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ASYMMETRIC SYNTHESIS OF 2-AMINONORBORNANE-2-CARBOXYLIC ACIDS BY DIELS-ALDER REACTION

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

Departamento de Química Orgánica. I. C. M. A. Universidad de Zaragoza. CSIC.50009 Zaragoza. Spain.

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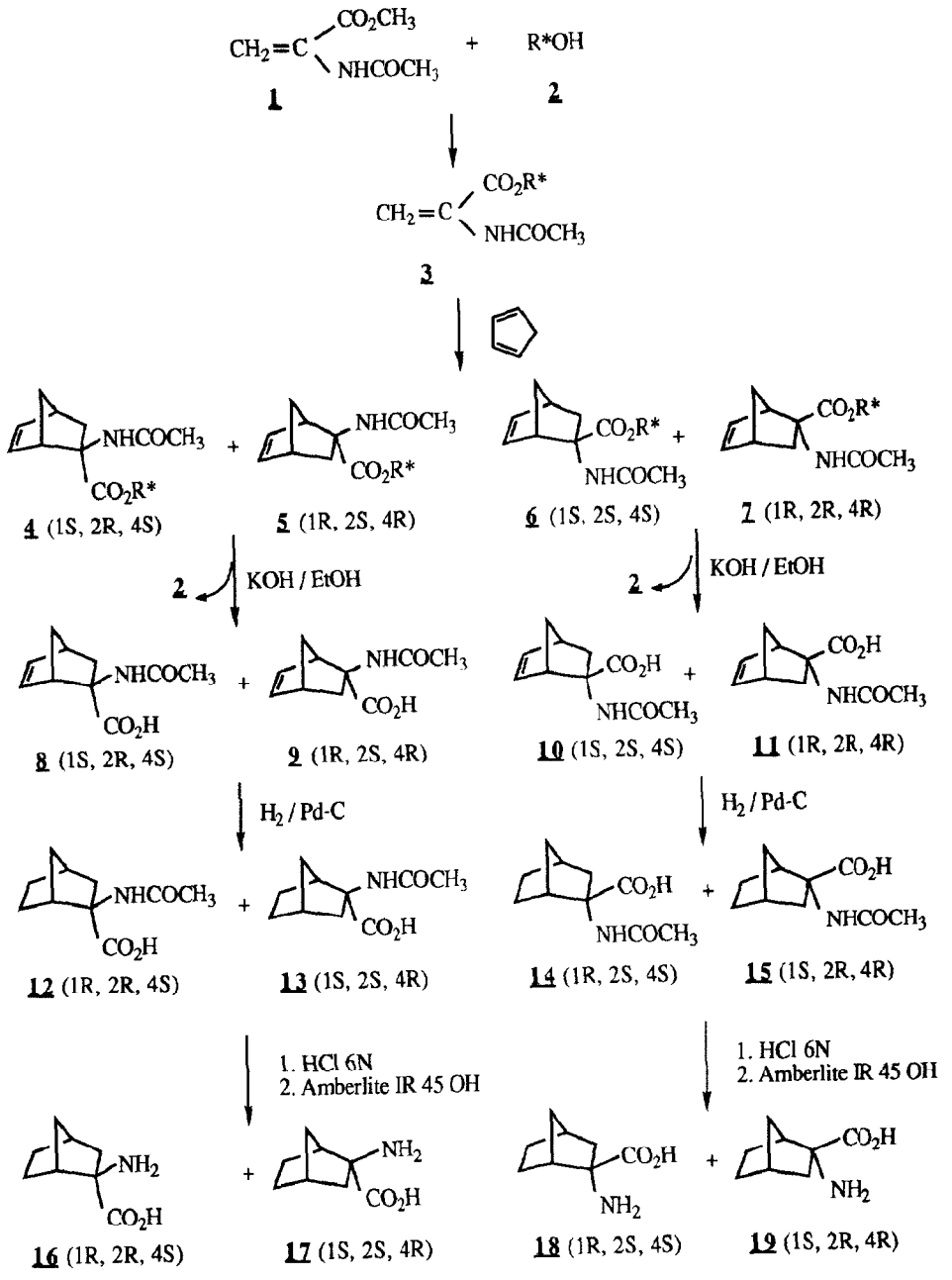
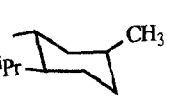
Abstract: The reaction between methyl N-acetyl-α,β-didehydroalaninate and cyclopentadiene in the presence of several chiral Lewis acids is studied and the results obtained are compared with those described for the reactions of the same diene with chiral N-acetyl-α,β-didehydroalaninates. In the presence of the titanium complex 24d methyl (1R,2R,4R) 2-acetamido-5-norbornen-2-carboxylate is preferably obtained. Thus, the reaction between methyl N-acetyl-α,β-didehydroalaninate and cyclopentadiene is a good method for the synthesis of (1S, 2R, 4R) 2-aminonorbornane-2-carboxylic acid.

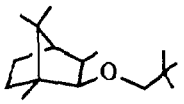
Cycloaliphatic amino acids with a norbornane skeleton are of interest because they display interesting biological properties as far as the transport of ions through biological membranes is concerned[1]. The parent compounds, 2-aminonorbornane-2-carboxylic acids, can be obtained by Diels-Alder reaction of N-acyl-α,β-didehydroalaninates with cyclopentadiene[2]. We have recently reported that the Diels-Alder reaction between cyclopentadiene and (-)-menthyl N-acetyl-α,β-didehydroalaninate (3a) is an excellent method for the asymmetric synthesis of 2-endo-aminonorbornane-2-exo-carboxylic acids[3], whereas the use of the N-acetyl-α,β-didehydroalaninate of (-)-cis-3-hydroxy isobornyl neopentyl ether (3b) as a dienophile is a better method for the asymmetric synthesis of 2-exo-aminonorbornane-2-endo-carboxylic acids[4] (Scheme 1). In this paper we wish to describe the reaction between methyl N-acetyl-α,β-didehydroalaninate and cyclopentadiene catalyzed by chiral Lewis acids.

RESULTS AND DISCUSSION

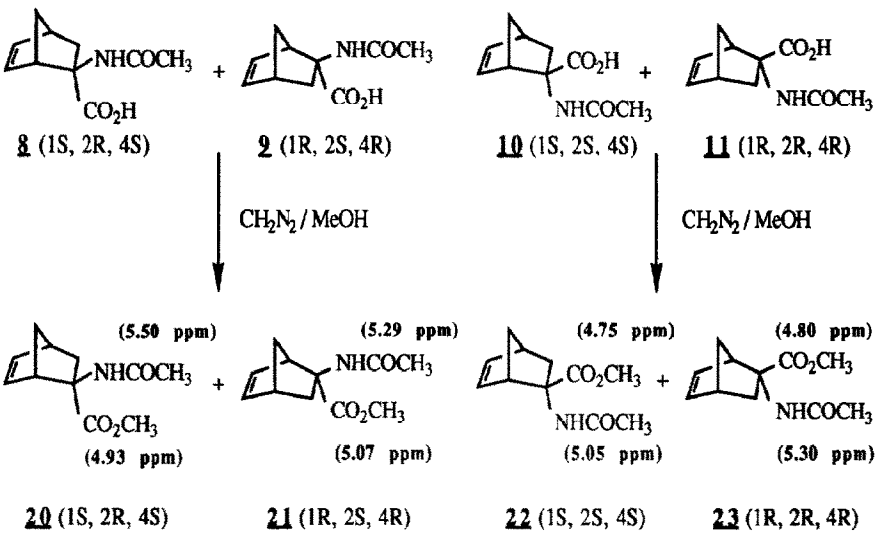
2-Acetamido-5-norbornen-2-carboxylic esters can be transformed, with high chemical yield and without epimerization, into the coresponding α-amino acids. Therefore, the asymmetric synthesis of these esters is the key step in the asymmetric preparation of 2-aminonorbornane-2-carboxylic acids. Table 1 gathers the results obtained in the reactions between chiral N-acetyl-α,β-didehydroalaninates and cyclopentadiene[3,4]. The absolute configuration of the cycloadducts (4-7) preferably obtained can be determined by transformation into the corresponding α-amino acids (16-19) and comparison of their optical rotations with the values given in the literature[1c]. Furthermore, the cycloadducts obtained (4-7) can easily be transformed into the corresponding methyl esters (20-23), whose analysis by ^{1}H-NMR in the presence of Eu(tfc)$_3$ (L/S molar relationship = 0.85, $CDCl_3$ as a solvent) allowed us to assign the singlets corresponding to the acetamido and ester methyls to each enantiomer[4] (Scheme 2). As can be seen from Table 1, in the reactions of 3a and 3b with cyclopentadiene, $TiCl_4$ is a more efficient catalyst than $AlCl_3$. With both dienophiles, high to excellent diastereofacial selectivities are obtained with the same direction of the asymmetric induction. The main difference between both chiral dienophiles is the exo-preference observed with 3a and the endo-preference obtained with 3b. Thus, whereas the reaction between 3a and cyclopentadiene is the key step in the asymmetric synthesis of (1R,2S,4S) 2-aminonorbornane-2-carboxylic acid (18), the reaction between 3b and cyclopentadiene is an excellent method for the asymmetric synthesis of (1S,2S,4R) 2-aminonorbornane-2-carboxylic acid (17).



a : R* = 

b : R* = 

Scheme 1



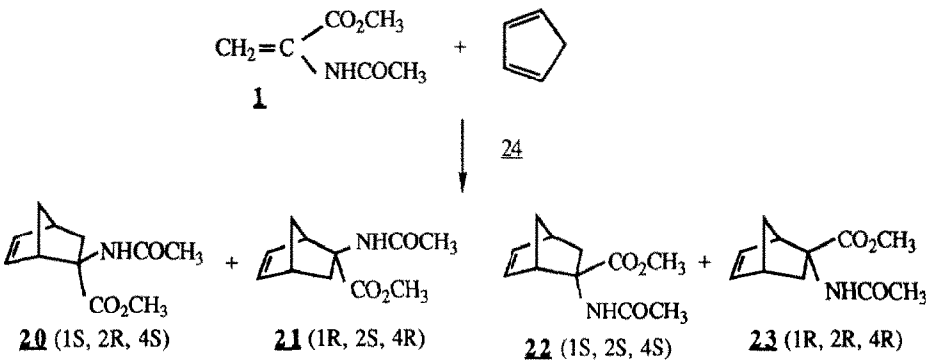
Scheme 2

Table 1. Diels-Alder reaction between 3a[a] and 3b[b] with cyclopentadiene.

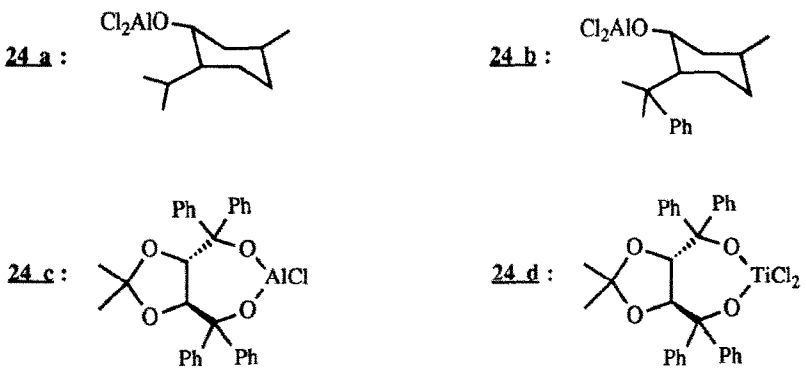
Lewis acid (eq)	Dienophile	T (°C)	t (h)	% Yield	ratio (4+5)/(6+7)	ratio 5/4	ratio 6/7
$TiCl_4$ (0.75)	3a	25	3	100	19/81	86/14	97/3
$TiCl_4$ (1.1)	3a	0	3	100	21/79	86/14	92/8
$TiCl_4$ (0.5)	3a	0	7	76	21/79	88/12	>99/1
$TiCl_4$ (1.1)	3a	-45	6	98	18/82	-	>99/1
$TiCl_4$ (1.1)	3b	0	1.5	94	62/38	>99/1	>99/1
$TiCl_4$ (0.5)	3b	0	4	100	62/38	>99/1	>99/1
$TiCl_4$ (0.75)	3b	-70	9	60	70/30	>99/1	>99/1
$AlCl_3$ (1.1)	3a	25	22	74	26/74	81/19	90/10
$AlCl_3$ (0.75)	3a	0	46	98	22/78	85/15	96/4
$AlCl_3$ (1.1)	3b	25	72	34	44/56	>99/1	>99/1
$AlCl_3$ (1.1)	3b	-45	72	20	55/45	>99/1	>99/1

a. Ref. 3 b. Ref. 4

The use of aluminium[5] and titanium[6] chiral Lewis acids has allowed the obtention of excellent results in asymmetric Diels-Alder reactions. In order to complete our program about the use of N-acetyl-α,β-didehydroalaninates as dienophiles in the asymmetric synthesis of amino acids with a norbornane skeleton, we have studied the reaction between methyl N-acetyl-α,β-didehydroalaninate (1) and cyclopentadiene in the presence of chiral Lewis acids (Scheme 3). The integration of the singlets corresponding to the acetamido and ester methyls allows the determination of the chemical yield and endo/exo selectivity[2]. In order to determine the enantiomeric excess and the absolute configuration of the major enantiomer, the reaction crude was separated into its endo and exo components by means of column chromatography on silica gel using AcOEt as an eluent. The endo and exo mixtures were analyzed by ^{1}H-NMR in the presence of Eu(tfc)$_3$.



1 :	$NHCOCH_3$	2.08 ppm (s)	CO_2CH_3	3.84 ppm (s)
20+21 :	$NHCOCH_3$	1.97 ppm (s)	CO_2CH_3	3.61 ppm (s)
22+23 :	$NHCOCH_3$	1.92 ppm (s)	CO_2CH_3	3.74 ppm (s)



Scheme 3

Table 2 gathers the results obtained in the reaction between methyl N-acetyl-α,β-didehydroalaninate (1) and cyclopentadiene catalyzed by chiral Lewis acids (24 a-d).

Table 2. Diels-Alder reaction between methyl N-acetyl-α,β-didehydroalaninate (1) and cyclopentadiene catalyzed by chiral Lewis acids[a].

Lewis acid (eq)	diene : 1	T (°C)	t (h)	% Yield [b]	(22+23)/(20+21) [b]	20/21 [c]	22/23 [c]
24a (0.5)	2:1	0	73	40	51/49	50/50	50/50
24a (1.0)	2:1	0	45	80	54/46	50/50	50/50
24b (1.0)	6:1	0	68	92	53/47	50/50	45/55
24c (1.0)	6:1	0	65	56	48/52	-	53/47
24d (1.0) [d]	6:1	0	71	73	79/21	85/15	15/85
24d (1.0) [d]	6:1	25	36	85	78/22	79/21	21/79
24d (1.0) [e]	6:1	0	24	93	76/24	72/28	21/79
24d (1.0) [e,f]	6:1	0	21	80	77/23	85/15	15/85
24d (0.5) [e,f]	6:1	0	21	64	78/22	85/15	15/85
24d (0.1) [e,f]	6:1	0	72	10	-	-	-

a. In toluene. b. Determined by ^{1}H-NMR. c. Determined by ^{1}H-NMR in the presence of Eu(tfc)$_3$.
d. With 0.21 g/(eq of Lewis acid) of 4Å molecular sieve. e. With 2.1 g/(eq of Lewis acid) of 4Å molecular sieve. f. In toluene:hexane = 1:1

It has been reported[5c] that the Diels-Alder reactions of α,β-unsaturated carbonyl compounds, catalyzed by chiral aluminium derivatives, gives rise to high levels of asymmetric induction when a syn-planar disposition of the double bond and the carbonyl group is favoured. It has been shown[7] that the most stable conformer of the methyl N-acetyl-α,β-didehydroalaninate presents a syn-planar disposition between the double bond and the carbonyl of the acetamido group, where the co-ordination of the catalyst must take place. In spite of this, neither exo/endo nor diastereofacial selectivity is obtained with the aluminium catalyst used (24 a-c). If the results obtained with 24a are compared with those described for the reaction between cyclopentadiene and methacrolein[5a] catalyzed by the same Lewis acids, it can be concluded that the presence of an extra bond between the double bond and the co-ordinating carbonyl group prevents the achievement of high levels of enantioselectivity. Probably the conformational equilibrium between B and C is shifted towards C because of a steric interaction of the catalyst with the methylenic hydrogens and the chiral auxiliary is far away from the double bond (Figure 1).

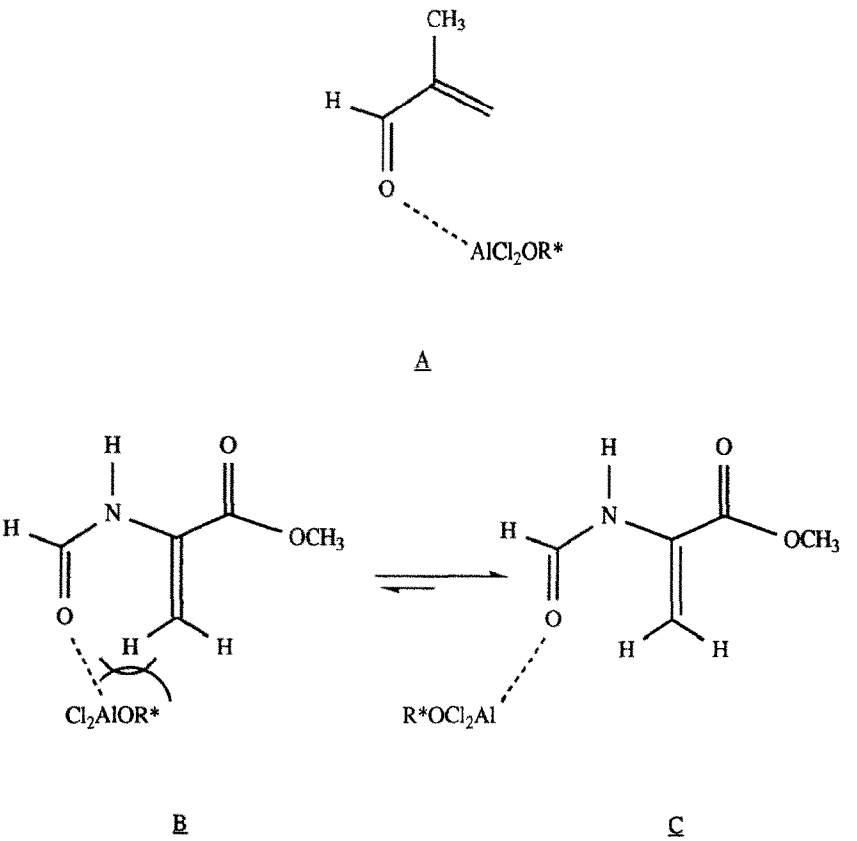
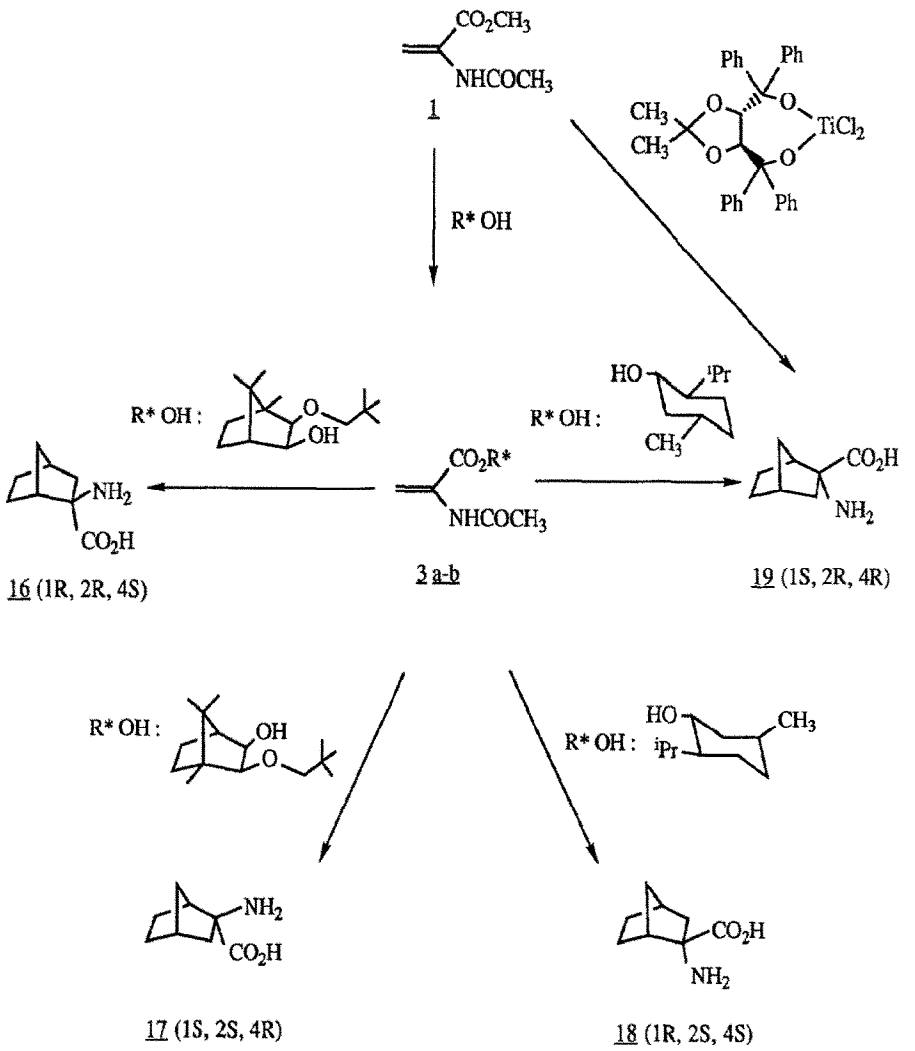


Figure 1

Nevertheless, when 24d is used as a catalyst, high exo/endo ratios and diastereofacial selectivities are obtained. It has been reported that the use of 4Å molecular sieves[6b-d] and toluene:hexane = 1:1 as solvent[6c-d] modifies the results of Diels-Alder reactions catalyzed by diol-$TiCl_2$ compounds. In our case, the best results are obtained by using a great excess of molecular sieves and toluene:hexane as solvent. In the titanium catalyzed reactions, 23 is the major cycloadduct; given that this compound can easily be converted into (1S,2R,4R) 2-aminonorbornane-2-carboxylic acid (19), this method complements the use of (-)-menthyl N-acetyl-α,β-didehydroalaninate as dienophile in the asymmetric synthesis of 2-endo-aminonorbornane-2-exo-carboxylic acids (18, 19).

Further work in order to explain and to improve the results obtained with chiral titanium catalyst is in progress.

To sum up, Scheme 4 shows how each of the four stereoisomers of the 2-aminonorbornane-2-carboxylic acid can be obtained starting from the easily available methyl N-acetyl-α,β-didehydroalaninate (1).



Scheme 4

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 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (20+21) and methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (22+23).**

General procedure for Diels-Alder reactions catalyzed by 24a and 24b: To a solution of the chiral alcohol (2 mmol) in anhydrous toluene (15 ml) at -78°C under argon atmosphere, 1 ml of a solution 1M of Cl_2AlEt in hexane is added. After 30 minutes stirring at room temperature under argon stream, the mixture is cooled to 0°C and a solution of methyl N-acetyl-α,β-didehydroalaninate (1) (1 mmol, 143 mg) in anhydrous toluene (7 ml) is added. The stirring is maintained for 20 minutes and then a solution of freshly distilled cyclopentadiene in anhydrous toluene (6 mmol in 3 ml or 2 mmol in 1 ml) is added and the reaction is stirred for the time reported in Table 2. The mixture is treated with $Na_2CO_3.10H_2O$ (400 mg), the solution is filtered and the solvent evaporated under vacuum to give a mixture, the composition of which was analyzed by ^{1}H-NMR.

General procedure for Diels-Alder reactions catalyzed by 24c: To a solution of the chiral diol (1 mmol) in anhydrous toluene (15 ml) at -78°C under argon atmosphere, 1 ml of a solution 1M of $ClAlEt_2$ in hexane is added. After 30 minutes stirring at room temperature under argon stream, the mixture is cooled at 0°C and the above procedure is followed.

General procedure for Diels-Alder reactions catalyzed by 24d: To a solution of $Ti(O^iPr)_4$ (142 mg, 0.5mmol) and $TiCl_4$ (0.5 ml of a solution 1M in hexane, 0.5 mmol) in anhydrous toluene (2 ml), a solution of the chiral diol (1.05 mmol) in dry toluene (5 ml) is added. After 1 hour stirring at room temperature the solution is added to a suspensión of 4Å molecular sieves (0.21 or 2.1 gr) in 2 ml of dry toluene kept under argon. The mixture is placed at the reaction temperature (Table 2), a solution of methyl N-acetyl-α,β-didehydroalaninate (1) (1 mmol, 143 mg) in anhydrous toluene (5 ml) is added and the stirring is maintained for 20 minutes. Then, a solution of freshly distilled cyclopentadiene (6 mmol, 396 mg) in anhydrous toluene or hexane (15 ml) is added and the reaction is stirred for the time reported in Table 2. The mixture is treated with $Na_2CO_3.10H_2O$ (400 mg), the solution is filtered, the solid is repeatedly washed with toluene and AcOEt and the solvent evaporated under vacuum to give a mixture, the composition of which was analyzed by ^{1}H-NMR.

Determination of the absolute configuration.

*** Separation of the reaction mixture into its endo and exo components.**

Endo and exo cycloadducts as well as the chiral auxiliary are separated by column chromatography on silica gel,using AcOEt as an eluent. The chiral diols are purified by column chromatography on silica gel using Et_2O: hexane = 2:8 as an eluent. In this way, the chiral auxiliary is recovered without loss of optical purity.

Methyl 2-exo-acetamidobicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (20+21)

^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.32 (dd, J=3.3 Hz, J'=5.7 Hz, 1H), 6.03 (bs, 1H), 5.85-5.81 (m, 1H), 3.61 (s, 3H), 2.93 (bs, 2H), 2.30 (dd, J=3.0 Hz, J'=12.6 Hz, 1H), 1.97 (s, 3H), 1.77-1.70 (m, 2H), 1.60-1.58 (m, 1H).

IR (nujol): ν (cm-1) = 3270 (N-H), 1755 (O-C=O), 1650 (N-C=O).

Found: C 63.39%, H 7.00%, N 6.50%. Calc. for $C_{11}H_{15}NO_3$: C 63.14%, H 7.23%, N 6.69%

Methyl 2-endo-acetamidobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (22+23)

^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.44 (dd, J=3.0 Hz, J'=5.4 Hz, 1H), 6.10 (dd, J=3.0 Hz, J'=5.4 Hz, 1H), 6.40 (bs, 1H), 3.74 (s, 3H), 3.33 (bs, 1H), 2.94 (bs, 1H), 2.69 (dd, J=3.9 Hz, J'=12.8 Hz, 1H), 1.92 (s, 3H), 1.78 (d, J=9.3 Hz, 1H), 1.55-1.52 (m, 1H), 1.17 (dd, J=3.3 Hz, J'=12.8 Hz, 1H).

IR (nujol): ν (cm-1) = 3290 (N-H), 1740 (O-C=O), 1650 (N-C=O).

Found: C 63.12%, H 7.09%, N 6.90%. Calc. for $C_{11}H_{15}NO_3$: C 63.14%, H 7.23%, N 6.69%

*** Determination of the enantiomeric excess and absolute configuration.**

The mixture of 20 and 21 was analyzed by ^{1}H-NMR in $CDCl_3$ in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85)

20 (1S,2R,4S) : $NHCOCH_3$ (5.50 ppm); CO_2CH_3 (4.93 ppm).

21 (1R,2S,4R) : $NHCOCH_3$ (5.29 ppm); CO_2CH_3 (5.07 ppm).

The mixture of 22 and 23 was analyzed by ^{1}H-NMR in $CDCl_3$ in the presence of Eu(tfc)$_3$ (L:S molar relationship = 0.85)

22 (1S,2S,4S) : $NHCOCH_3$ (5.05 ppm); CO_2CH_3 (4.75 ppm).

23 (1R,2R,4R) : $NHCOCH_3$ (5.30 ppm); CO_2CH_3 (4.80 ppm).

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. C. CATIVIELA, P. LOPEZ, J. A. MAYORAL, *Tetrahedron: Asymmetry 2 449 (1991).*
5. (a) S. HASHIMOTO, N. KOMESHIMA, K. KOGA, *J. Chem. Soc. Chem. Comm. 1979 437 ;* (b) H. TAKEMURA, N. KOMESHIMA, I. TAKAHASHI, S. HASHIMOTO, N. IKOTA, K. TOMIOKA, K. KOGA, *Tetrahedron Lett. 28 5687 (1987);* (c) C. J. NORTHCOTT, Z. VALENTA, *Can.J.Chem 65 1917 (1987);* (d) C. CHAPUIS, J. JURCZAK, *Helv.Chim.Acta 70 436 (1987);* (e) E. J. COREY, R. IMWINKELRIED, S. PIKUL, Y. B. XIANG, *J. Am. Chem. Soc.111 5493 (1989);* (f) F. FABIERE, O. RIANT, H. B. KAGAN, *Tetrahedron: Asymmetry 1 199 (1990).*
6. (a) K. NARASAKA, M. INOUE, N. OKADA, *Chem. Lett. 1986 1109;* (b) K. NARASAKA, M. INOUE, T. YAMADA, *Chem. Lett. 1986 1967 ;* (c) K. NARASAKA, N. IWASAKA, M. INOUE, T. YAMADA, M. NAKASHIMA, J. SUGIMORI, *J. Am. Chem. Soc.111 5340 (1989);* (d) K. NARASAKA, H. TAKANA, F. KANAI, *Bull. Chem. Soc. Jpn. 64 387 (1991);* (e) D. SEEBACH, A. K. BECK, R. K. IMWINKELRIED, S. ROGGO, A. WONNACOTT, *Helv.Chim.Acta 70 954 (1987);* (f) A. KETTER, G. GLAHSL, R. HERRMANN, *J. Chem. Res. 1990 278 .*
7. (a) D. AJO, G. GRANOZZI, E. TONDELLO, A. del PRA, G. ZANOTT, *J Chem. Soc. Perkin Trans. 2 1979 , 927;* (b) D. AJO, M. CASARIN, G. GRANOZZI, H. C. J. OTTENHEIJM, R. PLATE, *Recl. Trav. Chim. Pays-Bas 103 365 (1984).*