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ABSOLUTE CONFIGURATION OF HOMOISOFLAVANONES FROM MUSCARI SPECIES

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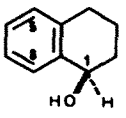
Abstract - The absolute configuration of homoisoflavanones isolated from Muscari species was determined by applying the chiral exciton coupling method to suitable derivatives. A negative Cotton effect in the 287-295 nm region of the CD curves of the natural compounds was shown to be indicative of 3R-configuration.

In the course of our studies (1) on the homoisoflavonoid content of Muscari species (Liliaceae), many compounds of this class of natural products have been isolated, both with the 3-benzylchroman-4-one skeleton and of the scillascillin type with a 3-spirocyclobutene ring, and their structure has been elucidated except for the absolute configuration at the chiral position C3.

In a recent paper (2), Namikoshi et al. have determined the absolute configurations at C3 and C4 of some 3,4-dihydroxyhomoisoflavans by establishing the relative configuration of these chiral centers and then applying the Horeau partial resolution method to elucidate the absolute configuration at C4. Comparison with the CD curves of these compounds was then used to establish the absolute configuration of two further compounds of the same structural class. On the grounds of this correlation to 3,4-dihydroxyhomoisoflavans by the CD curves, the absolute configuration of the C3 center of a 3-benzylchroman-4-one was also identified (3).

In principle, the absolute configuration of the homoisoflavanones isolated from Muscari might have been determined by reducing them to the corresponding 4-alcohols, applying the Horeau method to these latter and elucidating the configuration of center C3 relative to C4. However, it must be noted that in benzocyclanols of type 1 the presence of substituents in positions 5 and 8 may give rise to uncertainty about the classification of the phenyl group as "medium" or "large" when the Horeau rule is applied (4). Since all Muscari homoisoflavanones possess a hydroxyl group at position 5, we applied an absolute method to the elucidation of their absolute configuration. The chiral exciton coupling method (5) was preferred to the X-ray Bijvoet method, as the former does not require crystalline samples. Therefore, the procedure adopted for homoisoflavanones 2, 3, 4 and 5 and described in this paper implied the creation of a carbynolic chiral center at C4 by reduction of the carbonyl group, the determination of the absolute configuration at this center by



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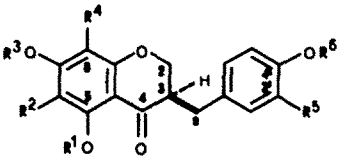
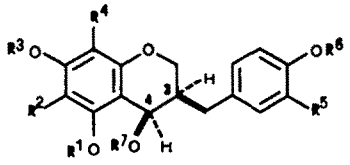
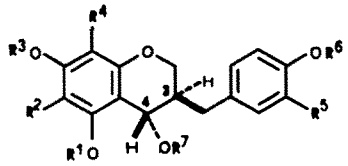


	R^1	R^2	R^3	R^4	R^5	R^6
2	H	H	CH_3	OH	H	H
3	H	CH_3	H	H	H	H
4	H	OCH_3	CH_3	H	H	H
5	H	H	H	H	OH	H
6	H	H	CH_3	OCH_3	H	CH_3
15	CH_3	OCH_3	CH_3	H	H	CH_3
16	H	OCH_3	$COCH_3$	H	H	$COCH_3$

	R^1	R^2	R^3	R^4	R^5	R^6
23	H	H	H	H	OH	CH_3
24	H	H	CH_3	OH	OH	H
25	H	OCH_3	H	H	OH	H
26	H	OCH_3	CH_3	CH_3	H	CH_3
27	CH_3	OCH_3	CH_3	OCH_3	H	CH_3
28	H	H	CH_3	H	OCH_3	CH_3





	R^1	R^2	R^3	R^4	R^5	R^6	R^7	
7	H	H	CH_3	OCH_3	H	CH_3	H	8
9	COC_6H_4Br	H	CH_3	OCH_3	H	CH_3	COC_6H_4Br	10
11	COC_6H_4Br	OCH_3	CH_3	OCH_3	H	CH_3	COC_6H_4Br	12
13	COC_6H_4Br	H	CH_3	H	OCH_3	CH_3	COC_6H_4Br	14
17	H	OCH_3	$COCH_3$	H	H	$COCH_3$	H	18
19	COC_6H_4Br	OCH_3	$COCH_3$	H	H	$COCH_3$	COC_6H_4Br	20
21	CH_3	OCH_3	CH_3	H	H	CH_3	H	22

applying the exciton coupling method to a 4,5-di-p-bromobenzoate derivative and, finally, the determination of the configuration at C3 relative to C4 by ^{1}H-nmr analysis.

Homoisoflavanone 2 was reacted with diazomethane/ether, that converted the hydroxyl groups into methoxyl groups, with the exception (6) of the 5-OH chelated with the (4)C=O group. Upon treatment with lithium aluminium hydride, the methylated derivative 6 (^{1}H-nmr: see Table 1) was converted to the 4-epimeric mixture of alcohols 7 and 8 ((4)CHOH: δ 4.74 d, J = 4.1 Hz and δ 4.81 d, J = 2.1 Hz) which, on treatment with p-bromobenzoyl chloride in pyridine and subsequent PLC separation, afforded di-p-bromobenzoates 9 and 10. ^{1}H-nmr data of 9 and 10 are summarized in Table 2. In the same way 4 and 5 were converted into di-p-bromobenzoates 11 and 12 and into di-p-bromobenzoates 13 and 14, respectively (^{1}H-nmr: see Table 2).

Contrarily to the cases of 2, 4 and 5, methylation at position 5 of 3 could not be avoided during the diazomethane/ether treatment, even in the cold, and permethylation product 15 was obtained in any case. However, acetylation of 3 in benzene with acetyl chloride and traces of pyridine gave the desired 4',7-diacetate 16, whose ^{1}H-nmr spectrum displayed the signal of the chelated 5-hydroxyl proton at δ 12.04. The crude mixture of the 4-epimeric alchols 17 and 18 (^{1}H-nmr carbinol proton signals at δ 4.72 d, J = 3.7 Hz and δ 4.77 d, J = 3.6 Hz) obtained from 16 by sodium borohydride reduction was then converted into the two 4,5-di-p-bromobenzoates 19 and 20, separated by PLC. ^{1}H-nmr data of 19 and 20 are summarized in Table 2.

Table 1. ^{1}H-nmr (300 MHz) data of homoisoflavanone derivative (9, 15, 16, 26, 27, and 28) in chloroform-d.[a]

	9	15	16
H-2	4.23 dd, J=11.5, 6.1	4.08 dd, J=11.0, 7.0	4.15 dd, J=11.3, 6.8
	4.37 dd, J=11.5, 4.1	4.27 dd, J=11.0, 3.7	4.40 dd, J=11.3, 4.0
H-3	2.83 m	2.72 m	2.85 m
H-9	2.76 dd, J=12.7, 10.1	2.64 dd, J=13.2, 10.7	2.80 dd, J=13.0, 10.5
	3.19 dd, J=12.7, 2.9	3.19 dd, J=13.2, 3.3	3.25 dd, J=13.0, 3.5
H-6/H-8	6.11 s, (H-6)	6.25 s, (H-8)	6.18 s, (H-8)
H-2',H-6'	7.16 d, J=8.9	7.14 d, J=8.5	7.25 d, J=8.8
H-3',H-5'	6.87 d, J=8.9	6.84 d, J=8.5	7.04 d, J=8.8
Others	3.78 s, 3.81 s, 3.90 s, 3 x OCH_3	3.79 s, 3.81 s, 3.87 s, 3.93 s, 4 x OCH_3	3.84 s, OCH_3
	12.02 s, 5-OH		2.30 s, 2.33 s, 2 x $OCOCH_3$
			12.04 s, 5-OH

	26	27	28
H-2	4.19 dd, J=11.3, 6.9	4.17 dd, J=11.3, 6.8	4.14 dd, J=11.6, 7.3
	4.35 dd, J=11.3, 4.1	4.36 dd, J=11.3, 4.1	4.30 dd, J=11.6, 3.7
H-3	2.86, m	2.79, m	2.83 m
H-9	2.76 dd, J=13.5, 10.7	2.67 dd, J=13.5, 10.7	2.72, dd, J=14.0, 11.0
	3.18 dd, J=13.5, 4.3	3.19 dd, J=13.5, 4.2	3.19, dd, J=14.0, 4.3
H-6/H-8			5.97 d/6.07d, J=2.4
H-2',H-6'	7.16 d, J=8.6	7.17 d, J=8.7	
			6.75/6.81
H-3',H-5'	6.87 d, J=8.6	6.85 d, J=8.7	
Others	3.80 s, 3.81 s, 3.86 s, 4.10 s, 4 x OCH_3	3.80 s, 3.84 s, 3.85 s, 3.90 s, 4.06, 5 x OCH_3	3.82 s, 3.88 s, 3.89 s, 3 x OCH_3
	11.87 s, 5-OH		11.42 s, 5-OH

[a] Apparent coupling constants J are given in Hz.

Identification of the stereoisomer with the cis-, and of that with the trans-relationship between the 3- and the 4-hydrogen in the epimeric pairs of the 4,5-di-p-bromobenzoates of 2 and 5 was achieved by analysis of their ^{1}H-nmr spectra, that implied consideration of the ring-C conformational mobility, as depicted in Figure 1. In the ^{1}H-nmr spectrum of one member of each pair, both the (2)CH_2 protons appear to be coupled to the 3-proton with a rather small coupling constant ($J \leq 2.2$ Hz), indicative of the equatorial orientation of the 3-proton, whereas for the other member the two $J_{2,3}$ are 4-4.6 Hz and ca. 11 Hz, this latter being indicative of the axial orientation of the 3-proton. In both epimeric pairs, both epimers exhibit a $J_{3,4}$ value of 1.8-3.6 Hz. This rules out the b2 conformation (Figure 1) with the axial 3-proton and the pseudoaxial 4-proton for the trans-epimers. Thus, in each epimeric pair the trans stereochemistry may be safely assigned to the member that displays the 3-proton with equatorial orientation (conformation b1). Consequently, the cis member is the compound with the axial 3-proton, with conformation a2. Confirming evidence for these conclusions comes from the W-coupling (1.2-1.8 Hz) between the 2_{eq}-H and the 4-H displayed in the spectra of 9, 13 and 14, that is consistent only with the conformation a2 for the cis-epimer and b1 for the trans-epimer.

Table 2. ^{1}H-nmr (300 MHz) data of cis- (9, 11, 13, 19, and 21) and trans-steroisomers (10, 12, 14, 20, and 22) in chloroform-d.[a]

	9	11	13	19	21[b]
H-2	4.08 dd, J=10.9, 11.3	4.05 dd, J=11.5, 11.0	4.06 dd, J=11.3, 11.0	4.03 dd[c], J= 11.7, 11.4	4.01 ddd, J=10.7, 3.7, 1.1
	4.24 ddd, J=10.9, 4.0, 1.2	4.21 ddd, J= 11.5, 3.7, 1.5	4.14 ddd, J=11.3, 4.6, 1.3	4.11 dd, J= 11.7, 2.9	4.17 dd, J=10.7, 11.8
H-3	2.48 m	2.47 m	2.50 m	2.51 m	2.14 m
H-4	6.51 dd, J=3.4, 1.2	6.5 b	6.50 dd, J=3.6, 1.3	6.5 b	4.84 dd, J=3.3, 1.1
H-9	2.25 dd, J=14.0, 10.7	2.25, dd, J=14.0, 10.6	2.37 dd, J=14.3, 10.8	2.30	2.57 dd, J=14.0, 7.3
	2.92 dd, J=14.0, 3.7	2.92, dd, J=14.0, 4.4	2.92 dd, J=14.3, 4.2	2.95 dd, J=14.0, 4.0	2.95 dd, J=14.0, 8.1
H-6/H-8	6.38 s (H-6)		6.35 d/6.39d, J=2.5	6.64 s (H-8)	6.33 s (H-8)
H-2',H-6'	7.04 d, J=8.8	7.04 d, J=8.8	6.65 (H-2', H-6')	7.13 d, J=8.4	7.11 d, J=8.4
H-3',H-5'	6.81 d, J=8.8	6.81 d, J=8.8	6.77 d (H-5'), J=8.6	7.01 d, J=8.4	6.82 d, J=8.4
Others	3.78 s, 3.84 s, 3.86 s, 3 x OCH_3	3.75 s, 3.78 s, 3.91 s, 3.97 s, 4 x OCH_3	3.78 s, 3.83 s, 3.86 s, 3 x OCH_3	2.29 s, 2.33 s, 2 x $OCOCH_3$	3.25 s, 3.33 s, 3.68 s, 3.70 s, 4 x OCH_3
	7.54d, 7.82d, J=8.5, p-BrC_6H_4COO-		7.56d, 7.82d, J=8.4, p-BrC_6H_4COO-	3.67 s, OCH_3	
	7.56d, 7.73d, J=8.5, p-BrC_6H_4COO-	7.5-7.9, 2 x p-BrC_6H_4COO-	7.55d, 7.74d, J=8.4, p-BrC_6H_4COO-	7.5-7.9, 2 x p-BrC_6H_4COO-	
	10	12	14	20	22[b]
H-2	4.18 dd, J=11.0, 2.1	4.09 d, J=10.7	4.05 dt, J=11.3, 1.8, 1.8	4.02 d, J= 11.0	3.94 ddd, J=10.7, 3.3, 1.1
	4.20 dd, J=11.0, 2.1	4.15 d, J=10.7	4.15 dd, J=11.3, 2.2	4.08 d, J= 11.0	4.31 dd, J=10.7, 2.2
H-3	2.30 m	2.28 m	2.31 m	2.31 m	2.23 m
H-4	5.99 d, J=2.1	5.96 bs	5.97 t, J=1.8, 1.8	5.96 bs	4.77 dd, J=2.9, 1.1
H-9	2.55 dd, J=13.4, 10.4	2.55 dd, J=13.5, 10.6	2.54 dd, J=13.9, 10.8	2.60 dd, J=13.6, 11.0	2.53 dd, J=14.0, 8.8
	2.78 dd, J=13.4, 6.1	2.81 dd, J=13.5, 5.4	2.79 dd, J=13.9, 5.5	2.84 dd, J=13.6, 4.8	2.63 dd, J=14.0, 7.3
H-6/H-8	6.52 s		6.48 d/6.49d, J=2.6	6.74 s	6.37 s
H-2',H-6'	7.15 d, J=8.5	7.15 d, J=8.5	6.75 d (H-2'), J=1.8; 6.78 dd (H-6'), J=8.0, 1.8	7.25 d, J=8.4	6.96 d, J=8.4
H-3',H-5'	6.85 d, J=8.5	6.85 d, J=8.5	6.82 d (H-5'), J=8.0	7.04 d, J=8.4	6.78 d, J=8.4
Others	3.79 s, 3.90 s, 3.96 s, 3 x OCH_3	3.79 s, 3.81 s, 4.00 s, 4.03 s, 4 x OCH_3	3.84 s, 3.87 s, 3.88 s, 3 x OCH_3	2.30 s, 2.37 s, 2 x $OCOCH_3$	3.27 s, 3.32 s, 3.71 s, 3.78 s, 4 x OCH_3
	7.49d, 7.65d, J=8.5, p-BrC_6H_4COO-		7.49d, 7.72d, J=8.6, p-BrC_6H_4COO-	3.73 s, OCH_3	
	7.47d, 7.73d, J=8.5, p-BrC_6H_4COO-	7.4-7.8, 2 x p-BrC_6H_4COO-	7.47d, 7.66d, J=8.6, p-BrC_6H_4COO-	7.4-7.7, 2 x p-BrC_6H_4COO-	

[a] Apparent coupling constants J are given in Hz.

[b] Measured in benzene-d_6.

[c] In acetone-d_6 this signal appears as ddd, J = 10.6, 3.9, 1.3 Hz, the 1.3 Hz constant being due to W-coupling with H-4.

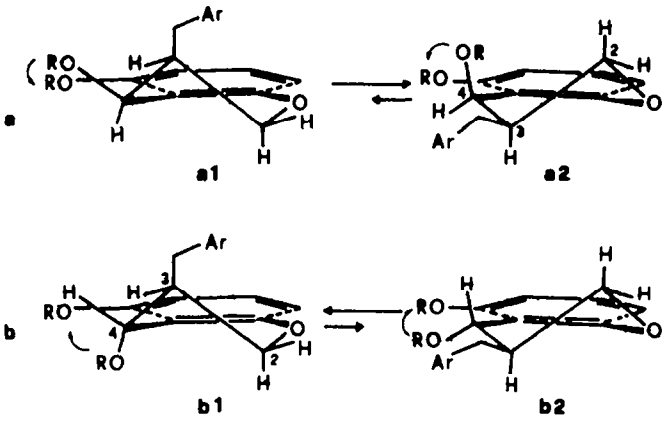


Figure 1. Conformations of the ring C of epimeric 4,5-di-p-bromobenzoates (R = p-BrC$_6$H$_4$CO-, Ar = ring B): a) 3,4-cis-isomer, b) 3,4-trans-isomer. Arrows indicate chirality (clockwise = positive, counterclockwise = negative) of the arrangement of the two p-bromobenzoate chromophores.

Table 3. CD data of di-p-bromobenzoates 9-14 and 19-20 in methanol.[a]

	λ_{ext}, nm	$\Delta\varepsilon$	A-value
9	253	-9.6	
	245	0	-15.7
	237	+6.1	
10	254	+9.5	
	244	0	+17
	237	-7.5	
11	254	-12.0	
	242	0	-21.2
	234	+9.2	
12	254	+13.1	
	242	0	+19.1
	233	-6.0	
13	253	-12	
	243	0	-20.6
	236	+8.4	
14	252	+16.3	
	242	0	+23.5
	237	-7.2	
19	253	-14.7	
	244	0	-22.2
	236	+7.5	
20	251	+12.0	
	242	0	+21.4
	232	-9.4	

[a] All di-p-bromobenzoates exhibit a UV absorption band at 246-247 nm, ε = 39000-39500.

Table 4. CD and UV data of homoisoflavanones 2-5 and 23-25 in methanol.

	λ_{ext}, nm	$[\theta]$	λ_{max}, nm	ε
2	315	0	366	2200
	292	-5940	286	12500
	260	+3300	248	8800
3	314	+50	330	4200
	287	-15500	286	18700
	252	+6930		
4	325	+10	380	4300
	293	-11550	360	4300
	262	+6930	290	17000
5	316	+165	325	4500
	294	-1700	287	19000
	262	+530		
23	312	+20	287	24000
	290	-7920		
	258	+2310		
24	325	0	365	3500
	295	-990	290	16200
	270	-330	244	9500
25	320	+10	286	21000
	293	-20450		
	258	+3960		

[a] Concentration : 10^{-4}-10^{-5} M; room temperature.

The 3-proton is displayed at δ 2.48-2.50 in the spectra of the cis-epimers 9 and 13 and at δ 2.30-2.31 in the spectra of the trans-epimers 10 e 14. In addition, the 4-proton signal appears at δ 6.50-6.51 in the spectra of the former and at δ 5.97-5.99 in the spectra of the latter compounds. The 9-proton signals also appear in the spectra of the cis- at quite different δ values than in the spectra of the trans-epimers. Distinction of the cis- from the trans-epimer in the di-p-bromobenzoate pairs obtained from 4 and 3 was safely achieved on the grounds of this chemical shift criterion, since in the ^{1}H-nmr spectra of these compounds the signal multiplicities (see Table 2) are not suitable for an assignment grounded on the coupling between protons 2, 3, and 4, as above in the cases of 9 and 10 and of 13 and 14.

Once the relative configuration of the chiral centers 3 and 4 had been established, the absolute configuration of the latter was determined from the sign of the A-value of the split Cotton effects exhibited by 9, 10, 11, 12, 13, 14, 19 and 20 (Table 3). Positive exciton chirality for the trans-epimers and negative exciton chirality for the cis-epimers indicate that the chiral center C4 possess the S-configuration in the former and the R-configuration in the latter. Consequently, the chiral center C3 is R in all eight compounds and in the parent natural homoisoflavanones 2, 3, 4 and 5.

The relative "size" of the groups linked to the secondary alcohol chiral center C4 in the case of presence of a 5-hydroxyl group was investigated, with the aim of applying the Horeau method. 15 was thus reduced with lithium aluminium hydride to the epimeric 4-alcohols 21 and 22, separated by PLC. The relative stereochemistry of the centers 3 and 4 in 21 and 22 was established to be that depicted in the respective formulae by analysis of the nmr coupling of protons 2-H_2, 3-H and 4-H, exactly as in the case of di-p-bromobenzoates 9, 10, 13 and 14. Configuration of the C3 center being R, that of the C4 center was R in the cis-epimer and S in the trans-epimer. Upon application of the gaschromatographic modification (7) of the Horeau partial resolution method, a positive increment of the peak of (+)-α-phenylethylamide of (-)R-phenylbutyric acid was observed for the cis-epimer 21 and a negative increment for the trans-epimer 22. Thus the phenyl ring must be the "medium" substituent group, and the grouping at C3 "large", in order to apply the Horeau rule to the secondary 4-alcohols bearing a hydroxyl group at C5.

CD curves of homoisoflavanones 2, 3, 4, and 5 all exhibit a negative Cotton effect in the 287-295 nm region (Table 4), that may be therefore taken as indicative of R-configuration at C3, since the dihydropyranone ring C may be assumed to have the same conformation for all four compounds. In fact, in the ^{1}H-nmr spectra of all homoisoflavanones (1, 6) the 3-proton appears coupled to one 2-proton with a J > 10 Hz and to the other 2-proton with a J < 4 Hz, that implies equatorial orientation of the 3-benzyl group in all cases. Measurement of the CD curves thus allowed the assignment of the absolute configuration of natural homoisoflavanones 23, 24, and 25 also, as they all exhibit a negative CD Cotton effect (Table 4).

The elucidation of the absolute stereochemistry scillascillin homoisoflavanones isolated from Muscari is in progress.

EXPERIMENTAL[1]

^{1}H-nmr spectra were recorded at 300.14 MHz with an AM-300 FT NMR spectrometer (Bruker) with TMS as an internal standard. UV spectra were measured in methanol with a Cary 210 spectrometer. CD curves were measured in methanol with a JASCO J-500 dichrograph. PLC was performed on precoated silica gel layers Merch F_{254}, 0.5 mm. GLC was carried out with a Carlo Erba Fractovap 4160 chromatograph.

Methyl derivatives 6, 26, 28 and 15. 2 (50 mg) in ether (5 ml) was treated with a solution of diazomethane in ether for 48 h at r.t.. PLC (5:2:3 hexane-dioxane-ether; two runs) of the crude product obtained after usual work-up gave pure 6 (41 mg). Analogously, 4 (100 mg) was converted into 26 (25 mg) and 27 (67 mg), separated by PLC (6:1:3 hexane-dioxane-ether; three runs), 5 (40 mg) into 28 (37 mg), purified by PLC (chloroform; two runs), and 3 (22 mg) into 15 (20 mg), purified by PLC (7:3 chloroform-ethyl acetate; one run).

Acetyl derivative 16. A soln of 3 (50 mg) in dry benzene (4 ml) was treated with acetyl chloride (0.5 ml) and pyridine (traces). After 12 h at r.t., methanol was added and the mixture was evaporated. The crude product, dissolved in ethyl acetate, washed with water and submitted to PLC (4:1 benzene-ethyl acetate; one run) gave pure 16 (30 mg).

Di-p-bromobenzoates 9-14. 6 (38 mg) was treated in ether with lithium aluminium hydride for 5 min at r.t. to give the epimeric mixture of 7 and 8 (4-C<u>H</u>OH: δ 4.74 d, J = 4.1 Hz and δ 4.81 d, J = 2.1 Hz) that, without purification, was treated with p-bromobenzoyl chloride in anhydrous pyridine for 12 h at r.t.. Usual work-up and PLC (4:1 hexane-ether; four runs) gave pure 9 (8 mg) and 10 (10 mg). Upon analogous treatment, 26 (25 mg) was converted into pure 11 (10 mg) and 12 (12 mg) (PLC: 4:1 benzene-ethyl acetate; two runs), and 28 (35 mg) into pure 13 (15 mg) and 14 (14 mg) (PLC: 5:2:3 hexane-dioxane-ether; four runs).

Di-p-bromobenzoates 19 and 20. 16 (25 mg) was treated in methanol with sodium borohydride for 5 min at 0° to give the epimeric mixture of 17 and 18 (4-C<u>H</u>OH: δ 4.72 d, J = 3.7 Hz and δ 4.77 d, J = 3.6 Hz) that, without purification, was treated with p-bromobenzoyl chloride in anhydrous pyridine for 12 h at r.t.. Usual work-up and PLC (95:5 benzene-ethyl acetate; four runs) gave pure 19 (8 mg) and 20 (7 mg).

Alcohols 21 and 22. Treatment of 15 (20 mg) in ether with lithium aluminium hydride for 5 min at r.t. and PLC (7:3 benzene-ethyl acetate; two runs) gave the pure epimeric 4-alcohols 21 (10 mg) and 22 (8 mg). Alcohols 21 and 22 were treated with (±)phenylbutyric anhydride and the excess of anhydride was analyzed by glc (25-m fused silica capillary OV1 column; T = 190°; flow: 1 mL/min, nitrogen) as (+)-R-phenylethylamides of (-)-R- and (+)-S-phenylbutyric acid, following the procedure described in ref. 7. Peak increments of +5 and -4 for R-acid were calculated for 21 and 22, respectively.

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