Tetrahedron: Asymmetry Vol. 2, No. 6, pp. 449-456, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

ASYMMETRIC SYNTHESIS OF 2-EXO-AMINONORBORNANE-2-ENDO-CARBOXYLIC ACID DERIVATIVES

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

Departamento de Química Orgánica. Instituto de Ciencia de Materiales de Aragón. Universidad de Zaragoza. CSIC. 50009 Zaragoza. Spain.

(*Received* 6 *May* 1991)

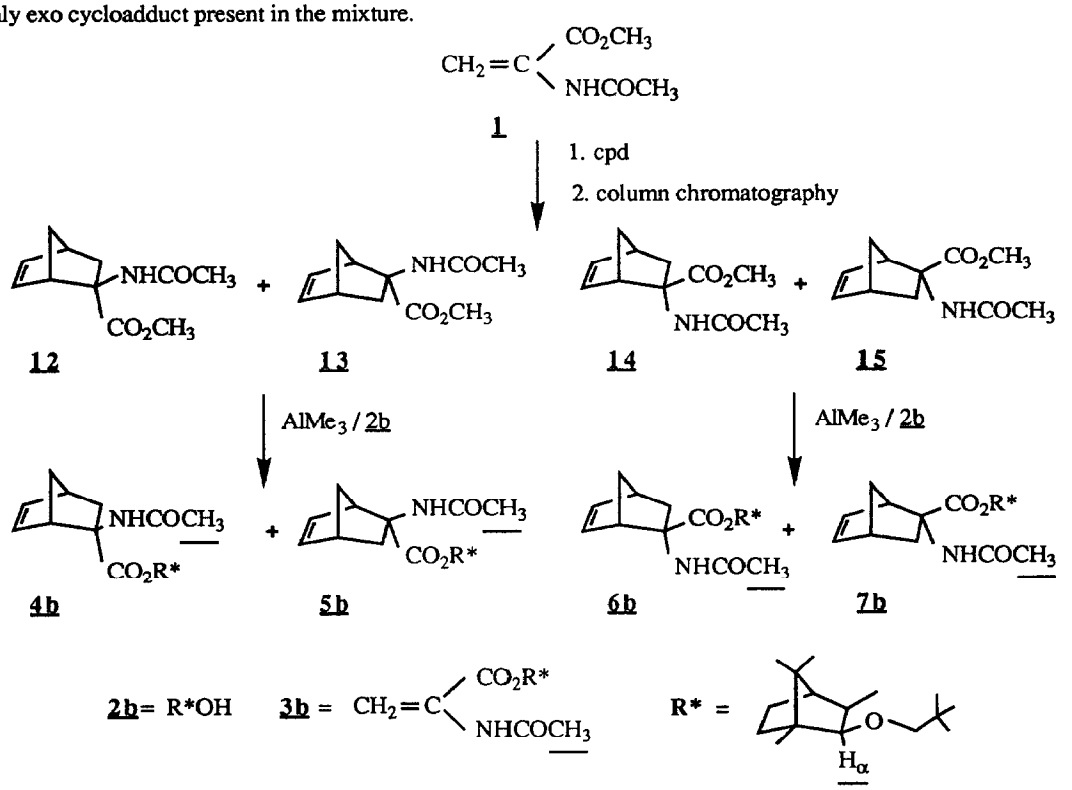
Abstract: The Diels-Alder reaction of cyclopentadiene with N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether yields the corresponding 2-endo(exo)-acetamido-5-norbornene-2-exo(endo)-carboxylates with total diastereofacial selectivity and with a preference for the cycloadduct with the ester group placed at the endo position. So this dienophile is complementary with the previously described (-)-menthyl N-acetyl-α,β-didehydroalaninate for the asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids, since with the latter dienophile exo cycloadducts are preferably obtained with a high diastereofacial selectivity.

Cycloaliphatic amino acids possessing a norbornane skeleton are of interest because of their biological properties[1] and they have been obtained by Diels-Alder reaction of N-acyl-α,β-didehydroalaninates and cyclopentadiene[2]. We have recently described the first asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids using (-)-menthyl N-acetyl-α,β-didehydroalaninate (3a) as a dienophile[3]. The Diels-Alder reaction of cyclopentadiene with this dienophile (Scheme 2) leads preferably to exo cycloadducts (6a + 7a) with high diastereofacial selectivity. However, endo cycloadducts (4a + 5a) are obtained in a minor proportion and with only a moderate diastereofacial selectivity. Therefore, this reaction is an excellent method for the asymmetric synthesis of 2-endo-aminonorbornane-2-exo-carboxylic acids, but it is not very efficient in the preparation of 2-exo-aminonorbornane-2-endo-carboxylic acids. In this paper we want to describe the use of the N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether (3b) as a dienophile that leads mainly to endo cycloadducts (4b + 5b) with total diastereofacial selectivity.

RESULTS AND DISCUSSION

The chiral dienophile (3b), obtained by the reaction of methyl N-acetyl-α,β-didehydroalaninate (1)[2b,4] with (-)-cis-3-hydroxy isobornyl neopentyl ether (2b)[5] in the presence of trimethylaluminium[6], was made to react with cyclopentadiene under several conditions. The results obtained from these Diels-Alder reactions were determined by ^{1}H-NMR. In order to assign the NMR signals to the corresponding cycloadducts, these were prepared , as endo (4b + 5b) and exo (6b + 7b) mixtures, by reaction of the corresponding endo (12 + 13) and exo (14 +15) methyl 2-acetamido-5-norbornen-2-carboxylates[2b] with the chiral auxiliary (2b) in the presence of trimethylaluminium, and analyzed by ^{1}H-NMR. Scheme 1 shows the signals that can be used to determine the relative amounts of dienophile and cycloadducts in the mixture. As can be seen the % conversion, the endo/exo and the endo/endo (4b : 5b) ratios can easily be determined by the integration of the acetamido singlets, but the determination of the exo/exo (6b : 7b) ratio is not so straightforward. Luckily the ^{1}H-NMR spectra obtained from the reaction mixtures were simpler than expected. So, only one endo cycloadduct was observed in the acetamido region (5b, 1.95 ppm), and the H_α region showed signals at 4.75 and 4.80 ppm. Furthermore, the

ratios between the peaks at 1.95 and 1.86 ppm (endo/exo) and that of the doublets at 4.75 and 4.80 ppm were the same, showing that the signal at 4.75 ppm corresponded to 5b, without contamination of 7b, and 6b was the only exo cycloadduct present in the mixture.

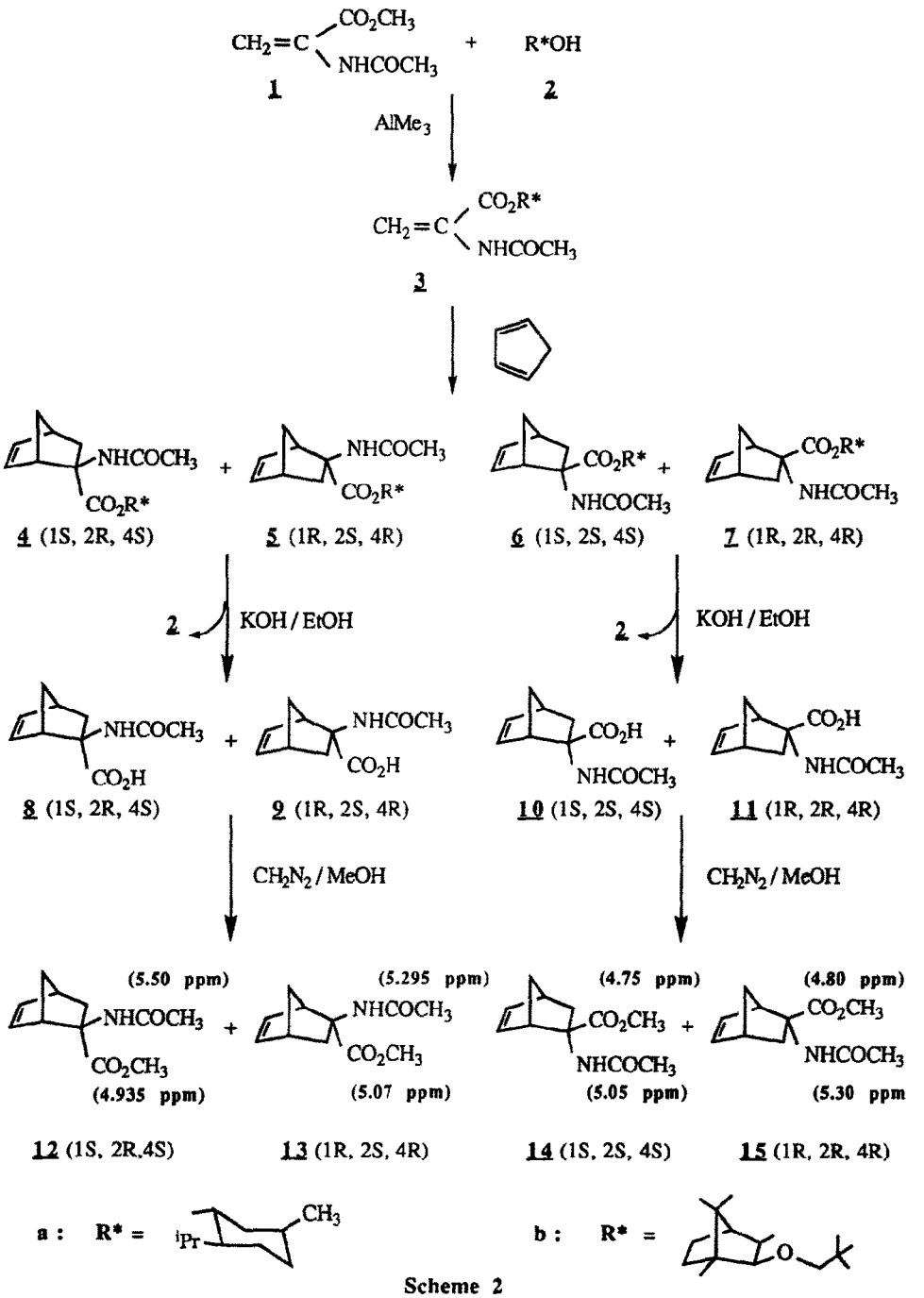


3b :	$NHCOCH_3$	2.08 ppm (s)	H_α	4.77 ppm (d, J = 8.0 Hz)
4b :	$NHCOCH_3$	1.97 ppm (s)	H_α	4.60 ppm (d, J = 6.8 Hz)
5b :	$NHCOCH_3$	1.95 ppm (s)	H_α	4.75 ppm (d, J = 6.8 Hz)
6b :	$NHCOCH_3$	1.86 ppm (s)	H_α	4.80 ppm (d, J = 6.4 Hz)
7b :	$NHCOCH_3$	1.86 ppm (s)	H_α	4.75 ppm (d, J = 6.4 Hz)

Scheme 1

In order to confirm these determinations and to determine the absolute configuration of the cycloadducts obtained, the following experiment was carried out. In a previous paper we have described how the reaction between cyclopentadiene and (-)-menthyl N-acetyl-α,β-didehydroalaninate[3] leads preferably to 5a and 6a. A mixture coming from this Diels-Alder reaction was separated into its endo and exo components by column chromatography (diethyl ether : n-hexane = 9:1 as an eluent), and the purified cycloadducts were almost quantitatively transformed into the corresponding methyl 2-acetamido-5-norbornene-2-carboxylates (12 + 13 and 14 + 15) by saponification and methylation with diazomethane. These mixtures were analyzed by ^{1}H-NMR in

the presence of $Eu(tfc)_3$ (L:S molar relationship = 0.85, CD_3CN as solvent) and the singlets corresponding to the acetamido and ester methyls were assigned to each enantiomer (Scheme 2).



Scheme 2

The mixtures of cycloadducts obtained from the Diels-Alder reactions of 3b with cyclopentadiene were separated into the endo (4b + 5b) and exo (6b + 7b) components by means of column chromatography ($CHCl_3$: diethyl ether = 7: 3 as an eluent). The purified cycloadducts were transformed into the corresponding methyl 2-acetamido-5-norbornene-2-carboxylates (12 + 13 and 14 + 15) by the above described procedure and they were analyzed by ^{1}H-NMR in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85, CD_3CN as solvent) showing that only one enantiomer is present in the mixture. In order to ensure the position of the signals, a known amount of racemic 12 + 13 (or 14 + 15) was added and the ^{1}H-NMR analysis was repeated. In this way it was determined that the Diels-Alder reaction of 3b with cyclopentadiene led to 5b and 6b.

Table 1 gathers the results obtained from the reaction between 3b and cyclopentadiene, together with some comparative results from the reaction between 3a and cyclopentadiene.

Table 1. Diels-Alder reaction between N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether (3b) and cyclopentadiene

Lewis acid (eq)	Dienophile	T°C	t h	% Yield[a]	ratio (4+5)/(6+7)[a]	ratio 5/4[a,b]	ratio 6/7[a,b]
$TiCl_4$ (0.75)	3a[c]	25	3	100	19/81	86/14	97/3
$TiCl_4$ (0.75)	3b	25	4	95	55/45	>99/1	>99/1
$TiCl_4$ (1.1)	3a[c]	0	3	100	21/79	86/14	92/8
$TiCl_4$ (1.1)	3b	0	1.5	94	62/38	>99/1	>99/1
$TiCl_4$ (0.5)	3b	0	4	100	62/38	>99/1	>99/1
$TiCl_4$ (0.3)	3b	0	21	7.5	-	-	-
$TiCl_4$ (0.75)	3b	-70	9	60	70/30	>99/1	>99/1
$AlCl_3$ (1.1)	3a[c]	25	22	74	26/74	81/19	90/10
$AlCl_3$ (1.1)	3b	25	72	34	44/56	>99/1	>99/1
$AlCl_3$ (0.75)	3b	25	72	0	-	-	-
$AlCl_3$ (1.1)	3b	-45	72	20	55/45	>99/1	>99/1

[a]. Determined by ^{1}H-NMR

[b]. No signals corresponding to 4b and 7b could be found.

[c]. Ref. 3

The rate of the Diels-Alder reaction depends on the Lewis acid used as a catalyst, and is faster with $TiCl_4$. With $AlCl_3$ an equimolecular amount of catalyst is needed to achieve low to moderate yields, suggesting a low constant of formation of the dienophile-$AlCl_3$ complex. The reaction of (-)-menthyl N-acetyl-α,β-didehydroalaninate (3a) with $AlCl_3$ is faster , but a similar dependence on the nature of the catalyst is observed[3].

Table 1 shows that , starting from 3a, 5a is obtained with an overall yield of about 20%, whereas the yield in 6a is about 70%. On the other hand, 3b leads to 5b with a yield of 62% and to 6b with a yield of 38%. Given that the cycloadducts can be easily transformed into the corresponding 2-aminonorbornane-2-carboxylic acids[3], both dienophiles are complementary for the asymmetric synthesis of the α-amino acids with the amino group placed at the endo or exo position.

Although, in Lewis acid-catalyzed reactions with cyclopentadiene the acrylate of (-)-cis-3-hydroxy isobornyl neopentyl ether[5] leads to better endo/exo ratios than (-)-menthyl acrylate[7],we cannot suggest an explanation for the different endo/exo selectivity obtained with 3a and 3b, and in particular for the unexpected behaviour of 3b.

In the Diels-Alder reaction between the acrylate of (-)-cis-3-hydroxy isobornyl neopentyl ether and cyclopentadiene, (1R,2S,4R)-5-norbornene-2-carboxylate is preferably obtained with high diastereofacial selectivity[7]. The stereochemical control may be explained by the similarity to the model proposed for classical acrylates[8] 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 neopentyl group of the chiral auxiliary and the attack of the diene takes place on the Si-face leading to 5b and 6b. If a preferable co-ordination of the Lewis acid to the acetamido group is admitted, the anti enoate conformer may be favoured by the formation of an intramolecular hydrogen bond (Figure 1).

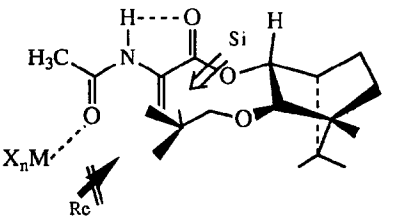


Figure 1

Acknowledgements: This work was made possible by the financial support of the Dirección General de Investigación Científica y Técnica (Project number PB88-0038).

EXPERIMENTAL SECTION

* **Methyl N-acetyl-α,β-didehydroalaninate (1)**
* **(-)-menthyl N-acetyl-α,β-didehydroalaninate (3a)**
* **N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether (3b)**

These compounds were prepared following the methods described in the literature[2b,6]

* **(1R,2S,4R)- 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (5b) and (1S,2S,4S)-2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (6b) of (-)-cis-3-hydroxy isobornyl neopentyl ether.**

General procedure for Diels-Alder reactions: To a solution of N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether (3b) (175.5 mg, 0.5 mmol) in anhydrous toluene (20 ml) under an inert atmosphere the catalyst was added. After 20 minutes stirring at the corresponding working temperature, a solution of freshly distilled cyclopentadiene (132 mg, 2 mmol) in anhydrous 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, the composition of which was analyzed by ^{1}H-NMR. The reaction mixture was separated into endo (5b) and exo (6b) adducts by column chromatography on a silica gel column using $CHCl_3$: diethyl ether = 7:3 as an eluent.

^{1}H-NMR ($CDCl_3$): **5b** δ = 0.75 (s,3H), 0.90 (s,3H), 0.94 (s,9H), 1.06 (s,3H), 1.40-1.78 (m,6H), 1.79 (bs,1H), 1.84 (d,1H), 1.96 (s,3H), 2.41 (dd,1H), 2.85 (d,1H), 2.91 (bs,1H), 2.96 (bs,1H), 3.25(d,1H), 3.39 (d,1H), 4.75 (d,1H), 5.78-5.83 (m, 1H), 5.87 (bs,1H), 6.34-6.39 (m, 1H).

6b δ = 0.77 (s,3H), 0.91 (s,12H), 1.08 (s,3H), 1.05-1.25 (m, 2H), 1.38-1.71 (m,4H), 1.75-1.85 (m,2H), 1.87 (s,3H), 2.79-2.94 (m,3H), 3.25-3.33 (m,3H), 4.81 (d,1H), 5.59 (bs, 1H), 6.05-6.12 (m,1H), 6.40-6.50 (m,1H).

Found: 5b C 71.65 , H 9.70 , N 3.12 % ; 6b C 72.03 , H 9.22 , N 3.16 %

Calc. for $C_{25}H_{39}NO_4$: C 71.91 , H 9.41 , N 3.35 %

m.p. : **5b** = 188 ± 2°C; **6b** = 156 ± 2°C.

5b : $[\alpha]_D^{24}$ (c = 6.4 x 10^{-1} , MeOH) = +32.8 ± 0.5

6b : $[\alpha]_D^{24}$ (c = 7.9 x 10^{-1} , MeOH) = -61.4 ± 0.5

Characterization and identification of adducts 4b, 5b, 6b, 7b.

*** Methyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (12+13) and methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (14+15).**

These products were prepared and identified as described in the literature[2b,3b].

*** Transesterification of (12+13) and (14+15) to give (4b+5b) and (6b+7b).**

To an anhydrous toluene solution (15 ml) of (-)-cis-3-hydroxy isobornyl neopentyl ether (2b) (600 mg, 2.5 mmol) kept in an inert atmosphere, a solution of $AlMe_3$ (1.37 ml solution 2N in hexanes, 2.75 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+13) [or the corresponding exo adducts (14+15)] (785 mg, 3.75 mmol) in anhydrous toluene (5 ml) was added. The reaction was refluxed for 4 days. After cooling, the reaction mixture was treated with $Na_2CO_3.10H_2O$ (500 mg), filtered and the solvent evaporated under reduced pressure. The corresponding products 4b + 5b [or 6b + 7b] were purified by column chromatography using $CHCl_3$: diethyl ether = 7:3 as an eluent.

Found: 4b+5b C 71.71 , H 9.58 , N 3.20 % ; 6b+7b C 72.10 , H 9.50 , N 3.12 %

Calc. for $C_{25}H_{39}NO_4$: C 71.91 , H 9.41 , N 3.35 %

Determination of the absolute configuration of 5b and 6b.

*** (-)-Menthyl 2-exo-acetamidobicyblo[2.2.1]hept-5-ene-2-endo-carboxylate (4a+5a) and (-)-menthyl 2-endo-acetamidobicyblo[2.2.1]hept-5-ene-2-exo-carboxylate (6a+7a).**

Mixtures of 4a + 5a and 6a + 7a of known stereochemical composition were prepared from (-)-menthyl N-acetyl-α,β,-didehydroalaninate (3a) and identified following the procedure described in the literature[3b].

*** 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (8+9) from 4a + 5a and 2-endo-acetamido-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid (10+11) from 6a + 7a.**

These reactions were performed following the method previously described[3b].

*** Methyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (12+13) from (4a+5a).**

To a solution of the mixture of 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (8+9) coming from (4a+5a) (195 mg, 1 mmol) in methanol, an ethereal solution of diazomethane is added until the yellow colour remains. The solution is stirred until the reaction is completed (monitored by TLC). The excess of diazomethane is destroyed with $CaCl_2$, the solution is filtered and the solvent eliminated under reduced pressure to afford quantitatively the mixture of methyl esters (12+13).

This mixture was identified by ^{1}H-NMR, which was in good agreement with the data described in the literature[2b], and were analyzed by ^{1}H-NMR in CD_3CN in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85).

12 (1S,2R) : $NHCOCH_3$ (5.50 ppm) ; CO_2CH_3 (4.935 ppm).
13 (1R,2S) : $NHCOCH_3$ (5.295 ppm) ; CO_2CH_3 (5.07 ppm).

*** Methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (14+15) from (6a+7a).**

The mixture was quantitatively prepared from the mixture (10+11), coming from (5a+7a), following the above described procedure. The mixture was analized by ^{1}H-NMR in CD_3CN in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85)

14 (1S,2S) : $NHCOCH_3$ (5.05 ppm) ; CO_2CH_3 (4.75 ppm).
15 (1R,2R) : $NHCOCH_3$ (5.30 ppm) ; CO_2CH_3 (4.80 ppm).

*** (1R,2S,4R)-2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (9).**

To a solution of (1R,4R)-2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate of (-)-cis-3-hydroxy isobornyl neopentyl ether (5b) (417 mg, 1 mmol) in EtOH (10 ml) was added 7 ml of a solution of KOH 3N in EtOH and the reaction mixture was refluxed for 2 days. The resulting reaction was cooled and the solvent was evaporated. The residue was diluted in water (30 ml) and washed with diethyl ether (3 x 15 ml).

The chiral auxiliary is recovered in 85% yield after washing the organic layer with a solution of NaOH 3N, drying with Na_2SO_4 and evaporation of the solvent.

The aqueous layer was acidified at pH=3 and the white precipitate filtered off. The filtrate was extracted with diethyl 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 120 mg of 9 (yield: 60%).

^{1}H-NMR and IR data are in agreement with those described in the literature[3b].

Found: 9 C 61.35 , H 6.89 , N 7.22 %
Calc. for $C_{10}H_{13}NO_3$: C 61.53 , H 6.71 , N 7.17 %
m.p. = 221 ± 2°C (dec.)
$[\alpha]_D^{24}$ (c = 11.4 x 10^{-1}, MeOH) = +156.0 ± 0.5

*** (1S,2S,4S)-2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid (10).**

The reaction was performed using the same conditions described for 9. Starting from 6b (417 mg, 1 mmol), 1 day for reaction, 2 days for continuous extraction, 140 mg of 10 were obtained (yield: 72%).

^{1}H-NMR and IR data are in agreement with those described in the literature[3b].

Found: 10 C 61.35 , H 6.51 , N 7.40 %
Calc. for $C_{10}H_{13}NO_3$: C 61.53 , H 6.71 , N 7.17 %

m.p. = 224 ± 2°C (dec.)

$[\alpha]_D^{24}$ (c = 12 x 10^{-1}, MeOH) = -106.2 ± 0.5°

*** Methyl (1R,2S,4R)-2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (13).**

The product was quantitatively obtained from 9, following the above described procedure of methylation with diazomethane.

^{1}H-NMR data are in good agreement with those described in the literature[2b].

Absolute configuration was assigned by comparing the ^{1}H-NMR analysis in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85, CD_3CN) with the above described data for 12 and 13.

Found: 13 **C** 63.09, **H** 7.20, **N** 6.55 %

Calc. for $C_{11}H_{15}NO_3$: **C** 63.14, **H** 7.23, **N** 6.69 %

m.p. = 123 ± 2°C.

$[\alpha]_D^{24}$ (c = 12.75 x 10^{-1}, MeOH) = +72.5 ± 0.5

*** Methyl (1S,2S,4S)-2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (14).**

The product was quantitatively obtained from 10, following the above described procedure of methylation with diazomethane.

^{1}H-NMR data are in good agreement with those described in the literature[2b].

Absolute configuration was assigned by comparing the ^{1}H-NMR analysis in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85, CD_3CN) with the above described data for 14 and 15.

Found: 14 **C** 63.15, **H** 7.30, **N** 6.89 %

Calc. for $C_{11}H_{15}NO_3$: **C** 63.14, **H** 7.23, **N** 6.69 %

m.p. = 132 ± 2°C.

$[\alpha]_D^{24}$ (c = 17.90 x 10^{-1}, MeOH) = -97.3 ± 0.5

REFERENCES

1. (a) H. N. CHRISTENSEN, M. E. HANDLOGTEN, I. LAM, H. S. TAGER, R. ZAND, *J.Biol.Chem. 244 1510 (1969);* (b) H. N. CHRISTENSEN, A. M. CULLEN, *J.Biol.Chem. 244 1521 (1969);* (c) H. S. TAGER, H. N. CHRISTENSEN, *J.Am.Chem.Soc. 94 968 (1972).*
2. (a) H. HORIKAWA, T. NISHITANI, T. IWASAKI, Y. MUSHIKA, I. INOUE, M. MIYOSHI, *Tetrahedron Lett. 21 4101 (1980);* (b) M. P. BUENO, C. CATIVIELA, C. FINOL, J. A. MAYORAL, C. JAIME, *Can.J.Chem 65 2182 (1987).*
3. (a) C. CATIVIELA, P. LOPEZ, J. A. MAYORAL, *Tetrahedron: Asymmetry 1 61 (1990);* (b) C. CATIVIELA, P. LOPEZ, J. A. MAYORAL, *Tetrahedron: Asymmetry 1 379 (1990).*
4. T. WIELAND, G. OHNACKER, W. ZIEGLER, *Chem .Ber. 90 194 (1957).*
5. W. OPPOLZER, C. CHAPUIS, G. MAO DAO, D. REICHLIN, T. GODEL, *Tetrahedron Lett. 23 4781 (1982).*
6. C. CATIVIELA, M. D. DIAZ DE VILLEGAS, J. A. GALVEZ, *Synthesis, 1990 198.*
7. W. OPPOLZER, M. KURTH, D. REICHLIN, F. MOFFATT, *Tetrahedron Lett. 27 2545 (1981).*
8. W.OPPOLZER, M. KURTH, D. REICHLIN, C. CHAPUIS, M. MOHNHAUPT, F. MOFFATT, *Helv.Chim.Acta 64 2802 (1981).*