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ASYMMETRIC 1,4-ADDITIONS TO 5-ALKOXY-2(5H)-FURANONES ENANTIOSELECTIVE SYNTHESIS AND ABSOLUTE CONFIGURATION DETERMINATION OF β-AMINO-γ-BUTYROLACTONES AND AMINO DIOLS

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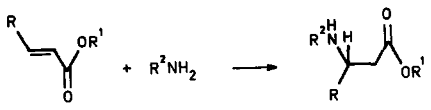
Abstract. The synthesis of enantiomerically pure β-amino-γ-butyrolactones via asymmetric conjugate addition of various amines to 5-menthyloxy-2(5H)-furanone is described. This route provides access to new multifunctional homochiral building blocks. The absolute configuration of the β-amino-γ-butyrolactones is established by X-ray analysis and ^{1}H NMR correlation. The conjugate addition of amines to 2[5H]-furanone, 5-alkyl-2[5H]-furanones and 5-alkoxy-2[5H]-furanones was studied and an enhanced reactivity was observed in 2[5H]-furanones due to a γ-alkoxy-effect. The synthetic utility of the asymmetric amine addition is illustrated in an efficient route to various optically pure 2-amino-1,4-butanediols.

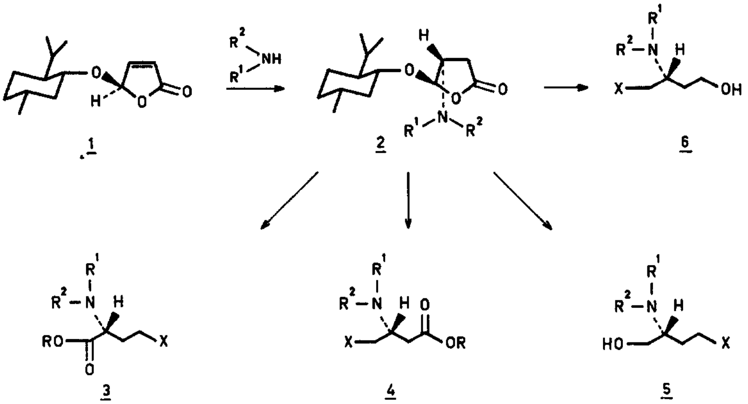
Chiral β-amino esters are increasingly important in organic synthesis since they are precursors to β-lactams[1], act as components in peptide synthesis[2] and are used as synthons in the preparation of antibiotics and antitumor agents[3]. Optically active amino alcohols derived from amino esters are essential structural entities in numerous pharmaceutical compounds[4]. In addition they have served as chiral building blocks, chiral auxiliaries or ligands in asymmetric synthesis[5]. An elegant method for the formation of β-amino esters is the enantioselective 1,4-addition of amines to conjugated esters (eq.1). The stereochemistry at the newly created asymmetric center could in principle be controlled by either using a chiral amine[6], a chiral α,β-ethylenic ester[7a] or vinylsulfoxide[7b] or a chiral catalyst[8].

(1)



A limited number of highly stereoselective syntheses of β-amino esters, following these routes, have been reported. Excellent diastereoselectivities (d.e.>99%) were achieved by d'Angelo and Maddalano[7a] in the conjugate addition of α-phenylbenzylamine to 8-(β-naphthyl)menthylcrotonate under 15 kbar pressure. The inter-and intramolecular additions of amine functionalities to α,β-unsaturated esters containing a chiral center in the γ-position proceed with high stereoselectivities[9]. Complete stereocontrol was furthermore found in the 1,4-addition of p-methoxybenzylamine to optically active 5-t-butyloxymethyl-2[5H]-furanone[10a]. Similar conversions of conjugated esters with optically active amines[11] and optically active fumaric diamides with achiral amines[12] resulted only in modest diastereoselectivities. A combined conjugate addition-resolution procedure for β-amino esters have been reported[13] as well as the synthesis of β-amino lactones from L-aspartic acid[14]. Despite these promising achievements we feel that their synthetic application might be restricted in several cases for instance by the high pressure required[7], the availability of the chiral auxiliaries[7] or the synthetic procedure necessary to obtain the optically pure conjugated esters[9]. In this paper we describe full details of a new synthetic strategy to enantiomerically pure β-amino lactones, that can serve as precursors to β-amino esters and amino alcohols[4,5]. Our approach is based on facile conjugate addition of amines to enantiomerically pure γ-menthyloxy-2[5H]-furanone 1 (scheme 1)[15]. Significant for the synthetic application of these new methods are the facts that the chiral butenolide 1 is easily prepared starting from l-menthol(9) as a chiral auxiliary (vide infra); both enantiomers of 9 are cheap and readily available. As the amine functionality is situated in a β-position with respect to the lactone and in an α-position with respect to the acetal moiety it is conceivable that selective modifications at the 2- and 5-positions in 2 would allow formation of optically active α- and β-amino esters (3,4) and 1,2- and 1,3-amino alcohols (5,6) (scheme 1).

scheme 1

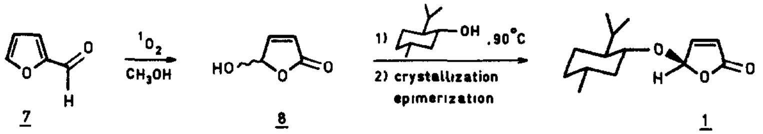


This approach will therefore allow flexible and enantioselective routes to these different chiral building blocks. The diastereofacial addition of several amines to butenolide 1 is reported as well as the absolute configuration determination by X-ray analysis. Furthermore we discuss the conversion of 2 into enantiomerically pure amino diols (6,X=OH).

Asymmetric Amine Additions

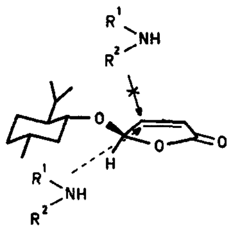
The new chiral synthon (l)-5-menthyloxy-2[5H]-furanone 1 (or its enantiomer, prepared starting from d-menthol) serves as the starting material for the asymmetric syntheses described here. Enantiomerically pure butenolide 1 is readily available in gram quantities through a three step procedure from furfural as was described previously[16] (eq.2). Singlet oxygen photooxidation of furfural[17] followed by acetalization with l-menthol yields two diastereomeric l-menthyloxyfuranones. Crystallization from petroleum ether 40/60 or hexane and in situ epimerization of the minor diastereoisomer provides enantiomerically pure 1.

(2)



7 8 1

In line with the observation of diastereofacial Diels-Alder reactions[18] and thiol additions[16] to 1 and stereocontrolled 1,4-additions to 5-t-butyloxymethyl-[5H]-furanone[10], we expected that the amine additions to 1 would also preferentially proceed anti to the C5-menthyloxy substituent.



Various primary and secondary amines indeed undergo a diastereoselective addition to chiral butenolide 1 to yield diastereomerically and enantiomerically pure β-amino butenolides 2 (scheme 1).

The results are summarized in table I. We have substantially improved the procedure for conjugate additions of amines to butenolides by the choice of dichloromethane or N,N-dimethylformamide as the solvent[19]. The same solvent effect is valid for the asymmetric amine additions described here. At room temperature quantitative conversions (as determined by ^{1}H-NMR) are reached in 0.5-8 hours using the solvents mentioned.

In several cases the products were purified by crystallization from petroleum ether 40/60, but in general we experienced that the crude adducts

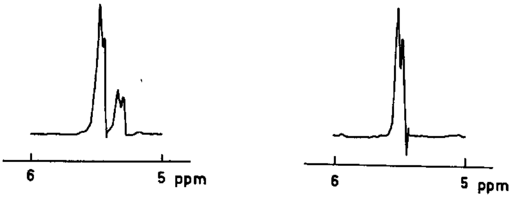
Table I

entry	Amine(R^1R^2NH) R^1	R^2	solvent	reaction time (hrs)	product yield[a] (%) 2	isolated yield (%) 2	6 (X=OH)
1	$(CH_2)_4$		CH_2Cl_2	0.5	100	76	73
2	$(CH_2)_5$		CH_2Cl_2	0.5	100	68	76
3	$(CH_2)_2O(CH_2)_2$		DMF	1	100	73	39
4	C_2H_5	C_2H_5	DMF	2[b]	100	95	62
5	H	n-C_4H_9	DMF	1	100	90	58
6	H	$C_6H_5CH_2$	DMF	8	>95	50	63
7	H	(l)-$C_6H_5CH(CH_3)$	DMF	8	>95	90	69

[a] yield by NMR; [b] two-fold excess amine was used.

were homogeneous by TLC and ^{1}H NMR and sufficiently pure for further conversions. Purification by distillation can lead to substantial losses as the amino butenolides 2 are prone to elimination. The diastereoselectivities and the relative configurations of the newly formed asymmetric centers were established by ^{1}H NMR. In all the adducts a singlet was observed for the acetal hydrogen or a doublet was found with a small ($J \leq 2$ Hz) coupling constant. This is consistent with a trans relationship of the substituents at the C4 and C5 chiral centers as a small coupling constant for the vicinal hydrogens is deduced from molecular models using Altona's method[20]. (A calculated value of $J\ H_{4-5}$ = 1.8Hz was found for 2 ($R^1R^2 = (CH_2)_4$). Furthermore this analysis is in accordance with the X-ray determination (vide infra). In contrast herewith two absorptions (40:60 ratio) were found for the two diastereoisomers of 2 when a 40:60 mixture of epimers of 1 was used as starting material. Figure 1 shows a typical case for (4R)-(1"-pyrrolidino-)-(5R)-(1'R,2'S,5'R)-menthyloxybutyrolactone. These observations indicate a diastereomeric excess (d.e.) greater than 96% for all the amino lactones 2 prepared so far.

Figure 1



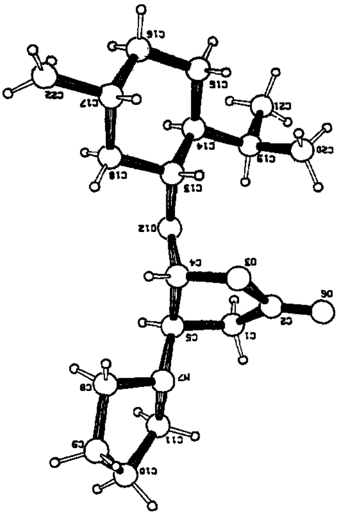
^{1}H NMR of C_{H-5} of $2(R^1,R^2=(CH_2)_4)$
a: Using a 60:40 mixture of epimers of 1; b: Using enantiomerically pure 1.

X-ray structure analysis and absolute configuration determination

The absolute configuration at the acetal center of butenolide 1 could not be obtained by direct means as we have not been able so far to grow crystals suitable for X-ray determination. In order to establish the absolute configuration of 1 unambiguously and to prove the π-face selectivity in the amine additions to 1 the structure of 2 ($R^1,R^2=(CH_2)_4$) was determined by X-ray analysis.

Suitable crystals were grown from petroleum ether 40/60, solvent was included in the crystals in small holes. Surprisingly solvent free crystals were unstable and not suited for X-ray analysis. The structure was solved by direct methods (see experimental section) and based on the known absolute configuration of the 1-menthyloxy-part[21]. Table II shows the bond distances, whereas the bond angles are included in table III. An ORTEP Plot of 2 ($R^1,R^2 = (CH_2)_4$) is shown in figure 2.

Figure 2



Envelope conformations are seen for both the lactone and pyrrolidine 5-membered rings. The tert.amine has C5,N7,C11 and C5,N7,C8 angles of 111.0(3) and 113.7(3)° respectively with the lone pair in a syn orientation with the butenolide oxygen atoms. The menthyloxy- and pyrrolidine substituents are in a trans-configuration. This finding confirms the complete π-face selective addition of the amine anti to the menthyloxy substituent in 1. Based on the (1R,2S,5R) configuration of 1-menthol[21] it is deduced from the structure shown in figure 2, that the R-configuration is present at the acetal chiral center in 1 and 2 as well as the R-absolute configuration at the newly created chiral center in 2 (scheme 1).

Epimerization during the amine addition was excluded as no trace of the epimer of 1 was observed under the conditions used. This can also be

Table II 2 $R^1,R^2=(CH_2)_4)$ Bond Distances in Angstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom4	Distance
03	C2	1,358(5)	C1	C2	1,535(6)	C14	C15	1,532(6)
03	C4	1,458(5)	C1	C5	1,537(6)	C14	C19	1,553(6)
06	C2	1,197(6)	C4	C5	1,545(6)	C15	C16	1,531(6)
012	C4	1,357(5)	C8	C9	1,527(7)	C16	C17	1,542(7)
012	C13	1,456(5)	C9	C10	1,515(8)	C17	C18	1,528(7)
N7	C5	1,462(5)	C10	C11	1,531(7)	C17	C22	1,538(7)
N7	C8	1,476(5)	C13	C14	1,526(6)	C19	C20	1,517(7)
N7	C11	1,478(6)	C13	C18	1,529(6)	C19	C21	1,536(7)

Numbers in parentheses are estimated standard deviations in least significant digits.

Table III **2** $(R^1,R^2=(CH_2)_4)$ Table of Bond Angles in Degrees

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C2	03	C4	110,0(3)	N7	C5	C1	110,1(3)	C15	C14	C19	113,1(4)
C4	012	C13	113,7(3)	N7	C5	C4	111,2(3)	C14	C15	C16	111,8(4)
C5	N7	C8	113,7(3)	C1	C5	C4	99,9(3)	C15	C16	C17	111,4(4)
C5	N7	C11	111,0(3)	N7	C8	C9	102,5(4)	C16	C17	C18	109,5(4)
C8	N7	C11	104,0(3)	C8	C9	C10	105,0(4)	C16	C17	C22	109,5(4)
C2	C1	C5	102,4(3)	C9	C10	C11	103,3(4)	C18	C17	C22	111,9(4)
03	C2	06	122,1(4)	N7	C11	C10	104,7(4)	C13	C18	C17	111,0(4)
03	C2	01	109,1(4)	O12	C13	C14	108,4(3)	C14	C19	C20	113,7(4)
06	C2	C1	128,8(4)	O12	C13	C18	110,1(3)	C14	C19	C21	110,8(4)
03	C4	O12	110,1(3)	C14	C13	C18	11,0(4)	C20	C19	C21	110,5(4)
03	C4	C5	104,7(3)	C13	C14	C15	107,3(3)				
012	C4	C5	107,3(3)	C13	C14	C19	113,8(3)				

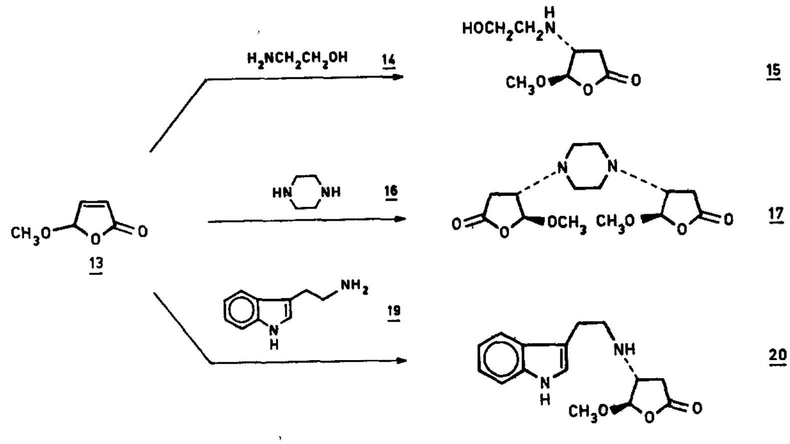
Numbers in parentheses are estimated standard deviations in the least significant digits.

concluded from the fact that a 60/40 mixture of epimers of 1 produces a 60/40 mixture of diastereoisomers 2 as indicated in figure 1. Finally a torsional angle of 78.0° was found for the C_4-H_4 and C_5-H_5 bonds. The vicinal coupling constant J_{H4-5} of 1.8 Hz that is calculated using this angle[20] corresponds well with the experimental data. Based on the structural analysis of 2 (R^1,R^2=$(CH_2)_4$) and the comparison of the ^1H NMR data it is evident that the 4R,5R absolute configuration is present in all amine-adducts 2 derived from l-menthoxybutenolide 1.

1,4-Addition of amines to 2[5H]-furanones

In a previous paper[19] we described a dramatic solvent effect on the rate of amine additions to 2[5H]-furanones i.e. quantitative conversions were reached in 8 hours and 15 minutes for primary and secondary amines respectively in contrast to 5-15 days with incomplete conversion in several instances as reported[22]. As expected it turned out that besides the solvent effect electronic and steric factors, govern the 1,4-addition. Hexamethyldisilazane (10); aniline (11) and dibenzylamine (12) seem to be to weak nucleophiles to give 1,4-additions to γ-alkoxybutenolides whereas also steric constrains may play an important role. No trace of adduct from 12 and 1 was observed even in boiling DMF. In contrast herewith the conjugate addition of ethanolamine (14) to γ-methoxybutenolide 13 gave racemic amino lactone 15 in 70% yield (scheme 2).

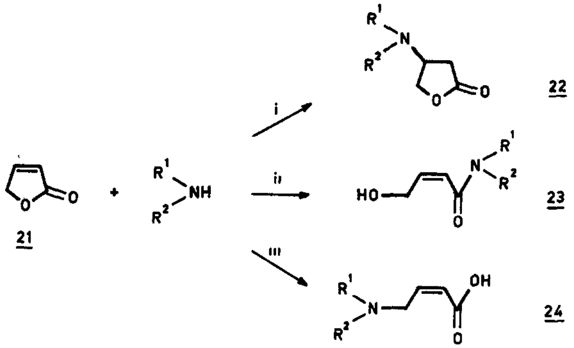
scheme 2



This product can serve as precursor to various amino triols. Similarly piperazine (16) reacts with two equivalents of 13 to provide diadduct 17 (95% yield) a useful precursor for diamino tetraols 18 and starbust molecules[23]. Surprisingly a single diastereomer 17 is formed although the starting material 13 is a racemate. No trace of the other isomer was observed (^1H-, ^{13}C-NMR, TLC). The configuration of 17, indicated in scheme 2 as the meso (R,S) isomer, has not yet been proven. It is conceivable that 17 is the racemic (RR,SS) adduct. We have at present no explanation for the high stereoselectivity in this addition reaction. The 1,4-addition of tryptamine 19 to γ-alkoxybutenolides could provide attractive precursors to various indole alkoloids. A facile stereoselective and quantitative addition of tryptamine to 13 was observed resulting in 97% isolated yield of trans adduct 20 after 1 hour. Acid catalyzed cyclization of 20 could lead to indole alkaloid building blocks. These routes are currently under investigation. A singlet or doublet (J = 1Hz) was found in the ^1H NMR spectra for the acetal hydrogens in 15, 17 and 20 pointing to trans stereochemistry for the vicinal substituents.

Amine additions to a number of γ-alkylsubstituted 2[5H]-furanones have been studied by Jones and Barker[25] e.q. the addition of benzylamine to angelica-lactone (15% yield after purification). Three modes of addition of amines to butenolides were envisaged: i. Michael addition on the enone; ii. amide formation and iii. attack at the γ-position; see scheme 3. The results depend strongly on solvent, reactant and temperature.

scheme 3



To compare the amine additions to γ-alkoxybutenolides with the additions to γ-alkylbutenolides and unsubstituted butenolides the reaction of three amines with 2[5H]-furanone 21 and 2-(5-n-butyl)furanone 25 was investigated under the conditions described above. The results are summarized in table IV.

The following conclusion can be drawn:

Conjugate addition is the major or exclusive pathway. Attack at the γ-position (the acetal carbon) was not observed. γ-Alkoxybutenolides are more reactive Michael type acceptors as compared to their unsubstituted or γ-alkyl substituted analogues.

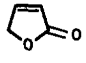
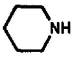
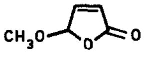
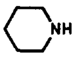
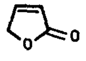
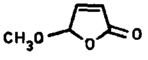
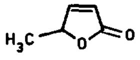
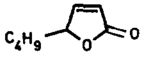
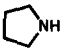
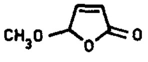
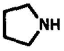
We attribute the rate enhancement to the inductive effect of the C_5-alkoxy-substituent with an antibonding C-O σ-orbital appropriate aligned for interaction with the π-orbital of the enone moiety. The effect found here is related to the inductive effect of allylic alkoxy-substituent in, for example, deprotonations and the stereocontrol by allylic oxygen substituent in 1,2-additions as described previously[26,27].

The "γ-alkoxy-effect" resulting in the rate enhancement and consequently facile conjugate addition will be explored in related systems.

Amino alcohol synthesis

Reduction of amino lactones 2 with lithium aluminium hydride in tetrahydrofuran affords optical active amino diols 27 in modest to good yields (scheme 4 and table I). The chiral auxiliary l-menthol (9) is readily recovered by distillation or chromatography. However some loss of amino diol is due to these purification procedures.

Table IV

entry	butenolide		amine	solvent	time (hr)	product yield (%) a)b)	isolated yield (%) c)
1		(21)		CH_2Cl_2	1	100	74
2		(13)		CH_2Cl_2	0.12	100	60
3		(21)	$C_6H_5CH_2NH_2$	DMF	12	100	65
4		(13)	$C_6H_5CH_2NH_2$	DMF	0 5	95	50
5		(26)	$C_6H_5CH_2NH_2$	–	2		15[25]
6		(25)		CH_2Cl_2	1	95	65
7		(13)		CH_2Cl_2	0 12	100	83

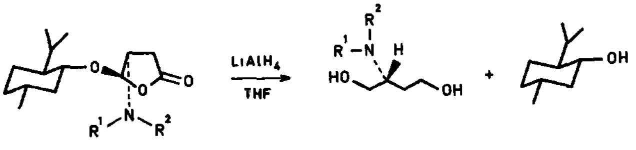
a) yield by ^1H NMR

b) only conjugate addition product (scheme 3, route i) was observed

c) isolated yield by distillation

The R configuration was assigned to all amino diols prepared via this route.

scheme 4



2 (a-g) 27 (a-g) 9

Furthermore all amino diols obtained from (4R,5R)-amino lactones 2 are optically pure. This is based on the assumption that the C_4-asymmetric center of the amino lactones 2 remains unaffected during the reduction. In order to determine the enantiomeric excess of the amino diols independently and to exclude possible racemization during the reduction step of the sensitive amino lactones 2 we studied the (l)-α-methylbenzylamine adducts (table 1, entry 7).

Addition of (S)-α-methylbenzylamine (28) to racemic (R,S)-methoxybutenolide 13 provided two diastereomeric adducts SS-2 and RS-2 (R^1 = H,R^2 = $C_6H_5CH(CH_3)$) in a 50:50 ratio. Similarly diastereomerically pure RS-2 (R^1=H,R^2=$C_6H_5CH(CH_3)$) was obtained from optically pure menthyloxybutenolide 1 and S(-)-28. Reduction of both adducts afforded amino diols 27 (R^1=H,R^2=$C_6H_5CH(CH_3)$). ^{1}H-NMR and ^{13}C-NMR revealed a 50:50 mixture of diastereoisomers of 27 obtained from racemic butenolide 13 and a single isomer when the addition, reduction sequence was started with R-1. This means a diastereomeric excess of > 96% in the latter case and furthermore that no racemization takes place during the reduction step.

Due to their widespread applicability several routes to amino alcohols have been devised. Generally amino acids[28] or chiral amino ketones[29] serve as starting material but also routes based on epoxides[30], hydroxy acids[31] or cyanohydrins[32] or via cycloadditions[33] have been developed. d'Angelo and coworkers have used the benzylamine adduct of 8-(β-naphthyl)menthylacrylester to obtain 3-amino butanol (e.e.95%)[7a] after reductive conversion. A two step procedure to racemic amino diols based on amine additions to β-benzylacrylicacid esters was described by Cromwelt et.al.[34]

The access to both enantiomers of chirale butenolides 1, the facile and diastereoselective addition of various amines and the reductive conversion to amino diols with complete retention of configuration make the route described here highly competitive with existing procedures. Selective conversions at either the lactone or acetal functionality in the adducts 2 will further extend the scope of this asymmetric synthesis. When mild methods for ringopening of 2 without epimerization at the sensitive C4 chiral center can be found, the synthesis of optically active functionalized 1,2- and 1,3-amino -alcohols and the formation of optically active β-lactams will be possible.

Investigations along these lines are currently in progress.

Experimental:

^{1}H NMR (200 MHz and 300 MHz) and ^{13}C NMR spectra were obtained on Nicolet NT200 and Varian VXR 300 spectrometers in deuterochloroform solution. Chemical shifts are reported as δ values relative to tetramethylsilane (δ=0 ppm). Infrared spectra were recorded on a Unicam SP200 infrared spectrophotometer. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus. Boiling points for amino diols given are Kugelrohr distillation temperatures. High resolution mass spectra (HRMS) were recorded on an AEI-MS-902 spectrometer. Elemental analyses were performed in the micro-analytical department of this laboratory. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. DMF was dried over molecular sieves (4A°). All other solvents were distilled before use. d- and l-Menthol were purchased from Janssen Chimica. Optical rotations were measured on a Perkin Elmer 241 Polarimeter. Photooxidation of furfural was performed using rose bengal or methylene blue as sensitizer and a 700 Watt high pressure mercury lamp (Hanau) analogous to procedures described before[16,17,35]. 2[5H]-furanone was prepared following the procedure described by Nasman and Pensar.[36] 5-n-Butyl-2[5H]-furanone was prepared as described by Marhado-Arango and Core.[37]

5-Hydroxy-2[5H]-furanone (8); 5-Methoxy-2[5H]-furanone (13); 5-(l)-Menthyloxy-2[5H]-furanone (1)

These compounds were prepared in 95%, 75% and 60% yield respectively using the procedures described before[16] from furfural (7).

Amine additions to γ-alkoxybutenolides; typical procedure.

To a solution of 1.0 g (4.1 mmol) 5-(l)-menthyloxy-2[5H]-furanone (1) in 10 ml of CH_2Cl_2 or DMF was added 0.29 g (4.1 mmol) of pyrrolidine. The reaction mixture was stirred at room temperature for the appropriate time (table I). The conversion of 1 was complete in this period as was indicated by ^1H NMR. Subsequently the solvent was removed under vacuo and the residue purified by crystallization from petroleum ether 40/60.

(4R,5R)-4-(1"-pyrrolidino)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone was obtained as white needles; 0.96 g (76%) m.p. 134.6-134.8°C; $[\alpha]_D^{20}$ - 150.1° (c 1.0,$CHCl_3$) Anal.Calcd. for $C_{18}H_{31}NO_3$: C,69.83; H,10.10; N,4.52. Found: C,69.85; H,10.10; N,4.45.

^1H NMR: 1.0-2.0 (m,18H, menthyl H's), 1.6-1.8 (m,4H,$H_{3",4"}$), 2.5 (m,6H,$H_{2",5"}$,H_3), 3.0 (m,1H,H_4), 3.5 (m,1H,H1'), 5.5 (d,1H,J=2Hz,H_5).

^{13}C NMR: 15.97 (q), 21.19 (q), 22.58 (q), 23.41 (t), 23.51 (t), 25.77 (d), 31.66 (d), 33.89 (t), 34.61 (t), 39.92 (t), 48.08 (d), 51.88 (t), 65.87 (d), 77.41 (d), 103.23 (d), 174.61 (s).

IR(KBr,cm^{-1}): 2800 (C-H), 1780 (C=O), 1200-1000 (C-O).

HRMS: calcd. 309.230, found 309.231.

(4S,5S)-4-(1"-pyrrolidino-)-5-((1'S,2'R,5'S)-menthyloxy)-butyrolactone; white crystalline solid, mp. 133.8-134.6°C; $[\alpha]_D^{20}$ + 150.0° (c 1.0,$CHCl_3$)

(5R)-4-(R)-(1"-piperidino-)5-((1'R,2'S,5'R)-menthyloxy-)-butyrolactone. white crystalline solid, m.p. 114.9-115.6°C; $[\alpha]_D^{20}$ -149.0° (c 1.0, $CHCl_3$).

^1H NMR: 1.0-2.0 (m,18H, menthyl-H's), 1.6 (m,6H,H_3",H_4", H_5"), 2.4-2.6 (m,,7H,H_2",H_6",H_3,H_4), 3.5 (m,1H,H_1'), 5.5 (d,1H,J= 2Hz,H_5).

^{13}C NMR: 15.90 (q), 21.14 (q), 22.54 (q), 23.38 (t), 24.46 (t), 25.73 (d), 26.12 (t), 31.64 (d), 33.38 (t), 34.58 (t), 39.90 (t), 47.99 (d), 50.97 (t), 66.93 (d), 77.16 (d), 101.30 (d), 174.99 (s).

IR(KBr,cm^{-1}): 2900-2800 (C-H), 1780 (C=O), 1200-1000 (C-O).

HRMS: calcd. 323.246, found 323.245.

(4R,5R)-4-(1"-morpholino)-5-((1'R,2'S,5'R)-menthyloxy-)-butyrolactone.

white crystalline solid, m.p. 109.4-110.2°C; $[\alpha]_D^{20}$-142.3° (c 1.0, $CHCl_3$).

^1H NMR: 0.8-1.8 (m,18H, menthyl-H's), 2.1-2.5 (m,6H,H_3, H_2",H_7"), 3.1 (m,1H,H_4), 3.5-3.7 (m,5H,H_1',H_3",H_5"), 5.5 (d,1H, J=2Hz,H_5).

^{13}C NMR: 15.59 (q), 20.73 (q), 22.15 (q). 23.07 (t), 25.44 (d), 31.28 (d), 34.11 (t), 34.58 (t), 39.54 (t), 47.69 (d), 50.20 (t), 66.38 (t), 66.63 (d), 78.02 (d), 101.15 (d), 174.38 (s).

IR(KBr,cm^{-1}): 2900-2800 (C-H), 1790 (C=O), 1200-1000 (C-O).

HRMS: calcd. 325.225, found 325.225.

(4R,5R)-4-(N,N-diethylamino-)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone.

oil., $[\alpha]_D^{20}$ - 148.1° (c 1.0,$CHCl_3$).

^1H NMR: 0.8-2.0 (m,18H, menthyl-H's), 1.0 (t,6H,J=10Hz,H_{16}), 2.1 H_3 (m,1H,H_2'), 2.5 (q,4H,J=10Hz,H_{15}), 2.6 (m,1H,H_3), 3.4-3.6 (m,2H,H_4,H_1'), 5.5 (d,1H,J=2Hz,H_5).

^{13}C NMR: 12.43 (q), 15.45 (q), 20.65 (q), 22.02 (q), 22.93 (t), 25.26 (d), 31.16 (d), 31.72 (t), 34.12 (t), 39.45 (t), 43.43 (t), 47.45 (d), 62.35 (d), 76.79 (d), 102.63 (d), 175.24 (s).

IR(neat,cm^{-1}): 2900-2800 (C-H), 1780 (C=O), 1200-1000(C-O).

HRMS: calcd. 311.246, found 311.247.

(4R,5R)-4-(N-butylamino-)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone.

semisolid., $[\alpha]_D^{20}$ - 134.1° (c 1.0, $CHCl_3$).

^1H NMR: 0.8-2.0 (m,21H,H_3",menthyl-H's), 1.4 (m,5H,H_3",H_4",NH), 2.4-2.6 (m,4H,H_2",H_3), 3.3 (m,1H,H_4), 3.4 (m,1H,$H_1{}^1$), 5.4 (s,1H, H_5).

^{13}C NMR: 13.79 (q), 15.54 (q), 20.23 (t), 20.75 (q), 22.13 (q), 23.04 (t), 25.45 (d), 31.27 (d), 32.12 (t), 34.23 (t), 34.99 (t), 39.66 (t). 47.07 (t), 47.66 (d), 59.99 (d), 76.78 (d), 103.94 (d), 175.29 (s).

IR(KBr,cm^{-1}): 2900-2800 (C-H), 1780 (C=O), 1200-1050 (C-O).

HRMS: calcd. 311.246, found 311.246.

(4R,5R)-4-(N-benzylamino-)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone.

yellow solid, m.p. 100.6-102.7°C;
$[\alpha]_D^{20}$ - 100.7° (c 1.0, $CHCl_3$).

^{1}H NMR: 0.7-2.0 (m,19H,NH,menthyl H's), 2.3 (dd,1H,J=3 Hz, J = 15Hz,H_3), 2.8 (dd,1H,J=15Hz,J=7Hz,H_3), 3.4-3.6 (m,2H,H_4,H_1), 3.8 (s,2H,H_2"), 5.4 (s,1H,H_5), 7.3 (m,5H,aryl-H's).
^{13}C NMR: 15.52 (q), 20.75 (q), 22.12 (q), 23.03 (t), 25.44 (d), 31.25 (d), 34.21 (t), 35.05 (t), 39.60 (t), 47.64 (d), 51.63 (t), 59.49 (d), 78.03 (d), 103.82 (d), 127.33 (d). 128.02 (d), 128.52 (d), 139.12 (s), 175.16 (s).
IR(KBr,cm^{-1}): 3350 (N-H), 3100-3000 (C-H aryl), 2950-2800 (C-H), 1780 (C=O).
HRMS: calcd. 345.230, found 345.229.

(4R,5R)-4-((2"R)-α-Methylbenzylamino-)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone.
oil, $[\alpha]^{20}_{D}$ - 109.1° (c 1.0, $CHCl_3$).
^{1}H NMR: 0.8-1.9 (m,18H,menthyl-H's), 1.4 (d,3H,J=9Hz,H_3"), 1.6 (s,1H,NH), 2.1 (dd,1H,J=15Hz, J=2Hz,H_3), 2.7 (dd,1H,J=15Hz,J=8Hz,H_3), 3.3-3.4 (m,2H,H_4,H_1), 3.8 (q,1H,J=9Hz,H_2"), 5.2 (s,1H,H_5), 7.3 (m,5H,aryl-H's).
^{13}C NMR: 15.41 (q), 20.64 (q), 21.99 (q), 22.93 (t), 24.45 (q), 25.33 (d), 31.11 (d), 34.13 (t), 34.98 (t), 39.21 (t), 47.44 (d), 56.18 (d), 58.67 (d), 76.40 (d), 104.13 (d), 126.49 (d), 127.26 (d), 128.58 (d), 144.61 (s), 175.50 (s).
IR(neat,cm^{-1}): 3370 (N-H), 3100-3000 (C-H aryl), 3000-2850 (C-H), 1790 (C=O).
HRMS: calcd. 350.243, found 350.243.

4-((2'R)-α-Methylbenzylamino)-5-methoxy-butyrolactone.
oil, mixture of 2'R,5R and 2'R,5S-diastereomers (50:50 ratio).
^{1}H NMR: 1.3-1.4 (dd,3H,J=3Hz,J=10Hz,H_3"), 2.1 and 2.3 (dd,1H,J=4Hz,J=14Hz,H_3), 2.6-2.7 (dd,1H,J=8Hz,J=14Hz,H_3), 3.3 (m,1H,H_4), 3.3 and 3.5 (s,3H,OCH_3), 3.7-3.9 (dq,1H,J=3Hz,J=10Hz,H_2"), 4.9 and 5.2 (s,1H,H_5), 7.0-7.4 (m,5H,aryl-H's).
^{13}C NMR: 23.98, 24.08 (q), 34.57, 35.11 (t), 55.97, 56.24 (d), 56.41, 56.52 (d), 57.18, 57.89 (q), 108.77, 109.08 (d), 126.34 (d), 127.10 (d), 128.39 (d), 144.24 (s), 174.92 (s).
IR(neat,cm^{-1}): 3350 (N-H), 3050-2950 (C-H), 1795 (C=O), 1200-1100 (C-O).
HRMS: calcd. 235.121, found 235.120.

X-ray structure analysis of (4R,5R)-4-(1"-pyrrolidino-)-5-((1'R, 2'S,5'R)-menthyloxy)-butyrolactone.
Suitable crystals were grown in the orthorhombic space group $P2_12_12_1$ from petroleum ether 40/60 by evaporation of the solvent.
However, the solvent is easily included in the crystals in small holes.
Crystal data for $C_{18}H_{31}NO_3$, 4(crystallographically independent) molecules per

unit cell; a = 5.305(3), b = 13.024(2), c = 25.467 (4), A°, α = 90.0°, β = 90.0°, = 90.0°, D_c = 1.168 g cm^{-3}; U = 1759.6 $A^{\circ 3}$; crystal dimensions 0.45 x 0.35 x 0.20 mm; (Mo-K_α) = 0.71073 A°.
Data were collected with graphite-monochromated Mo-K_α radiation on a CAD4F diffractometer and the structure was solved by direct methods (CAD4 SDP-Programs, Enraf-Nonius Dreux & Associates).
1883 unique reflections with I>3.0σ (I) were used in the refinements.
The structure was solved by direct methods[24] and based on the absolute configuration of the l-menthol part.[21] The positions of all the H-atoms could be revealed from a single final difference map based on all the non H-atoms.
Block diagonal least-squares of F, with unit weights, converged to a final R = 0.059 and R_w = 0.069 respectively, using anisotropic temperature factors for the non H-atoms and fixed isotropic temperature factors (B = 5.0 $A^{\circ 3}$) for the H-atoms. In the final refinements the H-atoms were constraint to their corresponding C-atoms at a distance of 0.095 Å.

1,4-Bis-4-(5-methoxy-2-butyrolactone)-piperazine (17).

A mixture of 1.0 g (8.8 mmol) of 5-methoxy-2[5H]-furanone 13 and 0.4 g (4.4 mmol) of piperazine 16 in 10 ml CH_2Cl_2 was stirred at room temperature for 1 hour. The solvent was removed in vacuo and the semisolid titrated from CH_2Cl_2. There was obtained 1.32 g (95%) of 17 as a yellow solid, homogeneous by TLC and ^1H NMR. m.p. 75.3-78.6°C.
^1H NMR: 2.5 (m,10H,H_2,H_3,H_5,H_7,H_3',H_3"). 2.7 (dd,J=6Hz,J=14Hz,2H, H_3',H_3"), 3.1 (m,2H,H_4,H_4"), 3.5 (s,6H,CH_3), 5.2 (d,J=1Hz,2H,H_5', H_5").
HRMS: calcd. 314.148, found 314.149.

4-(N-2-Hydroxyethylamino-)-5-methoxy-2-butyrolactone (15).

The experimential procedure described above was followed using N,N-dimethylformamide as a solvent and a reaction time of 2 hours. Yield 70% of 15 (viscous oil).
^1H NMR: 2.1-2.8 (m,3H,H_3,NH), 2.9 (m,3H,H_4,H_2'), 3.5 (s,3H,OCH_3), 3.7 (m,3H,H_3',OH), 5.2 (s,1H,H_5).

4-(N-2-(1-Indolyl-)ethylamino)-5-methoxy-2-butyrolactone 20.

Prepared from 0.25 g (2.20 mmol) 13 as described for 17 using DMF instead of CH_2Cl_2 as the solvent and a reaction time of 1 hour; yield 0.58 g (97%) of 20 (oil).
^1H NMR: 2.1 (dd,1H,J=2Hz,J=15Hz,H_3), 2.7 (dd,1H,J=8Hz,J=15Hz,H_3), 3.0 (m,4H,H_2',H_3'), 3.3 (m,1,H_4), 3.4 (s,3H,OCH_3), 5.0 (s,1H,H_5), 7.0-7.7 (m,5H,aryl-H's), 9.0 (s,broad,1H,NH).
^{13}C NMR: 25.67 (t), 34.37 (t), 47.03 (t), 56.37 (q), 59.17 (d), 108.44 (d),

111.12 (d), 112.16 (s), 118.13 (d), 118.67 (d), 121.42 (d), 122.20 (d), 126.81 (s), 136.15 (s), 175.31 (s).

4-(1-Pyrrolidino-)-5-n-butyl-butyrolactone.
From 0.35 g (2.5 mmol) 5-n-butyl-2[5H]-furanone and 0.17 g (2.4 mmol) pyrrolidine following the general procedure there was obtained 0.50 g (95%) of adduct as an oil.
^{1}H NMR: 0.9-1.1 (m,3H,H_8), 1.3-1.7 (m,6H,H_5,H_6,H_7), 1.9-2.0 (m, 4H,H_{10}), 2.6 (m,4H,H_9), 2.8 (m,2H,H_2), 3.5 (m,1H,H_3), 4.5 (m,1H, H_4).

4-Benzylamino-butyrolactone.
From 0.50 g (6.0 mmol) of 2[5H]-furanone and 0.69 g (6.0 mmol) of benzylamine was obtained the amine adduct: 1.2 g (100%), oil., homogeneous by ^{1}H NMR and TLC.
^{1}H NMR: 2.7 (m,2H,H_3), 3.7 (m,1H,H_4), 3.8 (s,2H,H_2'), 4.1-4.4 (m, 2H,H_5), 7.3 (m,5H,aryl-H's).
^{13}C NMR: 35.56 (t), 51.51 (t), 53.56 (d), 73.20 (t), 127.34 (d), 127.76 (d), 128.42 (d), 128.63 (s), 179.31 (s).
HRMS: calcd. 191.096, found 191.095.

4-Piperidino-butyrolactone.
Oil, yield 1.0 g (100%); homomogeneous by ^{1}H NMR and TLC; using the general procedure.
^{1}H NMR: 1.5 (m,6H,H_3',H_4',H_5'), 2.3 (m,4H,H_2',H_7'), 2.5 (m,2H,H_3), 3.2 (m,1H,H_4), 4.1-4.3 (m,2H,H_5).
^{13}C NMR: 23.75 (t), 25.30 (t), 32.25 (t), 51.33 (t), 60.78 (d), 71.01 (t), 175.63 (s).
HRMS: calcd. 169.110, found 169.110.

Synthesis of amino diols; typical procedure.
To a suspension of 0.30 g (8.0 mmol) lithium aluminium hydride in 50 ml THF under a nitrogen atmosphere was added, at 0°C under stirring, 1.24 g (4.0 mmol), (4R,5R)-4-(1"-pyrrolidino-)-5-((1'R,2'S,5'R)-menthyloxy)-butyrolactone dissolved in 15 ml THF.
The mixture was stirred at 0°C for 30 min. and subsequently at room temperature for 2 hours. The excess $LiAlH_4$ was destroyed by careful addition of 1 ml H_2O and 1 ml 10% aqueous KOH. The salts that precipitated were collected and extracted with diethyl ether for 20 hours using a continuous extraction procedure. The combined organic solutions were dried over Na_2SO_4 and the solvent removed in vacuo. The resulting oil was purified by Kugelrohr-distillation and in case that not all the menthol was separated by

distillation subsequent purification by flash chromatography was performed (silicagel, n-hexane followed by diethyl ether, methanol (90/10 ratio) as eluens). There was obtained pure **(R)-2-pyrrolidino-1,4-butanediol** as a colourless oil. 0.46 g (73%), b.p. 145°(0.01 mm Hg). oil, $[\alpha]_D^{20}$ +2.1° (c 1.8,$CHCl_3$).
^{1}H NMR: 1.5-2.0 (m,6H,H_2,H_6), 2.5-2.9 (m,5H,H_3,H_5), 3.3-3.7 (m,H_1,H_4), 4.7 (s,2H,br,OH).
^{13}C NMR: 22.95 (t), 30.83 (t), 49.67 (t), 60.21 (t), 61.67 (t), 62.25 (d).
IR(neat,cm^{-1}): 3500-3200 (O-H), 2950-2800 (C-H), 1100-1000 (C-O).
HRMS: calcd. 159.125, found 159.127.

(R)-2-Piperidino-1,4-butanediol.
Colourless oil, b.p. 140°C (0.01 mm Hg);$[\alpha]_D^{20}$ +1.9° (c 1.8,$CHCl_3$).
^{1}H NMR: 1.4-2.0 (m,8H,H_2,H_6,H_7), 2.5-3.0 (m,5H,H_3,H_5), 3.3-3.8 (m,4H,H_1,H_4), 4.4 (s,2H,br,OH).
^{13}C NMR: 24.29 (t), 26.33 (t), 28.02 (t), 49.54 (t), 60.46 (t), 62.21 (t), 65.97 (d).
IR(neat,cm^{-1}): 3500-3200 (O-H), 2950-2750 (C-H), 1200-1050 (C-O).
HRMS: calcd. 173.142, found 173.142.

(R)-2-Morpholino-1,4-butanediol.
Colourless oil, b.p. 140°C (0.01 mm Hg); $[\alpha]_D^{20}$ +2.0° (c 1.8,$CHCl_3$).
^{1}H NMR: 1.4-2.0 (m,2H,H_2), 2.5-2.9 (m,5H,H_3,H_5), 3.4-3.9 (m,8H, H_1,H_4,H_6, 4.2 (s,2H,OH).
^{13}C NMR: 28.16 (t), 48.69 (t), 60.51 (t), 61.42 (t), 64.68 (d), 67.13 (t).
IR(neat,cm^{-1}): 3600-3200 (O-H), 2900-2800 (C-H), 1200-1000 (C-O).
HRMS: calcd. 175.121, found 175.121.

(R)-2-Diethylamino-1,4-butanediol.
Colourless oil, b.p. 145°C (0.01 mm Hg); $[\alpha]_D^{20}$ +5.3° (c 1.8,$CHCl_3$).
^{1}H NMR: 1.0-1.2 (t,6H,J=9Hz,H_6), 1.5-1.8 (m,2H,H_2), 2.4-2.7 (q, 4H,J=9Hz,H_5), 2.8-3.1 (m,1H,H_3), 3.5-3.8 (m,4H,H_1,H_4), 3.6 (s, br,2H,OH).
^{13}C NMR: 13.95 (q), 28.73 (t), 43.00 (t), 60.41 (d), 60.58 (t), 61.85 (t).
IR(neat,cm^{-1}): 3600-3200 (O-H), 2950-2850 (C-H), 1200-1000 (C-O).
HRMS: calcd. 161.142, found 161.141.

(R)-2-n-Butylamino-1,4-butanediol.
Colourless oil, b.p. 130°C (0.01 mm Hg); $[\alpha]_D^{20}$ +12.2° (c 1.8, $CHCl_3$).
^{1}H NMR: 0.8-1.1 (q,3H,J=10Hz,H_8), 1.2-1.9 (m,6H,H_2,H_6,H_7), 2.5-

2.8 (m,3H,H_3,H_5), 3.4-3.9 (m,4H,H_1,H_4), 4.1 (s,2H,OH).
^{13}C NMR: 13.53 (q), 20.00 (t), 31.95 (t), 32.34 (t), 46.11 (t), 58.63 (d), 60.71 (t), 62.30 (t).
IR(neat,cm^{-1}): 3500-3100 (O-H), 3000-2800 (C-H), 1100-1050 (C-O).
HRMS: calcd. 130.123, found 130.121 (M^{+}-CH$_2$OH).

(R)-2-Benzylamino-1,4-butanediol.
Colourless oil, b.p. 170°C (0.005 mm Hg); [α]$^{20}_{D}$ +24.4° (c 1.8,CHCl$_3$).
^{1}H NMR: 1.5-1.8 (m,2H,H_2), 2.8-3.0 (m,1H,H_3), 3.4-3.7 (m,4H,H_1, H_4), 3.8 (s,2H,H_5), 3.9 (s,2H,OH), 7.3 (m,5H,H_7,H_8,H_9).
^{13}C NMR: 32.50 (t), 57.94 (d), 60.81 (t), 61.15 (t), 62.36 (t), 126.88 (d), 127.88 (d), 128.19 (d), 139.31 (s).
IR(neat,cm^{-1}): 3500-3200 (O-H), 3050-3000 (C-H,aromaat), 2950-2850 (C-H), 1100-1000 (C-O).
HRMS: calcd. 195.126, found 195.124.

(2R)-2-((1'S)-α-Methylbenzylamino-)-1,4-butanediol.
Colourless oil, b.p. 170°C (0.005 mm Hg); [α]$^{20}_{D}$ - 11.8° (c 1.8,CHCl$_3$).
^{1}H NMR: 1.3 (d,3H,J=9Hz,H_6), 1.6-1.8 (m,2H,H_2), 2.8 (m,1H,H_3), 3.3-3.4 (m,4H,H_1,H_4), 3.4 (s,2H,OH), 3.9 (q,1H,J=9Hz,H_5), 7.2 (m, 5H,H_8,H_9,H_{10}).
^{13}C NMR: 23.83 (q), 32.41 (t), 55.10 (d), 55.83 (d), 60.87 (t), 63.63 (t), 126.32 (d), 127.04 (d), 128.46 (d), 145.02 (s).

Mixture of (2R)- and (2S)-diastereoisomers of (2R)-2-((1'S)-α-Methylbenzylamino-)-1,4-butanediol.
^{1}H NMR: 1.3 (dd,3H,J=5,9Hz,H_6), 1.6-1.8 (m,2H,H_2), 2.5 en 2.7 (m, 1H,H_3), 3.3-3.4 (m,4H,H_1,H_4), 3.4 (s,br,2H,OH), 3.9 (dq,1H,J= 5,9Hz,H_5), 7.2 (m,5H,H_8,H_9,H_{10}).
^{13}C NMR: 23.82, 24.72 (q), 32.57, 34.05 (t), 54.86, 55.15 (d), 55.71, 55.81 (d), 60.85, 61.45 (t), 62.11, 63.68 (t), 126.30 (d), 127.02 (d), 128.44 (d), 145.07, 145.30 (s).
IR(neat,cm^{-1}): 3500-3400 (O-H), 3050-2900 (C-H), 1100-1000 (C-O).
HRMS: calcd. 178.123, found 178.121 (M^{+}-CH$_2$OH).

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