by chromatographic separation of the *O*-acetylmandelate esters[12] and individual reduction of the purified diastereomers. The indicated absolute configurational assignments to (+)-**11** and (−)-**14** follow from initial chirality transfer in the latter by hydroxyl-directed hydrogenation of the extraannular double bond.[13] Arrival at (−)-**15** was followed by Peterson olefination and ozonolysis to give the known (*S*)-(−)-**16**.[14]

In a companion series of reactions, (+)-**11** was subjected to oxidative phenylation as before. Once (−)-**12** was available, Haller–Bauer cleavage was seen to proceed with outstanding levels of retention (Table I). Direct evidence bearing on the optical purity of (−)-**13a** was gained by ozonolytic cleavage to (−)-**13b**, $[\alpha]^{28}_D$ −68.4° (*c* 0.45, $CHCl_3$), and independent kinetic resolution[15] of 3-(trimethylsilyl)cyclopentene (**17**)[16] by Brown's method.[17] Hydroboration–oxidation of (*S*)-(−)-**17** (34% ee)[2b] according to Larson[16a] gave (*S*)-(−)-**13b**, $[\alpha]^{26}_D$ − 62.3° (*c* 0.75, $CHCl_3$).

In summary, we detail herein a general method for preparing diastereomerically enriched samples of esters **5** and **6**, the phenyl ketones of which have the capacity for generating α-silyl carbanions in chiral condition. Protonation of these reactive species and those in cyclic structures occurs with high retention of configuration in nonpolar benzene solution. This phenomenon should perhaps be regarded as a fundamental chemical process, having earlier played a key role in Cram's development (through use of related processes) of the steric course of electrophilic substitution at saturated carbon.[18] An important and utilitarian route to optically active tertiary silanes such as **8** that possesses reliable stereochemical predictability has now been defined.

Acknowledgment. We express our gratitude to the National Science Foundation for financial support and the Fulbright Commission for a travel grant (to J.P.G.).

Registry No. **3**, 112297-88-8; **4**, 4951-48-8; **5a**, 112297-80-0; **5b**, 112297-81-1; **5c**, 112297-82-2; **5d**, 112297-83-3; **6a**, 112297-84-4; **6b**, 112297-85-5; **6c**, 112297-86-6; **6d**, 112297-87-7; **7a**, 112297-89-9; **7b**, 112297-90-2; **7c**, 112297-91-3; **7d**, 112297-92-4; **8a**, 112297-93-5; **8b**, 112297-94-6; **8c**, 112297-95-7; **8d**, 112297-96-8; **9**, 112297-97-9; **10a**, 112297-98-0; **10b**, 112297-99-1; **11**, 112298-00-7; **12**, 112298-01-8; **13a**, 112298-02-9; **13b**, 112298-03-0; **14**, 112298-04-1; **15**, 112298-05-2; **16**, 93451-75-3; (*S*)-(−)-**17**, 89576-21-6; $BrCH_2Ph$, 100-39-0; $BrCH_2CH{=}C(CH_3)_2$, 870-63-3; $BrCH_2CH_2Ph$, 103-63-9; $Br(CH_2)_4CH_3$, 110-53-2; $MeOCOCH_2SiMe_3$, 2916-76-9; Ph(AcO)CHCOCl, 49845-69-4; 3-bromomethyl-5-bromo-2-methyl-2-pentene, 85221-99-4.

(12) The use of *O*-acetylmandelate esters for resolution was first reported by Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

(13) Double irradiation of the Me_3Si singlet at 500 MHz had no effect on the CH_2OH absorption but enhanced the integration of the isopropyl peak by 7.8%.

(14) The (*R*)-(+) enantiomer of **16** has been reported to exhibit $[\alpha]^{20}_D$ +186° ($CHCl_3$): (a) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. (b) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1904. (c) Naves, Y.-R. *Bull. Soc. Chim. Fr.* **1958**, 1372. For the present sample: $[\alpha]^{23}_D$ −88° (*c* 0.28, $CHCl_3$).

(15) Compare the alternative procedure in ref 2b.

(16) (a) DeJesus, M.; Rosario, O.; Larson, G. L. *J. Organomet. Chem.* **1977**, *132*, 301. (b) Reuter, J. M.; Sinha, A.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 2438.

(17) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.

(18) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; Chapter IV and relevant references cited therein.

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Stereocontrolled Construction of the Hexahydrobenzofuran Subunit of the Avermectins and the Milbemycins: The Aldol Strategy

Summary: A novel route to the hexahydrobenzofuran subunit (**1**) of the avermectins and the milbemycins has been developed via two successive aldol reactions that proceed with high diastereoselectivity.

Sir: The avermectins[1] and the milbemycins[2] are of considerable current interest because of their unique structures and potent antiparasitic activities, and consequently many papers concerned with their total syntheses have appeared recently.[3,4] We describe herein a stereocontrolled synthesis of the crucial[5] hexahydrobenzofuran subunit **1**[4b,c] in optically active form, which is a versatile synthon for all of the avermectins[1] and the α series of the milbemycins.[2]

Our synthetic strategy for **1** outlined in Scheme I is based on the consideration of these natural products as nonaromatic alicyclic polyketides.[6] The two strategic bond disconnections (C2–C7 and C5–C6) of the retro-aldol type define chiral ketone **4** and achiral aldehyde **5** as building blocks for stereo- and enantioselective construction of **1**:[7] the single chiral center of **4** is designed to induce all of four chiralities essential to **1** via two key aldol reactions.

The kinetic aldol reaction, the first crucial step, of freshly prepared **4**[8] with **5**[9] exhibited good stereoselection

(1) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. For a recent review, see: Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(2) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A. *Tetrahedron Lett.* **1975**, 711. Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120. Mishima, H.; Junya, I.; Muramatsu, S.; Ono, M. *Ibid.* **1983**, *36*, 980.

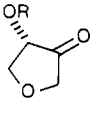
(3) For total syntheses of milbemycin β_3, see: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenburg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *Ibid.* **1982**, *104*, 4708. Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1326. Street, S. D. A.; Yeates, C.; Kocienski, P.; Campbell, S. F. *Ibid.* **1985**, 1386, 1388. Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840.

(4) (a) For syntheses of the spiroacetal subunit of avermectins, see: Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427. Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, *309*. Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.* **1986**, *27*, 5281. (b) For syntheses and synthetic studies of the hexahydrobenzofuran subunit, see: Prashad, M.; Fraiser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1556. (c) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Kozikowski, A. P.; MaloneyHuss, K. E. *Tetrahedron Lett.* **1985**, *26*, 5759. Crimmins, M. T.; Lever, J. G. *Ibid.* **1986**, *27*, 291. Hanessian, S.; Beaulieu, P.; Dube, D. *Ibid.* **1986**, *27*, 5071. Barrett, A. G. M.; Capps, N. K. *Ibid.* **1986**, *27*, 5571. Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273. Ardisson, J.; Ferezou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001. Crimmins, M. T.; Hollis, W. G., Jr.; Lever, J. G. *Ibid.* **1987**, *28*, 3647. (d) Recently a first relay synthesis of avermectin B_{1a} has been reported: Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P. J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776. Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299. See also ref 5.

(5) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.

(6) Cane, D. E.; Liang, T.-C.; Kaplan, L.; Nallin, M. K.; Schulman, M. D.; Hensens, O. D.; Douglas, A. W.; Albers-Schönberg, G. *J. Am. Chem. Soc.* **1983**, *105*, 4110.

(7) The tetrahydrofuranone **i** would appear to be a more straightforward synthon for the synthesis of **1**. However, this ketone proved to be extremely labile[8] under the conditions of enolate formation, irrespective of the hydroxyl protecting group R.



i

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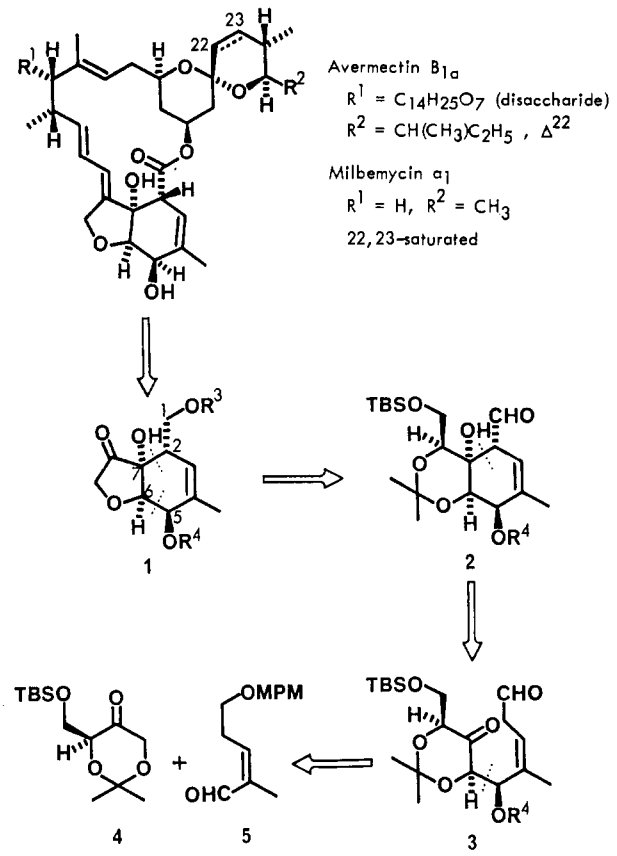
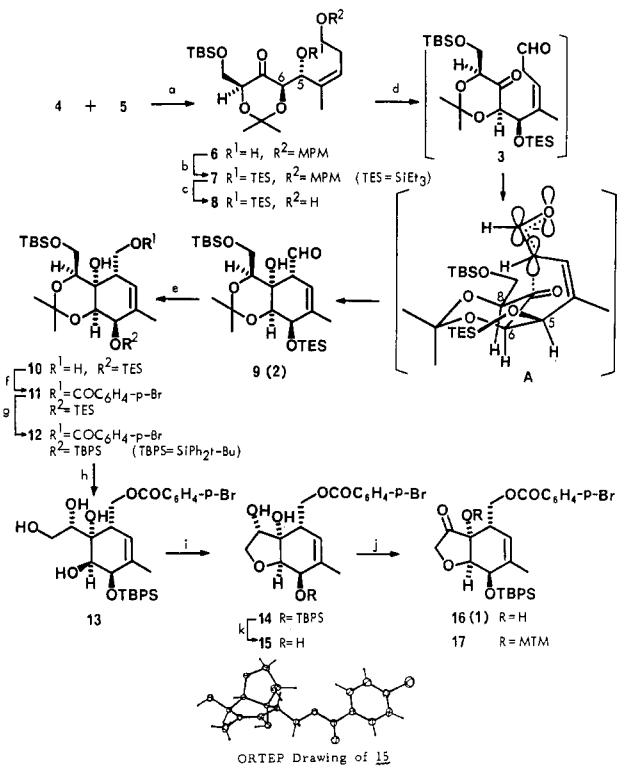
Scheme I



as expected.[10] Only two 5,6-antidiastereomers were detected in a 8.3:1 ratio. The major alcohol (47–56% yield), tentatively assigned as 5*R*,6*R* isomer **6**[11] (Scheme II), was silylated (Et_3SiCl, 83%) to **7** and its MPM ether[12] group was deprotected to give the homoallylic alcohol **8**[11] (76%).

Scheme II[a]



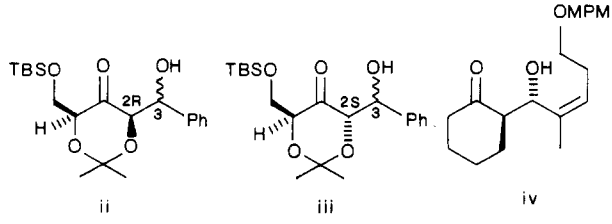
[a] (a) **4**, LDA, −78 °C, 30 s, then **5**, 5 s, 47–56%; (b) Et_3SiCl, imidazole, DMF, 22 °C, 5 min, 83%; (c) 1.5 equiv of DDQ, CH_2Cl_2–H_2O (20:1), 22 °C, 76%; (d) 1.5 equiv of Me_2SO, 1.5 equiv of $(COCl)_2$, 10 equiv of $(i\text{-}Pr)_2NEt$, −60 °C, then 22 °C, 10 h, 40–51%; (e) $NaBH_4$, MeOH, 0 °C, 85%; (f) $ClCOC_6H_4\text{-}p\text{-}Br$, Pyr, 22 °C, 73%; (g) (i) 5 equiv of Pyr·HCl, pyr, 22 °C, 28 h, 75%, (ii) *t*-$BuPh_2SiCl$, imidazole, DMF, 22 °C, 93%. (h) CF_3COOH–MeOH (1:2), 22 °C, 30 h, 82%; (i) 5 equiv of $2,4,6\text{-}(i\text{-}Pr)_3C_6H_2SO_2Cl$, Pyr, 22 °C, 23 h, 71%; (j) 6 equiv of Me_2SO, 3 equiv of $(COCl)_2$, 10 equiv of Et_3N, −60 °C, 20 min, **16**: 45%, **17**: 30%; (k) CF_3COOH–MeOH (1:2), 45 °C, 86%.

The intramolecular aldol condensation of **3**, the second crucial step in our sequence, required the generation of the two chiral centers C2 and C7 with retention of the delicate functionality in **3**. Of the possible modes of cyclization, transition state A leading to **2** seemed most likely for two reasons: (1) α-side (equatorial) attack on the ketone should be hindered by two axial hydrogens (H6, H8); (2) the bond formation through the *si* face of the aldehyde cis enolate would be more favorable due to both electrostatic and steric interactions between enolate ion and ether oxygens at C5, C6, and C8. In the event, clean and highly selective formation of **9** (**2**) was easily achieved by Swern oxidation of **8** in degassed CH_2Cl_2 at −60 °C using excess diisopropylethylamine and subsequent warming to room temperature afforded **9**[13] in 40–51% overall yield.[14] The stereochemical outcome of these aldol reactions was confirmed by X-ray crystallographic analysis of the crystalline *p*-bromobenzoate **15** (vide infra). Thus, destruction of the delicate functionality in **3** and **9** was avoided by taking advantage of an intramolecular reaction with a sterically hindered base. Reduction of **9** (85%) and protection of

(8) Prepared from D-glucose in five steps [46% overall yield, $[\alpha]^{17}_D$ −190° (*c* 1, $CHCl_3$); 1. $MeOCMe{=}CH_2$, H^+; 2. $NaIO_4$; 3. $NaBH_4$; 4. TBSCl, DMAP, NEt_3; 5. Me_2SO, $(COCl)_2$, NEt_3] and racemizes slowly at room temperature (22% in 18 h).

(9) Prepared from propane-1,3-diol via modified Wittig reaction (Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226) in five steps (34% overall yield, *Z*:*E* = 15:1) and used without purification: 1. $MeOC_6H_4CHO$, H^+; 2. $LiAlH_4$, $AlCl_3$; 3. Me_2SO, $(COCl)_2$, NEt_3; 4. $Ph_3P{=}CHMe$, *n*-BuLi, HCHO; 5. Me_2SO, $(COCl)_2$, NEt_3.

(10) Before performing the first key step, the stereoselectivity in the kinetic aldol reaction of each segment, **4** and **5**, was evaluated. The desired diastereoface selectivity (*re* face preference) of the lithium enolate from the (*S*)-ketone **4** was established by reaction with benzaldehyde (LDA, −78 °C, 70%, ii:iii ≈ 3.4:1). When reacted with the lithium enolate of cyclohexanone (−78 °C, 5 s), **5** gave single anti-aldol iv (78%): this high diastereoselectivity makes a striking contrast with that observed between cyclohexanone and benzaldehyde [52:48 ratio; see: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. Heathcock, C. H. *Asymmetric Organic Reactions*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Chapter 2]. These stereochemical results encouraged us to continue our synthetic plan.



(11) Tends to form hydrate, which looses water slowly in chloroform solution or in vacuo at 60 °C.

(12) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(13) Purified by flash chromatography without appreciable double-bond migration or vinylogous β-elimination.

(14) A small amount of a diastereomer of **9** and a γ-oxygenated Δ^2 isomer of **3** (each ratio to **9**, ≤1:15) was detected. The yield of the latter increased unless oxygen-free CH_2Cl_2 was used.

the resulting primary alcohol (73%) gave **11**, which by the exchange of the C5 protecting group with the more stable *t*-BuPh$_2$Si group afforded **12** (70% overall yield). The acetonide and *t*-BuMe$_2$Si groups were removed with CF$_3$COOH–MeOH (82%), and the resulting tetrol **13** was sulfonated in pyridine to yield diol **14** directly (71%).[4b] Deprotection of **14** with an acid gave the triol **15** (86%), X-ray analysis of which was described earlier. Subsequent Swern oxidation[4b] furnished the desired ketone **16** (**1**) and the corresponding (methylthio)methyl ether **17** in 45% and 30% yield, respectively.

Thus, the aldol strategy has been shown to provide an expedient stereocontrolled route to the "southern" hexahydrobenzofuran subunit **1**. Construction of seco acids of the avermectins and the milbemycins from **1** and subsequent lactonization, the last crucial step,[4d,5] are currently under investigation.

Supplementary Material Available: Spectral and analytical data for the new compounds shown in Scheme II (7 pages). Ordering information is given on any current masthead page.

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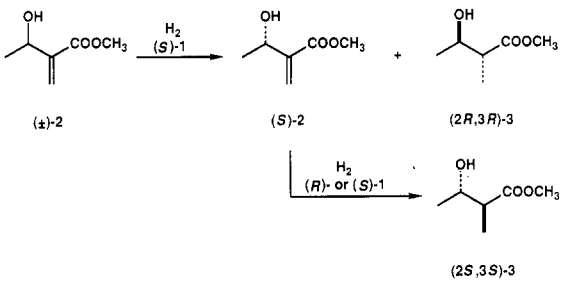
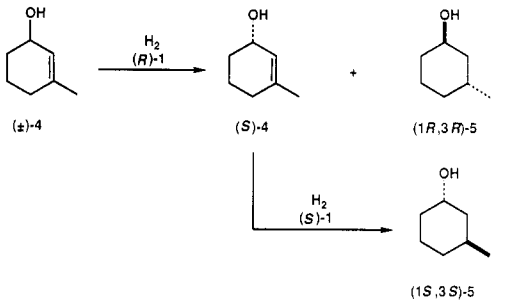
Received October 16, 1987

Scheme I



Scheme II

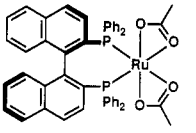


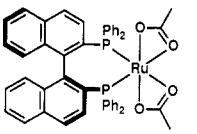
Kinetic Resolution of Racemic Allylic Alcohols by BINAP–Ruthenium(II)-Catalyzed Hydrogenation

Summary: Chiral allylic secondary alcohols have been resolved efficiently by homogeneous hydrogenation catalyzed by (*R*)- or (*S*)-BINAP–Ru diacetate complex. The combined effects of intramolecular and intermolecular asymmetric induction give up to 76:1 differentiation between the enantiomeric unsaturated alcohols.

Sir: Chemical kinetic resolution is now recognized as a viable tool for obtaining certain optically active compounds. In homogeneous hydrogenation of racemic allylic alcohols catalyzed by optically active phosphine–transition-metal complexes, the enantiomers react at different rates[1] and a chiral Rh catalyst has shown, at most, 6.5:1 discrimination for some acyclic substrates.[1,2] In view of the extremely high enantioface-differentiating ability of our BINAP–Ru(II) dicarboxylate complexes in hydrogenation of prochiral unsaturated alcohols,[3] we examined kinetic resolution of chiral substrates using the double stereodifferentiation[4] and found that appropriate substrate/catalyst chirality matching can achieve excellent enantiomer recognition.

The asymmetric hydrogenation of racemic allylic alcohols was conducted with BINAP–Ru(OCOCH$_3$)$_2$ (**1**)[5] as catalyst in methanol at 0–30 °C with substrate/catalyst mole ratio (S/C) of 200–1800. The catalytic reaction afforded a high level of kinetic enantiomer selection (k_f/k_s) for both cyclic and some acyclic substrates. Several characteristic features which deserve comment follow.





We first tested the resolution of the well-studied acyclic substrate **2**[1] (Scheme I). When racemic **2** was hydrogenated with the *S* Ru catalyst, (*S*)-**1**, at 76% conversion (4 atm, 25 °C, 11 h), there were obtained unreacted (*S*)-**2** in >99% ee and a 49:1 mixture of *threo*-**3** (2*R*,3*R* in 37% ee) and the erythro isomer. Although this threo/erythro ratio does not exceed the 100:1 ratio reported for racemic **3** with achiral DIPHOS-4–Rh as catalyst,[1] the rate ratio, k_f/k_s = 16:1, is greater than the 6.5:1 discrimination effected with chiral DIPAMP–Rh catalyst.[1] Notably, hydrogenation of (*S*)-**2** (>99% ee) with *either* antipodal Ru catalyst, (*R*)- or (*S*)-**1**, led to (2*S*,3*S*)-**3** with equally high threo selection (>23:1), indicating operation of overwhelming substrate control in the hydrogenation of this particular chiral allylic alcohol.

This asymmetric catalysis is applicable to the previously unexploited resolution of cyclic allylic alcohols as exemplified in Table I.[6] The Ru-catalyzed hydrogenation of 3-methyl-2-cyclohexenol (**4**) afforded *trans*- and *cis*-3-

(1) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190 and references cited therein.
(2) Up to 22-fold discrimination has been observed with an olefin having an acylamino directing group; see: Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett.* **1987**, *28*, 2179.
(3) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596; **1987**, *109*, 4129.
(4) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(5) Noyori, R.; Ohta, M.; Hsiao, Yi; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.*, in press.
(6) Hydrogenation of racemic 2-cyclohexenol catalyzed by {Rh[(*S*)-binap](CH$_3$OH)$_2$}$^+$ClO$_4^-$ or RhCl[(*S*)-binap](cod) in methanol (4 or 100 atm, 25 °C) gave only 1.1–1.6:1 enantiomer discrimination.

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