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Communications

Stereoselective Synthesis of 3-(Ethoxycarbonyl)-4-hydroxy-5-(1-hydroxyalkyl)-2-isoxazoline 2-Oxides by Reaction of 2,3-Epoxy Aldehydes and Ethyl Nitroacetate on Alumina Surface

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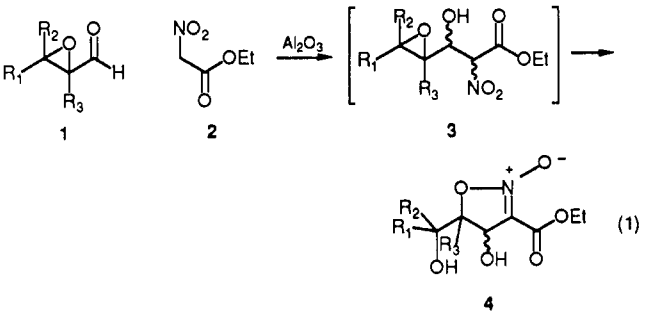
Summary: Treatment of racemic 2,3-epoxy aldehydes and ethyl nitroacetate with alumina affords title compounds through a nitroaldol reaction–cyclization process. While in the case of 3-trans-monosubstituted substrates, C4,C5-trans and cis isomers (dr = 1.5) with C5,C6-anti configuration are obtained, 3-cis-monosubstituted 2,3-epoxy aldehydes give C4,C5-trans and cis derivatives with a much higher diastereoselectivity (dr ≥ 20) and C5,C6-syn configuration. 5-Exo cyclization occurs also when 2,3-epoxy aldehydes are 2-substituted.

In the course of our studies toward the synthesis of polyhydroxylated molecules and related natural products from acyclic precursors, we require a practical methodology that permits diastereomeric control in the construction of three or more contiguous asymmetric centers, as well as the potential utilization of enantiomerically pure starting materials easily available without the use of enzymes.

Previous work from this laboratory[3,4] demonstrated that commercial chromatographic alumina is an excellent base to effect heterogeneous solvent-free nitroaldol reactions between functionalized nitroalkanes and aldehydes. This method has proved to be mild and convenient and was shown useful in the multistep synthesis of natural products.[5,6]

Here we report that 2,3-epoxy aldehydes **1** react stereoselectively with ethyl nitroacetate[7] (**2**) on alumina surface in the absence of solvent to give 3-(ethoxycarbonyl)-4-hydroxy-5-(1-hydroxyalkyl)-2-isoxazoline 2-oxides (**4**) (eq 1).



(1)

This reaction can be depicted as a base-catalyzed tandem nitroaldol cyclization process in which the chain-lengthening step affords a 2-nitroalkanol **3** and/or its *aci*-nitro form as transient species that undergoes a fast epoxide ring-opening cyclization to **4**.

The general procedure for the reaction reveals its simplicity.[8] Table I displays the results with a series of racemic substrates (**5–10**) which were chosen to demonstrate the generality of the procedure and to show the dependence of their configuration on the selectivity in the formation of products **11–21**. While the 2-isoxazoline 2-oxide

(1) Taken in part from the Tesi di Laurea of R. Galarini (November 1989) at the University of Bologna, Faculty of Industrial Chemistry.
(2) In partial fulfillment of requirements for Ph.D. Thesis in Chemical Sciences of the University of Bologna.
(3) Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014.
(4) Rosini, G.; Ballini, R.; Petrini, M.; Sorrenti, P. *Synthesis* **1985**, 515.
(5) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
(6) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261.
(7) Shipchandler, M. T. *Synthesis* **1979**, 666.

(8) **General Procedure.** Reactions are performed simply by mixing equimolar amounts of starting materials **1** and **2** and adding to the mixture, cooled at 0 °C and under vigorous stirring, sufficient commercial chromatographic alumina to absorb it completely. After standing for 2–20 h at room temperature with occasional stirring, products are isolated in fair to good yields by washing with dichloromethane, filtration of organic extracts, and evaporation of the solvent under reduced pressure. The separation of diastereomers is accomplished by flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) on silica gel using diethyl ether as eluent. For further characterization data, see the supplementary material.

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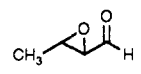
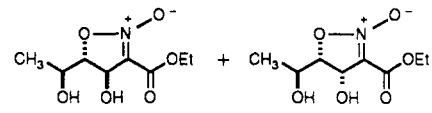
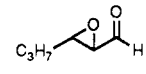
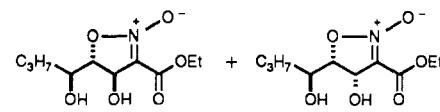
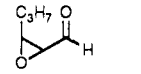
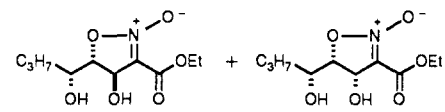
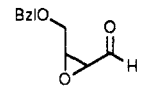
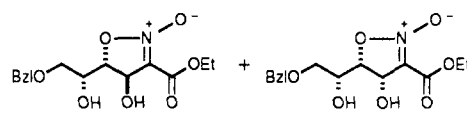
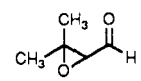
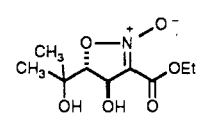
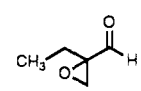
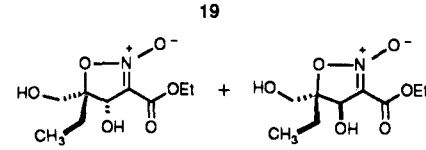
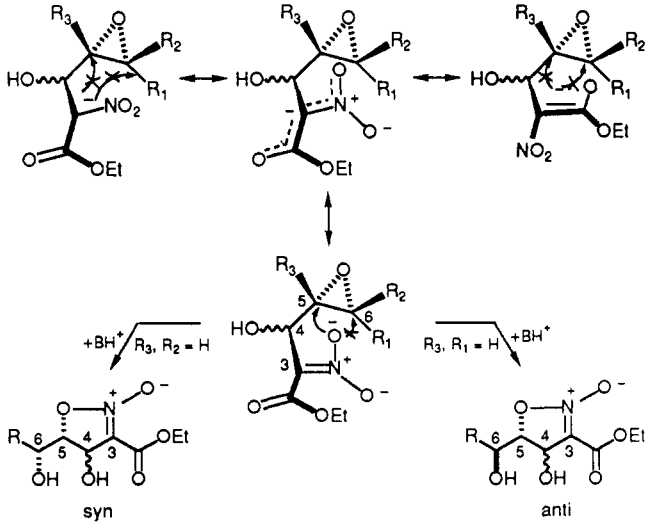
Table I. Tandem Nitroaldol Reaction–Cyclization of 2,3-Epoxy Aldehydes with Ethyl Nitroacetate on Alumina

entry	2,3-epoxy aldehyde	yield,[a] %	time, h	products[b,c]	dr[d]
1	 **5**	99	26	 **11** + **12**	1.5
2	 **6**	75	18	 **13** + **14**	1.5
3	 **7**	47[e]	21	 **15** + **16**[f]	20
4	 **8**	83	2	 **17** + **18**[f]	20
5	 **9**	56	15	 **19**	–
6	 **10**	65	20	 **20** + **21**	4

[a] The yield is based on the weight of a purified sample of the diastereomer mixture by a short column chromatography, before separation of each diastereoisomer. [b] The assignment of structure is based on IR, ^{13}C NMR, and ^{1}H NMR spectra. [c] Although only one enantiomer is depicted in each case, all structures represent racemates. [d] The ratio is based on integration of the ^{1}H NMR signal of the diastereoisomer mixture at ca. δ 5.2 + 5.3 ppm, due to the H at C4 after D_2O exchange. [e] The aldehyde has been recovered only in part after standing alone on alumina for the indicated reaction time. [f] Observed only in trace in ^{13}C NMR and in ^{1}H NMR spectra of the reaction mixture.

Scheme I. Ambido-, Regio-, and Stereospecificity in the Cyclization Step of the Reaction of 3-Trans- and 3-Cis-Monosubstituted 2,3-Epoxy Aldehydes and Ethyl Nitroacetate on Alumina



structure of compounds **11–21** is based on IR, ^{13}C NMR, and ^{1}H NMR spectra and trans and cis relationships between hydrogens on endocyclic C4 and C5 are apparent from ^{1}H NMR data ($J_{H_4H_5trans}$ = 2.2–3.3 Hz; $J_{H_4H_5cis}$ = 5.2–7.3 Hz), the syn and anti stereochemistry[9] of substituents at C5 and C6 ultimately rests on the assumption that in the intramolecular base-catalyzed epoxide opening the nucleophilic attack of nitronate oxygen occurs with inversion of configuration.[10,11]

(9) We prefer the prefixes syn and anti and use them according to Masamune, S.; Ali Sk. A.; Smitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. Argumentations on the several alternatives suggested for same stereostructural notation are reported: Heathcock, C. H. The Aldol Addition Reaction. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 112.

(10) Intramolecular openings of epoxides are well documented. See, for example: (a) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256. (b) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. (c) Schubert, J.; Schwesinger, R.; Prinzbach, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 167. (d) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (e) Sorokin, M. F.; Shodè, L. G.; Pavlyukov, S. A.; Ohosova, L. A. *Zh. Org. Khim.* **1980**, *16*, 1241. (f) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (g) Corey, E. J.; Sachder, H. S.; Gongontas, Z.; Saenger, W. *J. Am. Chem. Soc.* **1970**, *92*, 2488.

(11) For reviews on the chemistry of the epoxides and 2,3-epoxy alcohols, see: (a) Rossiter, B. E. Synthetic Aspects and Application of Asymmetric Epoxidation. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5, pp 194–243. (b) Fin, M. G.; Sharpless, K. B. On the Mechanism of Asymmetric Epoxidation with Titanium Tartrate Catalysts. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5, pp 247–301. (c) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. (d) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodward, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. (e) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67 and references cited therein.

Each of the reactions is ambido- and regiospecific. Isomeric products resulting from intramolecular substitution of the nitronate oxygen atom to the farther carbon of the epoxide (6-endo cyclization) are not detected. Scheme I illustrates the ambido-, regio-, and stereospecificity of the cyclization step. The pioneering studies relative to epoxynitrile cyclization[12] indicated that ring opening of the oxirane is easier when the nucleophilic end, which is attacking it from the rear side, is co-linear with the C–O bond due to be broken. In our systems the geometry of nitronate anion and the distance of oxirane ring from it allows an easy attainment of co-linearity C5–O bond of the intermediate **3**, and cyclization occurs to give 2-isoxazoline 2-oxide (5-exo cyclization) with C5,C6 syn conformation when the starting 2,3-epoxy aldehyde is cis-3-monosubstituted (entries 3 and 4) and with C5,C6 anti conformation in the case of trans-3-monosubstituted 2,3-epoxy aldehydes (entries 1 and 2). Five-membered ring rather than the six-membered ring isomer formation is preferred even though the cyclization to 2-isoxazoline 2-oxide derivative involves intramolecular nucleophilic attack to the more substituted end of oxirane as in entry 6.

In spite of the high selectivity of the intramolecular cyclization involving C–O σ-bond formation and ring-opening of oxirane moiety, a lack of selectivity can be ascribed to the chain-lengthening step. Although nitroaldol addition–cyclization of ethyl nitroacetate does show low diastereoselectivity with 3-monosubstituted trans-2,3-epoxy aldehydes (entry 1 and 2), much better results are observed when 2,3-epoxy aldehydes are cis-3-monosubstituted (entry 3 and 4) and 3-disubstituted (entry 5). Reactions of compound **5** and ethyl nitroacetate with a suspension of alumina in methanol or in diethyl ether at room temperature as well as at −20 °C revealed the same diastereoisomer ratio observed during room temperature experiments in the absence of solvent according to the general procedure.

The assignment of configuration of compounds **20** and **21** was achieved by means of differential NOE (nuclear Overhauser enhancement) experiments.[13]

2-Isoxazoline 2-oxides have been prepared using several different procedures starting from nitroacetic esters,[7,14] nitroalkenes,[15] or bromonitroalkenes.[16] However, our reaction stands out from the reported procedures as a useful tool to build stereoselectively polyhydroxylated linear molecules in a predictable way. In fact, 2-isoxazoline 2-oxides as cyclic nitronates have the richness of the chemistry of nitronates including Nef-type hydrolysis to open the ring. In addition 2-isoxazoline 2-oxide may be converted into the corresponding 2-isoxazoline.[14] These are central intermediates for their latent functionality that allow routes to, inter alia, γ-amino alcohols[17] and, in the case of 4-hydroxyisoxazoline, amino polyols and amino sugars by stereoselective reductive cleavage of the heterocyclic ring.[18]

The initial target of our project has been to study the selectivity of reactions of 2,3-epoxy aldehydes and ethyl nitroacetate and, for convenience, we have restricted our preliminary studies to the racemic 2,3-epoxy aldehydes presented in Table I. These are easily prepared by epoxidation of the corresponding 2,3-unsaturated aldehydes[19] or by oxidation of 2,3-epoxy alcohols by well-established procedures.[20] However, enantiomerically pure 2,3-epoxy alcohols could be prepared by Sharpless[11] enantioselective epoxidation of prochiral (*E*)- and (*Z*)-allylic alcohols; these being themselves easily available by using Wittig, Wittig–Horner, or Bestmann reagents.[21,22]

Additional research will be needed to better understand the operative stereochemical control elements and the limits of our reaction. However, it should be clear that the asymmetric epoxidation of prochiral allylic alcohols in conjunction with the richness of cyclic nitronates and 2-isoxazoline chemistry is very indicative of the usefulness of our stereoselective tandem nitroaldol cyclization process in synthesis.

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Supplementary Material Available: Characterization data (IR, ^{13}C NMR, and combustion analyses as Table II–IV, and actual ^{1}H NMR spectra) for compounds **11–17** and **19–21** (24 pages). Ordering information is given on any current masthead page.

(12) (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268. (b) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5272. See also: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(13) In the case of compound called **20** saturation of CH_2 signal of the ethyl group (δ = 1.73 ppm) bounded to C5 yielded a 11% enhancement of the proton on C4. This entails a configuration having the mentioned ethyl group and the C4H on the same side of the ring (cis configuration). This assignment has been confirmed by an analogous experiment carried out on the isomer **21** where saturation of the same CH_2 ethyl signal (δ = 1.77 ppm) yields a 10% enhancement of the OH proton in position 4. Accordingly configuration trans has been assigned to **21**.

(14) Melöt, J. M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1988**, 558 and references cited therein.

(15) (a) Glagett, M.; Gooch, A.; Graham, P.; Holy, N.; Mains, B.; Strunk, J. *J. Org. Chem.* **1976**, *25*, 4033. (b) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971.

(16) Matelkina, E. L.; Sopova, A. S.; Perckalin, V. V.; Ionin, B. I. *Zh. Org. Khim.* **1974**, *10*, 209.

(17) For reviews on the argument, see: (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857. (b) Jäger, V.; Grund, H.; Franz, R.; Ehrler, R. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *52*, 2137. (d) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5822.

(18) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601.

(19) Marschall, H.; Penninger, J.; Weyerstahl *Justus Liebigs Ann. Chem.* **1982**, 49.

(20) We found that the reagent of choice is the pyridinium dichromate (PDC) in dichloromethane in the presence of 4-Å molecular sieves: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(21) For recent reviews, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Bestmann, H. J.; Vostrowski, O. *Top. Curr. Chem.* **1983**, *109*, 85. (c) Wittig, G. *Angew. Chem.* **1980**, *92*, 671. (d) Cadogan, J. F. C. *Organophosphorus Reagents in Oranic Synthesis*; Academic Press: New York, 1979. (e) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515.

(22) Bestamnn, H. J.; Rock, K.; Ettlinger, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 687.