Finally, while on the subject of asymmetric epoxidations we note that the importance of achieving anhydrous conditions in these reactions cannot be overemphasized. We recently examined the effect of adding known amounts of water to a standard asymmetric epoxidation reaction using (*E*)-α-phenylcinnamyl alcohol as substrate. The enantiomeric excess was 99% with no water added and plummeted to 48% with 1 equiv of added water.[7] We believe that when substandard results are obtained in an asymmetric epoxidation, the first suspicion should be that water has somehow crept in. Small-scale and catalytic epoxidations will obviously be most vulnerable to the deleterious effect of adventitious water.

Experimental Section

Preparation of Anhydrous *tert*-Butyl Hydroperoxide (TBHP) in Toluene. CAUTION.[8] To a 1-L separatory funnel was added 325 mL of TBHP-70 (Aldrich or ARCO) [70% TBHP, 30% H_2O], and then 400 mL of reagent-grade toluene was added and the solution swirled (do not shake, otherwise an emulsion may form). The aqueous layer (75 mL) was separated and the organic layer transferred to a 1-L two-necked flask equipped with a Dean–Stark trap (15-mL side arm), a reflux condenser, and a thermometer (all set up in a well-ventilated hood). After addition of several boiling chips, the solution was refluxed by using a heating mantle (caution: prevent overheating the TBHP by avoiding high power settings and by not allowing the solvent level to drop below the level of the top of the mantle).

After 1 h of reflux, about 20 mL of water was removed (note: side arm must be emptied at least once). At this point there was no further accumulation of water. Water begins accumulating at a pot temperature of 84 °C, and after less than 1 h, a constant pot temperature at 107 °C was reached. After visible accumulation of water had stopped, the system was protected from atmospheric moisture by use of a drying tube filled with Drierite, and ca. 20 mL of distillate was removed through the side arm to ensure removal of the last traces of water. After cooling, the remaining (ca. 600 mL) TBHP/toluene solution was transferred to a brown glass bottle (polyethylene cone cap)[9] and stored at *room temperature*[10] over activated 4-Å molecular sieves (sieves optional, but *do not* use larger pore size sieves). This solution was approximately 3.3 M in TBHP,[11] and no change in titer was observed after storage for 3 months under these conditions.[12]

This procedure has been performed on up to four times this scale.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8007622) for financial support. Helpful discussions with Drs. Lendon Pridgen and Lee Webb of Smith Kline and French and with our colleague Professor Frederick D. Greene are gratefully acknowledged. We are indebted to Drs. Frank W. Long and John F. White of ARCO for generous gifts of TBHP.

Registry No. (*E*)-α-Phenylcinnamyl alcohol, 62668-02-4; TBHP, 75-91-2; toluene, 108-88-3.

(7) M. G. Finn and Jon Ellman, unpublished results.

(8) We have carried out this procedure many times without incident. However, solutions of oxidants and oxidizable substrates are potentially hazardous and possibly subject to violent decomposition by adventitious catalysts. We have previously discussed (see section V of ref 1) the safety considerations related to handling solutions of TBHP, but it seems appropriate to repeat some of the key points here.

The first rule is never add a strong acid (not even a drop) to high-strength TBHP solutions. The second rule is never add transition-metal salts known to be good autoxidation catalysts (e.g., Mn, Fe, and Co are particularly bad) to high-strength TBHP solutions. Alkyl hydroperoxides are sensitive to metal-catalyzed radical-chain decomposition. Among other things this produces a lot of oxygen gas. The third rule is never work with pure TBHP and avoid using high-strength solutions of it whenever possible.[1]

(9) Do not use polyethylene containers as they are permeable to these solutions (preferentially to the toluene) and one observes a constantly increasing peroxide titer.

(10) These solutions are perfectly stable for many months at room temperature and do not require refrigeration. In fact, we have observed that refrigeration actually reduces their useful lifetimes by accelerating the rate at which atmospheric moisture is introduced.

(11) The active oxygen content of these ca. 3 M solutions is near 5%. One can of course prepare more or less concentrated solutions by simply adjusting the initial toluene/TBHP ratio. However, we strongly recommend that concentrations of 3–4 M be regarded as the upper limit for these TBHP solutions.

(12) The exact molarity is best determined by titration as described in footnote 58a of ref 1 above. However, as before (see note 58b in ref 1), we have found NMR analysis to be reasonably accurate (±5%) and more convenient. The equation we use for toluene solutions is molarity = $X/[0.1X + 0.32Y]$ where X = integration of the *tert*-butyl resonance ($\delta \sim 1.25$) and Y = integration of the methyl resonance ($\delta \sim 2.4$).

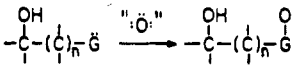
Communications

Kinetic Resolution of Racemic β-Hydroxy Amines by Enantioselective *N*-Oxide Formation

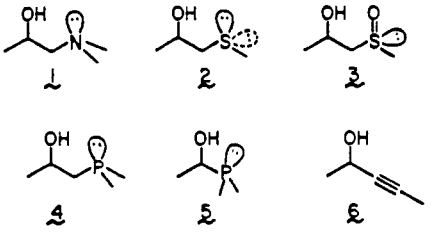
Summary: Enantioselective oxidation using TBHP and an asymmetric titanium–tartrate complex provides direct access to a variety of homochiral β-hydroxy amines.

Sir: Soon after the discovery of the asymmetric epoxidation of allylic alcohols,[1] we realized that the same titanium–tartrate catalyst might be effective for the larger class of asymmetric oxidations depicted in a most general manner in Scheme I.[2] In this conception, the only structural requirements for the substrate are a hydroxyl group for coordination to the chiral metal center and a proximate locus (G) in the molecule capable of accepting an oxygen atom.[2] Some tangible embodiments of this

Scheme I



Scheme II

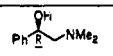
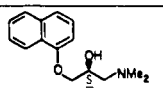
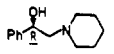
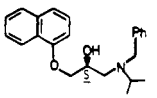
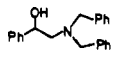
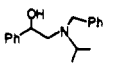
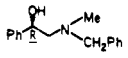
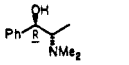
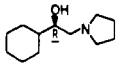
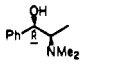
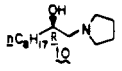
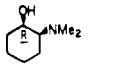
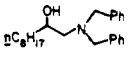
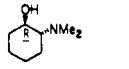
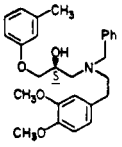
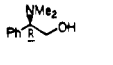
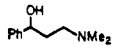


(1) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(2) Scheme I appears in U.S. Patent Application 175 786, "The First Practical Method for Asymmetric Epoxidation", filed August 6, 1980, assignee the Board of Trustees of Leland Stanford Junior University.

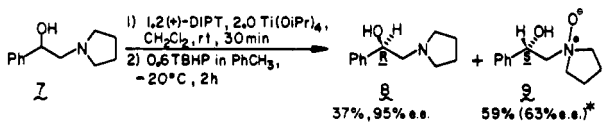
0022-3263/83/1948-3608$01.50/0

Table I[a]

run	slow reacting[b] (i.e., recovered) enantiomer	% ee[c]	run	slow reacting[b] (i.e., recovered) enantiomer	% ee[c]
1		95 (−47.8, *c* 1.16, MeOH)	9		92 (−2.6, *c* 2.4, EtOH)
2		97 (−51.3, *c* 1.12, EtOH)	10		32 (+8.5, *c* 1.84, EtOH)
3		0	11		0
4		79 (−41.0, *c* 2.19, EtOH)	12		98 (−26.3, *c* 1.08, MeOH)
5		92 (−20.7, *c* 1.37, EtOH)	13		75 (−32.4, *c* 1.52, MeOH)
6		94 (−1.19, *c* 1.26, EtOH)	14		>95 (−2.95, *c* 1.56, MeOH)
7		0	15		92 (−25.4, *c* 2.05, EtOH)
8		85 (+13.7, *c* 3.55, EtOH)	16		34 (−5.7, *c* 1.07, MeOH)
			17		0

[a] All these oxidative kinetic resolutions were carried to 60% conversion under the conditions described in the typical experimental procedure, except on a smaller scale (i.e., only 1 or 2 mmol instead of 10 mmol). [b] See the supplementary material for determination of absolute configuration. [c] Enantiomeric excess determined by using Eu(hfbc)$_3$ chiral shift reagent on the acetates[23] or via the Mosher esters, made from (+)-MTPACl. The $[\alpha]^{20}_D$ for each product is given in parentheses (rotation, concentration, solvent).

Scheme III



*Calculated e.e. for 2 based on 60% conversion and measured e.e. for 2

notion are encompassed by the potential substrates shown in Scheme II.

We recently described very modest success in oxidative kinetic resolutions of β-hydroxy sulfides **2** and α-acetylenic alcohols **6**.[3] Such poor results are in stark contrast to the dramatically successful kinetic resolutions of racemic allylic alcohols.[4] Our earlier experiments[5] with β-hydroxy amines **1** also suggested that they were not promising substrates for the kinetic resolution process. However, a recent closer look, under somewhat different conditions, has revealed that many β-hydroxy amines are excellent substrates for oxidative kinetic resolution. A typical result is shown in Scheme III.

The oxidation by TBHP of tertiary amines to *N*-oxides, catalyzed by early transition metals, is not new.[6] In fact, there is even one report of titanium alkoxide catalyzed oxidation of a β-hydroxy amine to its *N*-oxide by TBHP.[7]

What is new in the present work is the discovery that the oxidation can be effected in a highly enantioselective manner. Furthermore, examination of the results in Table I for various hydroxy amines reveals a process of both substantial scope and predictability. When the natural tartrate ester is employed, the slow reacting enantiomer is always that related to **8** in Scheme III (i.e., when the hydroxyl group is up, the amine group is on the right).[8] Thus the new system shares this desirable feature of predictability with the parent process for kinetic resolution of allylic alcohols.[4] *While having many features in common with the parent process for allylic alcohols, this new system exhibits one striking difference. Close inspection of Scheme III reveals that the titanium:tartrate ligand ratio is close to 2:1.* This contrasts with the asymmetric epoxidation systems[1,4] where the optimum ratio of titanium:ligand is close to 2:2. We have obtained considerable evidence that the 2:2 and 2:1 asymmetric catalysts have, as might be expected, quite different structures.[9] These structural studies will be reported elsewhere, but it is worth mentioning here that this new type of asymmetric catalyst (i.e., 2:1) may be more common than the original 2:2 type. We have also discovered, in addition to the process described herein, two[10,11] more new asymmetric oxidation processes that are based on the 2:1 type of catalyst.

A number of experiments with two different amino alcohol substrates **7** and **10** confirmed that the 2:1 catalyst

(3) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.
(4) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(5) Zilenovski, J. R.; Sharpless, K. B., unpublished results, Stanford University, 1980.
(6) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588.
(7) Kuhnen, L. *Chem. Ber.* **1966**, *99*, 3384.
(8) Since the *R* and *S* designation varies with the substrate, the need for this type of convention is obvious.
(9) Woodard, S. S.; Finn, M. G.; Sharpless, K. B., unpublished results.
(10) Lu, L. D.-L.; Finn, M. G.; Sharpless, K. B., unpublished results.
(11) Johnson, R. A.; Sharpless, K. B., unpublished results.

type is optimum. Use of the 2:2 type catalyst with **7** gave 71% ee instead of 95% ee at 60% conversion. The same experiment with the less hindered amino alcohol **10** gave 0% ee instead of the 94% ee reported in entry 6 of Table I. We believe that the oxidation is usually slow on the 2:2 catalyst but that when it does proceed it gives enantioselectivity opposite from the 2:1 catalyst.

The examples in Table I were in part chosen to demonstrate the exquisite sensitivity of this new process to the nature of the substituents on nitrogen. Smaller substituents obviously lead to better resolution, but the borderline separating success from failure can be surprisingly sharp (cf. entries 3 and 4, 7 and 8, and 10 and 11). The subtle features of this "steric window" are still under study, but we note here our suspicion that these β-hydroxy 3° amines are behaving, probably for similar reasons,[12] like the (*Z*)-allylic alcohols in previous investigations.[3,4] In keeping with the (*Z*)-allylic alcohol analogy (see ref 4, Table I, entries 5 and 6), the enantiomeric oxidation rate differences for most of the cases in Table I lie between 10:1 and 20:1. Such rate differences are sufficient to give excellent enantiomeric purity at 60–70% conversion.[13]

Precursors to the β-blocker class of molecules (i.e., entries 8,[14] 9, and 10) are generally good substrates, but a better protecting group than benzyl is being sought for those cases having an α-branched nitrogen substituent (e.g., the propranolol precursor in entry 10). *N*-Methylephedrine and *N*-methylpseudoephedrine (entries 12 and 13, see also entries 14 and 15) provide interesting examples of the "matched/mismatched"[15] influence of a second chiral center. In the one case examined (entry 16), a poorer result obtained when the carbinol carbon was not chiral. The single γ-hydroxy amine (entry 17) attempted was a convincing failure.

Even with the above-noted limitations, this new route to chiral β-hydroxy amines has many good characteristics. One of the most pleasing is the ease with which the *N*-oxide product and the unreacted amino alcohol are separated. Due to dramatic solubility differences these two substances can usually be separated by simple trituration or extraction, and chromatography is generally avoided. Furthermore, the *N*-oxide is easily reduced back to the amino alcohol of opposite configuration,[16] so that enriched samples of either enantiomer of the amino alcohol are available from a single kinetic resolution experiment.

Typical Experimental Procedure. A 300-mL, one-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar was oven-dried and then fitted with a serum cap and flushed with nitrogen while cooling. Addition of 2-pyrrolidino-1-phenylethanol (1.92 g, 10.0 mmol)[17a] and (+)-DIPT (2.84 g, 12.1 mmol)[17b] was followed by brief flushing with nitrogen.[17c] (The following procedures were carried out under a positive nitrogen pressure; reagents were added through the septum with hypodermic syringes.) The flask was then charged with 100 mL of dichloromethane (distilled from CaH_2) followed by titanium tetraisopropoxide (6.24 mL, 5.96 g, 21.0 mmol).[17b] *The mixture was stirred for 30 min at room temperature.*[18] After this aging period, the flask was cooled with stirring in a dry ice/CCl_4 bath (ca. −23 °C). To this solution was added 1.85 mL of an anhydrous toluene solution[19] (3.29 M in TBHP) containing 6.09 mmol of *tert*-butyl hydroperoxide (TBHP).[20] After stirring for 2 h[21a] in the cooling bath, the reaction was quenched by adding 100 mL of diethyl ether, 4 mL of water, and 4 mL of a 40% NaOH solution. This mixture was vigorously stirred for 10–15 h[21b] at room temperature, yielding a gelatinous precipitate which was filtered with ease through a pad of Celite and washed thoroughly with 200 mL of CH_2Cl_2.

The combined filtrates were concentrated to leave a pale yellow, viscous oil to which 3 mL of toluene was added followed by removal of the toluene under aspirator vacuum. This azeotropic drying process was repeated twice more to give a white solid.[22a] The solid was triturated in 40 mL of *n*-hexane,[22b] and the clear supernatant solution was decanted. The remaining solid was further triturated twice with 10-mL portions of *n*-hexane. This hexane-insoluble precipitate is the optically active *N*-oxide of 2-pyrrolidino-1-phenylethanol: 1.22 g (yield, 58.9% based on the starting racemic amino alcohol); $[\alpha]^{20}_D$ +35.8° (*c* 1.13, EtOH). The combined hexane extracts were diluted with 10 mL of ether, washed with water[22c] (ca. 1 mL × 3), and dried over anhydrous Na_2SO_4. The solvents were evaporated, and a trace of residual water was removed as the toluene azeotrope (vide supra) to afford optically active 2-pyrrolidino-1-phenylethanol: 0.71 g (yield 37.0% based on the starting racemic amino alcohol); $[\alpha]^{20}_D$ −40.3° (*c* 1.88, EtOH); mp 69.5–70.5 °C. Following acetylation (Ac_2O, pyridine), NMR analysis of the acetate in benzene-d_6 using Eu(hfbc)$_3$ chiral shift reagent revealed an enantiomeric excess of 95%.[23]

(12) Despite obvious differences, the transition states for both processes (i.e., epoxidation and *N*-oxide formation) bring one alkyl substituent into the same crowded area near the catalyst. For the allylic alcohol this is the (*Z*)-β-vinylalkyl substituent, and for the amine, it is the alkyl substituent on nitrogen which is syn to the coordinated amino alcohol oxygen in the transition state. The results to date suggest that this amino alcohol oxidative kinetic resolution is at least as sensitive to the size of this substituent as the corresponding process for allylic alcohols.

(13) See the graph in ref 4 for the relationship between % ee, % conversion, and relative rate.

(14) We thank Dr. Marvin S. Hoekstra of Warner-Lambert for a racemic sample of this *N*-benzyl derivative of their cardioselective β-blocker, bevantolol. The absolute configuration of the therapeutically active isomer of bevantolol has not yet been unambiguously established. However, by analogy to other β-blockers, one assumes it is the *S* enantiomer which happily is the slow-reacting enantiomer when using natural (+)-DIPT in these kinetic resolutions. For leading references on β-blockers, see: Frishman, W. H. *New Eng. J. Med.* **1981**, *305*, 500. Lefkowitz, R. J. *Annu. Rep. Med. Chem.* **1980**, *15*, 217. We are also grateful to Dr. David E. McClure of Merck for helpful discussions about β-blockers.

(15) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.

(16) There are many ways to reduce *N*-oxides to amines. We have found the use of $LiAlH_4$ in THF to be highly efficient and convenient; milder methods (e.g., catalytic hydrogenation) are also effective.

(17) (a) The amino alcohols should be dried by one of the following procedures: a, distillation; b, azeotropically by using benzene or toluene; or c, under high vacuum for 12–24 h. (b) (+)-DIPT and Ti(O-*i*-Pr)$_4$ were used as received from Aldrich. Because it is too viscous for a syringe, DIPT is delivered by weight using a Pasteur pipet. As in the kinetic resolution of allylic alcohols,[4] DIPT is superior to DET or DMT. (c) The system is not sensitive to O_2; the only purpose of the nitrogen atmosphere is to exclude moisture.

(18) This peculiar step for aging the catalyst *in the presence of the substrate* is necessary for obtaining good enantioselectivity. At present we have no explanation for this phenomenon.

(19) *See accompanying note* (Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.*, in this issue) *for preparation of anhydrous toluene solutions of TBHP. We now prefer these toluene solutions for all applications requring anhydrous TBHP*; however, TBHP in other dry organic solvents may also be used (as in ref 1).

(20) These oxidations are exothermic, and on scales any larger than the present 10-mmol example the TBHP solution should be added gradually while monitoring the reaction temperature to hold it below −15 °C.

(21) (a) These reactions may be kept at −20 °C for much longer than 2 h without affecting the results. (b) This length of time is usually required to ensure complete hydrolysis of the tartrate and to obtain a mixture that is more easily filtered.

(22) (a) In this case the *N*-oxide is less polar on TLC (100% CH_3OH) than the amino alcohol. In some cases, however, the relative polarities reverse, and in other cases the compounds coincide on TLC. Separation of the *N*-oxide from the amino alcohol was sometimes accomplished by silica gel chromatography. (b) Diethyl ether may be used instead of *n*-hexane. (c) This water wash is used to remove the final traces of the *N*-oxide, which is very soluble in water.

(23) See supplementary material for the determination of absolute configurations and of enantiomeric excesses.

Since β-hydroxy amines constitute one of the best recognized classes of pharmacologically active substances, this new method for *predictably* obtaining either desired enantiomer from a racemic mixture should find many practical applications. In addition, β-hydroxy amines are known precursors of epoxides via closure of the derived quaternary ammonium salts.[24] In this way the kinetically resolved amino alcohol in entry 9 was converted in 60% yield to the corresponding epoxide,[25] which was opened with isopropylamine in nearly quantitative yield to give (−)-propranolol.[26] Other chiral epoxides can be similarly prepared.[24,27]

With the emergence of a large new class of substrates the chiral titanium–tartrate complexes have now become asymmetric oxidation catalysts,[28] rather than simply asymmetric epoxidation catalysts.[29] This is the most significant development since the original discovery.[1] Furthermore, we noted earlier,[30] and are still exploring, nonredox asymmetric catalysis by these systems. Thus, we believe that the potential for new applications of these unique nonenzymic titanium catalysts is barely tapped and that before long they will be known simply as asymmetric catalysts.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM28384) and to Eli Lilly for financial support. S.M. thanks the Ministry of Education of Japan for the Overseas Research Fellowship (1982–1983), and S.M.V. thanks the National Science Foundation for a Graduate Fellowship. We thank Dr. Lee Weigel of Eli Lilly for a large sample of (*R*)-(−)-styrene oxide, which greatly eased problems associated with determinations of absolute configuration.

Registry No. (±)-**7**, 87040-32-2; (*R*)-**8**, 87069-57-6; (*S*)-**9**, 87040-33-3; TBHP, 75-91-2; (±)-DIPT, 2217-15-4; $Ti(OiPr)_4$, 546-68-9; (±)-*N*,*N*-dimethyl-β-hydroxyphenethylamine, 2202-68-8; (±)-2-piperidino-1-phenylethanol, 13626-20-5; (±)-*N*,*N*-dibenzyl-β-hydroxyphenethylamine, 87040-34-4; (±)-*N*-benzyl-*N*-methyl-β-hydroxyphenethylamine, 52026-30-9; (±)-1-cyclohexyl-2-pyrrolidinoethanol, 87050-10-0; (±)-1-pyrrolidino-2-decanol, 87040-35-5; (±)-*N*,*N*-dibenzyl-β-hydroxydecylamine, 87040-36-6; (±)-*N*-benzyl-*N*-(3,4-dimethoxyphenethyl)-2-hydroxy-3-(*m*-tolyloxy)propylamine, 87040-37-7; (±)-*N*,*N*-dimethyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 87040-38-8; (±)-*N*-benzyl-*N*-isopropyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 87069-61-2; (±)-*N*-benzyl-*N*-isopropyl-β-hydroxyphenethylamine, 87040-39-9; (±)-*N*-methylephedrine, 1201-56-5; (±)-*N*-methylpseudoephedrine, 87040-40-2; *cis*-(±)-2-(dimethylamino)cyclohexanol, 21651-80-9; *trans*-(±)-2-(dimethylamino)cyclohexanol, 21651-78-5; (±)-*N*,*N*-dimethyl-β-hydroxy-α-phenylethylamine, 2202-64-4; (±)-*N*,*N*-dimethyl-3-hydroxy-3-phenylpropylamine, 36296-95-4; (*R*)-*N*,*N*-dimethyl-β-hydroxyphenethylamine, 34469-09-5; (*R*)-2-piperidino-1-phenylethanol, 40116-77-6; (*R*)-*N*-benzyl-N-methyl-β-hydroxyphenethylamine, 87098-81-5; (*R*)-1-cyclohexyl-2-pyrrolidinoethanol, 87098-82-6; (*R*)-1-pyrrolidino-2-decanol, 87069-58-7; (*S*)-*N*-benzyl-*N*-(3,4-dimethoxyphenethyl)2-hydroxy-3-(*m*-tolyloxy)propylamine, 87069-59-8; (*S*)-*N*,*N*-dimethyl-2-hydroxy-3-(1-naphthyloxy)-propylamine, 87069-60-1; (*S*)-*N*-benzyl-*N*-isopropyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 53729-51-4; (−)-*N*-methylephedrine, 552-79-4; (−)-*N*-methylpseudoephedrine, 14222-20-9; (1*R*,2*S*)-2-(dimethylamino)cyclohexanol, 21651-71-8; (1*R*,2*R*)-2-(dimethylamino)cyclohexanol, 29783-02-6; (*R*)-*N*,*N*-dimethyl-β-hydroxy-α-phenylethylamine, 2202-65-5.

Supplementary Material Available: Determination of absolute configurations and details related to measurement of enantiomeric excesses of β-hydroxy amines (8 pages). Ordering information is given on any current masthead page.

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(24) (a) McClure, D. E.; Engelhardt, E. L.; Mensler, K.; King, S.; Saari, W. S.; Huff, J. R.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 1826. (b) Lyle, G. G.; Keefer, L, K. *Ibid.* **1966**, *31*, 3921. (c) Coke, J. L.; Richon, A. B. *Ibid.* **1976**, *41*, 3516 and references cited therein.

(25) The procedure of McClure et al.[24a] was followed.

(26) This step is identical with the final step in our previous synthesis of (−)-propranolol.[3]

(27) Of the various[24] procedures for closing a β-hydroxy quaternary ammonium salt to an epoxide, we find the NaH/DMF method of McClure et al.[24a] to be the most convenient, since DMF is also a good solvent for the alkylation with methyl iodide.

(28) In the present work, to realize a decent oxidation rate with only 0.6 equiv of TBHP, we use stoichiometric amounts of the titanium–tartrate complex. With more TBHP and/or longer reaction times we have seen more than one turnover per metal center, but under these conditions the enantioselectivity is also poorer. While the achiral oxidation of β-hydroxy amines with TBHP is the presence of $Ti(OR)_4$ is catalytic in the metal species,[7] it remains to be established whether this enantioselective version can be regarded as truly catalytic. The *N*-oxide product appears to be a strong inhibitor of the desired catalysis.

(29) We are now seeking to further generalize these enantioselective oxidations among the family of substrates shown in Scheme II.

(30) See footnote 16 in ref 4, which describes diastereo- and enantioselective openings of racemic epoxy alcohols by the titanium–tartrate catalyst.

Silicon-Mediated Synthesis of 11-Deoxyanthracyclines

Summary: The Hassall cyclization (**17** → **18**) has been used as a key step in the synthesis of 11-deoxycarminomycinone. Other steps include the unusual Diels–Alder addition **6** + **4a** → **7**, where the directing effect of dienol carbonate oxygen is dominated by other substituents. A benzylic silane serves as a latent leaving group and is converted into benzylic bromide (**14** → **15**) by treatment with Br_2/CsF.

Sir: We have developed a route to 11-deoxyanthracyclines based on the Hassall cyclization (as in **17** → **19**) approach to anthraquinones.[1] Key features of the sequence include good control of regiochemistry and the use of benzylic silicon as a latent leaving group.

Diels–Alder condensation of ynone **1**[2] with CH_2=CHC(OTBS)=CH_2 (Scheme I) affords the adduct **2** (75–80%, 185 °C).[5,6] Selective conversion of enol ether **2** to monoketal **3** (80%) occurs with 2,2-dimethylpropanediol (5 equiv) and camphorsulfonic acid (THF, 20 °C). Attachment of the remaining anthracycline carbons involves Diels–Alder condensations of dienyl ether derivatives such as **4**. Under the best enolization conditions found (LDA in THF + TMEDA, −100 °C), an 8:1 ratio of **4a** and the undesired γ-deprotonation product **5** is obtained after quenching with $ClCO_2Et$.[7]

(1) Davies, J. S.; Davies, V. H.; Hassall, C. H. *J. Chem. Soc. C* **1969**, 1873. Hassall, C. H.; Morgan, B. A. *J. Chem. Soc. D* **1970**, 1345; *J. Chem. Soc., Perkin Trans. 1* **1973**, 2853. Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Ibid.* **1977**, 2502.

(2) Prepared from 3-(trimethylsilyl)propionaldehyde[3] and lithioacetylide[4] (−78 °C, 30 min; warmed to 20 °C; distilled ynol product, bp 55–8 °C, 0.8 mm) followed by two-phase Jones oxidation (ether as organic phase, 10 °C) to give **1** (bp 57–8 °C, 3 mm), 70% overall yield.

(3) Picard, J.-P.; Ekouya, A.; Dunogues, J.; Duffaut, N.; Calas, R. *J. Organomet. Chem.* **1975**, *93*, 51.

(4) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

(5) **2**: crystallized from hexane, mp 32–5 °C; 270-MHz NMR ($CDCl_3$) δ 6.78 (br s, 1 H), 4.91 (br t, *J* = 2.5 Hz, 1 H), 2.94 (m, 4 H), 2.63 (m, 2 H), 0.94 (s, 9 H), 0.79 (m, 2 H), 0.16 (s, 6 H), 0.02 (s, 9 H).

(6) Correct composition by high-resolution mass spectroscopy.

0022-3263/83/1948-3611$01.50/0