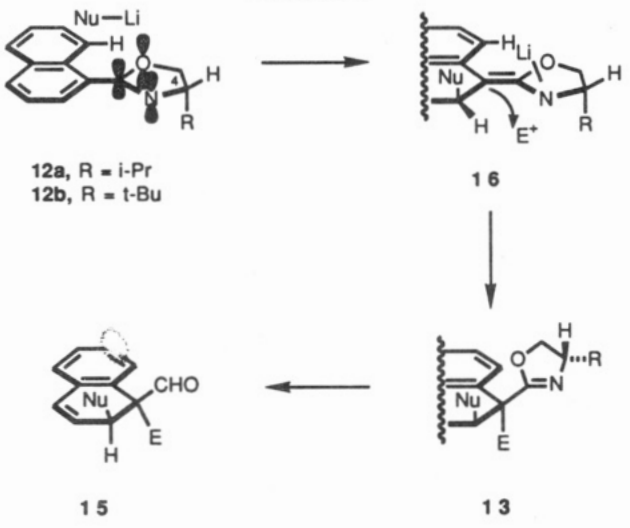
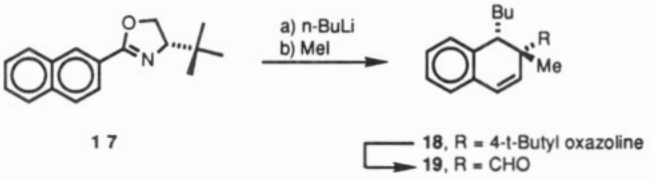
Scheme III



to the organolithium and delivery of the organo portion to the β-face of the naphthalene ring (**16**). The electrophile (i.e., MeI) is then added and enters from the more accessible α-face generating **13**, which is then observed as the overwhelmingly major product. Hydrolysis, after reduction of the C=N, gives the observed dihydronaphthalenes **15**. The steric effect in going from **12** to **16** must be very specific since the range of temperatures explored (−78 to 25 °C) has little effect on the outcome.[13]

(13) We have prepared and examined the alanine- and phenylalanine-derived oxazolines **12** (R = Me, Ph) to assess the sensitivity of the reaction to smaller steric influences. The de's (at −78 °C) for **12a** (R = Me) and **12b** (R = Ph) were 75:25 and 86:14 respectively.

Finally, we briefly examined the 2-naphthyl system[5] **17** that, upon addition of *n*-butyllithium at −78 or 25 °C gave, after methyl iodide addition, 94–98% yields of **18** and >99 and 97% diastereoselection, respectively. Here again, we observed a relatively small temperature effect. The reaction was complete in 2 h at −78 °C or 15 min at 25 °C. Removal of the oxazoline, in the manner stated earlier, gave the chiral aldehyde **19** in >98% ee from −78 °C reaction and >90% ee from the 25 °C reaction.



These impressive enantioselective results using a simple, easily prepared chiral oxazoline will now make these systems more convenient to utilize. Although the yields of product are comparable with all three oxazolines studied (**4**, **12a**, and **12b**), the stereochemical results using *tert*-butyl derivative appears to be overall superior and will ultimately be the system of choice. We are also examining these chiral oxazolines (**12b**) in other reactions (alkylations, aryl couplings, etc.).

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this work and to Merck, Sharpe & Dohme for a postdoctoral fellowship (D.J.R.).

Supplementary Material Available: Experimental details, spectral data, and HPLC data for enantiomeric determination (13 pages). Ordering information is given on any current masthead page.

A Simple Asymmetric Synthesis of 2-Substituted Pyrrolidines from 3-Acylpropionic Acids

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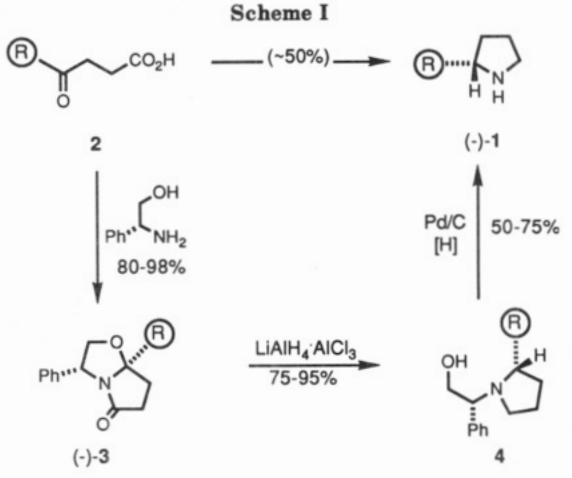
Received January 4, 1991

Summary: The title compounds have been prepared from 3-acylpropionic acids **2** and (−)-R-phenylglycinol in a three-step sequence in >98% enantiomeric excess. The R group in **2** ultimately becomes the 2-substituent in the chiral pyrrolidine.

In recent years, a number of laboratories have reported asymmetric and enantioselective routes to 2-substituted pyrrolidines.[1] In all these studies, either the enantiomeric purity of the final product or the inconvenience of a large number of synthetic steps, or both, detracted from the overall utility of the process. We wish to describe our preliminary results on a route to 2-substituted pyrrolidines

(1) (a) Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 29. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (c) Shiosaki, K.; Rapaport, H. *J. Org. Chem.* **1985**, *50*, 1229. (d) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (e) Arseniyadis, S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 631. (f) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775. (g) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (h) Ganem, B.; Liotta, L. J. *Synlett* **1990**, 503. (i) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (j) Morlacchi, F.; Losacco, V. *J. Heterocycl. Chem.* **1976**, *13*, 165. (k) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250. (l) Nordlander, J. E.; Njoroge, F. G.; Payne, M. S.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481.

Scheme I



which is both convenient to utilize and provides the final products in >98% enantiomeric excess. Scheme I portrays the overall three-step sequence which provides the nonracemic 2-substituted pyrrolidines in ~50% overall yield.

The starting keto acid **2**, if not commercially available, is readily prepared by using the elegant procedure of

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Table I. Formation of Lactams 3 and Pyrrolidines 4 and 1

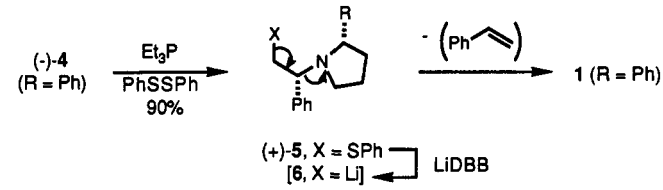
R	% yield, $[\alpha]_D$[a] (deg) 3	% yield 4	% yield 1	(conf)	$[\alpha]_D$[g] (deg)	lit. ref
$PhCH_2$	80, -181.8	85[b]	60	(S)[c]	+13.3 (CH_2Cl_2)	1a,l
n-heptyl	80, -142.2	90	75	(R)[d]	-15.7 ($CHCl_3$)	1e,f,b
cyclopentyl	83, -183.4	87	65	(R)	-6.0 (MeOH)	
n-Bu	91, -152.6	87	62	(R)[e]	-12.0 ($CHCl_3$)	1e,f
n-Pr	84, -145.2	75	78	(R)	-18.0 (MeOH)	1k
Ph	98, -99.6	95	51[f]	(S)	-22.0 (MeOH)	1i,j

[a] All rotations taken in CH_2Cl_2 (c = 2.0). [b] Prepared from 3 using only $LiAlH_4$; all other entries in this column were obtained using $LiAlH_3$·$AlCl_3$. [c] $[\alpha]_D$ = +20.0° (MeOH); $[\alpha]_D$ = +31.0° (2 N, HCl). [d] $[\alpha]_D$ = -13.8° (THF). [e] $[\alpha]_D$ = -8.2° (MeOH). [f] Obtained via β-lithio cleavage of 6. [g] All products are >98% ee via HPLC analyses and/or comparison with literature values.[1]

Larson.[2] It should be noted that the R group in the keto acid ultimately becomes the 2-substituent in the pyrrolidine 1. We examined a series of 3-acylpropionic acids and each was smoothly transformed into the bicyclic lactam 3 by simply heating an equimolar mixture of the keto acid with R-phenylglycinol[3] in toluene overnight (Table I). Related bicyclic lactams from valinol and *tert*-leucinol have been reported earlier to lead to a variety of chiral products.[4] All the bicyclic lactams in the table have been shown (NMR) to be comprised of a single diastereomer with the absolute configuration as written.

The synthetic value of lactams 3 was adequately demonstrated when we found that treatment with $LiAlH_4$·$AlCl_3$ (AlH_3) in THF[5] at -78 °C proceeded to reduce the carbonyl group and simultaneously cleave the oxazolidine ring to pyrrolidines, 4. In one instance 3 (R = CH_2Ph) was reductively cleaved using only lithium aluminum hydride in the absence of $AlCl_3$. However, reductions using $LiAlH_4$·$AlCl_3$ were consistently cleaner, affording 4 as stereochemically homogeneous materials. Transformation of 4 to the 2-substituted pyrrolidines 1 was accomplished by removing the *N*-alkyl substituent via reductive cleavage (ammonium formate–palladium-on-carbon in methanol, 19 h, 25 °C).[6] These mild hydrogenolyses proceeded smoothly and led to unoptimized reasonable yields (Table I) of 1 as pure, isolated materials. The enantiomeric purity of these products was evaluated via HPLC analysis using chiral columns.[7]

In the case of the 2-phenylpyrrolidine 4 (R = Ph), the reductive cleavage obviously could not be employed since there were two benzylic amino groups present. In order to circumvent this problem we transformed 4 into the thiophenyl derivative, 5, using triethylphosphine and diphenyl disulfide.[8] The crude thiophenyl derivative was next treated with lithio di-*tert*-butylbiphenyl[9] (LiDBB) affording the lithio derivative 6 which spontaneously underwent the expected fragmentation to 2-phenylpyrrolidine in 51% overall yield. This latter procedure for removing the chiral auxiliary now allows for extended latitude in reaching pyrrolidines which contain reducible 2-substituents (alkenyl, aryl, etc.).



We further examined the potential of this route to chiral pyrrolidines by asking whether one could insert a substituent into a bicyclic lactam containing only an angular hydrogen substituent, e.g. 3 (R = H). When we allowed the bicyclic lactam 3 (R = H), recently reported by our group,[10] to react with allyltrimethylsilane–$TiCl_4$ at -78 °C in CH_2Cl_2, we obtained the allylpyrrolidone 7 in 92% isolated yield. The ratio of diastereomers in 7 was assessed at >9:1 (NMR), and the pure isomer (82%) was obtained by radial chromatography (silica gel, EtOAc–hexane). After removal of the *N*-alkyl substituent via the thiophenyl derivative, 8, and LiDBB, the 2-allylpyrrolidone (+)-9 was obtained in >50% yield (from 3, R = H). Reduction of (+)-9 with lithium aluminum hydride gave 2-allylpyrrolidine 1 (R = allyl) in 80% yield. In order to assign the absolute configuration to the 2-allylpyrrolidine and also provide some insight into the stereochemical result using allyltrimethylsilane–$TiCl_4$, we sought to establish the stereochemistry of the allylated product (+)-7 with that prepared from 3 (R = *n*-Pr). This correlation was readily accomplished by reducing the allyl group in (+)-7 to the propyl derivative 10 under Pd/C–ammonium formate conditions which did not result in hydrogenolytic cleavage of the *N*-benzyl group of the pyrrolidone. The carbonyl group in 10 was reduced to the known *N*-alkylpyrrolidine 4, previously obtained by alane reduction of 3 (R = *n*-Pr). Both products were identical spectroscopically and in sign and magnitude of rotation ($[\alpha]_D$ = -120 ± 2°), indicating that *the allylsilane addition to 3 (R = H) proceeded with inversion, whereas alane additions to 3 (R = alkyl, aryl) proceeded with retention.*

Rationalization of the stereochemical results described herein is based on earlier studies of acetal-like ring openings.[11,12] We currently envision the alane coordinating with the ring oxygen in 3 resulting in an intramolecular

(2) Bentacourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039. For a related detailed procedure, see: Larson et al. *Org. Synth.* **1989**, *67*, 125.

(3) Aldrich, or reduction of phenylglycine using the procedure described for valinol (*Org. Synth.* VII, 530, Procedure A).

(4) Meyers, A. I.; Bienz, S. *J. Org. Chem.* **1990**, *55*, 791 and earlier papers cited.

(5) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.

(6) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.

(7) The percent enantiomeric excess of all pyrrolidines in Table I was compared to the specific rotations found in the literature[1] but for more precise and meaningful assessments, compounds 1 (R = Ph, $PhCH_2$, heptyl) were transformed into their respective *N*-naphthoyl derivatives (from 1-naphthoyl chloride) and subjected to HPLC analysis. Both racemic and enantiomeric pyrrolidines were prepared and their 1-naphthoyl derivatives examined (25% EtOH–hexane) on a Diacel OJ cellulose-based chiral column (Diacel Chemical Industries). Cf.: Okamoto, Y.; Hatada, K. *J. Chromatog.* **1987**, *95*, 389.

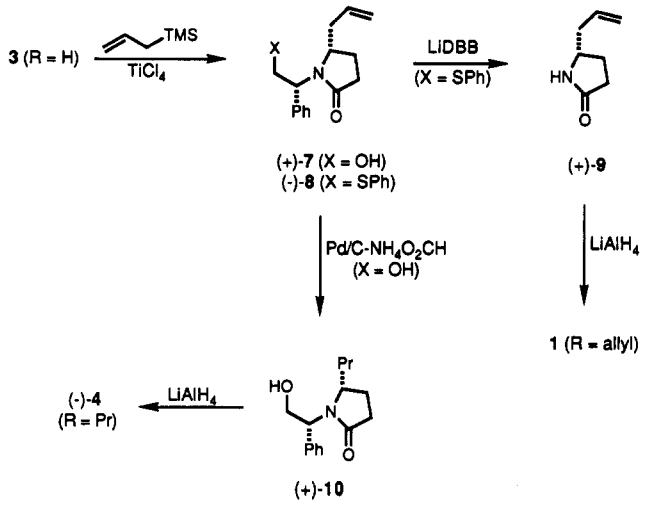
(8) (a) Hata, T.; Sekine, M. *Chem. Lett.* **1974**, 83. (b) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. (c) Cleary, D. G. *Synth. Commun.* **1989**, 737.

(9) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924; **1983**, *48*, 4705.

(10) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum L. J. *J. Org. Chem.* **1989**, *54*, 4243.

(11) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595 and earlier references. For a recent overview on this area, see: Alexakis, A.; Mangeney, P. *Tetrahedron-Asymmetry* **1990**, *1*, 477–511.

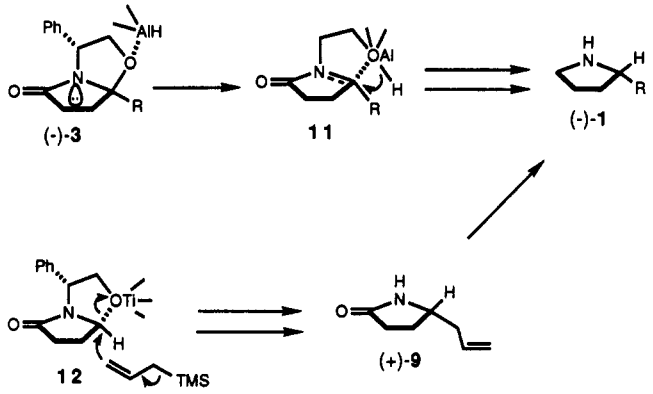
(12) Recent reports by Heathcock, Bartlett, Yamamoto, et al. (*J. Org. Chem.* **1990**, *55*, 6107) and Denmark (*J. Am. Chem. Soc.* **1989**, *111*, 3475) call attention to the fact that Lewis acid catalyzed acetal ring openings are highly substrate dependent and that many S_N2-like cleavages may in fact be proceeding through S_N1 transition states. In the present study, we can only state that the allyl pyrrolidinone 9 is a "S_N2 product" and whether or not the cleavage of 12 is a S_N1 or S_N2 process is not known for certain at this time.



hydride delivery as depicted by 11 thus furnishing the pyrrolidine 1. However, it is unknown at this time whether the carbonyl is reduced prior to or after the hydride is delivered at the angular position. The configuration of the resulting pyrrolidines agrees well with all the earlier assignments in this series.[1] In the case of the allylsilane addition the analogy is seen to work on acetals[11] where Lewis acid initiated ring opening proceeds in an S_N2-like fashion.[12] Thus, we consider 12 as the key step in the allylation reaction and this leads to 9 and ultimately to 1.

Once again, it is noteworthy to mention that the hydride cleavage proceeds with retention while the allylsilane proceeds with inversion resulting in both processes furnishing the same absolute stereochemical alignment in the pyrrolidines.

Further studies are in progress to reach more elaborate systems as well as 2,5-dialkylpyrrolidines.



Acknowledgment. Financial support by the National Institutes of Health is gratefully acknowledged.

Supplementary Material Available: Experimental details and physical properties of all compounds and an HPLC plot of enantiomeric 2-benzylpyrrolidine (14 pages). Ordering information is given on any current masthead page.

Asymmetric Olefin Epoxidation with Sodium Hypochlorite Catalyzed by Easily Prepared Chiral Mn(III) Salen Complexes

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Received January 15, 1991

Summary: A practical method is described for the asymmetric epoxidation of *cis*-β-methylstyrene by commercial bleach with up to 86% ee.

We recently reported a new method for the asymmetric epoxidation of simple olefins involving catalysis by chiral salen (*N,N'*-bis(salicylideneamino)ethane) Mn(III) complexes.[1] These constitute the most enantioselective nonenzymatic olefin epoxidation catalysts reported thus far in which asymmetric induction results solely from nonbonded interactions.[2] The utility of the initially reported method was restricted, however, by a technically difficult catalyst synthesis and by the prescribed use of iodosylarenes as stoichiometric oxidants. We describe herein key improvements to this technology, including a simplified synthesis of the chiral salen-based Mn(III) epoxidation catalysts and a highly practical epoxidation procedure that employs commercial bleach as the stoichiometric oxidant.

The chiral catalysts **1a–c** used in this study were prepared from the readily available chiral auxiliary (*R,R*)- or (*S,S*)-1,2-diamino-1,2-diphenylethane (**2**; Scheme I).[3,4] The requisite hindered salicylaldehydes **4a–c** were con-

(1) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

(2) For other studies directed toward the asymmetric catalytic epoxidation of unfunctionalized olefins, see refs 1 and 4 in ref 1. For more recent work, see: (a) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

(3) Williams, O. F.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 4464. Resolution: Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 931. An extremely convenient route to **2** was recently reported: Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(4) General procedure for the preparation of **1**. Salicylaldehyde derivative **4** (2.0 equiv) is added as a solid to a 0.2 M solution of (*R,R*)- or (*S,S*)-**2** (1.0 equiv) in absolute ethanol. The mixture is heated to reflux for 1 h and then H_2O is added dropwise to the cooled bright yellow solution (occasionally product begins to crystallize prior to addition of water). The resulting yellow crystalline solid is collected by filtration and washed with a small portion of 95% ethanol. The yields of analytically pure **5** obtained in this manner are in the range of 91–97%. The ligand **5** is redissolved in hot absolute ethanol to give a 0.1 M solution. Solid $Mn(OAc)_2 \cdot H_2O$ (2.0 equiv) is added in one portion and the solution is refluxed for 1 h. Approximately 3 equiv of solid LiCl are then added and, the mixture is heated to reflux for an additional 0.5 h. Cooling the mixture to 0 °C affords the Mn(III) complex **1** as dark brown crystals that are washed thoroughly with H_2O and isolated by filtration in ~75% yield. An additional crop of material can be obtained by dropwise addition of H_2O to the mother liquor. Combined yields of catalyst **1** are 89–96% for this step and 81–93% overall from the optically pure diamine **2**. Acceptable C, H, N, Cl, and Mn analyses of **1** have been obtained (±0.4%), but these vary according to the extent of water and ethanol incorporation in the powdery product. Enantioselectivities in the epoxidation reactions are invariant with different batches of a given catalyst, indicating that the solvent content of **1** does not influence its effectiveness.

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