1.31 (t, 3 H, J = 7.5 Hz), 1.45 (t, 3 H, J = 7.5 Hz), 3.35 (q, 2 H, J = 7.5 Hz), 3.39 (q, 3 H, J = 7.5 Hz); ^{19}F NMR ϕ -108.7 (t, 2 F, J = 1.5 Hz), -125.2 (t, 2 F, J = 1.5 Hz); mass spectrum, m/e 274.

Anal. Calcd for $C_9H_{10}F_4OS_2$: C, 39.41; H, 3.67. Found: C, 39.47; H, 3.62.

Reaction of 9 with Ethanethiol. Treatment of **9** with 1 equiv of ethanethiol and triethylamine as described above afforded an inseparable mixture of **9** and **20** in a 3:7 ratio.

3-Thioethoxy-2,4,4-trifluorocyclobutenone (21) and 2,3-Dithioethoxy-4,4-difluorocyclobutenone (22). Treatment of 1.59 g (11.35 mmol) of **2** with 0.7 g (11.35 mmol) of ethanethiol and 1.41 g (14 mmol) of triethylamine as described above gave a brown residue which was separated into two fractions by preparative thin-layer chromatography with 9:1 hexane-ether.

Fraction I, 22: 470 mg (20%); IR (neat) 1750 (C=O), 1735 (C=C) cm^{-1}; ^{1}H NMR δ 1.40 (t, 3 H, J = 8 Hz), 1.46 (t, 3 H, J = 7 Hz), 3.25 (q, 2 H, J = 8 Hz), 3.27 (q, 2 H, J = 7 Hz); ^{19}F NMR ϕ -102.65 (s); mass spectrum m/e 224; UV (isooctane) λ_{max} 215 nm (ϵ 6940), 230 (7970), 300 (15 500).

Anal. Calcd for $C_8H_{10}F_2OS_2$: C, 42.84; H, 4.49. Found: C, 43.15; H, 4.45.

Fraction II, 21: 130 mg (6.3%); IR (neat) 1820 (C=O), 1640 (C=C) cm^{-1}; ^{1}H NMR δ 1.48 (t, 3 H, J = 8 Hz), 3.25 (q, 2 H, J = 8 Hz); ^{19}F NMR ϕ -107.3 (A of AB_2, J = 23 Hz), -110.12 (B of AB_2, J = 23 Hz); mass spectrum, m/e 182; UV (isooctane) λ_{max} 221 nm (ϵ 1700), 270 (23 200), 310 (851).

Anal. Calcd for $C_6H_5F_3OS$: C, 39.56; H, 2.77. Found: C, 39.77; H, 2.84.

1,2-Dithiomethoxy-3,4,4-trifluorocyclobutenyl Hexafluoroantimonate (27). Under anhydrous conditions, 4.92 g (22.6 mmol) of **26** was added dropwise to a solution of 4.88 g (22.6 mol) of SbF_5 in 25 mL of sulfur dioxide at -65 °C. The resulting homogeneous, deep blue solution was warmed to room temperature, while the sulfur dioxide was removed in a slow stream of nitrogen. The hexafluoroantimonate salt **27** was deposited as a deep blue crystalline solid in 67% isolated yield.

Hydrolysis of 27. 2,3-Dithiomethoxy-4,4-difluorocyclobutenone (28) and 3,4-Dithiomethoxycyclobutene-1,2-dione (29). The hexafluoroantimonate salt **27** (6.55 g, 15 mmol) was added cautiously in portions to vigorously stirred ice-water. After dissolution of the salt, the mixture was extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to a yellow mass that was separated into two components by thin-layer chromatography with 5:1 hexane-ether.

Fraction I, 28: 470 mg (10%); yellow solid; mp 33.5-35.5 °C (petroleum ether); IR (KBr) 1760 (C=O) cm^{-1}; ^{1}H NMR (benzene) δ 1.92 (s, 3 H), 2.12 (s, 3 H); ^{19}F NMR ϕ -102 (s); mass spectrum, m/e 196; UV (isooctane) 229 nm (ϵ 9337), 299 (16 375).

Anal. Calcd for $C_6H_6F_2OS_2$: C, 36.72; H, 3.08. Found: C, 36.70; H, 3.06.

Fraction II, 29: 280 mg (7%); yellow solid; mp 135.5-137 °C (ether-ethyl acetate); IR (KBr) 1745 (C=O), 1725 (C=O) cm^{-1}; ^{1}H NMR δ 2.92 (s); mass spectrum, m/e 174.

Anal. Calcd for $C_6H_6O_2S_2$: C, 41.36; H, 3.47. Found: C, 41.50; H, 3.51.

Registry No. 1, 24807-10-1; **2**, 60838-92-8; **3**, 74835-63-5; **4**, 74843-74-6; **5**, 74835-64-6; **6**, 60407-11-6; **8**, 74835-65-7; **9**, 74835-66-8; **10**, 74835-67-9; **13**, 74835-68-0; **14**, 66463-35-2; **15**, 74835-69-1; **16**, 74835-70-4; **17**, 74835-71-5; **18**, 74835-72-6; **20**, 74835-73-7; **21**, 74835-74-8; **22**, 74835-75-9; **26**, 13888-99-8; **27**, 74877-68-2; **28**, 74835-76-0; **29**, 54131-97-4; aniline, 62-53-3; *p*-toluenesulfonylhydrazide, 1576-35-8; phenol, 108-95-2; *n*-decanol, 112-30-1; 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, 4064-06-6; PhONa, 139-02-6; perfluorocyclopentene, 559-40-0; KOAc, 127-08-2; PhSNa, 930-69-8; EtSH, 75-08-1.

Microbial Stereodifferentiating Reduction of Carbonyl Compounds; Proposed Quadrant Rule[1]

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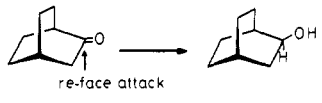
The stereochemistry of the isomeric alcohols obtained from microbial reduction (*Curvularia lunata* and *Rhodotorula rubra*) of the racemic modification of bicyclic (**5**, **8**, **23**), benzobicyclic (**11**, **14**, **17**), and tricyclic (**20**) ketones with a wide variation in molecular framework has led to the formulation of a quadrant rule which provides information on the absolute configuration of the substrate ketone.

Our continuing interest in the syntheses and chiroptical properties of various gyrochiral[2] cage-shaped molecules has led us to examine the stereochemistry of microbial reduction of tri- and pentacyclic cage-shaped C_2 ketones[3] (e.g., 9-*twist*-brendanone (**1**)) as well as that of the atropisomeric C_2 biphenyl-bridged ketone (**2**).[4]

Scheme I



3 (+)-(2S)-4

Illustrated in Figure 1 are the enantiomers **1** and **2**, which were found to be preferentially reduced by *Curvularia lunata* and *Rhodotorula rubra*, and they can be schematically represented by a *P*-C_2 ketone,[5] a quadrant projection formula obtained by looking from the oxygen side along the carbonyl axis (Figure 2).

Our formulation of the "C_2-ketone rule"[4b] stating that the microbes selectively reduce the *P*-C_2 ketones over the enantiomeric *M*-C_2 ketones[5] supplements the "Prelog

(1) Presented at the 26th IUPAC Congress, Sept 8, 1977, Tokyo, Japan, Abstracts p 63. For preliminary account of this work, see: Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Hirose, Y.; Shimizu, T.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 668-670. For review summarizing our studies on stereodifferentiating microbial reduction, see: Nakazaki, M.; Chikamatsu, H. *Kagaku no Ryoiki* **1977**, *31*, 819-833.

(2) This name is proposed to describe the symmetry of a shape which is chiral but not asymmetric. Cf.: Nakazaki, M.; Naemura, K.; Yoshihara, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3278-3284.

(3) In this paper, ketones are conveniently classified according to their symmetry: C_s ketones belong to the C_s point group and have the plane of symmetry coincident with the carbonyl plane; C_2 ketones belong to the C_2 point group and have the C_2 axis coincident with the carbonyl axis; C_1 ketones have no symmetry element passing through the carbonyl axis.

(4) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 667-668. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Org. Chem.* **1979**, *44*, 4588-4593.

(5) An inspection of the quadrant projection formula (Figure 1) should support the adequacy of our adopting *M* and *P* helicity[6] to describe these chiralities.

(6) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385-415.

0022-3263/80/1945-4432$01.00/0

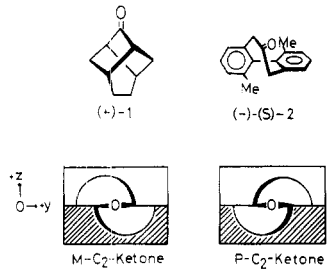


Figure 1. Microbial reduction of a C_2 ketone and the "C_2-ketone rule".

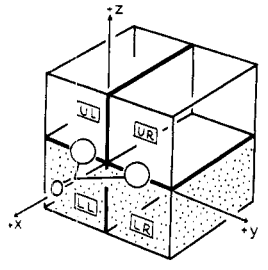


Figure 2. Quadrant orientation. Substrate ketone molecules are orientated in a three-dimensional system with the carbonyl plane on the xy plane and the carbonyl oxygen pointing in the $+x$ direction. Four quadrants are designated by UL (upper left), UR (upper right), LL (lower left), and LR (lower right).

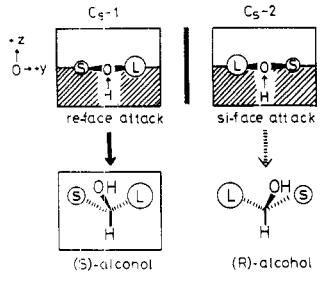


Figure 3. Microbial reduction of a C_s ketone and the "Prelog rule".

rule"[7] (Figure 3) which summarizes microbial behavior toward C_s ketones[3] by stating that the microbes prefer C_s-1 over C_s-2 quadrant orientation to yield the (*S*)-alcohol on hydrogen delivery from the low quadrant sections (*re*-face attack).

Having no symmetry element passing through the carbonyl axis, the stereochemical environment around the carbonyl group in the C_1 ketone[3] provides further complications. Since two faces around the carbonyl group in one of the enantiomers of the C_1 ketone are diastereotopic,[8] we can distinguish four stereochemically different faces in a racemic C_1 ketone to yield the corresponding four quadrant orientations: C_1-1 and C_1-2 for one enantiomer and C_1-3 and C_1-4 for another enantiomer (Figure 4).

Among the various cyclic C_1 ketones whose metabolites have been investigated to elucidate stereoselectivity in microbial reduction,[7,9] few have either the carbonyl group constrained in the nonchair form of a cyclohexane ring or rigid and well-defined molecular frameworks. This

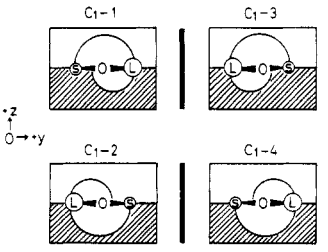


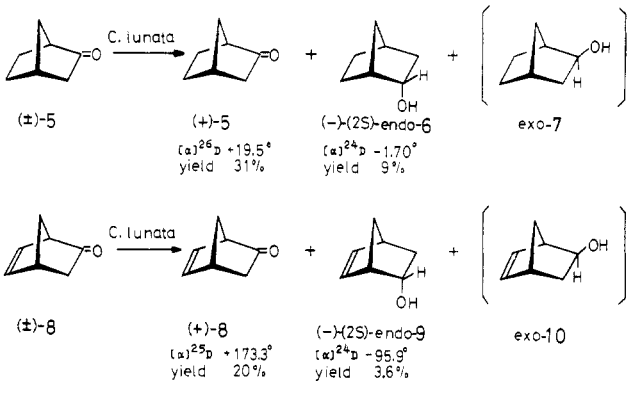
Figure 4. Schematic representation of four quadrant orientations for a racemic C_1 ketone.

Table I. Microbial Reduction of Bicyclo[2.2.2]octan-2-one (3) with Various Microbes

microorganisms	incubation period, h	compd 4 yield, %[a]	compd 4 $[\alpha]_D$ ($CHCl_3$), deg	compd 4 optical purity, %[b]
R. rubra	24	37	+31.3	98
C. lunata	48	37	+28.4	89
R. arrhizus	72	19	+16.8	53
baker's yeast	96	11	+25.0	78

[a] The recovered ketone 3 was not accounted for in these calculations. [b] The optical purity was calculated on adapting Goering's absolute rotation $[\alpha]_D$ + 32°,[14] which was incidentally found to be identical with Jacques' value[15] obtained by calorimetric analysis.

Scheme II



prompted us to examine the stereochemistry of microbiological reduction products of the cage-shaped C_1 ketones with these stereochemical characteristics.

Results[10]

Screening of Microbes. Microbial Reduction of Bicyclo[2.2.2]octan-2-one (3) (Scheme I). Before studying the microbial reduction of cage-shaped C_1 ketones, we made a screening of microbes to secure microbes which were "easy" microbes[11] and reduced these ketones with reasonable rates and high stereoselectivity. To avoid expected complications which should arise from possible formation of diastereomers, we selected bicyclo[2.2.2]octan-2-one (3) with C_s symmetry as a reference substrate. After trial incubations with these microbes, preparative-scale incubations were carried out with four microbes: *Rhodotorula rubra*, *Curvularia lunata*, *Rhizopus arrhizus*, and fermenting baker's yeast (*Saccharomyces cerevisiae*). The reaction process was monitored by GLC and termi-

(7) (a) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–130. (b) Acklin, W.; Prelog, V.; Schenker, F.; Serdarevic, B.; Walter, P. *Helv. Chim. Acta* **1965**, *48*, 1725–1746.

(8) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1–38.

(9) Concise reviews can be found in: (a) Bentley, R. "Molecular Asymmetry in Biology"; Academic Press: New York, 1970; Vol. 2, pp 41–50; (b) Sih, C. J.; Rosazza, J. P. "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part 1, pp 69–106; (c) Kieslich, K. *Synthesis* **1969**, *1*, 147–157; (d) Kieslich, K. "Microbial Transformations of Non-Steroid Cyclic Compounds"; Georg Thieme Verlag: Stuttgart, 1976; pp 16–28.

(10) Proper caution was paid in order to minimize errors due to optical fractionation on repeated recrystallization, and the optical purities cited in this paper are based on the specific rotations of sublimed or once-recrystallized materials.

(11) Fonken, G. S.; Johnson, R. A. "Chemical Oxidations with Microorganisms"; Marcel Dekker: New York, 1972; p 249.

Table II. Microbial Reduction of Bicyclic and Tricyclic Cage-Shaped C_1 Ketones with *C. lunata*, *R. rubra*, and Baker's Yeast

substr	microbe	incubation period,[a] h	recovered ketone optical purity, %	alcohol optical purity, % endo	alcohol optical purity, % exo	ratio[b] of endo/exo
(±)-5	*C. lunata*	15 (52)	67	91	*c*	25:1
	R. rubra	24 (33)	6.8	83	*c*	5.6:1
(±)-8	*C. lunata*	15 (34)	15	54	*c*	33:1
	R. rubra	24 (27)	1.3	12	*c*	12.5:1
(±)-11	*C. lunata*	12 (70)	53	82	*c*	endo[d]
(±)-14	*C. lunata*	20 (62)	95	85	77	30:1
	R. rubra	12 (63)	49	36	*c*	endo[d]
(±)-17	*C. lunata*	20 (62)	93	72	*c*	30:1
	R. rubra	8.5 (53)	3.7	8.6	*c*	11:1
(±)-20	baker's yeast	96 (53)	3.8	89	54	1:1.8
	R. rubra	30 (62)	92	94	81	1:4.2
(±)-23	*C. lunata*	48 (50)	15	71	69	1.3:1
	R. rubra	96 (51)	26	74	90	2.4:1

[a] Parenthesized values are the percentage extents of microbial reduction at the end of each incubation. [b] Estimated by GLC of crude ether extracts. [c] Insufficient material for characterization. [d] Almost pure endo alcohol with a trace amount of exo isomer detectable only by GLC.

nated after about 50% of the ketone had been reduced. Our results are summarized on Table I.

The absolute configuration shown in Scheme I was assigned on the basis of literature correlation[12] and confirmed the "Prelog rule".

Disturbing richness in extractable foreign materials together with producing a rather poor yield of the alcohol **4** with low optical purity made us exclude *R. arrhizus* and the baker's yeast from our further microbiological experiments.[13]

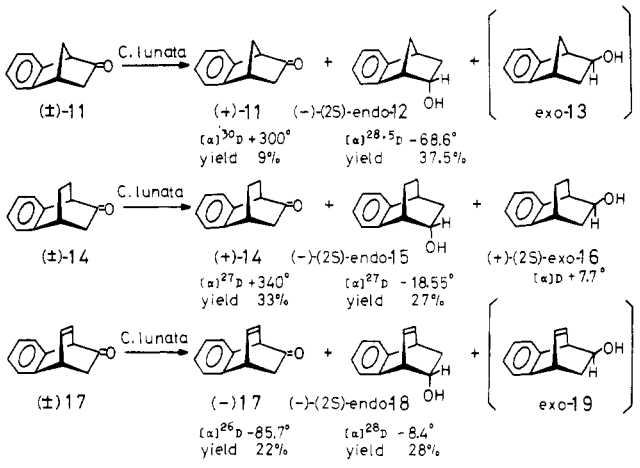
Microbial Reduction of Racemic Norbornane Ketones 5 and 8 (Scheme II). Racemic bicyclo[2.2.1]heptan-2-one (**5**) was subjected to incubation with *C. lunata*. The reaction was terminated when ~50% of the ketone had been consumed. The results are summarized in Table II.

After extraction of the metabolite, alumina chromatography and sublimation in vacuo yielded the recovered (+)-ketone **5** and the (−)-*endo*-alcohol **6** whose GLC indicated a 1.5% contamination with the exo isomer **7**. Its meager existence in the metabolite prevented us from isolating this exo isomer.

The absolute configurations shown in Scheme II are based on previous literature,[16] and the optical purities given in Table II were calculated from Jones' data.[17-19]

Table II also tabulates the results of microbial reduction of the unsaturated ketone (±)-bicyclo[2.2.1]hept-5-en-2-one (**8**). Literature correlations established the absolute configurations of the recovered ketone (+)-**8**[12a] and (−)-*endo*-alcohol **9**[20] (contaminated with 3% *exo*-alcohol **10**), and their optical purities were calculated from their reported absolute rotation values.[21,22]

Scheme III



Reduction of **5** and **8** with *R. rubra* was found to be poorer both in enantiomer and in endo–exo product selectivities compared with that with *C. lunata*.

Microbial Reduction of Racemic Benzobicyclic Ketones 11, 14, and 17 (Scheme III). An inspection of Figure 4 reasonably suggests that the larger the difference between molecular space occupations in the upper and lower quadrants, the higher will be microbial stereodifferentiation between the four quadrant orientations. This prompted us to examine the microbial reduction of the benzobicyclic ketones **11**, **14**, and **17** which appear to fulfil this stereochemical requirement.

Incubation of (±)-benzobicyclo[2.2.1]heptan-2-one (**11**) with *C. lunata* was terminated after 70% of reduction had occurred. The results are shown in Scheme III and Table II.

(12) (a) Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 1956–1961. (b) Berson, J. A.; Willner, D. *Ibid.* **1964**, *86*, 609–616.

(13) Preparative-scale incubation of (±)-4-twistanone (**20**) was carried out with *R. rubra* and baker's yeast.

(14) Goering, H. L.; Fickes, G. N. *J. Am. Chem. Soc.* **1968**, *90*, 2862–2868.

(15) Varech, D.; Jacques, J. *Tetrahedron* **1972**, *28*, 5671–5679.

(16) (a) For the absolute configurations of (+)-ketone **5** and (−)-*exo*-alcohol **7** see ref 12a. (b) For the absolute configurations of (+)-ketone **5** and (+)-*endo*-alcohol **6**, see: Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986–3997.

(17) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8476–8482. These authors gave maximum rotation values, $[\alpha]^{25}_D$ +29.1° for (+)-**5**, +1.87° for (+)-*endo*-**6**, and −3.14° for (−)-*exo*-**7**.

(18) Contamination (1.5%) with the exo isomer **7** was ignored in the optical purity calculation of **6**.

(19) Irwin and Jones[17] reported the completely opposite results in their horse liver alcohol dehydrogenase catalyzed reduction using sodium dithionite recycling of NADH, isolating (−)-ketone **5** (46% optical purity) and (+)-*endo*-alcohol **6** (64% optical purity).

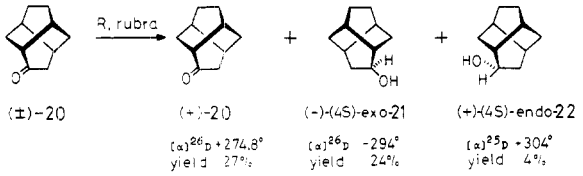
(20) Sandman, D. J.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 2924–2926.

(21) The optical purity of (+)-ketone **8** was calculated on the basis of the reported absolute rotation $[\alpha]_D$ 1160° (isooctane).[20]

(22) Our failure in isolating the exo isomer **10** prevented estimation of the accurate optical purity of the isolated (−)-*endo*-alcohol **9**. Fortunately, however, the small absolute rotation, $[\alpha]_D$ 13.4°,[23] of the contaminating exo isomer **10** compared with the reported absolute rotation, $[\alpha]_D$ −177°,[20] of the (−)-*endo*-alcohol **9** together with its minute quantity seems to give an approximate optical purity of 54% to this isolated specimen of **9**.

(23) From literature correlation between Irwin[17] and Mislow.[12a]

Scheme IV



The metabolite mixture was chromatographed to give the recovered (+)-ketone **11** and (−)-*endo*-alcohol **12**. Their absolute configurations shown are based on previous literature proofs,[24] and their optical purities were calculated from their reported absolute rotation values.[24]

Other benzobicyclic ketones, (±)-benzobicyclo[2.2.2]-octan-2-one (**14**) and (±)-benzobicyclo[2.2.2]oct-5-en-2-one (**17**), were also subjected to incubation with *C. lunata*. The results are shown in Scheme III and Table II.

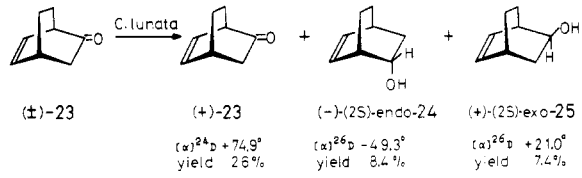
The absolute configuration and optical purity of the recovered ketone (+)-**14** are based on the previous literature.[25] Information on the absolute configuration as well as the optical purity of the metabolite alcohol, (−)-*endo*-**15**,[26] whose GLC indicated no trace of the exo isomer **16**,[26] was provided from the Jones oxidation which gave (−)-ketone **14**.[27] Although its meager existence prevented us from isolating *exo*-alcohol **16**, the stereochemical information of **16** shown in Scheme III and Table II was obtained from that of a speciemen of a 72:28 mixture of endo and exo isomers (see Experimental Section).[28]

The recovered (−)-ketone **17**[29] and the metabolite (−)-*endo*-alcohol **18** were hydrogenated on Pd/C to yield the saturated (+)-ketone **14** and the saturated (−)-*endo*-alcohol **15**, respectively, thereby establishing their absolute configurations and optical purities.[25,30,31]

Tabulated also in Table II is the result of incubation with *R. rubra*, which yielded the recovered (+)-ketone **14** of lower optical purity with almost no formation of the *exo*-alcohol **16**. *R. rubra* exhibited very low stereoselectivity toward the unsaturated ketone **17**, yielding the recovered (−)-ketone **17** and (−)-*endo*-alcohol **18** with extremely low optical purities.

Microbial Reduction of Racemic 4-Twistanone (Tricyclo[4.4.0.0^{3,8}]decan-4-one, 20; Scheme IV). The microbial reduction of the tricyclic cage-shaped C_1 ketone (±)-4-twistanone (**20**) was carried out with baker's yeast and *R. rubra*. The results are summarized in Table II. As a preliminary experiment, (±)-**20** was incubated with fermenting baker's yeast. The reaction was stopped when ~50% of the starting ketone had been consumed. Alumina chromatography of the metabolite afforded the recovered (−)-ketone **20**, (−)-*exo*-**21**,[32] and (+)-*endo*-**22**[32] which was contaminated with 10% of the exo isomer. The absolute configuration of the recovered (−)-ketone **20** is based on previous literature proofs,[34] and its optical purity was calculated from its newly established absolute rotation value.[35] Jones oxidation of (−)-*exo*-**21** and (+)-*endo*-**22** to (−)- and (+)-ketone **20**, respectively, allowed us to determine their absolute configurations and to calculate their optical purities.[36]

Scheme V



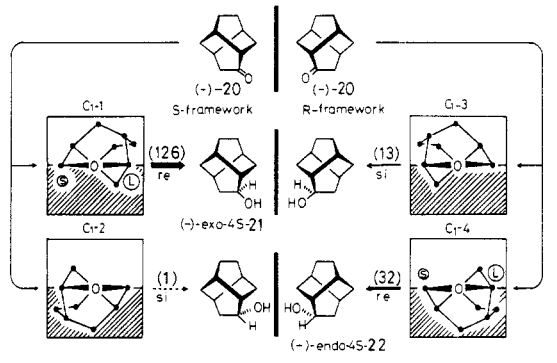


Figure 5. Quadrant orientations of (±)-4-twistanone (**20**). The parenthesized values are the calculated relative rates of formation of isomeric alcohols with *R. rubra*.

Incubation with *R. rubra* was found to reveal much higher enantiomer selectivity toward ketone **20**. A large part of (−)-**20** was metabolized to (−)-*exo*-**21** (optical purity 81%) which can be readily oxidized back to (−)-**20** chemically, and (+)-**20** (optical purity 92%) remained in the culture solution. Thus, *R. rubra*'s incubation is a convenient method of the optical resolution of (±)-4-twistanone (**20**).

Microbial Reaction of (±)-Bicyclo[2.2.2]oct-5-en-2-one (23) (Scheme V). Which enantiotopic[8] ethano bridges in C_s ketone **3** are replaced by an etheno bridge determine the chirality of the resulting bicyclo[2.2.2]oct-5-en-2-one (**23**), and incubation of this unsaturated ketone was carried out to see the microbes' ability to distinguish this subtle stereochemical difference between the ethano and etheno bridges.

Incubation with *C. lunata* was terminated when GLC monitoring showed the formation of a metabolite mixture composed of the recovered ketone **23**, *endo*-alcohol **24**, and

(24) Sandman, D. J.; Mislow, K.; Giddings, W. P.; Dirlam, J.; Hanson, G. C. *J. Am. Chem. Soc.* **1968**, *90*, 4877–4884. These authors also gave absolute rotation values of $[\alpha]_D$ +570° for the (+)-ketone **11** and +84° for the (+)-*endo*-alcohol **12**.

(25) For the absolute configuration of (−)-ketone **14**; see: Takeda, K.; Hagishita, S.; Sugiura, M.; Kitahonoki, K.; Ban, I.; Miyazaki, S.; Kuriyama, K. *Tetrahedron* **1970**, *26*, 1435–1451. Optical purity was calculated on the maximum rotation, $[\alpha]_D$ −356.2°, reported in this reference.

(26) For the characterization of *endo*-**15** and exo isomer **16**; see: (a) Kitahonoki, K.; Takano, Y. *Tetrahedron Lett.* **1963**, 1597–1603; (b) Tori, K.; Takano, Y.; Kitahonoki, K. *Chem. Ber.* **1964**, *97*, 2798–2815.

(27) This correlation automatically furnished an absolute rotation of $[\alpha]_D$ −21.8° to the (−)-endo isomer **15**.

(28) The calculation assigns $[\alpha]_D$ +10° as the absolute rotation of the (+)-*exo*-alcohol **16**.

(29) Takeda et al.[25] reported the preparation of (+)-ketone **17**, $[\alpha]^{22}_D$ +87.5 ± 1.2°.

(30) Optical purity was calculated from our newly estimated absolute rotation of $[\alpha]_D$ 21.8° for **15**.[27]

(31) These estimated optical purities of the ketone **17** and the *endo*-alcohol **18** indicate their maximum rotation to be $[\alpha]_D$ 92° and 11.6°, respectively.

(32) The exo and endo configurations were assigned by means of their NMR spectra.[33]

(33) (a) Tichy, M.; Kniezo, L. *Tetrahedron Lett.* **1971**, 1665–1670. (b) Tichy, M.; Kniezo, L.; Hapala, J. *Ibid.* **1972**, 699–702. (c) Tichy, M.; Kniezo, L. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1537–1550.

(34) For the synthesis and absolute configuration of (+)-ketone **20**, see: (a) Tichy, M.; Sicher, J. *Tetrahedron Lett.* **1969**, 4609–4613; (b) Tichy, M. *Ibid.* **1972**, 2001–2004; (c) Tichy, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2673–2684.

(35) Correlating with (−)-2-twistanol acetate, $[\alpha]_D$ −98.9° (MeOH), whose 34.5% optical purity was established by the enantiomers differential shifts observed in its NMR spectrum with a chiral shift reagent, Eu(facam)$_3$, we have assigned an absolute rotation of $[\alpha]_D$ +440° (EtOH) to (+)-twistane (Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1978**, *43*, 4745–4750) which eventually gives $[\alpha]_D$ +299° (EtOH) for the absolute rotation of (+)-4-twistanone (**20**). This value is close to Tichy's value of $[\alpha]^{25}_D$ +295.2° (EtOH).[34c]

(36) These estimated optical purities of *exo*-**21** and *endo*-alcohol **22** indicate their absolute rotation values to be $[\alpha]_D$ 364° and 323°, respectively.

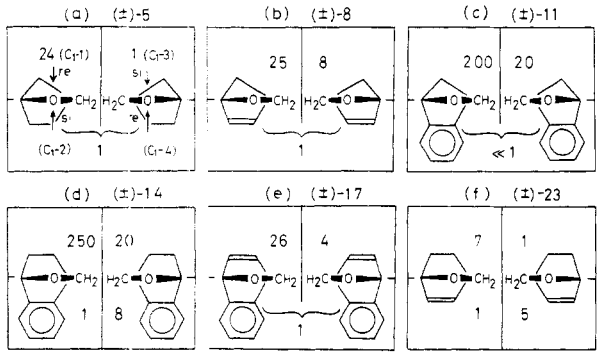


Figure 6. Quadrant orientations of cage-shaped ketones and relative rates of formation of the corresponding isomeric alcohols (*C. lunata*). The two quadrant orientations corresponding to each enantiomer in Figure 4 are combined, and each numeral indicates the relative rate of formation of the isomeric alcohol formed by hydrogen delivery from its side.

exo-alcohol **25** in a ratio of 50:28:22. Alumina chromatography followed by sublimation furnished the recovered (+)-ketone **23**, (−)-*endo*-alcohol **24**,[37] and (+)-*exo*-alcohol **25**.[37]

The absolute configuration of the (+)-ketone **23** has been assigned by Mislow and Berger[12a] and the optical purity was calculated on the basis of its reported absolute rotation value.[39] Literature correlations assigned the absolute configurations of (−)-*endo*-alcohol **24**[12a] and (+)-*exo*-alcohol **25**,[40] and their optical purities were determined by their direct conversion into the saturated alcohol **4** with known absolute rotation.[14,15,41]

Incubation with *R. rubra* showed a little higher stereodifferentiation as can be seen from Table II.

Discussion

Quadrant Rule for C_1 Ketones. In the case of *R. rubra*'s reduction of (±)-4-twistanone (**20**), the distribution ratio of *exo*-**21** and *endo*-**22** included in ether extract (4.2:1) and their estimated optical purities (exo, 81%; endo, 94%) permit calculation of their relative rates of formation: (−)-*exo*-**21**/(+)-*exo*-**21**/(−)-*endo*-**22**/(+)-*endo*-**22** ratio of 126:13:32:1. As this ratio corresponds to the preference for quadrant orientations C_1-1, C_1-3, C_1-4, and C_1-2, respectively, in the reduction process, the qualitative preference order of orientations is $C_1\text{-}1 \gg C_1\text{-}4 > C_1\text{-}3 \gg C_1\text{-}2$ (Figure 5).

The microbial reduction (e.g., *C. lunata*) of the other cage-shaped C_1 ketones **5**, **8**, **11**, **14**, and **17** (except **23**)[43] produced the endo alcohol preferentially, accompanied by a trace amount of exo isomer. Figure 6 shows the relative rates of formation of corresponding isomeric alcohols. It can be recognized that the preference order of orientations is $C_1\text{-}1 \gg C_1\text{-}3 > C_1\text{-}4 \gtrsim C_1\text{-}2$.

These analyses led us to assume that there appears to operate two steric requirements controlling the process.

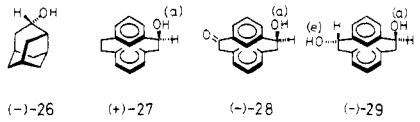


Figure 7. Major reduction products (C_1-1 metabolite alcohol) obtained by *R. rubra* incubation experiments: (−)-**26** from (±)-4-protoadamantanone, (+)-**27** from (±)-1-oxo[2.2]metacyclophane, and (−)-**28** and (−)-**29** from 1,10-dioxo[2.2]metacyclophane.

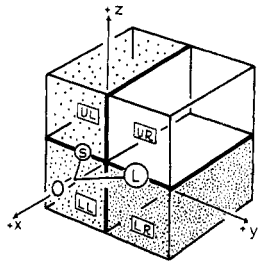


Figure 8. Proposed quadrant section of the "active site" of the redox system in *C. lunata* and *R. rubra*. The qualitative order of their resistance to occupation is LR > LL > UL > UR.

Toward hydrogen delivery from the lower quadrants (Figure 2), the microbe's redox system requires the substrate ketone molecule to be oriented in the position with (a) the larger carbonyl flanking group (L) on the $+y$ axis and the smaller flanking group (S) on the $-y$ axis and (b) the smaller part of the molecule in the lower quadrants. The first requirement corresponds to the Prelog rule operating in microbial reduction of a C_s ketone to result in the predominant formation of an *S* alcohol by *re*-face attack of hydrogen.

Fulfilling these two requirements simultaneously, the enantiomer corresponding to the C_1-1 quadrant orientation should be reduced preferentially, yielding the C_1-1 metabolite alcohol. The opposite situation is to be encountered in the C_1-2 quadrant orientation which cannot accommodate both these requirements, and this should promise a poor yield of the C_1-2 metabolite alcohol. These two steric requirements contradict in C_1-3 and C_1-4 orientations, and this should explain the observed medium and fluctuant yields of the diastereomeric C_1-3 and C_1-4 metabolite alcohols. In practice, incubation monitored by GLC or TLC is terminated at about the 50% stage of reduction, and suitable extraction and separation would provide the C_1-1 metabolite alcohol (*S* configuration) as the major reduction product accompanied by the optically active recovered ketone enriched in the enantiomer with the opposite molecular framework.[44]

Application of the Quadrant Rule To Determine the Absolute Configuration of a C_1 Ketone. A natural corollary of the "quadrant rule" is its application in the determination of the absolute configuration of a substrate C_1 ketone utilizing the racemic modification. Inspection of substrate behavior in quadrant section terms with the aid of molecular models indicates which enantiomer will be preferentially reduced, corresponding to the C_1-1 quadrant orientation, and which will be left intact to be recovered from the incubation mixture. Supplementing this procedure, the diastereomeric nature (syn/anti, endo/exo, and axial/equatorial, etc.) of the C_1-1 metabolite alcohol might be checked against the predicted structure.

(37) The endo and exo configurations were assigned by means of their NMR spectra[38] and relative order of retention times in GLC.[12a]

(38) (a) Fraser, R. R.; O'Farrell, S. *Tetrahedron Lett.* **1962**, 1143–1146. (b) Reference 26b.

(39) $[\alpha]_D$ +497°: Goering, H. L.; Towns, D. L. *J. Am. Chem. Soc.* **1963**, *85*, 2295–2298.

(40) Berson, J. A.; Wege, D.; Clarke, G. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 5594–5601.

(41) Catalytic hydrogenation of (−)-**24** and (+)-**25** yielded (+)-(2*S*)-alcohol **4**. Absolute rotations of $[\alpha]_D$ 69.8°[42] and 30.5° were assigned to *endo*-**24** and *exo*-**25**, respectively.

(42) This value is close to the absolute rotation value of $[\alpha]_D$ 74 ± 2° reported by Goering and Towns.[39]

(43) In the case of **23**, microbes showed a low stereodifferentiation between ethano and etheno bridges (Figure 6f) but preferentially gave *endo*-(2*S*)-**24** and *exo*-(2*S*)-**25**, confirming the "Prelog rule".

(44) Since the major reduction product, the C_1-1 metabolite alcohol, can be readily oxidized back to the enantiomeric ketone, this microbial stereodifferentiating reduction of the C_1 ketone affords a convenient single-step method for preparing substantially enantiomerically enriched cage-shaped ketones from their racemic precursors.

Our successful applications of the quadrant rule are illustrated in Figure 7 which shows the major reduction products isolated from *R. rubra*'s incubation with (±)-4-protoadamantanone,[1] (±)-1-oxo[2.2]metacyclophane,[45] and 1,10-dioxo[2.2]metacyclphane.[45]

As a rule of thumb for microbes in general, however, this quadrant rule for *C. lunata* and *R. rubra* should be applied with due caution, especially when the substrate ketones have substituents which are suspected to exert a disturbing effect by virture of electronic effects or hydrogen bond formation.

Quadrant Section Model of the Active Site of the Redox Systems in *C. lunata* and *R. rubra* (Figure 8). Since we used whole living cells in our microbial reduction, factors operating in the quadrant rule are undoubtedly vast and complicated, and it would be premature to present any definite idea on the possible "active site" of the redox systems in *C. lunata* and *R. rubra*. But the results accumulated in our laboratory prompted us to present a quadrant section model (Figure 8) which accommodates this "C_1-ketone rule" and the proposed "C_2-ketone rule".[4b]

Comparison of the relative rates of dehydrogenation of various cyclic alcohol substrates mainly with the chair-form cyclohexanol moiety led Prelog[7a,17,46] to propose a diamond lattice section of the active site of horse liver alcohol dehydrogenase (HLADH). Being formulated from incubation experiments with living microbes, our quadrant rule could not be directly compared with Prelog's diamond lattice section model. Nevertheless, it is interesting to notice that Prelog's diamond lattice section model, in its boldly simplified version,[4b] is fairly compatible with our quadrant model.

Experimental Section[47]

The cultures of *R. rubra* (IFO 0889), *R. arrhizus* (IFO 5780), and *C. lunata* (IFO 6288) were obtained from the Institute of Fermentation, Osaka, Japan, and the baker's yeast was purchased from Oriental Yeast Co., Tokyo. The general procedure of microbial reduction has been described previously.[4b,45]

Microbial Reduction of Bicyclo[2.2.2]octan-2-one (3). The substrate ketone **3** was prepared by catalytic reduction of (±)-bicyclo[2.2.2]oct-5-en-2-one (**23**) with 10% Pd/C; mp 173.5–175 °C (sealed tube) (lit. mp 176 °C,[48a] 178–179 °C,[48b] 175.5–177.5 °C[12a]).

(A) Reduction with *R. rubra*. The substrate ketone **3** (total 350 mg) was incubated for 24 h at 30 °C in four batches (4 × 200 mL of culture media). The metabolite mixture containing **3** and **4** in a ratio of 46:54 (GLC) was chromatographed over 15 g of alumina. Elution with *n*-pentane yielded the recovered ketone **3** which was sublimed: 71 mg (20% yield); mp 173–174.5 °C (sealed tube).

Further elution with *n*-pentane–ether (100:15) gave crude alcohol **4** whose sublimation in vacuo afforded 130 mg (37% yield) of (+)-bicyclo[2.2.2]octan-2-ol (**4**): mp 212.5–213.5 °C (sealed tube); $[\alpha]^{27}_D$ + 31.3° (*c* 1.4); optical purity (op) 97.8% (lit. mp 220 °C, $[\alpha]^{25}_D$ −32°[15]; mp 221–222 °C, $[\alpha]^{21}_D$ −28°[12a]). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.88; H, 11.28.

(B) Reduction with *C. lunata*. The substrate ketone **3** (total 510 mg) was incubated for 48 h at 30 °C in five batches (5 × 200 mL of culture media). The metabolite mixture containing **3** and **4** in a ratio of 33:67 (GLC) was worked up according to the procedure described in A to afford **3** (50 mg, 10% yield) and **4**: 190 mg (37% yield); mp 213–214 °C (sealed tube); $[\alpha]^{20}_D$ +28.4° (*c* 1.85); op 89%.

(C) Reduction with *R. arrhizus* ("Resting Cell" Suspension Method). A 24-h culture (25 mL) was transfered into 200 mL of medium solution and incubated for 24 h at 30 °C. The grown mycelium was collected, washed with sterilized water, and suspended again on 200 mL of $^1/_{15}$ N Sørensen's phosphate buffer solution (pH 7) containing 10 g of glucose. After an ethanolic solution (1.5 mL) of the ketone **3** (150 mg) was added, the incubation was maintained for 72 h at 30 °C. The combined six batches of the incubation afforded a crude metabolite extract (820 mg) containing **3** and **4** in a ratio of 66:34 (GLC). Treatment in the manner described in A gave **3** (300 mg, 33% yield) and **4**: 168 mg (19% yield); mp 213–215 °C (sealed tube); $[\alpha]^{14}_D$ + 16.8° (*c* 1.65); op 52.5%.

(D) Reduction with Actively Fermenting Baker's Yeast. A 90-g sample of fresh baker's yeast dispersed to a paste in 100 mL of tap water was placed in a 3-L, three-necked flask with 100 g of glucose in 400 mL of tap water. To this stirred and actively fermenting mixture was added 800 mg of the ketone **3** in 20 mL of EtOH, and the incubation was maintained at 34–35 °C for 48 h. After addition of the yeast slurry (100 g in 100 mL of water) with glucose solution (100 g in 100 mL of water), the incubation was resumed for another 48 h. Two batches were combined and the clear beer was extracted with ether to afford 3.5 g of a yellow oil containing **3** and **4** in a ratio of 62:38 (GLC). Alumina chromatography gave 367 mg of **3** (22.9% yield) and 180 mg of (+)-**4** (11% yield): mp 216–218 °C (sealed tube); $[\alpha]^{14}_D$ +25.0° (*c* 1.39); op 78%.

Microbial Reduction of (±)-Bicyclo[2.2.1]heptan-2-one (5). The racemic substrate ketone **5** was prepared by catalytic reduction of (±)-bicyclo[2.2.1]hept-5-en-2-one (**8**) with 10% Pd/C; mp 91–92 °C (sealed tube) (lit. mp 91–92 °C,[49a] 92.5–93.5 °C[49b]).

(A) Reduction with *C. lunata*. A total of 1.2 g of the racemic ketone **5** was incubated at 29 °C for 15 h in eight batches (8 × 200 mL of culture media). The metabolite mixture (1.35 g) containing **5–7** in a ratio of 48:50:2 (GLC) was placed on a column of alumina (30 g) with *n*-pentane and eluted with *n*-pentane (fractions 1–8) followed by *n*-pentane–ether (9:1, fractions 9–20) in fractions of 80 mL each.

The residue obtained from the former fractions was sublimed in vacuo to give 370 mg of (+)-ketone **5**: 30.8% yield; mp 95–96 °C (sealed tube); $[\alpha]^{26}_D$ + 19.54° (*c* 1.45); op 67% (lit.[17] mp 97–98 °C; $[\alpha]^{25}_D$ +29.1°).

Preparative TLC followed by sublimation (in vacuo) of the latter fractions gave 105 mg of (−)-*endo*-alcohol **6** containing 1.5% of exo isomer **7**: 8.75% yield); mp 148–149 °C (sealed tube); $[\alpha]^{24}_D$ −1.70° (*c* 2.37); op 91% (lit.[17] mp 151–152 °C; $[\alpha]^{25}_D$ +1.87°). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.90; H, 10.81.

(B) Reduction with *R. rubra*. The racemic ketone **5** (total 1.2 g) was incubated at 30 °C for 24 h in eight batches (8 × 200 mL of culture media) to afford a crude metabolite mixture (1.27 g) containing **5–7** in a ratio of 67:28:5 (GLC). Workup following the procedure described in A gave (a) 590 mg of (+)-ketone **5** [49% yield; mp 94–96 °C (sealed tube); $[\alpha]^{26}_D$ +1.98° (*c* 4.99); op 6.8%] and (b) 69 mg of (−)-*endo*-alcohol **6** containing 8% of exo isomer **7** [5.8% yield; mp 142–144.5 °C (sealed tube); $[\alpha]^{26}_D$ −1.55° (*c* 2.8); op 83%].

Microbial Reduction of (±)-Bicyclo[2.2.1]hept-5-en-2-one (8). The racemic ketone **8** was prepared by the method of Freeman et al.;[50] bp 65–66.5 °C (24 mm) [lit.[50] bp 80–81 °C (45 mm)].

(A) Reduction with *C. lunata*. A 15-h incubation of a total of 1.24 g of the racemic ketone **8** at 30 °C in eight batches (8 ×

(45) Nakazaki, M.; Chikamatsu, H.; Hirose, Y.; Shimizu, T. *J. Org. Chem.* **1979**, *44*, 1043–1048.

(46) Jones, J. B.; Beck, J. F. "Applications of Biochemical Systems in Organic Chemistry", Jones, J. B., Sih C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part 1, pp 295–319.

(47) Melting points are uncorrected. ^{1}H NMR spectra were determined on a JNM-NH-100 and a JNM-C-60-HL. Chemical shifts are reported as δ values in part per million relative to internal Me_4Si (δ 0). Coupling constants (*J*) are reported in hertz; s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, and m = multiplet. Optical rotations all refer to $CHCl_3$ solutions unless otherwise specified. GLC analyses were performed on a JGC-20K equipped with an FID and using a 2 m × 3 mm column of 10% Carbowax 20M on Chromosorb W. Preparative TLCs were carried out with E. Merck silica gel 60 $PF_{254+366}$ as an adsorbent. Woelm active alumina (neutral, activity III) was used for column chromatography as an adsorbent.

(48) (a) Komppa, G. *Chem. Ber.* **1935**, *68*, 1267–1272. (b) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1930**, *478*, 137–154.

(49) (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1929**, *470*, 62–103. (b) Wildman, W. C.; Hemminger, C. H. *J. Org. Chem.* **1952**, *17*, 1641–1645.

(50) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211–2214.

200 mL of culture media) afforded a crude metabolite mixture (1.01 g) containing 8–10 in a ratio of 66:33:1 (GLC). The metabolite mixture was taken up in *n*-pentane and chromatographed over 30 g of alumina.

The ketone 8 was eluted with *n*-pentane to yield an oil: 250 mg (20% yield); $[\alpha]^{25}_D$ +173.3° (*c* 0.45, isooctane); op 15% [lit.[20] bp 40–60 °C (2 mm); $[\alpha]^{23}_D$ −525° (isooctane)].

Further elution with *n*-pentane–ether (85:15) afforded 142 mg of crude 9 (11.5% yield), which was purified by preparative TLC followed by sublimation to give 45 mg of (−)-*endo*-alcohol 9 (3.6% yield) containing 3% of the exo isomer 10 (GLC): mp 112.5–114 °C (sealed tube); $[\alpha]^{24}_D$ −95.9° (*c* 0.66); op 54% (lit.[20] mp 105–111 °C; $[\alpha]^{23}_D$ −73.4°); mass spectrum, *m/e* 110 (M^+) [required for $C_7H_{10}O$ (M^+) *m/e* 110]. Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.12. Found: C, 75.21; H, 9.15. The material was homogeneous by TLC criteria, but the carbon content was low.

(B) Reduction with *R. rubra*. The racemic ketone 8 (total of 1.25 g) was incubated at 30 °C for 24 h in eight batches (8 × 200 mL of culture media) to afford a crude metabolite mixture containing 8–10 in a ratio of 73:25:2 (GLC). Treatment in the same way as described in A gave (a) 360 mg of (+)-ketone 8 [29% yield; bp 80–85 °C (20 mm); $[\alpha]^{21}_D$ +15.40° (*c* 1.13, isooctane); op 1.3%] and (b) 37 mg of (−)-*endo*-alcohol 9 containing 7% of exo isomer 10 (GLC) [3% yield; mp 105–110 °C (sealed tube); $[\alpha]^{24}_D$ −21.34° (*c* 1.14); op 12%].

Microbial Reduction of (±)-Benzobicyclo[2.2.1]heptan-2-one (11). The racemic ketone 11 was prepared by the method of Bartlett and Giddings,[51] bp 140–145 °C (21 mm). 2,4-Dinitrophenylhydrazone, mp 175–176.5 °C (lit.[51] 2,4-dinitrophenylhydrazone, mp 175.4–177 °C).

Reduction with *C. lunata*. A total of 560 mg of the racemic ketone 11 was incubated at 30 °C for 12 h in four batches (4 × 200 mL of culture media) to afford 620 mg of a crude metabolite mixture containing 11 (30%), 12 (70%), and a trace amount of 13 (GLC). The metabolite product was taken up in *n*-hexane and chromatographed over 25 g of alumina. Elution with *n*-hexane followed by *n*-hexane–ether (4:1) afforded the following 150-mL aliquot fractions.

Fractions 3–6 (108 mg, eluted with *n*-hexane) was distilled bulb-to-bulb (145 °C, 25 mm) to give 50 mg of (+) recovered ketone 11 (8.9% yield): n^{27}_D 1.5639; $[\alpha]^{30}_D$ +300.1° (*c* 0.4, isooctane); op 53% [lit.[24] bp 65–75 °C (0.02 mm); $[\alpha]^{25}_D$ +262° (isooctane)]. 2,4-Dinitrophenylhydrazone, mp 175–176.5 °C. Anal. Calcd for $C_{17}H_{14}O_4N_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.47; H, 4.15; N, 16.56.

Fractions 9–10 (265 mg, eluted with *n*-hexane–ether) were sublimed in vacuo (70 °C, 20 mm) to give 210 mg of (−)-*endo*-alcohol 12: 37.5% yield; mp 108–109 °C; $[\alpha]^{28.5}_D$ −68.6° (*c* 0.84); op 82% (lit.[24] mp 68–90 °C; $[\alpha]^{22}_D$ +39.1°); NMR[24] (60 MHz, CCl_4) δ 4.18–4.52 (m, 1 H, C-2 exo proton). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.23; H, 7.66.

Fraction 11 (eluted with *n*-hexane–ether) gave 20 mg of *endo*-12 containing 3.5% of exo isomer 13.

Microbial Reduction of (±)-Benzobicyclo[2.2.2]octan-2-one (14). The racemic ketone 14 was prepared by catalytic reduction of (±)-benzobicyclo[2.2.2]oct-5-en-2-one (17) with Pd/C: bp 167–174 °C (35 mm); mp 37–38 °C (lit.[26a] mp 30–31 °C). *p*-Nitrophenylhydrazone, mp 183.5–185 °C (lit.[26a] mp 183.5–184.5 °C).

(A) Reduction with *C. lunata*. The racemic ketone 14 (total 600 mg) was incubated at 30 °C for 20 h in four batches (4 × 200 mL of culture media). The metabolite mixture containing 14–16 in a ratio of 38:60:2 (GLC) was placed on a column of alumina (25 g) with *n*-hexane and eluted to give the following 80-mL aliquot fractions [fractions 1–8 with *n*-hexane and fractions 9–13 with *n*-hexane–ether (4:1)].

Fractions 1–8 provided 200 mg of (+)-ketone 14: 33% yield; mp 54–56 °C; $[\alpha]^{27}_D$ +340° (*c* 0.52); op 95% (lit.[25] mp 52–53 °C; $[\alpha]^{22}_D$ −356.2°). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.51; H, 7.05. Recrystallization from *n*-hexane afforded 82.6 mg of an optically pure specimen: mp 55–56 °C; $[\alpha]^{30}_D$ +356.8° (*c* 0.41); op 100%.

Fractions 9–10 yielded 242 mg of *endo*-alcohol 15 containing 5% of exo isomer 16 which was rechromatographed on a column of alumina (25 g) with *n*-hexane followed by *n*-hexane–ether (4:1) elution. From fast-moving fractions there was obtained 39 mg of a mixture of the isomeric alcohols 15 and 16 [endo/exo ratio of 72:28 (GLC); $[\alpha]^{28}_D$ −11.19° (*c* 0.755)] and 58 mg of *endo*-alcohol 15 containing 3% of exo isomer 16 (GLC). From slow-moving fractions there was obtained 107 mg of *endo*-15, $[\alpha]^{27}_D$ −14.2° (*c* 1.24).

Fractions 11–13 yielded 89 mg of *endo*-15 ($[\alpha]^{26}_D$ −15.65°) which was combined with 107 mg of the same described above. Recrystallization from *n*-hexane afforded 163 mg of (−)-*endo*-alcohol 15: 27% yield; mp 128–129 °C; $[\alpha]^{27}_D$ −18.55° (*c* 0.9); op 85%. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.64; H, 8.18. The NMR spectrum of the acetate from 15 was found to be in agreement with that reported by Tori:[26b] NMR (60 MHz, $CDCl_3$) δ 1.80 (s, 3 H, $OCOCH_3$), 5.08 (dt, J = 2.5, 8 Hz, 1 H, $HCOCOCH_3$), 7.15 (s, 4 H, aromatic H).

Since the isolated *exo*-alcohol 16 ($[\alpha]^{28}_D$ −11.19°) contained 72% of the (−)-*endo*-alcohol 15 with $[\alpha]^{27}_D$ −18.55°, calculation gave the specific rotation $[\alpha]_D$ +7.7° to the *exo*-alcohol 16 present in the original metabolite mixture.

(B) Reduction with *R. rubra*. A total of 630 mg of the racemic ketone 14 was incubated at 30 °C for 12 h in four batches (4 × 200 mL of culture media). The ether extract (620 mg) was shown to contain 14 (37%), 15 (63%), and a trace amount of *exo*-alcohol 16 (GLC). Separation and purification were carried out according to a procedure similar to A to give the following materials. (a) Recovered ketone 14: 200 mg (32% yield); mp 52–53 °C; $[\alpha]^{27}_D$ +174.8° (*c* 1.75); op 49%. (b) (−)-*endo*-Alcohol 15: 294 mg (47% yield); mp 114–117 °C; $[\alpha]^{26}_D$ −7.83° (*c* 0.84); op 36%.

(C) Oxidation of (−)-*endo*-Alcohol 15. The (−)-*endo*-alcohol 15 (85.5 mg, $[\alpha]^{27}_D$ −18.55°) obtained from experiment A was dissolved in 2.5 mL of acetone and treated with 0.6 mL of 8 N Jones reagent at room temperature. After 5 min, the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with dilute $NaHCO_3$ and water and then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative TLC followed by sublimation to give 45.5 mg of the (−)-ketone 14: mp 53–54 °C; $[\alpha]^{22}_D$ −302.23° (*c* 0.4); op 85%. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.61; H, 7.02.

(D) Oxidation of a Mixture of Isomeric Alcohols 15 and 16. According to the same procedure described above, 39 mg of the 72:28 mixture ($[\alpha]^{25}_D$ −11.19°) of the endo–exo isomeric alcohols 15 and 16 obtained from A was oxidized to give 22 mg of (−)-14: mp 41–42 °C; $[\alpha]^{22}_D$ −140.4° (*c* 0.49). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.61; H, 6.99. This ketone is composed of 72% of the (−)-ketone ($[\alpha]_D$ −302.23°) from the (−)-*endo*-alcohol 15 and the 28% of the ketone with unknown specific rotation from the original exo alcohol ($[\alpha]_D$ +7.7°); calculation assigned $[\alpha]_D$ +275.7° (optical purity 77%) to this ketone from the original *exo*-alcohol 16. This automatically assigned the absolute configuration of 16 as indicated in Scheme III and 77% optical purity to the (+)-*exo*-alcohol 16 originally present in the metabolite mixture.

Microbial Reduction of (±)-Benzobicyclo[2.2.2]oct-5-en-2-one (17). The racemic ketone 17 was prepared by the method of Kitahonoki;[26a] mp 56.5–58 °C (lit.[26a,52] mp 56.5–58 °C).

(A) Reduction with *C. lunata*. The racemic ketone 17 (total 685 mg) was incubated at 30 °C for 20 h in four batches (4 × 200 mL of culture media). The metabolite mixture (670 mg) containing 17–19 in a ratio of 38:60:2 (GLC) was taken up in *n*-hexane and chromatographed over alumina (25 g), yielding the following fractions.

(a) Elution with 800 mL of *n*-hexane gave a semicrystalline material, $[\alpha]^{26}_D$ −58.3° (*c* 1.3), which was recrystallized from *n*-hexane to afford 150 mg of the (−)-ketone 17: 22% yield; mp 67–68 °C; $[\alpha]^{30}_D$ −85.7° (*c* 1.35); op 93% (lit.[25] mp 68–69 °C; $[\alpha]^{22}_D$ +87.5 ± 1.2°). Anal. Calcd for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.49; H, 5.88. Further recrystallization from *n*-hexane afforded 96.4 mg of the optically purer specimen: mp 68–69 °C; $[\alpha]^{25}_D$ −89.0° (*c* 1.09); op 97%.

(51) Bartlett, P. D.; Giddings, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1240–1246.

(52) Plieninger, H.; Lehnert, W. *Chem. Ber.* **1967**, *100*, 2427–2434.

(b) Elution with *n*-hexane–ether (4:1, 160 mL) gave, after sublimation, 191.6 mg of (−)-*endo*-alcohol **18**: 28% yield; mp 111–114 °C; $[\alpha]^{28}_D$ −8.4° (*c* 0.7); op 72%. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.77; H, 7.02. Recrystallization from *n*-hexane gave the optically pure specimen: mp 128–129.5 °C; $[\alpha]^{27}_D$ −9.64° (*c* 1.26); op 83%.

(B) Reduction with *R. rubra*. A total of 908 mg of the racemic ketone **17** was incubated at 30 °C for 8.5 h in six batches (6 × 200 mL of culture media) to give a metabolite mixture (990 mg) containing **17–19** in a ratio of 47:48.5:4.5 (GLC). Separation afforded following materials. (a) Recovered ketone **17**: 349 mg (38% yield); mp 56.5–58 °C; $[\alpha]^{27}_D$ −3.38° (*c* 0.73); op 3.7%. (b) (−)-*endo*-Alcohol **18**: 190 mg (21% yield); mp 102–103 °C; $[\alpha]^{29}_D$ −1.0° (*c* 1.08); op 8.6%.

(C) Catalytic Reduction of (−)-Ketone 17. A 65-mg sample of (−)-ketone **17** ($[\alpha]^{25}_D$ −89.0°; obtained from experiment A) in 6 mL of EtOH was hydrogenated at atmospheric pressure over 10 mg of 10% Pd/C. After filtration of the catalyst, the solvent was evaporated to yield (+)-benzobicyclo[2.2.2]octan-2-one (**14**) in a crystalline form ($[\alpha]^{26}_D$ +346.5° (*c* 0.42); op 97%) which was recrystallized from *n*-hexane to give 48.4 mg of (+)-**14**: mp 54–55 °C; $[\alpha]^{25}_D$ +354.2° (*c* 0.4); op 99.4%. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.93; H, 7.08.

(D) Catalytic Reduction of (−)-*endo*-Alcohol 18. Hydrogenation of 69 mg of (−)-*endo*-alcohol **18** ($[\alpha]^{25}_D$ −9.64°, obtained from experiment A) was carried out under the same conditions as described above. The crude product was sublimed to give 55 mg of (−)-*endo*-benzobicyclo[2.2.2]octan-2-ol (**15**): mp 128–129 °C; $[\alpha]^{26}_D$ −18.14° (*c* 0.93); op 83%. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.69; H, 7.93.

Microbial Reduction of (±)-Tricyclo[4.4.0.0^{3,8}]decan-4-one (4-Twistanone, 20). The racemic ketone **20** was prepared following Deslongchamps' procedure;[53] mp 166–167 °C (sealed tube) (lit. mp 185–190 °C,[53] 173–174 °C[33c]).

(A) Reduction with *R. rubra*. A total of 800 mg of the racemic ketone **20** was incubated at 30 °C for 30 h in eight batches (8 × 200 mL of culture media) to give 800 mg of a metabolite mixture containing **20–22** in a ratio of 38:50:12 (GLC). The semicrystalline metabolite mixture was placed on a column of alumina (30 g) with *n*-pentane and chromatographed, 80-mL aliquot fractions being collected in the following order: 1–12 (*n*-pentane), 13–18 (*n*-pentane–ether, 5:1), 19–20 (ether).

Fractions 2–12 afforded a semicrystalline material which was sublimed in vacuo (105 °C, 20 mm) to give 213 mg of (+)-4-twistanone (**20**): 27% yield; mp 167–168 °C (sealed tube); $[\alpha]^{25}_D$ +284.2° (*c* 0.28); $[\alpha]^{26}_D$ +274.8° (*c* 0.44, EtOH); op 92% (lit.[34c] mp 172–174 °C; $[\alpha]^{25}_D$ +295.2° (EtOH)). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.90; H, 9.42.

Fraction 14 yielded 200 mg of a crystalline material which was sublimed in vacuo (100 °C, 20 mm), affording 193 mg of the (−)-*exo*-alcohol **21**: 24% yield; mp 192–194 °C (sealed tube); $[\alpha]^{26}_D$ −293.9° (*c* 0.51); op 81%; NMR[33c] (100 MHz, CCl_4) δ 3.98 (q, *J* = 4.2 and 7.5 Hz, 1 H, C-4 H). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.00; H, 10.66.

Fractions 15–16 eluted 120 mg of a mixture of the isomeric alcohols **21** and **22** (exo/endo ratio of 87:13, GLC).

Fractions 17–18 yielded 60 mg of a sample of **22** which was purified by preparative TLC followed by sublimation in vacuo to give 34 mg of (+)-*endo*-alcohol **22** containing 14% of the exo isomer **21** (GLC): yield 4.25%; mp 130–132 °C (sealed tube); $[\alpha]^{22}_D$ +220.0° (*c* 0.79) (calcd $[\alpha]_D$ +304°, op 94%); NMR[33c] (100 MHz, CCl_4) δ 4.08 (t, *J* = 7.2 Hz, 1 H, C-4 H). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.69; H, 10.67.

(B) Reduction with Fermenting Baker's Yeast. The racemic ketone **20** (total 1.65 g) dissolved in 60 mL of EtOH was incubated with actively fermenting baker's yeast in three batches (3-L, three-necked flasks) for 96 h following the procedure described for the reduction of **3** (vide supra). The metabolite product (3.5 g) containing **20–22** in a ratio of 47:34:19 (GLC) was worked up according to the procedure described in A to give following materials. (a) (−)-Ketone **20**: 253 mg (15% yield); mp 160–162 °C (sealed tube); $[\alpha]^{17}_D$ −11.4° (*c* 1.45, EtOH); op 3.8%. (b) (−)-*exo*-Alcohol **21**: 190 mg (11.5% yield); mp 194–196 °C (sealed tube); $[\alpha]^{25}_D$ −196.3° (*c* 0.72); op 54%. (c) (+)-*endo*-Alcohol **22** containing 10% of the exo isomer **21**: 60 mg (3.6% yield); mp 138–140 °C (sealed tube); $[\alpha]^{25}_D$ +239.2° (*c* 0.4) (calcd $[\alpha]_D$ +288°; op 89%).

(C) Oxidation of (−)-*exo*-4-Twistanol (21). A 40-mg sample of (−)-**21** ($[\alpha]^{25}_D$ −196.3°, obtained from experiment B) in 1 mL of acetone was treated with 0.1 mL of 8 N Jones reagent at 10 °C. After being allowed to stand for 1 h, the reaction mixture was diluted with water and extracted with *n*-pentane to afford, after sublimation, 20 mg of (−)-4-twistanone (**20**): mp 168–170 °C (sealed tube); $[\alpha]^{17}_D$ −161.6° (*c* 0.4, EtOH); op 54%. Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.96; H, 9.33.

(D) Oxidation of (+)-*endo*-4-Twistanol (22). Oxidation of a 40-mg sample of (+)-**22** containing 10% of the exo isomer **21** ($[\alpha]^{25}_D$ +239.2°, obtained from experiment B) in the same way as described above afforded 22 mg of (+)-4-twistanone (**20**): mp 163–165 °C (sealed tube); $[\alpha]^{15}_D$ +221.9° (*c* 0.42, EtOH). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.33.

This ketone supposedly contains 10% of the ketone **20** originating from the contaminating (−)-*exo*-alcohol **21** (optical purity 54%). Calculation afforded specific rotation $[\alpha]_D$ +265° (optical purity 89%) for ketone **20**, corresponding to the original endo alcohol, and this assigns the absolute configuration and an optical purity of 89% to the isolated (+)-*endo*-alcohol **22** (calcd $[\alpha]_D$ +288°).

Microbial Reduction of (±)-Bicyclo[2.2.2]oct-5-en-2-one (23). The racemic ketone **23** was prepared by following Freeman's[50] procedure; mp 79–81 °C (sealed tube) (lit.[50] mp 84–86 °C).

(A) Reduction with *C. lunata*. The racemic ketone **23** (total 2.7 g) was incubated at 30 °C for 48 h in 18 batches (18 × 200 mL of culture media). The crude metabolite mixture (2.4 g) containing **23–25** in a ratio of 50.3:28.3:21.4 (GLC) was taken up in *n*-pentane and chromatographed over 60 g of alumina; 80-mL-aliquot fractions being collected in the following order: 1–10 (*n*-pentane), 11–13 (*n*-pentane–ether, 100:15), 14–17 (*n*-pentane–ether, 100:50).

Fractions 2–10 yielded 700 mg of (+)-ketone **23**: 26% yield; mp 79–81 °C (sealed tube); $[\alpha]^{24}_D$ +74.9° (*c* 1.82); op 15% (lit.[12a] mp 90.5–92 °C; $[\alpha]^{28}_D$ +267°).

Fractions 11–13 yielded 480 mg of *exo*-alcohol **25** containing 25% of endo isomer which was rechromatographed over 40 g of alumina with *n*-pentane–ether (10:1). From fast-moving fractions there was obtained pure *exo*-alcohol **25** (GLC) which was sublimed in vacuo (120 °C, 20 mm) to give 199.6 mg of (+)-*exo*-alcohol **25**: 7.4% yield; mp 167–168 °C (sealed tube); $[\alpha]^{26}_D$ +21.0° (*c* 1.28); op 68.8%; NMR[38] (100 MHz, CCl_4) δ 3.72 (dt, *J* = 2, 4 Hz, 1 H, C-2 H), 6.02 (m, 2 H, vinyl H). Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.27; H, 9.79. From slow-moving fractions there was obtained a further 175 mg of **25** contaminated with endo isomer **24**.

Fractions 14–17 yielded 600 mg of crude *endo*-alcohol **24** containing 10% exo isomer which was rechromatographed over 40 g of alumina with *n*-pentane–ether (10:1) as the eluent. From slow-moving fractions there was obtained *endo*-alcohol **24** in pure form (GLC). Sublimation in vacuo (120 °C, 20 mm) yielded 227.2 mg of (−)-*endo*-alcohol **24**: 8.4% yield; mp 163-164 °C (sealed tube); $[\alpha]^{26}_D$ −49.3° (*c* 1.25); op 70.6%) (lit.[12a] mp 167.5–168 °C; $[\alpha]^{23}_D$ +68.2°); NMR[38] (100 MHz, CCl_4) δ 3.80 (dt, *J* = 2, 4 Hz, 1 H, C-2 H), 6.08 and 6.38 (each t, *J* = 4 Hz, each 1 H, vinyl H). Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.12; H, 9.78.

(B) Reduction with *R. rubra*. The substrate ketone **23** (total 2 g) was incubated at 30 °C for 48 h in 16 batches (16 × 200 mL of culture media) to give a metabolite mixture containing **23–25** in a ratio of 72:21:7 (GLC). Alumina chromatography gave 920 mg of **23** [46% yield; $[\alpha]^{30}_D$ +44.3° (*c* 1.9); op 8.9%] and 400 mg of a mixture of the isomeric alcohols. The recovered ketone (920 mg) was incubated again in eight batches (8 × 200 mL of culture media) at 30 °C for 48 h to provide a metabolite mixture containing **23–25** in a ratio of 49:35:16 (GLC) whose chromatography afforded 350 mg of crude **23** and 180 mg of a mixture of the isomeric alcohols.

Sublimation of the crude ketone yielded 220 mg of (+)-ketone **23**: 11% yield; mp 79–82 °C (sealed tube); $[\alpha]^{30}_D$ +128.9° (*c* 2.38); op 25.9%.

(53) Gauthier, J.; Deslongchamps, P. *Can. J. Chem.* **1967**, *45*, 297–300.

The combined mixtures of the isomeric alcohols from two runs (570 mg, endo/exo ratio of 71:29) were chromatographed to afford (a) (−)-*endo*-alcohol **24** [110.7 mg (5.5% yield); mp 162–163 °C (sealed tube); $[\alpha]^{28}_D$ −51.6° (*c* 0.81); op 74%] and (b) (+)-*exo*-alcohol **25** [47.3 mg (2.4% yield); mp 163.5–165.5 °C (sealed tube); $[\alpha]^{25}_D$ +27.4° (*c* 1.3); op 90%].

(C) Catalytic Reduction of (−)-*endo*-Alcohol 24 and (+)-*exo*-Alcohol 25. A solution of 62.6 mg of (−)-**24** ($[\alpha]^{26}_D$ −49.3°, obtained from experiment A) in 3 mL of EtOH was hydrogenated at atmospheric pressure over 15 mg of 5% Pd/C. After filtration and evaporation of the solvent, the residue was sublimed in vacuo to afford 51.8 mg of (+)-bicyclo[2.2.2]octan-2-ol (**4**): mp 212–213 °C (sealed tube); $[\alpha]^{23}_D$ +22.6° (*c* 1.1); op 70.6%. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.22; H, 11.17.

Hydrogenation of 65 mg of (+)-**25** ($[\alpha]^{26}_D$ +21.0°, obtained from experiment A) in EtOH with 5% Pd/C gave 52.2 mg of (+)-**4**: mp 213–215 °C (sealed tube); $[\alpha]^{23}_D$ +22.0° (*c* 1.08); op 68.8%. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.17; H, 11.31.

Registry No. 3, 5019-82-9; (+)-(2*S*)-**4**, 40335-86-2; (±)-**5**, 22270-13-9; (+)-**5**, 2630-41-3; (−)-(2*S*)-**6**, 36779-79-0; *exo*-**7**, 497-37-0; (±)-**8**, 51736-74-4; (+)-**8**, 16346-63-7; (−)-(2*S*)-**9**, 16620-80-7; *exo*-**10**, 2890-98-4; (±)-**11**, 74958-72-2; (±)-**11** DNP, 74925-11-4; (+)-**11**, 21159-73-9; (−)-(2*S*)-**12**, 74958-43-3; *exo*-**13**, 13153-47-4; (±)-**14**, 74958-44-4; (±)-**14** DNP, 74925-12-5; (+)-**14**, 29073-66-3; (−)-(2*S*)-**15**, 74958-45-5; (−)-(2*S*)-**15** acetate, 74958-46-6; (+)-(2*S*)-**16**, 74958-47-7; (±)-**17**, 74958-48-8; (−)-**17**, 74958-49-9; (−)-(2*S*)-**18**, 74958-50-2; *exo*-**19**, 16938-87-7; (±)-**20**, 69308-42-5; (+)-**20**, 25225-94-9; (−)-**20**, 74958-51-3; (−)-(4*S*)-**21**, 74958-52-4; (+)-(4*S*)-**22**, 74958-53-5; (±)-**23**, 68908-13-4; (+)-**23**, 16196-15-9; (−)-(2*S*)-**24**, 68069-65-8; (+)-(2*S*)-**25**, 74958-54-6; (−)-**26**, 69308-43-6; (+)-**27**, 68907-11-9; (−)-**28**, 68876-10-8; (−)-**29**, 68926-54-5; (±)-4-protoadamantanone, 74925-13-6; (±)-1-oxo[2.2]metacyclophane, 40143-99-5; 1,10-dioxo[2.2]metacyclophane, 68907-12-0.

Syntheses and Chiroptical Properties of Optically Active C_1-Methanotwistane, C_2-Ditwistane, C_1-Homobasketane, and C_2-3,10-Dehydroditwistane

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When applied to the tricyclic keto mesylate **23**, a modification of Deslongchamps' 4-twistanone synthesis gave (±)-3-C_2-ditwistanone (**24**, 7% yield) whose Wolff–Kishner reduction afforded (±)-ditwistane (**6**). Diazomethane ring expansion of (+)-C_2-bishomocubane-6,10-dione 6-ethylene ketal (**26**) with known absolute configuration followed by the Wolff–Kishner reduction afforded the (−)-ketal **28** which was converted, via (−)-4-C_1-homobasketanone (**29**), into (−)-C_1-homobasketane (**8**). A similar sequence of transformations converted (−)-**29** into (−)-C_2-3,10-dehydroditwistane (**9**). Hydrogenolysis of (−)-**8** and (−)-**9** gave (−)-C_1-methanotwistane (**5**) and (−)-C_2-ditwistane (**6**), assigning their respective (1*R*,4*S*,7*R*,8*R*) and (1*S*,4*S*,7*R*,8*R*) configurations.

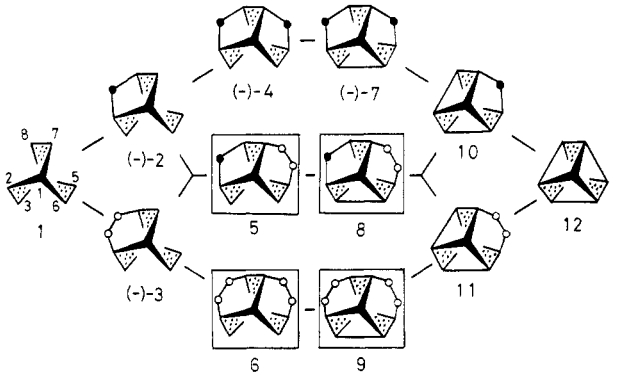
The C2–C8 diagonal bridging of bicyclo[2.2.2]octane (**1**) with methano (the closed circle) and ethano (the two open circles) bridges (Chart I)[1] furnishes two tricyclic cage-shaped hydrocarbons, *twist*-brendane (**2**) (C_2 symmetry) and twistane (**3**, D_2 symmetry), respectively, both with the D_3-twisted molecular framework **1** in a frozen conformation.

Further C5–C7 diagonal bridging of these gyrochiral[2] molecules with methano and ethano bridges gives three tetracyclic cage-shaped hydrocarbons, C_2-di-*twist*-brendane (**4**), C_1-methanotwistane (**5**), and C_2-ditwistane (**6**).

Final C3–C6 diagonal bridging with a single bond provides C_2-bishomocubane (**7**), C_1-homobasketane (**8**), and C_2-3,10-dehydroditwistane (**9**); all can be conceptually constructed, via homocubane (**10**) and basketane (**11**), on the desymmetrization of cubane (**12**) (O_h symmetry) which in turn can be envisaged to be composed of two D_3-twisted bicyclo[2.2.2]octane moieties with opposite chiralities.[3]

Among these chiral cage-shaped hydrocarbons possessing the D_3-twisted bicyclo[2.2.2]octane as a common structural feature, tricyclic *twist*-brendane (**2**)[4] and twistane (**3**)[5] were first synthesized in our laboratory in optically active modifications and their absolute configurations have been determined.[6] Natural extension of these studies led us to explore possible synthetic routes to the optically active gyrochiral tetracyclic **4** and pentacyclic **7** cage-shaped molecules with known absolute configurations, and

Chart I



(1) All structural formulas in this paper with (+) or (−) signs are presented in their absolute configurations.

(2) Nakazaki, M.; Naemura, K.; Kadowaki, H. *J. Org. Chem.* **1976**, *41*, 3725.

(3) Trivial names and symmetries of the pentacyclic hydrocarbons constructed by diagonal bridging of the D_3-twisted bicyclo[2.2.2]octane are listed in: Nakazaki, M.; Naemura, K.; Arashiba, N.; Iwasaki, M. *J. Org. Chem.* **1979**, *44*, 2433.

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(6) Tichy, M. *Tetrahedron Lett.* **1972**, 2001. Nakazaki, M.; Naemura, K.; Harita, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1907.

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