the proposed initially-formed tbp's analogous to **4** (e.g., **8**[11]) suffer from a severe steric interaction between an alkyl group on the ligand and an apical substituent within the tbp. In other words, though the corresponding transition structures for aldol reaction of **5** and **6** with benzaldehyde seem reasonable, there appears to be no low-energy pathway for their formation. Further consideration of structure **8**[11] suggests that a viable intermediate might be produced by epimerization of the methyl-bearing carbon, a proposal supported by experiment. (1*S*,2*S*)-Pseudoephedrine-derived ketene *N*,*O*-acetal **9** undergoes smooth aldol condensation with benzaldehyde at 60 °C to form the (2*S*,3*R*)-anti aldol product **10** (mp 156–158 °C) in 70% yield. X-ray analysis of **10** shows the structure to be analogous to **2**, supporting, though certainly not proving, a common reaction mechanism.

In summary, it is proposed that attack of benzaldehyde on **1** produces **4**, which then undergoes pseudorotation and (rate-determining) C–C bond formation to afford **2**. The formation of other tbp isomers by attack on a different tetrahedral face of **1** with subsequent pseudorotational isomerizations to **4** (at least two are required) is not ruled out; however, the proposed mechanism is simpler. This mechanism follows rationally from consideration of the experimental data and appears to correlate results obtained with several different substrates. Finally, in addition to providing mechanistic insight, the pseudoephedrine-derived *O*-silyl ketene *N*,*O*-acetal **9** is anticipated to be of value in the synthesis of enantiomerically pure anti aldol products.

Acknowledgment. Generous financial assistance from the National Science Foundation and the David and Lucile Packard Foundation is gratefully acknowledged. We are indebted to Professor Kurt Mislow for helpful discussions.

Supplementary Material Available: A Hammett plot of the reaction of **1** with a series of substituted benzaldehydes (1 page). Ordering information is given on any current masthead page.

(10) Structures **3** and **4** may represent energy minima or simply points along the surface leading to **2**; the data available at this time do not allow resolution of this issue.

(11) The enantiomer is depicted for visual comparison of homochiral structures.

Asymmetric Synthesis of (−)-Quinocarcin

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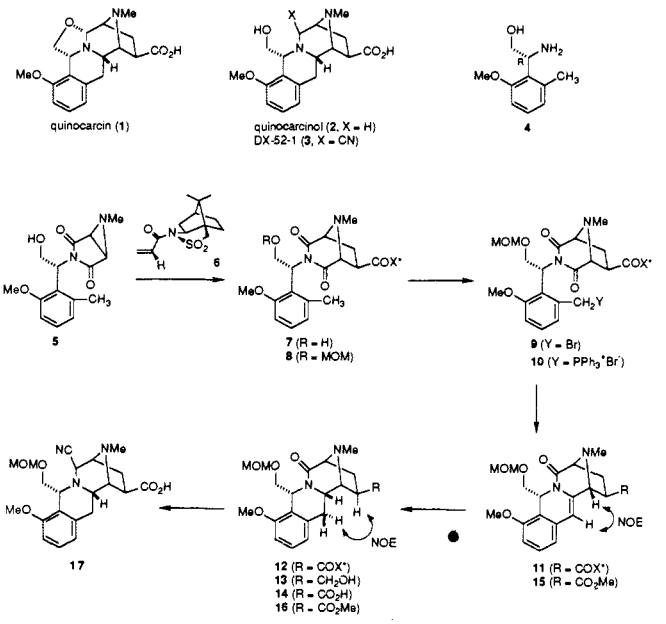
Quinocarcin (**1**)[1] is an antitumor antibiotic isolated from *Streptomyces melanovinaceus* whose structure was deduced from the X-ray analysis of quinocarcinol (**2**), an inactive homologue which lacks the hemiaminal function. Quinocarcin itself is rather labile but can be converted to a more stable amino nitrile derivative DX-52-1 (**3**) by treatment with CN^-, and **1** can be regenerated with $AgNO_3$ or strong acid.[2] The antitumor activity of **1** appears to be tied to the inhibition of DNA and/or RNA synthesis.[3] Quinocarcin's absolute configuration was not determined, but a computational study suggests that the enantiomer shown may be preferred for binding to DNA.[4] Although total syntheses of racemic **1** and **2** have been reported,[5] recent work has focused on developing enantiospecific approaches to these molecules.[6] We now report the first asymmetric synthesis of (−)-**1**.

The synthesis begins with (*R*)-phenylglycinol derivative **4**,[7] which is converted to the aziridine imide **5**[8] in 31% overall yield via a five-step sequence analogous to one used in our model studies.[9] Building on our previously elaborated strategy,[10] an auxiliary-controlled 1,3-dipolar cycloaddition reaction would be used to assemble the 3,8-diazabicyclo[3.2.1]octane moiety of **1**.[11] In the event, portionwise addition of (+)-acryloyl sultam **6**[12] to an irradiated (2537 Å, quartz) solution of **5** in 1,4-dioxane resulted in a very clean reaction to give **7** (X* = (+)-sultam), the cycloadduct resulting from addition of the intermediate azomethine ylide to the *exo-si* face of the dipolarophile **6**, in 61% isolated yield. At this juncture, the free hydroxyl function was masked (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 86%) to give the MOM ether **8**.



Benzylic bromination of **8** (0.01 M, NBS, $CHCl_3$, *hν*) afforded the monobromide **9**, which was directly converted to the phosphonium salt **10** (Ph_3P, $CHCl_3$, 56% over two steps). Treatment of **10** with *t*-BuOK resulted in the formation of a phosphonium ylide, which, upon heating (DMF, 120 °C), cyclized to give the required dihydroisoquinoline **11** in 79% yield.[13] The regioselectivity of this intramolecular imide olefination can be ascribed

(1) (a) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468. (b) Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1705.

(2) (a) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. (b) Saito, H.; Kobayashi, S.; Uosaki, Y.; Sato, A.; Fujimoto, K.; Miyoshi, K.; Morimoto, A.; Hirata, T. *Chem. Pharm. Bull.* **1990**, *38*, 1278.

(3) (a) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268. (b) Fujimoto, K.; Oka, T.; Morimoto, M. *Cancer Res.* **1987**, *47*, 1516. (c) Kanamaru, R.; Konishi, Y.; Ishioka, C.; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakui, A. *Cancer Chemother. Pharmacol.* **1988**, *22*, 197.

(4) Hill, G. C.; Wunz, T. P.; Remers, W. A. *J. Comput.-Aided Mol. Des.* **1988**, *2*, 6029.

(5) (a) (±)-**2**: Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neil, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421. (b) (±)-**1**: Fukuyama, T.; Nunes, J. J. *Ibid.* **1988**, *110*, 5196.

(6) (a) Saito, S.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1988**, *29*, 6301. (b) Saito, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Terashima, S. *Ibid.* **1989**, *30*, 7423. (c) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Ibid.* **1990**, *31*, 2105.

(7) This compound was prepared in >99% ee by asymmetric azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011) of the (1*S*,2*R*)-norephedrine derived oxazolidine imide of 2-methoxy-6-methylbenzeneacetic acid followed by reduction. Details will be provided in the full account of this work.

(8) All of the compounds depicted in this paper exhibited satisfactory spectral and/or analytical data.

(9) **4** → **5**: (1) maleic anhydride, Et_2O; (2) Ac_2O, NaOAc, 120 °C; (3) 5 N HCl, THF; (4) MeN_3, toluene; (5) *hν* (Hg, Pyrex), 1,4-dioxane. (See ref 10 for details.)

(10) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

(11) For a related approach to quinocarcin, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Ibid.* **1990**, *31*, 1012.

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(13) Flitsch, W.; Langer, W. *Liebigs Ann. Chem.* **1988**, 391. This application of Flitsch's imide olefination protocol to the synthesis of dihydroisoquinoline systems is, to our knowledge, unprecedented.

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to a transition state conformation that places the benzylic methine (rather than the CH_2OMOM group) in the imide plane so that the ylide approaches the *pro-R* imide carbonyl from the exo face.[14] Hydrogenation of **11** (1400 psi of H_2/Raney Ni (W2), EtOH, 65-70 °C) occurred from the exo face to afford nearly equal amounts of **12** and the overreduced byproduct **13** in 64% combined yield. Saponification of **12** (LiOH, THF-H_2O) produced the carboxylic acid **14** in quantitative yield. Alternatively, the sultam auxiliary could be removed from **11** (LiOH) and the resulting acid esterified (CH_2N_2, 63% overall) to provide **15**, which underwent clean hydrogenation to **16** in 67% yield. Select NOE experiments on both **15** and **16** served to confirm our structure assignments at this stage.

Following the protocol that Evans used in his cyanocycline A synthesis,[15] the hindered lactam of **14** could be partially reduced with Li/NH_3 and the resulting hemiaminal converted directly to the stable amino nitrile **17** (NaCN, H_2O, 60% overall). The racemic version of **17** was an intermediate in Fukuyama's synthesis of (±)-quinocarcin. Deprotection of **17** (NaI, TMSCl, MeCN, 72%) afforded a compound corresponding to **3**, which was then converted to (-)-quinocarcin (**1**) ($AgNO_3$, MeOH, H_2O, 89%). The ^1H and ^{13}C NMR data obtained for synthetic **1** matched those reported in the literature[1a] as well as those of an authentic sample. Comparison of the optical rotation of synthetic **1** ($[\alpha]^{25}_D$ -30° (*c* 0.2, H_2O)) with that of natural quinocarcin (lit.[1a] $[\alpha]^{25}_D$ -32° (*c* 0.50, H_2O)) confirms that the absolute configuration of the natural product is as shown.

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Supplementary Material Available: HPLC, ^1H NMR, ^{13}C NMR, and HRMS data for synthetic (-)-quinocarcin (**1**) (4 pages). Ordering information is given on any current masthead page.

(14) For a similar argument governing a highly stereoselective *intramolecular* cycloaddition, see: Garner, P.; Sunitha, K.; Ho, W. B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041.

(15) (a) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478. (b) Illig, C. R. The Total Synthesis of (±)-Cyanocycline A and (+)-Cyanocycline A. Ph.D. Dissertation, Harvard University, 1987.

Chiral Lewis Acid Catalysis. Enantioselective Addition of Azide to Meso Epoxides

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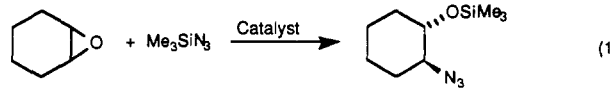
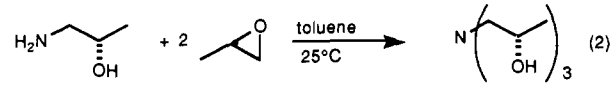
Chiral Lewis acid catalysis is emerging as a powerful tool for enantioselective synthesis.[1] One potentially useful class of reactions has heretofore proven elusive. The asymmetric cleavage of meso epoxides exemplified by eq 1 simultaneously establishes two contiguous stereogenic centers.[2] We now report a successful approach to this problem utilizing a novel type of chiral Lewis acid.



(1)

It has been reported[3,4] that eq 1 proceeds in modest enantiomeric excess in the presence of a stoichiometric amount of titanium isopropoxide/dimethyl tartrate. However, use of a catalytic amount of the titanium alkoxide resulted in essentially racemic product.[3] This suggested to us that the chiral ligand was being lost in the presence of excess azidotrimethylsilane and that this might be overcome by use of a tightly binding multidentate ligand. Trialkanolamines seemed an especially advantageous choice as ligand; they are easy to prepare, and the parent triethanolamine is known to form stable alkoxides with many early transition metals.[5] To test this notion, (+)-(*S*,*S*,*S*)-triisopropanolamine[6,7] (88% de) was prepared quantitatively by the reaction of commercially available (*S*)-(+)-1-amino-2-propanol (Aldrich, 91% ee) and (*S*)-(-)-propylene oxide (Aldrich, 98.6% ee) according to eq 2.[8]



(2)

Treatment of zirconium *tert*-butoxide in THF with this trialkanolamine (LH_3 in eq 3) followed by distillation of the solvent affords **1** as a white powder. As expected,[9] the spectroscopic

(3)

(1) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481-1483. Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789. Review: Narasaka, K. *Synthesis* **1991**, 1-11.

Table I. Effect of Catalyst and Promoter on Enantioselectivity of Eq 1[a]

catalyst/ promoter	enantiomeric excess (%) and sign of rotation			
	none	HOAc[b]	HO_2CCF_3[c]	$Me_3SiO_2CCF_3$[d]
1	6 (+)	19 (-)	13 (+)	3 (+)
2	3 (+)	2 (+)	19 (-)	11 (-)
3	19 (-)	70 (-)	87 (-)	86 (-)

[a] All runs contain cyclohexene oxide (1.2 mmol), Me_3SiN_3 (1.2 mmol), and catalyst (0.1 mmol of Zr) in 1,2-dichlorobutane (3.0 mL), 18 h, 25 °C. [b] Additionally contains 1.0 μL of 50% aqueous acetic acid. [c] Additionally contains 1.0 μL of 50% aqueous trifluoroacetic acid. [d] Additionally contains 3.0 μL of trimethylsilyl trifluoroacetate.

(2) For other examples of "the meso trick", see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320-1367.

(3) Emziane, M.; Sutowardoyo, K. I.; Sinou, D. *J. Organomet. Chem.* **1988**, *346*, C7-C10. See also: Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett* **1991**, 774-776.

(4) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213.

(5) (a) Bostwick, C. O. U.S. Patent 2,824,114, 1958; *Chem. Abstr.* **1958**, *52*, 7734. (b) Taube, R.; Knoth, P. *Z. Anorg. Allg. Chem.* **1990**, *581*, 89. (c) Astakhov, A. I.; Kas'yanenko, A. I. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1972**, *15*, 1620; *Chem. Abstr.* **1973**, *78*, 66407. (d) Mehrota, R. C.; Kapoor, P. N. *J. Indian Chem. Soc.* **1967**, *44*, 467. (e) Mehrota, R. C.; Kapoor, R. N. *Indian J. Chem.* **1967**, *5*, 5051. (f) Menge, W. M. B. P.; Verkade, J. G. *Inorg. Chem.* **1991**, *30*, 4628-4631.

(6) (*S*,*S*,*S*)-Triisopropanolamine has been used previously as a chiral auxiliary for the asymmetric reduction of ketones with metal hydrides: Morrison, J. D.; Grandbois, E. R.; Weisman, G. R. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series 185; American Chemical Society: Washington, DC, 1982.

(7) For diastereoisomeric mixtures of transition metal alkoxides prepared from racemic triisopropanolamine: Tandura, S. N.; Voronkov, M. G.; Kisin, A. V.; Shestakov, E. E.; Ovchinnikova, Z. A.; Baryshok, V. P. *Zh. Obshch. Khim.* **1984**, *54*, 2010. Voronkov, M. G.; Faitel'son, F. D. *Khim. Geterotsikl. Soedin.* **1967**, 39; *Chem. Abstr.* **1967**, *67*, 64321.

(8) Alternatively, this trialkanolamine could be made directly (in 94% de) from (-)-(*S*)-propylene oxide and ammonia: Grassi, M.; Di Silvestro, G.; Farina, M. *Tetrahedron* **1985**, *41*, 177-181.

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