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ASYMMETRIC SYNTHESIS OF CYCLOALIPHATIC a-AMINO ACIDS WITH A NORBORNANE SKELETON

Carlos Cativiela*, Pilar López, José A. Mayoral.

Department of Organic Chemistry. Instituto de Ciencia de Materiales de Aragón. Universidad de Zaragoza. CSIC. 50009 Zaragoza. Spain.

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Abstract: The asymmetric synthesis of endo and exo 2-aminonorbornane-2-carboxylic acids is carried out via the Diels-Alder reaction between cyclopentadiene and (-)-menthyl N-acetyl-α,β-dehydroalaninate. It is shown that this dienophile is more reactive than the corresponding methyl ester, which opens the way for the use of chiral N-acetyl-α,β-dehydroalaninates as dienophiles in asymmetric Diels-Alder reactions. As high diastereofacial selectivity is obtained with what was previously considered a mediocre chiral auxiliary, the acetamido group must play an important role, which is discussed.

In spite of the interesting biological properties of cycloaliphatic amino acids possessing a norbornane skeleton with regard to the ion transport through biological membranes[1], there is very little in the literature regarding the synthesis of these structures. The parent compounds, 2-aminonorbornane-2-carboxylic acids, have been obtained by Diels-Alder reaction of N-acyl-a$-dehydroalaninates and cyclopentadiene[2]. As high levels of diastereofacial selectivity have been achieved in asymmetric Diels-Alder reactions using chiral acrylates as dienophiles[3], it is interesting to determine whether chiral N-acyl-a$-dehydroalaninates can be used as chiral dienophiles in the asymmetric synthesis of the above-mentioned a-amino acids. We have recently communicated our preliminary results in this field4 and we want now to report the complete work in the first asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids, using (-)-menthyl N-acetyl-α,β-dehydroalaninate as a chiral dienophile. Given that in most the asymmetric syntheses of a-amino acids, a$-dehydroamino acid derivatives are used as the starting material[5], this work opens the way for the use of chiral N-acyl-a$-dehydroalaninates as reagents in asymmetric reactions, the aim of which is the enantioselective synthesis of a-amino acids.

RESULTS AND DISCUSSION

The chiral dienophile, obtained by reaction of N-acetyl-a$-dehydroalaninate (1)[2b,6] with (-)-menthol (2) in the presence of trimethylaluminium[7], was reacted with cyclopentadiene in toluene under several conditions (Table 1).

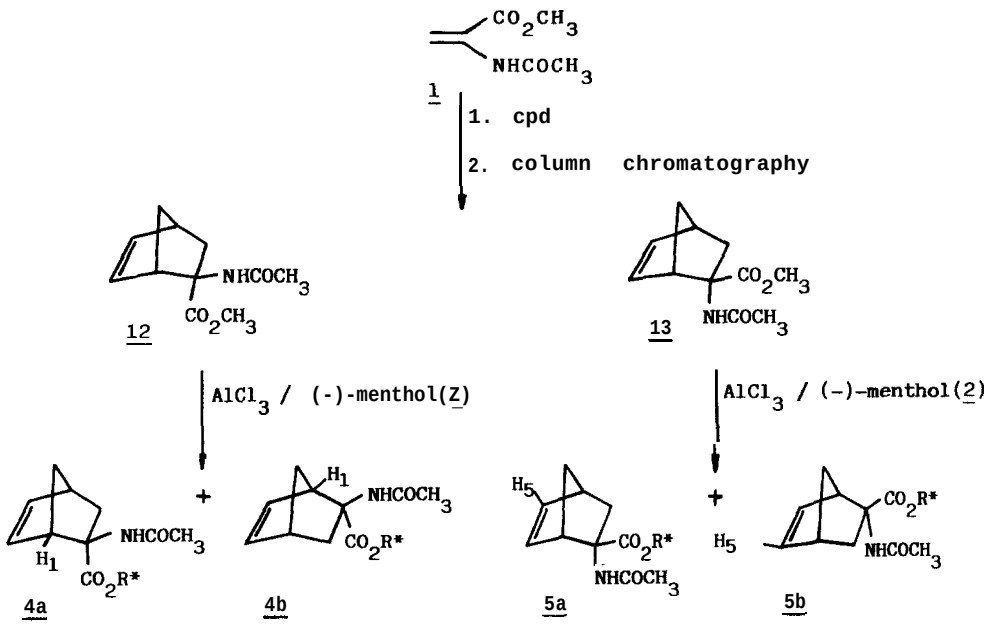
Table 1. Diels-Alder reaction between (-)-menthyl N-acetyl-a$-dehydroalaninate (2) and cyclopentadiene

Lewis acid (eq)	T °C	t h	% Yield[a]	ratio 5/4[a]	ratio 4b/4a[a]	ratio 5a/5b[a]
$TiCl_4$ (1.1)	25	3	100	69/3 1	77/23	95/5
$TiCl_4$(0.75)	25	3	100	81/19	86/14	97/3
$TiCl_4$ (0.5)	25	7	75	79/21	83/17	>99/1[b]
$TiCl_4$ (1.1)	0	3	100	79/21	86/14	92/8
$TiCl_4$(0.75)	0	3	99	8 1/19	89/1 1	90/10
$TiCl_4$ (0.5)	0	7	76	79/21	88/12	>99/1[b]
$TiCl_4$ (1.1)	-20	5	98	78/22	86/14	92/8
$TiCl_4$(0.75)	-20	5	100	8 1/19	87/13	91/9
$TiCl_4$ (1.1)	-45	6	98	82/18		99/1
$TiCl_4$(0.75)	-45	7	99	78/22		98/2
$TiCl_4$(0.75)	-70	22	99	78/22		97/3
AIC13 (1.1)	25	10	30			
$AlCl_3$ (1.1)	25	22	74	74/26	81/19	90/10
$AlCl_3$(0.75)	25	10	43	82/18	79/21	98/2
Alc13 (0.5)	25	23	< 5			
$AlCl_3$ (0.5)	25	93	20			
AlC13 (1.1)	0	22	90	82/18	85/15	97/3
$AlCl_3$(0.75)	0	46	98	78/22	85/15	96/4
Alc13 (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 ^{1}H-NMR

b. No signals corresponding to 5b could be found.

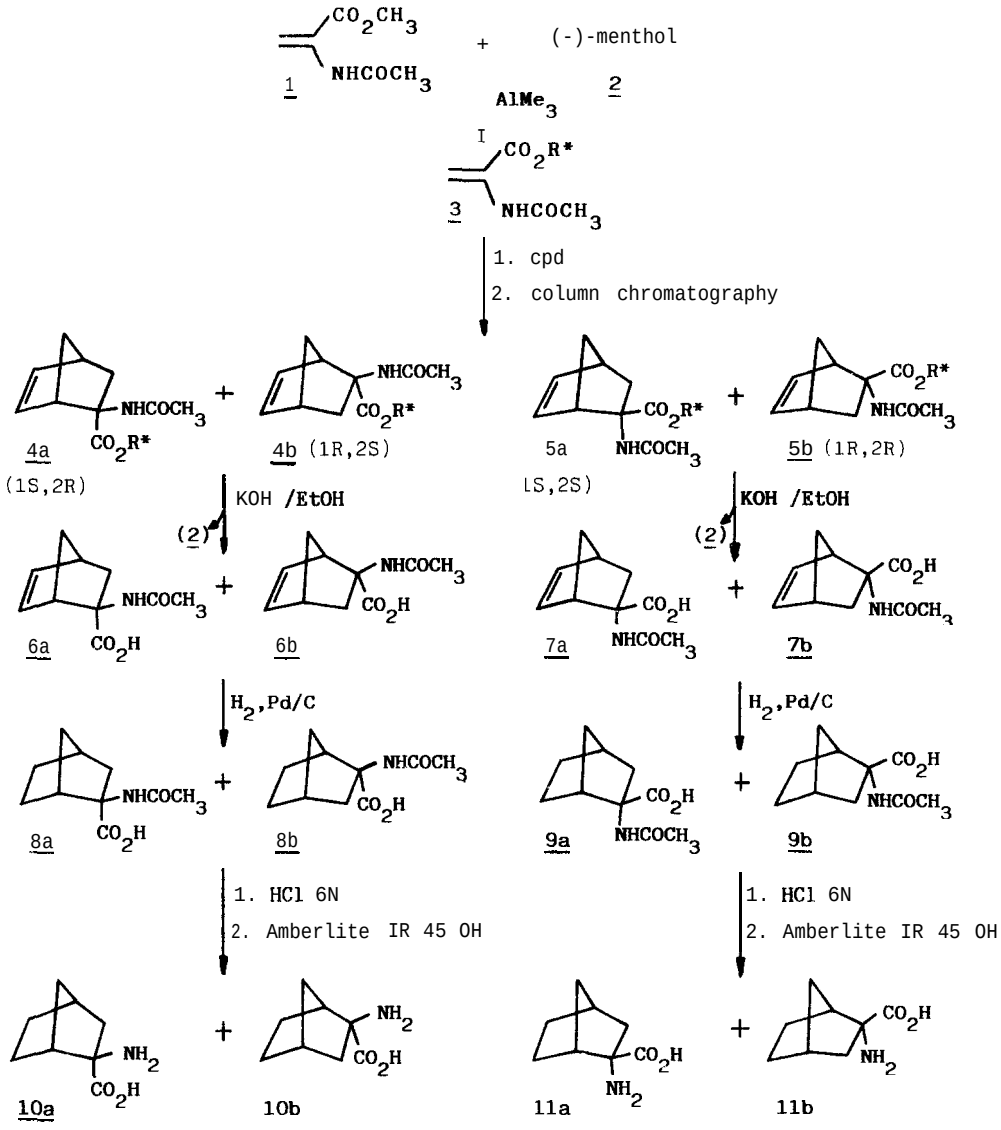
In order to find a way of determining the results of the Diels-Alder reaction, the endo (4) and exo (5) cycloadducts were prepared by reaction of the corresponding endo (12) and exo (13) methyl 2-acetamido-5-norbornen-2-carboxylates [obtained by Diels-Alder reaction of methyl N-acetyl-α,β-dehydroalaninate (1) with cyclopentadiene, followed by column chromatography[2b]] with (-)-menthol (2) in the presence of timethylaluminium (Scheme 1). The mixtures of endo (4a + 4b) and exo (5a + 5b) thus obtained were analyzed by ^{1}H-NMR; Scheme 1 shows the signals that can be used to determine the relative amounts of these compounds. Given that the singlet corresponding to the acetamido group of (-)-menthyl N-acetyl-α,β-dehydroalaninate appears at 2.13 ppm, the results were determined by integration of the signals of the acetamido group methyl corresponding to the different compounds present in the reaction mixture.



4a : **2.38** (dd, 1H, H_1); 1.98 (s, 3H, $COCH_3$); 0.75 (d, 3H, CH_3)
4b : 2.32 (dd, 1H, H_1); 1.96 (s, 3H, $COCH_3$); 0.70 (d, 3H, CH_3)
5a : 6.04 (m, 1H, H_5); 2.03 (s, 3H, $COCH_3$)
5b : 6.10 (m, 1H, H_5); 1.89 (s, 3H, $COCH_3$)

Scheme 1

The mixture of cycloadducts obtained from the Diels-Alder reaction was separated into its endo (4) and exo (5) components by means of column chromatography (diethyl ether : n-hexane = 9:1 as an eluent), and the corresponding purified adducts were almost quantitatively transformed into the corresponding a-amino acids (10 and 11) by saponification, hydrogenation, acid hydrolysis of the acetamido group and elution through an ionic exchange resin Amberlite® IR 45 OH (Scheme 2).



Scheme 2

The optical rotations of the a-amino acids (10 and 11) obtained were compared with those given in the literature[1c]: starting from a mixture of 4b : 4a = 89 : 11 the optical rotation measured for 10 was $[\alpha]_D^{25}$ (1% water) = +46.3{$[\alpha]_D^{25}$ (1% water) = -61.4 (10a), +61.2 (10b)}[1c] which gives 10b : 10a = 87.7 : 12.3; starting from a mixture of 5a : 5b = 90 : 10 the optical rotation measured for 11 was $[\alpha]_D^{25}$ (1% water) = -19.1 ($[\alpha]_D^{25}$ (1% water) = -24.7 (11a), +24.4 (11b)}[1c] which gives 11a : 11b = 88.7 : 11.3. These results show that there is no epimerization during the process and enabled us to determine the absolute configuration of the major cycloadducts resulting from the Diels-Alder reaction. In the saponification step, the chiral auxiliary (2) was recovered without loss of optical purity.

The rate of the Diels-Alder reaction depends on the nature of the Lewis acid used as a catalyst (Table 1), and is faster with $TiCl_4$ .In fact, the use of this catalyst leads to high chemical yields in short reaction times, even at low temperatures and using catalyst : dienophile ratios lower than the equimolecular. It is well known* that $TiCl_4$ can form seven membered chelate complexes with dienophiles that have two carbonyl groups in suitable positions. Whereas the coordination between (-)-menthyl N-acetyl-α,β-dehydroalaninate and $AlCl_3$ must take place at the most basic amido group[2b], $TiCl_4$ can coordinate both carbonyl groups to give a chelate intermediate (Figure 1). This difference may account for the greater efficiency of $TiCl_4$. With methyl N-acetyl-α,β-dehydroalaninate the reaction rate is affected in the same way by the nature of the catalyst, but the reaction is slower[2]. So the (-)-menthyl N-acetyl-α,β–dehydroalaninate is a more reactive dienophile, which makes it possible to use chiral N-acetyl-a$-dehydroalaninates in asymmetric Diels-Alder reactions.

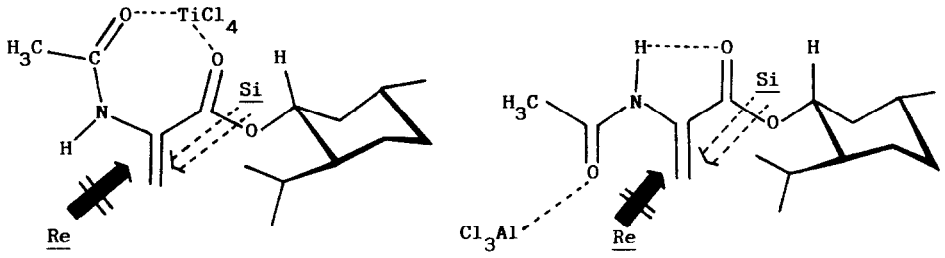


Figure 1

As expected[2b], the exo cycloadducts (5) are obtained in greater proportion and the exo : endo ratio is not noticeably modified either by the nature of the catalyst, the catalyst : dienophile ratio or the reaction temperature.

In the Diels-Alder reaction between (-)-menthyl acrylate and cyclopentadiene, (-)-menthyl (1R,2R)-5-norbornene-2-carboxylate is the major cycloadduct[9]. In comparison with the reaction carried out at the same temperature, better selectivity is obtained in the reaction between (-)-menthyl N-acetyl-a$-dehydroalaninate and cyclopentadiene, but the same face of the dienophile is shielded by the chiral auxiliary and 4b and 5a are the major cycloadducts. The stereochemical control may be explained by the

similarity to the model proposed for acrylates[10] where the carbonyl group is antiplanar to the olefinic double bond and synplanar to the alcoxy C-H group (Figure 1). Accordingly, the Re-face of the dienophile is shielded by the isopropyl group of the chiral auxiliary and the attack of the diene on the Si-face leads to 4b and 5a. It is difficult to account for the better selectivity obtained with (-)-menthyl N-acetyl-a$-dehydroalaninate, but the acetamido group must play an important role. It has been shown that, unlike methyl acrylate[11], where the syn enoate conformer is favoured by about 0.7 Kcal/mol, in methyl N-acetyl-a$-dehydroalaninate the anti enoate conformer is favoured by about 0.6 Kcal/mol[2b,12]. Nevertheless, the Lewis acid complexes of methyl acrylate show a preference of about 1.3 Kcal/mol for the anti enoate conformer[11], which is explained by steric hindrance. In the case of N-acetyl-a$-dehydroalaninates, coordination with the acetamido group is preferred. It is therefore difficult to believe that this coordination can substantially change the 0.6 Kcal/mol preference for the anti enoate conformer for steric reasons and, consequently, to explain the better selectivity obtained. Therefore, we suggest that there are two possible reasons why the preference for this conformer can be increased. When $TiCl_4$ is used as a catalyst, the anti enoate conformer would be greatly favoured by the formation of the above-mentioned chelate complex between the Lewis acid and the dienophile (Figure 1). In the case of AlC13, the formation of a hydrogen bond between the N-H and the carbonyl of the ester group (favoured by coordination at the acetamido group which must increase N-H acidity) would account for the results.

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 5b. A similar reason has been used to explain the exo preference in the cycloaddition between cyclopentadiene and methyl methacrylate[13].

Further work to clarify the role of the acetamido group and improve the results by use of different chiral auxiliaries is in progress

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EXPERIMENTAL SECTION

*** Methyl N-acetyl-α,β-dehydroalaninate (1)**

*** (-)-menthyl N-acetyl-a$-dehydroalaninate (3)**

Both compounds were prepared following the methods described in the literature[2b,7]

*** (-)-menthyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (4) and (-)-menthyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (5).**

General procedure for Diels-Alder rections: To a solution of (-)-menthyl N-acetyl-α,β-dehydroalaninate (3) (133.5 mg, 0.5 mmol) in anhydrous toluene (15 ml) under an inert atmosphere was added the catalyst. After 20 minutes stirring at the corresponding working temperature, a solution of freshly distilled cyclopentadiene (198 mg, 3 mmol) in toluene (0.5 ml) was added and the reaction was stirred for the time reported in Table 1. The mixture was treated with $Na_2CO_3.10H_2O$ (200 mg), the solution was filtered and the solvent evaporated under vacuum to give a mixture, composition of which was analyzed by ^{1}H-NMR. The

reaction mixture can be separated into endo and exo adducts (4 and 5) by column chromatography on silica gel column using diethyl ether : n-hexane (9:1) as an eluent

Identification and characterization of adducts 4a, 4b, 5a, 5b.

*** Methyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (12) and Methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (13).**

To an anhydrous toluene solution (100 ml) of methyl N-acetyl-+dehydroalaninate (1) (3.5g, 25mmol) kept in an inert atmosphere, a solution of $TiCl_4$ (19 ml solution 1M in CH_2Cl_2, 19 mmol) was added dropwise. After 20 minutes stirring at 0°C, a solution of freshly -distilled cyclopentadiene (6.6 g, 100 mmol) in toluene (5 ml) was added and the reaction was stirred at 0°C. After 14 hours, the reaction was treated with $Na_2CO_3.10H_2O$ (2 g) until the colour was removed. The mixture was filtered and the solvent was evaporated under reduced pressure. The rough was separated into endo and exo adducts (12 and 13) by column chromatography using ethyl acetate as an eluent to afford 1.3 g of 12 (yield: 26%) and 2.3 g of 13 (yield:44%).

The corresponding endo and exo adducts were identified by means of their ^{1}H-NMR spectra and melting points, which were in good agreement with the data described in the literature[2b].

*** Transesteriflcation of (12) and (13) to give (4) and (5).**

(-)-Menthyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (4) and (-)-menthyl 2-endo-acetamido-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (5) were prepared from the corresponding 12 and 13 by means of the following procedure:

To an anhydrous toluene solution (25 ml) of (-)-menthol (2) (780 mg, 5 mmol) kept in an inert atmosphere, a solution of $AlMe_3$ (2.25 ml solution 2N in hexanes, 5.5 mmol) was added dropwise at 0°C. After stirring at this temperature for 30 min., the ice-bath was removed and a solution of methyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (12) [or methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (13) (1.57 g, 7.5 mmol)] in anhydrous toluene (5 ml) was added. The reaction was refluxed for 4 days. After cooling, the reaction mixture was treated with $Na_2CO_3.10H_2O$ (1 g), filtered and the solvent evaporated under reduced pressure. The corresponding (-)-menthyl adducts 4a + 4b [or 5a + 5b] were purified by column chromatography using diethyl ether : n-hexane (9: 1) as an eluent.

^{1}H-NMR ($CDCl_3$): **4a+4b** δ = 0.70 (d,3H 4b), 0.75 (d,3H 4a), 0.81-0.95 (m,6H 4a + 6H 4b), 0.96-1.85 (m,9H 4a + 9H 4b), 1.96 (s,3H 4b), 1.98 (s,3H 4a), 1.86-2.04 (m,1H 4a + 1H 4b), 2.32 (dd,lH 4b), 2.38 (dd,lH 4a), 2.94 (bs,2H 4a + 2H 4b), 4.45-4.70 (m,lH 4a + 1H 4b), 5.96 (bs,lH 4a + 1H 4b), 5.82-5.90 (m, 1H 4a + 1H 4b), 6.30-6.38 (m, 1H 4a + 1H 4b).

5a+5b δ = 0.75 (d,3H 5a + 3H 5b), 0.89 (d,6H 5a + 6H 5b), 0.98-1.80 (m, 9H 5a + 9H 5b), 1.89 (s,3H 5b), 2.03 (s,3H 5a), 1.95-2.10 (m,lH 5a + 1H 5b), 2.64 (dd,1H 5a), 2.70 (dd,1H 5b), 2.88-2.98 (m, 2H 5a+1H 5b), 3.31 (bs,lH 5b), 4.68 (ddd,lH 5a), 4.71 (ddd,1H 5b), 5.61 (bs,1H 4a + 1H 4b), 6.04 (m, 1H 5a), 6.10 (m,1H 5b), 6.42 (m, 1H 5a + 1H 5b).

Found: 4a+4b C 71.75, H 9.62, N 4.24 % ; 5a+5b C 71.85, H 9.50, N 4.00%

Calc. for $C_{20}H_{31}NO_3$: C 72.04, H 9.37, N 4.20 %

Transformation of amido esters (4) and (5) into amino acids (10) and (11).

*** 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acids (6).**

To a solution of (-)-menthyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylates (4) (999mg, 3 mmol) in EtOH (10 ml) was added a solution of KOH (KOH 3N in EtOH, 20 ml) and the reaction mixture was refluxed for 2 days. The resulting solution was cooled and the solvent was evaporated. The residue was diluted in water (30 ml) and washed with ether (3 x 15 ml). The aqueous layer was then acidified at pH=3 and the white precipitate was filtered off. The filtrate was extracted with ether (20 ml) in a Soxhlet apparatus for 4 days. After extraction, the organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford 500mg of 6a + 6b (yield: 85%).

The ethereal layer obtained in the first extraction was evaporated and the (-)-menthol (2) was recovered by sublimation under vacuum without epimerization.

^{1}H-NMR (CDC13): δ = 1.25 - 1.50 (m,2H), 1.65 (bs,1H), 1.75 (s,3H), 1.90 (bs,1H), 2.80 (bs,1H), 2.95 (bs,lH), 5.80 (dd,1H), 6.20 (dd,lH), 8.27 (s,1H).
IR (nujol): 3325 cm-t (N-H), 1703 cm-t (C=O), 1620 cm^{-1} (C=O).
Found: 6a+6b C 61.81, H 7.00, N 6.95 %
Calc. for $C_{10}H_{13}NO_3$: C 61.53, H 6.71, N 7.17 %

*** 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acids (7).**

The reaction was performed using the same conditions described for (6). Starting from (5) (999 mg, 3 mmol), $2^{1/2}$ days for reaction, 2 days for continuous extraction, 350 mg of 7a + 7b were obtained (yield: 60%).

^{1}H-NMR (CDC13): δ = 1.27 (s,1H), 1.37 (s,1H), 1.75 (s,3H), 2.20-2.58 (m,2H), 2.83 (bs,1H), 3.25 (bs,lH), 6.13 (m,1H), 6.33 (m,1H), 7.90 (s,1H).
IR (nujol): 3353 cm-t (N-H), 1694 cm-t (C=O), 1620 cm^{-1} (C=O).
Found: 7a+7b C 61.27, H 6.47, N 6.92 %
Calc. for $C_{10}H_{13}NO_3$: C 61.53, H 6.71 , N 7.17 %

*** 2-exo-acetamidobicyclo[2.2.1]heptane-2-endo-carboxylic acids (8).**

A solution of 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acids (6) (390 mg, 2 mmol) in MeOH (15 ml) was hydrogenated under atmospheric pressure with Palladium-Charcoal activated (10% Pd) (50 mg) as a catalyst. The reaction was shaken overnight. The catalyst was then filtered and the solvent was evaporated under reduced pressure to afford 390 mg of acids 8a + 8b as a white solid (yield: 99%).

^{1}H-NMR (DMSO): δ = 1.05-1.85 (m,7H), 1.75 (s,1H), 2.13 (bs,lH), 2.23 (bs,1H), 2.45 (bs,1H), 8.18 (s,1H).
IR (nujol): 3332 cm^{-1} (N-H), 1696 cm^{-1} (C=O), 1620 cm^{-1} (C=O).
Found: 8a+8b C 60.72, H 7.95 , N 6.90 %
Calc. for $C_{10}H_{15}NO_3$: C 60.90 , H 7.66 , N 7.10 %

*** 2-endo-acetamidobicyclo[2.2.1]heptane-2-exo-carboxylic acids (9).**

The reaction was performed using the same conditions described for (8). Starting from (7) (390 mg, 2 mmol),375 mg of 9a + 9b were obtained (yield: 95%).

^{1}H-NMR (DMSO): δ = 1.05-2.10 (m,8H), 1.78 (s,3H), 2.45 (bs,1H), 2.60 (bs,1H), 8.00 (s,1H).
IR (nujol): 3353 cm-t (N-H), 1709 cm-t (C=O), 1614 cm-r (C=O).
Found: 9a+9b C 61.09, H 7.85, N 6.98 %
Calc. for $C_{10}H_{15}NO_3$: C 60.90, H 7.66, N 7.10 %

*** 2-exo-aminobicyclo[2.2.1]heptane-2-endo-carboxylic acids (10).**

2-exo-acetamidobicyclo[2.2.1]heptane-2-endo-carboxylic acids (8).(197 mg, 1 mmol) were suspended in HCl 5N (5 ml) and the solution was heated to 80-85°C for 5 hours. After this time the solvent was evaporated under vacuum and the remaining solid was dried under reduced pressure to yield the corresponding amino acid hydrochlorides (130 mg, 93% yield).

The mixture of amino acid hydrochlorides was diluted in water (15 ml) and the solution was passed through an Amberlite IR 45 column (0.5 g, OH- form). The column was eluted with water until the eluate was neutral. After evaporation of the eluates, the remaining residue was dried under vacuum to yield the amino acids 10a + 10b as a white solid.

When the synthetic route started from (-)-menthyl N-acetyl-a$-dehydroalaninate (3) with $TiCl_4$ (0.75eq.) as a catalyst and the reaction was carried out at 0°C, the measurement by polarimetry of the mixture of amino acids 10a + 10b gave an enantiomeric excess of 75.4% ($[\alpha]_D^{25}$ (1% water) = +46.3, 10b being the major adduct}.

'H-NMR (D_2O): δ = 0.45 (d,1H), 0.48 (d,1H), 0.55(bs,1H), 0.63 (bs,1H), 1.05 (bs,1H), 1.00 (bs,1H), 1.98-2.10 (m,2H), 2.50-2.67 (bs,2H).
IR (nujol): 3115 cm^{-1} (NH_3^+), 1654 cm-t (CO_2^-), 1463 cm-t (NH_3^+), 1381 cm-t (CO_2^-).
Found: 10a+10b C 61.65, H 8.70, N 9.00 %
Calc. for $C_8H_{13}NO_2$: C 61.91 , H 8.44, N 9.02 %

*** 2-endo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acids (11).**

The amino acids 11a + 11b were similarly prepared from the 2-endo-acetamidobicyclo[2.2.1]heptane-2-exo-carboxylic acids (9).

When the synthetic route started from (-)-menthyl N-acetyl-a$-dehydroalaninate (3) with $TiCl_4$ (0.75eq.) as a catalyst and the reaction was carried out at 0°C, the measurement by polarimetry of the mixture of amino acids 11a + 11b gave an enantiomeric excess of 77.4% ([a]$ (1% water) = -19.1, 11a being the major adduct}.

'H-NMR (D_2O): δ = 0.57 (d,lH), 0.64 (d,lH), 0.73 (bs,1H), 0.96 (dd,lH), 1.29 (bs,1H), 1.33 (bs,lH), 1.54 (dd,1H), 1.61 (dd,1H), 1.65 (bs,1H), 1,81 (bs,1H).
IR (nujol): 3357 cm^{-1} (NH_3^+), 1581 cm-t (CO_2^-), 1522 cm^{-1} (NH_3^+), 1378 cm^{-1} (CO_2^-).
Found: 11a+11b C 61.85, H 8.50, N 9.10 %
Calc. for $C_8H_{13}NO_2$: C 61.91 , H 8.44, N 9.02 %

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