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N-[Bis(methylthio)methylene]-Didehydroalanine Methyl Ester a New and Excellent Dienophile for the Synthesis of 2-Aminonorbornene-2-Carboxylic Acid

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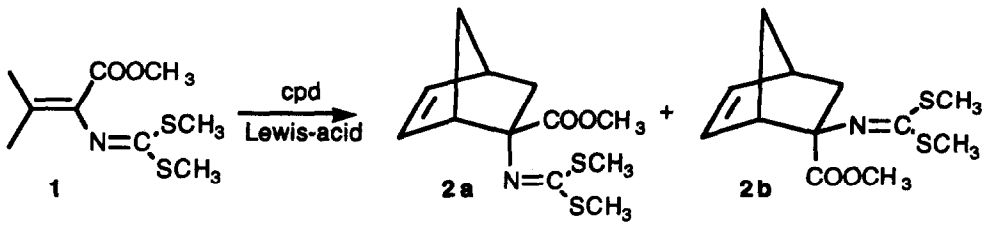
Abstract: *N-[Bis(methylthio)methylene]-didehydroalanine methyl ester behaves as an excellent dienophile with cyclopentadiene to afford methyl N-[Bis(methylthio)methylene]-2-aminonorbornene-2-carboxylate in excellent yield and with high selectivity.*

Alicyclic non-metabolizable amino acids with a norbornane skeleton are known to possess unique biological properties that affect the transport of ions through biological membranes.[1] These amino acids have been prepared by two different routes: Strecker or Bucherer synthesis[2] and the Diels-Alder reaction with cyclopentadiene of α,β-didehydroalanine derivatives.[3] The latter is the synthetic approach that has allowed[4] the asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids.

In the course of our research into the synthesis of α-amino acids we have developed a synthetic route[5] to N-[Bis(methylthio)methylene]-didehydroalanine methyl ester **1** which is a stable derivative of α,β-didehydroalanine and behaves as a new synthon in the synthesis of α-amino acids. It has proved to be an excellent dipolarophile in 1,3-dipolar cycloaddition of diazomethane directed towards the synthesis of 1-aminocyclopropanecarboxylic acid.[6] We now wish to report the unusual reactivity of this compound in Diels-Alder reactions with cyclopentadiene in the presence of a catalytic amount of Lewis-acid.

N-[Bis(methylthio)methylene]-didehydroalanine methyl ester **1** was easily prepared from serine methyl ester hydrochloride according to the previously described procedure[5] and allowed to react with cyclopentadiene in the presence of a sub-stoichiometric amount of a Lewis-acid catalyst as shown in Scheme 1.



Scheme 1

The experiments were performed on 3-6:1 mixtures of cyclopentadiene and dienophile **1** in dichloromethane and in all the Lewis-acid catalyzed Diels-Alder reactions the concentration of the dienophile was 0.25 M. Table 1 shows the reaction conditions and the results of selected experiments. Reactions were monitored by HPLC and the ratio of stereoisomers and the level of conversion were determined in the crude reaction spectra by integration of the signals as singlets at 3.62, 3.68 and 3.73 ppm corresponding to the carbomethoxy group of **2b**, **2a** and **1** respectively in the ^{1}H-NMR (300 MHz) spectrum. The results are summarised in Table 1.

Table 1: Lewis-Acid Catalyzed Diels-Alder Reaction between Ester **1** and Cyclopentadiene.

Lewis-acid (eq)	Ratio diene/1	Temp °C	Reaction time/h[a]	Conversion %	Ratio 2a/2b
-	6:1	25	100	0	-
$TiCl_4$(0.2)	6:1	25	0.5	100	80/20
$TiCl_4$(0.2)	3:1	25	0.5	100	80/20
$TiCl_4$(0.2)	3:1	0	24	90	80/20
$TiCl_4$(0.2)	3:1	- 25	120	72	80/20
$TiCl_4$(0.5)	3:1	- 25	0.5	100	80/20
$TiCl_4$(0.2)	3:1	- 40	96	60	80/20
$AlCl_3$(0.2)	3:1	25	24	18	70/30
$AlCl_3$(0.5)	3:1	25	4	90	55/45
$AlCl_3$(1.0)	3:1	25	4	100	50/50
$EtAlCl_2$(0.5)	3:1	25	0.5	100	48/52
$EtAlCl_2$(1.0)	3:1	25	0.5	100	44/56
Et_2AlCl(1.0)	3:1	25	24	100	-

[a] The reaction was monitored by HPLC until no evolution was detected. Column radial pack silica (8 mp 10 µm). Eluent hexane-ethyl acetate 98/2. Flow rate 3 ml/m. Detection 254 nm.

No reaction was observed when no catalyst was used. However, a sub-stoichiometric amount of the Lewis-acid catalyst $TiCl_4$ was enough to obtain cycloadducts in good yields and with excellent stereoselectivity. When the reaction was carried out at low temperatures there was a decrease in catalytic activity as can be seen in the kinetic curves (Figure 1), although the stereoselectivity of the reaction did not change, and a greater amount of catalyst was needed to reach the total conversion at a lower temperature.

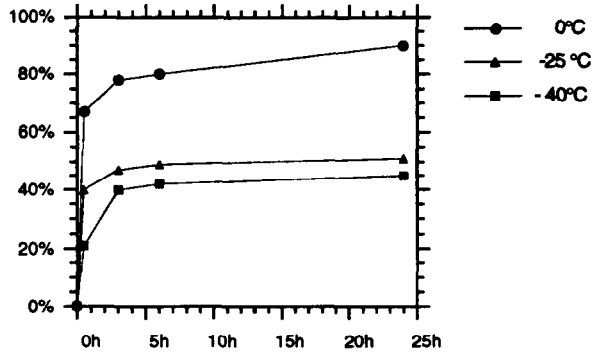


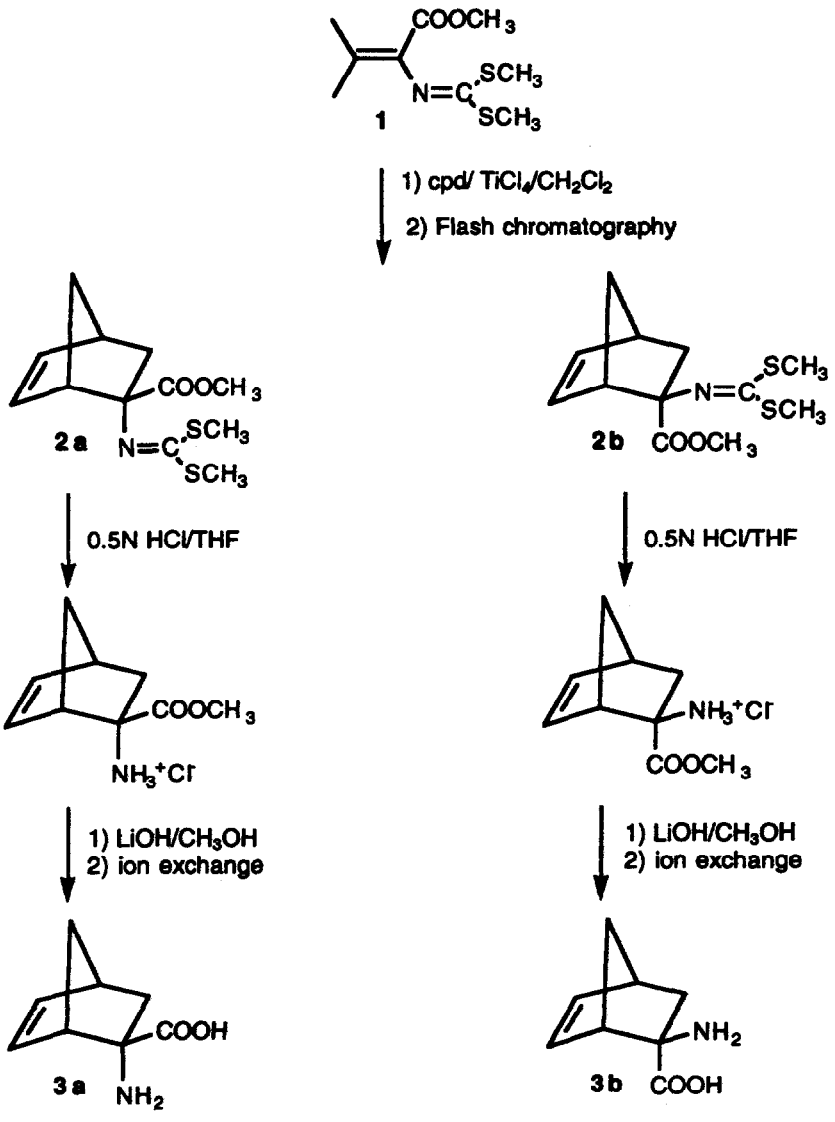
Figure 1

When $AlCl_3$ was used as a catalyst longer reaction times and higher dienophile/catalyst ratios were needed to obtain good conversions. In this case stereoselectivity decreased noticeably and a lot of competing polymerization was observed which increased when a higher dienophile/catalyst ratio was used.

We also studied the Diels-Alder reaction of cyclopentadiene and compound **1** catalyzed by the soluble organoaluminum complexes Et_2AlCl and $EtAlCl_2$ which have been widely used in Diels-Alder reactions. $EtAlCl_2$ showed good catalytic activity and total conversion was reached in 30 min at room temperature, but stereoselectivity was not observed and a lot of polymerization occurred. When Et_2AlCl was used dienophile **1** disappeared in 2 h but no cycloadducts were detected in the crude reaction spectrum.

The cycloadducts were readily separated by column chromatography on silicagel, and the structural assignments were made on the basis of NOE experiments which involved irradiation of the $COOCH_3$ of the two separated isomers **2a** and **2b**. Only the isomer, in which the methyl of the carbomethoxy group resonated upfield, exhibited a significant NOE enhancement in the absorption of the vinylic proton at $\delta = 5.81$ on pre-saturation of the methyl protons at $\delta = 3.62$, indicating that the protons are spatially close to each other and allowing firm identification of **2b** as the cycloadduct with the carbomethoxy group in an endo position.

When the reaction was carried out in multigram scale we obtained 72% of isolated **2a** and 15% of isolated **2b**.The advantage of using this new dienopile is the mild removal of the protecting groups which allowed the transformation of the adducts into the free unsaturated amino acids **4a** and **4b** without noticeable decomposition of the starting material. (Scheme 2)



Scheme 2

Mild acid hydrolysis of **2a** and **2b** with 0.5N hydrochloric acid in THF at room temperature provided methyl 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate hydrochoride **3a** and methyl 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate hydrochoride **3b** respectively in nearly quantitative yield.

A smooth transformation in their free-amine with lithium hydroxyde in methanol at room temperature gave methyl 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate and methyl 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate, which were hydrolyzed under these basic conditions to the lithium salt of the amino acids and subsequently transformed into 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylic acid **4a** and 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylic acid **4b** in nearly quantitative yield.

In summary we have developed a protocol for the syntheis of 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylic **4a** and 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylic **4b**, new non-proteinogenic and unsaturated aminoacids based on Diels-Alder reaction of N-[Bis(methylthio)methylene]-didehydroalanine methyl ester **1** with cyclopentadiene in the presence of a catalyic amount of $TiCl_4$ and selective removal of the N-[Bis(methylthio)methylene] and the carbomethoxy groups under very mild conditions.

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EXPERIMENTAL SECTION

Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H-NMR spectra at 300 MHz and ^{13}C-NMR spectra at 75 MHz were recorded on a Varian Unity-300 in $CDCl_3$ solution. Mass spectra (MS) were determined on a high-resolution VG-AutoSpec spectrometer.
All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Titanium (IV) chloride 1.0 M solution in dichloromethane, ethyl aluminum dichloride 1.0 M solution in hexanes, diethyl aluminum chloride 1.0 M solution in hexanes, aluminum chloride and dicyclopentadiene were purchased from Aldrich Chemical Co. TLC was performed on Merk precoated silica-gel plates. Flash chromatography was performed using 230-400 mesh (Merk) silica-gel.

N-[Bis(methylthio)methylene]-didehydroalanine methyl ester (1)

The compound was prepared from the commercial serine methyl ester hydrochloride according to the procedure previously described by the authors.[5]

General procedure for catalyzed Diels-Alder cycloaddition.

A typical experiment was run as follows: The Lewis-acid catalyst in solution (0.2 mL of a 1.0 M solution) was added to a solution of ester **1** (1 mmol) in 4 mL of dry dichloromethane under argon.

The mixture was stirred at the appropriate temperature for 0.5 h. Then cyclopentadiene (3 mmol) was added and the resulting solution was stirred at the appropriate temperature until no evolution was detected by HPLC. For analysis the mixture was treated with $Na_2CO_3.10H_2O$ (400 mg), the solution filtered and the solvent evaporated under vacuum to give a mixture, the composition of which was analyzed by ^{1}H-NMR.

Methyl N-[bis(methylthio)methylene]-2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate (2a) and methyl N-[bis(methylthio)methylene]-2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate (2b).

The Lewis-acid catalyst in solution (2 mL of a 1.0 M solution) was added to a solution of ester **1** (10 mmol) in 40 mL of dry dichloromethane under argon. The mixture was stirred at room temperature for 0.5 h. Then cyclopentadiene (30 mmol) was added and the resulting solution was stirred at the room temperature for 0.5 h. After completion the solution was quenched with 20 mL of 1N HCl. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), the combined extracts were dried ($MgSO_4$), and evaporated to dryness in vacuo to afford a mixture of cycloadducts **2a** and **2b** as a pale yellow oil ; yield: 2.57 g (95%). Flash chromatography on silica-gel using hexane-ethyl acetate 9/1 as an eluent afforded 1.95 g (72 %) of **2a** as a white oil and 406 mg (15%) of **2b** as a white oil.

Methyl N-[bis(methylthio)methylene]-2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate (2a).

HRMS (EI): m/z = 271.0703 (M^+, calc for $C_{12}H_{17}NO_2S_2$ 271.0700).
IR (neat): ν = 1724, 1577 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.13 (dd, 1H, J = 3.3, J = 12 Hz), 1.33-1.38 (m, 1H), 1.62-1.66(m, 1H), 2.30 (s, 3H), 2.47 (s, 3H), 2.81 (dd, 1H, J = 3.6, J = 12 Hz), 2.89-2.91 (m, 1H), 3.22-3.25 (m, 1H), 3.69 (s, 3H), 6.18-6.23 (m, 2H).
^{13}C NMR ($CDCl_3$): δ = 14.8, 15.7, 41.2, 42.9, 45.6, 52.4, 53.8, 74.9, 135.4, 138.4, 158.9, 175.4.

Methyl N-[bis(methylthio)methylene]-2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate (2b).

HRMS (EI): m/z = 271.0719 (M^+, calc for $C_{12}H_{17}NO_2S_2$ 271.0700).
IR (neat): ν = 1726, 1569 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.54 (dd, 1H, J = 3.3, J = 12.3 Hz), 1.52-1.57 (m, 1H), 1.77-1.82 (m, 1H), 2.24 (dd, 1H, J = 3, J = 12.3 Hz), 2.37 (s, 3H), 2.50 (s, 3H), 2.82-2.85 (m, 1H), 3.14-3.18 (m, 1H), 3.61 (s, 3H), 5.82 (dd, 1H, J = 3, J = 6 Hz), 6.27 (dd, 1H, J = 3, J = 5.7 Hz).
^{13}C NMR ($CDCl_3$): δ = 14.9, 15.7, 38.5, 42.1, 48.8, 52.0, 55.6, 73.1, 131.4, 140.6, 159.6, 173.8.

Methyl 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate hydrochloride (3a).

A solution of methyl N-[Bis(methylthio)methylene]-2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate **2a** (1 mmol) in 10 mL of THF and 20 mL of 0.5 N hydrochloric acid was stirred at room temperature for 4 days. Concentration to dryness afforded crude methyl 2-endo-amino[2.2.1]hept-

5-ene-2-exo-carboxylate hydrochloride **3a** as a white solid, m. p. 195 °C, in 95% yield, which was used without further purification.
IR (nujol): ν = 1745 cm^{-1}.
^1H NMR (D_2O): δ = 1.22 (dd, 1H, J = 3.6, J = 13.5 Hz), 1.44-1.49 (m, 1H), 1.84 (d, 1H, J = 9.6 Hz), 2.39 (dd, 1H, J = 3.6, J = 13.5 Hz), 2.98-3.00 (m, 1H), 3.11-3.13 (m, 1H), 3.71 (s, 3H), 6.06 (dd, 1H, J = 3, J = 5.7 Hz), 6.47 (dd, 1H, J = 3, J = 5.7 Hz).
^{13}C NMR (D_2O/CD_3COCD_3): δ = 36.8, 42.6, 48.4, 50.9, 53.9, 65.0, 131.2, 143.6, 172.9.

Methyl 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate hydrochloride (3b).
A solution of methyl N-[Bis(methylthio)methylene]-2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate **2b** (1 mmol) in 10 mL of THF and 20 mL of 0.5 N hydrochloric acid was stirred at room temperature for 4 days. Concentration to dryness afforded crude methyl 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate hydrochloride **3b** as a white solid, m. p. 184 °C, in 90% yield, which was used without further purification.
IR (nujol): ν = 1748 cm^{-1}.
^1H NMR (D_2O): δ = 1.58-1.62 (m, 2H), 1.73 (dd, 1H, J = 3.6, J = 13.5 Hz), 1.93 (dd, 1H, J = 2.4, J = 13.5 Hz), 2.93-2.99 (m, 1H), 3.08-3.12 (m, 1H), 3.62 (s, 3H), 5.82 (dd, 1H, J = 3.3, J = 5.7 Hz), 6.28 (dd, 1H, J = 3.3, J = 5.7 Hz).
^{13}C NMR (D_2O/CD_3COCD_3): δ = 35.9, 42.4, 47.5, 50.9, 52.4, 65.8, 131.6, 140.2, 174.7.

2-Endo-amino[2.2.1]hept-5-ene-2-exo-carboxylic acid (4a).
Methyl 2-endo-amino[2.2.1]hept-5-ene-2-exo-carboxylate hydrochloride **3a** was dissolved in 2 mL of methanol and lithium hydroxyde (2.5 mmol) was added. The reaction mixture was stirred at room temperature for 3 days and the solvent was evaporated in vacuo. The residue was dissolved in water then 5% hydrochloric was added to adjust the acidity to about pH 5. The solution was loaded into a cation exchange resin column (Dowex-50H^+) and after washing with water the free amino acid was eluted with 2N aqueous ammonia. Removal of the solvent in vacuo yielded the free amino acid **3a** as a white solid, m. p. > 300 °C, in nearly quantitative yield.
HRMS (EI): m/z = 153.0782 (M^+, calc for $C_8H_{11}NO_2$ 153.0789).
IR (nujol): ν = 1576 cm^{-1}.
^1H NMR (D_2O): δ = 1.13 (dd, 1H, J = 3, J = 12.9 Hz), 1.38-1.46 (m, 1H), 1.90 (d, 1H, J = 9 Hz), 2.26 (dd, 1H, J = 3.6, J = 12.9 Hz), 2.89-2.94 (m, 1H), 2.95-2.98 (m, 1H), 6.07 (dd, 1H, J = 3, J = 5.7 Hz), 6.41 (dd, 1H, J = 3, J = 5.7 Hz).
^{13}C NMR (D_2O/CD_3COCD_3): δ = 36.7, 42.4, 48.8, 50.4, 66.1, 132.2, 142.6, 177.4.
Calc. for $C_8H_{11}NO_2$: C: 62.73; N: 7.23; N: 9.14;. Found: C: 62.86; H, 7.09; N: 9.02

2-Exo-amino[2.2.1]hept-5-ene-2-endo-carboxylic acid (4b).
Methyl 2-exo-amino[2.2.1]hept-5-ene-2-endo-carboxylate hydrochloride **3b** was dissolved in 2 mL of methanol and lithium hydroxyde (2.5 mmol) was added. The reaction mixture was stirred at room temperature for 15 days and the solvent was evaporated in vacuo. The residue was dissolved in water then 5% hydrochloric was added to adjust the acidity to about pH 5. The

solution was loaded into a cation exchange resin column (Dowex-50H$^+$) and after washing with water the free amino acid was eluted with 2N aqueous ammonia. Removal of the solvent in vacuo yielded the free amino acid **3a** as a white solid, m. p. > 300 °C, in nearly quantitative yield.
HRMS (EI): m/z = 153.0795 (M^+, calc for $C_8H_{11}NO_2$ 153.0789).
IR (nujol): ν = 1578 cm^{-1}.
^1H NMR (D_2O): δ = 1.52-1.54 (m, 2H), 1.61 (dd, 1H, J = 3.6, J = 13.2 Hz), 1.81 (dd, 1H, J = 1.8, J = 13.2 Hz), 2.90-2.91 (m, 2H), 5.82 (dd, 1H, J = 3, J = 5.7 Hz), 6.19 (dd, 1H, J = 3, J = 5.7 Hz).
^{13}C NMR (D_2O/CD_3COCD_3): δ = 35.7, 42.5, 47.5, 51.0, 55.6, 66.5, 131.9, 139.8, 176.0.
Calc. for $C_8H_{11}NO_2$: C: 62.73; N: 7.23; N: 9.14;. Found: C: 62.96; H, 7.07; N: 9.17

REFERENCES

1. a) Christensen, H. N.; Handlogten, M. I.; Lam, I.; Tager, H. S.; Zand, R. *J.Biol.Chem.*, **1969**, *244*, 1510-1520. b) Christensen, H. N.; Cullen, A. M. *J.Biol.Chem.*, **1969**, *244*, 1521-1526. c) Tager, H. S.; Christensen, H. N. *J.Am.Chem.Soc.*, **1972**, *94*, 968-972.
2. Layton, W. J.; Smith, S. L.; Crooks, P. A.; Deeks, T.; Waigh, R. D. *J.Chem.Soc.Perkin Trans I*, **1984**, 1283-1287.
3. a) Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Moyoshi, M. *Tetrahedron Lett.*, **1980**, *21*, 4101-4104. b) Bueno, M. P.; Cativiela, C.; Finol, C.; Mayoral, J. A.; Jaime, C. *Can.J.Chem.*, **1987**, *65*, 2182-2186. c) Effenberger, F.; Baugartner, C.; Kühlwein, J. *Angew.Chem.Int.Ed.Eng.*, **1989**, *28*, 1053-1055. d) Cativiela, C.; Fraile, J. M.; Mayoral, J. A. *Bull.Chem.Soc.Jpn.*, **1990**, *63*, 2456-1457.
4. a) Cativiela, C.; Lopez, M. P.; Mayoral, J. A. *Tetrahedron: Asymmetry*, **1990**, *1*, 61-64 b) Cativiela, C.; Lopez, M. P.; Mayoral, J. A. *Tetrahedron: Asymmetry*, **1990**, *1*, 379-388. c) Cativiela, M. P. Lopez, J. A. Mayoral, *Tetrahedron: Asymmetry*, **1991**, *2*, 449-456. d) Cativiela, M. P. Lopez, J. A. Mayoral, *Tetrahedron: Asymmetry*, **1991**, *2*, 1295-1304.
5. Cativiela, C.; Diaz de Villegas, M. D. *Tetrahedron*, **1993**, *49*, 497-506
6. Buñuel, E.; Cativiela, C.; Diaz de Villegas, M. D.; Jimenez, A. I. *Synlett*, **1992**, 579-580.