Tetrahedron Letters,Vol.26,No.1,pp 83 - 84,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

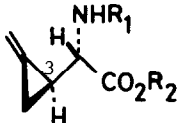
THE PALLADIUM(II)-ASSISTED SYNTHESES OF (±)-α-(METHYLENECYCLOPROPYL)GLYCINE AND (±)-TRANS-α-(CARBOXYCYCLOPROPYL)GLYCINE, TWO BIOACTIVE AMINO ACIDS.

Natsuko Kurokawa and Yasufumi Ohfune*
Suntory Institute for Bioorganic Research
Shimamoto-cho, Mishima-gun, Osaka 618, Japan

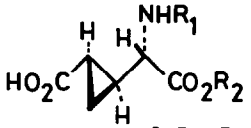
Summary: Title compounds 1 and 2 have been synthesized efficiently from β-hydroxyallylglycine derivative 3 via the Pd(II)-catalyzed reactions.

α-(Methylenecyclopropyl)glycine (1) and trans-α-(carboxycyclopropyl)glycine (2) have been found in the seeds of Sapindaceae family by Fowden et al.[1,2] In view of the significant biological activity of 1[2a] which causes hypoglycemic symptoms in animals, and since 2[2b] incorporates an L-glutamic acid moiety with a partially restricted conformation within its structure, both 1 and 2 have recently been shown to exhibit interesting bioactive properties.[3,4] We have reported the stereoselective synthesis of β-hydroxyallylglycine derivative 3 by an efficient SeO_2/t-BuOOH oxidation of N-t-butoxycarbonylallylglycine methyl ester.[5] We approached to the syntheses of 1 and 2 by using 3 via the Pd(II)-assisted migration of C4 double bond to C3 followed by cyclopropanation.

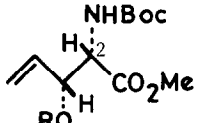
The Pd(II)-catalyzed [3,3] sigmatropic rearrangement of allylic acetate 4 to 5 was carried out as follows. Allylic alcohol 3[6] was converted (Ac_2O/Py, 100%) into allylic acetate 4 and treated with a catalytic amount of bis(acetonitrile)palladium(II) chloride (0.04 equiv) in benzene (60°C, 40h).[7] Workup provided the desired product 5 [oil; ^1H NMR($CDCl_3$) δ5.81(1H, dd, J=5.06, 15.95 Hz), 5.86(1H, ddd, J=4.74, 5.68, 15.95 Hz)] in 60% yield, and 35% of recovered starting material. The cyclopropane ring was introduced by using excess diazomethane (Et_2O, room temperature) in the presence of the same catalyst as above



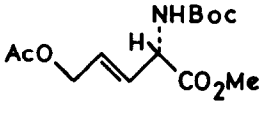
1 R_1=R_2=H
8 R_1=Boc, R_2=Me



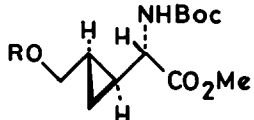
2 R_1=R_2=H
9 R_1=Boc, R_2=Me



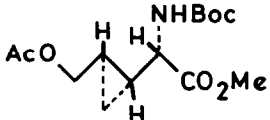
3 R=H
4 R=Ac



5



6a R=Ac, 6b R=H



7

to give a 1:1 mixture of (2S*,3S*,4S*)6a (Rf=0.31 in AcOEt/hexane=2/3) and (2S*, 3R*,4R*)7 (Rf=0.29) in 68% yield.[8,9] Both isomers were separated by medium pressure column chromatography on SiO_2 (elution with AcOEt/hexane=1/5). The configuration of the desired less polar isomer 6a was unambiguously determined by converting it to 1. This was accomplished by removal of the acetoxyl group of 6a (0.1 equiv K_2CO_3/MeOH, 97%), subsequent o-nitro-phenylselenenylation (o-NO_2-PhSeCN/n-Bu_3P, 100%), and oxidative elimination of the selenide (O_3/CH_2Cl_2, -78°C and then toluene, 110°C, 76%) yielding the exomethylenecyclopropane 8. Finally, the N- and O-protective groups were removed in two steps: (i) 0.5N KOH/THF; (ii) CF_3COOH. Treatment of the resultant trifluoroacetate with Dowex 50W x 4 and elution with 1N NH_3 provided (±)-1: mp 250°C(decomp); EIMS, m/z 128 $(M+1)^+$. Synthetic 1 showed identical 360MHz ^1H NMR, IR, and MS data with those of natural 1.[10]

On the other hand, oxidation of the alcohol 6b (Jones reagent, 83%) followed by deprotection as mentioned above afforded the corresponding monoammonium salt. Treatment with pH 4 buffer provided (±)-2: mp 245°C(decomp).[11]

ACKNOWLEDGEMENT: We are grateful to Prof. L.Fowden for a sample of natural 2. We wish to thank Dr. H.Komura of this Institute for spectral data of natural 1 and Dr. S.Yogai for assistance of experimental parts.

REFERENCES AND FOOTNOTES

1. For a review, see: I.Wagner and H.Musso, Angew.Chem.Int.Ed.Engl., 22, 816 (1983).
2. (a) D.O.Gray and L.Fowden, Biochem.J., 82, 385 (1962). (b) L.Fowden, A.Smith, D.S.Millington, and R.C.Sheppard, Phytochemistry, 8, 437 (1969).
3. Screening of numerous plants for antimutagenic activity has disclosed that 1 is the active principle in certain plants: H.Komura, et al., submitted for publication.
4. Biological activity of 2 was briefly reported.[2b] Moreover, the neurotransmitting activity of 2 as compared with that of L-Glu is of interest: to be described elsewhere.
5. Y.Ohfune and H.Nishio, Tetrahedron Lett., 4133 (1984).
6. A mixture of (2S*,3R*)3 and its (2S*,3S*)isomer (3.8:1 ratio)[5] was used.
7. (a) L.E.Overman and E.M.Knoll, ibid., 321 (1979). (b) P.A.Grieco, T.Takigawa, S.L.Bongers, and H.Tanaka, J.Am.Chem.Soc., 102, 7588 (1980).
8. Pd(II)-catalyzed cyclopropanation of terminal olefins,[8a] α,β-unsaturated carbonyls,[8b] and strained alkenes[8b] have been reported: (a) M.Suda, Synthesis, 714 (1981). (b) U.Mende, B.Radüchel, W.Skuballa, and H.Vorbrüggen, Tetrahedron Lett., 629 (1975).
9. The [2+3] cycloaddition of vinylglycine derivatives with nitrile oxide results in poor stereoselectivity: P.A.Wade, S.M.Singh, and M.K.Pillay, Tetrahedron, 40, 601 (1984).
10. 360MHz ^1H NMR(D_2O) data of 1: δ1.285(1H, dddd, J=2.0, 2.5, 5.0, 10.0 Hz), 1.56(1H, dddd, J=2.0, 2.5, 10.0, 10.2 Hz), 3.40(1H, d, J=8.5 Hz), 5.55(1H, m), 5.60(1H, m). C3 epimer of 1 (synthesized from 7 in the same manner with those of 1): δ3.25(1H, d, J=10.0 Hz).
11. 360MHz ^1H NMR and IR spectra of synthetic 2 were identical with those of authentic material. ^1H NMR(D_2O) data of 2: δ1.27(1H, ddd, J=5.2, 6.0, 8.7 Hz), 1.38(1H, dt, J=5.2, 8.7 Hz), 1.75(1H, m), 1.82(1H, ddd, J=4.0, 5.2, 8.7 Hz), 3.60(1H, d, J=10.0 Hz).
12. Satisfactory spectroscopic data were obtained for all new compounds in this text.

(Received in Japan 20 September 1984)