoronamic acid

(a) Glycine-methylester hydrochloride, TEA, Et_2O, r.t. 12h (b) 1. ^{t}BuOK, CH_2Cl_2 (argon), -70°C; 2. propionaldehyde, CH_2Cl_2, r.t., 2 h, Z/E=9/1 (c) Ac_2O, 130°C, 12 h (d) TEA, DMAP, $(^t BuCO_2)_2O$, CH_2Cl_2(argon), r.t., 12 h (e) CH_2N_2, benzene, r.t., 3 or 8 d (f) hv, benzene, 7 h (g) 1. 6N HCl-AcOH, 100°C, 2 d; 2. AMBERLITE CG-120(Na^+ form)

preparation of the N-acetyl derivative **2b** was first attempted (Scheme 2), but this compound was unstable and gave the pyrazoline **5b** in low yield. Finally the N-(*tert*-butoxycarbonyl)-diketopiperazine **2c** was synthesized in 75% yield, by treatment of derivative **3** with di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and triethylamine in 75% yield. Compound **3** was obtained, either reacting **2a** with glycine-methyl ester hydrochloride and triethylamine (85% yield),[10] or by treatment of the phosphonodiketopiperazine **4**[12] with potassium *tert*-butoxide and propionaldehyde (Z/E=9/1, 75% yield).

The N-Boc diketopiperazine **2c** was reacted with diazomethane to give an almost single diastereoisomer (>95%) of the pyrazoline **5c**[14] in 95% yield. This product, on photolysis in the usual way,[6e] produced the spirocyclopropane **6c** in almost quantitative yield. Acid hydrolysis of **6c** gave, after removing the starting proline through an ion-exchange column[17] and recrystallization from ethanol/diethyl ether, (+)-(1R,2S)-1-amino-2-ethyl-cyclopropanecarboxylic acid **7** (66% yield) [$[\alpha]_D$ +64° (*c* 1.1, $CHCl_3$), lit.[16] $[\alpha]_D$ +65° (*c* 1.83, $CHCl_3$)]. Unalterated L-proline was recovered in 76% yield.

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References and Notes

1. Burroughs, L.F., *Nature* **1957**, 360.
2. Adams, D.O.; Yang, S.F., *Proc. Natl. Acad. Sci. USA*, **1979**, *76*, 170.
3. For a recent review, see Stammer, C.H., *Tetrahedron*, **1990**, *46*, 2231 and references therein.
4. (a) Shiraishi, K.; Konoma, K.; Sato, H.; Ichibara, A.; Sakamura, K.; Nishiyama, N.; Sakai,P., *Agric. Biol. Chem.*, **1976**, *43*, 1753.
   (b) Adlington, R.M.; Baldwin, J.E.; Rawlings, B.J., *J. Chem. Soc., Chem. Commun.*,**1983**, 290.
   (c) Suckling, C.J., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27, 537* and references cited therein.
5. Mapelli, C.; Newton, M.G.; Ringold, C.E.; Stammer, C.H., *Int. J. Peptide Protein Res.*, **1987**, *30*, 498.
6. (a) Hill, R.K.; Prakash, S.R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H.W.; Walsh, C.T., *J. Am. Chem. Soc.*, **1984**, *106*, 795.
   (b) Pirrung, M.; McGeehan, G.M., *J. Org. Chem.*, **1986**, *51*, 2103.
   (c) Woodard, R.W.; Subramanian, P.K., *J. Org. Chem.*, **1987**, *52*, 15.
   (d) Marco, J.L., *Heterocycles*, **1987**, *26*, 2579.
   (e) Fernández, M.D.; de Frutos, M.P.; Marco, J.L.; Fernández-Alvarez, E.; Bernabé, M., *Tetrahedron Lett.*, **1989**, *30*, 3101.
   (f) Alami, A.; Calmes, M.; Daunis, J.; Escale, F.; Jacquier, R.; Roumestant, M.L.; Viallefont, P., *Tetrahedron: Asymmetry*, **1991**, *2*, 175.
   (g) Gaucher, A.; Ollivier, J.; Salaün, J., *Synlett*, **1991**, 151.
   (h) Williams, R.M.; Fegley, G.J., *J. Am. Chem. Soc.*, **1991**, *113*, 8796.
7. Marco, J.L.; Sánchez, B.; Fernández, M.D.; Bernabé, M., *Liebigs Ann. Chem.*, **1991**, 1099.
8. Baltazzi, E.; Robinson, R., *Chem. Ind.*, **1954**, 191.

9. Hoffman, N.E.; Yang, S.F.; Ichihara, A.; Sakamura, S., *Plant Physiol.*, **1982**, *70*, 195.
10. Poisel, H.; Schmidt, U., *Chem. Ber.*, **1973**, *106*, 3408.
11. Unpublished results.
12. (a) Zoller, U.; Ben-Ishai, D., *Tetrahedron*, **1975**, *31*, 863.
(b) Schmidt, U.; Lieberknecht, A.; Wild, J., *Synthesis*, **1984**, 53.
(c) Lieberknecht, A.; Griesser, H., *Tetrahedron Lett.*, **1987**, *28*, 4275.
13. All new compounds gave satisfactory spectroscopic and analytical data. Relevant ^{1}H-NMR parameters of selected derivatives were as follows: Compound **2a**: $\delta(CDCl_3)$: 7.74-7.37 (m, 5H, arom.); 6.24 (dd, 1H, olef., J=9.0, J=5.8 Hz); 4.22 (t, 1H, proline, J=7.9 Hz); 3.58 (m, 2H, proline); 2.24-1.72 (m, 6H, CH_2 proline and ethyl); 0.88 (t, 3H, CH_3, J=7.5 Hz). Compound **2c**: $\delta(C_6D_6)$: 6.47 (dd, 1H, olef., J=8.7, J=6.3 Hz); 3.18 (dd, 1H, proline, J=7.3, J=8.5 Hz); 3.12-2.95 (m, 2H, proline); 2.04 (m, 2H, proline); 1.8 (m, 1H, proline); 1.52 (m, 1H, proline), 1.40 (s, 9H, Boc); 1.04 (m, 2H, proline); 0.85 (t, 3H, CH_3, J=7.5 Hz). Compound **3**: $\delta(CDCl_3)$: 8.91 (bs, 1H, NH); 6.05 (t, 1H, olef., J=7.75 Hz); 4.19 (dd, 1H, proline, J=9.7, J=6.5 Hz); 3.76 (m, 1H, proline); 3.57 (m, 1H, proline); 2.42 (m, 1H, proline); 2.15 (q, 2H, CH_2 ethyl, J=7.5 Hz); 2.09-1.87 (m, 3H, proline); 1.10 (t, 3H, CH_3, J=7.5 Hz). Compound **5c**: $\delta(C_6D_6)$: 4.51 (dd, 1H, pyrazoline, J=17.9, J=8.4 Hz); 4.38 (dd, 1H, pyrazoline, J=17.9, J=5.3 Hz); 3.45 (dd, 1H, proline, J=10.0, J=6.8 Hz); 3.00 (m, 2H, proline); 1.85 (m, 2H, proline, pyrazoline); 1.55 (m, 3H, proline, CH_2 ethyl); 1.36 (s, 9H, Boc); 1.00 (m, 2H, proline); 0.54 (t, 3H, CH_3, J=7.4 Hz). Compound **6c**: $\delta(C_6D_6)$: 3.77 (t, 1H, proline, J=7.8 Hz); 3.39-3.05 (m, 2H, proline); 2.28 (dd, 1H, cyclopropane, J=9.5, J=6.6 Hz); 2.08 (m, 1H, proline); 1.76 (m, 1H, proline); 1.34 (s, 9H, Boc); 1.31-1.11 (m, 5H, cyclopropane, proline, CH_2 ethyl); 1.01 (m, 1H, cyclopropane); 0.80 (t, 3H, CH_3, J=7.4 Hz). Compound **7**: $\delta(D_2O)$: 1.83 (m, 1H, cyclopropane); 1.69 (dd, 1H, cyclopropane, J=9.9, J=6.1 Hz); 1.60 (m, 1H, CH_2 ethyl); 1.44 (m, 1H, CH_2 ethyl); 1.15 (dd, 1H, cyclopropane, J= 8.0, J= 6.1 Hz); 1.06 (t, 3H, CH_3, J=7.3 Hz).
14. Diastereomeric excesses were determined by ^{1}H-NMR analysis on the crude reaction mixtures.
15. Meltings points and $[\alpha]_D$ values of relevant compounds were as follows: Compound **2a**: mp 94-96°C; $[\alpha]_D$ +71° (*c* 0.7, $CHCl_3$). Compound **2c**: mp 93-94°C; $[\alpha]_D$ -6° (*c* 1.53, $CHCl_3$). Compound **3**: mp 195-197°C; $[\alpha]_D$ +17° (*c* 1.09, $CHCl_3$). Compound **5c**: mp 138°C; $[\alpha]_D$ -7° (*c* 0.76, $CHCl_3$). Compound **6c**: mp 71-73°C; $[\alpha]_D$ -9° (*c* 0.6, $CHCl_3$). Compound **7**: mp 212-214°C (dec.); $[\alpha]_D$ +64° (*c* 1.1, H_2O).
16. Baldwin, J.E.;Adlington, R.M.; Rawlings, B.J.; Jones, R.H., *Tetrahedron Lett.*, **1985**, *26*, 485.
17. Hirs, C.H.W.; Moore, S.; Stein, W.H., *J. Biol. Chem.*, **1952**, *195*, 669.

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