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High Diastereofacial Selectivity in the 1,3-Dipolar Cycloaddition of Chiral Azomethine Ylides

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Abstract : Excellent diastereofacial and endo/exo stereoselectivities have been obtained in cycloaddition of the chiral azomethine ylide generated from 4-phenyloxazolidine acetic acid (-)-8-phenylmenthyl ester ***1e****.*

The 3+2 cycloaddition reactions of azomethine ylides are very well documented and widely studied. Surprisingly, very little work has been concerned with facial diastereoselectivity and furthermore successes in this area remain modest or are limited to isolated instances[1] (intramolecular processes for example).

We recently introduced a new facile method for the generation of ylides under very mild conditions using *N*-methoxycarbonylmethyl-4-phenyloxazolidine **1a**[2]. Cycloaddition to various activated dipolarophiles occurred in high yield within 4 h at - 78°C. This represented one of the first examples of a chiral azomethine ylide and we undertook a study of the diastereoselectivity of the cycloaddition[3]. Using *N*-phenylmaleimide as dipolarophile, it was shown that cycloaddition proceeded with complete *exo* selectivity on the stabilized U-shaped ylide **Y1** (Scheme 1) derived from **1a** but without any facial selectivity (two cycloadducts **2a** and **3a** are formed in a 48:52 ratio).

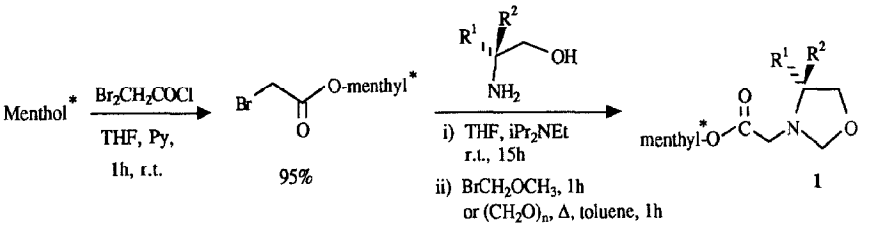
1
a) R = CH_3, R^1 = Ph, R^2 = H

Y1

Scheme 1

This low diastereofacial selectivity was not improved on by modification of substituents R^1 and R^2 on the oxazolidine ring of **1**.[3] A possible explanation is that in the *exo* mode of cycloaddition the chiral center cannot interact with the dipolarophile because of its remote position. We thus proposed the introduction of a chiral group in the ester moiety and we present herein our preliminary results obtained in cycloaddition reactions of such derivatives with *N*-phenylmaleimide.

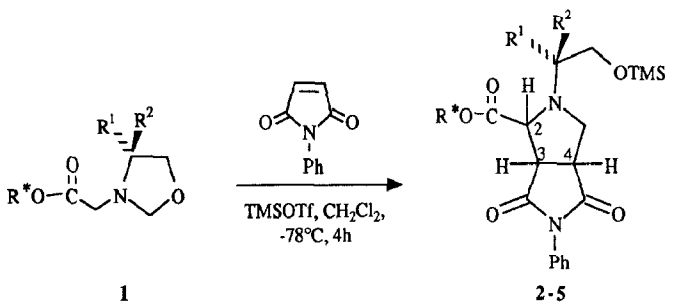
Esters **1b-e** were easily synthesized in good yields from commercially available (+)-menthol, (-)-menthol and (-)-8-phenylmenthol (Scheme 2). *R*-(-)-Phenylglycinol and 2-amino-2-methyl propanol were *N*-monoalkylated with menthyl bromoacetate (obtained by treatment of the appropriate menthol with bromoacetic acid in the presence of pyridine) in THF with 1 eq of iPr_2NEt followed by treatment with bromomethyl methyl ether in the same medium or by condensation with paraformaldehyde in refluxing toluene (Table 1).



Scheme 2

Table 1 : Preparation of chiral menthyl esters **1**.

Menthol*	R^1	R^2	Oxazolidine	Overall yield (%)	$[\alpha]_D^{20}$
(+)-menthol	CH_3	CH_3	**1b**	45	+57 (c 1, $CHCl_3$)
(+)-menthol	Ph	H	**1c**	58	-41 (c 5, $CHCl_3$)
(-)-menthol	Ph	H	**1d**	50	-144 (c 1.2, $CHCl_3$)
(-)-8-phenylmenthol	Ph	H	**1e**	77	-59 (c 3, $CHCl_3$)



Scheme 3

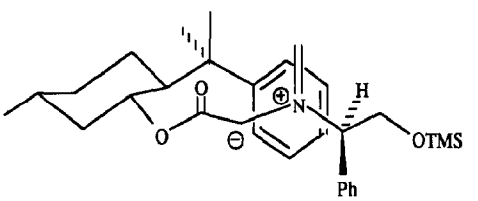
Table 2 : Isomeric ratio of different cycloadducts of *N*-phenylmaleimide with different chiral esters **1**.

	R	R^1	R^2	Overall yield	H-2/H-3 cis exo		H-2/H-3 trans endo		exo/endo	d.e.
					2	**3**	**4**	**5**		
(a)	Me	Ph	H	85	48	52	-	-	100:0	4
(b)	(+)-Menthyl	Me	Me	52	55	-	45	-	55:45	-
(c)	(+)-Menthyl	Ph	H	83	84	9	7	-	93:7	80
(d)	(-)-Menthyl	Ph	H	79	20	80	-	-	100:0	60
(e)	(-)-8-Ph Menthyl	Ph	H	86	-	≥98	-	-	100:0	≥95

We first used ester **1b** wich had no chiral group on the oxazolidine ring and it can be seen from Table 2 that two cycloadducts **2b** and **4b** [4] (Scheme 3) were obtained in a 45:55 ratio.[5] We deduced that major compound **2b** arose from an *exo* cycloaddition whereas **4b** was an *endo* cycloadduct. This result was in agreement with previous results from this laboratory [3] showing that small R^1 and/or R^2 groups led to a fair *endo/exo* selectivity. We then used oxazolidines derived from *R*-(-)-phenylglycinol in the hope of obtaining only *exo* cycloadducts. The two diastereomeric esters **1c** and **1d** obtained respectively from (+)- and (-)-menthol were investigated. The cycloaddition of *N*-phenylmaleimide with **1d** (derived from (-)-menthol) gave an 80% yield of two *exo* adducts [4] (**2d** and **3d**) with 60% d.e.[5] showing the determinant role of the menthyl group. On the other hand, ester **1c** (derived from (+)-menthol) gave a very good facial diastereoselectivity : d.e. = 80% [In this instance the cycloaddition was not completely *exo* : the *exo-endo* ratio was 93:7].

Although this process is not strictly speaking a double induction - the two chiral groups are placed on the same reactive species - it clearly proceeds on the same principle.

We finally tried oxazolidine **1e** derived from (-)-8-phenylmenthol which has proved to be a much more effective chiral directing group than menthol, in the Diels-Alder reaction of menthyl acrylates for instance.[6] We were pleased to find that a single cycloadduct **3e** [7,8] was obtained in 86% yield from the reaction of **1e** with *N*-phenylmaleimide. This indicates that, in this case, one face of the ylide is completely masked by the phenyl ring of the 8-phenylmenthyl group. The stereochemistry of **3e** implicates an *exo* transition state.To explain the stereochemical course of the reaction, we propose the model shown on Figure. Determination of the absolute configuration of cycloadduct **3** will give us new elements to confirm this model. Work is in progress in this field and will be reported later.



Figure

We have thus designed and synthesized a new stable synthon **1e** [9] which is easily transformed to an azomethine ylide constrained in a U-shaped conformation, and bearing two chiral moieties. The first chiral center borne by the nitrogen atom forces the exclusive *exo* addition of dipolarophile while the second chiral center on the ester group permits diastereofacial selectivity.

Oxazolidine **1e** was treated with a variety of dipolarophiles to check the generality of the reaction. Cycloadditions with dimethyl acetylenedicarboxylate and 2,2-dimethyl cyclopentene-1,3-dione occurred in good yield (respectively 81% and 56%) giving in each case a single product, but dimethylmaleate did not react.

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3. Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* submitted.
4. The relative stereochemistry of each cycloadduct was determined by ^1H NMR at 250 MHz on the separated derivatized alcohols obtained after desilylation (citric acid in MeOH).
5. The diastereomeric ratio was determined by ^1H and ^{13}C NMR on the crude reaction mixture.
6. a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. b) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffat, F. *Helv. Chim. Acta*, **1981**, *64*, 2802.
7. The crude reaction mixture was examined by ^1H NMR (250 MHz) and ^{13}C NMR in which the presence of only one product was apparent. HPLC analysis showed small impurities which exhibited UV spectra different of those of cycloadduct.
8. **3e** : mp : 134°C ; $[\alpha]_D^{20}$ = -106 (c 0.6, $CHCl_3$); RMN ^1H ($CDCl_3$, 250 MHz) : 0.1 (s, 9H, TMS), 0.85 (d, J=7Hz, 3H, CH_3), 1.1 (m, 2H, H ment), 1.25 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 1.5 (m, 4H, H ment), 2.1 (m, 1H, H ment), 2.35 (m, 1H, H ment), 2.65 (t, J=9Hz, 1H, H-5), 2.9 (d, J=7Hz, 1H, H-2), 3.1 (m, 2H, H-3, H-4), 3.55 (d, J=9Hz, 1H, H-5), 3.95 (d, J=6.5Hz, 2H, H-7), 4.35 (t, J=6.5Hz, 1H, H-6), 4.8 (td, J=4.5Hz, 10.5Hz, 1H, H ment), 7.35 (m, 15H, H arom); RMN ^{13}C ($CDCl_3$) : -0.6 (TMS), 21.8 26.1 27.1 31.4 34.7 39.8 40.6 (C ment), 42.6 46.5 50.3 (C ment, C-3, C-4), 50.3 (C-5), 63.2 64.7 (C-2, C-6), 64.6 (C-7), 77.1 (C ment), 124.8 125.4 126.6 127.8 127.9 128.2 128.5 129.0 129.4 132.0 136.1 151.8 (C arom), 168.3 174.8 177.5 (C=O); MS (CI) m/z : 667 (MH^+, 100), 475 (10), 473 (10); IR (cm^{-1}) : 1715, 1735; Anal. Calcd. for $C_{40}H_{30}N_2O_5Si$: C 72.03, H 7.35, N 4.20, Found C 71.81, H 7.43, N 4.21.
9. **1e** : $[\alpha]_D^{20}$ = -59 (c 3.7, $CHCl_3$); RMN ^1H ($CDCl_3$, 250 MHz) : 0.90 (d, J=7Hz, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 1.5 (m, 3H, H ment), 1.9 (m, 4H, H ment), 2.1 (m, 1H, H ment), 2.65 (d, J=17Hz, 1H, H-6), 3.0 (d, J=17Hz, 1H, H-6), 3.8 (t, J=7Hz,1H, H-5), 4.0 (t, J=7Hz, 1H, H-4), 4.3 (t, J=7Hz, 1H, H-5), 4.4 (d, J=3Hz, 1H, H-2), 4.9 (d, J=3Hz, 1H, H-2), 5.0 (td, J=4.5Hz, 10.5Hz, 1H, H ment), 7.35 (m, 10H, H arom) ; RMN ^{13}C ($CDCl_3$) : 21.8 24.4 26.5 28.7 31.3 34.6 39.6 41.8 50.3 (C ment), 52.5 (C-6), 66.4 (C-4), 73.2 (C-5), 74.6 (C ment), 86.6 (C-2), 125.1 125.4 127.6 127.8 128.0 128.7 139.2 151.7 (C arom), 169.8 (C=O) ; MS (CI) m/z : 422 (MH^+, 100), 302 (5),215 (10) ; IR (cm^{-1}) : 1735 ; Anal. Calcd. for $C_{27}H_{31}NO_3$: C 76.92, H 8.36, N 3.32, Found : C 76.58, H 8.38, N 3.12.