The combined ether extracts were washed with 5% NaOH (3 × 40 mL), dried (Na_2SO_4), and concentrated to afford 0.650 g (99%) of white solidified foam: mp 147–149 °C; IR (mull) 3335, 1098, 820, 778, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.02–7.94 (m, 4 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.50–7.43 (m, 4 H), 7.31–7.23 (m, 2 H), 3.85 (d, J = 11.7 Hz, 2 H), 3.53 (d, J = 11.7 Hz, 2 H), 2.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 134.80, 134.63, 132.84, 131.17, 128.69, 128.08, 127.12, 126.84, 125.55, 125.16, 48.40.

(*S*)-(+)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (2c). A solution of 2.09 g (7.09 mmol) of (±)-**2c** in 235 mL of methanol was added slowly with gentle mixing to a solution of 2.67 g (7.09 mmol) of (−)-dibenzoyl-L-tartaric acid monohydrate in 400 mL of methanol at room temperature. White needles began to form upon standing 1 h. After 24 h, the mixture was cooled to 0 °C for 30 h and then to −20 °C for 15 h. Filtration yielded 2.12 g of pale yellow needles: mp 170–175 °C (dec).

A 0.992 g sample of this material was slurried in 70 mL of ether and treated with 50 mL of 5% NaOH (aqueous) with stirring, giving two cloudy phases. The ether phase was separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined ether phases were washed with 5% NaOH (2 × 40 mL) and water (2 × 30 mL), dried (Na_2SO_4), and concentrated to give 0.444 g (45% = 90% of theory, based on (±)-**2c**) of white solidified foam: mp 73–84 °C; $[\alpha]^{20}_D$ +620° (*c* 0.78, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ +574.8° (*c* 0.7, $CHCl_3$)]; IR (mull) 1090, 1030, 819, 770, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.99–7.94 (m, 4 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.50–7.44 (m, 4 H), 7.30–7.24 (m, 2 H), 3.86 (d, J = 12.1 Hz, 2 H), 3.52 (d, J = 12.1 Hz, 2 H), 1.82 (br s, 1 H).

A small sample of free base was derivatized with 1-naphthoyl chloride (pyridine, ca. 95 °C, 45 min) and analyzed by chiral stationary-phase HPLC (Regis Pirkle Type 1-A, 25 cm × 4.6 mm i.d., two columns in series; 10% isopropyl alcohol in hexane, 2.6 mL/min, retention times of racemate: 27.6 and 33.0 min), indicating 100% ee favoring the first eluted enantiomer.

Thermal Michael Additions. A solution of 0.150 g (0.508 mmol) of (±)-**2c** in 5.4 mL (51 mmol) of dry methyl crotonate was heated at reflux for 21 h. The resulting clear orange solution was cooled and concentrated in vacuo (rotory evaporator followed by 0.5 mm overnight) to 0.199 g of brown oil. Flash chromatography (50% ethyl acetate in hexane) yielded 0.137 g (68%) of very pale yellow oil: IR (neat film) 1733, 1200, 1143, 819, 754, 735, 503 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (dd, J = 4.0, 7.7 Hz, 4 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.47–7.40 (m, 4 H), 7.27–7.22 (m, 2 H), 3.82–3.64 (m, 5 H), 3.52–3.32 (m, 3 H), 2.70–2.60 (m, 1 H), 2.40–2.29 (m, 1 H), 1.20 (d, J = 6.2 Hz, 1.0 H, diastereomeric methyl protons), 1.13 (d, J = 7.0 Hz, 2.0 H, diastereomeric methyl protons); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.80, 172.72, 134.79, 134.73, 134.27, 134.16, 132.95, 131.22, 128.55, 128.19, 127.87, 127.41, 125.65, 125.32, 56.86, 56.74, 56.56, 56.45, 51.94, 51.52, 40.38, 40.26, 18.30, 18.19; HPLC (Regis Pirkle Type 1-A, 25 cm × 10 mm i.d.; 5% isopropyl alcohol in hexane, 1 mL/min, retention times 41.13 and 44.02 min) 3.48:1, favoring the first eluted diastereomer.

Aliquots, 0.5 mL, were syringed from an identical reaction, rapidly cooled in an ice bath, passed through a plug of silica gel with 50% ethyl acetate in hexane, and analyzed by HPLC as above: diastereomer ratio (time); 4.16:1 (1 h), 3.79:1 (4 h), 3.50:1 (23 h), 2.91:1 (51 h), 1.36:1 (114 h), 1.28:1 (148 h), 1.00:1 (218 h), 1.09:1 (264 h).

Lithium Amide Michael Additions. To 5 mL of dry tetrahydrofuran in a −78 °C bath was added 0.219 mL (0.508 mmol) of *n*-butyllithium (2.32 M in hexane). The resulting solution was added dropwise via cannula over 3 min to a solution of 0.150 g (0.508 mmol) of (±)-**2c** in 5 mL of dry tetrahydrofuran rapidly stirred in a −78 °C bath. The resulting dark green solution was stirred 25 min at −78 °C before treatment with a solution of 13.5 μL (12.7 mg, 0.127 mmol) of dry methyl crotonate in 2.3 mL of dry tetrahydrofuran precooled in a −78 °C bath dropwise via cannula over 1.3 min. The resulting brown solution was stirred 30 min at −78 °C before quenching with a solution of 27.2 mg (0.508 mmol) of NH_4Cl in 7 mL of water and warming to room temperature. The majority of tetrahydrofuran was removed in vacuo before the solution was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo (1 mm, overnight) to 0.169 g of orange oil. Flash chromatography (50% ethyl acetate in hexane) yielded 44.2 mg (88%) of yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.95–7.92 (m, 4 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.47–7.40 (m, 4 H), 7.27–7.21 (m, 2 H), 3.80 (d, J = 12.3 Hz, 2 H), 3.66 (s, 3 H), 3.42 (d, J = 12.3 Hz, 2 H), 3.40–3.30 (m, 1 H) 2.66 (dd, J = 5.3, 14.4 Hz, 1 H), 2.37 (dd, J = 8.7, 14.4 Hz, 1 H), 1.20 (d, J = 6.6 Hz, 3 H); HPLC (as above) 94:1, favoring the second eluted diastereomer.

A similar procedure employing (*S*)-**2c** yielded 40.8 mg (81%) of clear oil: $[\alpha]^{25}_D$ +267° (*c* 2.46, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.95–7.91 (m, 4 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.48–7.40 (m, 4 H), 7.27–7.21 (m, 2 H), 3.79 (d, J = 12.3 Hz, 2 H), 3.66 (s, 3 H), 3.42 (d, J = 12.3 Hz, 2 H), 3.40–3.30 (m, 1 H), 2.65 (dd, J = 5.4, 14.5 Hz, 1 H), 2.37 (dd, J = 8.7, 14.5 Hz, 1 H), 1.20 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.82, 134.85, 134.16, 132.99, 131.30, 128.60, 128.21, 127.86, 127.44, 125.69, 125.37, 56.55, 51.99, 51.58, 40.40, 18.31; HPLC (as above) 61:1, favoring the second eluted diastereomer.

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Registry No. (±)-**2c**, 102518-95-6; (*S*)-(+)-**2c**, 97551-09-2; (*S*)-**2c** (dibenzoyl L-tartrate salt), 102493-59-4; **3**, 64091-25-4; **5**, 102493-57-2; **6** (diastereomer 1), 102518-96-7; **6** (diastereomer 2), 102493-60-7; CF_3CONH_2, 354-38-1; $CH_3CH{=}CHCO_2CH_3$, 18707-60-3.

Regio- and Stereoselective Dehydrogenation of α,ω-Diols Catalyzed by a Rhodium Hydride Complex

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The hydrogen-transfer reaction from an alcohol to a hydrogen acceptor catalyzed by transition-metal complexes giving the oxidized product[1] has attracted much interest and now is recognized to be one of useful processes in organic synthesis. When a diol was used as the starting alcohol the corresponding lactones could be readily obtained.[2] Very recently we have found that certain ruthenium complexes are excellent catalysts for the stereo-[3] and regioselective[4] lactone formation reaction from substituted diols. It is of interest that for the lactone formation reaction from unsymmetrically substituted diols, the ruthenium-catalyzed system using an α,β-unsaturated ketone as a hydrogen acceptor exhibits a regioselectivity

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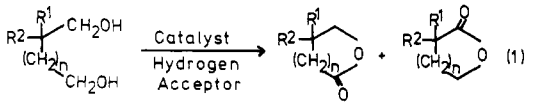
Table I. Rhodium-Catalyzed Regioselective Dehydrogenation of Unsymmetrical Diols[a]

entry	diol	catalyst	yield,[b] %	ratio[c] 2/3
1[d]	1a	$RhH(PPh_3)_4$	77	78/22
2	1a	$RhH(PPh_3)_4$	95	98/2
3[e]	1a	$RhH(PPh_3)_4$	80	97/3
4[f]	1a	$RhH(PPh_3)_4$	66	94/6
5[g]	1a	$RhH(PPh_3)_4$	88	95/5
6[d]	1a	$RhCl(PPh_3)_3$	0	
7	1a	$RhH(CO)(PPh_3)_3$	18	61/39
8	1a	$RhH((-)\text{-DIOP})_2$	34	92/8
9	1b	$RhH(PPh_3)_4$	82	86/14
10	1c	$RhH(PPh_3)_4$	100	85/15
11	1d	$RhH(PPh_3)_4$	80[h]	89/11[i]
12	1e	$RhH(PPh_3)_4$	94	92/8
13	1f	$RhH(PPh_3)_4$	90	90/10
14	1g	$RhH(PPh_3)_4$	95	91/9
15	1h	$RhH(PPh_3)_4$	86	73/27
16	1i	$RhH(PPh_3)_4$	57[h]	79/21[i]

[a] For the details of the procedure, see the Experimental Section. [b] GC yield based on the starting diol. [c] Determined by GC. [d] 110 °C. [e] 20 °C. [f] 4-Methyl-3-penten-2-one was used as a hydrogen acceptor. [g] 1,3-Diphenyl-2-propen-1-one was used as a hydrogen acceptor. [h] Isolated yield. [i] Determined by ^1H NMR (400 MHz).

(major product = **2**) completely opposite to that found for the palladium-catalyzed one using aryl halides as a hydrogen acceptor[5] (major product = **3**) (eq 1). However,



(1)

1 2 3

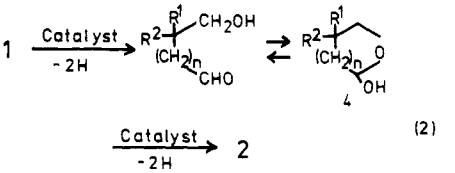
1, 2, 3	R	R′	n
a	CH_3	CH_3	1
b	CH_3	H	1
c	$(CH_3)_2CH$	H	1
d	C_6H_5	H	1
e	CH_3O	H	1
f	$CH_3CH_2CH_2CH_2O$	H	1
g	CH_3	CH_3	2
h	CH_3	H	2
i	C_6H_5	H	2

no rhodium complex has been applied to such lactone syntheses in spite of its well-documented high catalytic activity for the hydrogen-transfer reaction.[1c,d,6] In this paper we wish to report the rhodium hydride complex catalyzed oxidation of diols especially with views to reveal the selectivity in forming regio- and enantioisomeric lactones and to exhibit its versatility as a synthetic tool.

The oxidation of 2-alkyl-1,4-diols or -1,5-diols **1a–i** catalyzed by $RhH(PPh_3)_4$ in the presence of α,β-unsaturated ketones, such as 4-phenyl-3-butene-2-one, as a hydrogen acceptor provided preferentially β-substituted γ-lactones or γ-substituted δ-lactones **2a–i**. As shown in Table I the regioselectivity for substituted 1,4-butanediols increased in the order of 2-methyl- $\simeq$ 2-isopropyl- < 2-phenyl- < 2,2-dimethyl-1,4-butanediol, which is the order of the steric bulkiness of the substituents. 2,2-Dimethyl-1,4-butanediol (**1a**) exhibited a quite high regioselectivity up to 98/2. These results clearly indicate that the main factor which governs the regioselectivity should be the steric repulsion between the phosphine ligands and the substituent(s) of the diol. The same trend in the selectivity was observed in the ruthenium complex catalyzed lactone formation reaction.[4]

In contrast to the hydride complex, $RhCl(PPh_3)_3$ was found ineffective for the lactone formation from diols. It is supposed that the ω-hydroxy aldehydes formed as the dehydrogenation intermediates of the lactone formation are decarbonylated to provide the carbonyl complex $RhCl(CO)(PPh_3)_2$, which is a poor catalyst for the present reaction.[6]

In ruthenium-catalyzed reaction systems, hemiacetals were shown to be the intermediate,[2b,c,3] and this suggests that the stepwise dehydrogenation involving the formation of the hemiacetals **4** followed by the successive dehydrogenation of them to afford the lactones would be a possible mechanism (eq 2). In contrast to the ruthenium-catalyzed

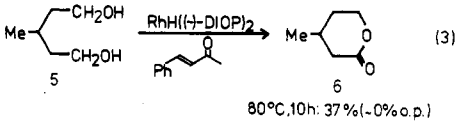


4 (2)

reactions no hemiacetals were detected in reaction mixtures catalyzed by the rhodium complex by GC analyses. However, the close similarity in the regioselectivity between the ruthenium and the rhodium systems suggests that the stepwise mechanism shown in eq 2 could be the case for the latter reaction system. It was reported that the equilibrium constants for the coordination of hindered benzyl alcohols to $RhH(PPh_3)_4$ are rather small so that they suffer slow dehydrogenation.[7] In the present lactonization reaction, it is plausible that the regioselectivity is determined at the step of the coordination of one of the hydroxyl group of a diol to the rhodium complex, followed by the first dehydrogenation of the coordinated hydroxymethyl group.

When the diol having either prochiral or meso structure undergoes dehydrogenation by a chiral phosphine rhodium complex, the formation of an optically active lactone is expected. This reaction involving such transformation as the dehydrogenation of one of the enantiotopic hydroxymethyl group to give an optically active product belongs to the *enantiotopos* differentiating reaction,[8] which is a rare type of asymmetric reaction with respect to transition metal complex catalysis.[9]

The hydrogen transfer from 3-methyl-1,5-pentanediol (**5**) to 4-phenyl-3-buten-2-one using $RhH((-)\text{-DIOP})_2$ ((-)-DIOP = (4*R*,5*R*)-2,2-dimethyl-4,5-bis[(diphenylphosphino)methyl]-1,3-dioxolane[10]) as the catalyst gave practically optically inactive tetrahydro-4-methyl-2*H*-pyran-2-one (**6**, eq 3). On the other hand, a similar re-



5 6 (3)

action with *cis*-1,2-bis(hydroxymethyl)cyclohexane (**7**) gave optically active lactone, (3_aR,7_aS)-hexahydro-1(3*H*)-isobenzofuranone **8** (eq 4). The lactone **8** obtained at 80 and 50 °C is of 19% and 29% optical purity, respectively. The optical yield of the latter reaction is higher than that obtained by the $Ru_2Cl_4((-)\text{-DIOP})_3$-catalzyed reaction.[3] Although chemical and optical yield of this reaction are still not satisfactory, this asymmetric reaction is interesting

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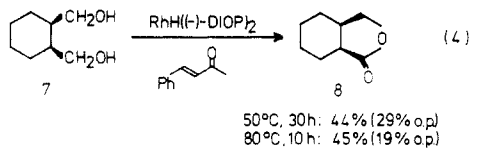

as a transition metal complex catalyzed counterpart of enzymatic reaction.[11]

Experimental Section

Proton NMR spectra were taken on a Hitachi R-40 (90 MHz) spectrometer or a JEOL JNM-GX400 (400 MHz) spectrometer using chloroform-*d* as a solvent. IR spectra were taken on a Shimadzu IR-400 spectrophotometer as neat film. Analyses by gas chromatography were performed on a Shimadzu GC-6AM instrument equipped with a frame ionization detector and a Shimadzu Chromatopac C-E1B calculating integrator using an adequate internal standard. A 2-m steel column filled with 60/80 mesh Uniport HB with 2% carbowax 40M was used. A Hitachi 163 instrument fitted with a thermal conductivity detector was used for preparative GC.

All of the diols were prepared by $LiAlH_4$ reduction of corresponding dicarboxylic acids, diesters, or cyclic anhydrides. $RhH(PPh_3)_4$,[12] $RhCl(PPh_3)_3$,[13] $RhH(CO)(PPh_3)_3$,[14] and $RhH((-)\text{-DIOP})_2$[15] were prepared according to the literature methods. Toluene was dried over sodium, distilled, and stored under argon. Other chemicals were reagent-grade commercial products.

An Example of Catalytic Regioselective Dehydrogenation of a Diol. A mixture of 2,2-dimethyl-1,4-butanediol (**1a**) (1.0 mmol) and 4-phenyl-3-buten-2-one (2.0 mmol) was dissolved in toluene (5 ml) under argon, and $RhH(PPh_3)_4$ (0.04 mmol) was added in one portion. Resulting yellow solution was stirred for 10 h at 50 °C. GC analysis of the reaction mixture indicated that the dehydrogenation of the diol gave a mixture of dihydro-4,4-dimethyl-2(3*H*)-furanone (**2a**) and dihydro-3,3-dimethyl-2-(3*H*)-furanone (**3a**) in the ratio of 98:2 in 95% yield. The structure of the products were fully characterized by ^1H NMR and IR spectra after purification by preparative GC.

An Example of Catalytic Enantioselective Dehydrogenation of a Diol. A mixture of *cis*-1,2-bis(hydroxymethyl)-cyclohexane (**7**) (5 mmol) and 4-phenyl-3-buten-2-one was dissolved in toluene (25 mL) under argon, $RhH((-)\text{-DIOP})_2$ (0.2 mmol) was added in one portion, and the solution was stirred for 30 h at 50 °C. The solvent was evaporated off, and the product was purified by column chromatography (silica gel, 6:4 ether–hexane) followed by bulb-to-bulb distillation to give (3_aR,7_a*S*)-hexahydro-1(3*H*)-isobenzofuranone (**8**) (44%), and the optical yield was determined to be 29% from its optical rotation.[11b]

Acknowledgment. This work was supported by Grants in Aid for Developmental Scientific Research from the Ministry of Education of Japan (58550556).

Registry No. **1a**, 32812-23-0; **1b**, 2938-98-9; **1c**, 39497-66-0; **1d**, 6837-05-4; **1e**, 13942-68-2; **1f**, 63842-86-4; **1g**, 3121-82-2; **1h**, 42856-62-2; **1i**, 101999-42-2; **2a**, 13861-97-7; **2b**, 1679-49-8; **2c**, 10547-88-3; **2d**, 1008-73-7; **2e**, 20514-72-1; **2f**, 101999-37-5; **2g**, 1679-55-6; **2h**, 3123-98-6; **2i**, 62618-74-0; **3a**, 3709-08-8; **3b**, 1679-47-6; **3c**, 1608-63-5; **3d**, 6836-98-2; **3e**, 25600-25-3; **3f**, 25600-27-5; **3g**, 4830-05-1; **3h**, 10603-03-9; **3i**, 13019-37-9; **5**, 4457-71-0; (±)-**6**, 62989-38-2; **7**, 15753-50-1; **8**, 65376-02-5; $RhH(PPh_3)_4$, 18284-36-1; $RhH((-)\text{-DIOP})_2$, 102490-04-0; $PhCH{=}CHCOCH_3$, 122-57-6.

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Stereoselective Synthesis of the Novel Bisnorditerpene Grindelistrictic Acid, Isolated from *Grindelia stricta*

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Most of the diterpenes isolated from plants of the genus *Grindelia* are structurally related to grindelic acid (**1a**)[1] (Chart I). Recently, however, a new type of terpenoids carrying a spiroketal moiety, namely strictanonic acid (**2a**) and the bisnorditerpene grindelistrictic acid (**3a**), were isolated in very small amounts from *G. stricta*.[2] Considerable attention has been given to the natural products containing spiroketal moieties, from the point of view of biological and synthetic interests.[3-5] In addition, since the **2a** and **3a** structures were proposed only on the basis of NMR data, unambiguous syntheses were needed for their confirmation. We have already succeeded in the synthesis of **2b**,[6] and now, we wish to report the stereoselective synthesis of **3b**.

We examined the synthesis of **3b** via the intramolecular ketalization of the C-18 precursor **4**, which could be obtained by oxidative cleavage of ester **5a**,[7] the reduction product of the known ketol **6**.[8] The latter possesses three of the four chiral centers present in **3b**.

For the preparation of **6** we used a three-step procedure, involving the reductive cleavage of **1a** to give **7**, followed by methylation and Jones oxidation to afford **6** in a 43% overall yield. Sodium borohydride reduction of **6** produced mainly the equatorial allylic alcohol **5a**, as shown by the half-band width of its H-7 signal. However, when **5a** was submitted to ozonolysis, compound **8** was obtained, after workup, as an epimeric mixture at C-7. The production of **8** indicated, in agreement with our previous experience in the synthesis of **2b**,[6] that the keto group formed by cleavage of the carbon–carbon double bond is immediately trapped as an intramolecular ketal, which then precludes the further cleavage of the α-ketol moiety.

In order to avoid the formation of **8** during the ozonolysis workup, we protected the allylic alcohol as an acetate (**5a** → **5b**).[9] In this case **5b** afforded **9** in 77% yield. The removal of the extra two-carbon unit of **9** would require the hydrolysis of the acetate under conditions that would favor cleavage over ketalization. The use of mild alkaline conditions in the presence of the cleaving agent ($NaIO_4$,

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(9) Compound **5b** was also prepared by direct oxidation of **1b**, according to the procedure described in ref 8, followed by $NaBH_4$ reduction and acetylation, in an overall yield of 40%.

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