Pergamon

Tetrahedron 54 (1998) 10537–10554

TETRAHEDRON

NEW ACYLNITROSO COMPOUNDS FOR THE ASYMMETRIC OXYAMINATION OF DIENES

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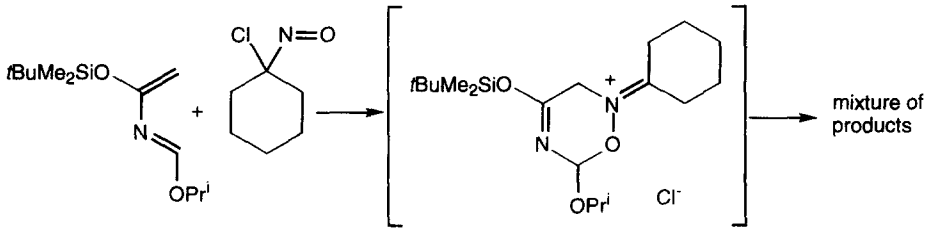
Received 17 March 1998; revised 7 April 1998; accepted 17 April 1998

Abstract : a series of new enantiomerically pure acylnitroso compounds have been prepared and tested as dienophiles for the asymmetric oxyamination of dienes. Very high selectivities were obtained with acylnitroso compounds derived from diphenylmethoxymethyl pyrrolidine **2c** , the C_2-symmetric pyrrolidines **2d-e** and camphorsultam **2f**. © 1998 Elsevier Science Ltd. All rights reserved.

Key words : asymmetric amination, Diels-Alder reaction, acylnitroso compounds.

INTRODUCTION AND PRELIMINARY RESULTS

The asymmetric addition of dienes to nitroso compounds is a useful route towards enantiomerically pure amino alcohols and amino acids. Excellent results have been obtained with α-chloronitroso compounds derived from epiandrosterone and D-mannose.[1] However, α-chloronitroso compounds cannot be added to highly nucleophilic dienes which decompose under the reaction conditions.[2] This has been ascribed to the intermediate formation of an iminium adduct which reacts with the nucleophilic diene (Scheme 1).



Scheme 1

In a preliminary attempt to overcome this problem, we had selected nitroso compound **1** as a potential oxyamination reagent of these sensitive dienes (Scheme 2). It was readily prepared by nitrosation of the commercial Oppolzer's sultam. Surprisingly, it was totally inert towards a wide variety of reactive dienes even in the presence of a Lewis acid catalyst. This probably results from the fact that the SO_2 group does not suppress electron donation from the nitrogen atom to the highly electrophilic nitroso group.

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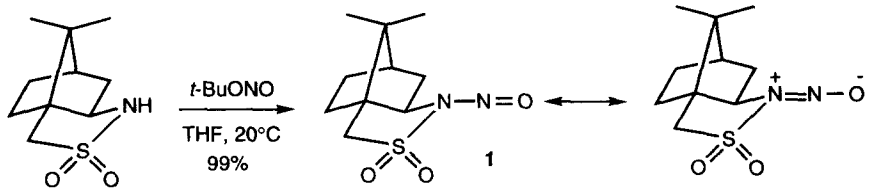
PII: S0040-4020(98)00504-3



Scheme 2

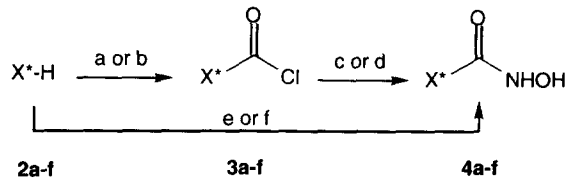
In contrast, acylnitroso compounds have been shown to be excellent dienophiles. However, only moderate facial selectivities were obtained by using enantiomerically pure acylnitroso compounds derived from mandelic acid or proline.[3,4] In two preliminary communications, we reported the efficiency of acylnitroso compounds **5d** and **5f** for the asymmetric amination of dienes.[5,6] The full details and extensions of these studies are presented here.

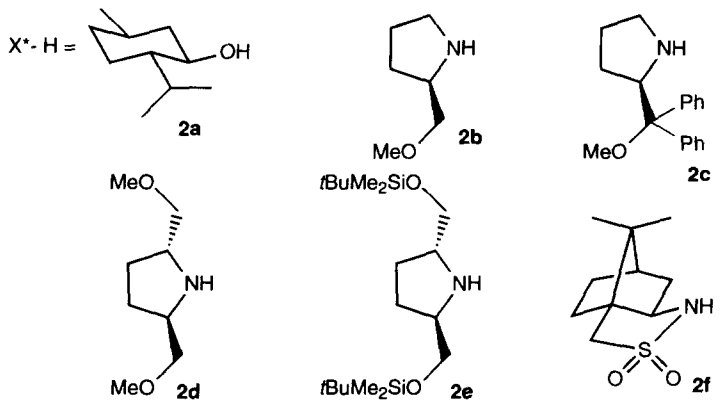
RESULTS

1. Synthesis of enantiomerically pure hydroxamic acids

Acylnitroso compounds are usually unstable and must be generated *in situ* by oxidation of the corresponding hydroxamic acids. A series of hydroxamic acids derived from enantiomerically pure compounds **2a-f** were prepared by the routes described in Scheme 3 and Table 1.

Compounds **2a**, **b**, **d**, **e** and **f** were first transformed into their corresponding carbamoyl chlorides **3**. The chlorocarboxylation of **2f** required the deprotonation of the sultam nitrogen prior to acylation with triphosgene. With **2b**, **d** and **e**, conversion to the carbamoyl chlorides proceeded cleanly and without rearrangement.[7] The crude carbamoyl chlorides were converted into their corresponding hydroxamic acids using either hydroxylamine hydrochloride in the presence of sodium hydroxide or N,O-*bis*(trimethylsilyl)hydroxylamine. The acid sensitive pyrrolidine **2c** was directly converted into **4c** by transacylation with *p*-nitrophenoxyhydroxamic acid. This transacylation could not be applied to D-bornane-2,10-sultame **2f** for the preparation of compound **4f** (3 % yield) because of the weaker nucleophilicity of the nitrogen atom of the sultam function. For compound **4f**, we also developed a one-pot procedure using diisopropylethylamine and triphosgene in ether, then hydroxylamine hydrochloride and K_2CO_3 in water. This one-pot procedure gave a much better yield (85 %) than the two step sequence described above (41 % overall yield).





Reagents : (a) : $COCl_2$, toluene or ether, -30° C; (b) : NaH, toluene then triphosgene; (c) : $NH_2OH.HCl$, NaOH, $MeOH/H_2O$; (d) : $Me_3SiNHOSiMe_3$ then MeOH; (e) : NaHMDS, THF, *p*-O_2N-C_6H_4-O-CO-NHOH, -78° C to rt; (f) : triphosgene, $NEt(iPr)_2$ then $NH_2OH.HCl$, K_2CO_3, H_2O/ether.

Scheme 3

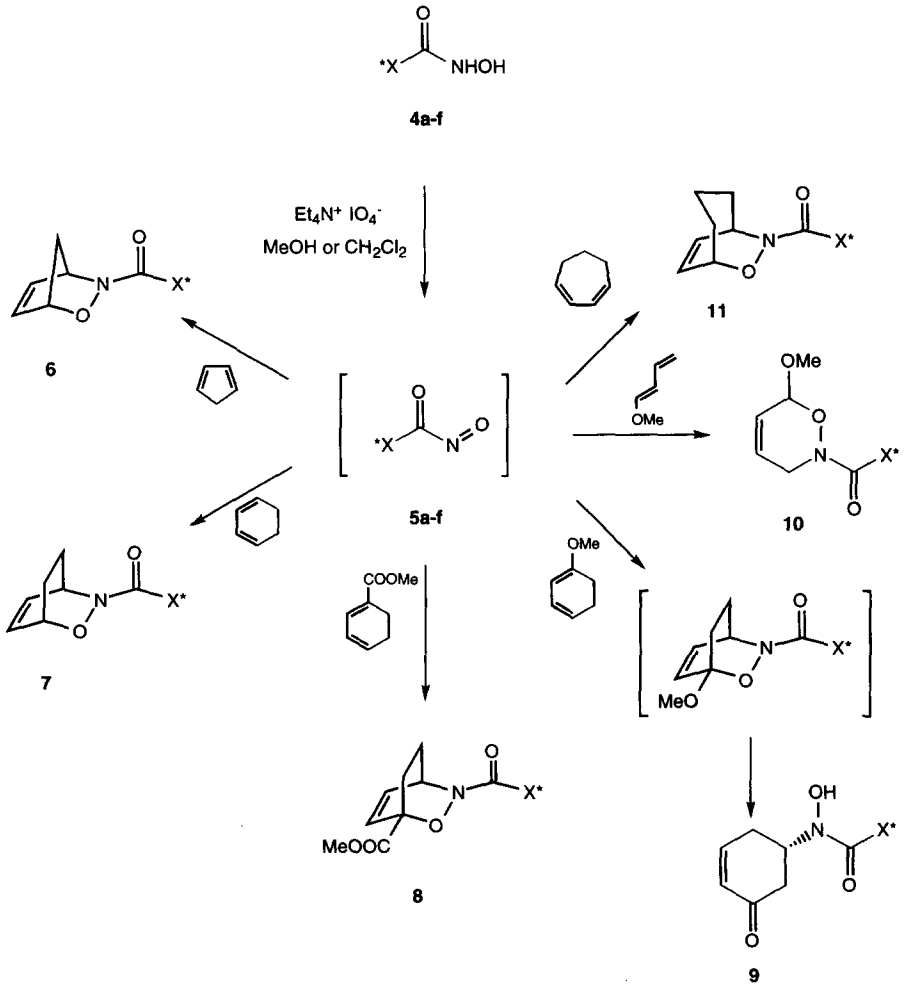
Table 1 : Synthesis of Enantiomerically Pure Hydroxamic Acids

Starting material	Conditions	Yield **3** (%)	Yield **4** (%)	global yield **4** (%)
2a	a then c	82	76	62
2b	a then d	91	71	64
2c	e	--	--	40
2d	a then d	95[a]	64	61
2e	a then d	95[a]	82	78
2f	b then d	51	80	41
2f	f	--	--	85

a : yields of crude compounds

2. Asymmetric cycloadditions

Acylnitroso compounds **5a-f** were generated in the presence of excess diene by oxidation of hydroxamic acids **4a-f** with tetraethylammonium periodate. These very reactive dienophiles gave good yields of cycloadducts under these very mild conditions (Scheme 4, Table 2).



Scheme 4

Acylnitroso compound **5a** derived from menthol gave very low diastereomeric excesses (Table 2, entries 1 and 2), a result which can be explained by several reactive conformations. For similar reasons, poor diastereoselectivities were obtained with acylnitroso **5b** derived from proline (Table 2, entries 3 and 4). This had been previously observed by Streith *et al.*[4]

Several possibilities were considered in order to improve the diastereoselectivities. We have selected a pyrrolidine derivative bearing a bulkier group α to the nitrogen. Dienophile **5c** derived from α,α-diphenylmethoxymethylpyrrolidine reacted at 0° C with cyclohexadiene to give adduct **7c** as a single diastereomer (d.e. > 98 %, Table 2, entry 5). Complete control of the diastereoselectivity was also observed with functionalised dienes (Table 2, entries 6, 7 and 8). For those reactions involving non symmetrical dienes, only one regioisomer was detected by ^{1}H NMR analysis of the crude mixtures. The primary adduct from the reaction of 1-methoxycyclohexadiene with **5c** was not isolated but directly hydrolysed to yield **9c**. These results showed that the presence of a large substituent on the pyrrolidine ring significantly enhanced the diastereomeric excess of the cycloaddition.

Table 2 : Cycloadditions of Acylnitroso Compounds with Dienes

Entry	Acylnitroso **5**	Diene	t (° C)	Adduct	Yield (%)[a]	d.e. (%)[b]
1	**5a**	cyclopentadiene	0	**6a**	65	12[c]
2	**5a**	cyclohexadiene	0	**7a**	74	20[c]
3	**5b**	cyclopentadiene	0	**6b**	71	34
4	**5b**	cyclohexadiene	0	**7b**	80	72
5	**5c**	cyclohexadiene	0	**7c**	75	> 98
6	**5c**	1-carboxymethylcyclohexadiene	0	**8c**	40	> 98
7	**5c**	1-methoxycyclohexadiene	0	**9c**	68	> 98
8	**5c**	1-methoxybutadiene	0	**10c**	51	> 98
9	**5d**	cyclopentadiene	- 25	**6d**	83	87 (98[d])
10	**5d**	cyclohexadiene	20	**7d**	88	> 98
11	**5d**	cycloheptadiene	20	**11d**	70	> 98
12	**5e**	cyclohexadiene	20	**6e**	82	> 98
13	**5f**	cyclopentadiene	0	**6f**	91	> 98
14	**5f**	cyclohexadiene	0	**7f**	94	> 98
15	**5f**	1-carboxymethylcyclohexadiene	- 20	**8f**	75	> 98

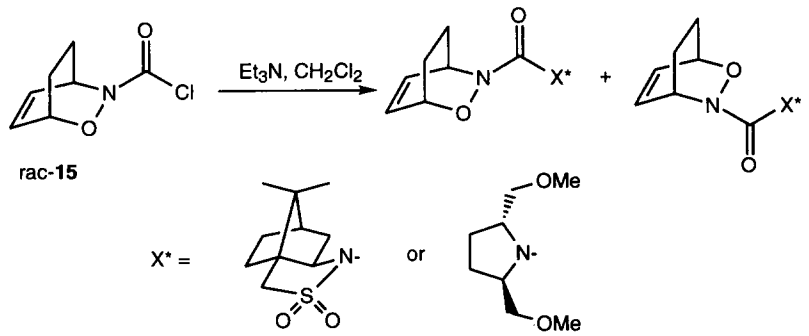
a : yields of purified compounds; b : determined by ^{1}H NMR on the crude compounds; c : approximated by quantitative ^{13}C NMR; d : after purification.

Excellent levels of asymmetric induction were also observed with acylnitroso compounds **5d** and **5e** derived from C_2-symmetric pyrrolidines (Table 2, entries 9-12).[8]

Finally, nitroso compound **5f** derived from camphor sultam also proved to be an efficient stereodirecting chiral heterodienophile. It reacted with cyclohexadiene, cyclopentadiene and 1-carboxymethylcyclohexadiene to give the expected adducts with more than 98 % d.e. (Table 2, entries 13, 14 and 15). The reaction with 1-carboxymethylcyclohexadiene was also totally regiospecific (Table 2, entry 15).

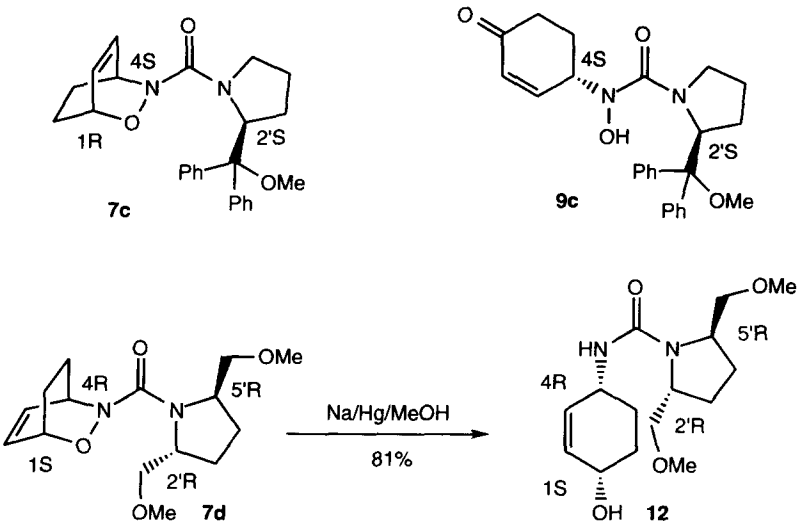
The determination of the diastereomeric excesses rested upon the ^{1}H NMR analysis of the crude mixtures. For the bicyclic adducts, the d.e. were deduced from the examination of the signals of the bridgehead protons. A control experiment was performed on an equimolecular mixture of diastereomers prepared independently following Scheme 5. This authentic mixture showed well separated ^{1}H NMR signals for the bridgehead protons (Scheme 5).

The hydrolysed product **9c** showed only one signal at 58.9 ppm for the newly created asymmetric carbon atom. Similarly product **10** showed only one signal at 100.1 ppm for the new asymmetric carbon atom.



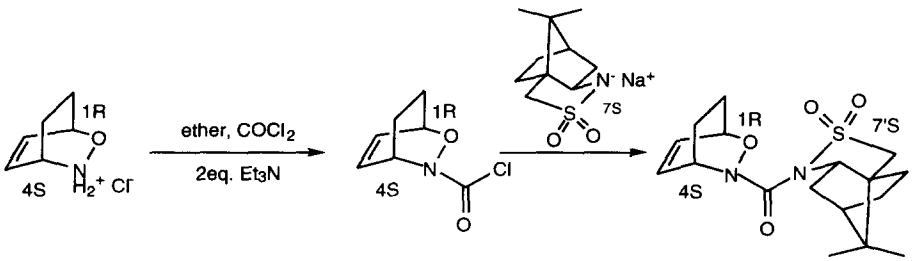
Scheme 5

The structure and absolute configurations of adducts **7c**, **9c** were assigned by X-ray diffraction analysis by reference to the known absolute configuration of the asymmetric carbon atoms of the pyrrolidine ring.[9] We also obtained an X-ray diffraction analysis on compound **12** resulting from the reduction of **7d** (Scheme 6).[10]



Scheme 6

The absolute configuration of adduct **7f** was established by an independent synthesis from the known enantiomerically pure (1R,4S)-oxazine[1d] (Scheme 7).



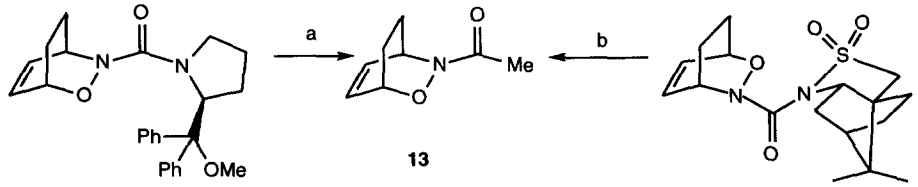
Scheme 7

3. Cleavage of the chiral auxiliaries

We have previously described that the hydrolytic cleavage of the chiral auxiliary from adducts prepared by cycloaddition of acylnitroso compound **5d** and 2-azadienes was possible by refluxing the adduct in 6M HCl. Under those conditions, concomitant demethylation of the methoxymethyl groups of the pyrrolidine ring was observed.[10]

In a preliminary study, we have found that similar strong acidic conditions only gave a poor yield in the case of **7c**. This is probably due to the instability of the bicyclic oxazine under these conditions.

On the other hand, the cleavage of the imide bond of **7f** could be effected with H_2O_2 - LiOH as shown earlier.[11] Here again we observed some decomposition of the oxazine. Further studies are in progress to optimise these steps.



7c **7f**

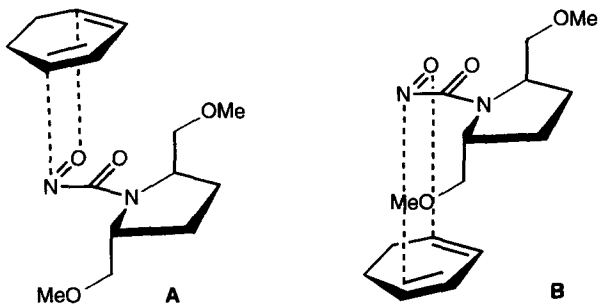
(a) HCl/MeOH then CH_3COCl, Et_3N, 28 %; (b) H_2O_2, LiOH then CH_3COCl, Et_3N, 35 %

Scheme 8

4. Transition state models

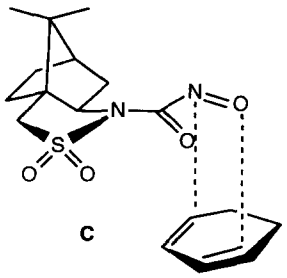
The excellent diastereoselectivities observed for the reactions of acylnitroso **5c**, **5d** and **5f** with cyclohexadiene, cyclopentadiene or functionalised dienes could be rationalised in the following manner.

For acylnitroso compound **5d**, one could consider the two *endo* transition states **A** and **B**.

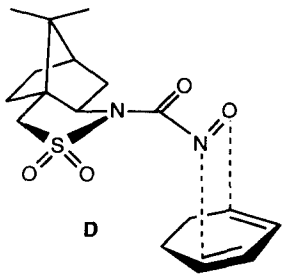


In contrast with other acylnitroso compounds, the carbamoyl nitroso prefers a *syn* conformation. *Ab initio* calculations using the basis sets MINI-1'[12,13] and 6-31G[14] predict this *syn* conformation to be 7.039 and 6.911 Kcal (AG) more stable than the corresponding *anti* conformation. The *anti* conformation corresponds to an energy maximum in both basis sets. This results from repulsive interactions between the oxygen atom of the N=O group and the bulky substituent on the pyrrolidine ring atom. In transition state **A**, the diene approaches in an *endo* fashion from the less hindered side of the dienophile. Transition state **A** is clearly lower in energy than transition state **B** and leads to the experimentally observed adduct.

The facial diastereoselectivity observed for the cycloaddition of dienophile **5f** with cyclohexadiene is consistent with transition state models **C** or **D**.



C



D

Transition state **C** results from an *endo* approach of the dienophile from the less hindered side of the dienophile in a *syn-syn* conformation around the SO_2N-CO and CO-NO bond. Transition state **D** results from an *exo* approach of the diene from the less hindered face of the dienophile in an *anti-syn* conformation. The four conformers resulting from the rotation around the SO_2N-CO and CO-NO bonds have been fully optimised by *ab initio* calculations using minimal MINI-1'[12-13], double 6-31G[14] and 6-31G* basis sets[15] (Table 3). Except for the *syn-anti* conformer which corresponds to an energy maximum following the reaction coordinate, all three other conformers are true minima.

Table 3 : Conformational Energy Differences (kcal) for Dienophile 5f

		Syn-Syn	Anti-Syn	Syn-Anti	Anti-Anti
MINI-1'	ΔE	1.458	0.000	8.363	3.269
	ΔG	1.433	0.000	9.044	3.787
6-31G	ΔE	3.989	0.000	9.954	4.621
	ΔG	3.900	0.000	10.487	5.029
6.31G*	ΔE	3.167	0.000	8.514	1.660
	ΔG	3.001	0.000	9.326	1.530

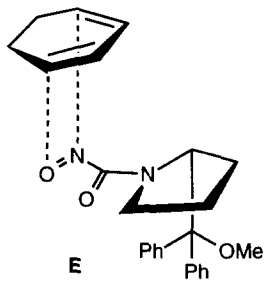
Inspection of molecular models suggests that in transition state **D** the large SO_2 group could interact with the approaching diene. This should not be the case in transition state **C** which should therefore be preferred. Furthermore, an *endo* approach of diene and nitroso dienophile would be in agreement with what was previously observed for other chiral acylnitroso compounds.

For acylnitroso compound **5d**, *ab initio* calculations using the basis sets MINI-1 and 6-31G predicted the *anti-syn* conformation as the most stable one (Table 4).

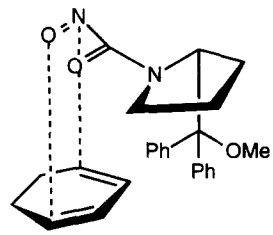
Table 4 : Conformational energy differences (kcal) for dienophile **5d**

		Syn-Syn	Anti-Syn	Syn-Anti	Anti-Anti
MINI-1	ΔE	1.164	0.000	5.874	3.398
	ΔG	0.682	0.000	6.042	3.310
6-31G	ΔE	6.075	0.000	10.289	2.477
	ΔG	4.814	0.000	10.113	2.415

Both transition states **E** and **F** resulting from an *endo* approach of the dienophile in an *anti-syn* conformation have been considered. Transition state **E** resulting from the approach from the less hindered face of the pyrrolidine ring should be favoured. It leads to the experimentally observed adducts.



E



F

CONCLUSION

Among the various acylnitroso compounds we have prepared, **5c**, **5d** and **5f** yielded cycloadducts with high facial selectivity. Transition state models have been proposed which allow prediction of the absolute configuration of an adduct starting from a given chiral auxiliary. The acylnitroso compound derived from the commercial Oppolzer's sultam presently appears to be the best choice : it gives high yields of cycloadducts with excellent diastereomeric excesses. However a proper evaluation of the new chiral nitroso compounds with respect to those described earlier[16,17,18] also rests upon a study of the cleavage and recovery of the chiral auxiliary.

EXPERIMENTAL SECTION

IR spectra were recorded on Perkin-Elmer 297 or 681 spectrophotometers. ^{1}H NMR spectra were obtained if not specified otherwise on Varian XL-200 or VXR-200 spectrometers (δ=0(TMS), $CDCl_3$, J in Hertz). ^{13}C-NMR spectra were recorded at 20MHz on Varian CFT-20 and at 50MHz on Varian XL-200 or VXR-200 (δ in ppm relative to internal TMS, *J* in Hertz). Mass spectra were measured on Varian MAT-44 or Finnigan MAT-TSQ70 spectrometers (electronic impact 70eV or chemical ionisation 100V with 200μBar isobutane as ionising gas). Optical rotations were measured on polarimeter Perkin-Elmer 241 MC. Column chromatographies were performed on Merck 60 silicagel (70-230 Mesh) and flash-chromatography on Merck 60 silicagel (230-400 Mesh). Chromatographic solvents were distilled before use. TLC were performed on Merck 60 F_{254} plastic or glass plates. All dry solvents were distilled under argon or *in vacuo*. Benzene, toluene, tetrahydrofurane (THF) and ether (Et_2O) were distilled from benzophenone ketyl. Dichloromethane, chloroform and acetonitrile were distilled from P_2O_5. Cyclohexane was dried by azeotropic distillation. Ethyl acetate was refluxed on solid K_2CO_3 and distilled. Methanol and ethanol were distilled from their respective magnesium alkoxides.

(2S)-Methoxymethylpyrrolidine[19], (2S)-methoxydiphenylmethylpyrrolidine[20], (2R,5R)-methoxymethylpyrrolidine[21], (7S)-10,10-dimethyl-5-thia-4-aza-tricyclo(5,2,1,0) decane-5,5-dioxide[22], carboxyethylcyclohexadiene[23] have been prepared following the procedures described in the literature.

For the theoretical calculations, all the geometric degrees of freedom have been fully optimised at *ab initio* level using the minimal basis set MINI-1'[12,13] and the double zeta basis sets 6-31G[14] and 6-31G*[15]. The nature of the critical point was determined by analytical frequency calculation available in Gaussian 94[24]. The free energy calculations were performed at 298.15K and 1atm.

4-(N-Nitroso)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,03,7]-decane-5,5-dioxide 1

To a solution of 0.33g(1.52mmol, 1eq.) of sultam **2f** in 2ml THF was added dropwise a solution of 0.3ml(2.28mmol, 1.5eq.) of *t*-butylnitrite in 2ml THF. The mixture immediately turned yellow. After 30 min, all starting material had disappeared (TLC). After evaporation, the yellow solid was washed with pentane, filtered and dried *in vacuo*. It was used without further purification. Yield: 0.37g(99 %); Rf: 0.92(ethylacetate); IR (film, cm^{-1}): 1460, 1360; m/z(E.I.) 244(M); ^{1}H NMR (200MHz, $CDCl_3$): 3.60 and 3.47(2H, AB, *J*=13.9), 2.1(2H,m), 1.9(3H,m), 1.4(2H,m), 1.08(3H,s), 0.99(3H,s); ^{13}C NMR (50MHz, $CDCl_3$): 63.5, 51.9, 48.2, 48.1, 44.8, 36.8, 32.6, 26.3, 20.6, 19.7; $[\alpha]_D^{20}$ -116° (c=0.48, CH_3OH).

1) SYNTHESIS OF OPTICALLY PURE HYDROXAMIC ACIDS

Synthesis of (l)-menthyloxycarbohydroxamic acid 4a

To a solution of 3.2ml (0.045mole, 3eq) of phosgene and 20ml of toluene at -20° C, was added dropwise 2.3g (0.015mole, 1eq.) of l-(-)-menthol dissolved in 10ml of toluene. After the addition, the mixture was stirred for 5 hours at -10° C and then at room temperature for one hour. After evaporation of the solvent and the excess of phosgene, the residual oil was purified by column chromatography to give 2.7g of (l)-menthylchloroformate **3a** (82 %); Rf: 0.84 (ethylacetate/cyclohexane:2/8); IR (film, cm^{-1}): 1775, 1470, 1370; To a suspension of 4.24 g (0.0611mole, 5eq) of hydroxylamine hydrochloride in a mixture 1/1 methanol/water (30ml) was added at once 3.42g (7eq.) of NaOH dissolved in 20ml of a 1/1 mixture of methanol/water. After addition of 2.7g (0.0122mole, 1eq) of (l)-menthyl chlorocarbamate **3a**, the reaction mixture was stirred overnight. The solvents were evaporated and the residue was treated with 1N HCl until acidic pH. After three extractions with dichloromethane, the organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give a residual solid which was purified by column chromatography and recristallised in a mixture of ethylacetate/cyclohexane; yield: 1.99g (76 %); Rf:0.55 (ethylacetate/cyclohexane; 1/1); IR(film, cm^{-1}) 3430, 1725; ^{1}H NMR (200MHz, $CDCl_3$): 7.26(1H, br s), 6.89 (1H, br s), 4.65 (1H, dxt, *J*=4.5, *J*=10.9), 2.08 to 0.76 (9H, m), 0.91 (3H, d, *J*= 6.4), 0.88 (3H, d, *J*=7.1), 0.76 (3H, d, *J*=6.9);

^{13}C NMR (50MHz, $CDCl_3$): 159.3, 76.6, 47.2, 41.0, 34.1, 31.4, 26.2, 23.4, 21.9, 20.7, 16.3; $[\alpha]_D^{20}$= -78.7° (c=0.5, $CHCl_3$).

(2S)-(methoxymethyl)pyrrolidinocarbohydroxamic acid 4b

Same procedure as for **3a** with 3g(0.026mmol) of (2S)-methoxymethylpyrrolidine, 5.5ml (0.078mol) of phosgene; yield: 2.1g(91 %) of crude N-(carbamoyl)-2(S)-(methoxymethyl)pyrrolidine **3b**; IR(film, cm^{-1}) 1740; A mixture of 2.1g(0.012mol) of carbamoyl chloride **3b**, 4.6g(5.6ml, 0.026mol, 2.2eq.) of N,O-*bis*(trimethylsilyl)hydroxylamine and 4eq. of methanol was heated for 2 hours at 60° C; After addition of 1ml of methanol, the mixture was stirred for another 15 minutes then evaporated *under vacuo*; the residue was purified by column chromatography; yield:1.46g (71 %);white solid; recristallised in cyclohexane; m.p. 90.8° C; IR (film, cm^{-1}) 3280, 1655; ^1H NMR (500MHz, $CDCl_3$) 8.28(1H, br s), 6.94(1H, br s), 3.93(2H,m), 3.61(5H,m), 3.4(6H, dxd, *J*=5.9, *J*=3.4); 3.33(3H, s), 3.37(1H, m), 3.26(1H, dxd, *J*=9.3, *J*=9.3), 1.97(1H,m), 1.81(1H,m), 1.61(1H,m); ^{13}C NMR(50MHz, $CDCl_3$): 161.7, 76.9, 59.2, 56.4, 46.8, 28.6, 23.2; m/z(EI) 174 (M, 20 %); EA($C_7H_{14}N_2O_3$) %C(48.27, found 48.22), %H(8.10, found 8.12), %N(16.08, found, 16.13); $[\alpha]_D^{20}$ = -93.1° (c=1.99, CH_3OH).

Diphenylmethoxymethylpyrrolidino carbohydroxamic acid 4c

NaHMDS 1.0M in THF (0.67ml, 0.67mmol) was added dropwise to a suspension of 2-diphenylmethoxymethylpyrrolidine hydrochloride (100mg, 0.33mmol) in 10ml THF at -78° C under an Argon atmosphere. The mixture was stirred for 30 minutes in which time the solid went into solution. A solution of *p*-nitrophenyl-N-hydroxycarbamate (72mg, 0.36mmol) in THF was added dropwise, this was accompanied by the solution turning yellow in colour due to the liberation of *p*-nitrophenol. The reaction was allowed to warm to room temperature over several hours, and the reaction was quenched with 10ml saturated $NH_4^+Cl^-$ solution. The organic phase was extracted with Et_2O (25ml) and was washed with water (2x10ml) and brine (10ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a yellow solid. The crude product was purified by flash column chromatography using ethylacetate/cyclohexane(2/1) as eluant, this was repeated a second time as further purification was necessary; white foam; 40 % yield (43mg, 0.13mmol), m.p. 72-74° C; IR(film, cm^{-1}) 3291, 1656; ^1H NMR (200MHz, $CDCl_3$): 0.83(1H,m), 1.35(1H,m), 1.67-2.20(3H,m), 2.92(3H,s), 3.63(1H, m), 4.98(1H, dxd, *J*=2.9, *J*=9.2), 6.93(1H, br s), 7.4(8H,m, Ar), 7.53(2H, m, Ar) and 9.04(1H, br s, OH): ^{13}C NMR (50MHz, $CDCl_3$) 162.7, 137.0, 135.7, 129.9, 128.2, 89.2, 64.5, 51.7, 47.4, 28.8, 22.0; LRMS(FAB) 327$(M+1)^+$; $[\alpha]_D^{20}$ = -126.4° (c=0.97, $CHCl_3$).

(2R,5R) *bis*(methoxymethyl)pyrrolidinocarbohydroxamic acid 4d

Same procedure as for **3a** with 2.2g(0.014mmol) of (2R, 5R)-*bis*(methoxymethyl)pyrrolidine, 5.5ml (0.07mol, 5eq.) of phosgene; yield: 1.46g (95 %) of crude N-(carbamoyl)-(2R,5R)-methoxymethyl)pyrrolidine **3d** as a colourless oil; IR(film, cm^{-1}) 1745; ^1H (200MHz, $CDCl_3$) 4.09 (2H, m), 3.50 (4H, m), 3.37 (3H, s), 3.34 (3H, s), 2.19-1.92 (4H, m); ^{13}C NMR(50MHz, $CDCl_3$) 146.5, 73.2, 71.2, 60.4, 61.3, 59.4, 28.9, 26.7;then same procedure as for **4b** with 1.46g (0.007mol, 1eq.) of carbamoyl chloride **3d**, 2.58g(0.015mol, 2.2eq) of N,O-*bis*(trimethylsilyl)hydroxylamine; yield: 0.97g(64 %); colourless oil; Rf:0.23(ethylacetate); IR(film, cm^{-1}) 3260, 1650; ^1H NMR(500MHz, $CDCl_3$) 8.65(1H, br s), 6.32(1H, br s), 4.01(2H, m), 3.44(4H, m), 3.33(6H,s), 2.05 to 1.15 (4H,m); ^{13}C(50MHz, $CDCl_3$) 161.5, 74.1, 59.0, 57.1, 26.6; m/z(E.I.) 218; E.A.($C_9H_{18}N_2O_4$) %C(49.53, found 49.50), %H(8.31, found 8.33), %N(12.84, found 12.87); $[\alpha]_D^{20}$ = +111.6°(c=0.62, CH_3OH).

(2,5)-*bis*-*t*-butyldimethylsilyloxymethyl)pyrrolidinocarbohydroxamic acid 4e

Same procedure as for **3a** with 2.0g(0.057mol) of (2,5)-*bis*-(*t*-butyldimethylsilyloxymethyl)pyrrolidine **2e**, 1.3ml (0.0184mol, 3.3eq.) of phosgene, 5ml ether; yield: 2.23g(95 %) of crude **3e** as a colourless oil; IR(film, cm^{-1}): 1740; then same procedure as for **4b**: 2.23g (0.0053mol) of carbamoyl chloride **3e**, 2.05g (0.012mol, 2.2eq.) of N,O-*bis*(trimethylsilyl)hydroxylamine; yield: 1.81g(82 %); colourless solid; m.p. 125.5° C; Rf=0.5(ethylacetate/cyclohexane, 1/2); IR(film, cm^{-1}) 3260, 1655; ^1H NMR (500MHz, $CDCl_3$) 8.72(1H,s), 6.19(1H,s), 3.98(2H, br s), 3.67(4H, br s), 2.03 to 1.76(4H,m), 0.85(18H, s), 0.11(12H, s); ^{13}C NMR (125MHz, $CDCl_3$): 161.6, 68(br s), 59.7(br s), 26.5, 25.8, 18.2, - 5.6; E.A.($C_{19}H_{42}N_2O_4Si_2$) %C(54.50, found 54.34), %H(10.11, found 10.10), %N(6.69, found 6.72); m/z(E.I.) 418.

4-(N-carbohydroxamic acid)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,$0^{3,7}$]-decane-5,5-dioxide 4f

The two steps procedure : **1st step**: 0.105g(0.002mol) of NaH 60 %; 2ml toluene; 0.5g(0.0023mol) of sultam **2f**, 0.23g(0.77mmol; 0.3eq.) of triphosgene; yield: 0.288g(51 %) of crude carbamoyl chloride **3f** ; **2nd step**: 0.225ml(0.93mmol, 2eq.) of N,O-*bis*(trimethylsilyl)hydroxylamine; 0.1g of carbamoyl chloride **3f**, cat DMAP; yield: 1.81g (82 %);

The one-pot procedure : To a solution of 1g (4.64mmol, 1eq.) of sultam **2f**, 2.43 ml (13.9 mmol, 3eq.) and iPr_2EtN in 35ml dry ether at 0° C was added in once 1.38g (4.64mmol) of triphosgene. After 15 minutes at 0° C, the reaction mixture was stirred at rt for 18 hours. 1.61g (23.2mol, 5eq.) of hydroxylamine hydrochloride was then added all at once as well as a solution of K_2CO_3 (1.92g, 13.93mmol in 5ml H_2O). After 5 hours at rt, the organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chomatography; yield: 1.08g (85 %); white solid; m.p. 250° C(dec); Rf=0.25 (ethylacetate/cyclohexane:1/1); IR (film, cm^{-1}) 3260, 1660, 1360; ^1H NMR (500MHz, $CDCl_3$) 8.30(br s, 1H), 6.80(br s, 1H), 3.87(1H, dxd, J=7.7, J=5.1), 3.39(2H,s), 2.1-1.8 and 1.5-1.2 (7H,m), 1.1 (3H,s), 0.95 (3H,s); ^{13}C NMR (50MHz, $CDCl_3$): 152.9, 64.2, 51.7, 49.5, 47.9, 44.3, 37.3, 32.1, 26.6, 20.3, 19.8; m/z(E.I.) 274 $M^{+\cdot}$; $[\alpha]_D^{20}$ = -69° (c=1.05, $CHCl_3$).

2) ASYMMETRIC CYCLOADDITIONS

General procedure: A solution of tetraethylammonium periodate in CH_2Cl_2 was added over a 15 min period to a stirred solution of hydroxamic acid and of the diene at the given temperature. After completion of the reaction (disappearance of the hydroxamic acid according to TLC), the reaction mixture was diluted with CH_2Cl_2, washed with 10 % aqueous $NaHSO_3$, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography.

3-(menthyloxycarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,1]-hept-2-ene 6a

0.2g(0.93mmol, 1eq.) of **4a**, 0.35g(1.2mmol, 1.2 eq.) of $Et_4N^+IO_4^-$, 1ml of cyclopentadiene; 0° C; d.e.=12 % estimated by quantitative ^{13}C NMR; yield: 65 %; Rf=0.49 (AcOEt/cyclohexane:3/7); IR(film, cm^{-1}) 1725; ^1H NMR (500MHz, $CDCl_3$): 6.43-6.37(2H, m), 5.24(1H,m), 5.04(1H,m),4.61(4.49*)(1H, txd, *J*=10.9, *J*=4.4), 2.00-0.75(9H, m), 0.9(0.93*) (3H, d,*J*= 7.4 (*J*=6.4*)), 0.87(0.89*)(3H, d, *J*=6.9 (*J*=6.3*)), 0.76(0.78*) (3H, d, *J*=7.0 (*J*=7.0*)); ^{13} C NMR (125MHz, $CDCl_3$): 159.4(159.2*), 134.3(134.1*), 132.9(132.8*), 83.5(83.47*), 76.4(76.6*), 65.0(64.8*), 53.0(53.1*), 51.9(52.1*), 45.9, 39.1(39.2*), 36.3(36.33*), 31.2(31.1*), 28.5(20.2*), 26.9(27.0*), 25.6(25.8*°, 21.3(20.9*) m/z(E.I.): 280$(M+1)^+$ (*: minor diastereomer).

3-(menthyloxycarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,2]-oct-2-ene 7a

0.32g(1.5mmol, 1eq) of **4a**, 0.56g(1.8mmol, 1.2eq.) of $Et_4N^+IO_4^-$,0.36g(4.5mmol, 3eq) of cyclohexadiene; rt; d.e.=20 % estimated by quantitative ^{13}C NMR; yield: 0.33g(74 %); Rf=0.6(AcOEt/cyclohexane: 3/7);); IR(film, cm^{-1}) 1725; ^1H NMR (500MHz, $CDCl_3$): 6.01(2H,m), 4.26(1H, m), 4.21(1H,m), 4.09(1H,txd,*J*=10.9, *J*=4.4), 2.00-0.75(13H, m), 0.90 (3H,d, *J*=6.5), 0.88(3H, d, *J*=7.0), 0.75 (3H, d, *J*=6.9); ^{13} C NMR (125MHz, $CDCl_3$) : 158.4(158.2*), 131.7(131.4*), 131.3(131.2*), 75.9, 70.4, 50.0, 46.8, 40.7(40.69*), 33.9, 31.1, 26.0(25.9*), 23.4, 23.0(23.3*), 21.7, 20.3(20.5*), 20.1(20.2*), 16.2(15.0*); m/z(E.I) : 293$(M)^{+\cdot}$ (* : minor diastereomer).

3-(2'S-methoxymethyl)pyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,1]hept-5-ene 6b

0.085g(0.49mmol, 1eq.) of **4b**, 0.154g(0.49mmol, 1.2 eq.) of $E_4N^+IO_4^-$, 0.12ml (0.15mmol, 3eq.) of cyclopentadiene; -25° C; d.e.= 34 %; yield: 0.083g(71 %); 2 diastereomers not separated by column chromatography ***major diastereomer***: Rf=0.46 (AcOEt); IR(film, cm^{-1}) 1680, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.58(1H, m), 6.31(1H,m), 5.05(1H,br s), 4.15(1H,m), 3.58(1H, m), 3.50(1H, dxd, *J*=9.5, *J*=3.6), 3.35(1H, m), 3.31(3H, s), 3.26(1H, dxd, *J*=9.5, *J*=7.1), 2.1-1.6(6H, m); ***minor diastereomer***:

Rf=0.57 (AcOEt); ^{1}H NMR (500MHz, $CDCl_3$) 6.47(1H, m), 6.41(1H,m), 5.12(1H,br s), 5.10(1H, br s), 4.05(1H, m), 3.66(1H, m), 3.52(1H, dxd, *J*=9.4, *J*=3.4), 3.33(3H, s), 3.24(1H, dxd, *J*=9.5, *J*=7.1), 2.1-1.6(6H, m).

3-(2'S-methoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,2]-oct-5-ene 7b
0.12g(0.7mmol, 1eq.) of **4b**, 0.22g(0.7mmol, 1.2 eq.) of $Et_4N^+IO_4^-$, 0.17g(0.2mmol, 3eq.) of cyclopentadiene; 0° C; d.e.= 72 %; recristallisation in CH_2Cl_2/ether; yield(2 diastereomers): 0.14g(80 %); 2 diastereomers separated by column chromatography (105mg major; 17mg minor) ***major diastereomer***: Rf=0.52 (AcOEt); IR(film, cm^{-1}) 1680, 1640; ^{1}H NMR (500MHz, $CDCl_3$) 6.60(1H, dxdxd, *J*=8.3, *J*=5.8, *J*=1.7), 6.53(1H, dxdxd, *J*=8.3, *J*=5.7, *J*=1.8), 4.64(1H,m), 4.62(1H, m), 4.14(1H, m), 3.62(1H, m), 3.54(1H, dxd, *J*=9.3, *J*=3.4), 3.36(1H, m), 3.34(3H, s), 3.30(1H, dxd, *J*=9.3, *J*=7.7), 2.14(2H, m), 1.86(3H, m), 1.7(1H, m), 1.49(1H, m), 1.35(1H,m); ^{13}C NMR (125MHz, $CDCl_3$): 161.9, 133.3, 131.3, 73.3, 70.2, 58.9, 57.8, 50.2, 48.4, 27.6, 24.1, 23.5, 20.1; ***minor diastereomer***: Rf=0.64(AcOEt); IR(film, cm^{-1}) 1680, 1640; ^{1}H NMR (500MHz, $CDCl_3$) 6.69(1H, dxdxd, *J*=7.5, *J*=5.8, *J*=1.6), 6.46(1H, dxdxd, *J*=8.3, *J*=5.8, *J*=1.8), 4.73(1H,m), 4.54(1H, m), 4.18(1H, m), 3.56-3.54(2H, dxd+ m, *J*=9.5, *J*=3.5), 3.45(1H,m), 3.33(3H, s), 3.28(1H, dxd, *J*=9.5, *J*=7.2), 2.14(1H, m), 2.04(1H, m), 1.96(1H, m), 1.83(1H, m), 1.77(1H, m), 1.68(1H, m), 1.51(1H, m), 1.35(1H, m); ^{13}C NMR (125MHz, $CDCl_3$): 162.9, 134.9, 130.7, 73.3, 70.4, 59.1, 57.6, 49.5, 49.4, 27.9, 24.7, 24.5, 20.1; m/z(E.I.): 252($M^{+\cdot}$).

3-(2-(α,α)-diphenylmethoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-bicyclo [2,2,2] oct-5-ene 7c
0.05g(0.153mol, 1eq.) of **4c**; 0.049(0.153mol, 1eq.) of $Et_4N^+IO_4^-$; 21.9µl(0.23mmol) of 1,3-cyclohexadiene; 2ml dry CH_2Cl_2; -70° C then 0° C; white solid; yield: 46mg (75 %) recrystallised in ethylacetate/cyclohexane (2/1); yield: 44.2mg (72 %) ; d.e.>98 % ; m.p. 140° C; IR(KBr, cm^{-1}) 2938, 1641, 1396; ^{1}H NMR (500MHz, $CDCl_3$): 0.84(1H,m), 1.41(2H,m), 1.45(1H,m), 1.90(1H,m), 2.11(1H,m), 2.17(2H,m), 2.25(1H,m), 2.31(1H,m), 2.97(3H,s), 3.31(1H,m), 4.45(1H, dxd, *J*=1.5, *J*=5.8), 4.74(1H, dxd, *J*=1.53, *J*=5.8), 5.59(1H, dxd, *J*=3.5, *J*=9.0), 6.5(1H,dxd, *J*=1.5, *J*=5.8, *J*=8.2), 6.63(1H, dxdxd, *J*=1.5, *J*=5.8, *J*=8.2), 7.2-7.5(10H, m); ^{13}C NMR(125MHz, $CHCl_3$) 20.5, 23.5, 24.1, 26.2, 50.4, 51.5, 51.9, 59.2, 70.1, 85.8, 126.9, 127.1, 127.4, 127.6, 129.4, 129.8, 130.0, 132.1, 140.9, 142.4, 163.7; LRMS(FAB) 405 $(M+1)^+$; $C_{25}H_{28}N_2O_3$: calculated: C, 74.25; H, 6.93; N, 6.93; Found: C, 74.54; H, 6.75; N, 6.95; Absolute Configuration by X-Ray: 1R, 4S, 2'S; $[\alpha]_D^{20}$ = -139.4° (c=1.25, $CHCl_3$).

1-methoxycarboxylate-3-(2-(α,α)-diphenylmethoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-bicyclo [2,2,2] oct-5-ene 8c
0.05g(0.153mol, 1eq.) of **4c**; 0.049(0.15mol, 1eq.) of $Et_4N^+IO_4^-$; 28mg(0.18mmol) of ethyl cyclohexa-1,3-diene carboxylate; 1ml dry CH_2Cl_2; -70° C then 0° C; d.e. >98 %; colourless oil; purification by column chromatography (AcOEt/dichloromethane: 20/80); yield: 29.1mg (40 %); IR(KBr, cm^{-1}) 2940, 1758, 1695, 1645, 1447; ^{1}H NMR (500MHz, $CDCl_3$): 0.71(1H,m), 1.34(3H,t, *J*=7.0Hz), 1.41(2H,m), 1.67(1H,m), 1.89(1H,m), 2.06(1H,m), 2.26(2H,m), 2.53(1H,m), 2.97(3H,s), 3.27(1H,m), 4.34(2H,m), 4.57(1H, dxd, *J*=1.4, *J*=6.3), 5.57(1H, dxd, *J*=3.1, *J*=8.9), 6.60(1H, dxd, *J*=6.3, *J*=8.2), 6.75(1H, dxd, *J*=1.4, *J*=8.2), 7.2-7.5(10H, m); ^{13}C NMR (125MHz, $CHCl_3$): 14.1, 20.6, 22.7, 23.8, 26.2, 27.6, 50.4, 51.3, 52.2, 59.9, 61.7, 68.2; 85.7, 127.0, 127.3, 127.4, 127.6, 127.8, 129.3, 129.5, 129.8, 129.9, 131.0, 132.2, 140.4, 141.9, 163.0, 169.7; $[\alpha]_D^{20}$= -74.3°(c=0.6, $CHCl_3$).

N,N,N-(hydroxy-4'cyclohexenonyl-(α,α)-diphenylmethoxymethylpyrrolidino-carbonyl)amine 9c
0.05g(0.153mol, 1eq.) of **4c**; 0.049(0.15mol, 1eq.) of $Et_4N^+IO_4^-$, 54.4µl(0.18mmol) of 1-methoxycyclohexa-1,3-diene; 2ml dry CH_2Cl_2; -50° C then 0° C; d.e. >98 %; purification by column chromatography (AcOEt/cyclohexane: 2/1); yield: 47mg (68 %); recrystallisation in CH_2Cl_2/EtOAc/cyclohexane; white solid; 42mg (65 %); m.p.197° C; IR(KBr, cm^{-1}): 3333, 2932, 1695, 1445; ^{1}H NMR (500MHz, $CHCl_3$): 1.15(1H,m), 1.56(1H,m), 1.96(2H,m), 2.46(2H,m), 2.69(1H,m), 2.97(3H,s), 3.35(1H,m), 4.42(1H, dxd, *J*=2.2, *J*=2.5), 5.6(1H, dxd, *J*=3.1, *J*=9.0), 6.2(1H, dxdxd, *J*=1.6, *J*=2.2, *J*=10.5), 6.89(1H, dxdxd, *J*=0.8, *J*=2.5, *J*=10.5), 7.02(1H, s, OH), 7.24-7.4(10H,m); ^{13}C NMR(125 MHz, $CDCl_3$): 23.8, 26.7, 27.0, 36.6, 49.8, 51.9, 58.9, 61.1, 86.4, 127.2, 127.7, 127.9,

128.0, 129.2, 129.7, 132.1, 139.4, 140.3, 149.5, 163.9, 198.1; d.e.>98 %; Absolute configuration attributed by X-ray: 1S, 2'S; $[\alpha]_D^{20}$= -160.8°(c=0.65, $CHCl_3$).

N-((α,α)-diphenylmethoxymethylpyrrolidino-carbonyl)-1-oxa-2-aza-6-methoxy-cyclohex-4-ene 10c

0.05g(0.15mol, 1eq.) of **4c**; 0.05g(0.15mol, 1eq.) of $Et_4N^+IO_4^-$; 38.8 µl(0.18mmol) of 1-methoxycyclohexa-1,3-diene; 2ml dry CH_2Cl_2; -30° C then 0° C; d.e. >98 %;purification by column chromatography (AcOEt/cyclohexane: 1/2); white foam; yield: 32mg (51 %); IR(KBr, cm^{-1}) 2975, 1654; ^1H NMR(500MHz, $CHCl_3$): 1.07(1H,m), 1.49(1H,m), 1.89(1H,m), 2.14(1H,m), 2.34(1H,m), 2.97(3H,s), 3.45(3H,s), 3.58(1H,m), 3.83(1H, dxdxd, *J*=1.5, *J*=4.9, *J*=17.1), 7.2-7.5(10H, m); ^{13}C NMR(125MHz, $CDCl_3$): 24.3, 26.4, 45.8, 49.9, 51.9, 57.7, 59.7, 86.1, 100.1, 123.4, 126.8, 126.9, 127.4, 127.5, 127.6, 129.9, 140.5, 141.5, 162.0; $[\alpha]_D^{20}$= -2.27° (c=0.75, $CHCl_3$).

3-((2'R,5'R)-*bis*(methoxymethyl)pyrrolidinocarbonyl-2-oxa-3-aza-3bicyclo-[2,2,1] hept-5-ene 6d

0.15g(0.70mmol, 1.1eq.) of **4d**, 0.27g (0.77mmol, 1.1eq.) of $Et_4N^+IO_4^-$, 0.18ml of cyclopentadiene; -25° C; d.e. crude mixture 87 % ; >98 % after purification by column chromatography; yield: 0.164g (83 %); recrystallisation in pentane afforded 101mg (51 %) of the major diastereomer as a white solid and 52mg of a mixture of both diastereomers as an oil; ***major diastereomer*** Rf:0.58 (ethylacetate); IR(film, cm^{-1}) 1680, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.40(1H, dxdxd, *J*=5.7, *J*=3.7, *J*=1.9), 6.35(1H, dxdxd, *J*=5.6, *J*=4.4, *J*=2.0), 5.12(2H,m), 4.23(2H,m), 3.43(2H, dxd, *J*=9.4, *J*=3.2), 3.3(6H,s), 3.22(2H, dxd, *J*=9.3, *J*=7.9), 1.98(2H,m), 1.86(2H,m), 1.80(1H,m), 1.70(1H,m); ^{13}C NMR (125MHz, $CDCl_3$): 161.3, 134.9, 134.6, 83.2, 72.5, 64.5, 58.9, 57.7, 48.1, 25.8; Absolute configuration: 1S, 4R, 2'R, 5'R; $[\alpha]_D^{20}$ = +149.5° (c=0.19, CH_3OH); ***minor diastereomer*** (colourless oil): Rf:0.54(ethylacetate); IR(film, cm^{-1}) 1680, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.45(1H, dxdxd, *J*=5.45, *J*=2.16, *J*=1.00), 6.39(1H, dxdxd, *J*=5.7, *J*=4.4, *J*=1.0), 5.08(1H,m), 5.03(1H,m), 4.04(2H,m), 3.49(2H, dxd, *J*=9.4, *J*=3.2), 3.35(6H,s), 3.20(2H, dxd, *J*=9.4, *J*=8.4), 2.10-1.70(6H,m); Absolute configuration: 1R, 4S, 2'R, 5'R; m/z(E.I.): 282(M^+).

3-((2'R,5'R)-*bis*(methoxymethyl)pyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo [2,2,2] oct-5-ene 7d

0.12g(0.55mmol, 1eq.) of **4d**, 0.2g (0.63mmol, 1.1eq.) of $Et_4N^+IO_4^-$, 0.16ml (.189mmol, 3eq.) of cyclohexadiene; rt; d.e. >98 %; yield: 0.143g(88 %); Rf:0.48(ethylacetate); IR(film, cm^{-1}) 1680, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.58(1H, dxdxd, *J*=8.2, *J*=5.7, *J*=1.7), 6.52(1H, dxdxd, *J*=8.2, *J*=6.1, *J*=1.6); 4.7(2H,m), 4.23(2H,m), 3.41(2H, dxd, *J*=9.3, *J*=8.0), 3.33(6H,s), 3.21(2H, dxd, *J*=9.3, *J*=5.4), 2.15(2H,m), 1.98(2H,m), 1.86(2H,m), 1.45(2H,m); ^{13}C NMR (125MHz, $CDCl_3$): 159.9, 131.7, 131.3, 72.9, 70.3, 58.8, 57.8, 50.7, 25.6, 23.4, 20.4; Absolute configuration: 1S, 4R, 2'R, 5'R; $C_{15}H_{24}N_2O_4$: Calculated: C, 60.79; H, 8.16; N, 9.45, Found: C, 60.81; H, 8.20; N, 9.49; $[\alpha]_D^{20}$ = +106.8° (c=1.24, CH_3OH); m/z(E.I.): 296(M^+).

Diastereomer (1R, 4S, 2'R, 5'R) prepared by independent synthesis IR(film, cm^{-1}) 1680, 1640; Rf: 0.65(ethylacetate); ^1H NMR (500MHz, $CDCl_3$) 6.68(1H, dxdxd, *J*=8.3, *J*=5.7, *J*=1.6), 6.47(1H, dxdxd, *J*=8.3, *J*=5.8, *J*=1.8); 4.77 (1H,m), 4.57 (1H,m), 4.36(2H,m), 3.47(2H, dxd, *J*=9.3, *J*=3.3), 3.33(6H, s), 3.19(2H, dxd, *J*=0.3, *J*=8.4), 2.13(1H,m), 2.03(1H,m), 1.95(2H,m), 1.84(2H,m), 1.51(1H,m), 1.35(1H,m); ^{13}C NMR (125MHz, $CDCl_3$): 161.6, 134.9, 130.7, 72.2, 70.4, 58.9, 57.8, 49.3, 25.6, 24.5, 20.2; Absolute configuration: 1R, 4S, 2'R, 5'R.

3-((2'R,5'R)-*bis*(methoxymethyl)pyrrolidinocarbonyl-2-oxa-3-aza-3-bicyclo [3,2,2] non-5-ene 11d

0.176g(0.81mmol, 1eq.) of **4d**, 0.176g (0.89mmol, 1.1eq.) of $Et_4N^+IO_4^-$, 0.084g(0.89mmol, 1eq.) of cycloheptadiene; rt; d.e.>98 %; yield: 0.18g(70 %); Rf:0.45(ethylacetate); recrystallisation in pentane; IR(film, cm^{-1}) 1680, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.24(1H, m), 4.76(1H, m), 4.71(1H,m), 4.23(2H,m), 3.41(2H, dxd, *J*=9.1, *J*=3.2), 3.32(6H,s), 3.21(2H, dxd, *J*=9.2, *J*=8.1), 2.10-1.3(10H,m); ^{13}C NMR (125MHz, $CDCl_3$): 158.6, 127.8, 74.9, 73.1, 58.9, 57.9, 55.3, 31.1, 27.9, 25.7, 18.5; Absolute configuration: 1S, 4R, 2'R, 5'R; $C_{16}H_{26}N_2O_4$: Calculated: C, 61.91; H, 8.44; N, 9.03, Found: C, 61.95; H,

8.47; N, 9.07; $[\alpha]_D^{20}$ = +94.9 ° (c=0.69, CH_3OH); Absolute configuration: 1S, 4R, 2'R, 5'R; m/z(E.I.): 310($M^{+\cdot}$).

N-(1'S,4'R-hydroxycyclohex-2'-en)-2,5-*bis*(methoxymethyl)pyrrolidino-carboxamide 12
To a solution of 0.115g(0.39mmol) of **7d** in 3 ml of dry methanol was added portionwise 1.2g of 5 % Na/Hg; After 25 minutes, the reaction mixture was filtered on celite; After evaporation under reduced pressure, the solid residue was crystallised in EtOAc; yield:0.094g(81 %); white solid; m.p. 104.2° C; Rf:0.34 (ethylacetate); IR(film, cm^{-1}) 3350, 1640; ^1H NMR (500MHz, $CDCl_3$) 6.68(1H, dxdxd, *J*=7.5), 5.78(2H,m), 4.28(1H,m), 4.18(1H,m), 3.95(2H,m), 3.55(2H,m), 3.34(2H,m), 3.3(6H,s), 2.25(1H, br s), 2.05-1.50(8H,m); ^{13}C NMR (125MHz, $CDCl_3$): 156.8, 131.8, 131.5, 75, 64.9, 58.8, 57.3, 45.1, 28.9, 27.1, 26.2; Absolute configuration: 1'S, 4'R, 2R, 5R; $C_{15}H_{26}N_2O_4$: Calculated: C, 60.38; H, 8.78; N, 9.39, Found: C, 60.41; H, 8.82; N, 9.45; $[\alpha]_D^{20}$ = +151.73° (c=0.66, CH_3OH); m/z(E.I.) 298($M^{+\cdot}$).

3-(2,5-*bis*(*t*-butyldimethylsilyloxy)pyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,2]oct-5-ene 7e
0.1g(0.24mmol, 1eq.) of **4e**, 0.12g (0.72mmol, 1.5eq.) of $Et_4N^+IO_4^-$, 0.07g(0.72mmol, 3eq.) of cyclohexadiene; rt; d.e. >98 %; yield: 0.097g(82 %); Rf:0.47(ethylacetate:cyclohexane/3:7); IR(film, cm^{-1}) 1660; ^1H NMR (500MHz, $CDCl_3$) 6.54(1H, dxdxd, *J*=8.2, *J*=5.8, *J*=1.7), 6.47(1H, dxdxd, *J*=8.2, *J*=6.2, *J*=1.6), 4.63(1H,m), 4.88(2H,m), 3.61(2H, dxd, *J*=9.71, *J*=3.29), 3.38(2H, dxd, *J*=9.7, *J*=7.4), 2.15(2H,m), 1.94-1.84(4H,m), 1.37(2H,m), 0.86(18H,s), 0.018(6H,s), 0.071(6H,s); ^{13}C NMR (125MHz, $CDCl_3$) : 160.1, 131.9, 131.3, 70.3, 63.4, 60.2, 50.8, 25.9, 25.3, 23.6, 20.6, 18.3, -5.34; Absolute configuration: 1S, 4R, 2'R, 5'R; m/z(E.I.): 496($M^{+\cdot}$).

4-(2'-oxa-3'-aza-bicyclo[2,2,1]hept-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,03,7]decane-5,5-dioxide 6f
0.1g(0.36mmol, 1eq.) of **4f**, 0.176g(0.54mmol, 1.5eq.) of $E_4N^+IO_4^-$, 0.3ml(3.6mmol, 10eq.) of cyclopentadiene; 0° C during 10min; d.e. >98 %; recristalisation in CH_2Cl_2/ether; yield: 0.11g(91 %); m.p. 160° C (dec); Rf=0.33 (AcOEt/cyclohexane:1/1); IR(film, cm^{-1}) 1720, 1340; ^1H NMR(500MHz, $CDCl_3$) 6.47(1H, dxdxd, *J*=5.5, *J*=4.0, *J*=1.6), 6.23(1H, dxdxd, *J*=5.5, *J*=3.9, *J*=2.1), 5.55(1H,m), 5.35(1H,m), 3.99(1H, dxd, *J*=7.7, *J*=4.3), 3.44(2H,s), 2.13(1H,m), 1.9(3H,m), 1.8-1.7(2H,m), 1.46(1H,m), 1.35(2H,m), 1.25(3H,s), 0.99(3H,s); ^{13}C NMR (125MHz, $CDCl_3$): 156.1, 133.5, 131.3, 84.6, 69.0, 64.9, 52.7, 48.5, 48.3, 47.9, 44.7, 37.2, 32.4, 26.7, 20.5, 19.9; Absolute configuration: 7S, 1'R, 4'S; $[\alpha]_D^{20}$ = -89.4° (c=0.06, CH_3OH); m/z(FAB): 677(2M+1).

4-(2'-oxa-3'-aza-bicyclo[2,2,2]oct-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,03,7]decane-5,5-dioxide 7f
0.1g(0.36mmol, 1eq.) of **4f**, 0.176g(0.54mmol, 1.5eq.) of $E_4N^+IO_4^-$, 0.3ml(3.6mmol, 10eq.) of cyclohexadiene; 0° C; d.e. >98 %; recristallisation in AcOEt; mp 195-200° C(dec); Rf:0.42(AcOEt/cyclohexane:1/1); IR(film, cm^{-1}) 1710, 1345; ***diastereomer 7S, 1'R, 4'S*** : ^1H NMR(500MHz, $CDCl_3$) 6.60(1H, dxdxd, *J*=8.2, *J*=5.8, *J*=1.8), 6.39(dxdxd, *J*=8.2, *J*=5.9, *J*=1.8); 4.99(1H,m), 4.87(1H,m), 4.01(1H, dxd, *J*=7.7, *J*=4.3), 3.39(2H,s), 2.34-2.23(2H,m), 1.93(1H,m), 1.90(1H,m), 1.88(1H,m), 1.80(1H,m), 1.83(1H,m), 1.47(2H,m), 1.30(2H,m), 1.21(3H,s), 0.97(3H,s); ^{13}C NMR (125MHz, $CDCl_3$): 154.7, 132.3, 129.4, 71.6, 65.1, 54.1, 52.7, 48.5, 47.9, 44.7, 37.4, 32.5, 26.7, 23.2, 20.7, 20.5, 19.9; Absolute configuration: 7S, 1'R, 4'S; $C_{25}H_{28}N_2O_3$: calculated: C, 57.93; H, 6.86; N, 7.95; S,9.10 Found: C, 57.84; H, 6.94; N, 7.84; S,9.20; $[\alpha]_D^{20}$ = -57.9° (c=0.66, $CHCl_3$); m/z(E.I.) 353(M+1); ***Diastereomer 7S, 1'S, 4'R prepared by the independent synthesis*** ^1H NMR(500MHz, $CDCl_3$) 6.69(1H, dxdxd, *J*=8.2, *J*=6.0, *J*=1.6), 6.54(1H, dxdxd, *J*=8.3, *J*=5.7, *J*=1.6); 5.03(1H,m), 4.83(1H,m), 4.10(1H, dxd, *J*=7.5, *J*=4.8), 3.36 and 3.34(2H, AB, *J*=13.5), 2.40-2.20(2H,m), 2.09(1H,m), 1.96-1.80(4H,m), 1.47(2H,m), 1.26(2H,m), 1.20(3H,s), 0.97(3H,s); ^{13}C NMR (125MHz, $CDCl_3$): 154.3, 133.3, 131.9, 71.5, 66.7, 53.3, 51.1, 48.3, 47.6, 45.4, 38.2, 33.3, 26.4, 23.6, 21.5, 20.8, 19.9.

4-(1'-methoxycarbonyl-2'-oxa-3'-aza-bicyclo[2,2,2]oct-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,03,7]decane-5,5-dioxide 8f
0.24g(1.5mmol, 1.5eq) of methyl cyclohexa-1,3-dienecarboxylate, 0.3g(1eq) of **4f**, 1 eq. of $E_4N^+IO_4^-$; yield:75 %; -20° C; d.e.>98 %; m.p.: 155.5° C (dec); IR(film, cm^{-1}) 1740, 1720, 1340; ^1H NMR (500MHz, $CDCl_3$) 6.79 (1H, dxd, *J*=8.3, *J*=1.7), 6.45(1H, dxd, *J*=8.3, *J*=5.9); 5.04(1H,m), 4.32(2H, m), 3.98(2H, dxd, *J*=7.6, *J*=4.4), 3.4(2H,s),2.50-2.30(2H, m), 2.00-1.40(9H, m), 1.35(3H, t, *J*=7.13), 1.19(3H, s), 0.97(3H, s); ^{13}C NMR (125MHz, $CDCl_3$): 168.8, 154.9, 131.9, 129.4, 78.0, 64.8, 61.9, 54.4, 52.5, 48.3, 47.7, 44.4, 37.2, 32.2, 27.7, 26.5, 20.4, 20.3, 19.7, 13.9; $C_{20}H_{28}N_2O_6S_1$: Calculated: C, 56.58; H, 6.65; N, 6.60, Found: C, 56.46; H, 6.61; N, 6.55; ; $[\alpha]_D^{20}$ = -83.1° (c=1.00, $CHCl_3$); m/z(E.I.) 425(M, 100 %).

(1R, 4S)-N-acetyl-3-aza-2-oxabicyclo[2,2,2] oct-5-ene 13
From adduct **7f**: To a solution of **7f** (100 mg) in THF was added H_2O_2 (30 % solution in water) and then a solution of LiOH in H_2O. After stirring at r.t. for 24h, $Na_2S_2O_4$ was added and the mixture was extracted twice with ethylacetate. After evaporation, the residue was treated with CH_3COCl and Et_3N; yield: 15mg (35 %); From adduct **7c**: Adduct **7c** (100mg) was dissolved in a solution of HCl 5M in MeOH; the solution was refluxed in a sealed vial; After 10h, the mixture was evaporated and the residue treated with CH_3COCl and Et_3N; yield: 9mg (28 %); ^1H NMR(200MHz): 6.69-6.40(m, 2H), 1.98(s, 3H), 1.67-1.39(m, 2H).

Acknowledgements

This work was generously supported by the Ministère de l'Education et de la Recherche Scientifique de la Communauté française de Belgique (Action Concertée 86/91-84), by the "Fonds pour la formation à la Recherche dans L'industrie et dans l'Agriculture" (fellowship to C.M.) and by the University of Louvain (assistantship to V.G., fellowships to D.B. and S.McC). This text also presents research results of the Belgian programme on Interuniversity Poles of Attraction initiated by the Belgian State, Prime Minister's Office, Science Policy Programming.

REFERENCES

1. (a) Sabrini, M.; Kresze, G.; Braun, H. *Tetrahedron Lett.* **1984**, *25*, 5377; (b) Felber, H.; Kresze, G.; Braun, H.; Vasella, A. *Tetrahedron Lett.* **1984**, *25*, 5381; (c) Felber, H.; Kresze, G.; Prewo, R.; Vasella, A. *Helv. Chim. Acta.* **1986**, *69*, 1137; (d) Braun, H.; Charles, R.; Kresze, G.; Sabuni, M.; Winlker, J. *Liebigs Am. Chem.* **1987**, 1129; (e) Defoin, A.; Sarazin, H.; Streith, J. *Tetrahedron* **1997**, *53*, 13769.
2. Gouverneur, V.; Ghosez, L. *Tetrahedron* **1996**, *21*, 7585.
3. (a) Kirby, G.W.; Nazeer, M. *Tetrahedron Lett.* **1988**, *29*, 6173; (b) Kirby, G.W.; Nazeer, M. *J. Chem. Soc. Perkin Trans. I* **1993**, *13*, 1397; (c) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, *75*, 109; (d) Miller, A.; Mc Paterson, T.C.; Procter, G. *Synlett* **1989**, 32; (e) Choy, W.; Reed, L.A.; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137.
4. Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, *75*, 109; Brouillard-Poichet, A.; Defoin, A.; Streith, J. *Tetrahedron Lett.* **1989**, *30*, 7061.
5. Gouverneur, V.; Ghosez, L. *Tetrahedron:Asymmetry* **1990**, *6*, 363.
6. Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron:Asymmetry* **1991**, *12*, 1173.
7. Banks, R.; Brookes, R.F.; Godson, D.H. *J. Chem. Soc. Perkin Trans I* **1975**, 1836.
8. (a) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *39*, 5349; (b) see also : Defoin, A.; Pires, J.; Tissot, I.; Tschamber, T.; Bar, D.; Zehnder, M.; Streith, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1209.
9. We thank Prof. Declercq, J.P. and Dr. Tinant, B. for the crystallographic studies.
10. Declercq, J.P., Gouverneur, V. *Bull. Soc. Chim. Belg.* **1996**, *6*, 359.

11. (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603; (b) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1535.
12. Tatewaki, H.; Huzinaga, S.; *J. Comp. Chem.* **1980**, *1*, 205.
13. Dive, G.; Dehareng, D.; Ghuysen, J.M. *Theoret. Chim. Acta* **1993**, *85*, 409.
14. Hehre, W.J.; Ditchfield, R.; Pople, J.A. *J. Chem. Phys.* **1972**, *56*, 3265.
15. Frisch, M.-J.; Pople, J.A.; Binkley, J.S. *J. Chem. Phys.* **1984**, *80*, 3265.
16. Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* **1992**, *33*, 3583.
17. (a) Shustov, G.V.; Rauk, A. *Tetrahderon Lett.* **1995**, *36*, 5449; (b) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 103.
18. Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1535.
19. Seebach, D.; Kalonowski, H.O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; Dupreez, N.P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301.
20. Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L.J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1988**, *97*, 691.
21. (a) Kawanami, Y.; Kitagawa, T.; Tamiguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *24*, 857; (b) Chen, L.Y.; Tran, T.V.; Schils, D.; Perry, M. ; Ghosez, L. unpublished results.
22. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397; (b) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035.
23. Hünig, S.; Kahanek, H. *Chem. Ber.* **1957**, *90*, 238.
24. Gaussian 94, Revision D.4, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Gill, P.M.W.; Johnson, B.G.; Robb, M.A.; Cheeseman, J.R.; Keith, T.; Petersson, G.A.; Montgomery, J.A.; Raghavachari, K.; Al-Laham, M.A.; Zakrzewski, V.G.; Ortiz, J.V.; Foresman, J.B.; Cioslowski, J.; Stefanov, B.B.; Nanayakkara, A.; Challacombe, M.; Peng, C.Y.; Ayala, P.Y.; Chen, W.; Wong, M.W.; Andres, J.L.; Replogle, E.S.; Gomperts, R.; Martin, R.L.; Fox, D.J.; Binkley, J.S.; Defrees, D.J.; Baker, J.; Stewart, J.P.; Head-Gordon, M.; Gonzalez, C. and Pople, J.A. Gaussian, Inc., Pittsburgh PA, **1995**.