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A GENERAL ASYMMETRIC CYCLIZATION. ASYMMETRIC SYNTHETHIS OF OPTICALLY ACTIVE 2-OXO-5-PYRROLIDINEACETIC ACID DERIVATIVES

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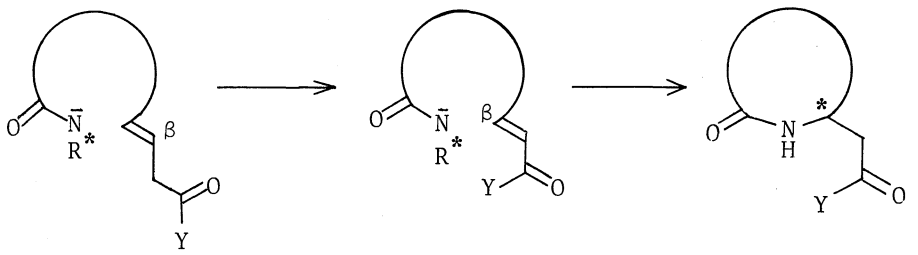
Novel asymmetric intramolecular Michael addition by chiral amide anion to α,β-unsaturated ester was performed for the asymmetric synthesis of (S)-2-oxo-5-pyrrolidineacetic acid. The acid was related to (S)-(-)-ecgoninic acid in order to determine its absolute configuration. Much higher diastereoselectivity of the chiral amide than that of the chiral ester was also demonstrated.

Althogh different approaches for asymmetric cyclization in carbon-carbon bond formation to yield optically active alicyclic compounds have been explored,[1] a study on an asymmetric cyclization in carbon-nitrogen bond formation has few examples.[2] We describe herein the first asymmetric intramolecular Michael Addition of the chiral amide anion onto the β-carbon of an α,β-unsaturated carbonyl compound or a β,γ-unsaturated carbonyl compound which is convertible to α,β-unsaturated one. This concept is outlined in eq. 1.



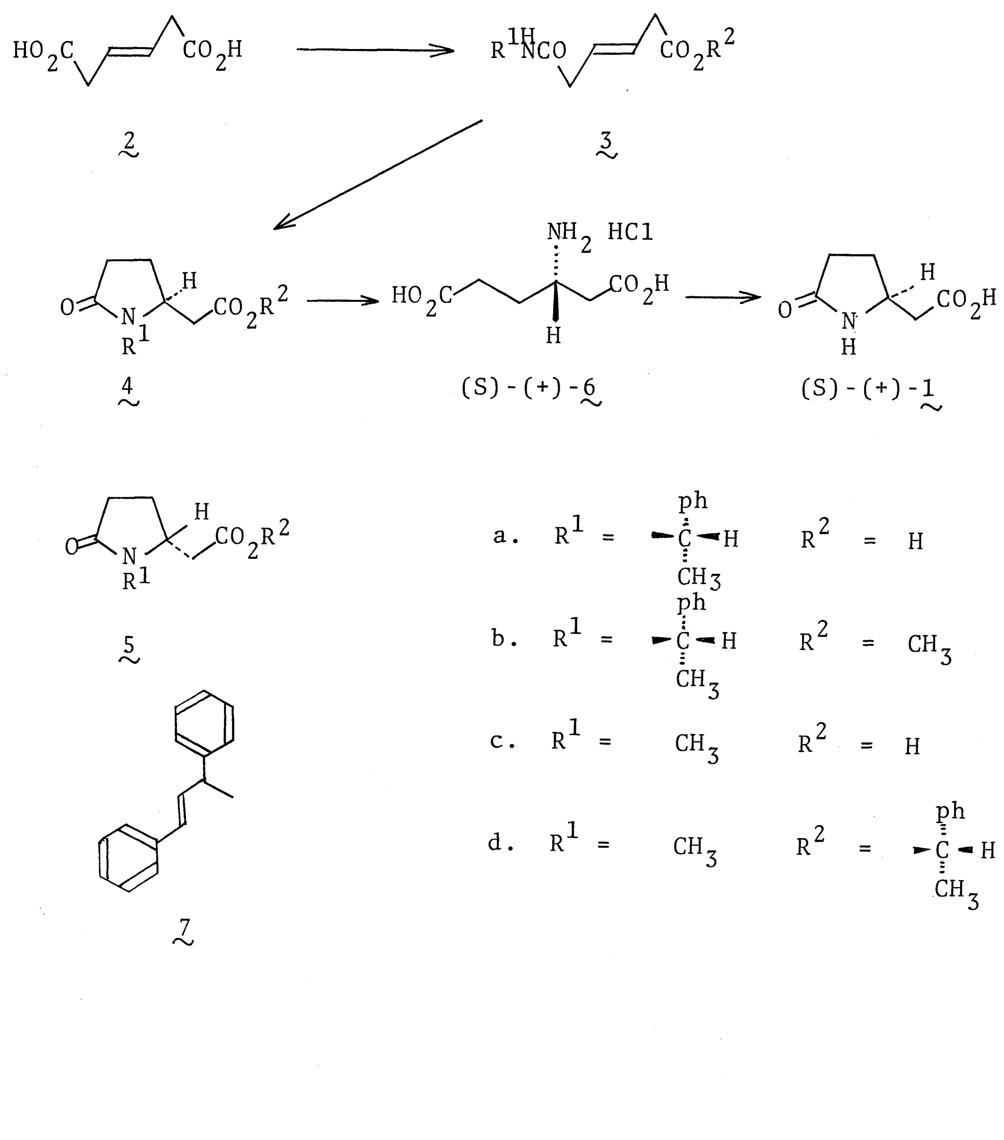
(1)

R*: chiral controlling group

This report deals with the asymmetric synthesis of (S)-(+)-2-oxo-5-pyrrolidineacetic acid (1)[3], which is a potential intermediate for optically active pyrrolidine derivatives, by the cyclization process utilizing a readily available and efficient chiral controlling group.

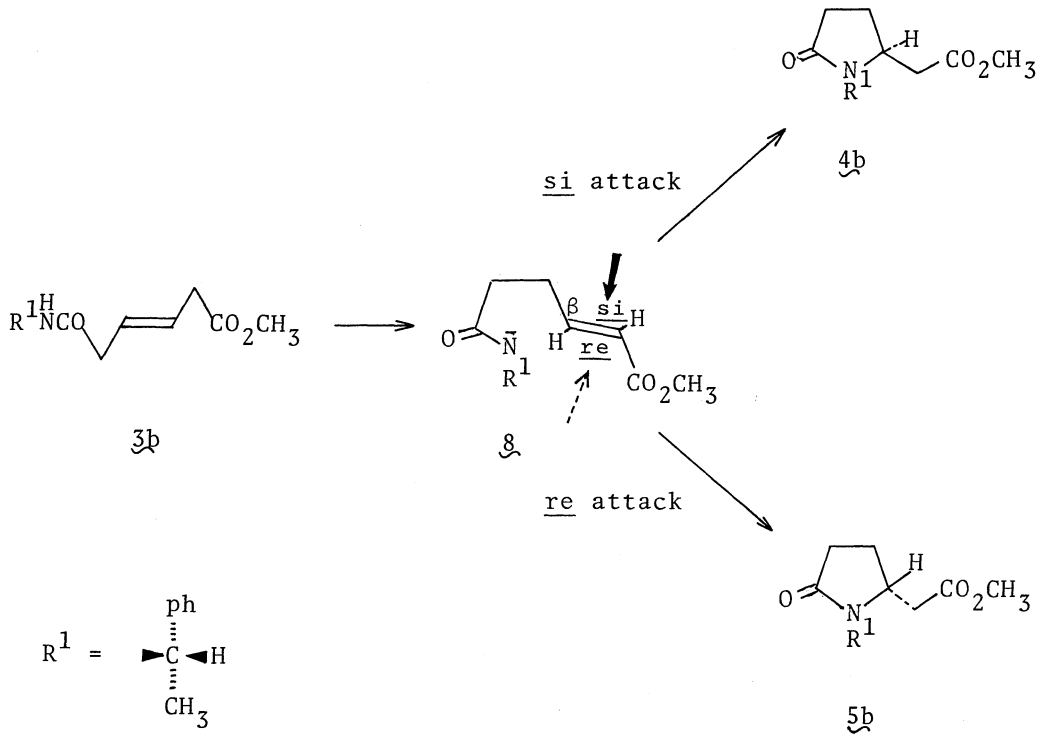
Treatment of β-hydromuconic acid (2) with (S)-(-)-α-phenethylamine and diethyl phosphorocyanidate (DEPC)[4] in dimethylformamide (DMF) gave the optically active acid 3a, mp 66-67°, $[\alpha]_D^{23}$ - 63.5° (c=1.0[5], EtOH), in 41% yield. Initial attempts of the asymmetric cyclization of the acid 3a with sodium hydride (NaH) or triethylamine, or with p-toluene sulfonic acid gave neither the amide 4a nor the amide 5a. Then, the acid 3a was esterified with diazomethane to the ester 3b, which was treated with 0.2 equiv. of NaH in THF at 4°C for 19 hr to give a mixture of methyl ester 4b and its diastereomer 5b in 72% yield. To determine the ratio of

Scheme I

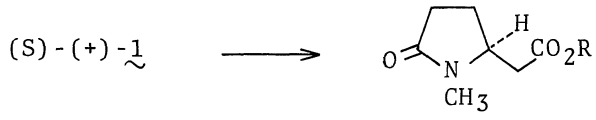


4a and 5a the corresponding mixture of methyl esters 4b and 5b prepared by treatment with diazomethane was submitted to an nmr assay. The 100-MHz nmr spectra of the above mixture of methyl esters 4b and 5b in deuterochloroform showed chemical shift differences (3.53 and 3.61 ppm) in the methyl ester region and showed 44% diastereomeric purity[6] for 4b (4b : 5b = 72 : 28). Hydrolysis of the latter mixture of the methyl ester 4b and 5b with aqueous methanolic KOH gave a mixture of amides 4a and 5a which yielded 96% optically pure 4a, mp 205-206°, $[\alpha]_D^{27}$ - 159.9° (EtOH), after recrystallizations from ethanol. The above transformation of the ester 3b to the diastereoisomeric mixture of the amides 4b and 5b is outlined in Scheme II. Migration of the double bond of the ester 3b by NaH generates the probable intermediate 8 which has a chiral amide anion functionality discriminating si-face from re-face[7] at the β-carbon to afford the amide 4b diasteroselectively.[8]

Scheme II



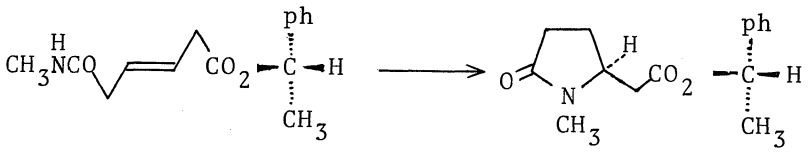
The 96% optically pure amide 4a was treated with 6N-HCl under reflux to give (S)-(+)-β-aminoadipic acid hydrochloride (6)[9] in 94% yield [mp 173-175°, $[\alpha]_D^{26}$ + 18.8°(water)] and the compound 7 [UV: λ_{max}(hexane) 251(ε 16,600), 284 (ε 1,400), MS: m/e 208 (M^+)] in 35% yield. Cyclization of 6 in pyridine under reflux for 1.5 hr afforded (S)-(+)-2-oxo-5-pyrrolidineacetic acid (1), mp 103-105°, $[\alpha]_D^{26}$ + 17.6°(EtOH), in 96% yield. Methylation of the resulting acid 1 with methyl iodide and sodium hydride in DMF gave (S)-(-)-methyl ecgoninate (9b) as an oil, $[\alpha]_D^{23}$ - 40.1° (EtOH), in 86% yield. Alkaline hydrolysis of 9b gave (S)-(-)-ecgoninic acid[10] (9a), mp 121-122°, $[\alpha]_D^{23}$ - 41.6°(EtOH), the degradation product of natural (-)-ecgonine (eq. 2).



(S)-(+)-1 (2)

9 a = H
b = CH_3

On the other hand, the ester 3d was prepared by the treatment of β-hydromuconic acid (2) with methylamine and DEPC followed by the esterification of the acid 3c with (S)-(-)-α-phenethyl alcohol, N, N'-dicyclohexylcarbodiimide and pyridine in methylene chloride. Cyclization of the ester 3d with NaH in THF at 20°C gave the ester 10 in 85% yield (eq. 3).



3d 10 (3)

Saponification of the ester 10 afforded (S)-(-)-ecgoninic acid (9a), mp 90-93°, $[\alpha]_D^{23}$ - 0.9° (EtOH) in 2% optical purity and in 68% yield from 3d.

The above results demonstrate that the 1,6-asymmetric induction by the amide anion in 8 at the sp^2 carbon atom is more efficient than 1,5-asymmetric induction by that from 3d. Thus, the geometry of the transition state for the above 1,6-asymmetric induction seems to resemble the product 4b.

In conclusion, it should be pointed out that the new asymmetrically induced intramolecular Michael reaction using a chiral amide has major potential for biomimetic asymmetric alkaloid syntheses.[11]

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References and Notes

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3. S-configuration of this compound 1 was determined by converting 1 to (S)-(-)-ecgoninic acid 9a whose absolute configuration is already known.[10]
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5. All the optical rotation measurement was carried out at c=1.0.

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