Further elution with 800 mL of $CHCl_3$–MeOH (100:1) gave the crude *cis,trans*-diol **12** followed by the *trans,trans*-diol **11**.

The crude *cis,trans*-diol **12** (210 mg) was purified by preparative TLC [developed with $CHCl_3$–MeOH (100:3)] followed by distillation to afford the (+)-*cis,trans*-diol **12**: 110 mg (5.5% yield); bp 120–140 °C (10 mm); $[\alpha]^{20}_D$ +46.7° (*c* 0.75, EtOH); optical purity 73% [lit.[7b] (±)-**12** mp 43–43.5 °C].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.74; H, 10.38.

Bis(*p*-nitrobenzoate) of (+)-**12**, mp 183–184 °C (from AcOEt–EtOH) [lit.[7b] (±)-bis(*p*-nitrobenzoate) mp 192–192.5 °C).

Anal. Calcd for $C_{23}H_{22}N_2O_8$: C, 60.79; H, 4.88; N, 6.17. Found: C, 60.89; H, 4.85; N, 6.06.

The crude *trans,trans*-diol **11** (120 mg) was sublimed in vacuo [95 °C (0.08 mm)] to give the (+)-*trans,trans*-doil **11**: 110 mg (5.5% yield); mp 126–129 °C; $[\alpha]^{20}_D$ +48.5° (*c* 0.54, EtOH); optical purity 80% [lit. mp 133–134 °C, $[\alpha]_D$ –53° (*c* 0.3, EtOH);[5a] mp 131–132 °C, $[\alpha]_D$ +61° (*c* 0.3, EtOH)[21]].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.91; H, 10.11.

(c) Jones Oxidation of the (+)-*cis,trans*-Diol 12. The (+)-*cis,trans*-diol **12** (35.5 mg) was dissolved in 5 mL of acetone and treated with 0.4 mL of 8 N Jones reagent at 0 °C. The crude product was sublimed in vacuo [50 °C (5 mm)] to afford 12 mg of the (–)-diketone **8**: mp 59–61 °C; $[\alpha]^{20}_D$ –98.9° (*c* 0.33, cyclohexane); optical purity 73%.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.01; H, 7.85.

Microbial Reduction of (±)-*cis*-6-Hydroxyspiro[4.4]nonan-1-one (10) with *C. lunata*. The racemic ketol **10** was prepared by the method of Carruthers et al.:[24] bp 115 °C (7 mm); n^{24}_D 1.4928 [lit.[24] bp 112 °C (0.05 mm)].

A total of 1 g of the racemic ketol **10** was incubated at 30 °C for 48 h in eight batches (8 × 200 mL of culture media). GLC of the crude metabolite extract (720 mg) indicated its constitution containing the recovered ketol **10** and diols **12** plus **13** in a ratio of 72:28.

The mixture was taken up in *n*-hexane–$CHCl_3$ (2:1) and chromatographed on 25 g of silica gel. Elution with 150 mL of $CHCl_3$ afforded the (+)-*cis*-ketol **10**: 335 mg (34% yield); bp 110 °C (4 mm); $[\alpha]^{26}_D$ +4.8° (*c* 1.5, EtOH); optical purity 17%.[19]

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.07; H, 9.29.

p-Nitrobenzoate of (+)-**10**, mp 77–78 °C (from EtOH–H_2O).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.31; H, 5.61; N, 4.68.

Further elution with 200 mL of $CHCl_3$ afforded 107 mg of a mixture of the *cis,trans*-diol **12** and *cis,cis*-diol **13**: bp 130 °C (4 mm); $[\alpha]^{27}_D$ +21.3° (*c* 0.85, EtOH).

Acknowledgment. This research was partially supported by grants from the Ministry of Education, Japan (449015), the Yamada Science Foundation, and the Suntory Institute for Bioorganic Research to which the authors' thanks are due.

Registry No. (±)-**8**, 39746-33-3; (–)-**8**, 21932-23-0; (+)-**8**, 36551-90-3; (±)-*trans*-**9**, 76215-54-8; (–)-*trans*-**9**, 76248-64-1; (–)-*trans*-**9** *p*-nitrobenzoate, 76248-65-2; (+)-*trans*-**9**, 76248-66-3; (+)-*trans*-**9** *p*-nitrobenzoate, 76248-67-4; (±)-*cis*-**10**, 65427-11-4; (–)-*cis*-**10**, 76248-68-5; (–)-*cis*-**10** *p*-nitrobenzoate, 76248-69-6; (+)-*cis*-**10**, 76248-70-9; (+)-*cis*-**10** *p*-nitrobenzoate, 76248-71-0; (+)-*trans,trans*-**11**, 39746-37-7; (+)-*cis,trans*-**12**, 65167-79-5; (+)-*cis,trans*-**12** bis(*p*-nitrobenzoate), 76232-16-1; *cis,cis*-**13**, 76318-77-9; **14**, 14727-58-3; (+)-**15**, 21945-22-2; (+)-**16**, 21945-21-1.

(24) Carruthers, W.; Orridge, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2411–6.

Microbial Stereodifferentiating Reduction of 2,6-Adamantanedione and Hexahydrodibenzoheptalene-5,11-dione, Diketones with Two Homotopic Carbonyl Groups on a C_2 Symmetry Axis

Masao Nakazaki,* Hiroaki Chikamatsu, Masayoshi Nishino, and Hiroshi Murakami

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

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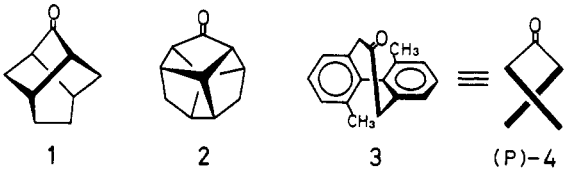
The microbial stereodifferentiating aptitude toward diketones with two homotopic carbonyl groups on a C_2 symmetry axis was studied. Incubation of 2,6-adamantanedione (**6**) with *Curvularia lunata* yielded, via the ketol **10**, (–)-(*R*)-2,6-adamantanediol (**11**), and incubation with *Rhodotorula rubra* converted the (±) doubly bridged biphenyl diketone **7** into a mixture of the recovered (+)-(*R*)-diketone **7**, the (+)-(*R*)-ketol **18**, and the (–)-(*S*)-*cis*-diol **19**. These stereoselectivities were analyzed to test the proposed "C_2-ketone rule".

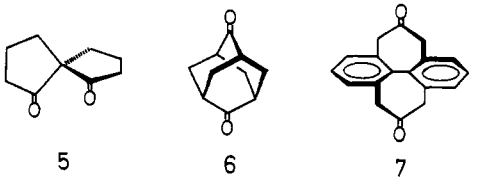
Analysis of the stereodifferentiating aptitude of *Curvularia lunata* and *Rhodotorula rubra* toward various C_2 ketones[1] [e.g., 9-*twist*-brendanone (**1**), 2-trishomocubanone (**2**), and the bridged biphenyl ketone **3**, Chart I] has led us to summarize their enantiomer selectivity in a "C_2-ketone rule"[2] which states that these microbes preferentially reduce the enantiomer with *P* helicity[3] (Figure 1).

Chart I



1 2 3 (P)-4

Chart II



5 6 7

These findings together with our continuing interests in the stereochemistry of gyrochiral molecules[4] prompted

(1) 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.

(2) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 667–8. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Org. Chem.* **1979**, *44*, 4588–93.

(3) As the quadrant projection formulas (Figure 1) indicate, the enantiomer with *P* helicity corresponds to that possessing the larger parts of molecule in the upper right and lower left quadrants.

0022-3263/81/1946-1151$01.25/0

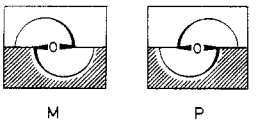
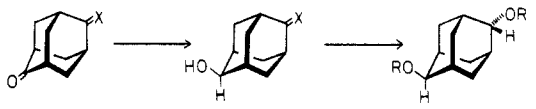


Figure 1. Two quadrant orientations for the enantiomers with *M* and *P* helicity of a C_2 ketone.

Scheme I



6 X = O
8 X = H_2
9 X = H_2
10 X = O
(−)-11 R = H
(−)-12 R = COC_6H_5
(−)-13 R = COC_6H_4-p-$N(CH_3)_2$

us to study microbial reduction of 1,6-spiro[4.4]nonanedione (**5**,[5] Chart II), a diketone with two homotopic carbonyl groups, and in the present paper we report the microbial stereodifferentiating reduction of two other diketones, 2,6-adamantanedione (**6**) and the doubly bridged biphenyl diketone **7** which share a rather unique stereochemical feature in possessing two homotopic carbonyl groups on the opposite ends of C_2 symmetry axis.

Results and Discussion

Microbial Reduction of 2,6-Adamantanedione (6, Scheme I). After satisfying ourselves by observing facile reduction of 2-adamantanone (**8**) to 2-adamantanol (**9**)[6] in preliminary test incubations both with *C. lunata* and *R. rubra* (see Experimental Section), we incubated 2,6-adamantanedione (**6**) with *C. lunata* for 48 h at 30 °C. GLC analysis of the ethereal extract revealed no trace of the ketol **10**, and column chromatography (SiO_2) followed by preparative TLC (SiO_2) of the extract afforded an 18% yield of the (−)-diol **11**: mp 253–261 °C; $[\alpha]_D$ −0.88°. For isolation of the intermediate ketol **10**, we resorted to the incubation with *R. rubra* which was found to be much more reluctant in reducing the diketone **6** than *C. lunata*.

Incubation of **6** with *R. rubra* was terminated after 48 h of shaking at 30 °C when GLC monitoring indicated the formation of a 1:9 mixture of **6** and the ketol **10** in the culture solution, and column chromatography of the metabolite mixture afforded a 25% yield of the ketol **10** (mp 310–311 °C) whose incubation in turn with *C. lunata* for 48 h at 30 °C yielded a specimen of the diol **11** with $[\alpha]_D$ −0.86°.

Although the nature of axial chirality in **11** has been discussed repeatedly,[7] our microbial preparation of the (−)-diol **11** was the first that obtained this interesting compound in an optically active modification, and this prompted us to secure information on its absolute configuration.

Because of the gyrochiral nature of the molecule, the two hydroxyl groups of **11** are disposed around the C_2 symmetry axis so as to be correlated by C_2 rotational operation around this symmetry element, and this geometry seemed to promise the diol **11** to be an ideal compound for applying various "C_2-symmetry rules",[7,8] especially the "dibenzoate rule".[9]

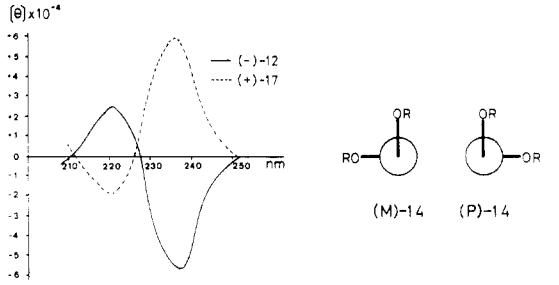
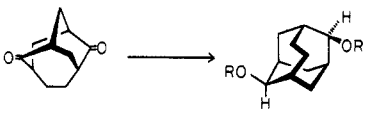


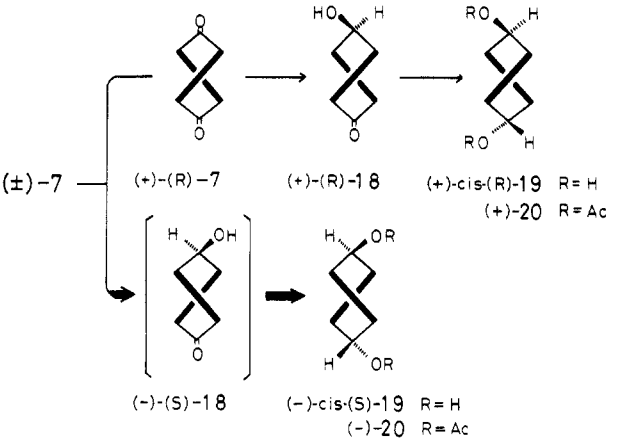
Figure 2. CD spectra of (−)-2,6-bis(benzoyloxy)adamantane (**12**) and (+)-(2*S*,7*S*)-2,7-bis(benzoyloxy)homoadamantane (**17**).

Scheme II



(+)-15
(+)-16 R = H
(+)-17 R = COC_6H_5

Scheme III



(±)-7
(+)-(R)-7
(+)-(R)-18
(+)-cis-(R)-19 R = H
(+)-20 R = Ac
(−)-(S)-18
(−)-cis-(S)-19 R = H
(−)-20 R = Ac

As reproduced in Figure 2, the (−)-dibenzoate **12** ($[\alpha]_D$ −41.8°) prepared from **11** exhibited a typical coupled Cotton effect with $[\Theta]_{237}$ −5.77 × 10^4 and $[\Theta]_{221}$ +2.51 × 10^4, and this automatically assigned the *R* configuration (*M* helicity) to the (−)-dibenzoate **12**.

While preparation of the (−)-bis[*p*-(dimethylamino)-benzoate] **13** ($[\alpha]_D$ −200°), which exhibited a bathochromic coupled Cotton effect[10] with $[\Theta]_{314.5}$ −1.95 × 10^5 and $[\Theta]_{288}$ +8.61 × 10^4, further confirmed this conclusion, convincing evidence came from the comparison of the Cotton effect of (−)-**12** with that of 2,7-bis(benzoyloxy)homoadamantane (**17**, Scheme II) which has an established absolute configuration.

By correlating with (+)-*twist*-brendane, we had assigned[11] the 1*S*,3*R*,6*R*,8*S* configuration to (+)-2,7-homoadamantanedione (**15**), whose $LiAlH_4$ reduction provided (+)-(2*S*,7*S*)-*endo*,*endo*-diol **16**[11] ($[\alpha]_D$ +18.8°), which was further converted into the (+)-dibenzoate **17**: mp 95–96 °C; $[\alpha]_D$ +30.1°.

(4) 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*, 3278–84.

(5) (a) Nakazaki, M.; Chikamatsu, H.; Nishino, M.; Asao, M. "Abstracts of Papers", 41st Annual Meeting of the Chemical Society of Japan; Osaka, Apr 1980; Chemical Society of Japan: Tokyo, 1980; No. II, p 1137. (b) Nakazaki, M.; Chikamatsu, H.; Asao, M. *J. Org. Chem.*, preceding paper in this issue.

(6) For enzymatic reduction of 2-adamantanone (**8**) mediated by alcohol dehydrogenase: (a) Ringold, H. J.; Bellas, T.; Clark, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 361–7; (b) Jones, J. B.; Sneddon, D. W.; Higgins, W.; Lewis, A. J. *J. Chem. Soc., Chem. Commun.* **1972**, 856–7; (c) Jones, J. B.; Beck, J. F. "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perman, D., Eds.; Wiley: New York, 1976; Part 1, pp 306–7.

(7) Krow, G. *Top. Stereochem.* **1970**, *5*, 31–68.

(8) Hug, W.; Wagniere, G. *Tetrahedron* **1972**, *28*, 1241–8.

(9) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257–63.

(10) (a) Chen, S. L.; Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1974**, *96*, 7352–4. (b) Harada, N.; Chen, S. L.; Nakanishi, K. *Ibid.* **1975**, *97*, 5345–52.

(11) Nakazaki, M.; Naemura, K. *J. Org. Chem.* **1977**, *42*, 4108–13.

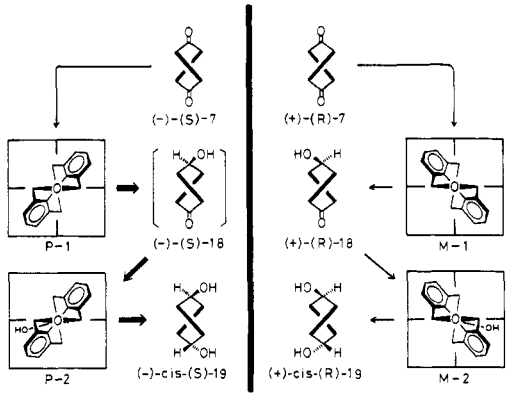


Figure 3. Schematic representation of the C_2-ketone rule applied on the microbial reduction of (±)-hexahydrodibenzoheptalene-5,11-dione (7).

An inspection of the molecular model reveals that in (+)-dibenzoate **17** the two benzoyloxy groups are aligned with *P* helicity ((*P*)-**14**, Figure 2), and the "dibenzoate rule" predicts its (+) and (-) Cotton effects at longer and shorter wavelength regions, respectively. The observed coupled Cotton effect of **17** with $[\theta]_{236}$ $+5.91 \times 10^4$ and $[\theta]_{221}$ -1.97×10^4 supported this prediction, and the completely enantiomeric Cotton effects exhibited by (-)-**12** and (+)-**17** (Figure 2) confirmed our assignment of the *R* configuration to (-)-2,6-adamantanediol (**11**).

Attempts to secure information on the optical purity of the (-)-diol **11** by the routine NMR method using chiral shift reagents failed, and we were forced to resort to the molecular rotation and CD spectrum of (-)-**12**, which when compared with those of (+)-**17** (80% optical purity[11]) permitted us to estimate rougly a 70–80% optical purity for (-)-**11**.

Microbial Reduction of (±)-4,5,6,10,11,12-Hexahydrodibenzo[*ef*,*kl*]heptalene-5,11-dione (7, Scheme III). Our previous experiences with the bridged biphenyl ketone **3**[2] indicate that *R. rubra* should exceed *C. lunata* in enantiomer selectivity in reducing the doubly bridged biphenyl diketone **7** with axial chirality, and this prediction was supported by small-scale test incubations.

After 76 h of incubation of the (±)-diketone **7** with *R. rubra* at 30 °C, the culture solution was extracted with ether, and concentration of the extract deposited almost racemic *cis*-diol **19** (20% yield; for the cis–trans stereochemistry, vide infra). The filtrate was chromatographed over alumina, and elution with benzene–$CHCl_3$ separated the diketone **7**, the ketol **18**, and the *cis*-diol **19** fractions. Rechromatography of these fractions afforded the (+)-diketone **7** (mp 205–207 °C; $[\alpha]_D$ +939°; 7% yield), the (+)-ketol **18** (mp 199–201 °C; $[\alpha]_D$ +610.5°; 14% yield), and the (-)-*cis*-diol **19** (mp 240–241 °C; $[\alpha]_D$ -293.5°; 15% yield).

The optically active (-)-diol **19** was converted into the diacetate **20** ($[\alpha]_D$ -271°) whose IR and NMR spectra were found to be indistinguishable from those of the diacetate ($[\alpha]_D$ -25.4°) prepared from the earlier isolated almost racemic *cis*-diol **19**, and this collectively indicated that the microbe produced a 35% yield of (-)-*cis*-diol **19** with an average rotation $[\alpha]_D$ -142°.

Absolute Configuration and Optical Purity of the Metabolites (Figure 3). Applying asymmetric Meerwein–Ponndorf–Verley reduction to the doubly bridged diketone **7**, Mislow[12] succeeded in assigning the axial *S* configuration to (-)-**7** which, according to our C_2 ketone definition, can be classified as the enantiomer with *P* helicity. Since our C_2-ketone rule (Figure 3) predicts that *R. rubra* preferentially reduces this *S* enantiomer (*P* helicity), the (-)-*cis*-diol **19**, our final reduction product, should be derived from this enantiomer and, consequently, have the same axial *S* configuration.

This was supported by Jones oxidation of the (-)-*cis*-diol ($[\alpha]_D$ -293.5°) into the (-)-diketone **7** ($[\alpha]_D$ -1558°) whose repeated recrystallization from *n*-hexane provided a speciment with a maximal $[\alpha]_D$ -1622°.

The opposite *R* configuration was assigned to the isolated (+)-ketol **18** by its Jones oxidation to the (+)-diketone **7**. On the assumption of the observed maxial $[\alpha]_D$ -1622° of the diketone **7** as its absolute rotation,[13] calculation allowed us to estimate that the incubation of (±)-**7** with *R. rubra* furnished the (+)-(*R*)-diketone **7**, the (+)-(*R*)-ketol **18**, and the (-)-(*S*)-*cis*-diol **19** with 58%, 72%, and 46% optical purities, respectively.[13,14]

Recovery of the (+)-diketone **7** and isolation of the (+)-ketol **18** with same axial *R* configuration (*M* helicity) can be explained by their unfavorable M-1 and M-2 quadrant orientations (Figure 3) with the larger parts of molecule in upper left and lower right quadrants, and this deduction also suggests that in the early stage of incubation the microbe should produce the ketol **18** enriched in the (-)-(*S*)-enantiomer corresponding to the favored P-1 quadrant orientation. Once formed, this (*S*)-ketol **18** should rapidly be converted into the final (-)-(*S*)-*cis*-diol **19**, corresponding to the favored P-2 orientation.

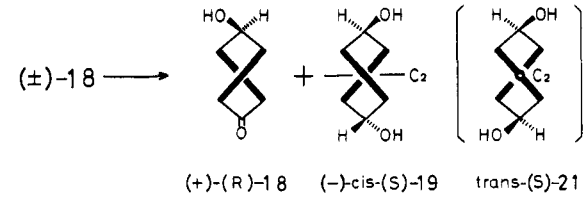
Although successful isolation of the ketol **18** enriched in this (-)-(*S*)-enantiomer from the culture solution of a test incubation experiment interrupted at an earlier stage (ca. 30 h) supported this conclusion, more convincing evidence emerged from the incubation experiment with the intermediate racemic ketol **18**.

Microbial Reduction of the (±)-Ketol 18 (Scheme IV). The racemic ketol **18** (mp 195.5–197.5 °C) prepared by $NaBH_4$ reduction of (±)-**7** was incubated with *R. rubra* for 46 h at 30 °C. Concentration of the ethereal extract of the culture solution again deposited crude racemic *cis*-diol **19**, and column chromatography of the filtrate afforded the (+)-(*R*)-ketol **18** (21% yield) and the (-)-(*S*)-*cis*-diol **19** (30% yield) with respective 92% and 90% optical purities.[15]

Totaling the amounts of these diols permitted us to estimate that the microbe furnished a 68% yield of the (-)-(*S*)-*cis*-diol **19** with 41% optical purity.

Figure 3 summarizes the observed enantiomeric selectivity exhibited by *R. rubra* toward these doubly bridged

Scheme IV



(12) Mislow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1710–33.

(13) Comparison of chiroptical properties of his specimen of the (-)-diketone 7 ($[\alpha]_{435}$ -894°) with those of single-bridged biphenyl ketones enable Mislow[12] to estimate its 15–20% optical purity, eventually assigning an absolute rotation of $[\alpha]_{435}$ -6000 to -4000° to the (-)-diketone 7. Our specimen of the (-)-diketone 7 with a maximal rotation $[\alpha]_D$ -1622° exhibited $[\alpha]_{435}$ -4514°, close to Mislow's estimation, and this seems to justify our adopting ca. $[\alpha]_D$ -1622° as an approximate absolute rotation of (-)-diketone 7.

(14) These data automatically assign absolute rotations $[\alpha]_D$ +851°, -305.5°, and -282° for the (+)-ketol **18**, the (-)-*cis*-diol **19**, and the (-)-diacetate **20**, respectively.

(15) Calculated from our reported absolute rotations.[14]

Table I

incubation period, h	% reduction	
	C. lunata	*R. rubra*
3	80	14
10	99	40
24	99.2	68
48	99.4	96
96	100	100

C_2 ketones with axial chirality and emphasizes the main pathways with thick lines.

Finally, it appears pertinent to discuss here the cis–trans stereochemistry of the isolated (–)-diol **19**. As depicted in Scheme IV, theoretically we have two diastereomeric diols, **19** and **21**, and these may be conveniently called the cis and trans isomers, respectively, referring to the relative orientation of two hydroxyl groups with respect to the plane of a hypothetically flattened molecular framework. Originating from the diketone with D_2 symmetry, these diols both belong to the C_2 point group and can be characterized by their specific C_2 symmetry axes, the one perpendicular to and the other coincident with the inherent pivot bond of the biphenyl moiety.

Although their separation was found unsuccessful, a mixture of these diols could be prepared by $LiAlH_4$ reduction of the (±)-diketone **7**, and an NMR spectrum of its diacetate revealed that this is a 1:1 mixture of two diacetates (see Experimental Section). Careful comparison of this spectrum with that of the optically active (–)-diacetate **20** revealed that this diacetate from the incubation corresponds to one of these diacetates.

So far we have had no conclusive evidence to support our assigning the cis configuration to the (–)-diol **19**, except for the fact that the optically active *cis*-diol **19** is the one supposed to be formed via the P-2 quadrant orientation (Figure 3) with the hydroxyl group in rear, lower section, and our detailed analysis of the stereochemical metabolite pathway of 2,6-spiro[4.4]nonanedione (**5**)[5] has clearly demonstrated the importance of this polar group effect in directing the steric course of the microbial reduction.

Experimental Section[16]

Our general procedure for microbial reduction and extraction of the metabolites had been described elsewhere.[2b] The cultures of *Curvularia lunata* and *Rhodotorula rubra* used in following experiments were obtained from the Institute of Fermentation, Osaka, Japan, and were identified by their IFO catalog numbers, IFO 6288 and IFO 0889, respectively.

Microbial Reduction of 2-Adamantanone (8). Erlenmyer flasks (100 mL), each containing 25 mL of the culture medium,[2b] were inoculated with spores of the microbe and were shaken for 48 h at 30 °C until a sufficient mass of mycelium had been developed. Then 2-adamantanone (**8**) (10 mg) dissolved in EtOH (0.5 mL) was added to each flask, and the incubation was resumed at 30 °C. The reduction rate was obtained by GLC analysis of the culture solutions whose incubations were terminated at suitable periods (see Table I).

Microbial Reduction of 2,6-Adamantanedione (6). The diketone **6** was prepared by the method of Janku and Landa,[17] mp 309–311 °C (in a sealed tube) [lit.[17] mp 323–323.4 °C (in a sealed tube)].

(a) Incubation with *R. rubra*. Aliquots of a solution of the substrate **6** (2 g) in 80 mL of EtOH were added to 16 flasks each containing 200 mL of a culture of *R. rubra*. After 48 h of incubation at 30 °C, the combined beers were extracted with ether to afford a metabolite mixture (990 mg) containing diketone **6** and ketol **10** in a ratio of 1:9 (GLC analysis).

The metabolite mixture was chromatographed on silica gel (24 g), and elution with 100 mL of $CHCl_3$ afforded the recovered diketone **6** (54 mg). Further elution with 150 mL of $CHCl_3$–MeOH (100:1) afforded the ketol (744 mg) which was recrystallized from *n*-hexane–benzene to give 495 mg (25% yield) of 6-hydroxyadamantan-2-one (**10**): mp 310–311 °C (in a sealed tube); IR (KBr) 3400, 1715, 1690, 1045, 980 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.2 (m, 8 H), 2.2–2.8 (m, 4 H), 2.65 (br s, 1 H, OH), 3.9–4.2 (m, 1 H, HCOH).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.50; H, 8.43.

(b) Incubation with *C. lunata*. Aliquots of a solution of the substrate **6** (1 g) in 40 mL of EtOH were added to eight flasks each containing 200 mL of a culture of *C. lunata*. After incubation for 48 h at 30 °C, the combined beers were extracted with ether to afford a metabolite mixture (0.5 g) containing the diol **11** with no trace of the diketone **6** or the ketol **10**.

The mixture was taken up in $CHCl_3$ and chromatographed on 8 g of silica gel. Elution with 150 mL of $CHCl_3$–MeOH (100:2) gave the crude diol (380 mg) which was purified by preparative TLC [$CHCl_3$–MeOH (100:5) development] followed by sublimation in vacuo (140 °C, 5 mm) to afford 175 mg (17.5% yield) of (–)-2,6-adamantanediol (**11**): mp 253–261 °C (in a sealed tube); $[\alpha]^{27}_D$ –0.878° (*c* 2.28, MeOH); IR (KBr) 3300, 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.48.

Microbial Reduction of 6-Hydroxyadamantan-2-one (10) with *C. lunata*. A total of 400 mg of the substrate **10** was incubated for 48 h at 30 °C in four batches (4 × 200 mL). The metabolite extract (420 mg) was chromatographed on 10 g of silica gel. Elution with $CHCl_3$–MeOH (100:2) afforded the crude diol (160 mg) whose preparative TLC followed by sublimation gave 45 mg (11% yield) of (–)-2,6-adamantanediol (**11**): mp 253–259 °C (in a sealed tube); $[\alpha]^{27}_D$ –0.857° (*c* 1.28, MeOH).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.59.

(–)-2,6-Bis(benzoyloxy)adamantane (12). A mixture containing the (–)-diol **11** (50 mg, $[\alpha]^{27}_D$ –0.878°), benzoyl chloride (0.2 g), and pyridine (3 mL) was allowed to stand at room temperature overnight, and the routine workup gave an oil which was purified by preparative TLC ($CHCl_3$ development) to give 41 mg of (–)-**12** as a glassy solid: $[\alpha]^{28}_D$ –41.8° (*c* 0.643, $CHCl_3$); CD (*c* 1.59 × 10^{-4} M, MeOH) $[\Theta]_{max}$ (λ, nm) +2.51 × 10^4 (221), –5.77 × 10^4 (237); UV (*c* 6.38 × 10^{-5} M, MeOH) λ_{max} 234 nm (ε 1.44 × 10^4), 272 (1.85 × 10^4), 280 (1.49 × 10^3).

Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.47; H, 6.36.

(–)-2,6-Bis[[*p*-(dimethylamino)benzoyl]oxy]adamantane (13). The mixture of the (–)-diol **11** (50 mg, $[\alpha]^{27}_D$ –0.878°) and *p*-(dimethylamino)benzoyl chloride[10b] (280 mg) in 10 mL of pyridine was heated at 80 °C for 4 h. After cooling, the reaction mixture was poured onto ice–water, neutralized with dilute H_2SO_4, and then extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. Removal of the solvent afforded 290 mg of the crude product which was chromatographed on silica gel ($CHCl_3$ elution) followed by preparative TLC ($CHCl_3$ development) to give 70 mg of (–)-**13**: mp 186–191 °C; $[\alpha]^{27}_D$ –195.6° (*c* 0.89, $CHCl_3$). Recrystallization from MeOH furnished an analytical specimen: mp 207–208 °C; $[\alpha]^{30}_D$ –199.8° (*c* 0.47, $CHCl_3$); CD (*c* 1.25 × 10^{-4} M, dioxane) $[\Theta]_{max}$ (λ, nm) +8.61 × 10^4 (288), –1.95 × 10^5 (314.5); UV (*c* 1.09 × 10^{-5} M, dioxane) λ_{max} 308 nm, (ε 5 6 × 10^4).

Anal. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.37; H, 7.32; N, 6.09.

(16) Melting points are uncorrected. ^1H NMR spectra were determined on a JNM-NH-100 and a JNM-C-60-HL. Chemical shifts are reported as δ values in parts per million relative to internal Me_4Si (δ 0). Coupling constants (*J*) are reported in hertz; s = singlet, d = doublet, dd = doublet of doublet. Optical rotations were measured with a JASCO DIP-SL polarimeter. Circular dichroism (CD) spectra were determined on a JASCO J-40 spectropolarimeter. 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 Merck silica gel 60 $PF_{254+366}$ as an adsorbent. Woelm alumina (neutral, activity III) and Merck silica gel 60 (70–230 mesh) were used for column chromatography as adsorbents.

(17) Janku, J.; Landa, S. *Collect. Czech. Chem. Commun.* **1970**, *35*, 375–7.

(+)-2,7-Bis(benzoyloxy)homoadamantane (17).[18] Benzoyl chloride (1.12 g) was added to a cooled (0 °C) solution of (+)-2,7-homoadamantanediol (**16**; 380 mg; $[\alpha]^{20}_D$ +18.8°; optical purity 80%)[11] in 4 mL of pyridine. After being stirred at 0 °C for 3 h, the reaction mixture was allowed to stand overnight at room temperature. The routine workup gave an oil which was chromatographed on silica gel. Elution with benzene gave an oil which was tritulated with *n*-hexane to afford a crystalline mass (530 mg). Recrystallization of this material from *n*-hexane–benzene gave (+)-**17**: mp 95–96 °C; $[\alpha]^{28}_D$ +30.1° (*c* 0.585, $CHCl_3$); CD (*c* 2.07 × 10^{-4} M, MeOH) $[\Theta]_{max}$ (λ, nm) −1.94 × 10^4 (221), +5.91 × 10^4 (236); UV (MeOH) λ_{max} 232 nm (ε 1.86 × 10^4), 266 (sh, 1.59 × 10^3), 274 (1.79 × 10^3), 280 (1.45 × 10^3).

Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.78; H, 6.64.

Microbial Reduction of the (±)-Diketone 7. The racemic substrate **7** was prepared by the method of Mislow et al.,[12] mp 210–215 °C dec (in a sealed tube) [lit.[12] mp 215–225 °C dec (in a sealed tube)].

(a) Incubation with *R. rubra*. Aliquots of a solution of the (±)-diketone **7** (1 g) in 32 mL of DMF were added to 16 flasks each containing 200 mL of a culture of *R. rubra*. After 76 h of incubation at 30 °C, the culture was filtered through a layer of Hyflo-super-cel, and the collected mycelium was extracted with acetone (2 L). Concentration in vacuo gave an oil which was diluted with water and extracted with ether (1 L). The culture solution freed from the mycelium was extracted with ether, and the extract was combined with the extract of the mycelium. The combined extracts (5 L) were washed with 5% $NaHCO_3$ and water and then dried over $MgSO_4$. Upon concentration of the solvent to 200 mL, there was deposited a crystalline mass which was collected by filtration to give 200 mg (20% yield) of the almost racemic *cis*-diol **19**. The filtrate was concentrated further and the residue (1 g) was taken up into benzene and chromatographed on 20 g of alumina.

Elution with 160 mL of benzene gave a semicrystalline mass (330 mg) which was rechromatographed on alumina to afford 70 mg (7% yield) of the (+)-diketone **7**: mp 205–207 °C; $[\alpha]^{30}_D$ +938.8° (*c* 0.085, $CHCl_3$); optical purity 58%; CD (*c* 1.96 × 10^{-4}M, dioxane) $[\Theta]_{max}$ (λ, nm) +5.91 × 10^4 (257), +1.67 × 10^5 (306); NMR ($CDCl_3$, 60 MHz) δ 3.50 (s, 8 H), 7.25 (s, 6 H).

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.16; H, 5.33.

Further elution with 240 mL of benzene gave a crystalline mass (179 mg) which was rechromatographed on alumina to afford 140 mg (14% yield) of the (+)-ketol **18**: mp 199–201 °C; $[\alpha]^{30}_D$ +610.5° (*c* 0.12, $CHCl_3$); optical purity 72%; CD (*c* 3.85 × 10^{-4} M, MeOH) $[\Theta]_{max}$ (λ, nm) +7.94 × 10^4 (255), +8.85 × 10^4 (296); IR (KBr) 3480, 1700, 1040 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.80 (s, 1 H, OH), 2.3 (dd, *J* = 9, 12 Hz, 1 H), 2.78 (d, *J* = 3 Hz, 2 H), 3.2 (dd, *J* = 6, 12 Hz, 1 H), 3.59 (d, *J* = 1 Hz, 4 H), 4.6 (m, 1 H), 7.38 (d, *J* = 1.5 Hz, 6 H).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.64; H, 5.97.

Final elution with 240 mL of benzene–$CHCl_3$ (1:1) gave a crystalline mass (290 mg) which was rechromatographed on alumina followed by preparative TLC [$CHCl_3$–MeOH (100:5) development] to afford 150 mg (15% yield) of the *cis*-diol **19**: mp 240–241 °C; $[\alpha]^{30}_D$ −293.5° (*c* 0.22, MeOH); optical purity 96%; CD (*c* 3.92 × 10^{-4} M, MeOH) $[\Theta]_{max}$ (λ, nm) −4.2 × 10^4 (231), −1.3 × 10^5 (253), −1.66 × 10^4 (275, sh), −1.99 × 10^4 (285.5); IR (KBr) 3350, 1050 cm^{-1}; NMR (pyridine-d_5, 60 MHz) δ 2.7 (dd, *J* = 6, 10 Hz, 2 H), 2.9 (d, *J* = 3 Hz, 4 H), 3.2 (dd, *J* = 6, 12 Hz, 2 H), 4.7 (m, 2 H), 7.3 (m, 6 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.93; H, 6.54.

(b) (−)-Diacetate 20 of the (−)-*cis*-Diol 19. A mixture of the (−)-*cis*-diol **19** (46 mg, $[\alpha]^{30}_D$ −293.5°) and acetic anhydride (1 mL) in 2 mL of pyridine was allowed to stand for 40 h at room temperature. The mixture was diluted with water. A deposited solid was collected, washed with water, and dried to give the (−)-diacetate **20**: 60 mg; mp 184.5–185.5 °C; $[\alpha]^{26}_D$ −271° (*c* 0.3, $CHCl_3$); optical purity 96%; CD (*c* 2.86 × 10^{-4} M, MeOH) $[\Theta]_{max}$ (λ, nm) +2.62 × 10^5 (210), −3.85 × 10^5 (221), −1.27 × 10^5 (251.5), −1.42 × 10^4 (275), −1.77 × 10^4 (285); IR (KBr) 1720, 1250 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 2.03 (s, 6 H), 2.33 (dd, *J* = 10, 12 Hz, 2 H), 2.72 (d, *J* = 3.5 Hz, 4 H), 2.95 (dd, *J* = 8, 12 Hz, 2 H), 5.47 (m, 2 H), 7.22 (s, 6 H).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.20; H, 6.31.

The ether-insoluble *cis*-diol **19** (200 mg) obtained during ether extraction (vide supra) was acetylated to give 256 mg of the diacetate **20**: mp 169–170 °C; $[\alpha]^{30}_D$ −25.4° (*c* 0.39, $CHCl_3$); optical purity 9%. Its NMR spectrum was indistinguishable from that of the optically purer diacetate.

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.37; H, 6.30.

(c) $LiAlH_4$ Reduction of the (±)-Diketone 7. A solution of the (±)-diketone **7** (89 mg) in 5 mL of anhydrous THF was added to a stirred suspension of 45 mg of $LiAlH_4$ in 5 mL of anhydrous THF. After the mixture was heated under reflux for 6 h, a small amount of water was added to the chilled reaction mixture to deposit an inorganic solid. The filtrate freed of the solid was dried over $MgSO_4$, and the solvent was evaporated to give 90 mg of a mixture of diols **19** and **21**; mp 214–218 °C (in a sealed tube, from EtOH).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.98; H, 6.86.

A mixture of the diols (35 mg) and acetic anhydride (0.3 mL) in 0.6 mL of pyridine was allowed to stand for 48 h at room temperature. Workup in the usual way afforded the crude product which was purified by preparative TLC ($CHCl_3$ development) to give a 1:1 mixture (35 mg) of the diacetates of diols **19** and **21**: mp 167–169 °C; NMR ($CDCl_3$, 60 MHz) δ 2.03 (s, 6 H), 2.33 (cis) and 2.37 (trans) (each dd, *J* = 10, 12 Hz, total 2 H), 2.70 (trans) and 2.72 (cis) (each d, *J* = 3.5 Hz, total 4 H), 2.95 (cis) and 2.98 (trans) (each dd, *J* = 8, 12 Hz, total 2 H), 5.47 (m, 2 H), 7.22 (s, 6 H).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.52; H, 6.27.

(d) Jones Oxidation of the (+)-Ketol 18. The (+)-ketol **18** (21 mg, $[\alpha]^{30}_D$ +610.5°) was dissolved in 5 mL of acetone and treated with 0.05 mL of 8 N Jones reagent at room temperature for 30 min. The routine workup gave a crystalline product which was purified by preparative TLC [$CHCl_3$–MeOH (100:4) development] to afford the (+)-diketone **7**: 15 mg; mp 205–207 °C; $[\alpha]^{23}_D$ +1164.0° (*c* 0.067, $CHCl_3$); optical purity 72%.

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.57; H, 5.13.

(e) Jones Oxidation of the (−)-*cis*-Diol 19. Oxidation of the (−)-*cis*-diol **19** (22 mg, $[\alpha]^{30}_D$ −293.5°) in the same way as described above afforded the (−)-diketone **7**: 17 mg; mp 205–207 °C; $[\alpha]^{23}_D$ −1558.4° (*c* 0.078, $CHCl_3$); optical purity 96%; CD (*c* 1.98 × 10^{-4} M, dioxane) $[\Theta]_{max}$ (λ, nm) −8.8 × 10^4 (257), −28.34 × 10^4 (306).

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.60; H, 5.14.

Several recrystallizations from *n*-hexane provided a specimen with $[\alpha]^{23}_D$ −1622 ± 2° (*c* 0.05, $CHCl_3$) and $[\alpha]^{20}_{435}$ −4514° (*c* 0.3, $CHCl_3$) [lit.[12] $[\alpha]^{25}_{435}$ −894° (*c* 1.5, $CHCl_3$)].

Microbial Reduction of the (±)-Ketol 18. (a) Preparation of the (±)-Ketol 18. To a stirred solution of the (±)-diketone **7** (900 mg) in 160 mL of EtOH was added $NaBH_4$ (27 mg) at room temperature. After being stirred for 2 h at 50 °C, the solution was acidified with 2 N HCl and concentrated in vacuo to yield an oily residue which was taken up in ether. The ethereal extract was washed with water, dried over $MgSO_4$, and then concentrated to give a solid (850 mg) which was dissolved in *n*-hexane–benzene (1:2) and chromatographed on alumina (40 g, activity II). Elution with *n*-hexane–benzene (1:2, 720 mL) gave the recovered diketone **7** (260 mg). Further elution with benzene–$CHCl_3$ (4:1, 400 mL) gave 400 mg (44% yield) of the (±)-ketol **18**, mp 195.5–197.5 °C (from MeOH).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.62; H, 6.10.

(b) Incubation with *R. rubra*. Aliquots of a solution of the (±)-ketol **18** (400 mg) in 16 mL of DMF were added to eight flasks each containing 200 mL of a culture of *R. rubra*. After 46 h of incubation at 30 °C, the combined culture solutions were filtered through a layer of Hyflo-super-cel. The ethereal extracts of the

(18) This experiment was carried out by Dr. Koichiro Naemura in this laboratory.

filtrate and the collected mycelium were combined and evaporated to dryness to afford a metabolite mixture (700 mg). The mixture was dissolved in 200 mL of benzene under reflux and allowed to stand at room temperature to deposit an insoluble material which was collected by filtration to afford 150 mg (37.5% yield) of the *cis*-diol **19**.

The benzene-soluble part was chromatographed on alumina (20 g), and elution with benzene (320 mL) gave 85 mg (21% yield) of the (+)-ketol **18**: mp 194–195 °C; $[\alpha]^{30}_D$ +780° (*c* 0.13, $CHCl_3$); optical purity 92%.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.49; H, 6.01.

Further elution with benzene–$CHCl_3$ (1:1, 160 mL) gave 120 mg (30% yield) of the (−)-*cis*-diol **19**: mp 239–240 °C; $[\alpha]^{30}_D$ −274.9° (*c* 0.24, MeOH); optical purity 90%.

Anal. Calcd for $C_{18}H_{18}O_2$:C, 81.17; H, 6.81. Found: C, 81.22; H, 6.78.

(c) (−)-Diacetate 20. The benzene-insoluble *cis*-diol **19** (150 mg) was acetylated with acetic anhydride and pyridine to afford 195 mg of diacetate **20**: mp 169–169.5 °C; $[\alpha]^{30}_D$ −6.2° (*c* 0.41, $CHCl_3$); optical purity 2.2%.

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.39; H, 6.37.

The benzene-soluble (−)-*cis*-diol **19** (30 mg, $[\alpha]^{30}_D$ −274.9°) was acetylated in the same way to afford 38 mg of the (−)-diacetate **20**: mp 184.5–185.5 °C; $[\alpha]^{28}_D$ −254° (*c* 0.3, $CHCl_3$); optical purity 90%.

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.21; H, 6.31.

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Registry No. 6, 39751-07-0; (±)-**7**, 76250-82-3; (+)-**7**, 76318-61-1; (−)-**7**, 76318-62-2; **8**, 700-58-3; **10**, 67092-78-8; (−)-**11**, 76250-83-4; (−)-**12**, 76250-84-5; (−)-**13**, 76250-85-6; (+)-**16**, 63902-07-8; (+)-**17**, 76250-86-7; (±)-**18**, 76250-87-8; (+)-**18**, 76318-63-3; (±)-**19**, 76250-88-9; (−)-**19**, 76318-64-4; (−)-**20**, 76250-89-0; (−)-**21**, 76318-65-5; (−)-**21** diacetate, 76318-66-6; *p*-(dimethylamino)benzoyl chloride, 4755-50-4.

Carbon–Phosphorus Heterocycles. Conformational Analysis of Substituted 1-Phenyl-4-phosphorinanones and Derivatives. Single-Crystal, X-ray Diffraction Analysis of 1-*r*,*cis*-2(a),*trans*-6(e)-Triphenyl-4-phosphorinanone 1-Sulfide

Jang B. Rampal,[1a] Gary D. Macdonell,[1b] James P. Edasery,[1c] and K. Darrell Berlin*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078

Asadur Rahman and Dick van der Helm*

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73109

K. Michal Pietrusiewicz

Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Boczna 5, 90-362 Poland

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A series of substituted 1,2,6-triphenyl-4-phosphorinanones has been prepared, and a conformational analysis was performed on these systems. Condensation of phenylphosphine or bis(hydroxymethyl)phenylphosphine with appropriately substituted 1,4-pentadien-3-ones gave the final products. For example, 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone was obtained which could be oxidized, sulfurized, or alkylated to give the corresponding oxide, sulfide, or phosphonium salt. 1,2,6-Triphenyl-4-phosphorinanone was also obtained and was oxidized and sulfurized by standard procedures. ^1H, ^{13}C, and ^{31}P NMR analysis on all of the compounds indicated that flattened chairs were the major conformation in all cases. Two isomers of 1,2,6-triphenyl-4-phosphorinanone were obtained from the original condensation as indicated by ^{31}P NMR analysis, but only one isomer could be isolated in pure form. Oxidation and sulfurization of this phosphine gave only one oxide and sulfide, respectively. The NMR data are most supportive of an axial C(2)–C_6H_5 bond and an equatorial C(6)–C_6H_5 bond in the phosphine, the oxide, and the sulfide. The ^{13}C NMR chemical shift for the C(6) atom is suggested to be at higher field than that for the C(2) atom from normal compression effects. A single-crystal, X-ray diffraction analysis of 1-*r*,-*cis*-2(a),*trans*-6(e)-triphenyl-4-phosphorinanone 1-sulfide was completed. The crystal is triclinic, the space group is $P\bar{1}$, and unit cell dimensions (at −135 °C) are a = 9.600 (5) Å, b = 10.219 (7) Å, c = 10.490 (4) Å, α = 103.02 (3)°, β = 109.77 (2)°, and γ = 76.29 (3)°, and Z = 2. Reduction of the ketone group in the tetramethyl-substituted series was accomplished smoothly and gave solid alcohols in the case of the corresponding *P*-oxide, *P*-sulfide, and *P*-$CH_2C_6H_5$ phosphonium salts. A conformational study was made on these systems, and a model compound, 1-phenyl-2,2,6,6-tetramethyl-4-*tert*-butyl-4-phosphorinanol 1-oxide, was also synthesized for the sake of comparison of spectral properties. These examples are the first highly substituted phosphorinanones and phosphorinanols to be examined by ^{13}C NMR analysis in which the phosphorus atom is highly hindered by large groups at C(2) and at C(6).

The chemistry and conformational analysis of six-membered heterocycles containing phosphorus as the heteroatom are an area of active interest.[2-4] Herein we report the syntheses of new derivatives of **1a** and **2a** as well as a conformational analysis, via ^1H, ^{13}C, and ^{31}P NMR examination, with regard to configurational preferences of groups attached to phosphorus and those located at C(2,6)

(1) (a) Postdoctorate, 1979–1980. (b) Predoctoral candidate, 1976–1978, Conoco Fellow, January–June 1976, and Dow Fellow, summers of 1975 and 1977. (c) Postdoctorate, 1979.

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