Asymmetric Microbial Reduction of Tetralones

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The reduction of α- and β-tetralones [3,4-dihydronaphthalen-2(1*H*)-ones] and of 4-substituted-α-tetralones with *Sporobolomyces pararoseus* and *Rhodotorula rubra* is described. Both strains were grown in well aerated fermentors, in some cases improving the conversion yields up to 100%, and modifying the known selectivity of the reductions performed with *S. pararoseus*. All the reductions performed with *R. rubra* are enantioselective giving rise to (*S*)-alcohols, but they are weakly influenced by substituents at the 4-position. With this strain (*S*)-β-tetralol could be obtained with 90% ee and 100% conversion yield. Reductions performed with *S. pararoseus* are not enantioselective giving rise to (*S*)- and (*R*)-alcohols indicating the possible action of two reductases. These two reductases are strongly influenced by substituents at the 4-position, allowing only *anti* entry of the hydride, giving rise to *cis*-alcohols. *cis*-(1R,4R)-4-Methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthol **12** could be obtained enantiomerically pure with an excellent conversion yield. The crystal structure of the Mosher ester derivative of compound **12** is described.

α- and β-Tetralols (1,2,3,4-tetrahydro-1-naphthols) and their derivatives are useful molecules as starting material for the synthesis of drugs, since they can be converted easily into other functions. For example, a series of 1-(methylamino)-4-aryltetralines has been studied as antidepressants, of which the most promising is the 4-(3,4-dichlorophenyl)-derivative.[1] Of the four possible isomers only the *cis*-(1*S*,4*S*)-isomer showed high selectivity for serotonin uptake. This result and the fact that the development of chirally pure drugs is of great current interest in the pharmaceutical industry prompted us to investigate an enantioselective synthesis of β-tetralols, and of 4-substituted-α-tetralols. We have attempted to synthesize these tetralols by asymmetric microbial reductions of the corresponding tetralones.

Ziffer *et al.*[2] had already investigated the microbial reduction of different hydroaromatic ketones and more particularly α-tetralone using *Sporobolomyces pararoseus* and *Cryptococcus macerans*. They found that the microbial reductions afforded (*S*)-alcohols following the rule formulated by Prelog.[3] Moreover substituents near the carbonyl group have been shown to decrease the reduction yields without any alteration of the configuration of the alcohols produced. However conversion yields are generally low and nothing was described on the reduction of β-tetralones, and of α-tetralones substituted at the 4-position.

In this paper we wish to report on the growing conditions allowing improved conversion yields, the stereochemistry of the microbial reduction of β-tetralone, and the influence of substituents on the reduction of 4-substituted-α-tetralones.

Results and Discussion

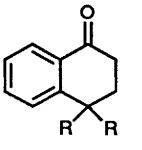
In order to study the enantioselectivity of the microbial reduction of β-tetralone, and the influence of substituents on the stereochemistry of the reduction of 4-substituted-α-tetralones, we have used *S. pararoseus* (ATCC 11386) and *Rhodotorula rubra* (ATCC 4056) which is a microorganism related to *C. macerans*. Since the conversion yield of the reduction of α-tetralone with *C. macerans* reported by Ziffer were rather low, we intended to improve this yield by modification of the culture conditions classically used by this author. Therefore, we have used a well-aerated fermentor which allowed a rapid growth of the strain, and after 30 h the aeration was stopped and the culture medium transferred into Erlenmeyer flasks for the bioconversion step.

Table 1 Reduction of achiral tetralones

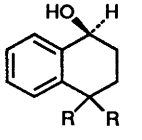
Ketone	Strain	Conversion (%)	Alcohol $[\alpha]_D^{25}$	Alcohol ee (%)	Alcohol Abs. conf.
1a	*R. Rubra*	53	+23[a]	96[b]	*S*
1a	*S. para*	90	−6[a]	23	*R*
1b	*R. rubra*	40	+17	98[b]	*S*
1b	*S. para*	55	−5.6	64[b]	*R*
2	*R. rubra*	100	−55[d]	90[c]	*S*
2	*S. para*	81	0	0	

[a] Lit.,[2] +26.8 ($CHCl_3$). [b] Measured by GC using a chiral column. [c] Measured by GC and ^{19}F NMR spectroscopy of Mosher ester derivatives. [d] Lit.,[5] −72 (*c* 1.6, EtOH).

Table 1 summarizes the results of the microbial reduction of ketones **1a**, **1b** and **2**[4] which do not contain an asymmetric carbon. Both strains gave rise to alcohols with fairly good conversion yields, in particular ketone **2** was quantitatively converted with *R. rubra*. According to the results described by Ziffer[2] reduction of ketone **1a** by *R. rubra* produces (*S*)-**6a**[5]

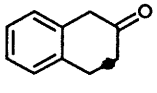


1a R = H
1b R = Me



(*S*)-**6a** R = H
(*S*)-**6b** R = Me

with 96% ee. *S. pararoseus* produced the other enantiomer (*R*)-**6a** which was surprising since all the literature results had reported that this strain produces the (*S*)-enantiomer. A similar observation was made regarding the reduction of β-tetralone **2**. *R. rubra* produced the enantiomer (*S*)-7[6] with 90% ee, while *S.*



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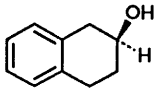
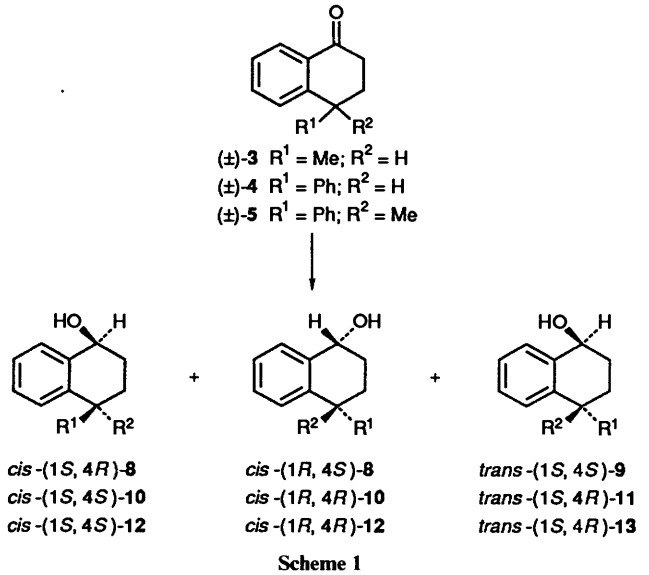


(*S*)-**7**

Table 2 Reduction of chiral tetralones

Ketone	Strain	Conversion (%)	Alcohol	Residual ketone
(±)-3	*R. rubra*	44	*c*-(1*S*,4*R*)-**8** (67%)[a]	4*S*[b]
			t-(1*S*,4*S*)-**9** (33%)	(ee 23%)
	S. para	60	*c*-(1*R*,4*S*)-**8** (67%)[c]	4*R*[d]
			c-(1*S*,4*R*)-**8** (33%)	(ee 38%)
(±)-4	*R. rubra*	34	*c*-(1*S*,4*S*)-**10**	(73%)
			t-(1*S*,4*R*)-**11**	(27%)
	S. para	30	*c*-(1*R*,4*R*)-**10** (60%)[e]	?[f]
			c-(1*S*,4*S*)-**10**	(40%)
(±)-5	*R. rubra*	22	*c*-(1*S*,4*S*)-**12**	(73%)[g]
			t-(1*S*,4*R*)-**13**	(27%)
	S. para	45	*c*-(1*R*,4*R*)-**12**[h]	4*S*[i]

[a] Determined by NMR spectroscopy. [b] Determined by GC using a chiral column, observed $[\alpha]_D^{25}$ −7 (*c* 2.5, MeOH), lit.,[7] $[\alpha]_D^{25}$ −15.4 (*c* 3.4, dioxane). [c] Determined by ^{19}F NMR spectroscopy of the Mosher esters, $[\alpha]_D^{25}$ −1.4 (*c* 2.5, MeOH). [d] Chiral GC, observed $[\alpha]_D^{25}$ +7 (*c* 2.5, MeOH). [e] $[\alpha]_D^{25}$ of the mixture −17 (*c* 2, EtOH). [f] $[\alpha_D^{25}$ +37 (*c* 2, EtOH). [g] GC and ^1H NMR spectroscopy, *cis* and *trans* diastereoisomers have ee >98% determined by ^{19}F NMR spectroscopy of the Mosher esters. [h] Determined by X-ray structure of the Mosher ester, ee >98%, $[\alpha]^{25}$ −43 (578), −49 (546), −82 (436) (*c* 2.5, MeOH). [i] $[\alpha]^{25}$ −2.4 (578), +1.7 (546), +70 (436) (*c* 2.5, MeOH).



Scheme 1

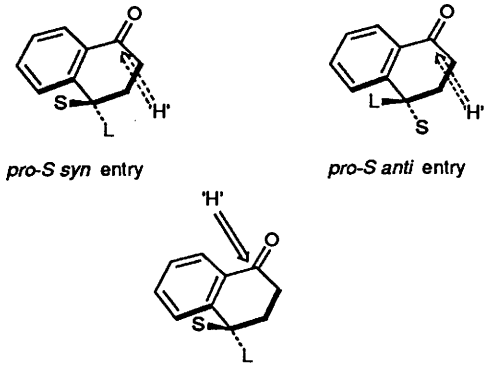


Fig. 1

pararoseus gave the racemic tetralol **7**. These two sets of results highlight first that the influence of the aromatic ring is still strong in the β-position to the ketone for the *R. rubra* reductase, and second that in our culture conditions, the reduction by *S. pararoseus* should occur by two reductases which have opposite enantioselectivities. Since the reduction by *R. rubra* of **2** occurs quantitatively, this method could be a good enantioselective preparative method for β-tetralol (*S*)-**7**.

The reduction of 4,4-dimethyl-1-tetralone **1b** with *R. rubra* produced an alcohol **6b**[7] (98% ee) found to have an optical rotation of opposite sign compared with that of the alcohol produced with *S. pararoseus*. As the reductions of tetralones with *R. rubra* are in good agreement with literature results and with Prelog's rule, we assumed that the laevorotatory alcohol produced by reduction of **1b** with this strain has the *S* configuration. With this assumption, it appears that the reductase from *S. pararoseus* which produced the *S*-alcohol is more sensitive to substituents at the 4-position than is the other reductase since this strain gives rise preferentially to the alcohol (*R*)-**6b** with 65% ee.

With ketones **3**–**5** which have an asymmetric carbon at the 4-position (Scheme 1), the two faces of the molecules are not sterically equivalent since the substituents R^1 and R^2 have different sizes. As reduction of the carbonyl group can yield both *cis*- and *trans*-isomers, we were interested in determining whether one or two stereoisomers were formed and also in determining the absolute configuration of the products. The stereochemistry of the alcohols *cis*-**8** and *trans*-**9** yielded by reduction of the 4-methyltetralone (±)-**3** was assigned from their NMR spectra[8] (Table 2). Reduction with *S. pararoseus* yielded only *cis*-**8** alcohol with a conversion yield of 60%, while *cis*-**8** and *trans*-**9** isomers (67:33) were produced by reduction with *R. rubra* with a conversion yield of 44%. The Mosher esters analysis showed that the *cis*-**8** alcohol produced by *S. pararoseus* reduction is a mixture of the two enantiomers, while the *cis*-**8** and *trans*-**9** alcohols produced by *R. rubra* reduction are enantiomerically pure. The absolute configuration of each alcohol was deduced from the enantiomeric composition of the corresponding unchanged ketone already described. The unchanged ketone from the *R. rubra* reduction of (±)-**3** has the 4*S*-configuration (23% ee),[9] and that from the *S. pararoseus* reduction has the 4*R*-configuration (38% ee). Therefore we deduced that *R. rubra* reduction produced the alcohols *cis*-(1*S*,4*R*)-**8** and *trans*-(1*S*,4*S*)-**9**, and that *S. pararoseus* reduction produced *cis*-(1*R*,4*S*)-**8** with 34% ee. In other words, these results show that the reductase from *R. rubra* which is *pro-S* enantioselective, is not diastereoselective but the rate of the reduction is influenced by the substituent at the 4-position, since the *trans*-(1*S*,4*S*) isomer resulting from the *pro-S syn* entry of the 'hydride' is less produced than is the *cis*-(1*S*,4*R*) isomer resulting from the less hindered *pro-S anti* entry (Fig.1). On the other hand the *pro-S* and *pro-R* reductases of *S. pararoseus* are diastereoselective since only the less hindered *anti* entry of the 'hydride' occurs (Fig. 1).

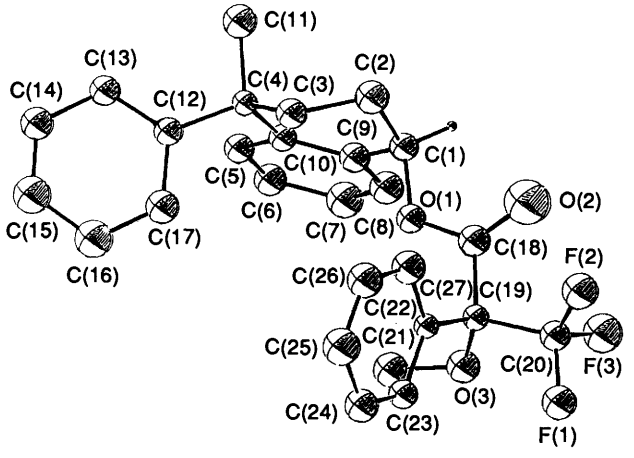


Fig. 2 Crystal structure of the Mosher ester of compound **12**

Synthesis of the unknown ketone **5** was performed classically by oxidation of 1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene [10] with sodium persulfate and copper(II) sulfate.

The reduction of (±)-**5** with *S. pararoseus* produced only the *cis* diastereoisomer **12** with a conversion yield of 45%. X-Ray analysis of the Mosher ester (Fig. 2) allowed us to attribute to this compound the *cis*-(1*R*,4*R*)-configuration, and ^{19}F NMR spectroscopic analysis showed it to be 98% ee.

The reduction of (±)-**5** with *R. rubra* produced a mixture of *cis*-**12** (73%) and *trans*-**13** (27%) alcohols as determined by ^1H NMR spectroscopy and gas chromatography, with a conversion yield of only 22%. ^{19}F NMR spectroscopy of the Mosher esters of the mixture showed that each stereoisomer has an ee of 98%. These results confirm the previous observations showing that *R. rubra* has only one enantioselective *pro-S* reductase albeit nondiastereoselective and influenced by the size of the substituents at the 4-position. Of the two reductases of *S. pararoseus*, only the *pro-R* is active in a diastereoselective way, giving rise to almost enantiomerically pure alcohol *cis*-(1*R*,4*R*)-**12**, corresponding to *anti* entry of the hydride. This method is a good asymmetric synthesis of this particularly complex tetralol.

The reduction of (±)-**4** with *R. rubra* gave rise to a mixture of two alcohols **10** and **11** in a 73:27 ratio as indicated by gas chromatography and ^1H NMR spectroscopy, while the reduction of (±)-**4** by *S. pararoseus* afforded only the major product **10**. The configuration of both alcohols was deduced from the chemical shift of the proton on the 4-position. As seen from Table 3, the protons of the 4-methyl group have different chemical shifts depending whether the methyl is *cis* or *trans* with respect to the hydroxy group: in all cases the protons of the *cis*-methyl appear at lower field. Likewise, for alcohols **8** and **9** the proton directly attached to carbon-4 appears at lower field when it is *cis* with respect to the hydroxy group. For alcohols **10** and **11**, the 4-H proton appears as a triplet at 4.05 and 3.91 ppm, respectively. The results reported in Table 3, allow the attribution of the triplet at 4.05 ppm to the *trans*-alcohol **11** and the triplet at 3.91 ppm to the *cis*-alcohol **10**.

The two alcohols **10** and **11** obtained with *R. rubra* are found to be enantiomerically pure using their Mosher esters. Considering that this strain is *pro-S*-enantioselective, we have deduced that the alcohol **10** has the absolute configuration (1*S*,4*S*), and the alcohol **11** the absolute configuration (1*S*,4*R*). The crude mixture of the two diastereoisomers was fractionated by thin layer chromatography in two fractions **a** (93:7), $[\alpha]_D^{25}$ +54.8* (*c* 0.79, EtOH) and **b** (2:98), $[\alpha]_D^{25}$ −9 (*c* 0.2, EtOH) of the alcohols **10** and **11**. For the alcohol *cis*-(1*S*,4*S*)-**10** the calculated $[\alpha]_D^{25}$ value is +60 and for the alcohol *trans*-(1*S*,4*R*)-**11** this value is −10.

Table 3 ^1H NMR spectroscopic chemical shifts of the protons of the 4-methyl or at the 4-position

Alcohol	δ_H
6b	1.24, 1.31
8	(CH_3) 1.31
9	(CH_3) 1.22
8	(H) 2.75
9	(H) 2.86
12	1.70
13	1.80

The Mosher ester method also indicated that the alcohol **10** obtained with *S. pararoseus* is a 60:40 mixture of the two *cis* enantiomers (1*R*,4*R*) and (1*S*,4*S*).

From the results described here three conclusions can be drawn. First, compared with the culture conditions reported by Ziffer, our well aerated conditions have probably greatly modified the metabolism of *S. pararoseus* since this strain produced two reductases of opposite enantioselectivity. Second, the *pro-S* reductase from *R. rubra* is weakly influenced by substituents at the 4-position since *syn* and *anti* entry of hydride can occur, whereas the two reductases from *S. pararoseus* are highly sensitive to this substitution since the *syn* entry is forbidden. Moreover the *pro-S* reductase of *S. pararoseus* is completely inhibited by the strain hindrance introduced when the 4-position is disubstituted. Finally, our culture conditions are well suited to obtaining some tetralols with both fairly good ee and conversion yields, allowing us to propose this method as a practical asymmetric synthesis of those alcohols.

Experimental

Culture Conditions.—A 1 dm^3 Erlenmeyer flask containing a solution (200 cm^3) of 2% yeast extract, 2% peptone, 2% malt extract and 3% glucose was inoculated with *S. pararoseus* or *R. rubra* and stirred (150 rpm) at 28 °C for 48 h. These cultures were used for inoculating the fermentors. A well-aerated (4 dm^{-3} min^{-1}) 7.5 dm^3 fermentor containing the culture medium (4 dm^3), inoculated with preculture (120 cm^3) was vigorously stirred (500 rpm) at 28 °C for 28 h.

Microbiological Reductions (General Procedure).—To a 2 dm^3 Erlenmeyer flask containing culture (1 dm^3) was added tetralone (1 g) and the flask was stirred (150 rpm) at 28 °C for 8 h. The suspension was extracted with methylene dichloride (3 × 200 cm^3) and the organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in diethyl ether and the solution filtered through silica gel. The filtrate was evaporated giving rise to crude alcohol and eventually unchanged ketone.

(cis)-4-*Phenyl*-1,2,3,4-*tetrahydro*-1-*naphthol* **10**. Bioconversion of ketone **4** (1 g) with *S. pararoseus* gave crude product (0.96 g) which was fractionated by chromatography on silica gel with diethyl ether–pentane (0.5:9.5) as the eluent. Pure alcohol **10** (0.26 g, 26%) was obtained as a waxy solid (Found: C, 85.35; H, 7.0. $C_{16}H_{16}O$ requires C, 85.65; H, 7.2%); δ_H†(200 MHz; $CDCl_3$) 1.8–2.2 (4 H, m), 3.9 (1 H, t, *J* 7), 4.75 (1 H, t, *J* 4) and 6.7–7.4 (9 H, m); *m/z* 224 (M^+), 206 ($M^+ - 18$) and 120 ($M^+ - 104$, 100%).

4-*Phenyl*-1,2,3,4-*tetrahydronaphthol* **10**, **11**. Bioconversion of ketone **4** (1 g), with *R. rubra*, gave after chromatography a mixture of the two alcohols **10** and **11** (0.28 g, 28%) as a waxy solid; δ_H(200 MHz; $CDCl_3$) 1.9–2.2 (4 H, m), 3.9 (0.7 H, t, *J* 7), 4.05 (0.3 H, t, *J* 7), 4.8 (1 H, m) and 6.8–7.5 (9 H, m).

* $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.
† *J*-Values are given in Hz throughout.

Table 4 Fractional atomic coordinates for compound **12**

Atom	*x/a*	*y/b*	*z/c*
O(1)	0.6789(8)	0.970(1)	0.4213(8)
O(2)	0.562(1)	1.034(2)	0.534(1)
O(3)	0.8572(9)	1.051(1)	0.6230(8)
F(1)	0.8118(7)	0.950(1)	0.8208(7)
F(2)	0.6276(8)	0.907(1)	0.7424(7)
F(3)	0.6996(9)	0.136(1)	0.7415(8)
C(1)	0.586(1)	1.010(2)	0.319(1)
C(2)	0.520(1)	0.866(2)	0.270(1)
C(3)	0.601(1)	0.763(2)	0.217(1)
C(4)	0.639(1)	0.848(2)	0.116(1)
C(5)	0.744(1)	1.091(2)	0.079(1)
C(6)	0.783(1)	1.240(2)	0.105(1)
C(7)	0.758(2)	1.316(2)	0.200(2)
C(8)	0.693(1)	1.240(2)	0.266(1)
C(9)	0.655(1)	1.086(2)	0.241(1)
C(10)	0.679(1)	1.013(2)	0.150(1)
C(11)	0.527(1)	0.864(2)	0.015(1)
C(12)	0.736(1)	0.757(2)	0.078(1)
C(13)	0.721(1)	0.680(2)	−0.025(1)
C(14)	0.818(1)	0.599(2)	−0.051(1)
C(15)	0.925(2)	0.598(2)	0.020(2)
C(16)	0.944(2)	0.670(2)	0.125(2)
C(17)	0.849(1)	0.750(2)	0.155(1)
C(18)	0.659(1)	0.994(2)	0.521(1)
C(19)	0.761(1)	0.947(2)	0.621(1)
C(20)	0.723(1)	0.985(2)	0.732(1)
C(21)	0.924(1)	1.040(2)	0.535(1)
C(22)	0.793(1)	0.779(2)	0.621(1)
C(23)	0.906(1)	0.734(2)	0.679(1)
C(24)	0.936(1)	0.578(2)	0.688(1)
C(25)	0.855(2)	0.466(2)	0.635(1)
C(26)	0.744(2)	0.512(2)	0.579(1)
C(27)	0.709(1)	0.668(2)	0.571(1)

4-Methyl-4-phenyl-3,4-dihydronaphthalen-1(2H)-one **5**. A solution of 1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene (20 g, 90 mmol)[10] in water–acetonitrile (1:1) was oxidised with sodium persulfate (72.8 g, 31 mmol) and copper(II) sulfate (22.5 g, 90 mmol) at reflux for 45 min, and at room temperature until the blue colour turned green. The organic phase was separated, diluted in diethyl ether, washed with water, dried and concentrated to dryness. Chromatography on silica gel with pentane–ethyl ether (9:1) yielded **5** (10.6 g, 50%) as an amorphous solid (Found: C, 86.2; H, 6.7. $C_{17}H_{16}O$ requires C, 86.4; H, 6.8%); δ_H(200 MHz; $CDCl_3$) 1.28 (3 H, s), 2.2–2.7 (4 H, m) and 7.0–7.1 (9 H, m); *m/z* 236 (M^+), 221 ($M^+ - 15$, 100%), 193 ($M^+ - 43$) and 165 ($M^+ - 71$).

4-Methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthol **12** *and* **13**. A solution of **5** (3 g, 12.7 mmol) in anhydrous ethyl ether (20 cm^3) was added slowly to a solution of $LiAlH_4$ (0.24 g, 6.4 mmol) in diethyl ether (0.1 dm^3). After hydrolysis with diethyl ether–water (1:1), the organic phase was washed with water, dried and concentrated to dryness. Chromatography on silica gel with ethyl ether–pentane (1:1) yielded **12** and **13** (2.7 g, 90%) (Found: C, 85.4; H, 7.6. $C_{17}H_{18}O$ requires C, 85.7; H, 7.6%); δ_H(300 MHz; $CDCl_3$), 1.7 (1.8 H, s), 1.8 (1.2 H, s), 1.8–2.4 (4 H, m), 4.84 (1 H, m) and 7–7.5 (9 H, m); *m/z* 238 (M^+), 205 ($M^+ - 33$, 100%) and 120 ($M^+ - 118$).

(1R,4R)-4-*Methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthol* **12**. Bioconversion of ketone **5** (1 g) with *S. pararoseus* gave after chromatography the alcohol **12** (0.42 g, 0.42% as a crystalline product, m.p. 104–106 °C; δ_H(300 MHz; $CDCl_3$), 1.7 (3 H, s), 1.8–2.4 (5 H, m), 4.8 (1 H, m) and 6.9–7.5 (9 H, m).

X-Ray Analysis of Mosher Ester Derivative of cis-(1R,4R) **12**.—*Crystal data*. $C_{27}H_{25}F_3O_3$, M = 454.5. Monoclinic, a = 11.393(2), b = 8.6279(9), c = 12.061(3) Å, β = 102.90(2)°, V = 1155.6(6) Å^3, space group $P2_1$, Z = 2, D_x = 1.30 g cm^{-3}, μ = 0.94 cm^{-1}, reflections for lattice parameters 25, 12–13.5, $F(000)$ = 476, crystal size: 0.65 × 0.50 × 0.20 mm. Non-hydrogen coordinates are given in Table 4. Hydrogen co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the CCDC.*

Data collection and processing. CAD4 diffractometer, graphite monochromator, ω–2θ scan type, 0.8 + 0.34 tanθ scan width, 1–25° θ range, 2 standard reflections measured every two hours, 2177 reflections measured, giving 891 reflections with $I \geqslant 3\sigma(I)$, min–max height in final $\Delta\rho$ = −0.29, −0.55.

Structure analysis and refinement. 134 Refined parameters, $R = [\Sigma\Delta F/\Sigma F_0] = 0.077$, $R = [\Sigma w(\Delta F)^2/\Sigma w F_0^2]^{\frac{1}{2}} = 0.077$, w = 1.

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† For full details of the Cambridge Crystallographic Data Centre deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1922, issue 1.

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