Stereochemistry of Horse Liver Alcohol Dehydrogenase (HLADH) Mediated Oxido Reduction in Cage-Shaped Carbonyl Compounds[1]

Masao Nakazaki,* Hiroaki Chikamatsu, and Yasuyuki Sasaki

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

Received September 8, 1982

The stereochemistry of HLADH-catalyzed oxido reduction of 4-twistanone (1), 4-brendanone (4), 8-deltacyclanone (7), 4-protoadamantanone (10), and the related alcohols has been examined to reveal that the stereospecificity of HLADH toward these cage-shaped compounds can be summarized by the same "quadrant rule" found in the microbial reduction with C_1-1 > C_1-4 ≫ C_1-2 ≈ C_1-3 quadrant orientation preference.

Two completely opposite stereospecificities toward C_2-ketones[2] which were found in microbial reduction and HLADH-catalyzed[3] oxido reduction have led us to propose the microbial *P*-C_2-ketone rule[4] and the HLADH *M*-C_2-ketone rule[5] to summarize their respective stereochemical behavior.

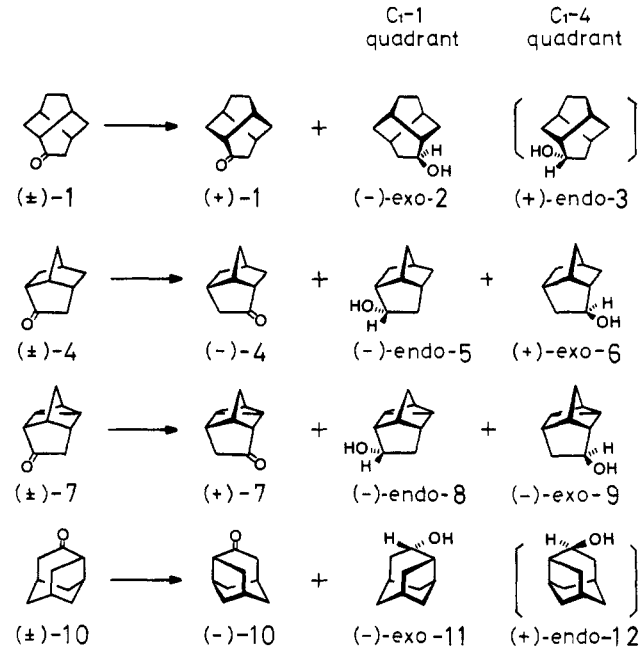
A natural extension of these studies, when coupled with the "quadrant rule"[6] found in microbial reduction of a number of cage-shaped C_1-ketones,[2] has prompted us to examine whether the stereochemistry of HLADH-mediated oxido reduction of cage-shaped C_1-ketones should be governed by the same "quadrant rule" observed in the microbial reduction which states that hydrogen attack from the lower quadrants is most favored for the C_1-1 quadrant orientation (Figure 1) followed by that for the C_4-4 quadrant orientation.

In this paper, we report the HLADH-catalyzed reduction of (±)-4-twistanone (1), (±)-4-brendanone (4), (±)-8-deltacyclanone (7), and (±)-4-protoadamantanone (10) as well as the HLADH-catalyzed oxidation of the related (±)-4-*exo*-twistanol (2), (±)-4-*exo*-protoadamantanol (11), and (±)-4-*endo*-protoadamantanol (12).

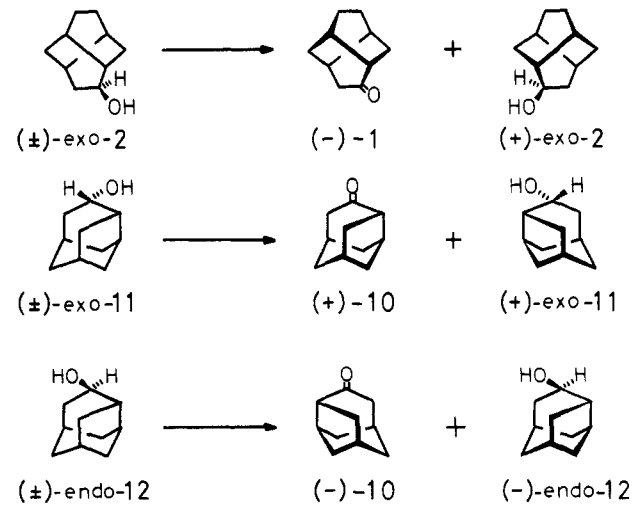
Results and Discussion

HLADH-Mediated Reduction of (±)-4-Twistanone (1), (±)-4-Brendanone (4), (±)-8-Deltacyclanone (7), and (±)-4-Protoadamantanone (10) (Scheme I). The reduction was initiated by adding a catalytic amount of HLADH preparation to a phosphate buffer solution (pH 7.0) which contained (±)-C_1-ketone substrate, NAD^+ coenzyme,[3] and sodium dithionite ($Na_2S_2O_4$), a recycling reagent of the coenzyme.[7] The incubation was terminated when GLC monitoring indicated ca. 50% conversion of the substrate. Extraction with ether was followed by con-

Scheme I



Scheme II



(1) Presented at the 45th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1982; Abstracts, Vol. II, p 708.

(2) In this paper, we conveniently classify ketones according to their symmetry around the carbonyl center: C_2-ketones belong to C_2 point group and have a C_2 symmetry axis coincident with the carbonyl axis, and C_1-ketones belong to C_1 point group and have no symmetry element passing through the carbonyl center.

(3) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; NADH and NAD^+, reduced and oxidized forms, respectively, of nicotinamide adenine dinucleotide; FMN, flavin mononucleotide.

(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) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Sasaki, Y.; Fujii, T. *J. Chem. Soc., Chem. Commun.* **1980**, 626–627. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Suzuki, T.; Iwasaki, M.; Sasaki, Y.; Fujii, T. *J. Org. Chem.* **1981**, *46*, 2726–2730.

(6) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Hirose, Y.; Shimizu, T.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 668–670. (b) Nakazaki, M.; Chikamatsu, H.; Hirose, Y.; Shimizu, T. *J. Org. Chem.* **1979**, *44*, 1043–1048. (c) Nakazaki, M.; Hirose, Y.; Shimizu, T.; Suzuki, T.; Ishii, A.; Makimura, M. *Ibid.* **1980**, *45*, 1428–1435. (d) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Asao, M. *Ibid.* **1980**, *45*, 4432–4440. (e) Nakazaki, M.; Chikamatsu, H.; Fujji, T.; Nakatsuji, T. *Ibid.* **1981**, *46*, 585–589.

(7) For a review of nicotinamide coenzyme recycling methods, see: Jones, J. B.; Beck, J. F. "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. H., Perlman, D., Eds.; Wiley: New York, 1976; Part 1, pp 357–376.

0022-3263/83/1948-2506$01.50/0

Table I. HLADH-Catalyzed Reduction of (±)-4-Twistanone (1), (±)-4-Brendanone (4), (±)-8-Deltacyclanone (7), and (±)-4-Protoadamantanone (10)

substrate	biological system	incubation period,[a] h	% conversion	recovered ketone (% optical purity)	alcohol (% optical purity) endo	alcohol (% optical purity) exo	ratio of endo/exo[b]
(±)-1	HLADH	45 (25)	43	(+)-1 (68)		(−)-2 (90)	exo[e]
(±)-1	*R. rubra*[c]	30 (30)	62	(+)-1 (85)	(+)-3 (78)	(−)-2 (77)	1:4.2
(±)-4	HLADH	25 (20)	49	(−)-4 (24)	(−)-5 (78)	(+)-6 (66)	3.5:1
(±)-4	*C. lunata*[d]	48 (30)	33	(−)-4 (35)	(−)-5 (85)		endo[e]
(±)-7	HLADH	100 (25)	63	(+)-7 (30)	(−)-8 (83)	(−)-9 (18)	2.7:1
(±)-7	*C. lunata*[d]	32 (30)	47	(+)-7 (33)	(−)-8 (54)		6.8:1
(±)-10	HLADH	50 (25)	48	(−)-10 (59)		(−)-11 (50)	exo[e]
(±)-10	*C. lunata*	48 (30)	50	(+)-10 (29)	(+)-12 (34)	(+)-11 (30)	1.4:1
(±)-10	*R. rubra*	24 (30)	34	(+)-10 (0.7)	(+)-12 (28)	(−)-11 (16)	1:2.4

[a] Parenthesized are incubation temperatures (°C). [b] Estimated by GLC of crude ether extract. [c] Taken from the data reported in ref 6d. [d] Taken from the data reported in ref 6e. [e] Only endo or exo isomer was isolated.

Table II. HLADH-Catalyzed Oxidation of (±)-4-*exo*-Twistanol (2) and (±)-4-*exo*- (11) and (±)-*endo*-Protoadamantanol (12)

substrate alcohol	incubation period, h (incubation temp, °C)	% conversion	product (% optical purity) ketone	product (% optical purity) alcohol
(±)-*exo*-2	15.5 (25)	53	(−)-1 (83)	(+)-*exo*-2 (100)
(±)-*exo*-11	7.5 (25)	55	(+)-10 (49)	(+)-*exo*-11 (46)
(±)-*endo*-12	49.0 (25)	52	(−)-10 (57)	(−)-*endo*-12 (54)

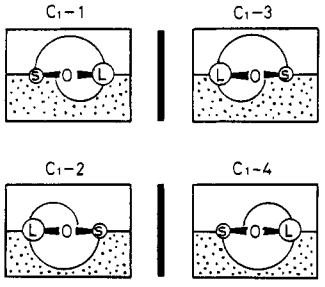


Figure 1. Four quadrant orientations for enantiomers of C_1-ketones. Hydrogen is to be delivered from the lower quadrants.

ventional separation of the metabolites by alumina column chromatography and sublimation in vacuo with due precaution to their optical purities.

The absolute configuration and the absolute rotation of these optically active substrate ketones and their related endo–exo isomeric alcohols have been reported from our laboratory[8,10] except for those of (−)-4-*exo*- (11) and (−)-4-*endo*-protoadamantanol (12).

Manganese dioxide oxidation of these optically active alcohols to (+)-4-protoadamantanone (10)[11] provided the information on their configurations as well as their absolute rotations (see Experimental Section).

Scheme I and Table I summarize the results of HLADH-catalyzed reduction of those cage-shaped C_1-ketones, and an inspection of these should indicate that the "quadrant rule" found in microbial reduction can predict the steric course of HLADH-mediated reduction of these cage-shaped ketones; C_1-1 quadrant orientation is most favored followed by C_1-4 orientation, affording a metabolite mixture which contains (a) the recovered C_1-ketone corresponding to C_1-3 and C_1-4 quadrant orientations, (b) the isomeric alcohol corresponding to C_1-1 orientation, and (c) a small amount of another isomeric alcohol corresponding to C_1-4 orientation.

HLADH-Mediated Oxidation of (±)-4-*exo*-Twistanol (2), (±)-4-*exo*-Protoadamantanol (11), and (±)-4-*endo*-Protoadmantanol (12) (Scheme II). To initiate the HLADH-mediated oxidation, a catalytic amount of HLADH preparation was added to a glycine–NaOH buffer solution (pH 9.0) containing (±)-alcohol substrate, NAD^+ coenzyme, and FMN,[3] a recycling reagent of the coenzyme.[7] The reaction was followed by GLC monitoring and was stopped when ca. 50% coversion had been reached. The product distribution summarized in Scheme II and Table II.

Among the C_1-1 and C_1-3 quadrant orientations possible for (±)-4-*exo*-twistanol (2), the "quadrant rule" predicts the C_1-1 orientation to be most favored, and this was shown to be the case by our isolating an 83% optically pure specimen of (−)-4-twistanone (1) (corresponding to C_1-1 orientation) along with recovering (+)-*exo*-alcohol 2 (corresponding to the unfavorable C_1-3 orientation) with almost 100% optical purity.

The same preference of C_1-1 over C_1-3 orientation, with a poorer stereoselectivity, was also demonstrated in an incubation experiment of (±)-4-*exo*-protoadamantanol (11). For isomeric (±)-4-*endo*-protoadamantanol (12), however, only the unfavorable C_1-2 and C_1-4 orientations are available, and this should explain the fact that while 49 h was required to achieve a 52% conversion of (±)-*endo*-12, 7.5 h was found to be enough for a 55% conversion of (±)-*exo*-11.

The C_1-4 > C_1-2 orientation preference, which is to be operative in this case, was proved by actual isolation of the (−)-ketone 10 and recovery of the (−)-*endo*-alcohol 12 in an incubation experiment utilizing the (±)-*endo*-alcohol 12.

Finally, it would be mentioned passingly that a mere comparison between the last two rows in Scheme II will be sufficient to convince one that the strictness of HLADH's stereoselectivity in this case is such that an apparently slight exo–endo stereochemical difference in

(8) For the absolute configurations of 4-twistanone (1) and 4-*exo*- (2) and 4-*endo*-twistanol (3), see ref 6d. The optical purity of these compounds was calculated from their respective absolute rotation value;[9] $[\alpha]_D$(abs) 324.5° (EtOH), 383° ($CHCl_3$), and 390° ($CHCl_3$).

(9) Nakazaki, M.; Chikamatsu, H.; Taniguchi, M. *Chem. Lett.* **1982**, 1761–1764.

(10) For the absolute configuration of 4-brendanone and 8-deltacyclanone derivatives, see ref 6e. Brown's oxidation of (+)-4-*exo*-brendanol (6) established its absolute configuration and optical purity (see Experimental Section).

(11) The Wolff–Kishner reduction of (−)-4-protoadamantanone (10) to (+)-protoadamantane[12] established its absolute configuration and absolute rotation (see Experimental Section). Optical purities of 4-protoadamantanone (10) and 4-*exo*- (11) and 4-*endo*-protoadamantanol (12) were calculated from their respective absolute rotation values: $[\alpha]_D$(abs) 15.2°, 200°, and 131.6°.

(12) Nakazaki, M; Naemura, K. *J. Org. Chem.* **1977**, *42*, 4108–4113.

Table III. Relative Rates of HLADH-Mediated Oxido Reduction of 4-Twistanone (1), 4-Brendanone (4), 8-Deltacyclanone (7), 4-Protoadamantanone (10), and the Related Alcohols

substrate ketone[a]	V_{rel}[b]	substrate alcohol[a]	V_{rel}[c]
(±)-1	9.9	(±)-*exo*-2	82
(−)-1 (83)	15.6	(−)-*exo*-2 (90)	123
(+)-1 (68)	6.8	(+)-*exo*-2 (100)	8
(±)-4	2.4	(±)-*endo*-3[d]	47
(±)-7	2.5	(±)-*exo*-11	133
(±)-10	7.5	(−)-*exo*-11 (50)	223
(+)-10 (49)	17.5	(+)-*exo*-11 (46)	23.5
(−)-10 (59)	7.5	(±)-*endo*-12	23
		(−)-*endo*-12 (54)	0.9

[a] Parenthesized are optical purities (in percent) of substrates. [b] Velocities are relative to cyclohexanone; V(cyclohexanone) = 100. [c] Velocities are relative to cyclohexanol; V(cyclohexanol) = 100. [d] The substrate is contaminated with 12% of exo isomer 2.

substrates directs the reaction in opposite directions, affording the products of enantiomeric molecular frameworks.

Relative Rates of HLADH-Catalyzed Oxido Reduction of Various Cage-Shaped C_1-Ketones and Related Alcohols. Further support for the "HLADH-quadrant rule" deduced from these preparative scale experiments were furnished by kinetic studies of HLADH-mediated oxido reduction utilizing either racemic or optically active cage-shape C_1-ketone and the related isomeric alcohol substrates.

The left part of Table III tabulates the observed relative reduction rates of the ketones 1, 4, 7 and 10, and an inspection of this reveals that (a) their reduction rates are far smaller than that of cyclohexanone and that (b) the enantiomeric ketones corresponding to C_1-1 quadrant orientation (e.g., (−)-1) are reduced 2–3 times faster than the opposite enantiomers.

Survey of the right part of Table III which summarizes observed relative oxidation rates of various isomeric alcohols reveals that also in this oxidative mode the enantiomeric alcohols corresponding to C_1-1 quadrant orientation (e.g. (−)-*exo*-2) are oxidized exceedingly faster than the opposite enantiomers.

"Microbial Quadrant Rule" and "HLADH-Quadrant Rule". Combination of the preparative-scale incubation experiments with the kinetic studies described above appears to indicate that stereochemistry of HLADH-catalyzed oxido reduction is governed by a similar "quadrant rule" as discovered in the microbial reduction with *Curvularia lunata* and *Rhodotorula rubra*: reaction proceeds according to C_1-1 > C_1-4 ≫ C_1-2 ≈ C_1-3 quadrant orientation preference.

Parallelism between these two "quadrant rules" can be seen from Table I which lists product distribution in the metabolite mixtures obtained from incubation of (±)-4-twistanone (1), (±)-4-brendanone (4), and (±)-8-deltacyclanone (7) with either *R. rubra* or *C. lunata* alongside of those observed in HLADH-mediated reduction employing the same substrates. These product distribution data in the microbial reduction of (±)-1, (±)-4, and (±)-7 are taken from our preceding papers,[6d,e] and lack of data for the microbial reduction of (±)-4-protoadamantanone (10) prompted us to carry out incubation experiments of this cage-shaped ketone with *C. lunata* and *R. rubra*.

Reproduced in the last two rows in Table I are the product distribution data obtained from these incubation experiments which surprised us by (a) a rather low enantiomer selectivity of these microbes toward this specific cage-shaped ketone 10 and (b) an unusual C_1-4 preference over C_1-1 quadrant orientation.

Nevertheless, as far as the cage-shaped C_1-ketones and their related alcohols described in this paper are concerned, the "quadrant rule" with C_1-1 > C_1-4 ≫ C_1-2 ≈ C_1-3 orientation preference has held satisfactorily in predicting the steric course of HLADH-mediated oxido reduction.

Survey of literature[13] reveals a quite number of substrates whose stereochemistry in HLADH-mediated reduction can be nicely explained by this "quadrant rule". They include (±)-*cis*-1-decalone,[13a] (±)-*cis*-2-decalone,[13a] (±)-*trans*-2-decalone,[13] (±)-2-bicyclo[3.2.1]octanone,[14] and *cis*-decalin-2,7-dione,[9] and exceptions which have come to our notice are (±)-2-norbornanone[14] and (±)-2-benzonorbornenone[15] whose product distribution in HLADH-mediated reduction cannot be explained by the "HLADH-quadrant rule".

Jones and co-workers[14] were the first to analyze the stereochemistry of HLADH-catalyzed oxido reduction of various substrates not constructed from chair-form cyclohexane molecular moieties by applying the Prolog's diamond lattice section theory.[13a,16] Having been deduced from the kinetic data for the substrates composed of the chair-form cyclohexane moieties, Prelog's diamond lattice is not necessarily suited to accommodate itself to the substrates constituted of nonchair-form cyclohexane moieties. To overcome this difficulty, Jones and coworker[17] have recently proposed a novel cubic-space section model based on the X-ray diffraction studies of the active site of crystalline HLADH enzyme.

On comparison of these rather elaborate models which are not, of necessity, easily applied to common substrates, we believe that our "HLADH-quadrant rule" is a reliable and easily applicable rule of thumb in predicting the specificity of HLADH-catalyzed oxido reduction of a variety of carbonyl compounds.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were determined on a JNM NH-100. Chemical shifts are reported as δ values in parts per million relative to internal Me_4Si (δ 0). Optical rotations were measured with a JASCO DIP-140 polarimeter. GLC analyses were performed on a JGC-20K equipped with an FID and a 2 m × 3 mm column of 10% Carbowax 20M on Chromosorb W or 15% silicone DC QF-1 on Uniport B. Column chromatography was carried out with Woelm active alumina (neutral, activity III). Preparative TLC was carried out with silica gel 60 $PF_{254+366}$ (Merck).

HLADH was purchased from Boehringer (Mannheim) as a crystalline suspension in phosphate buffer containing 10% ethanol. Immediately before each experiment, the enzyme suspension was freeze-dried to a powder whose average activity was found to be 1.37–1.95 U/mg.[18]

$NAD^+ \cdot 3H_2O$ and $NADH \cdot 3H_2O$ were obtained from Kohjin Co., Ltd., Tokyo, Japan.

(13) For a concise review covering stereochemistry of HLADH-catalyzed oxido reduction, see: (a) ref 7, pp 260–319. (b) Jones, J. B. "Enzymic and Non-Enzymic Catalysis"; Dunnill, P., Wiseman, A., Blakebrough, N., Eds.; Ellis Horwood: Chichester, 1980; Chapter 3.

(14) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8476–8482.

(15) Nakazaki, M.; Chikamatsu, H., presented at the 45th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1982; Abstracts, Vol. II, p 709.

(16) (a) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–130. (b) Graves, J. M. H.; Clark, A.; Ringold, H. J. *Biochemistry* **1965**, *4*, 2655–2671. (c) Bentley, R. "Molecular Asymmetry in Biology"; Academic Press: New York, 1970; Vol. 2, pp 22–31.

(17) Jones, J. B.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 19–28.

(18) Bonnichsen, R. K.; Brink, B. G. "Methods in Enzymology"; Colowick, S. P., Kaplan, N. O., Eds.; Academic Press: New York, 1955; Vol. 1, pp 495–500.

The cultures of *R. rubra* (IFO 0889) and *C. lunata* (IFO 6288) were obtained from the Institute of Fermentation, Osaka, Japan.

General Procedure for the Preparative-Scale HLADH-Catalyzed Oxido Reduction. While the reduction experiments were carried out in $^1/_{15}$ M Sørensen phosphate buffer solution (pH 7.0), the oxidation experiments were performed in 0.05 M glycine–NaOH buffer solution (pH 9.0). The reactions were monitored by GLC, and the incubation was terminated when monitoring indicated a ca. 1:1 ratio of alcohol to ketone in the reaction mixture. Extraction of the mixture with ether was followed by drying with $MgSO_4$, and removal of the solvent left a residue whose chromatography furnished ketone and alcohol fractions.

Kinetic Studies. The reductive runs were carried out in $^1/_{15}$ M Sørensen phosphate buffer (pH 7.0) containing NADH (1.8×10^{-4} M) and the substrate ketone (3.6×10^{-4} M). The oxidative runs were performed in 0.05 M glycine–NaOH buffer (pH 9.0) containing NAD^+ (5.0×10^{-4} M) and the substrate alcohol (3.5×10^{-4} M). The reaction was initiated by adding a 100-μL aliquot of HLADH stock solution (1 mg/1 mL in 0.05 M Tris–HCl buffer, pH 7.4) to give a 3-mL assay solution in a 1-cm cell. The absorbance change was monitored at 340 nm at 25 °C, and a reference assay was performed, for each substrate, by employing cyclohexanone or cyclohexanol.

HLADH-Catalyzed Reduction of (±)-4-Twistanone (1). NAD^+ (80.9 mg, 0.12 mmol), $Na_2S_2O_4$ (26.1 g, 0.15 mol), and HLADH (12.5 mg) were added to a solution of the (±)-1[19] (153.5 mg, 1.0 mmol) in phosphate buffer (1.5 L), and the mixture was incubated at 25 °C for 45 h. Extraction with ether, drying ($MgSO_4$), and removal of the solvent gave a metabolite mixture (150 mg) which was shown to be a 57:43 mixture of the ketone 1 and *exo*-2 (GLC). The mixture was chromatographed over alumina (6 g), and elution with pentane (150 mL) afforded crude (+)-4-twistanone (1) which after sublimation (65–70 °C, 25 mm) melted at 165–166 °C (in a sealed tube): 58 mg (35% yield); $[\alpha]^{24}_D$ +220° (*c* 0.92, EtOH), 68% optical purity (lit.[9] $[\alpha]_D$(abs) 324.5°). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.43.

Further elution with pentane–ether (4:1, 75 mL) gave (−)-4-*exo*-twistanol (2) which was sublimed (80–85 °C, 25 mm) to melt at 190–192 °C (in a sealed tube): 52 mg (34% yield); $[\alpha]^{25}_D$ −343° (*c* 0.97, $CHCl_3$), 90% optical purity (lit.[9] $[\alpha]_D$(abs) 383°). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.71; H, 10.53.

HLADH-Catalyzed Oxidation of (±)-4-*exo*-Twistanol (2). To a glycine–NaOH buffer solution (1 L) containing (±)-4-*exo*-twistanol (2)[21] (100.9 mg, 0.67 mmol), NAD^+ (49.8 mg, 0.075 mmol), and FMN (750 mg, 1.5 mmol) was added HLADH (7.44 mg), and the reaction was allowed to proceed at 25 °C until GLC monitoring indicated 53% oxidation (15.5 h). The ethereal extract (100 mg) was dissolved in pentane and chromatographed over alumina (5.5 g). Elution with pentane (120 mL) gave (−)-4-twistanone (1) which was sublimed in vacuo (70–75 °C, 25 mm): mp 159–161 °C (in a sealed tube); 36 mg (36% yield); $[\alpha]^{27}_D$ −270° (*c* 0.97, EtOH), 83% optical purity (lit.[9] $[\alpha]_D$(abs) 324.5°). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.87; H, 9.40.

Further elution with pentane–ether (4:1, 70 mL) gave (+)-4-*exo*-twistanol (2) which was purified by sublimatin in vacuo (80–85 °C, 25 mm): mp 192–194 °C (in a sealed tube); 28 mg (28% yield); $[\alpha]^{25}_D$ +383.6° (*c* 0.60, $CHCl_3$), 100% optical purity (lit.[9] $[\alpha]_D$(abs) 383°). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.61; H, 10.57.

HLADH-Catalyzed Reduction of (±)-4-Brendanone (4). To a 1-L phosphate buffer solution containing the (±)-ketone 4[23] (500 mg, 3.7 mmol), NAD^+ (350 mg, 0.51 mmol), and $Na_2S_2O_4$ (17.4 g, 0.1 mol) was added HLADH (40 mg), and the mixture was incubated at 20 °C for 25 h. GLC of the ethereal extract (440 mg) indicated that this was a 51:11:38 mixture of the ketone 4, *exo*-6, and *endo*-5. The extract was taken up in pentane and chromatographed over alumina (15 g). Elution with pentane (500 mL) gave (−)-4-brendanone (4) which was sublimed in vacuo (80 °C, 20 mm): mp 113–116 °C (in a sealed tube); 152 mg (30% yield); $[\alpha]^{22}_D$ −18.3° (*c* 0.56, $CHCl_3$), 24.4% optical purity (lit.[6e] $[\alpha]_D$(abs) 75°). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.42; H, 8.88.

Further elution with pentane–ether (4:1, 300 mL) was carried out to separate isomeric 4-*endo*- (5) and 4-*exo*-brendanol (6). Crude (−)-4-*endo*-brendanol (5) obtained from the earlier fractions was purified by preparative TLC (silica gel, 50:1 $CHCl_3$–MeOH) followed by sublimation in vacuo (90 °C, 20 mm): mp 136–137 °C (in a sealed tube); 95 mg (19% yield); $[\alpha]^{22}_D$ −28.2° (*c* 0.71, $CHCl_3$), 78% optical purity (lit.[6e] $[\alpha]_D$(abs) 36°). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.13; H, 10.22.

The slow-moving fractions provided crude 4-*exo*-brendanol (6) which melted at 104–107 °C after sublimation in vacuo (90 °C, 20 mm): $[\alpha]^{22}_D$ −4.2° (*c* 0.67, $CHCl_3$); 51 mg (10% yield). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.30.

GLC of this specimen of *exo*-6 indicated that this was a 74:26 mixture of *exo*-6 and *endo*-5. Calculation based on these data, when coupled with the result of Brown's oxidation (vide infra) of this specimen, showed that 4-*exo*-brendanol (6) in the original metabolite mixture is dextrorotatory with 66% optical purity.

Brown's Oxidation of the Crude 4-*exo*-Brendanol (6). To the crude 4-*exo*-brendanol (6: $[\alpha]^{22}_D$ −4.2°; 32 mg) dissolved in ether (25 mL) was added Brown's reagent[25] (0.21 mL) at 0 °C during 15 min. The ethereal layer was separated, washed with water and 7% $NaHCO_3$, and then dried ($MgSO_4$). Removal of the solvent and sublimation of the product (80 °C, 20 mm) gave (−)-4-brendanone 4: 17 mg; mp 107–109 °C (in a sealed tube); $[\alpha]^{20}_D$ −21.5° (*c* 0.34, $CHCl_3$), 29% optical purity (lit.[6e] $[\alpha]_D$(abs) 75°). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.37; H, 8.87.

HLADH-Catalyzed Reduction of (±)-8-Deltacyclanone (7). After HLADH (30 mg) was added to a phosphate buffer solution (500 mL) containing (±)-7[26] (300 mg, 2.2 mmol), NAD^+ (240 mg, 0.36 mmol), and $Na_2S_2O_4$ (8.7 g, 0.05 mol), the mixture was incubated at 25 °C for 100 h. Extraction with ether gave a metabolite mixture whose GLC indicated that this is a 37:17:46 mixture of 7, *exo*-9, and *endo*-8. The mixture was chromatographed over alumina (20 g), and elution with pentane (800 mL) afforded (+)-8-deltacyclanone (7) which was purified by vacuum distillation: bp 120 °C (20 mm); 55 mg (18% yield); $[\alpha]^{25}_D$ +86.2° (*c* 0.93, $CHCl_3$), 30% optical purity (lit.[6e] $[\alpha]_D$(abs) 290°). Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 79.85; H, 7.72.

Elution with pentane–ether (10:1, 80 mL) gave (−)-8-*exo*-deltacyclanol (9): bp 120 °C (20 mm); 22 mg (7% yield); $[\alpha]^{25}_D$ −1.6° (*c* 1.0, $CHCl_3$), 18% optical purity (lit.[6e] $[\alpha]_D$(abs) 9°). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.44; H, 9.30.

Further elution with pentane–ether (10:1, 560 mL) eluted a 1:2 mixture (95 mg) of 9 and 8 which was followed by (−)-8-*endo*-deltacyclanol (8): 55 mg (18% yield); bp 100 °C (6 mm); $[\alpha]^{25}_D$ −45.8° (*c* 0.69, $CHCl_3$), 83% optical purity (lit.[6e] $[\alpha]_D$(abs) 55°). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.60; H, 9.16.

HLADH-Catalyzed Reduction of (±)-4-Protoadamantanone (10). After HLADH (18 mg) was added to a phosphate buffer solution (2 L) containing (±)-10[27] (198 mg, 1.32 mmol), NAD^+ (96 mg, 0.14 mmol), and $Na_2S_2O_4$ (34.8 g, 0.2 mol), the mixture was incubated at 25 °C for 50 h. Extraction with ether afforded a metabolite mixture (200 mg) whose GLC indicated that this was a 52:48 mixture of 10 and *exo*-11.

The mixture was chromatographed over alumina (14 g), and elution with pentane (840 mL) gave (−)-4-protoadamantanone (10)

(19) The racemic ketone 1 was prepared by following Deslongchamps' procedure;[20] mp 160–162 °C (in a sealed tube) (lit.[20] mp 185–190 °C).

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

(21) Prepared by $LiAlH_4$ reduction of (±)-4-twistanone (1) followed by chromatographic separation of isomeric *exo*-2 and *endo*-3, mp 190–191 °C (in a sealed tube) (lit.[22] mp 202–203 °C (in a sealed tube)).

(22) Tichý, M.; Kniezo, L. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1537–1550.

(23) The racemic ketone 4 was prepared by the method of Nickon et al.;[24] mp 108–110 °C (in a sealed tube) (lit.[24] mp 120–120.5 °C).

(24) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904–3916.

(25) (a) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952–2953. (b) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387–390.

(26) The racemic ketone 7 was prepared by the method of Nickon et al.;[24] bp 61–62 °C (2 mm) (lit.[24] bp 88–90 °C (11 mm)).

(27) The racemic ketone 10 was prepared by the method of Lunn;[28] mp 208–210 °C (in a sealed tube) (lit.[28] mp 210–212 °C).

(28) Lunn, W. H. W. *J. Chem. Soc. C* **1970**, 2124–2126.

which was purified by sublimation in vacuo (70–75 °C, 30 mm): mp 208–210 °C (in a sealed tube); 60 mg (30% yield); $[\alpha]^{24}_D$ −8.9° (*c* 0.55, $CHCl_3$), 59% optical purity (lit.[11] $[\alpha]_D$(abs) 15.2°). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.80; H, 9.21.

Further elution with 700 mL of pentane–ether (10:1) gave (−)-4-*exo*-protoadamantanol (**11**)[29] which was purified by sublimation in vacuo (90–100 °C, 30 mm): mp 204–206 °C (in a sealed tube); 80 mg (40% yield); $[\alpha]^{24}_D$ −100° (*c* 0.58, $CHCl_3$), 50% optical purity (lit.[11] $[\alpha]_D$(abs) 200°); NMR[29] (100 MHz, $CDCl_3$) δ 4.16 (1 H, d of d, *J* = 3.3, 5.1 Hz, OH–C–$\mathbf{H}_{endo}$). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89: H, 10.60. Found: C, 78.77; H, 10.49.

Microbial Reduction of (±)-4-Protoadamantanone (10) with *R. rubra*.[30] An ethanol solution (40 mL) containing (±)-**10** (810 mg, 5.4 mmol) was distributed to eight batches of *R. rubra* culture solution (each 200 mL), and the mixtures were incubated at 30 °C for 24 h. Filtration through a layer of Hyflo Super Cel collected the mycelium which was extracted with ether. The ethereal extract of the beer filtrate was combined with the extract of the mycelium, washed with water, and dried ($MgSO_4$). Removal of the solvent left a metabolite mixture (650 mg) which was analzyed by GLC to reveal that this is a 66:24:10 mixture of **10**, *exo*-**11**, and *endo*-**12**. The mixture was dissolved in pentane and chromatographed over alumina (20 g). Elution with pentane (880 mL) afforded (+)-4-protoadamantanone (**10**) which was purified by sublimation in vacuo (100 °C, 20 mm): mp 204–206 °C (in a sealed tube); 486 mg (60% yield): $[\alpha]^{23}_D$ +0.1° (*c* 6.1, $CHCl_3$), 0.7% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.32.

Further elution with pentane–ether (10:1, 240 mL) gave (−)-4-*exo*-protoadamantanol (**11**) which melted at 229–231 °C (in a sealed tube) after sublimation in vacuo (100 °C, 20 mm): 108 mg (13% yield); $[\alpha]^{24}_D$ −32.3° (*c* 1.07, $CHCl_3$), 16% optical purity.[11] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.78; H, 10.57.

Final Elution with pentane–ether (10:1, 240 mL) provided (+)-4-*endo*-protoadamantanol (**12**)[29] which was purified through TLC (silica gel, 20:1 $CHCl_3$–MeOH) followed by sublimation in vacuo (100 °C, 20 mm): mp 210–212 °C (in a sealed tube); 27 mg (3% yield); $[\alpha]^{24}_D$ +36.0° (*c* 0.77, $CHCl_3$), 28% optical purity (lit.[11] $[\alpha]_D$(abs) 131.6°). GLC analysis showed this specimen was contaminated with 2.7% of *exo*-**11**: NMR[29] (100 MHz, $CDCl_3$) δ 4.02 (1 H, d of t, *J* = 3, 8 Hz, OH–C–$\mathbf{H}_{exo}$). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.64.

Microbial Reduction of (±)-4-Protoadamantanone (10) with *C. lunata*.[30] A total of 1.70 g (11 mmol) of (±)-**10** dissolved in 80 mL of ethanol was added to 16 batches of *C. lunata* culture solution (each 200 mL), and the mixtures were incubated at 30 °C for 48 h. The metabolite mixture (1.3 g) obtained via ether extraction was shown by GLC to be a 50:21:29 mixture of **10**, *exo*-**11**, and *endo*-**12**. Workup of the metabolite mixture following the procedure described for the *R. rubra* culture afforded the following.

(a) (+)-4-Protoadamantanone (10): 440 mg (26% yield); mp 204.5–206.5 °C (in a sealed tube); $[\alpha]^{24}_D$ +4.47° (*c* 3.5, $CHCl_3$), 29% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.37.

(b) (+)-4-*exo*-Protoadamantanol (11): 137 mg (8% yield); mp 231–233 °C (in a sealed tube); $[\alpha]^{27}_D$ +60.6° (*c* 1.43, $CHCl_3$), 30% optical purity.[11] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.68; H, 10.60.

(c) (+)-*endo*-Protoadamantanol (12): 204 mg (12% yield); mp 217–218.5 °C (in a sealed tube); $[\alpha]^{23}_D$ +44.3° (*c* 1.39, $CHCl_3$). The GLC analysis revealed that this specimen is contaminated with 2% of (+)-4-*exo*-**11**, assigning ca. 34% optical purity to this specimen.[11] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.63; H, 10.50.

HLADH-Catalyzed Oxidation of (±)-4-*exo*-Protoadamantanol (11). To 1 L of glycine–NaOH buffer solution containing (±)-*exo*-**11**[31] (101 mg, 0.66 mmol), NAD^+ (50 mg, 0.07 mmol), and FMN (660 mg, 1.3 mmol) was added HLADH (8 mg), and the mixture was incubated at 25 °C. The incubation was terminated after 7.5 h when GLC monitoring indicated 55% oxidation, and the mixture was extracted with ether. The extract (100 mg) was taken up in pentane and was chromatographed over alumina (7 g). Elution with pentane (420 mL) gave (+)-4-protoadamantanone (**10**) which was sublimed in vacuo (70–80 °C, 30 mm): mp 208–210 °C (in a sealed tube); 30 mg (30% yield); $[\alpha]^{23}_D$ +7.5° (*c* 0.53, $CHCl_3$), 49% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.78; H, 9.37.

Further elution with pentane–ether (10:1, 280 mL) afforded, after sublimation in vacuo (90–100 °C, 30 mm), (+)-4-*exo*-protoadamantanol (**11**): 40 mg (40% yield); mp 204–206 °C (in a sealed tube); $[\alpha]^{23}_D$ +92.0° (*c* 0.51, $CHCl_3$), 46% optical purity.[11] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.71; H, 10.55.

HLADH-Catalyzed Oxidation of (±)-4-*endo*-Protoadamantanol (12). To 1 L of glycine–NaOH buffer solution containing (±)-*endo*-**12**[31] (102 mg, 0.67 mmol), NAD^+ (52 mg, 0.08 mmol), and FMN (660 mg, 1.3 mmol) was added HLADH (8.3 mg), and the mixture was incubated at 25 °C. After 49 h when GLC monitoring indicated 52% oxidation, the incubation was terminated, and the mixture was extracted with ether. The extract (100 mg) was taken up in pentane and chromatographed over alumina (7 g). Elution with pentane (420 mL) gave, after sublimation in vacuo (70–80 °C, 30 mm), (−)-4-protoadamantanone (**10**): 25 mg (25% yield); mp 208–209 °C (in a sealed tube); $[\alpha]^{25}_D$ −8.7° (*c* 0.54, $CHCl_3$), 57% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.83; H, 9.33.

Further elution with pentane–ether (10:1, 420 mL) gave, after sublimation in vacuo (90–100 °C, 30 mm), (−)-4-*endo*-protoadamantanol (**12**): 40 mg (40% yield); mp 204–207 °C (in a sealed tube), $[\alpha]^{25}_D$ −71° (*c* 0.57, $CHCl_3$), 54% optical purity.[11] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.69; H, 10.55.

Manganese Dioxide Oxidation of (−)-4-*exo*-Protoadamantanol (11). A mixture of (−)-4-*exo*-protoadamantanol (**11**: 30 mg; $[\alpha]^{24}_D$ −100°) and activated manganese dioxide[32] (1.5 g) in methylene dichloride (10 mL) was stirred at room temperature for 16 h. The manganese dioxide collected by filtration was washed with methylene dichloride, and the washing was combined with the filtrate. Removal of the solvent left a residue which was taken up in pentane and chromatographed over alumina (5 g). Elution with pentane (420 mL) gave, after sublimation in vacuo (60–70 °C, 30 mm), (+)-4-protoadamantanone (**10**): 15 mg (50% yield); mp 202–204 °C (in a sealed tube); $[\alpha]^{20}_D$ +7.6° (*c* 0.3, $CHCl_3$), 50% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.55; H, 9.49.

Manganese Dioxide Oxidation of (−)-4-*endo*-Protoadamantanol (12). Following the same procedure as described above for (−)-exo-isomer **11**, (−)-4-*endo*-protoadamantanol (**12**: 25 mg; $[\alpha]^{25}_D$ −71°) was converted into (+)-4-protoadamantanone (**10**): 10 mg (40% yield); mp 204–206 °C (in a sealed tube); $[\alpha]^{20}_D$ +8.2° (*c* 0.3, $CHCl_3$), 54% optical purity.[11] Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.77; H, 9.39.

(+)-Protoadamantane. A mixture of (−)-4-protoadamantanone (**10**: 50 mg, 3.3 mmol; $[\alpha]^{24}_D$ −8.9°), KOH (30 mg), 80% hydrazine hydrate (0.1 mL), and triethylene glycol (1 mL) was heated at 100–120 °C for 30 min. The bath temperature was gradually raised to 200 °C which was maintained for an additional 3 h. The mixture was cooled, and a white solid which condensed on the inner wall of the condenser was taken into pentane. Removal of the solvent gave a crystalline mass (25 mg) which was chromatographed over alumina (3 g). Elution with pentane (150 mL) afforded, after sublimation in vacuo (50 °C, 30 mm), (+)-protoadamantane: 15 mg (33% yield); mp 213–215 °C (in a sealed tube); $[\alpha]^{21}_D$ +101.8° (*c* 0.28, EtOH), 59% optical purity [lit.[12] mp 212.5–214 °C (in a sealed tube); $[\alpha]^{26}_D$ −118° (EtOH),

(29) Racemic 4-*exo*- (**11**) and 4-*endo*-protoadamantanol (**12**): (a) Boyd, J.; Overton, K. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2533–2539. (b) Lenoir, D.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 2138–2148.

(30) The general procedure of the microbial reduction has been described previously.[4b,6b]

(31) The racemic substrate alcohols **11** and **12** were prepared by the method of Schleyer et al.:[29b] *exo*-**11**, mp 204–206 °C (in a sealed tube); *endo*-**12**, mp 214–216 °C (in a sealed tube) (lit.[29b] *exo*-**11**, mp 204–206 °C; *endo*-**12** mp 214–216 °C).

(32) Freshly prepared by the method of Attenburrow et al.[33]

(33) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Janesn, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111.

68% optical purity, $[\alpha]_D$(abs) 174°]. Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.96; H, 12.00.

Registry No. (±)-1, 69308-42-5; (+)-1, 25225-94-9; (−)-1, 74958-51-3; (±)-*exo*-2, 86022-51-7; (−)-*exo*-2, 74958-52-4; (+)-*exo*-2, 86022-54-0; (±)-4, 75768-03-5; (−)-4, 75801-50-2; (−)-*endo*-5, 75768-04-6; (+)-*exo*-6, 86087-01-6; (±)-7, 75768-02-4; (+)-7, 75801-41-1; (−)-*endo*-8, 75801-44-4; (−)-*exo*-9, 75801-47-7; (±)-10, 69308-42-5; (−)-10, 86022-55-1; (+)-10, 86022-56-2; (−)-*exo*-11, 69308-43-6; (±)-*exo*-11, 86022-52-8; (+)-*exo*-11, 86022-57-3; (±)-*endo*-12, 86022-53-9; (−)-*endo*-12, 86022-58-4; (+)-protoadamantane, 86022-59-5; HLADH, 9031-72-5.

A Novel Approach to the Synthesis of Xylomollin

James K. Whitesell,* Paul K. S. Wang, and Daniel A. Aguilar

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

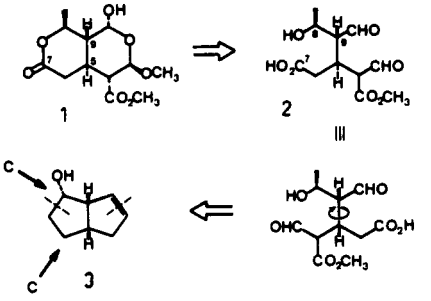
Received September 20, 1982

An approach to the natural product xylomollin (1) is described. The cis-fused bicyclo[3.3.0]octane ketone 4 was modified by the addition of one carbon and sequential cleavage of each of the carbocyclic rings to form the cis-fused bislactone 18. Treatment of 18 with zinc chloride in methanol effected cleavage of both lactone rings with reformation of a new bislactone 20, with the trans ring fusion in the natural product. Carbon NMR spectral data and assignments are provided for all intermediates.

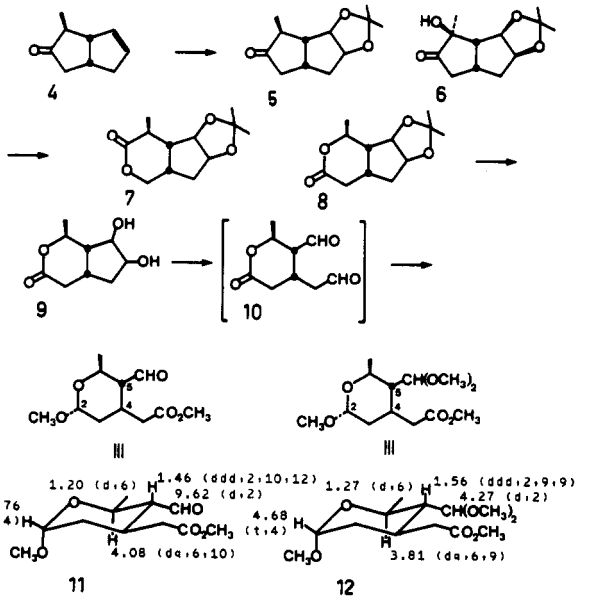
The iridoid mono- and sesquiterpenes represent interesting synthetic challenges, especially the more highly oxygenated examples such as sarracenin,[1] xylomollin,[2] and allamandin.[3] We have been involved for some time in the synthesis of these functionally rich natural products, starting from readily available *cis*-bicyclo[3.3.0]octanes. This approach has the advantage that the highly favored, cis fusion of the [3.3.0] ring fusion matches that found in all but one of the iridoids.[4] The one exception is xylomollin (1) and we were especially fascinated by the possibility that a *cis*-bicyclo[3.3.0]octane might ultimately be transformed into the trans-fused natural product. Such a sequence would formally require inversion of stereochemistry at one or the other of the bridgehead carbons, a process that could be accomplished by actual epimerization or by interconversion of the two, equal length chains attached to the lower bridgehead atom as illustrated in Scheme I. We choose the latter option both because it is stereochemically unambiguous[5] and because to our knowledge it represents a unique means of stereochemical control.

Our initial efforts were directed at a model study of the interconversion. The dialdehyde **10** was prepared from ketone **4** by the sequence shown in Scheme II. Two points concerning these transformations are worthy of note. First, while the oxidation of alkene linkage in **4** with catalytic osmium tetraoxide proceeded in high yield and with good exo face stereoselectivity (5.5:1), a small amount of the tertiary alcohol **6** was also generated, presumably by oxidation of the enolic form of the ketone. Second, Baeyer–Villager oxidation of ketone **5** led to an abnormally large amount (10%) of the lactone **7** resulting from migration of the less substituted carbon atom.

Scheme I



Scheme II



Treatment of dialdehyde **10** with acidic methanol led to a facile transformation the lactolide ester **11** as an anomeric mixture at C-2. Further conversion to the acetal **12** (again obtained as an anomeric mixture) could be achieved by prolonged treatment with the same medium. Analysis of the interproton coupling data for the major isomers of **11** and **12** led unequivocally to the assignment of the transoid relationship between the substituents at C-4 and C-5 (for **11**, $J_{4,5}$ = 10 Hz; for **12**, $J_{4,5}$ = 9 Hz). There are two independent reasons for the greater stability

(1) Miles, D. H.; Kokpol, U.; Bhattacharya, J.; Atwood, J. L.; Stone, K. E.; Bryson, T. A.; Wilson, C. *J. Am. Chem. Soc.* **1976**, *98*, 1569.
(2) Kubo, I.; Muira, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704.
(3) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477.
(4) Bobbitt, J. M.; Segebarth, K.-P. In "Cyclopentanoid Terpene Derivatives"; Taylor, W. I., Battersby, A. R., Ed.; Marcel Dekker: New York, 1969; Chapter 1.
(5) The stereochemistry originally reported for xylomollin was in error. See the following: Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S.; Helbling, A. M. "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, March, 1978; American Chemical Society: Washington, DC, 1978; ORGN 176. Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079.

0022-3263/83/1948-2511$01.50/0