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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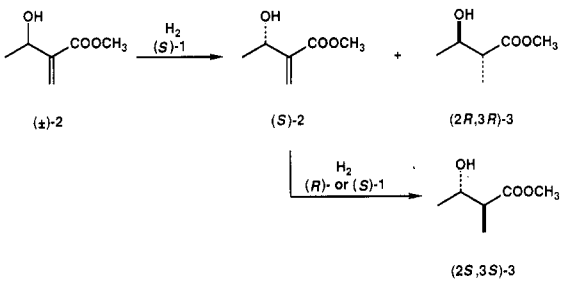
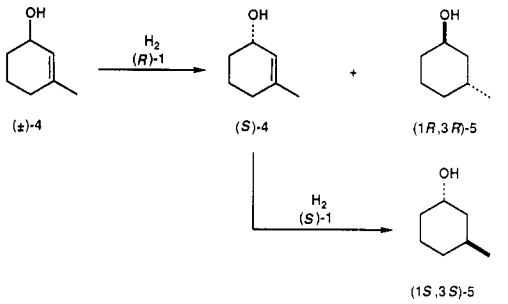
Scheme I



Scheme II

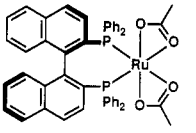


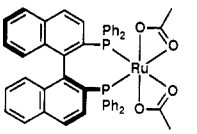
Kinetic Resolution of Racemic Allylic Alcohols by BINAP–Ruthenium(II)-Catalyzed Hydrogenation

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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Table I. Kinetic Resolution of Allylic Alcohols by $Ru(OCOCH_3)_2$(binap)-Catalyzed Asymmetric Hydrogenation[a]

substrate	catalyst	S/C	conditions			unreacted substrate			k_f/k_s[d]
			H_2, atm	temp, °C	time, h	% recovery[b]	% ee[c]	config[c]	
methyl 3-hydroxy-2-methylenebutanoate (2)	(S)-1	1700	4	25	11	24[e]	>99[f]	S	16
	(S)-1	1000	50	20	2.5	37[g]	97[f]	S	14
2-methyl-2-nonen-4-ol	(S)-1	400	4	20	3.0	47	66	S	7.2
	(S)-1	400	100	25	0.5	36	95	S	11
1-octen-3-ol	(S)-1	450	4	20	0.8	34	9	R	1.2
	(S)-1	200	100	0	1.2	46	21	R	1.7
2-cyclohexenol	(S)-1	300	1	30	0.7	48	96	R	62
	(S)-1	300	100	5	1.0	44	84	R	13
3-methyl-2-cyclohexenol (4)	(R)-1	600	4	26	56	46[h]	>99	S	74
	(R)-1	1800	100	26	40	49[i]	95	S	76
2-cyclopentenol	(S)-1	400	1	25	3.0	50	79	R	20
	(S)-1	500	100	20	1.0	44	82	R	11
4-hydroxy-2-cyclopentenone (6)	(S)-1	1000	4[j]	30	21	32	98	R	11
	(S)-1	1000	50[j]	25	2.0	18	94	R	4.3

[a] The reaction was carried out in 0.3–1 M methanol solution of the substrate (3–10 mmol). [b] Determined by 270-MHz ^1H NMR and/or GC analysis. [c] The enantiomeric excess was determined by HPLC analysis of the (S)-1-(1-naphthyl)ethyl carbamate or (R)-MTPA ester. The absolute configuration was deduced from rotation of the alcohol or its derivative. The details are given in the supplementary material. [d] Calculated by the Kagan's equation (Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 5152). [e] Threo:erythro = 49:1. [f] ^1H NMR analysis using $Eu(hfc)_3$ shift reagent. [g] Threo:erythro = 31:1. [h] Trans:cis = 300:1. [i] Trans:cis = 66:1. [j] Two equiv of acetic acid to 1 was added.

methylcyclohexanol in a 300:1 ratio. The excellent diastereoselectivity, as has been seen in other transition-metal catalyses,[1,7] suggests that the hydrogenation is occurring via coordination of the hydroxyl function to the Ru atom of the catalyst. In addition, hydrogenation of racemic **4** exhibited an extremely high enantiomer differentiation up to 76:1. The double stereodifferentiation method allows ready access to both antipodal unsaturated and saturated alcohols in high enantiomeric purity (Scheme II). Thus reaction of racemic **4** with 0.17 mol % of the *R* catalyst, (*R*)-**1**, under an initial hydrogen pressure of 4 atm (26 °C, 49 h), gave the trans saturated alcohol (1*R*,3*R*)-**5** in 95% ee in 46% yield and unreacted (*S*)-**4** in 80% ee with 54% recovery. The *S* enantiomer in >99% ee was obtained at 54% conversion. Hydrogenation of the partially resolved (*S*)-**4** (80% ee) with 0.5 mol % (*S*)-**1** (4 atm, 28 °C, 12 h) in turn afforded the enantiomeric saturated alcohol (1*S*,3*S*)-**5** in >99% ee (68%) together with (*S*)-**4** (40% ee, 32%).

The degree of enantiomer differentiation is considerably influenced by hydrogen pressure, in some cases (Table I).[8] With many substrates, higher k_f/k_s values were obtained at lower pressure. This trend is compared to *enantioface*-discriminating hydrogenation of geraniol or nerol with which hydrogen pressures as high as 100 atm are preferred.[3] Most notably, as seen from Schemes I and II respectively, the sense of the diastereoface selection with (*S*)-**1** and (*R*)-**1** as catalysts is opposite, if one assumes similar OH/C=C spatial relationships. Obviously different transition-state structures are involved in the hydrogenation of **2** and **4**.

The ready resolution of cyclic allylic alcohols is synthetically complementary to the Sharpless epoxidation procedure which is effective for flexible, acyclic substrates.[9]

A significant application of the present method includes a practical resolution of 4-hydroxy-2-cyclopentenone (**6**), a readily available[10] but sensitive compound.[11] Thus hydrogenation of racemic **6** with 0.1 mol % of (*S*)-**1** at 4 atm proceeded with k_f/k_s = 11:1 and, at 68% conversion, gave slow-reacting (*R*)-**6** in 98% ee and *R*-enriched hydrogenation product **8**. Sequential treatment of the mixture with *tert*-butyldimethylsilyl chloride (triethylamine and 4-(dimethylamino)pyridine, dichloromethane, 26 °C, 2 h) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (dichloromethane, 26 °C, 4 h), converting **8** to 2-cyclopentenone, gave after recrystallization the homochiral (*R*)-**7**, mp 29 °C, $[\alpha]^{21}_D$ + 66.6° (*c* 1.0, methanol). This compound serves as an important building block for the three-component coupling prostaglandin synthesis.[12]

(*R*)-**6**, R = H
(*R*)-**7**, R = $Si(CH_3)_2$-*t*-C_4H_9

8

Supplementary Material Available: Description of the general procedure for the asymmetric hydrogenation and de-

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termination of the enantiomeric excesses and absolute configurations of the products (7 pages). Ordering information is given on any current masthead page.

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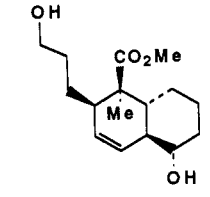
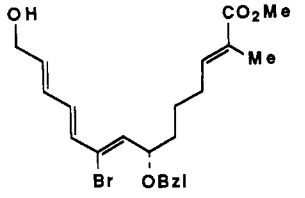
Enantioselective Synthesis of the Bottom Half of Chlorothricolide. 2. A Comparative Study of Substituent Effects on the Stereoselectivity of the Key Intramolecular Diels-Alder Reaction

Summary: The intramolecular Diels-Alder reactions of trienes **4-7** were studied to evaluate the ability of diene (TMS, Br) and dienophile (CHO, CO_2Me) substituents to influence Diels-Alder stereoselectivity and thereby define the optimal precursor to the bottom half of chlorothricolide.

Sir: In continuation of efforts to complete an enantioselective total synthesis of chlorothricolide, it became apparent that an improved synthesis of the bottom-half fragment **1** was required.[1] The key step of our previously



1



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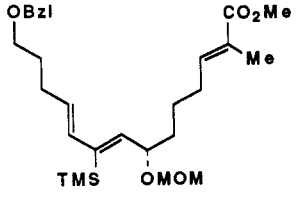
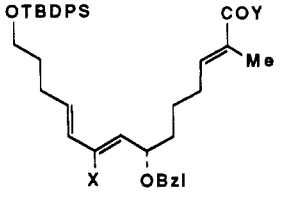


3



4, X = TMS, Y = OMe
5, X = Br, Y = OMe
6, X = TMS, Y = H
7, X = Br, Y = H

reported approach was the intramolecular Diels-Alder reaction of tetraene **2** that proceeded with only marginal stereoselection (55:45). Selective removal of the C(12)-C(13) double bond following cyclization was also problematic. Because Boeckman had reported that the Diels-Alder reaction of **3** proceeded with >100:1 stereoselection for a single trans-fused product,[2] we targeted the related TMS-substituted triene **4** as the key intermediate in an improved synthesis. *Much to our surprise, and in contrast to Boeckman's results, however, we found that the cyclization of 4 provided a 78:14:8 mixture of three cycloadducts.* This prompted us to broaden the scope of the present investigation and examine the effects of both the diene steric directing group X and the dienophile activating group[3] Y on the stereoselectivity of this key reaction (trienes **4-7**). In this way we hoped to define the optimal precursor to **1** and clearly evaluate the ability of substituents X and Y to influence intramolecular Diels-Alder stereoselectivity.[4]

Trienes **4-7** were synthesized as summarized in Scheme I.[5] Benzyl ether **8**, prepared as described previously from D-glyceraldehyde acetonide,[1] was smoothly elaborated to dibromo diene **9** ($[\alpha]^{23}_D$ -16.4° (*c* 1.0, $CHCl_3$)). After conversion[6] of **9** to the corresponding TMS alkyne, (iodovinyl)silane **10** ($[\alpha]^{23}_D$ -73.6° (*c* 1.1, $CHCl_3$)) was obtained via a hydroalumination-iodination sequence.[7] A very critical step followed, namely, the palladium-catalyzed cross-coupling reactions of **9** and **10** with vinylboronate **11**. Under the conditions described by Suzuki (aqueous 2 N NaOH, C_6H_6),[8] it was possible to prepare **12** ($[\alpha]^{23}_D$ -22.5° (*c* 1.0, $CHCl_3$)) and **13** ($[\alpha]^{23}_D$ -14.4° (*c* 1.2, $CHCl_3$)) in maximum yields of 55% and 36%, respectively. Considerable improvements, however, were realized by using the TlOH modification recently developed by Kishi.[9] Under optimal conditions, **12** (2 equiv each of **11** and TlOH, dioxane, 74%) and **13** (1.7 equiv each of **11** and TlOH, THF, 65%) were thus readily prepared. It is noteworthy that this synthesis of **13** represents the first successful example of a selective[10] mono-cross-coupling reaction of a 1,1-dibromo olefin[11] and may define a useful method for synthesis of 2-bromo 1,3-dienes for a range of synthetic objectives. Intermediates **12**/**13** were then elaborated to nitriles **14** ($[\alpha]^{23}_D$ -29.6° (*c* 0.9, $CHCl_3$)) and **15** ($[\alpha]^{23}_D$ -21.1° (*c* 1.2, $CHCl_3$)) by using Buchwald's zirconium-mediated hydrocyanation procedure[12] and finally to trienes **4** ($[\alpha]^{23}_D$ -21.2° (*c* 1.14, $CHCl_3$)), **5** [$(\alpha]^{23}_D$ -15.2° (*c* 2.67, $CHCl_3$)), **6**, and **7** via standard operations. It should be noted that alternative methods for synthesis of unsaturated aldehydes **6**/**7** involving Wittig or Petersen-type olefination procedures[12] gave considerably lower yields (43%) of less

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(10) A single isomer was obtained. The stereochemistry was assigned by conversion of **13** to **12** (2 equiv of *t*-BuLi, THF, -78 °C, then TMSCl, 53%).
(11) (a) The high selectivity of this reaction was anticipated on the basis of the known rate difference for the palladium-catalyzed cross-couplings of (*E*)- vs (*Z*)-1-bromoalkenes: Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 2529. (b) While our work was in progress, the selective monosubstitution of 1,1-dichloroethylene was reported: Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649. (c) See also: Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (d) For another recently reported example where a 1,1-dibromovinyl group undergoes a selective monosubstitution intramolecularly, see: Trost, B. M.; Chan, C.; Ruhter, S. *J. Am. Chem. Soc.* **1987**, *109*, 3486.
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