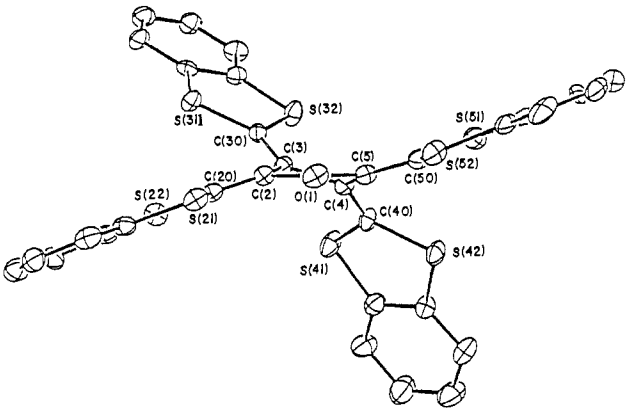

Figure 1. Molecular structure of **4b** by an ORTEP drawing with thermal ellipsoid at 20% probability level for the non-hydrogen atoms. The hydrogen atoms were omitted for clarity.

at 95–155 °C gave the unsubstituted compound **4c** in 88% yield.[5] The molecular structure of **4b** was determined by X-ray diffraction method.[6] Figure 1 shows the molecular structure projected along the O(1)–C(1) bond of the CO group. The molecule takes half-chair conformation with an approximate twofold symmetry passing through O(1)–C(1) bond. The torsional angles included in the central five-membered ring are smallest around the C(1)–C(2) (7.8°) and C(1)–C(5) (11.1°) bonds and are largest around the C(3)–C(4) (29.9°) bond, while those around the C(2)–C(3) (23.5°) and the C(4)–C(5) (25.7°) bonds take the intermediate values. The two 1,3-dithiole rings at the 3- and 4-positions show a relatively large dihedral angle (61.8°), while those at the 2- and 5-positions are coplanar. The C=O bond distance is 1.22 Å, and the mean values of the endocyclic C–C bond and the exocyclic C=C bond distances are 1.47 and 1.35 Å, respectively.

The redox behavior was investigated by using cyclic voltammetry (solvent, PhCN; room temperature). In all cases two pairs of waves were observed, and the two redox potentials were as follows: **4a**, +0.64 and +1.35 V vs. Ag/AgCl; **4b**, +0.38 and +1.22 V; **4c**, +0.17 and +1.14 V. From the fact that the two peak currents in the oxidation side are almost equal and the dication[7] shows the cyclic voltammogram corresponding to the pair of waves in the lower voltage, it is evident that both pairs of waves are due to two sequential redox processes accompanying a two-electron migration simultaneously.[8] In comparison of these potentials with those of already known compounds containing 1,3-dithiole moieties, the first potentials of **4**'s are lower by 0.05–0.1 V than those of corresponding **1** and **2**. In particular, **4c** has the lowest first potential as compared with TTF (+0.42 V),[9] 2,2'-(ethanediylidene)bis(1,3-dithiole) (+0.23),[10] 2,2'-(2-cyclohexene-1,4-diylidene)bis(1,3-dithiole) (+0.23),[11] and an unsubstituted **1** (+0.23).[1] This is quite unusual, if it is taken into consideration that a strong electron-withdrawing CO group is involved in the central five-membered ring.[12] Furthermore, **4** constructs the same four-electron redox system with **1**, in which the first two electrons migrate simultaneously. A marked difference between both systems is seen in the migration behavior of the two remaining electrons. Thus, **1** involves two one-electron processes, whose energy difference (ΔE) is large (0.43–0.50 V), while in **4** the processes overlap, indicating almost zero ΔE. Considering these results together with the fact that the antiaromatic cyclobutadiene and cyclopentadienone structures participate in the respective tetracation states ($\mathbf{1}^{4+}$ and $\mathbf{4}^{4+}$), it can be deduced that cyclopentadienone is less antiaromatic than cyclobutadiene.[13]

Judging from the first low oxidation potentials, **4b** and **4c** are expected as new electron donors for organic metals. In accord with this expectation, with a 2,3,5,6-tetrafluoro-TCNQ electron acceptor they formed the 1:2 CT complexes,[14] but their room temperature electrical conductivities on compressed pellets were not so high (10^{-8}–10^{-5} s/cm). However, the radical cation salts (**4b**·I_3 and $(\mathbf{4c})_2{\cdot}(I_3)_3$), obtained by electrolysis of **4b** and **4c** in CH_2Cl_2 containing $(n\text{-Bu})_4NI_3$, showed fairly high electrical conductivities of ca. 10^{-2} s/cm at room temperature on compressed pellets.[15]

Supplementary Material Available: Molecular structure of **4b** with full atomic numberings and tables of fractional atomic coordinates and interatomic bond distances in **4b** (3 pages). Ordering information is given on any current masthead page.

(6) Crystal data of **4b**: $C_{33}H_{16}OS_8$, fw = 685.0, monoclinic, space group $P2_1/c$, a = 18.596 (3) Å, b = 8.358 (2) Å, c = 25.488 (6) Å, β = 114.38 (1)°, U = 3608.5 (1.3) Å^3, D_x = 1.260 g cm^{-3}, Z = 4. X-ray diffraction data were measured on a Rigaku four-circle diffractometer by using graphite-monochromatized Mo Kα radiation. A total of 6338 reflections were collected up to 2θ = 50° by the θ–2θ scan technique. The crystal structure was solved by the direct method (MULTAN-78) (Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. *MULTAN-78: A System Computer Program for the Automatic Solution of Crystal Structures from X-ray Diffractometer Data*; University of York: England, and Louvain, Belgium, 1978) and refined by the full-matrix least-squares method (XRAY-76) (Stewart, J. M. *XRAY-76*; University of Maryland, 1976; report TR-446) by using the 3853 observed reflections [$|F_o| > 3\sigma(F_o)$] of the R index of 0.133 with anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms were not located. The difficulty of the interpretation of diffused electron densities, which resulted presumably from the crystal solvent, limited the accuracy of the refinement.

(7) The chemical oxidation of **4c** with 1.2 equiv of Br_2 in CH_2Cl at 0 °C gave the dibromide salt of dication ($\mathbf{4c}^{2+}{\cdot}2Br^-$) as a greenish blue solid (mp 280 °C dec) quantitatively.

(8) The first process was electrochemically reversible for **4b** and **4c** but quasireversible for **4a**. On the other hand, the second process was irreversible in all cases.

(9) Wudl, F.; Smith, G. M.; Hufnagel, E. *Chem. Commun.* **1970**, 1453.

(10) Yoshida, Z.; Kawase, T.; Awaji, H.; Sugimoto, I.; Sugimoto, T.; Yoneda, S. *Tetrahedron Lett.* **1983**, 3469.

(11) This compound was synthesized by decarbomethoxylation of the tetracarbomethoxy derivative already obtained by Sato et al. (Sato, M.; Gonnella, N. C.; Cava, M. P. *J. Org. Chem.* **1979**, *44*, 930).

(12) Presumably, this unusual observation should be related to the markedly increasing change of the central five-membered ring to the planar configuration in one- and two-electron oxidations of **4** to its radical cation and dication.

(13) (a) Breslow, R. *Pure Appl. Chem.* **1971**, *28*, 111. (b) Breslow, R.; Oda, M.; Sugimoto, T. *J. Am. Chem. Soc.* **1974**, *96*, 1974.

(14) **4c** formed no CT complex with TCNQ.

(15) Their perchlorate salts were also obtained, but the electrical conductivities were very low (ca. 10^{-8} s/cm). The detailed electrical properties of **4b**·I_3 and $(\mathbf{4c})_2{\cdot}(I_3)_3$ in single crystals are under investigation.

Homogeneous Asymmetric Hydrogenation of Functionalized Ketones

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Homogeneous asymmetric hydrogenation of ketones has remained far less fruitful than the catalysis of olefinic substrates.[2] However, now with the BINAP–Ru(II) complexes[3,4] effecting

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(2) Reviews: Kagan, H. B. In *Asymmetric Synthesis*: Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 1. Halpern, J. In *Asymmetric Synthesis*; Vol. 5, Chapter 2. Koenig, K. E. In *Asymmetric Synthesis*; Vol. 5, Chapter 3. *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff Publishers: Dordrecht, 1986. Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

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Table I. Catalytic Asymmetric Hydrogenation of Functionalized Ketones Using BINAP–Ru Complexes[a]

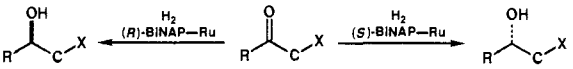
substrate	catalyst	S/C	conditions		product		
			H_2, atm	time, h	% yield[b]	% ee[c]	config[c]
$CH_3COCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-binap]	780	50[d,e]	12	72	96	*S*
$(CH_3)_2CHCOCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-binap]	390	100[d,e]	24	83	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	$RuBr_2[(S)$-binap]	490	100[d,e]	24	85	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-tolbinap][f]	530	100[d,e]	8	92	93	*S*
CH_3COCH_2OH	$RuCl_2[(R)$-binap]	230	93[d]	32	100	92	*R*
$CH_3COCO_2CH_3$	$RuCl_2[(R)$-binap]	780	96[d]	46	97	83	*R*
$CH_3COCH_2CH_2OH$	$RuCl_2[(R)$-binap]	900	70	42	100	98	*R*
$CH_3COCH_2CO_2C_2H_5$	$RuBr_2[(R)$-binap]	1260	86	51	100	>99	*R*
$CH_3COCH_2CON(CH_3)_2$	$RuBr_2[(S)$-binap]	680	63	86	100	96	*S*
$CH_3COCH_2COSC_2H_5$	$RuCl_2[(R)$-binap]	540	95	86	42[g]	93	*R*
$(i\text{-}C_3H_7)_3SiOCH_2COCH_2CO_2C_2H_5$	$RuBr_2[(S)$-binap]	290	100[h]	86	100	95	*R*
$C_6H_5CH_2OCH_2CH_2COCH_2CO_2CH_3$	$RuBr_2[(S)$-binap]	370	50[d]	185	94	99	*S*
$o\text{-}CH_3COC_6H_4CO_2H$	$Ru_2Cl_4[(R)\text{-binap}]_2(C_2H_5)_3N$	220	43[i]	15	100[g]	92	*R*
$o\text{-}BrC_6H_4COCH_3$	$RuBr_2[(R)$-binap]	1100	100	62	97	92	*R*
$CH_3COCOCH_3$	$RuBr_2[(S)$-binap]	680	80	61	100[j]	100[k]	*S,S*
$CH_3COCH_2COCH_3$	$RuCl_2[(R)$-binap]	2000	72[l]	89	100, 95[g,m]	100[k]	*R,R*
$CH_3COCH(CH_3)COCH_3$	$RuCl_2[(S)$-binap]	2200	94	62	100[m]	99	*S,S*

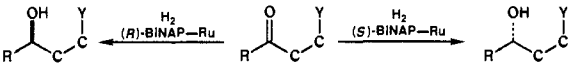
[a] Reaction was carried out at 20–32 °C in 1–4 M ethanol solution of the substrate (3–21 mmol). [b] Determined by 270-MHz or 400-MHz ^1H NMR analysis. [c] The enantiomeric excesses and absolute configurations of the products were determined by combination of HPLC and ^1H NMR analysis of the appropriate MTPA esters and rotation measurement. The details are given in the Supplementary Material. [d] Methanol as solvent. [e] The substrate concentration was 0.15–0.3 M. [f] Tolbinap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. [g] Isolated yield. [h] The substrate concentration was 0.5 M. [i] A 5:2 methanol–tetrahydrofuran mixture as solvent. [j] dl:meso = 26:74. [k] The minor isomer was not detectable by HPLC analysis of the MTPA ester. [l] A 10 M solution of the substrate (0.2 mol) was used. [m] dl:meso = 99:1.

highly enantioselective hydrogenation of β-keto carboxylic esters in hand,[5] we are now in the stage to extend the scope and application of this chiral multiplication method. As disclosed herein, the BINAP–Ru-catalyzed hydrogenation exhibits wider scope than reactions with any other chiral transition-metal complexes so far designed[6] and is capable of producing a variety of functionalized alcohols in synthetically useful enantiomeric excesses. With many substrates, this homogeneous hydrogenation procedure is superior to the heterogeneous version[7] and compares well with the biochemical transformations,[8] whose chemical and optical yields are often variable.

In the BINAP–Ru-catalyzed reaction, diverse polar functionalities facilitate hydrogenation of a neighboring carbonyl group and allow the efficient enantioface differentiation. The halogen-containing complexes of type RuX_2(binap),[9] the dimeric triethylamine complex,[10] or the dicarboxylate complexes, Ru(OCOR)$_2$(binap),[4] may be used as catalysts, depending on the ketonic substrates. Methanol or ethanol was the solvent of choice. The reaction with a substrate:catalyst mole ratio (S/C) of 230–2200 proceeded at a reasonable rate at room temperature by using an initial hydrogen pressure of 40–100 atm.

As exemplified in Table I, excellent levels of enantioselection have been observed with a wide range of functionalized ketones. The general sense of the asymmetric induction, illustrated in eq 1 and 2, suggests that the key factor in the stereodifferentiation





is the simultaneous coordination of the carbonyl oxygen and heteroatom, X or Y (C = sp^2 or nonstereogenic sp^3 carbon), to the Ru atom making a five- and six-membered chelate ring, respectively.[11] Some nitrogen- and oxygen-containing directing groups include dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, carboxyl, etc. The oxygen-triggered hydrogenation was accomplished smoothly with the halogen-containing Ru complexes as catalysts, whereas the reaction of more basic amino ketones was effected equally well with the Ru dicarboxylate complexes.

With the multifunctionalized ketones, the competitive ligation of the functionalities to Ru tends to decrease the enantioselectivity. The overall directivity of functionalities is critically affected by the donicity and orientation of the nonbonding orbitals of X or Y, bulkiness of the functional groups, and, of course, kinetic properties of the resulting chelate complexes. Ethyl 5-(benzyloxy)-3-oxopentanoate was hydrogenated in 99.1:0.9 enantioselectivity (RuBr$_2$[(*S*)-binap], S/C 700, ethanol, 100 atm, 28 °C), whereas the reaction of the lower homologue, ethyl 4-(benzyloxy)-3-oxobutanoate, exhibited only 89:11 selectivity. When the benzyl group in the latter substrate was replaced by the bulkier

(3) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-dinaphthyl. See: Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(4) Noyori, R.; Ohta, M.; Hsiao, Yi.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. Kitamura, M.; Hsiao, Yi.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829. Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.*, in press.

(5) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(6) Reactions with Rh complexes: Solodar, J. *Chem. Tech.* **1975**, 421. Ojima, I.; Kogure, T.; Terasaki, T.; Achiwa, K. *J. Org. Chem.* **1978**, *43*, 3444. Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395. Tōrōs, S.; Kollár, L.; Heil, B.; Markó, L. *J. Organomet. Chem.* **1982**, *232*, C17. Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4477. Takahashi, H.; Morimoto, T.; Achiwa, K. *Chem. Lett.* **1987**, 855. For homogeneous hydrogenation using chiral Co complexes, see: Ohgo, Y.; Natori, Y.; Takeuchi, S.; Yoshimura, J. *Chem. Lett.* **1974**, 1327.

(7) Tai, A.; Harada, T.; Hiraki, Y.; Murakami, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1414.

(8) Reviews: Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570. Oishi, T.; Akita, H. *J. Synth. Org. Chem., Jpn.* **1983**, *41*, 1031. Mori, K.; Sugai, T. *J. Synth. Org. Chem., Jpn.* **1983**, *41*, 1044. Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. Fujisawa, T.; Sato, T.; Ito, T. *J. Synth. Org. Chem., Jpn.* **1986**, *44*, 519. Butt, S.; Roberts, S. M. *Nat. Prod. Rep.* **1986**, 489 and references cited therein. See, also: Seebach, D.; Roggo, S.; Zimmermann, J. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; Verlag Chemie: Weinheim, 1987. Brooks, D. W.; Kellogg, R. P.; Cooper, C. S. *J. Org. Chem.* **1987**, *52*, 192.

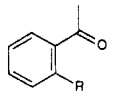
(9) Empirical formula with unknown molecular weight. Prepared by mixing Ru(OCOCH$_3$)$_2$(binap) and HX in a 1:2 ratio.[5]

(10) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

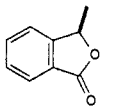
(11) For stereoselective stoichiometric reductions of functionalized ketones, see: Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.

triisopropylsilyl group, the extent of stereocontrol was increased to 97.4:2.6. In all cases, effect of the ester group overrode the directivity of the alkoxyl or siloxyl functionality, and the sense of the chiral delivery consistently followed eq 2.

Certain aromatic substituents also affect the steric course. For example, when *o*-acetylbenzoic acid (**1**) was hydrogenated in the presence of an (*R*)-BINAP-Ru complex, the (*R*)-phthalide **3** was



1, R = COOH
2, R = Br



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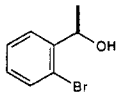

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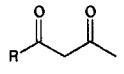
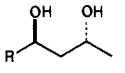
obtained in 92% ee and quantitatively. Surprisingly, *o*-bromoacetophenone afforded the (*R*)-alcohol **4** in 92% ee and in 97% yield, although unsubstituted acetophenone and the *m*- or *p*-bromo derivative failed to be hydrogenated in a satisfactory manner under the comparable conditions (<1% chemical yields and 74, 30, and 54% optical yield, respectively, with *opposite* enantioselection). The great rate enhancement with the *o*-bromo compound as well as the sense of enantioselection, following eq 2, indicates that even halogen atoms placed at appropriate positions in the substrates exert significant directing influence through interaction with Ru. The aromatic halogen atom can be removed without racemization by $CeCl_3$–$LiAlH_4$ reduction.[12]

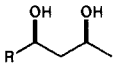
When prochiral, symmetrical α- or β-diketones were subjected to the asymmetric catalysis, mixtures of the diols possessing meso and dl structures were obtained. The enantiomeric excesses of the dl isomers were uniformly high (99–100% ee). In a like manner, hydrogenation of unsymmetrical β-diketone **5** catalyzed by $RuCl_2$[(*R*)-binap] afforded (1*S*,3*R*)-diol **7** (92% yield, 94% ee) together with a small amount of (1*S*,3*S*)-diol **9** (6% yield, 54% ee).[13]



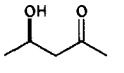
5, R = C_6H_5
6, R = CH_3



7, R = C_6H_5
8, R = CH_3



9, R = C_6H_5
10, R = CH_3



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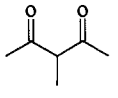

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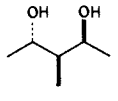

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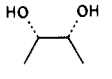

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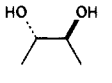

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In such two-step asymmetric hydrogenation of diketones, the overall stereochemical outcome is determined by both efficacy of catalyst/carbonyl chirality transfer (catalyst control) and structures of the initially created hydroxy ketones including chirality of the stereogenic center (substrate control). Hydrogenation of acetylacetone (**6**) catalyzed by $RuCl_2$[(*R*)-binap] produced first the (*R*)-hydroxy ketone **11** (98.5% ee at 10% conversion), as expected from eq 2, and then resulted in a 99:1 mixture of (*R*,*R*)-diol **8** in 100% ee and *meso*-diol **10**. In contrast, hydrogenation of the isolated *R* intermediate **11** (>99% ee) with the enantiomeric, (*S*)-BINAP-based catalyst led to the isomeric diols **8** and **10** in only 15:85 ratio. Thus the high enantiomeric purity of **8** obtained by the (*R*)-BINAP-Ru catalysis of **6** appears to be a result of double stereodifferentiation.[14] The analysis indicates that, in the second step, the catalyst control (>33:1) is much more dominant over the substrate control favoring formation of *dl*-diols (~6:1). 3-Methyl-2,4-pentanedione (**12**), an α-alkylated β-diketone, behaved like simple unsubstituted analogues. This asymmetric hydrogenation, viewed formally as triple stereodifferentiation, led to the *dl*-diol **13** (99% yield, 99% ee) and *meso*-diols (trace). In the reaction of α-diketones, substrate control in the second hydrogenation step, favoring *meso*-diol formation, becomes much more important, which results in high enantiomeric purities of the minor *dl*-diol products. Thus, (*S*)-BINAP-Ru aided hydrogenation of diacetyl (**14**) gave a 74:26 mixture of the *meso*-diol **15** and (*S*,*S*)-diol **16** in 100% ee.

Thus the BINAP-Ru complexes have excellent kinetic chiral recognition ability and are capable of hydrogenating a series of functionalized ketones in a predictable manner and with satisfactory chemical and chiral efficiency. The high synthetic applicability is obvious.

Supplementary Material Available: Descriptions of the general procedures of the asymmetric hydrogenation using a 20-g scale reaction of acetylacetone as an example and determination of the enantiomeric excesses and absolute configurations of the products (13 pages). Ordering information is given on any current masthead page.

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Synthesis of the Bicyclic Core of the Esperamicin/Calichemicin Class of Antitumor Agents

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Over the past 10 years, considerable effort has been devoted to the elucidation of structure and mechanism of action of the potent antitumor protein complex neocarzinostatin (ncs)[1,2] and its relative, auromomycin.[3] The biological properties of ncs reside completely within the highly unusual nonproteinal component, ncs chromophore, **1** (Scheme I). Edo has demonstrated that the DNA damaging properties of **1** can be traced to the bicyclic core comprised of an oxygenated enediyne.[4] Recently, the structures of several members of a related class of DNA binding/damaging agents were simultaneously reported by chemists at Bristol-Myers[5] and Lederle.[6,7] The esperamicins (e.g., esperamicin A_1, **2**) and calichemicins share a common bicyclic core structure equipped with an enediyne bridge that is integral to the DNA damaging and extreme tumoricidal properties of these compounds. A novel

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(2) The absolute stereochemistry of substituents on the methylene cyclopentene core is unknown. The *R*,*R*-stereochemistry depicted in **1** is the configuration predicted by a DNA binding model developed in our laboratory (manuscript in preparation). Modeling and synthesis research in this area was presented (by S.L.S.) at the 30th National Organic Chemistry Symposium of the American Chemical Society, Vancouver, Canada, June 21–26, 1987.
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