

Asymmetric Synthesis of 2-Aminonorbornane-2-carboxylic Acids by Diels-Alder Reaction

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Abstract: Reaction of (-)-menthyl N-acetyl- α,β -dehydroalaninate with cyclopentadiene takes place with good chemical yields and diastereofacial selectivity. The cycloadducts are easily transformed into the corresponding amino acids.

Cycloaliphatic amino acids with a norbornane skeleton are of interest because they display interesting biological properties as far as the transport of ions through biological membranes is concerned¹. These amino acids can be obtained by Diels-Alder reactions using N-acyl- α,β -dehydroalaninates as dienophiles². To the best of our knowledge there are no references dealing with the asymmetric synthesis of these amino acids, so we have concentrated on the preparation of these compounds via asymmetric Diels-Alder reactions.

High levels of diastereofacial selectivity have been achieved in asymmetric Diels-Alder reactions using dienophiles with a removable, chiral-directing auxiliary³, so it is interesting to determine whether chiral N-acyl- α,β -dehydroalaninates can be used as chiral dienophiles in the asymmetric synthesis of cycloaliphatic amino acids via asymmetric Diels-Alder reactions. This communication reports the first asymmetric synthesis of bicycloaliphatic amino acids, 2-aminonorbomane-2-carboxylic acids, by Diels-Alder reaction, using (-)-menthyl N-acetyl- α,β -dehydroalaninate **1** as a dienophile. The chiral dienophile **1** obtained by the reaction of methyl N-acetyl- α,β -dehydroalaninate^{2b,4} with (-)-menthol in the presence of trimethylaluminum⁵, was made to react with cyclopentadiene in toluene, under several conditions; the products were separated into endo **2** and exo **3** cycloadducts by column chromatography using diethyl ether : n-hexane = 9:1 as an eluent and were almost quantitatively transformed into endo **6** and exo **7** amino acids by saponification, hydrogenation, acid hydrolysis of the acetamido group and elution through an ionic exchange resin Amberlite® IR 45 OH.

Table 1

Lewis acid(eq)	T°C	t.h	Yield^a	ratio 3/2^a	ratio 2b/2a^b	ratio 3a/3b^a
TiCl ₄ (1.1)	25	3	100	69/31	77/23	95/5
TiCl ₄ (1.1)	0	3	100	79/21	86/14	92/8
TiCl ₄ (0.75)	0	3	99	81/19	89/11	90/10 ^b
TiCl ₄ (0.5)	0	7	76	79/21	88/12	>99/1 ^c
TiCl ₄ (0.75)	-20	5	100	81/19	87/13	91/9
TiCl ₄ (1.1)	-45	6	98	82/18	-	99/1
AlCl ₃ (1.1)	25	22	74	74/26	81/19	90/10
AlCl ₃ (0.75)	25	10	43	82/18	79/21	98/2
AlCl ₃ (1.1)	0	22	90	82/18	85/15	97/3
AlCl ₃ (0.75)	0	46	98	78/22	85/15	96/4
AlCl ₃ (1.1)	-20	54	28	-	-	-
ZnCl ₂ (1.1)	25	138	52	77/23	84/16	91/9
ZnCl ₂ (1.1)	0	68	18	-	-	-

- a. Determined by ¹H-NMR in a Bruker® AC-200 apparatus by integration of the methyl of the N-acetyl group.
- b. Polarimetric measurements of the α-amino acids obtained from these adducts show no epimerization
- c. No signals corresponding to **3b** could be found

The reaction rate does depend on the nature of the Lewis acid used and, as was to be expected^{2b}, the reaction is faster when TiCl₄ is used as a catalyst. As this reaction is faster than the reaction of methyl N-acetyl-α,β-dehydroalaninate, this result opens the possibility of using chiral α,β-dehydroalaninates as dienophiles in asymmetric Diels-Alder reactions.

As expected², exo products **3** were favoured under all the reaction conditions we tried, and the exo/endo ratio was not greatly improved either with lower temperatures or when different Lewis acids were used as catalysts.

In the Diels-Alder reaction between (-)-menthyl acrylate and cyclopentadiene, (-)-menthyl (1R,2R)-5-norbornene-2-carboxylate is preferably obtained⁷. In comparison with the reaction carried out at the same temperature, better selectivity is obtained in the reaction between (-)-menthyl N-acetyl-α,β-dehydroalaninate and cyclopentadiene, but the same face of the dienophile is shielded by the chiral auxiliary, and **2b** and **3a** are preferably obtained. The stereochemical control can be explained by the similarity to the model proposed for acrylates⁸ (Scheme 1). Accordingly, the Re-face of the dienophile is shielded and the attack of the diene on the Si-face leads to **2b** and **3a**. It is difficult to account for the better selectivity obtained with (-)-menthyl N-acetyl-α,β-dehydroalaninate, because of the existence of several

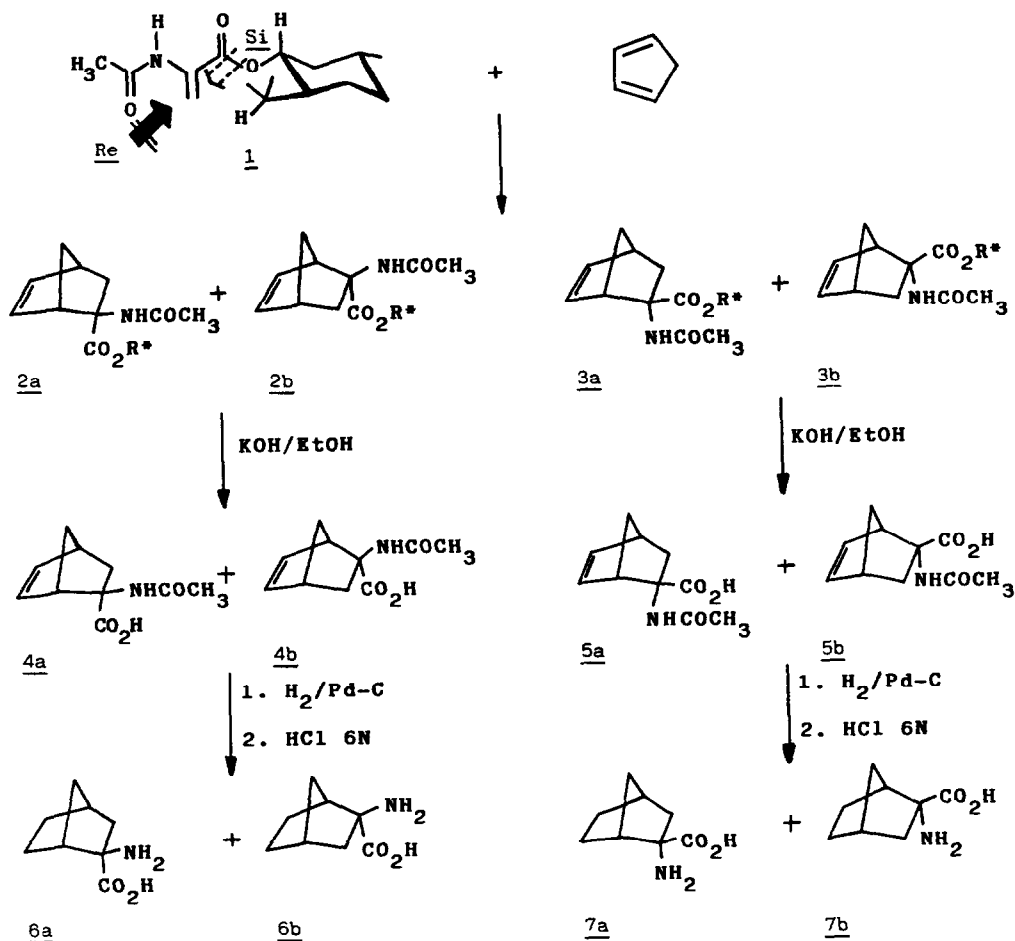
**Scheme 1**

Table 1 shows the results obtained in the Diels-Alder reaction. The endo/exo configuration of the cycloadducts was determined by $^1\text{H-NMR}$ of their methyl esters, obtained by the reaction of endo **4** and exo **5** acids with diazomethane, taking into account the shielding effect² of the double bond of 2-substituted-5-norbornene derivatives, which leads the protons of the endo substituent to resonate at a higher field than those of the exo substituent. The absolute configuration of the major cycloadducts was determined by comparing the specific rotations of the amino acids obtained (**6** and **7**) with those given in the literature⁶.

places where the catalyst can be coordinated. In any case, the coordination at the acetamido group is favoured^{2b}, and this group must play an important role. In fact it has been shown that, contrary to the situation in acrylates⁹, the anti enoate conformation is favoured in N-acyl- α,β -dehydroalanines¹⁰.

Furthermore, a higher diastereofacial selectivity is obtained in the exo approximation, which may be due to the steric interaction between the methylenic protons of the cyclopentadiene and the (-)-menthol moiety of the dienophile that is only present in the transition state leading to **3b**. A similar reason has been used to explain the exo preference in the cycloaddition between cyclopentadiene and methyl methacrylate¹¹.

Further work directed at explaining the results and improving the method by the use of different chiral auxiliaries is in progress.

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