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Stereoselective Synthesis of 2,3-Epoxy-amides by Aldol-like Condensation of 2,3-O-isopropylidene-D-glyceraldehyde with N,N-Diethyl Diazoacetamide

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Abstract: The 1:1 mixture of cis:trans epoxy-amides **5c** was obtained quantitatively by condensation of 2,3-O-isopropylidene-D-glyceraldehyde **1** with N,N-diethyl diazoacetamide. Similarly, the reaction of **1** with methyl diazopropionate was studied and gave as the main product the β-ketoester **4b** (product of a 1,2-hydrogen shift) and, in a low yield, the glycidic ester **5b** (intramolecular nitrogen displacement). The configuration at C-3 of the resultant epoxides of both reactions revealed that the addition step was completely stereoselective. Under similar conditions, compound **6**, methyl 3-hydroxy-2-diazopropionate was unreactive , but with heating gave **7**.

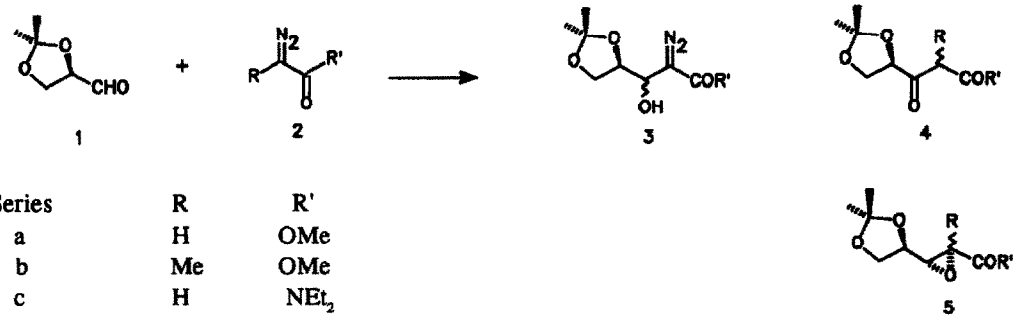
Highly stereoselective aldol reactions can be used for the acyclic asymmetric synthesis of a number of important natural products[1]. Reactions of diazoacetates with aldehydes, with or without catalyst, are of this type.The present work continues an extensive study of these reactions, many of which we have used in this laboratory to synthesize polyhydroxyl β-ketoesters, important intermediates in the preparation of C-nucleosides and related compounds[2]. Earlier work in this laboratory investigated the stereochemical course of reactions of 2,3-O-isopropylidene-D-glyceraldehyde **1** with alkyl diazoacetates[3] **2** and explored their potential for synthesis. Without acid catalysis, these reactions gave (3S)-β-hydroxy-α-diazo esters **3a** as the main products together with two minor products, the β-ketoester **4a** (11%) and trace amounts of the epoxide **5a** (< 5%). On the other hand, photochemistry of β-oxy-α-diazo methyl ketone, synthesized from **1** and diazoacetone, provided 3-oxy-2-methyl ester with *threo* configuration[4]. Our special interest in the epoxide product with two chiral centres and also in other glycidic derivatives led us to study the reaction of **1** with partially-stabilized sulphur ylides[5] that produce with high stereoselectivity the trans glycylamides **5c**. These epoxides are interesting synthetic intermediates for the preparation of polyacetates, polypropionates, aminoacids and other natural derivatives[6].

In our previous work[3] we conjectured about several possible mechanisms that might be involved in this reaction type. This thinking led us to suggest the replacement of the diazoacetate **2a** by its homologue 2-diazopropionate **2b** to avoid the H-2 intramolecular abstraction from the intermediate adduct and prevent the formation of the β-hydroxy-α-diazo ester **3a** and also improve the yield of the epoxide **5b**. Moreover, the synthesis of this new type of epoxide by the sulphur ylide method would need a very difficult and expensive preparation of the appropiate propionamide sulphur ylide. As we expected, the reaction of **1** with methyl 2-diazopropionate[7] without solvent and catalyst gave a 78:22 mixture of the β-ketoester **4b** and the epoxide **5b** respectively; just two of the three possible types of products. Unfortunately, the β-ketoester **4b** is of little interest for us at this time because the chirality initially developed at C-3 is lost.To increase the proportion of epoxide we carried out a simple theoretical study using Molecular Mechanic to try to explain the interdependence between the conformation of the intermediate adduct of the reaction and the dielectric constant, ε,of the solvent. We found that solvents with small ε should favour the coulombic interaction between the alkoxy ion at C-3 and

the diazonium group at C-2 in the intermediate adduct, to favour a antiperiplanar conformation of that diazonium group with the hydrogen at C-3. In this way, the conformation would facilitate the 1,2-hydrogen shift that in turn favours the production of the β-ketoester **4b**. On the other hand, any increase of ε would give rise to the epoxide. Thus, in practice, whereas the absence of solvent leads to a 22% of epoxide, when we reduced the polarity of the reaction medium by employing n-hexane, dichloromethane, or diethylether solvents we obtained as the sole reaction product the β-ketoester **4b**. Unfortunately, no reaction took place when the more polar solvents, methanol or DMF, were used, possibly because the reactants were solvated. Methanol slowly decomposed **2b**, while DMF permitted both starting products to be recovered.

At this point, for two reasons, we decided to study the reaction of **1** with diazoacetamides. Firstly, because we knew that aldol condensation with acid catalysis of aldehydes with 2-diazo β-lactams[8] gave the epoxides but in low yield and without stereoselectivity. Secondly, the electronic effect of the amide group would decrease the acid character of the diazo carbon and this should prevent the formation of β-hydroxy-α-diazo amide. Moreover, it would decrease the tendency of the hydrogen to migrate. Thus, the reaction of **1** with N,N-diethyl diazoacetamide **2c**[9] was carried out as above, and gave a mixture of the compound **4c** together with *Z:E* epoxy amides **5c** in a 2:3:5 ratio. The fact that we did not find the corresponding β-hydroxy-α-diazo amide confirmed our predictions. A wider study of this reaction in different conditions is summarized in Table I, and these results led us to seek the optimum conditions that would produce a quantitative yield of the mixture of both *Z:E* epoxides in an approximately 1:1 ratio. These epoxides were later separated by flash chromatography. We established their respective configurations by comparing them with epoxides obtained from condensation with the corresponding sulphur ylide [5]. The ratio of *Z:E* epoxides was not modified significantly when we used different solvents (chloroform, THF, TBME, DMF or DMSO) or different temperatures (r.t, 4ºC, -30ºC).

SCHEME I



Series	R	R'
a	H	OMe
b	Me	OMe
c	H	NEt_2

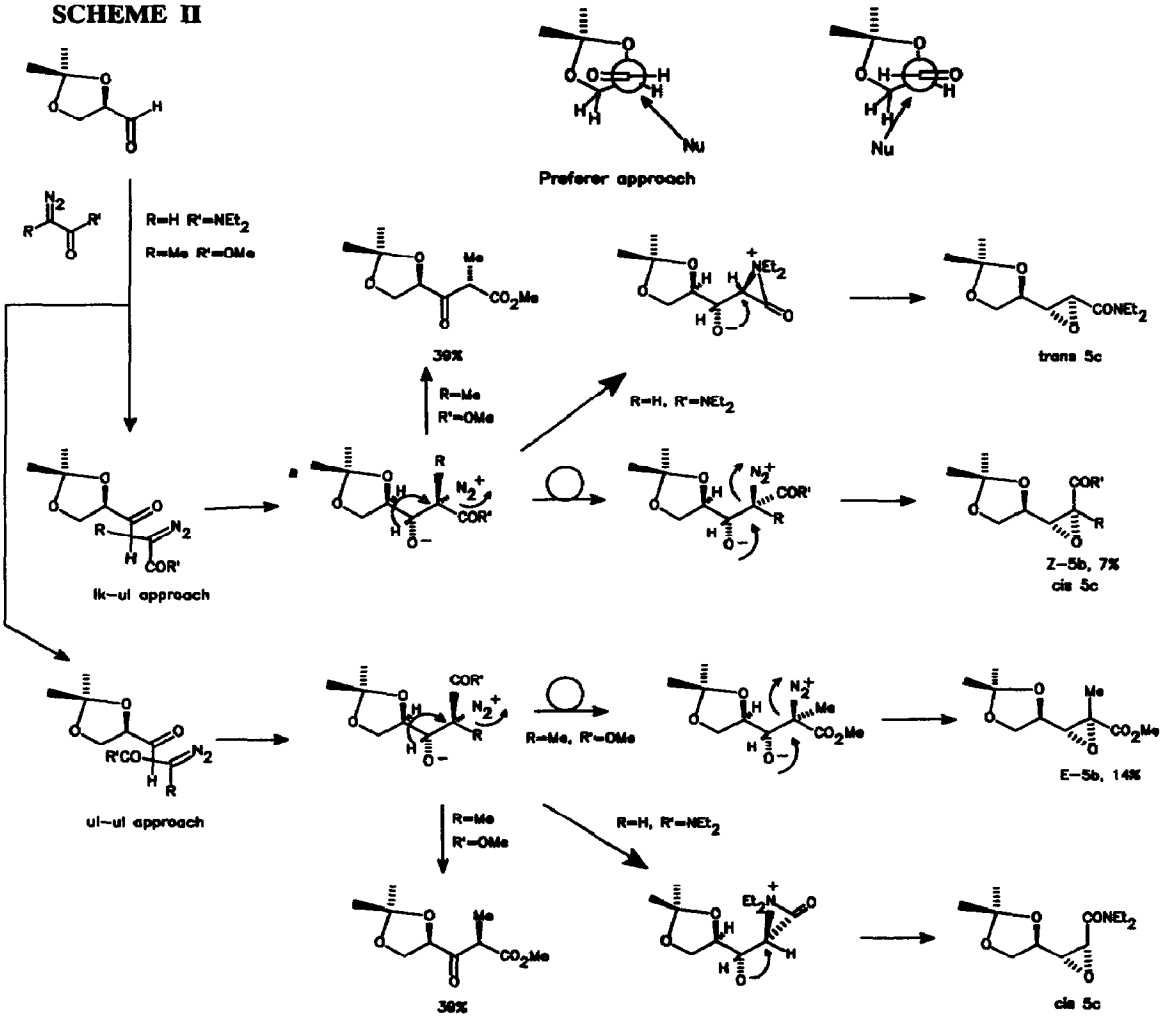
Stereochemically, the fact that in both reactions only two epoxides were formed can be interpreted as the result of an earlier highly stereoselective addition of methyl diazopropionate and N,N-Diethyl diazoacetamide to the *si* face of the aldehyde **1** as the Felkin-Ahn model predicts [10]. In the case of diazopropionate, this addition is followed by a second, less stereoselective process of intramolecular nitrogen displacement. The values of the coupling constants $J_{3,4}$ of the epoxides **5b** (8.2 Hz major isomer and 7.6 Hz minor isomer) served to assign the absolute configurations at C-3. The configurations at C-2 are tentative and are based on scheme 2. In the case of diazoacetamide, we postulated the formation of a quaternized α-lactam intermediate that would be opened by alkoxy group in antiperiplanar disposition to form the final epoxides. This push-pull mechanism would explain the exclusive formation of the cis:trans epoxides **5c** and the absence of β-ketoamide **4c** when the reaction took place in solution. A similar mechanism is proposed for the reaction of nitrous acid with 2-amino-2-deoxyaldonic acids[11]. Similarly, the formation of the *lk-ul* intermediate[3] as the result of the more favoured approach could explain also the isolation of both epoxides because the direct displacement of diazonium group by the alkoxy would give rise to the cis epoxy-amide and the trans epoxide could be formed by the quaternary α-lactam ring formation as explained before (Scheme II). Compound **4c** only was formed in small yield (12-14%) when this reaction took place without solvent or when heated while being refluxed with THF.

TABLE I

Conditions	Reaction time (hours)	trans-5c	cis-5c	4c
Without solv. and catalyst, r.t.	24	27.7 (a)	17.7 (a)	12 (a)
Without solv. and catalyst, 4°C	24	58 (b)	32 (b)	10 (b)
Chloroform, r.t.	48	48 (b)	52 (b)	traces
THF, reflux	1	48 (b)	38 (b)	14 (b)
Methanol, r.t.	48	traces (c)	traces (c)	---
Methanol/KOH 10%	2	not reaction	not reaction	not reaction
THF/Boron trifluoride	12	52	48	traces

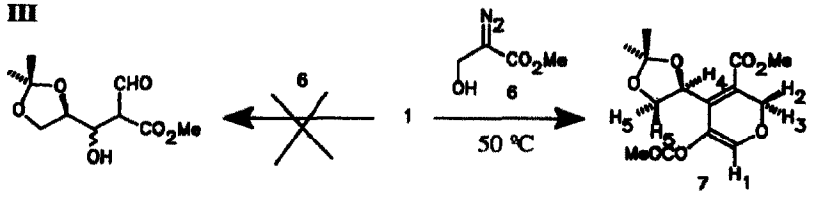
a.- Yield after purification. b.- Ratio determined by GC-MS analysis. c.- N,N-Diethyl diazoacetamide decomposed by the solvent to give N,N-Diethyl 2-methoxy acetamide.

SCHEME II



We employed a different approach to reduce the 1,2 migration of the H-3 hydrogen in diazopropionate derivative to preserve the chiral character of the C-3 carbon of the initial adduct. This led to the introduction of a hydroxyl group at C-3 of **2b**. In this way, in an analogous reaction, we used methyl 3-hydroxy-2-diazopropionate **6**[12],to introduce two new hydrogens in the alpha positions (relative to the diazonium group) that could compete with the hydrogen at C-3 (C-1 of the initial aldehyde) in the transposition step. However, after one week at r. t. and without solvent, **6** had not reacted with **1**. Even after heating the reaction mixture at 50ºC for one day, the only product isolated was the pyrane derivative **7**[13] in a low yield (10%).

SCHEME III



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REFERENCES

1. [a]D. A. Evans, *Aldrichimica Acta*, **15**, 318 (1982);[b] C.H. Heathcock, K. T. Hug and L.A. Flippin, *Tetrahedron Lett.*, **25**, 5973-6 (1984); [c] E. J. Corey and S. S. Kim, *Tetrahedron Lett.*, **31**, 3715-18 (1990);[d]C. Gennari, F. Molinari, P.G. Cozzi and A. Oliva, *Tetrahedron Lett.*, **30**, 5163-66 (1989);[e] H. Danda, M.M. Hansen and C. H. Heathcock, *J. Org. Chem.*, **55**, 173-181 (1990);[f] S.G. Davies, I.M. Dodor-Hedgcock and P. Warner, *Tetrahedron Lett.*, **26**, 2125-28 (1985);[g] A. I. Meyers and Y. Yamamoto, *Tetrahedron*, **40**,2309-2315 (1984); [h] Y. Ito, M. Sawamura and T. Hayashi, *Tetrahedron Lett.*, **28**, 6215-18 (1987); [i] S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem Int. Ed. in Engl.* **24**, 1-76 (1985); [j] M. Braun, *Angew. Chem. Int. Ed. Engl.*, **26**, 24-37 (1987).
2. [a] F. J. López-Aparicio, F.J. López-Herrera and M. Valpuesta-Fernández, *Carbohydr. Res.* **69**, 235 (1979);[b] M. Valpuesta-Fernández, F.J. López-Herrera and C. Gómez-Pérez, *Carbohydr. Res.*, **124**, 333 (1983).
3. F.J. López-Herrera; M. Valpuesta-Fernández and S. García-Claros; *Tetrahedron*, **46**, 7165-7174 (1990).
4. F.J. López-Herrera and F. Sarabia-García; *Tetrahedron Lett.*; **34**, 3467 (1993).
5. M. Valpuesta-Fernández; P. Durante-Lanes and F.J. López-Herrera; *Tetrahedron*, **46**, 7911-7922 (1990).
6. S. Masamune and W. Choy; *Aldrichimica Acta*, **15**, 335-352 (1982)
7. Synthesis of methyl 2-diazopropionate : J. García, J. González, R. Segura and J. Vilarrasa, *Tetrahedron*, **40**, 3121 (1984).
8. [a]J.C. Sheehan, E. Chacko, Y.S. Lo, D.R. Ponzi and E. Sato; *J Org. Chem.*; **43**, 4856 (1978); [b] V.J. Jephcote, D.I. John, P. Edwards, K. Lug and D.J. Williams; *Tetrahedron Lett.*; **25**, 2915 (1984).
9. Synthesis of N,N-Diethyl diazoacetamide: M. Regitz, J. Hocker and A. Liedhegener; *Org. Synth.*, **48**, 36 (1968).
10. [a] M. Cherest; H. Felkin and N. Prudent, *Tetrahedron Lett.*, 2201 (1968); [b] Nguyen Trong Ahn and O. Einstein; *Tetrahedron Lett.*, 155 (1976).
11. [a]J. Defaye; *Adv. in Carbohydr. Chem. and Biochem.*; **25**; 181 (1970); [b] J.M. Williams; *Adv. in Carbohydr. Chem. and Biochem.*; **31**, 9 (1975).
12. E. Wenkert and C.A. McPherson; *J. Am. Chem. Soc.*; **94**, 8084 (1972).
13. The ^{1}H-N.M.R. data of **7** were the following ($CDCl_3$, δ ppm): 7.49 (t, 1H, J=1Hz, H-1); 5.65 (dd, 1H, J=5.4Hz, J=7.1 Hz,H-4); 5.04 (dd, 1H, J=1 Hz,J=12.9Hz, H-2); 4.89 (dd, 1H, J=1 Hz, J=12.9Hz,H-3); 4.34 (dd,1H, J=7.1Hz,J=8.6Hz, H-5); 3.92 (dd, 1H, J=5.4Hz, J=8.6Hz, H-6); 3.76 (s, 6H, 2 -COOMe); 1.47 and 1.39 (2s, 6H, $-CMe_2$). M.S., m/z= 283 (M^+ -15).

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