ORGANIC LETTERS

2000
Vol. 2, No. 9
1193−1196

A Solution to the Cyclic Aldol Problem

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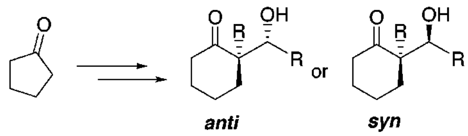
Received January 10, 2000

ABSTRACT



A protocol for achieving stereoselective aldol reactions with cyclic ketones is presented. In terms of yield, the process is particularly effective when a quaternary center at the α-carbon of the *β*-hydroxy ketone product is created. The stereochemical outcome, *anti* or *syn*, is achieved by the Lewis acid-mediated ring expansion of stereochemically homogeneous epoxides in a reaction related to the pinacol rearrangement.

One of the more important and vital contributions to synthetic organic methodology in the past 20−25 years has been the large body of work detailing the stereochemical outcome of the aldol and related reactions.[1] In the acyclic aldol condensation, the reaction between an acyclic carbonyl enolate or equivalent and an aldehyde, the conventional mnemonic holds that the relative stereochemistry of the *β*-hydroxyl carbonyl product (*syn*/*anti*; *erythro*/*threo*) is usually the result of a closed transition state (Zimmerman−Traxler)[2] in which enolate geometry is transferred to the product by minimizing nonbonded interactions. It is interesting that recent work has focused on the aggregated nature of the enolates[3] as well as the aldol product alkoxides,[4] and the strong indication that in the usual organic solvents the reaction may actually be occurring within a molecular aggregate.[5] Absolute stereochemistry in acyclic aldol reactions can often be controlled by incorporating chiral auxiliaries in either reaction partner, or in both to take advantage of double diastereoselection processes.[6]

In contrast to the regularity and predictability associated with the aldol condensations of acyclic carbonyl compounds, cyclic ketones have often proved to be more fractious. In general, cyclic aldol reactions run under equilibrating conditions favor the *anti* (*threo*) diastereomer as seen for the thermodynamic reaction of the lithium and zinc chloride enolates of cyclohexanone with benzaldehyde to give *anti*/*syn* ratios of 67/33 and 83/17, respectively.[7] As expected for an enolate constrained in the *E* configuration, one would also expect aldol condensations run under kinetic conditions to favor the formation of the *anti* product, in accord with the results of the acyclic aldol reactions summarized above. In general this is true, although the diastereomeric ratios are particularly sensitive to the nature of the counterion and reaction conditions. Representative results for the reaction between a variety of cyclohexanone enolates and benzaldehyde show only barely recognizable trends,[8] and even these results do not extrapolate to other cyclic ketones or carbonyl

(1) For comprehensive discussions of the various aspects of the aldol condensation see: (a) Meckleburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 2, pp 99−131. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 2, pp 133−179. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 2, pp 181−238. (d) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 2, pp 239−275.

(2) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920.

(3) (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc*. **1988**, *110*, 3829.

(4) An excellent summary of pertinent literature and definitive physical organic studies of the aldol reaction can be found in: Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribiero, A. A. *J. Am. Chem. Soc*. **1990**, *112*, 801.

(5) (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) C. H. Heathcock, C. H.; J. Lampe, J. *J. Org. Chem*. **1983**, *48*. 4330. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc*. **1987**, *109*, 5539. (d) Wei, Y.; Bakthavatchalam, R. *Tetrahedron Lett*. **1991**, *32*, 1535.

(6) (a) See, for example: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem Soc*. **1981**, *103*, 2127. (b) For a review of double diastereoselection in organic synthesis, see: Masamune, S. *Ang. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(7) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc*. **1985**, *95*, 3310 and references therein.

10.1021/ol005525a CCC: $19.00
Published on Web 04/04/2000

electrophiles. Results become even less predictable when the cyclic enolate is fully substituted so that the aldol reaction would generate a quaternary center as in the formation of aldol product **2** from 2-methylcyclohexanone (**1**). It is this problem that is of particular concern in the context of this work. Furthermore, the problem of absolute stereochemistry in these reactions has not been adequately solved. The good facial selectivities that have been observed in the alkylation reactions of chiral imine and hydrazone-derived cyclic enolates[1] do not transfer to the hydroxyl-bearing carbons of their aldol condensation counterparts.

While considering possible alternative solutions to the cyclic aldol problem, it became clear that epoxides such as **5** possess all of the stereochemical information on the target aldol products provided that a Lewis acid-mediated rearrangement/ring expansion could be effected under controlled conditions (Figure 1). In a relative sense the stereochemistry

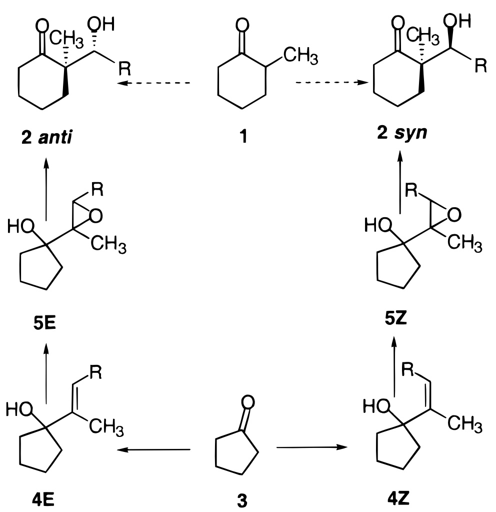


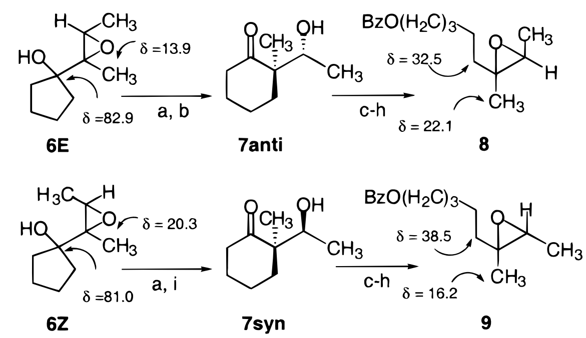
Figure 1. Alternative routes to cyclic aldol products.

of the ring-expanded products would be established by employing an allylic alcohol with specified alkene geometry (**4*E*** or **4*Z***) as precursor to the rearrangement substrate epoxides (**5*E*** or **5*Z***). Because the stereospecific preparation of alkenes is well established and alkene epoxidations are stereospecific processes, a high degree of overall stereochemical control would be possible if the rearrangement could be accomplished in a synchronous fashion. The opportunity for absolute stereochemical control also exists because of a variety of possibilities for enantioselective epoxidation of the prochiral allylic alcohols, e.g., **4**.

The literature on this kind of ring expansion is interesting, although rather sparse, and dates back more than 30 years to work by Julia[9] as well as Johnson and Goldsmith.[10] Formally related to the pinacol rearrangement,[11] it was expected that the reaction would proceed with inversion of configuration at the migration terminus. More recent indirect precedent for the stereochemical integrity of the rearrangement,[12] including an acyclic aldol-equivalent process, is encouraging.[13] Otherwise there has been no systematic study of this reaction. The results of our studies to better define its scope and stereochemical parameters are presented here.

Preparation of the initial test substrates **6*E*** and **6*Z*** was accomplished by the addition of the vinyllithium reagents derived from the *E* and *Z* isomers of commercially available 2-bromo-2-butene to cyclopentanone (~7/1 mixture of isomers) followed by epoxidation with mCPBA (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (a) TMS−imidazole, CH_2Cl_2, 20 °C, 12 h; (b) $BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, −78 °C, 2.5 h; (c) Ac_2O, DMAP, EtOAc, 14 h; (d) mCPBA, CH_2Cl_2, 20 °C, 40 h; (e) $LiAlH_4$, THF, 20 °C, 6 h; (f) BzCl, DMAP, $CHCl_3$, 20 °C, 16 h; (g) MsCl, DMAP, CH_2Cl_2, 0 °C, 14 h; (h) Triton B/CH_3OH, THF, −23 °C, 15 min; (i) $SnCl_4$ (1 equiv), CH_2Cl_2, −78 °C, 2.5 h.

Separation of the individual isomers could be accomplished at either the allylic alcohol or epoxide stage. Verification of the stereochemical assignments for the epoxides was based on ^{13}C NMR chemical shift data for the indicated carbons associated with the epoxide group, as has been observed in similar systems.[14] Particularly diagnostic were the resonances

(8) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem*. **1980**, *45*, 1066. (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nazaki, H. *J. Am. Chem. Soc*. **1977**, *99*, 7705. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *J. Am. Chem. Soc*. **1981**, *103*, 3099. (d) T. Mukaiyama, T.; K. Banno, K.; K. Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503. (e) Y. Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett*. **1980**, 4607. (f) S. Murata, S.; M. Suzuki, M.; R. Noyori, R. *J. Am. Chem. Soc*. **1980**, *102*, 3248. (g) Gennari, C.; Cardani, S.; Colombo, L.; Scolastico, C. *Tetrahedron Lett*. **1984**, *25*, 2283.

(9) Julia, S.; Julia, M.; Linares, H.; Blondel, J.-C. *Bull. Soc. Chim. Fr*. **1962**, 1952.

(10) (a) Johnson, C. R.; Cheer, C. J.; Goldsmith, D. J. *J. Org. Chem*. **1964**, *29*, 3320. (b) Cheer, C. J.; Johnson, C. R. *J. Org. Chem*. **1967**, *32*, 428.

(11) (a) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 3, pp 721−732. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 3, pp 733−775. (c) Coveney, D. J. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 3, pp 777−801.

(12) (a) Hwang, C.; Reusch, W. *Heterocycles* **1987**, *25*, 589. (b) Hwang, C.; Ward, D. L.; Reusch, W. *J. Org. Chem.* **1989**, *54*, 4318.

(13) An *acyclic* version of the epoxy alcohol rearrangement described above, and thus another solution to the *acyclic* aldol problem, has been described: (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc*. **1986**, *108*, 3827. (b) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett*. **1987**, *28*, 3515. (c) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett*. **1987**, *28*, 5891. (d) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc*. **1989**, *111*, 6431.

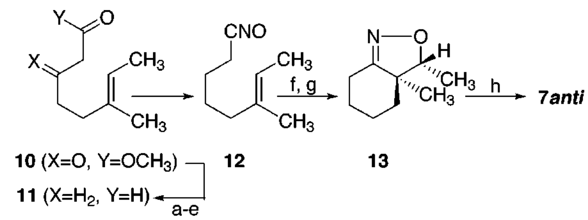
for the quaternary methyl carbons which were observed at δ 13.9 and δ 20.3 for **6*E*** and **6*Z***, respectively. Similarly, the alcohol-bearing ring carbons for these two isomers were observed at δ 82.9 and δ 81.0. It is worth noting that for the pairs of trisubstituted epoxide isomers examined in this study, such ^{13}C NMR chemical shift comparisons provide a convenient handle for assigning epoxide stereochemistry. In particular, it was found that the ^{13}C NMR chemical shifts of the carbons attached to the disubstituted end of the epoxide are sensitive to their spacial relationship to the methyl group on the monosubstituted epoxide carbon. Specifically, the resonance for the carbon that is *cis* to the secondary methyl group occurs upfield relative to the corresponding resonance for its stereoisomer (Scheme 1).

Although direct rearrangement of the epoxy alcohols gave satisfactory results, the derived TMS ethers (TMS imidazole) proved to be more reliable substrates, both in terms of yield and diastereomeric ratios. Furthermore, although a wide range of Lewis acids could be used to effect the rearrangement, no single promoter system was consistently superior. In general, however, the best promoters were $SnCl_4$, BF_3·OEt_2, and ClTi(O*i*Pr)$_3$.[15] Thus, rearrangement of the TMS ether of **6*E*** afforded an 88% yield of keto alcohols **7*anti*** and **7*syn*** in a 94/6 ratio, from which pure **7*anti*** was isolated in 81% yield after chromatography. The diastereomeric ratio from the rearrangement of the free alcohol **6*E*** was only 68/32. Similarly, rearrangement of the TMS ether of **6*Z*** yielded the same two products in a <1/99 ratio, the major isomer **7*syn*** being isolated in 89% yield after chromatography. Again, the ratio from rearrangement of the free alcohol was only 20/80. Similar results were obtained for the analogous ring expansion processes beginning with cyclobutanone, cyclohexanone, cycloheptanone, and cyclodocecanone, where the rearrangements (1.3 equiv $SnCl_4/CH_2Cl_2/-78$ °C) of the trimethylsilyl ethers of the four sets of *E* and *Z* dimethyl epoxides proceeded in high yield (>85%) and with high diastereostereoselectivities (>95/5).[16] These details of these results will be reported in due course.

Because the rearrangement products **7*anti*** and **7*syn*** had not been previously characterized and because definitive stereochemical assignments based on spectral comparisons were difficult, compounds **7*anti*** and **7*syn*** were converted to the stereoisomeric epoxides **8** and **9** by the reactions outlined in Scheme 1. As was the case for the original rearrangement substrates **6*E*** and **6*Z***, unambiguous stereochemical assignments were made on the basis of the indicated ^{13}C NMR chemical shifts, in accord with literature precedent.[14] Specifically, the quaternary methyl carbons of epoxides **8** and **10** were observed at δ 22.1 and δ 14.1, respectively, while the methylene carbons adjacent to the epoxide ring in these two compounds were seen at δ 32.5 and δ 38.5, in accord with the trend described previously.

Independent verification was obtained by the alternative synthesis of **7*anti*** outlined in Scheme 2. Starting with known

Scheme 2[a]

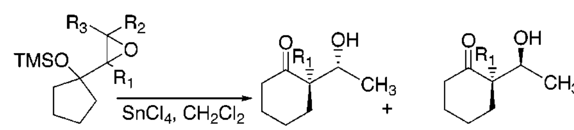


[a] Reagents and conditions: (a) $NaBH_4$, CH_3OH, 0 °C, 1 h; (b) MsCl, Et_3N, CH_2Cl_2, 20 °C, 24 h; (c)Mg, CH_3OH, 20 °C, 1 h;[20] (d) $LiAlH_4$, Et_2O, 0 °C, 3 h; (e) PDC, CH_2Cl_2, 20 °C, 24 h; (f) NH_2OH·HCl, $NaHCO_3$, H_2O, 20 °C, 1 h; (g) NaOCl, H_2O, CH_2Cl_2, 20 °C, 30h; (h) Raney Ni, CH_3OH, HOAc, 20 °C, 3 h.

ester **10** with secure alkene geometry,[17] aldehyde **11** was prepared in five unenventful steps. Conversion to the oxime followed by oxidation with NaOCl then afforded isoxazoline **13** through the intermediacy of the nitrile oxide **12**.[18] Raney nickel hydrogenolysis of **13** and hydrolysis according to the protocol of Curran[19] then yielded **7*anti***, identical with the same material derived from the epoxide rearrangement of **6*E***. As expected for the substitution pattern of compound **12**, the yield of the nitrile oxide cycloaddition reaction was low (~10%). It did, however, provide unambiguous confirmation of our previous stereochemical assignments. There was no indication of the formation of a second isomer in the nitrile oxide cycloaddition reaction; rather the remaining material appeared to be largely the result of nitrile oxide dimerization.

In an effort to determine the importance of the nature of the substituent at the migration terminus, two additional rearrangement substrate types were studied (Scheme 3). Thus,

Scheme 3



14E (R_1=Ph, R_2 =CH_3, R_3=H)
14Z (R_1=Ph, R_2=CH_3, R_3=H)
16E (R_1=R_3=H, R_2=CH_3)
16Z (R_1=R_2=H, R_3=CH_3)

15*anti* (R_1=Ph) **15*syn*** (R_1=Ph)
17*anti* (R_1=H) **17*syn*** (R_1=H)

rearrangement of phenyl-substituted epoxides **14*E*** and **14*Z***, prepared as before by epoxidation of the parent alkenes,[21]

(14) (a) Havesi, L.; Nagy, J. B.; Krief, A.; Derouane, E. G. *Org. Magn. Res.* **1977**, *10*, 14. (b) Pri-Bar, I.; Pearlman, P. S.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4629. (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(15) The rearrangements were carried out in the presence of 0.3−1.5 equiv of Lewis acid, the indicated amounts being the best for the particular experiment in question. Other Lewis acids surveyed include $TiCl_4$, $ZnCl_2$, and TMSOTf, although the diastereomeric ratios with these promoters were generally lower.

(16) The ratios of the diastereoisomers were determined by a combination of capillary gas chromatography and ^{1}H NMR spectroscopy. In the latter analyses, the quartet for the proton on the hydroxyl-bearing carbon was diagnostic, occurring between 0.1 and 0.2 ppm downfield in the *syn* isomers as compared to the *anti* isomers (e.g., δ 4.08 and δ 3.98 for **7*syn*** and **7*anti***, respectively).

(17) Snider, B. B.; Patricia, J. J. *J. Org. Chem.* **1989**, *54*, 38.

was accomplished by exposure to $SnCl_4$ in CH_2Cl_2 (1.2 equiv, −78 °C, 2 h). Epoxide **14*E*** afforded the two *β*-hydroxy cyclohexanone products in 87% yield, the ratio of **15*syn*** and **15*anti*** being <2/98. Similar treatment of **14*Z*** yielded the same two products (88% yield) in a 95/5 ratio. As before, rearrangement of the free alcohols afforded lower diasteroisomeric ratios as well as significant amounts of chlorohydrin byproducts.

The final rearrangement substrates for these initial studies were epoxides **16*Z*** and **16*E*** in which the rearrangement migration terminus is unsubstituted (R_1=H). Prepared by epoxidation of the alkene derived from low temperature addition of (*E*)- and (*Z*)-1-lithio-1-propene to cyclopentanone, this substrate was intended to determine whether a fully substituted migration terminus is required for successful reaction. In the event, rearrangement of **16*E*** with $SnCl_4$ at −40 °C afforded the cyclohexanone products **17*anti*** and **17*syn*** in a ratio of 3/97, although the yield was only 50−60%. The remaining material was largely chlorohydrin. Other Lewis acid promoters produced either decomposition of starting material (BF_3·OEt_2) or no reaction ($AlEt_3$, TiCl(O*i*Pr)$_3$, Ti(O*i*Pr)$_4$). Similar rearrangement of **16*Z*** afforded **17*anti*** and **17*syn*** in a ratio of 99/1, although again in 50−60% yield. The identity of **17*syn*** and **17*anti*** as the major products of these two reactions was confirmed by comparison of the ^{1}H NMR spectrum with that reported for authentic material. Specifically, the quartet for the proton on the hydroxyl-bearing carbon of **17*syn*** was observed at δ 3.95, in agreement with the literature value of δ 3.94 for authentic material.[18] The corresponding proton for the *anti* isomer was observed at δ 4.26 as compared with the literature value δ 4.27.

In summary, the epoxide ring expansion protocol described here provides a reasonable method for achieving *β*-hydroxy cycloalkanone (cyclic aldol) products in good yields and with high levels of diastereoselection, particularly in those cases in which the α carbon is fully substituted. Further developments and applications of this work will be reported subsequently, including protocols for achieving enantiomerically enriched epoxide rearrangement subtrates.[22]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work (26532-AC1). We also gratefully acknowledge NSF (CHE 95 22580) for financial assistance in the purchase of the 400 MHz NMR instrument used in support of this work.

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(18) For a discussion of intramolecular nitrile oxide/alkene cycloaddition (INOC) reactions, see: Wade, P. A. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 4, pp 1124−1134.

(19) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

(20) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287.

(21) The phenyl-substituted allylic alcohol precursors to epoxides **14** were prepared by lithiation of (*Z*)-1-bromo-1-phenylpropene followed by addition to cyclopentanone. At −78 °C the *Z*/*E* ratio of the stereoisomeric products was ∼4/1; at −22 °C the ratio was ∼1/4. Krop, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102.

(22) The structures of all new compounds reported in this work were confirmed by ^{1}H and ^{13}C NMR analysis and IR where appropriate. Suitably purified samples also exhibited consistent combustion analyses and/or high-resolution mass spectral data.