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THE ABSOLUTE CONFIGURATION OF 6,8-DIOXABICYCLO[3.2.1]OCTANE AND SEVERAL METHYL SUBSTITUTED DERIVATIVES

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Abstract - The enantiomers of 6,8-dioxabicyclo[3 2 1]octane and the alkyl substituted derivatives, *exo*- and *endo*-7-methyl, *exo*- and *endo*-5,7-dimethyl, 7,7-dimethyl, and *exo*- and *endo*-7-ethyl-5-methyl (*exo*- and *endo*-brevicomin), were synthesized stereoselectively with known configuration by standard synthetic methods, or with baker's yeast, or both The correlation between the absolute configuration of the bicyclic rings and the optical rotation was established by means of chiral complexation gas chromatography for two molecules for which this correlation was not known previously In all cases, the (1R) enantiomer exhibits positive rotation The absolute configurations were established for the yeast products which were always produced in high optical purity

We have recently reported the vibrational circular dichroism (VCD) spectra of four exo-7 derivatives of 5-methyl-6,8-dioxabicyclo[3 2 1]octane with the aim of determining the absolute configuration of related molecules utilizing only certain features in those spectra.[1] While this may be possible in principle, sufficient background information is needed initially which relates the observed signs of the VCD bands with the configuration at specific chiral centers For the four bicyclic ketals dealt with in that paper it was possible to make such correlations with certainty since the absolute configuration of one of them, namely (+)-(1R,5S,7R)-*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3 2 1]octane (**Ia** in Figure 1, also known as (+)-*exo*-brevicomin), had already been determined previously,[2] and the other three were derived from the

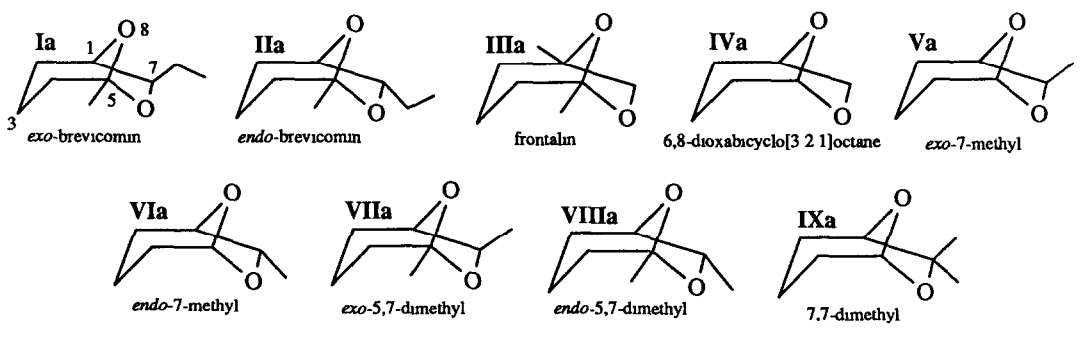


Figure 1 Substituted derivatives of 6,8-dioxabicyclo[3 2 1]octane with the (R) configuration at C(1), the antipodes having the (S) configuration at C(1) are designated "b" in the text

same precursor without change in configuration [1] In order to unravel the VCD spectra of these bicyclics

properly, however, it is necessary to first understand in detail the spectra of simpler analogs including the unsubstituted parent compound (**IV** to **IX** in Figure 1) Although we were able to synthesize the pure enantiomers of **V**, **VI**, **VII**, and **VIII** with selected yeasts, the VCD spectra showed discrepancies which made it uncertain whether the optical rotations could be relied upon as the sole indicators of the absolute configurations We found it necessary, therefore, to synthesize the enantiomers of **IV** to **IX** in ways which left no doubt about the configuration Those syntheses are described below, together with the related syntheses using baker's yeast, and the optical rotation and chiral g c data

The absolute configurations of **Ia** and **b** ((+)-(1R,5S,7R)- and (-)-(1S,5R,7S)-*exo*-brevicomin) were first deduced by Mori[2] starting from D-(-)- and L-(+)-tartaric acid, respectively Various values for the

Table 1 Literature syntheses of enantiomers of *exo*- and *endo*-brevicomin

route or chiral precursor	no steps	overall yield/% (steps)	ref [a]	$[\alpha]_D^{22}$/ degrees (concentrations in moles/L)
(+)-*exo*-brevicomin				
R-(-)-glutamic acid	11	35	3	+64 8 (c 1 25, $CHCl_3$)
R-isopropylideneglyceraldehyde	7	49	4	+80 9 (c 2 18, ether)
6-iodohexopyranoside	5	54	5	+82 4 (c 1 5, ether)
isopropylidene dioxybutyraldehyde	9	14 (6)	6	+74 (c 0 7, ether)
diacetone glucose	7	20	7	+81 5
(-)-diethyltartrate and Sharpless epoxidation	7	28	8	+59 0 (c 2 5, $CHCl_3$)[b]
α,β-dialkoxy erythro/threo aldehydes	7	57 (3)	9	+70 (c 2, ether)
partial resolution of an acid intermediate	5	42	10	+52 (c 1 2, ether)
(-)-tartaric acid	14	0 2	2	+84 1 (c 2 2, ether)
(-)-diethyltartrate and Sharpless epoxidation	7	31 (3)	11	+67 5 (c 1 052, ether)
(-)-*exo*-brevicomin				
(+)-diethyltartrate via Sharpless epoxidation	7	56	12	-66 5 (c 1 112, ether)[c]
R-isopropylidene glyceraldehyde	7	52	4	-80 3 (c 2 23, ether)
R-(-)-dihydrocarvone	8	33 (5)	13	-60 0 (c 2 57, ether)
(+)-diethyltartrate via Sharpless epoxidation	7	40 (27)	8	-60 6 (c 2 3, $CHCl_3$)[b]
α,β-dialkoxy erythro/threo aldehydes	7	57 (4)	9	-66 (c 2, ether)
(+)-diethyltartrate	9	10	14	-67 5 (c 2 15, ether)[d]
(+)-tartaric acid	14	0 2	9	-80 0 (c 1 6, ether)
(+)-*endo*-brevicomin				
R-isopropylideneglyceraldehyde	9	32	2	+96 6 (c 0 98, ether)
(+)-diethyltartrate via Sharpless epoxidation	7	63	10	+74 6 (c 1 06, ether)[c]
α,β-dialkoxy erythro/threo aldehydes	7	57 (4)	7	+76 7 (c 2, ether)
(+)-diisopropyltartrate via Sharpless epoxidation	5	7	15	+78 8 (c 0 5, ether)
(-)-*endo*-brevicomin				
R-isopropylideneglyceraldehyde	9	36	2	-93 1 (c 1 01, ether)
α,β-dialkoxy erythro/threo aldehydes	7	57 (4)	7	-74 (c 2 2, ether)
(-)-diisopropyltartrate via Sharpless expoxidation	5	5	15	-75 9 (c 0 717, ether)

[a] See Reference section in text
[b] 95% ee by complexation gas chromatography
[c] 78 5% optical purity
[d] 80-86% optical purity

optical rotation have been reported (Table 1), with that of Johnston and Oehlschlager[8] being supported by a precise determination of an optical purity of 95% ee by means of chiral complexation gas chromatography The first stereoselective synthesis of **IIa** and **b** ((+)-(1R,5S,7S)- and (-)-(1S,5R,7R)-*endo*-brevicomin) was

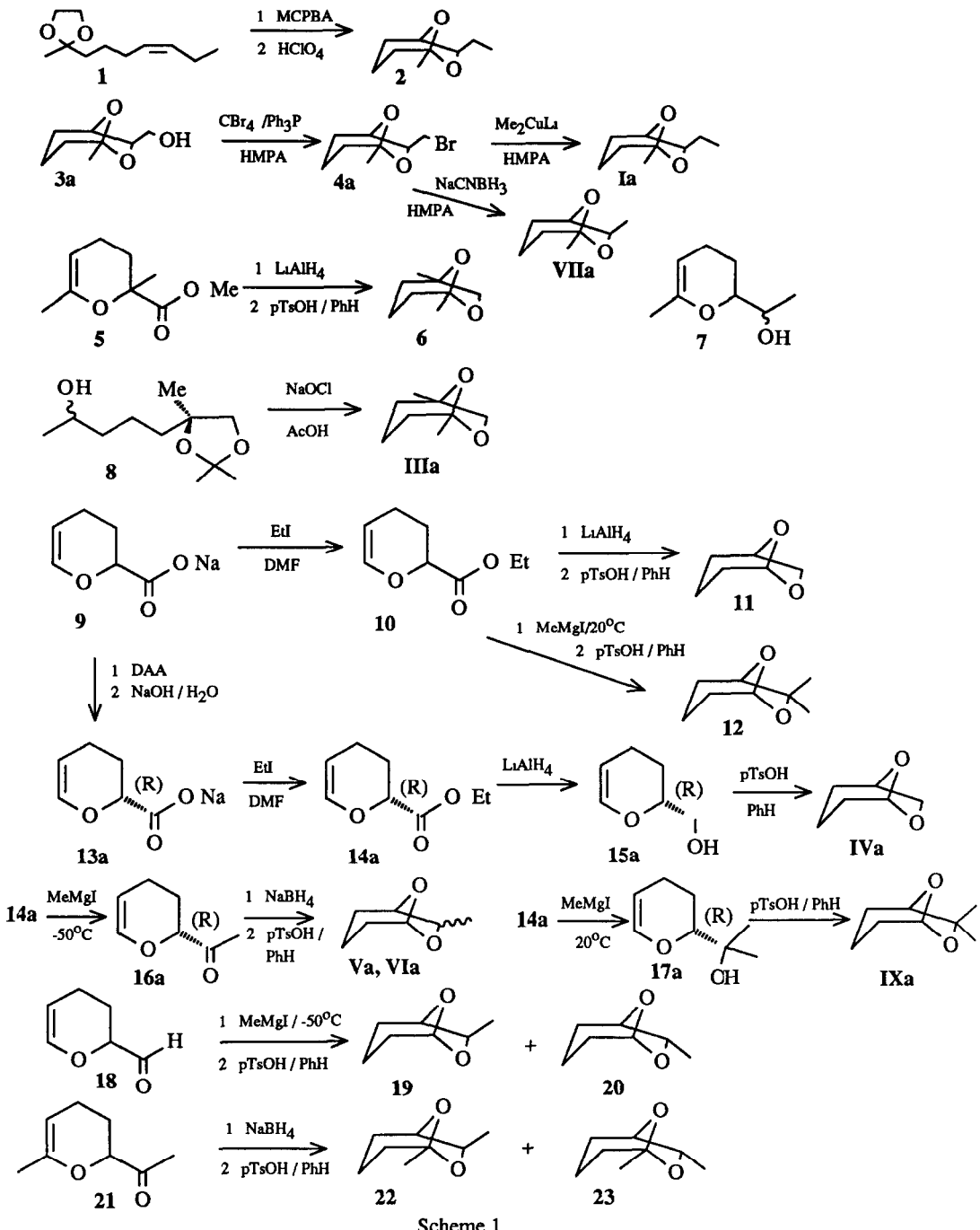
described by Mori and Sue,[15] using kinetic resolution of racemic 1-penten-3-ol by Sharpless epoxidation with diisopropyl L-(+)- and D-(-)-tartrate, respectively, and reporting an estimated optical purity of 96-97% based on the HPLC analysis of the MTPA ester of one of the intermediates Lastly, the absolute configuration of frontalin was established by Mori[16] as (+)-(1R,5S) and (-)-(1S,5R) (**IIIa** and **IIIb**, respectively) by resolution of racemic lactonic acid with quinine and cinchonine, respectively While the optical purity in this case was not stated quantitatively, the enantiomers were judged to be equally optically pure based on NMR spectra using the chiral shift reagent $Eu(facam)_3$

To confirm the absolute configurations of **IV** to **VI** and **IX** by synthetic means, we started with the resolution of the sodium salt of racemic 3,4-dihydro-2H-pyran-2-carboxylic acid (**9**) with dehydroabietylamine (DAA),[17] separating the enantiomers of the dihydropyran carboxylate with known configuration at C(2) of the dihydropyran ring (Scheme 1) Lithium aluminum hydride reduction of the ester (**14a**) derived from the (-)-(R) salt (**13a**), or Grignard reaction at -50°C to give the methyl ketone (**16a**) followed by reduction, or Grignard reaction at room temperature, afforded the primary (**15a**), secondary (not shown), or tertiary (**17a**) alcohol, respectively, which cyclized readily to the desired bicyclic ketals in mild acidic conditions [18,19] Cyclization of these (2R)-dihydropyran alcohols yields consistently the bicyclic systems with the (R) configuration at C(1), fixing simultaneously the configuration at C(5) Note that by normal convention, C(5) is designated as (S) for **IVa**, **Va**, and **VIa**, and (R) for **IXa** The antipodes of these four compounds were derived in the same manner starting with the (+)-(S) enantiomer of the sodium salt (**13b**)

The enantiomers of **IV** and **IX** were made in large enough quantities to obtain the optical rotations For **V** and **VI** it was sufficient to confirm the retention times on the chiral g c column which could then be correlated with the materials made by reaction with yeast (see below) The enantiomers of **VII** ((+)-(1R,5S,7R) and (-)-(1S,5R,7S) corresponding to **VIIa** and **VIIb**, respectively) were synthesized[1] with the procedure of Johnston and Oehlschlager[8] up to the 7-*exo* bromide (**4a** and **b**), starting with the ketal of commercially available 5-chloro-2-pentanone and utilizing asymmetric epoxidation by the Sharpless method (not shown in Scheme 1), followed by reaction with sodium cyanoborohydride with retention of configuration Since the yeast reaction described below yielded **VIIb** in very high optical purity and sufficient quantity to record the optical rotation, we surmised initially that the crucial step in the yeast reduction must also produce predominantly **VIIIa**, allowing us to assign the rotation and the corresponding chiral g c peak accordingly This assumption was verified later by the VCD spectra [20] The optical rotations and retention times are listed in Table 2

The stereoselective synthesis of **Ib**, **IIa**, **Vb**, **VIa**, **VIIb**, and **VIIIa** was achieved also with baker's yeast (*Saccaromyces cerevisiae*) using the racemic substituted dihydropyrans **21**, **26** and **28** as the precursors (Scheme 2) The Diels-Alder [4+2] cycloaddition of methyl vinyl ketone (**25**) gives **21** in a straightforward way The corresponding synthesis of **26** from acrolein (**24**) and **25** afforded four major products They were identified by g c /ms as acrolein dimer (**18**), methyl vinyl ketone dimer (**21**), and the two cross-products **26** and **27**, in the approximate ratio of 8 1 10 1, respectively, for a molar ratio of the monomers n_{24}/n_{25} = 2 5 Compound **27**, which was observed during the reaction at higher concentration but was not found after the work up, appeared to undergo a Cope rearrangement to yield **26** at high temperatures [21] The ethyl ketone **28** was prepared from **21** by an established alkylation procedure [22]

The formation of 5,7-disubstituted dioxabicyclo[3 2 1]octanes from 2-keto-dihydropyrans with



Scheme 1

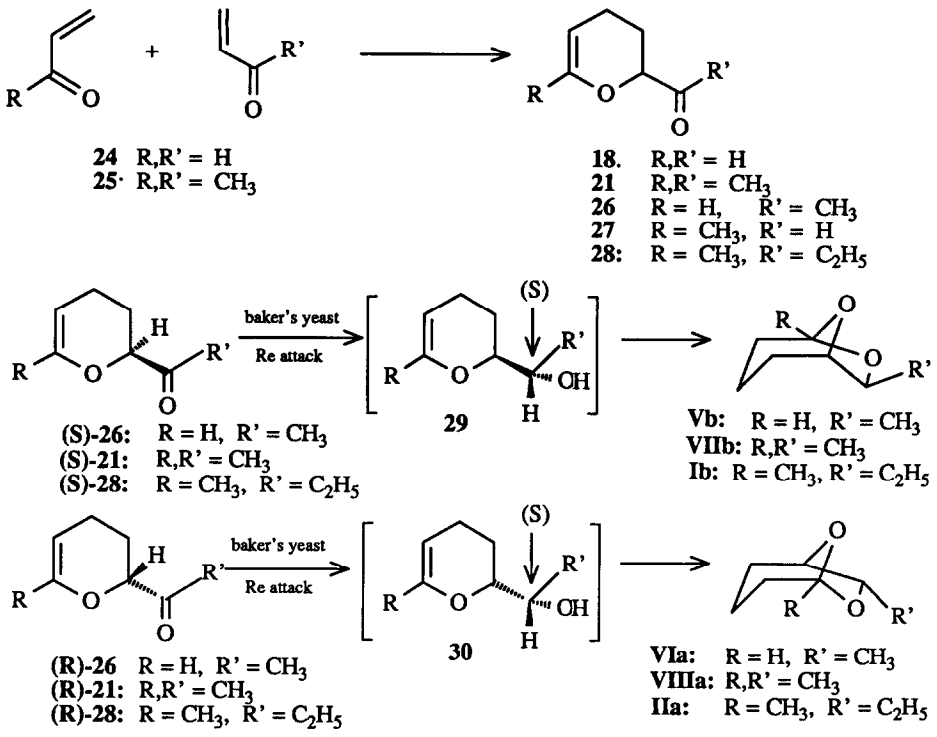
Letters "a" and "b" in combination with roman numerals refer to the enantiomers of the designated compounds, while arabic numbers indicate racemic mixtures except for **8**, **13**, **14**, **15**, **16**, and **17**

Table 2 Observed optical rotations, enantiomeric purities, and chiral column retention times

cmpd	config	$[\alpha]_D^a$ / %ee[b]				ret. time/min			chiral column[c]	
		synth		yeast		rac (c)	synth	yeast	synth.	yeast
Ia	1R,5S,7R	+ 60 3°	89 9			3 47 (4)	3 45		4	
Ib	1S,5R,7S	- 60 5°	91 0			4 35 (4)	4 36		4	
IIa	1R,5S,7S				100					
IVa	1R,5S	+113 8°	90			4 63 (1)	4 6		1	
IVb	1S,5R	- 86 8°	75[d]			4 98 (1)	no			
Va	1R,5S,7R	no	89 8			0 97 (2)	0 98		2	
Vb	1S,5R,7S			- 93 5°	99	1 35 (3)		1 41	2	3
VIa	1R,5S,7S	no	87	+ 107 0°	99	6 04 (2)	6 01	6 00	2	3
VIb	1S,5R,7R					3 58 (2)				
VIIa	1R,5S,7R	+ 58 5°	90 6			4 03 (5)	2 31			
VIIb	1S,5R,7S	no	90 4	- 65 6°	98 5	4 22 (5)	2 83	2 86	4	4
VIIIa	1R,5S,7S			+ 86 5°	100	5 1 (4)		5 24		4
VIIIb	1S,5R,7R					6 1 (4)				
IXa	1R,5R	+ 82 1°	91 4			0 80 (2)	0 76		2	
IXb	1S,5S	- 69 7°	76[e]			0 93 (2)	no		2	

[a] Conditions of measurement given in the Experimental section under the appropriate compound
[b] Determined by chiral g c unless stated otherwise
[c] Column/condition 1 Ni-Nop / 75°, 16 psi 3 Ni-Nop / 85°, 16 psi 5 Ni-4-pin / 80°, 10 psi
2 Ni-Nop / 80°, 16 psi 4 Ni-4-pin / 80°, 20 psi
[d] Based on published optical rotation of -115°
[e] Estimated on the basis of (-)-(1S,5R)-6,8-dioxabicyclo[3 2 1]octane.

baker's yeast has been reported very recently.[23] The reaction appears to be controlled by a selective enzymatic reduction from the Re face of the carbonyl group of either the dihydropyran, as shown in Scheme 2 for the purpose of demonstration, or of its ring opened form, as suggested by Ramaswamy and Oehlschlager,[23] or both These latter authors obtained nearly racemic *exo*-brevicomin, whereas we found the (-)-enantiomer in high optical purity With the exception of this detail, the two investigations generally agree with one another, suggesting that the configuration at the new chiral center after reduction, i e at the former carbonyl carbon, is always (S) yielding invariably the exo-(1S,5R,7S) and endo-(1R,5S,7S) enantiomers upon cyclization, depending upon the absolute configuration of the dihydropyran originally Consequently, the stereochemical course for both enantiomers of the racemic precursors **21**, **26** and **28** must be a selective enzymatic hydrogen transfer to the Re face to give the isolated optically pure diastereoisomers, agreeing with previous observations with baker's yeast and using other substrates [24] The intermediate alcohols **29** and **30** or the corresponding ring opened derivatives[23] cyclize very rapidly to the ketals in acidic solution and in our hands were not observed during the course of this reaction Further, we observed that the exo/endo ratios depended on the reaction time and on the pH of the yeast slurry The results presented here were obtained for unbuffered fermentation mixtures after the reduction had proceeded for two days The lower yields may be attributed to incomplete reaction and/or to biodegradation of the



Scheme 2

intermediates To our knowledge, the formation of the *exo*- and *endo*-7-methyl derivatives by means of yeast reductions has not been reported before, but seems to follow the same mechanism as for the 5,7-disubstituted analogs Incorporating **26** into a suspension of actively fermenting baker's yeast afforded a mixture of **Vb** and **VIa** in the ratio 1 3 with enantiomeric purities of at least 99% and with a total yield of the purified products of 3 7%

Comparison of the chiral g c retention times and the optical rotation signs with the corresponding data from the chemically prepared compounds allowed us to assign the absolute configurations of all the products unambiguously except **VIII** Based on the VCD spectra, optical rotation, and the chiral g c traces we believe that the (+)-enantiomer of **VIII**, which is produced in the reaction with baker's yeast, has the (1R,5S,7S) configuration (i e **VIIIa**)

EXPERIMENTAL

Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored over 3Å molecular sieves Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use Dehydroabietylamine (90+%, Aldrich) was purified before use

NMR spectra Bruker AC 200 or Perkin-Elmer R24B (60 MHz) spectrometer Analytical g c 12 foot SE30 column, Varian Model 3700 gas chromatograph connected to a Varian 4290 integrator Mass spectra VG-7070 coupled to a Shimadzu 9A g c , ionization potential 70 eV Preparative g c Varian 90P Aerograph, 8 foot carbowax column Complexation g c 25 m x 0 25 mm fused silica OV-1, 0 25 μm coated with "Chira-Metal" phase Ni-4-pin or Ni-Nop (CC&CC, FRG), splitter ratio 1 100 Optical rotations

Rudolph Autopol III automatic polarimeter, 1 cm or 1 dm cell.

Racemic exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2 1]octane (exo-brevicomin, 2)

(Z)-Non-6-ene-2-one ethylene ketal (**1**)[25] was epoxidized with m-chloroperbenzoic acid and the resulting epoxy ketal was stirred with dilute $HClO_4$ to give, after work up, crude product Purification by flash chromatography (ether in pentane) gave pure *exo*-brevicomin, b p 79-80°/30 mm (lit.[25] 70°/20 mm), ^1H nmr (200 MHz, $CDCl_3$) δ 4 14 (broad s, 1H), 3 94 (t, 1H), 1 45-2 06 (m, 8H), 1 43 (s, 3H), 0 95 (t, 3H), ^{13}C nmr (200MHz, $CDCl_3$) δ 108, 81 1, 78 3, 35, 28 6, 28, 25, 17 2, 9 7 ppm, ms, m/e (%) molecular ion 156 (9), major fragments 114 (76), 98 (26), 86 (23), 85 (60), 43 (100)

Exo-(1R,7S)-7-(bromoethyl)-5-methyl-6,8-dioxabicyclo[3.2 1]octane (4a)

A solution of (1R,7R) alcohol (**3a**) was treated with CBr_4 and triphenylphosphine in HMPA [8] After the usual work up the product (**4a**) was isolated by distillation, b p. 76-79°/0 1 mm (lit [8] 82-85°/0 1 mm) The NMR spectrum was identical to the reported one The (-)-exo-(1S,7R) antipode was made as above from the corresponding (1S,7S) alcohol

Exo-(1R,5S,7R)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2 1]octane ((+)-exo-brevicomin, Ia)

An ether solution of methyllithium (120 mL, 1 4 M, 0 166 mol) was added dropwise to purified cuprous iodide in ether (300 mL) under N_2 The resulting orange solution was then treated with a solution of **4a** (12 8 g, 0 058 mol) in dry HMPA (80 mL) [8] The reaction mixture was stirred under N_2 for 48 hours and then poured into saturated NH_4Cl solution The ether layer was separated and the aqueous layer was extracted with ether The extracts were combined, washed with water and saturated NaCl, and dried ($MgSO_4$) After removing the solvent by fractionation, the residue was distilled to give 3 4 g (54%) of 95% pure **Ia**, b p 67-69°/20 mm (lit [3] 60-62°/15 mm), $[\alpha]_D^{22}$ +60 3° (c 2 42, $CHCl_3$) (lit [8] +59 0 ± 0 5° (c 2 5, $CHCl_3$)), complexation g c (Ni-4-pin) showed 89 9% ee

(-)-*Exo*-brevicomin (1S,5R,7S, **Ib**) was made in 59% yield from the corresponding (-)-(1S,5R)-*exo* bromide (**4b**), b p 67-70°/20 mm, $[\alpha]_D^{22}$ -60 8° (c 1 2, $CHCl_3$) (lit [8] -60 5 ± 0 5° (c 2 3, $CHCl_3$)), chemical purity 97%, complexation g c (Ni-4-pin) showed 91% ee

Racemic 1,5-dimethyl-6,8-dioxabicyclo[3.2 1]octane (frontalin, 6)

The reaction of methyl vinyl ketone and methyl methacrylate at 180° gave a mixture of methyl vinyl ketone dimer (**21**) and ester **5** Attempts to separate the mixture were unsuccessful The mixture was then treated with sodium borohydride to reduce the dimer The resulting mixture containing alcohols **7** and ester **5** was easily separated by flash chromatography (ether in pentane) The pure ester **5** (31 g, 0 183 mole) was reduced with $LiAlH_4$ (8 1 g, 0 213 mol) in ether After the usual work up the crude product was cyclized using p-tosic acid in benzene Racemic frontalin was obtained in 86% yield, b p 64-65°/37 mm (lit [26] 76-78°/50 mm), chemical purity >97% ^1H nmr (200 MHz, $CDCl_3$) δ 3 92 (d, 1H), 3 46 (m, 1H), 1 13-2 12 (m, 6H), 1 45 (s, 3H), 1 35 (s, 3H), ^{13}C nmr (200 MHz, $CDCl_3$) δ 108, 80, 74 2, 34 6, 34, 24 7, 23, 18 ppm

(1R,5S)-1,5-Dimethyl-6,8-dioxabicyclo[3 2 1]octane ((+)-frontalin, IIIa)

A mixture of the (2R) dioxolane **8** (7 6 g, 0 038 mol) in glacial acetic acid (33 mL) was treated with

5% sodium hypochlorite (53 mL) [27] The reaction mixture was stirred at room temperature overnight and at 50° for 5 hours It was diluted with water and extracted with ether The combined extracts were washed successively with 5% NaOH, water, and saturated NaCl After drying ($MgSO_4$) and removal of the solvent, the residue was distilled to give 2 8 g (52 4%) of >98% pure **IIIa**, b p 67-72°/30-35 mm (lit [27] 65-67°/30 mm), $[\alpha]_D^{22}$ +54 1° (c 4 5, ether) (lit.[27] +50 7° (c 4 6, ether); complexation g c (Ni-Nop) showed 95% ee

(-)-(1S,5R)-Frontalin (**IIIb**) was made in the same manner in 51% yield, b p 78-79°/45 mm (lit [27] 66-67°/30 mm), $[\alpha]_D^{22}$ -55 2° (c 4 7, ether) (lit[27] -52.9° (c 4 7, ether)), complexation g c (Ni-Nop) showed 96% ee

Racemic 6,8-dioxabicyclo[3.2 1]octane (11)

Racemic sodium 3,4-dihydro-2H-pyran-2-carboxylate (**9**) was converted to the corresponding ethyl ester (**10**) in 90% yield [17] $LiAlH_4$ reduction of this ester and subsequent cyclization gave racemic **11** in 57% yield, m p. 45-47° (lit [27] 49°), ^1H nmr (200MHz, $CDCl_3$) δ 5 5 (broad s, 1H), 4 49 (m, 1H), 3 95 (d, 1H), 3 77 (t, 1H), 1 3-2 05 (m, 6H), ^{13}C nmr (200 MHz, $CDCl_3$) δ 101 7, 73 4, 68 0, 31 1, 28 7, 15 4 ppm, ms, m/e (%) molecular ion 114 (18), major fragments 86 (27), 68 (40), 58 (32), 57 (100), 41 (25)

Resolution of racemic sodium 3,4-dihydro-2H-pyran-2-carboxylate (9)

The resolution of racemic **9** with purified dehydroabietylamine was carried out according to the published procedure [17] The resulting crude salt was recrystallized five times from methanol to give white crystals of the (R) salt of DAA, m p 169-170° (lit [17] 173-177°), $[\alpha]_D^{22}$ +11 7° (c 1 05, ethanol) (lit [17] +10 7° (c 1 06 ethanol))

Partially resolved (S) salt was obtained from concentrating the mother liquor of above recrystallizations followed by two recrystallizations from ether/pentane to give about 75% ee salt

(R)-Ethyl-3,4-dihydro-2H-pyran-2-carboxylate (14a)

A solution of the (R) salt of DAA (43 5 g, 0 134 mol) and sodium hydroxide (5 5 g, 0 138 mole) in water (100 mL) was shaken vigorously until all the crystals dissolved The aqueous layer was separated, extracted with ether and concentrated to dryness The resulting (R) sodium salt (**13a**) (19 g, 0 127 mol) was heated in DMF (150 mL) at 70-80° and treated with ethyl bromide (38 8 g, 0 205 mole) The reaction mixture was heated at 70-80° for 3 hours, cooled and added to water The product was isolated by extraction with ether Pure (R) ester (**14a**) was obtained in 18% yield by flash chromatography (ether/pentane) of the crude material, $[\alpha]_D^{22}$ - 63 4° (c 0 17, ethanol) (lit [17] -69 3° (c 1 53, ethanol)) The NMR was identical to the racemic ester

The (S) ester (**14b**) was made in a similar way with the exception that methyl iodide was used, $[\alpha]_D^{22}$ +55 6° (c 0 18, ethanol)

(1R,5S)-6,8-dioxabicyclo[3 2 1]octane (IVa)

A solution of (R)-ester **14a** (2 3 g, 0 015 mol) in ether was added to an ether solution of $LiAlH_4$ (0 61 g, 0 16 mol) After the usual work up and concentration, the resulting alcohol (**15a**) was cyclized with p-tosic acid in benzene Pure **IVa** was obtained in 35% yield as a white solid, $[\alpha]_D^{22}$ +113 8° (c 0 72, n-hexane) (lit [17] +111 4° (c 0 75, n-hexane)), complexation g c (Ni-Nop) >90% ee

The (1S,5R) antipode (**IVb**) was made as described above, $[\alpha]_D^{22}$ -86 8° (c 0 72, n-hexane) (lit [29] -115° (c 0 41, hexane))

Racemic exo- and endo-7-methyl-6,8-dioxabicyclo[3 2 1]octane (19 and 20)

The reaction of acrolein dimer (**18**) with methyl magnesium iodide in ether gave, after work up and distillation, a mixture of threo and erythro alcohols, b p 72-75°/12 mm (lit [30] 73-75°/13 mm) The mixture was cyclized with p-tosic acid in benzene to **19** and **20**, respectively Prep g c separated the two isomers to a purity of >98% ^{1}H nmr (200 MHz, $CDCl_3$) *exo* δ 5 55 (broad s, 1H), 4 23 (q, 1H), 4 03 (broad s, 1H), 1 40-2 03 (m, 6H), 1 22 (d, 3H), *endo* δ 5 50 (5 50, broad s, 1H), 4 10-4 21 (m, 2H), 1 40-2 05 (m, 6H), 1 37 (d, 3H), ^{13}C nmr (200 MHz, $CDCl_3$) *exo* δ 102 5, 78 5, 75, 31, 28 6, 21 5, 16 1, *endo* δ 101 8, 75 7, 75 1, 30 3, 24 3, 15 8, 13 5 ppm, ms, m/e (%) *exo* molecular ion 128 (4), major fragments 86 (10), 68 (9), 58 (11), 43 (100), 41 (16), *endo* molecular ion 128 (13), major fragments 84 (33), 71 (100), 67 (35), 57 (51), 43 (34)

(1R,5S,7R)-exo- and (1R, 5S, 7S)-endo-7-methyl-6,8-dioxabicyclo[3 2 1]octane (Va and VIa)

A solution of (R)-ester **14a** (1 3 g, 0 0084 mol) in ether (5 mL) was added to a cooled solution (-50°) of methyl magnesium iodide in ether, made from magnesium (0 41 g, 0 017 mol) and methyl iodide (3 6 g, 0 025 mol) When the addition was complete the reaction mixture was immediately quenched with saturated NH_4Cl solution The ether layer was separated and the aqueous phase was extracted with ether The combined extracts were dried and the solvent was removed fractionally G c analysis of the residue showed the presence of the (R)-ketone **16a** (14%), (R)-alcohol **17a** (26%), and unreacted (R)-ester **14a** (40%) The desired ketone **16a** was isolated from the mixture by flash chromatography (ether/pentane) Reduction of **16a** with $NaBH_4$ followed by cyclization of the resulting alcohols with p-tosic acid in benzene gave a mixture of **Va** and **VIa** Complexation g c (Ni-Nop) showed 89 8% ee for **Va** and >87% ee for **VIa**

Racemic 7,7-dimethyl-6,8-dioxabicyclo[3 2 1]octane (12)

Racemic ethyl ester **10** was added at room temperature to excess methyl magnesium iodide in ether The resulting alcohol was cyclized with p-tosic acid in benzene to give **12** in 73% yield Final purification by prep g c gave >98% pure sample ^{1}H nmr (200 MHz, $CDCl_3$) δ 5 49 (broad s, 1H), 3 32 (broad s, 1H), 1 46-2 13 (m, 6H), 1,42 (s, 3H), 1 28 (s, 3H), ^{13}C nmr (200MHz, $CDCl_3$) δ 102, 80 4, 76 5, 30 2, 29, 25, 20 5, 15 6 ppm

(1R,5R)-7,7-Dimethyl-6,8-dioxabicyclo[3 2 1]octane (IXa)

A solution of (R)-ester **14a** (0 70 g, 0 0064 mol) in ether was added at room temperature to an ether solution of methyl magnesium iodide, made from magnesium (0 31 g, 0 013 mol) and methyl iodide (2 73 g, 0 019 mol) After heating under reflux for 1 hour, the reaction mixture was worked up in the usual manner and the resulting (R)-alcohol **17a** was cyclized with p-tosic acid in benzene Prep g c gave 0 66 g of >98% pure **IXa**, $[\alpha]_D^{22}$ +82 1° (c 0 78, $CHCl_3$), complexation g c (Ni-Nop) showed 91% ee

The (S)-ester (**14b**) was converted in the same manner to the (1S,5S) antipode, $[\alpha]_D^{22}$ -69 7° (c 0 75, $CHCl_3$) This rotation value represents about 75-77% ee optical purity

Racemic exo- and endo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (22 and 23)

Methyl vinyl ketone was heated at reflux temperature for 6 days[31] and the dimer (**21**) was isolated by distillation (40% yield), b p 66-69°/20 mm, ^{1}H nmr (60MHz, CCl_4) δ 4 24 (broad m, 1H), 3 89 (m, 1H), 2 0 (s, 3H), 1 74 (broad m, 4H), 1 58 (s, 3H), ms, m/e (%) molecular ion 140 (14), major fragments 97 (76), 69(15), 43 (100), 41 (72), 27 (18) Reduction of **21** with $NaBH_4$ in methanol gave a mixture of threo and erythro alcohols (**7**) which were cyclized with p-tosic acid in benzene to give a crude mixture of **22** and **23**, respectively, b p 54-60°/25 mm (lit [32] 48°/15 mm) Prep g c. gave pure (>98%) exo and endo isomers ^{1}H nmr (200 MHz, $CDCl_3$) *exo* δ 4 14 (broad s, 1H), 3 94 (t, 1H), 1 45-2 06 (m, 8H), 1 43 (s, 3H), 1 20 (d, 3H), *endo* δ 4 11-4 25 (m, 2H), 1 50-2 05 (m, 6H), 1 41 (s, 3H), 1 32 (d, 3H), ^{13}C nmr (200 MHz, $CDCl_3$) *exo* δ 108, 80 1, 75 8, 35, 27 7, 25.3, 21 9, 17 1, *endo* δ 107 77 4, 75 5, 34.3, 24 9, 23 6, 17 3, 13 8 ppm, ms, m/e (%) *exo* molecular ion 142 (2), major fragments 100 (30), 72 (16), 71 (33), 55 (12), 43 (100), *endo* molecular ion 142 (10), major fragments 98 (25), 72 (44), 71 (27). 43 (100), 41 (23)

(1R,5S,7R)-exo-5,7-dimethyl-6,8-dioxabicyclo[3 2 1]octane (VIIa)

Sodium cyanoborohydride (3 4 g, 0 054 mol) was added to a solution of the (1R,7S)-*exo*-bromide **4a** (3 0 g, 0 013 mol) in dry HMPA [33] The reaction mixture was heated at 105-110° for 3 days, cooled, and added to water The product was extracted with ether and the extracts were washed with water and dried ($MgSO_4$) The solvent was removed fractionally and the residue was distilled to give 3 0 g of **VIIa**, b p 82-90°/80 mm Prep g c gave a sample of 99% purity, $[\alpha]_D^{22}$ +58 5° (c 0 94, $CHCl_3$), complexation g c (Ni-4-pin) showed 90 6% ee

The (1S,5R,7S) antipode was made as above, chemical purity 98%, 90 4% ee by complexation g c (Ni-4-pin)

2-Acetyl-3,4-dihydro-2H-pyran (26)

Methyl vinyl ketone (30 g, 0 43 mol) and acrolein (60 g, 1 1 mol), both freshly distilled, and hydroquinone (1 g) were dispersed in 160 mL of benzene The emulsion was heated in a 2 L Parr bomb at 190° for 2 hours and subsequently concentrated The crude mixture contained 17 1 g (32%) of **26** and was vacuum distilled to remove the polymers The distillate collected between 28 to 66° (30 mm) was distilled twice with a spinning band column (20 cm x 6 mm, R ≈ 1 12) The fraction boiling at 77-78° (35 mm) was used for the microbial reduction (9 8 g, 18%), purity 97% by g c , ^{1}H nmr (60 MHz, $CDCl_3$) δ 6 46 (m, 1H), 4 71-4 89 (m, 1H), 4 16-4 37 (m, 1H), 2 26 (s, 3H), 2 03 (broad, 4H), ms m/e (%) molecular ion 126 (23), major fragments 83 (100), 55 (69), 43 (54), 29 (28), 27 (21)

2-Propionyl-6-methyl-3,4-dihydro-2H-pyran (**28**)

The synthesis was carried out following the procedure given by Chaquin et al [22] with 21 g (0 15 mol) of **21** The product from the first step was vacuum distilled and 22 7 g (68 6%) of imine still containing some starting material were obtained The imine (14 g, 0 063 mol) was used without further purification for the alkylation with equimolar amounts of ethyl magnesium bromide and methyl iodide as described [22] Distillation yielded 4 6 g of a mixture containing 75% of **28** (36% yield) and 25% of **21** This mixture was used directly in the yeast reduction step ^{1}H nmr (60 MHz, $CDCl_3$) δ 4 62-4 45 (m, 1H), 4 39-4 16 (m, 1H), 2 63 (q, 2H), 1 96 (broad, 4H), 1 79 (s, 3H), 1 06 (t, 3H), ms (from g c /ms of the product mixture), m/e (%)

molecular ion 154 (23), major fragments 97 (90), 69 (27), 43 (100), 41 (88), 27 (50)

*Yeast reductions (**Ib, IIa, Vb, VIa, VIIb, VIIIa**)*

Typically 10 g of racemic precursor (**21**, **26**, or **28**) were added to a suspension of actively fermenting baker's yeast (60 g of Fleischmann's fast rising dry yeast) and sucrose (126 g) in deionized unbuffered water (800 g) open to air. After 20 hours, another 20 g of sucrose were added and the reaction was stopped after 46 hours The slurry was divided into four batches which were centrifuged The supernatant from each batch was extracted with diethyl ether (3x100 mL) Most of the solvent was evaporated with a rotavapor and the remaining liquid dried with molecular sieves (3 Å) This solution was distilled with a small Vigreux column to yield a relatively small sample containing a mixture of exo and endo isomers and ether The separation and final purification were achieved by preparative g c

Products **21** gave **VIIIa** and **VIIb** in the ratio of 1 1 8 in the crude mixture, yielding after prep g c 100 and 98 5% ee optical purity (98 and 100% chemically pure), respectively, with a total yield of 3 6% relative to the precursor; **26** afforded **VIa** and **Vb** in the ratio of 3 1 before work up, yielding 0 35 and 0 10 g (80 and 87% chemical purity) of the products, respectively, corresponding to a total yield of 3 7%, another purification step with prep g c gave 0 15 g of 98 7% pure **VIa**, enantiomeric purities of both isomers were 99% or better, the mixture of 75% **28** and 25% **21** yielded after purification and isolation **Ib** and **IIa** in the ratio 1 12, and **VIIb** and **VIIIa** in the ratio 1 1 3, with enantiomeric purities of 99, 100, 93, and 99% ee, respectively Infrared absorption and mass spectra of all products were identical to those of the corresponding racemic compounds

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