Tetrahedron: Asymmetry Vol. 2, No. 12, pp. 1209-1221, 1991
Printed in Great Britain

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

Single and Double Asymmetric Induction in Diels-Alder Cycloadditions with Chiral Acylnitroso Dienophiles

Albert Defoin[a], Joaquim Pires[a], Isabelle Tissot[a], Théophile Tschamber[a], Daniel Bur[b], Margareta Zehnder[b], Jacques Streith[a]*

[a] Ecole Nationale Supérieure de Chimie, 3, rue Alfred Werner F-68093 Mulhouse Cédex, FRANCE.

[b] Institut für Anorganische Chemie, Universität Basel, Spitalstrasse 51, CH-4056 Basel, SWITZERLAND.

(*Received* 24 *September* 1991)

Abstract : Diels-Alder reaction of the achiral 1-silyloxybutadiene **1a** with the chiral acylnitroso dienophile **2a** gave cycloadduct **4** in high diastereomeric excess (*d.e.* > 98 %), a result which is undoubtedly due to the C-2 symmetrical chiral dimethylpyrrolidine inductor. Excellent *d.e.* was also observed when the (R)-prolinol dienophile **2d** was reacted with the chiral diene **1b** (*d.e.* = 96 %), whereas cycloaddition of the (S) enantiomer **2e** with **1b** gave only poor asymmetric induction (*d.e.* = 4 %). These two latter examples nicely illustrate the influence of "matched pair" (**1b/2d**) *versus* "mismatched pair" (**1b/2e**) upon double asymmetric induction. All herein reported Diels-Alder cycloadditions were regiospecific.

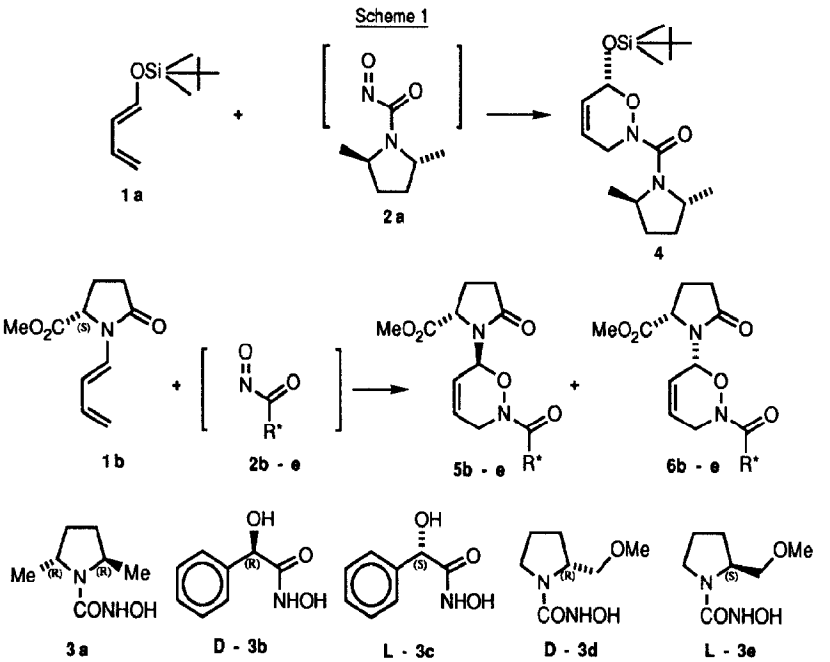
Introduction. - Single asymmetric Diels-Alder cycloadditions can in principle be achieved according to the following three methodologies : i) with a chiral diene ; ii) with a chiral dienophile ; iii) with a chiral Lewis acid catalyst. The concept of *double asymmetric induction* has been developed by S. Masamune who made use of a combination of any two of the above cited three methodologies[1]. In actual fact double asymmetric induction in Diels-Alder reactions are mostly performed by letting a chiral diene react with a chiral dienophile. Along these lines it was found that a given enantiomer (of, say, a diene) may lead to a pronounced diastereoselectivity when reacted with one enantiomer of a given dienophile, whereas reaction with the second enantiomer led to a strongly reduced diastereoselectivity. By convention the first pair of reactants is called a *matched pair*, the second one a *mismatched pair*[1].

We describe herein two types of stereospecific syntheses, the primary step being in all instances an asymmetric hetero-Diels-Alder cycloaddition with a chiral acylnitroso dienophile. The first approach we used is a *single asymmetric Diels-Alder cycloaddition* in which the achiral 1-siloxybutadiene **1a**[2] was reacted with the chiral acylnitroso dienophile **2a**. The handedness of **2a** is due to the C-2 symmetrical 2,5-dimethyl-pyrrolidine[3]. This latter type of chiral acylnitroso dienophiles is known to lead to excellent asymmetric induction (*d.e.* values of up to 99 %)[4,5].

In the second approach one takes advantage of *double asymmetric synthesis*, as defined above, by using : i) enantiomerically pure acylnitroso dienophiles **2b/2c**, and **2d/2e**, which were easily formed from D- and L-mandelic acid, and from D- and L-O-methylprolinol, respectively[6] ; ii) enantiomerically pure N-dienyl-L-methylpyroglutamate **1b** as the common and unique chiral diene partner[7,8]. When reacted with cyclohexa-1,3-diene (achiral partner) the chiral acylnitroso dienophiles **2b/2c** and **2d/2e** were known to give the expected cycloadducts with moderate asymmetric induction : *d.e.* = 58-75 % with **2b/2c**[6,9], *d.e.* = 68 % with **2d/2e**[6,10]. As to the chiral diene **1b**, when reacted with achiral acylnitroso dienophiles, it was shown to lead to *d.e.* values of up to 84 %[7].

The acylnitroso derivatives **2a-2e** are highly reactive and short-lived entities. They must be prepared *in situ* (in the presence of their diene partners) by oxidation of the corresponding hydroxamic acids **3a-3e** with tetra-n-propylammonium periodate in chloroform or in methylene chloride[11].

Scheme 1



Asymmetric Diels-Alder cycloaddition reactions. - Cycloaddition of siloxydiene **1a** with the dimethylpyrrolidine dienophile **2a** gave cycloadduct **4** as the only reaction product (*d.e.* > 98 %). This result is reminiscent of those reported recently when **2a** had been reacted with cyclohexadiene[5]. In both instances asymmetric induction proved to be excellent.

As to double asymmetric induction with diene **1b** ((S) configuration), it proved to be strongly dependent on the (R) or the (S) configuration of the dienophiles (see **Table 1**). Asymmetric induction turned out to be poor when **1b** was reacted with the L-mandelic acid derivative **2c** ((S) configuration) or with the L-O-methyl-prolinol derivative **2e** ((S) configuration), since the corresponding diastereomers **5c/6c** and **5e/6e** were formed in about equal amounts (**Table 1**).

When using the enantiomeric dienophiles ((R) configuration), *i.e.* **2b** and **2d**, the results were quite different. Dienophile **2b** led to a moderate asymmetric induction which proved to be similar in magnitude to the one observed with cyclohexadiene[6,9]. As to cycloaddition of diene **1b** with dienophile **2d**, it turned out to be almost diastereospecific (*d.e.* = 96 %), the minor cycloadduct **6d** being formed in trace amounts only (*ca.* 2 %). The pronounced discrepancy which is observed when comparing these two series is best explained by considering the results which had been obtained when **1b** was reacted with the acylnitroso derivative of phenylacetic acid whose structure is comparable to mandelic acid. In this latter instance the asymmetric induction was poor too[7].

Since single asymmetric induction was quite acceptable when **1b** was reacted with the achiral carbamoyl derivative Me_2N-CO-N=O (*d.e.* = 84 %)[2], the concept of double asymmetric induction[1] was expected to lead to a high *d.e.* value when using a chiral carbamoyl dienophile. This could be nicely checked with the chiral dienophile **2d** which forms a *matched pair* with the chiral diene **1b** (*d.e.* = 96 %) : clearly steric interactions in the transition state leading to **5d** must be minimized. The *mismatched pair*, *i.e.* **1b** and **2e**, was then predicted to lead to a poor asymmetric induction, which is indeed observed (*d.e.* = 2 %).

The same concept seems to apply - to a lesser extend though - to the mandelic acid series, the *matched pair* being **1b** + **2b** (*d.e.* = 46 %), the *mismatched pair* **1b** + **2c** (*d.e.* = 10 %).

Table 1. - *Single asymmetric cycloaddition of achiral diene* ***1a*** *with chiral dienophile* ***2a****, and double asymmetric induction of chiral diene* ***1b*** *with chiral dienophiles* ***2b-2e****.*

Dienes	Chiral dienophiles	Cycloadducts formed	Relative amounts (%)[a]	*d.e.* (%)
1a	**2a**	**4**	> 99	>98
1b	**2b**	**5b/6b**	73:27	46
1b	**2c**	**5c/6c**	55:45[b]	10
1b	**2d**	**5d/6d**	98:2	96
1b	**2e**	**5e/6e**	52:48[b]	4

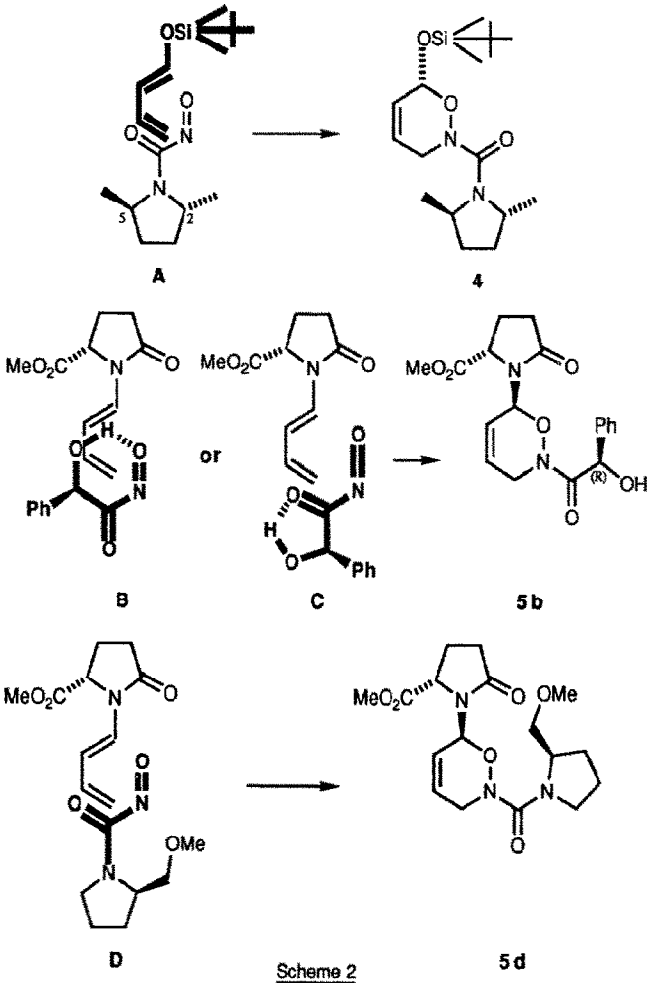
a) as determined by ^{13}C-NMR on the crude reaction products

b) or *vice versa*.

Mechanistic interpretations. - The absolute configuration has been established for adducts **4**, **5b** and **6b** (see below : last chapter). Therefore we feel entitled to propose reasonable geometries for the transition states (**TS**) which lead to these cycloadducts. With one prerequisite though : *endo* approach is postulated in all instances, since secondary orbital interactions should occur between the diene-MO and the acyl-MO (of the acylnitroso partner).

Single asymmetric induction. - Along this line of thought the absolute stereostructure of **4** can only be accounted for if the dienophile reacts from its *s-cis* conformation, as depicted in the postulated transition state **A** (**Scheme 2**) : Me-C(2) plays the dominant role as a directing group, the diene approaching from the less hindered side. A very similar interpretation had also been reached to account for the asymmetric cycloaddition of chiral carbamoylnitroso dienophiles with cyclohexadiene[4,5,6,10].

Double asymmetric induction with the D-mandelic acid series. - As described above, only in the D-series of the mandelic acid derivatives does one observe a certain degree of asymmetric induction (*d.e.* = 46%). The absolute stereostructure of the major cycloadduct **5b** being known (see below), we postulate either geometry **B** or geometry **C** for the transition state which leads to **5b**, steric interactions being kept at a minimum in both instances. The conformation of the chiral diene **1b**, has already been discussed in a previous paper;[7] the amide of the γ-lactam should be coplanar, and in the *s-trans* conformation, with respect to the butadienyl moiety, as indicated in **B** and **C** (**Scheme 2**). The conjugation is then strongest between these two π-functionalities[12].



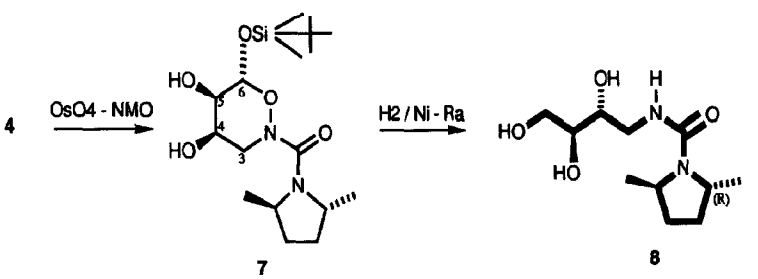
Scheme 2

Intramolecular hydrogen bonding of the D-mandelic acid derivative **2b** induces a conformational stiffening, either in the *s-trans* conformation which leads to **TS B**, or in the *s-cis* conformation which leads to **TS C**. Both H-bonded conformations of **2b** permit to explain the formation of the major cycloadduct **5b**. Some similar conclusions had been reached in order to explain the asymmetric Diels-Alder cycloaddition of **2b** with cyclohexadiene[6].

Double asymmetric induction with the O-methylprolinol series. - The absolute stereostructure of the major cycloadduct **5d** is not known with certainty. Nevertheless two arguments point to the absolute configuration as depicted in **5d (Scheme 2)** : i) let us assume an *s-trans* conformation between the amide and the butadienyl moieties of **1b**, as already discussed above ; ii) by analogy with the *s-cis* conformation of **2a** (Diels-Alder **TS**), let us assume that the acylnitroso dienophile occurs in its *s-cis* conformation too. It follows that the most likely **TS** for the cycloaddition of **1b** with **2d** is as indicated in **D (Scheme 2)**, with steric interactions being kept at a minimum in the D-series only.

Synthesis of chiral aminoerythritol 8. - Starting from the major Diels-Alder cycloadduct **4**, the reaction sequence leading to the expected aminoerythritol **8** was straightforward[2]. *cis*-Hydroxylation of **4** was achieved with OsO_4 (catalytic amounts) in the presence of N-methylmorpholine N-oxide (NMO) as the cooxidant. It led to **7** in which the *cis*-diol functionality is *anti* with respect to the silyloxy group. Raney nickel catalysed hydrogenolysis of the N-O bond, followed by two consecutive reaction steps (i) elimination of the silyloxy group ; ii) catalytic reduction of the ensuing aldehyde) gave ultimately the expected chiral L-amino-1-desoxy-erythritol derivative **8**.

Scheme 3



7 8

Structural analyses. - That all Diels-Alder cycloadducts *i.e.* **4**, **5b-5e**, and **6b-6e** - which are described herein, are formed diastereospecifically could easily be demonstrated by ^{13}C-NMR (see **Table 3**). In all instances the methylene C(3) atom appears at δ 40-45 ppm, proving thereby that it is connected to the N-atom of the former nitroso dienophile.

Conformation and stereostructure of diol **7** was ascertained in a straightforward manner by ^1H-NMR (**Table 2**) : a large $^3J_{5,6}$ and a rather small $^3J_{4,5}$ are measured : clearly H-C(5) and H-C(6) are in a *trans*-, C(4) and H-C(5) in a *cis*-topology.

The absolute stereostructures of diol **7** and of the minor cycloadduct **6b** were ascertained by X-ray diffraction analyses (**Figure 1** and **Figure 2**).

Table 2 : ^{1}H-NMR -Data of adducts **4**, **5b-e**, **6b-e**[a] and of diol **7** . 250 MHz, *CDCl3* ; δ *in ppm, J in Hz, internal standard TMS.*

	Hax-C(3)	Heq-C(3)	H-C(4)	H-C(5)	H-C(6)	H-C(3')	H-C(5')	CO_2Me	H-C(2")	H-C(5")	CH_2-C(2")	OMe	Other data	T(K)
4	4.16	3.68	5.98	5.69	5.47	-	-	-	4.39	4.39	-	-	SiMe2:0.15;tBu:0.92,Me-C(2"),Me-C(5"): 1.15,H-C(3"),H-C(4"):1.49,2.11	
5b	4.16	4.26	6.04	5.66	6.22	2.40,2.10	3.97	3.69	5.46	-	-	-	Ar:7.2-7.4,OH:2.22,H-C(4'):1.49,1.72	323
6b	4.05	4.18	6.15	5.63	5.68	2.82,2.39	4.18	3.75	5.41	-	-	-	Ar:7.3-7.4,OH:4.16,H-C(4'):2.1-2.4	323
5c or **6c**,A[b]	3.92	4.54	6.06	5.69	6.05	2.5	4.35	3.74	5.36	-	-	-	Ar:7.3-7.4,OH:1.44,H-C(4'):2.05,2.5	303
6c or **5c**,B[b]	3.71	4.59	6.14	5.67	6.26	2.75,2.43	4.19	3.31	5.48	-	-	-	Ar:7.2-7.4,OH:3.77,H-C(4'):2.1-2.3	328
5d	4.02	3.90	6.13	5.61	6.16	2.58, 2.3	4.55	3.75	4.23	3.58,3.46	3.56,3.33	3.34	H-C(4'),H-C(3"),H-C(4"):1.7-2.3	323
6d	3.83		6.19	5.46	6.26	2.74,2.40	4.21	3.67	4.23	3.52	3.52,3.37	3.33	H-C(4'),H-C(3"),H-C(4"):1.6-2.2	328
5e or **6e**,A[b]	3.89		6.11	5.61	6.27	2.57,2.40	4.39	3.76	4.20	3.51	3.51,3.35	3.35	H-C(4'),H-C(3"),H-C(4"):2.35,1.7-2.0	303
6e or **5e**,B[b]	3.80	4.09	6.23	5.61	6.15	2.78,2.39	4.23	3.69	4.19	3.55-3.35	3.58,3.33	3.34	H-C(4'),H-C(3"),H-C(4"):1.7-2.5	303
7	3.39	4.29	4.05	3.36	4.77	-	-	-	4.34	4.34	-	-	SiMe2:0.17;tBu:0.94;Me-C(2"),Me-C(5"): 1.17,H-C(3"),H-C(4"):1.55,2.13	300

	J3ax,3eq	J3ax,4	J3eq,4	J3ax,5	J3eq,5	J3ax,6	J3eq,6	J4,5	J4,6	J5,6
4	17.8	3.1	3.7	2.0	1.9	2.1	1.8	10.2	1.1	2.4
5b[c]	18.1	3.2[d]		2.2[d]		2.2[d]		10.4	1.8	3.0
6b	18.0	3.1	3.3	2.3	2.1	2.2	1.8	10.2	1.4	3.0
5c or **6c**,A	18.1	2.4	3.8	2.1	2.1	2.1	1.2	10.3	1.4	3.6
5c or **6c**,B	17.8	1.9	4.5	2.2	2.2	2.9	nd	10.4	1.8	2.5
5d	17.8	3.2	3.7	2.2	2.2	2.4	2.0	10.2	1.8	3.0
6d	17.4	3.2[d]		2.6[d]		2.3[d]		10.0	2.0	2.6
5e or **6e**,A	nd	3.2[d]		2.1[d]		2.5[d]		10.2	1.8	2.3
5e or **6e**,B	17.9	2.7	4.0	2.1	2.1	2.6	1.8	10.2	1.8	2.6
7	15.2	2.1	2.4	-	-	-	-	3.7	-	7.7

a) C(') refers to the pyroglutamate moiety, C(") to the pyrrolidine or mandelic acid moiety
b) A is the isomer of highest Rf, B the isomer of lowest Rf
c) for the pyroglutamate moiety (the a index refers to the more shielded protons) : J3'a,3'b=17.0 ; J4'a,4'b=13.2 ; J3'a,4'a=9.4 ; J3'a,4'b=2.2 ; J3'b,4'a=11.3 ; J3'b,4'b=9.1 ; J4'a,5'=9.4 ; J4'b,5'=1.8
d) mean values

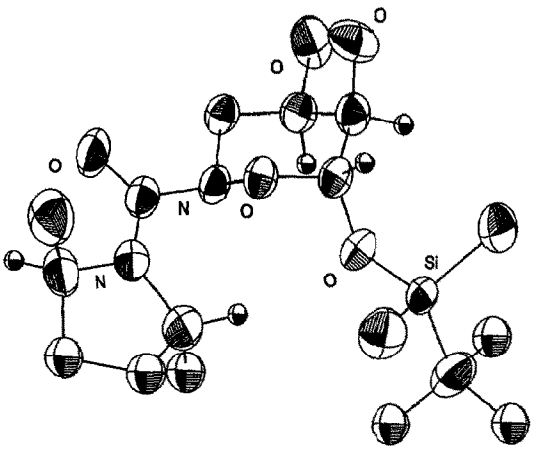


Figure 1.- *ORTEP* plot of **7** : 50 % probability ellipsoids. Most H-atoms omitted for clarity.

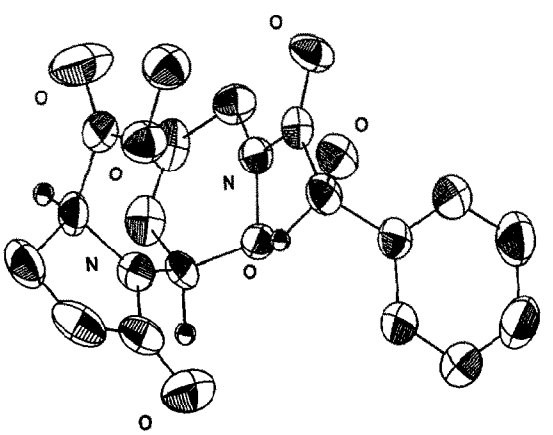


Figure 2.- *ORTEP* plot of **6b** : 50 % probability ellipsoids. Most H-atoms omitted for clarity.

Crystal Data. - Compound **7** $C_{17}H_{34}O_5N_2Si$, M=374.55, monoclinic, a=8.928(5), b=8.939(4), c=13.937(7) Å, β=102.99(5)°, U=1071.24 Å^3 (by least squares refinement of diffractometer angles for 25 independent, automatically centered reflections, λ=0.71069 Å), space group $P2_1$ (no.4), Z=2, D_c=1.162 g cm^{-3}, F(000)=408. Colourless crystals mounted in a 0.3 mm Lindemann capillary, μMo-Kα=1.0 cm^{-1}. Intensity data were collected on a Enraf-Nonius CAD4 diffractometer, ω-2θ scan, graphite-monochromated MoKα radiation ; 2346 independent reflections measured [± h,k,l) ; 2<θ<27°], 2213 with $F>3\sigma(F)$. No correction for absorbance was applied. The structure was solved by direct methods. Anisotropic full-matrix least-squares refinement for all non-hydrogen atoms. Hydrogen atoms were calculated and fixed with isotropic thermal U-values of 0.07. Final R=0.07 using unit weights.

Compound **6b** $C_{18}H_{20}N_2O_6$, M=360.367, orthorhombic, a=7.678(5), b=12.682(3), c=17.746(6) Å, U=1727.96 Å^3 (by least squares refinement of diffractometer angles for 25 independent, automatically centered reflections, λ=0.71069 Å), space group $P2_12_12$ (no. 18), Z=4, D_c=1.386 g cm^{-3}, F(000)=760. Colourless crystals mounted in a 0.3 mm Lindemann capillary, μMo-Kα=0.65 cm^{-1}. Data were collected using the same scan mode as above ; 1840 independent reflections measured [h,k,l) ; 2<θ<28°], 1428 with $F>2\sigma(F)$. No correction for absorbance was applied. The structure was solved by direct methods. Anisotropic full-matrix least-squares refinement for all non-hydrogen atoms. Hydrogen atoms were calculated and fixed with isotropic thermal U-values of 0.07. Final R and R' $[w=\sigma^2(2Fo+g(Fo)^2]^{-1}$=0.069 and 0.065.

Programs used (Microvaxll, Cryst. Lab. Chemistry Department, University of Basle) and sources of scattering factors were reported in refs[13,14]. Fractional atomic coordinates and Ueq values [$Beq=8\pi^2$ (U11+U22+U33)/3] for structure **7** and **6b** are listed in a separate **Table** which is available upon request (supplementary material).

It follows that the absolute configurations of **4** and of **5b** are known too. As to the most likely absolute configuration of the major cycloadduct **5d**, we discussed it in terms of mechanistic considerations (see above).

Acknowledgement. - The support of the **Centre National de la Recherche Scientifique** (URA-135) is gratefully acknowledged.

Experimental Part

General. - Flash chromatography (FC) : silica gel (Merck 60 ; 230-400 mesh). TLC : Al roll silica gel (Merck 60 F254). M.p. : Kofler hot bench or Büchi SMP 20 apparatus ; corrected. IR spectra (cm^{-1}) : Perkin-Elmer 157-G. ^1H- and ^{13}C-NMR spectra : Bruker AC-F-250 ; tetramethylsilane TMS (^1H-NMR) and $CDCl_3$ or C_6D_6 ($\delta(CDCl_3) = 77.0$ or $\delta(C_6D_6) = 128.0$ with respect to TMS ; ^{13}C-NMR) as internal references ; δ in ppm and J in Hz. High resolution (HR) MS were measured on a MAT-311 spectrometer at the University of Rennes. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS, Vernaison.

Starting Materials. - Raney-nickel (slurry in H_2O), nPr_4NIO_4, N-methylmorpholine-N-oxide (NMO), D- and L-mandelic acid were purchased from Fluka, (S) and (R)-2(methoxymethyl)pyrrolidine from Merck-Schuchardt.

The usual solvents were freshly distilled. The chlorinated ones were kept over Na_2CO_3.

Hydroxamic acids. -

D- or L-Methylmandelate : to a soln. of HCl 10 % in MeOH (25 ml) was added D- or L-mandelic acid (5 g, 33 mmol). After 2h at r.t., toluene was added and the soln. evaporated to give the esters (5.3-5.4 g, 96-100 %).

D(-)-Methylmandelate : m.p. : 50-52° (cyclohexane/benzene 20:1) ; $[\alpha]_D^{20} = -176$ (c=1.0, $CHCl_3$). (ref[15] : m.p. : 55.5° (petrol-ether) ; $[\alpha]_D^{23} = -174.2$ (c=0.58, $CHCl_3$)). IR(KBr) : 3525, 1735, 1260, 1185, 1080, 690. ^1H-NMR (250 MHz, $CDCl_3$) 7.36 (m, Har.) ; 5.18 (s, H-C(2)) ; 3.76 (s, OMe).

L(+)-Methylmandelate : m.p. = 52° (cyclohexane/benzene 20:1) ; $[\alpha]_D^{20} = +178$ (c=1.0, $CHCl_3$). (ref[15] : m.p. = 55.5° (petrol-ether) ; $[\alpha]_D^{25} = +173.5$ (c=0.97, $CHCl_3$). IR(KBr) : 3450, 1735, 1200, 1090, 1060, 735, 690. ^1H-NMR (250 MHz, $CDCl_3$) ; 7.36 (m, Har.) ; 5.19 (s, H-C(2)) ; 3.76 (s, OMe).

D(-) and L(+)-2-hydroxy-2-phenylacetohydroxamic acid **3b,c** were prepared from the corresponding methyl mandelate according to [6] :

(2R)-(-)-2-hydroxy-2-phenylacetohydroxamic acid **3b** : (beige crystals ; 73 %) ; m.p. = 155°, dec. (AcOEt/MeOH 8:1) ; $[\alpha]_D^{20} = -61$ (c = 2.5, H_2O) ; $[\alpha]_D^{20} = -48$ (c=0.6, MeOH) (lit.[6] : m.p. = 157.8, dec. (AcOEt) ; $[\alpha]_D^{20} = -46$ (c=0.6, MeOH)). IR(KBr) (other allotropic form of product described in [6]) : 3300, 1680, 1630, 1070, 735, 700.

(2S)-(+)-2-hydroxy-2-phenylacetohydroxamic acid **3c** : (beige crystals, 75 %) ; m.p. = 158°, dec. (AcOEt/MeOH 8:1) ; $[\alpha]_D^{20} = +63$ (c = 2.5, H_2O) ; $[\alpha]_D^{20} = +46$ (c = 0.6 ; MeOH) (lit.[9b] : m.p. = 137.8°, $[\alpha]_D = -164$ (c = 2.5, H_2O)). IR(KBr) : 3475, 3290, 1675, 1625, 1450, 1070, 720, 690. ^1H-NMR (250 MHz, $CDCl_3/CD_3OD$ 3:1) : 7.36 (m, Har.) ; 5.08 (s, H-C(2)) ; 3.01 (bs, OH, NHOH).

(2R)-(+)-2-(methoxymethyl)pyrrolidine-N-carbohydroxamic acid **3d** : a soln. of (R)-(+)-2-(methoxymethyl)pyrrolidine (0.86 ml, 6.95 mmol) and C-phenoxy-carbohydroxamic acid[6] (1.41 g, 9.2 mmol, 1.32 eq.) in anh. pyridine (10 ml) was stirred overnight under Ar at 30°. The pyridine was evaporated by azeotropic distillation with toluene. Acid **3d** was separated by FC (AcOEt/EtOH 8:2) and isolated as pinkish

crystals (1.43 g, 95 %) ; m.p. = 89-90° (AcOEt/*i*Pr$_2$O 2:1). $[\alpha]_D^{20}$ = +92.5 (c = 1.0, MeOH). IR(KBr) : 3290, 3200, 1650, 1450, 1375, 1090, 765, 655. ^{1}H-NMR : (250 MHz, $CDCl_3$) : 8.08 and 6.41 (2bs, NHOH) ; 3.97 (m, H-C(2)) ; 3.65 (m, Hb-C(5)) ; 3.25-3.45 (m, 3H, Ha-C(5), H-C(α)) ; 3.37 (s, OMe) ; 2.01 (m, Ha-C(3)), 1.84 (Hb-C(3), Ha-C(4)) ; Hb-C(5) ; 1.63 (m, Hb-C(4)).

-(2S)-(-)-2-(methoxymethyl)pyrrolidine-N-carbohydroxamic acid **3e** was prepared according to[6], (2R,5R) 2,5 dimethylpyrrolidine N-carbohydroxamic acid **3a** according to 5.

Cycloadducts

General procedure : to a stirred soln. of diene **1a** or **1b** in CH_2Cl_2 (1 g in 10 ml) at 0°C, containing *ca* 50 beads of 4 Å molecular sieves, was added *n*Pr$_4$NIO$_4$ (1/3 mol/mol of acid **3**) and then portionwise the hydroxamic acid (1-3 eq.). After ca. 4h the red soln. was diluted with ether, treated with 1*N* Na_2CO_3 and finally with brine (3x). The aq. phases were extracted again with Et_2O and the combined org. soln.dried over $MgSO_4$ and evaporated. The rate of minor to major adduct was determinated by ^{1}H and ^{13}C-NMR with the crude residue.

(6S)-6-(t-butyldimethylsilyloxy)-2-[(2R,5R)-2,5-dimethylpyrrolidine-1-carbonyl]-3,6-dihydro-2H-1,2-oxazine **4**. - Was prepared from **1a** (0.49 g, 2.7 mmol) in CH_2Cl_2 (5 ml), *n*Pr$_4$NIO$_4$ (0.34 g, 0.8 mmol) and (R)-acid **3a**[5] (0.42 g, 2.7 mmol). The crude product was purified by FC (AcOEt/cyclohexane 2:8) to give **4** (0.455 g, 50 %) as colourless crystals, m.p. : 55° (pentane at -20°). IR(KBr) : 2950, 2920, 2880, 2850, 1650, 1460, 1400, 1365, 1335, 1260, 1250. ^{1}H-NMR : see **Table 2**. ^{13}C-NMR : see **Table 3**. Anal calc. for $C_{17}H_{32}N_2O_3Si$ (340.55) : C 59.96, H 9.48, N 8.22 ; found : C 59.9, H 9.6, N 8.1.

(6S)-2-[(R)-2-hydroxy-2-phenylacetyl]-6-[(S)-5-methoxycarbony-2-oxo-pyrrolidine-1-yl]-3,6-dihydro-2H-1,2-oxazine **5b** and its (6R) diastereoisomer **6b**. - Compounds **5b/6b** were prepared from **1b** (56 mg, 0.28 mmol) in CH_2Cl_2 (0.5 ml), nPr$_4$NIO$_4$ (38 mg, 0.1 mmol) and (R)-acid D-**3b** (47 mg, 0.28 mmol, 1 eq.). The crude product was separated by TLC (AcOEt) to give **1b** (22 mg, 41 %), **5b** (Rf=0.4, 22 mg, 22 %), **6b** (Rf=0.25, 10 mg, 10 %). Larger scale experiments were performed with 2 eq. of acid **D-3b**.

Compound **5b** : yellow resin. $[\alpha]_D^{25}$ = +101 (c = 1.0, $CHCl_3$). IR(film) : 3450, 2950, 1740, 1715, 1705, 1685, 1670, 1650, 1435, 1395, 1375, 1280, 1205. ^{1}H-NMR : see **Table 2**. ^{13}C-NMR : see **Table 3**. MS, m/z (%) : 360(10), 196(40), 195(100), 144(44), 136(95), 108(19), 107(54), 105(15), 84(69), 83(25), 79(42), 77(32). HR-MS : 360.1316 ($C_{18}H_{20}N_2O_6$, M$^{+\cdot}$, calc. 360.1321).

Compound **6b** : colourless prisms, m.p. : 144°. $[\alpha]_D^{25}$ = +14 (c = 1.0, $CHCl_3$). IR(film) : 3450, 2950, 1735, 1715, 1705, 1685, 1670, 1650, 1435, 1395, 1275, 1205. ^{1}H-NMR : see **Table 2**. ^{13}C-NMR : see **Table 3**. MS, m/z (%) : 196(19), 195(43), 144(25), 136(45), 108(10), 107(29), 84(100), 83(14), 79(21), 77(16). HR-MS : 360.1316 ($C_{18}H_{20}N_2O_6$, M$^{+\cdot}$, calc. 360.1321).

(6S)-2-[(S)-2-hydroxy-2-phenylacetyl]-6-[(5S)-methoxycarbonyl-2-oxo-pyrrolidin-1-yl]-3,6-dihydro-2H-1,2-oxazine **5c** and its (6R) diastereomer **6c**. - Compounds **5c/6c** were prepared from **1b** (268 mg, 1.37 mmol) in CH_2Cl_2 (1.5 ml), nPr$_4$NIO$_4$ (282 mg, 0.74 mmol) and (S)-acid L-**3c** (334 mg, 2.0 mmol, 1.5 eq.). The crude product was separated by TLC (AcOEt) to give adduct A (Rf = 0.35 ; 92 mg, 19 %) and adduct B (Rf = 0.2 ;

69 mg, 14 %).

Adduct A (**5c** or **6c**) : yellow resin, $[\alpha]_D^{25}$ = -87 (c = 1.0, $CHCl_3$). IR(film) : 3440, 2950, 1740, 1710, 1670, 1650, 1395, 1280, 1210. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.** MS, m/z (%) : 196(26), 195(53), 144(27), 136(69), 107(46), 105(16), 91(21), 84(100), 83(22), 79(37), 77(19), 55(15). HR-MS : 360.1333 ($C_{18}H_{20}N_2O_6$, $M^{+\cdot}$, calc. 360.1321).

Adduct B (**6c** or **5c**) : yellow resin, $[\alpha]_D^{25}$ = -128° (c = 0.65, $CHCl_3$). IR(film) : 3450, 2980, 1740, 1720, 1705, 1690, 1670, 1650, 1435, 1400, 1375, 1275, 1210. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.** MS, m/z (%) : 196(14), 195(34), 144(18), 136(34), 107(14), 84(100), 79(10), 77(10). HR-MS : 360.1316 ($C_{18}H_{20}N_2O_6$, $M^{+\cdot}$, calc. 360.1321).

(6S)-6-[(S)-5-methoxycarbonyl-2-oxo-pyrrolidin-1-yl]-2-[(R)-2-(methoxymethyl)-pyrrolidin-1-carbonyl]-3,6-dihydro-2H-1,2-oxazine **5d** and its (6R)-diastereomer **6d**. - Compounds **5d** and **6d** were prepared from **1b** (128 mg, 0.66 mmol) in CH_2Cl_2 (2 ml), nPr$_4$NIO$_4$ (144 mg, 0.38 mmol) and (R)-acid D-**3d** (191 mg, 1.1 mmol, 1.7 eq.). The crude product was separated by FC (AcOEt) to give successively **1b** (13 mg, 10 %), **5d** (106 mg, 44 %) and **6d**. **6d** (3 mg, ~1 %) was purified by TLC (AcOEt, Rf of **5d** = 0.30, Rf of **6d** = 0.2).

Compound **5d** : yellow resin. $[\alpha]_D^{20}$ = - 18 (c = 1.0, $CHCl_3$). IR(film) : 3480, 2950, 1740, 1710, 1650, 1400, 1205. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.** MS, m/z (%) : 195(8), 142(100), 136(13), 114(11), 84(8), 82(21), 71(12). HR-MS : 367.1740 ($C_{17}H_{25}N_3O_6$, $M^{+\cdot}$, calc. 367.1743).

Compound **6d** : yellow resin, caracterised only by ^{1}H- and ^{13}C-NMR. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.**

(6S)-6-[(S)-5-methoxcarbonyl-2-oxo-pyrrolidin-1-yl]-2-[(S)-2-(methoxymethyl)-pyrrolidin-1-carbonyl]-3,6-dihydro-2H-1,2-oxazine **5e** and its diastereomer **6e**. - Compounds **5e** and **6e** were prepared from **1b** (57 mg, 0.29 mmol) in CH_2Cl_2 (0.5 ml), nPr$_4$NIO$_4$ (34 mg, 0.09 mmol) and (S)-acid L-**3e** (51 mg, 0.29 mmol, 1 eq.). The crude product was separated by TLC (AcOEt) to give **1b** (47 mg, 55 %), adduct A (Rf = 0.3, 18 mg, 17 %), Adduct B (Rf = 0.2, 20 mg, 19 %).

Adduct of highest Rf, **A**, **5e** (or **6e**) : yellowish resin. $[\alpha]_D^{20}$ = -71 (c = 0.9 ; $CHCl_3$). IR(film) : 3390, 2960, 2890, 1745, 1715, 1650, 1405, 1365, 1205, 1180, 1115, 1080, 1065. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.** MS, m/z (%) : 195(7), 142(100), 136(14), 114(16), 110(7), 82(34), 70(69), 55(9). HR-MS : 367.1740 ($C_{17}H_{25}N_3O_6$, $M^{+\cdot}$, calc. 367.1743).

Adduct of lowest Rf **B** **6e** (or **5e**) : yellowish resin. $[\alpha]_D^{20}$ = -68 (c = 1.4 ; $CHCl_3$). IR(film) : 3490, 2960, 2890, 1740, 1715, 1640, 1405, 1370, 1200, 1110. ^{1}H-NMR : see **Table 2.** ^{13}C-NMR : see **Table 3.** MS, m/z (%) : 211(7), 142(100), 136(7), 114(12), 110(5), 82(24), 70(16). HR-MS : 367.1740 ($C_{17}H_{25}N_3O_6$, $M^{+\cdot}$, calc. 367.1743).

[4R, 5R, 6S]-6-(t-Butyldimethylsilyloxy)-2-[2R,5R)-2,5-dimethylpyrrolidine-1-carbonyl]-tetrahydro-2H-1,2-oxazine-4,5-diol **7**. - To a stirred solution of **4** (0.52 g, 1.54 mmol) in acetone/H_2O (8 ml/1 ml) was added

NMO (0.42 g, 3.08 mmol) and a solution of OsO_4 [16] (12 ml). After 1 d, acetone (10 ml) and silicagel (2 g) were added. After filtration and evaporation of the solvent, the residue was puified by FC (AcOEt/cyclohexane 7:3) to give pure **7** (0.54 g, 94 %). Colourless crystals : m.p. 102-102.5° (hexane). $[\alpha]_D^{25}$ = -63 (c = 1.0, $CHCl_3$). IR(KBr) : 3590, 3365, 2960, 2930, 2880, 2855, 1640, 1420, 1250, 1135, 1105, 1090. ^{1}H-NMR : see **Table 2**. ^{13}C-NMR ($CDCl_3$, 62.8 MHz) : 161.1(CO), 98.1(C(6)), 73.3(C(5)), 68.3(C(4)), 54.8(C(2'),C(5')), 50.2(C(3)), 30.6(C(3'), C(4')), 25.6(($\underline{C}H_3$)$_3$C), 19.6(CH_3-C(2'), CH_3-C(5')), 19.0 ($Me_3\underline{C}$) -4.5, -4.7(2CH_3-Si). Anal. calc. for $C_{17}H_{34}N_2O_5Si$ (374.56) ; C 54.56, H 9.16, N 7.49, Si 7.51 ; found : C 54.3, H 9.3, N 7.3, Si 7.5.

[2S,3R]-4-[(2R,5R)-2,5-Dimethylpyrrolidine-1-carbonyl] aminobutane-1,2,3 triol **8**. - A solution of **7** (139 mg, 0.37 mmol) in EtOH (5 ml) was hydrogenolysed with H_2 (1 atm.) 1d. at 40°C over Ni-Ra (previously washed under H_2 in EtOH). After filtration on celite, the solvent was evaporated, the solid recrystallised : **8** (66 mg, 72 %) ; colourless crystals. m.p. = 110° (AcOEt, iPr_2O). $[\alpha]_D^{25}$ = -36.4 (c = 1.0, MeOH). ^{1}H-NMR (D_2O, 250 MHz) : 3.90 (m, H-C(2'), H-C(5')), 3.75-3.55 (m, 2H, H-C(1), H-C(2), H-C(3)) ; 3.30 (m, 2H, H-C(4)), 2.12 and 1.53 (2m, 4H, H-C(3'), H-C(4')), 1.05 (d, Me-C(2'), Me-C(5')). ^{13}C-NMR (D_2O, 62.8 MHz) : 159.3(CO), 74.0 (C(2)), 72.4 (C(3)), 63.8 (C(1)), 54.1 (C(2'),C(5')), 43.8 (C(4)), 30.8 (C(3'), C(4')), 20.1 (CH_3-C(2'), CH_3-C(5')). Anal. calc. for $C_{11}H_{22}N_2O_4$ (246.31) : C 53.64, H 9.00, N 11.37 ; found : C 53.5, H 9.0, N 11.2.

References

[1] S. Masamune, W. Choy, J.S. Petersen, L.R. Sita, *Angew. Chem.* **1985**, *97*, 1 ; ibid. *Intern. Ed.* **1985**, *24*, 1.

[2] A. Defoin, J. Pires, J. Streith, *Synlett* **1990**, 111 ; A. Defoin, J. Pires, J. Streith, *Helv. Chim. Acta*, submitted for publication

[3] R.P. Short, R.M. Kennedy, S. Masamune, *J. Org. Chem.* **1989**, *54*, 1755.

[4] V. Gouverneur, L. Ghosez, *Tetrahedron : Asymmetry* **1990**, *1*, 363.

[5] A. Defoin, A. Brouillard-Poichet, J. Streith, *Helv. Chim. Acta* **1991**, *74*, 103.

[6] A. Defoin, A. Brouillard-Poichet, J. Streith, *Helv. Chim. Acta* in press.

[7] A. Defoin, J. Pires, J. Streith, *Synlett* **1991**, 417.

[8] Ch. A. Zezza, M.B. Smith, *J. Org. Chem.* **1988**, *53*, 1161.

[9] a) A. Miller, T. McC. Paterson, G. Procter, *Synlett* **1990**, 32 ;
b) G.W. Kirby, M. Nazeer, *Tetrahedron Lett.* **1988**, *29*, 6173.

[10] A. Brouillard-Poichet, A. Defoin, J. Streith, *Tetrahedron Lett.* **1989**, *30*, 7061.

[11] G.W. Kirby, *Chem. Soc. Rev.* **1977**, *6*, 1.

[12] W. Oppolzer, W. Fröstl, *Helv. Chim. Acta* **1975**, *58*, 587.

[13] G.M. Sheldrick, programs SHELX-76 and SHELXS-86 respectively, University of Göttingen, Germany.

[14] D.T. Cromer, J.B. Mann, *Acta Crystallogr.*, Sect. A, **1968**, *24*, 321 ; D.T. Cromer, D. Libermann, *J. Chem. Phys.*, **1970**, *53*, 1891.

[15] W.A. Bonner, *J. Am. Chem. Soc.* **1951**, *73*, 3125.

[16] A. Defoin, H. Fritz, Ch. Schmidlin, J. Streith, *Helv. Chim. Acta* **1987**, *70*, 554.

Table 3 : ^{13}C-NMR-Data of adducts **4, 5b-e, 6b-e**[a]. 62.9 MHz, $CDCl_3$, 300 K ; δ in ppm, internal standart TMS or $CDCl_3$ ($\delta CDCl_3 = 77.0$ ppm)

	C(3)	C(4)	C(5)	C(6)	C(2')	C(3')	C(4')	C(5')	CO2Me	CO2Me	NC=O	C(2")	C(3")	C(4")	C(5")	Other data
4	44.3	126.6	126.7	92.7	-	-	-	-	-	-	159.3	54.1	30.3	30.3	54.1	Me3C:18.2,CMe3:20.1,SiMe2:-4.1,-5.0, MeC(2"),MeC(5"):25.7
5b	43.3	122.0	126.7	77.7	173.0	29.0	23.3	52.5	175.9	57.3	nd	71.2	-	-	-	Ar:C_s:139.4 C_o:127.5 C_m:128.6 C_p:128.3
6b	42.6	121.8	126.7	78.8	172.8	29.5	24.3	52.9	176.2	58.0	nd	71.5	-	-	-	Ar:C_s:138.4 C_o:127.5 C_m:128.5 C_p:128.1
5c or 6c,A[c]	42.1	121.6	127.1	78.1	172.9[b]	29.1	24.2	52.7	175.9	58.5	172.1[b]	70.6	-	-	-	Ar:C_s:138.5 C_o:127.0 C_m:128.6 C_p:128.6
6c or 5c,B[c]	41.4	122.5	127.3	79.5	171.8[b]	29.4	23.0	52.2	176.0	56.6	171.4[b]	71.2	-	-	-	Ar:C_s:139.4 C_o:127.3 C_m:128.3 C_p:127.9
5d	45.3	121.6	128.7	76.2	172.8	28.7	24.0	51.9	175.2	57.4	159.0	57.4	27.2	23.5	48.0	CH_2-C(2") : 72.6, OMe : 58.4
6d	46.1	123.4	129.9	76.5	172.5	27.7	24.8	52.2	175.8	58.0	159.4	56.9	29.7	23.5	48.9	CH_2-C(2") : 73.2, OMe : 59.0
5e or 6e,A[c]	45.9	122.8	129.2	78.3	~173	27.9	24.5	52.6	176.0	57.9	~159	56.9	29.4	24.2	48.8	CH_2-C(2") : 73.2, OMe : 59.0
6e or 5e,B[c]	45.3	122.4	130.3	76.9	172.7	27.7	24.6	52.4	176.0	58.0	159.0	57.3	29.7	23.8	48.8	CH_2-C(2") : 73.1, OMe : 59.0

a : C(') refers to the pyroglutamate moiety, C(") to the pyrrolidine or mandelic acid moiety.
b : C(2') or N-C=O.
c : A is the isomer of highest Rf, B the isomer of lowest Rf.