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ASYMMETRIC SYNTHESIS OF 2-AMINO-1,4-DIOLS

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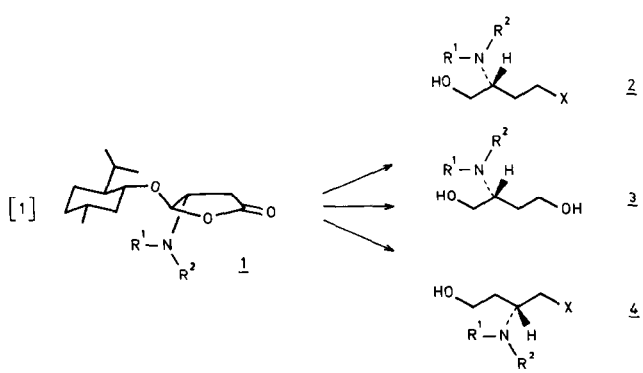
SUMMARY. Diastereoselective addition of amines to (1)-5-menthyloxy-2-(5H)-furanone yields aminolactones that upon reduction with $LiAlH_4$ provide enantiomerically pure aminodiols.

Chiral aminoalcohols are widely found as essential structural units in natural products and are of great importance in pharmaceutical research.[1] In addition optically active aminoalcohols have served as chiral building blocks in synthesis.[2] In recent years various successful asymmetric syntheses were based on the application of aminoalcohol derived chiral auxiliaries[3-7] or ligands.

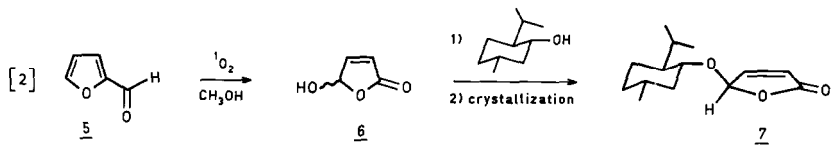
Optically active β-aminoalcohols are usually prepared from aminoacids[8] or chiral aminocarbonyl compounds.[9] Functionalized chiral aminoalcohols have been made via ringopening of epoxides,[10] from hydroxyacids,[11] cyanohydrines[12] or via cycloaddition procedures.[2,13] Only a limited number of highly diastereoselective syntheses of β-aminoesters through addition of amines to α, β-ethylenic esters were reported as far as we know.[14] Although very promising for the synthesis of γ-aminoalcohols, there applications will be restricted for instance by the high pressures required and the availability of the chiral auxiliary.[14]

We devised a new synthetic strategy to optically active 1,2- and 1,3-aminoalcohols as well as 2-amino-1,4-diols based on enantiomerically pure 4-amino-5-menthoxy-butyrolactones 1 (eq. 1). Reduction of both lactone and acetal functionalities in 1 would result in

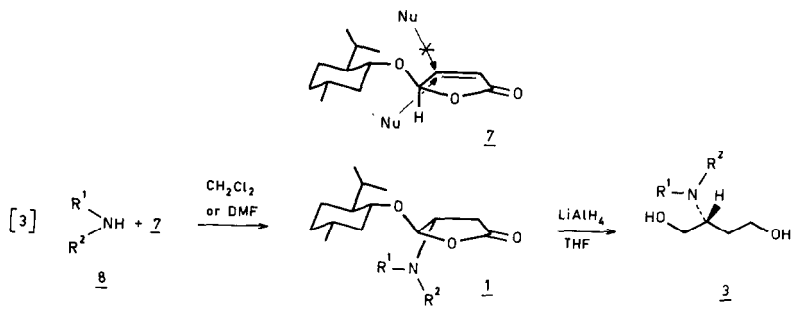


aminodiols 3. Selective modifications at the 2- and 5-positions in 1 allows formation of 1,2-aminoalcohols 2 or 1,3-aminoalcohols 4, respectively.

This paper describes an efficient procedure for the preparation of optically pure aminodiols 3. (1-)-(5)-Menthyloxy-2-(5H)-furanone 7, a new chiral synthon which we recently developed,[17] was used as a starting material. Enantiomerically pure menthoxylactone 7 is readily available through photooxidation of furfural,[15] followed by acetalization of hydroxylactone 6 with l-menthol and subsequently crystallization from petroleum ether (40-60) (eq. 2).[16,17]



With the observation of highly diastereofacial selective Diels Alder additions to 7[17] we recognized that nucleophilic additions at the C_4 position in 7 would also preferentially proceed anti to the C_5 menthoxy-substituent (eq. 3). This expectation has been realized in the diastereoselective addition reaction of various amines to 7. Enantiomerically pure



adducts 1 are obtained in quantitative yields at room temperature[18] (eq. 3; table). The configuration of the products and the diastereoselectivity of the reaction were established by ^{1}H-NMR. The trans relationship of the substituents at the C_4 and C_5 chiral centers is based on the small coupling constant ($J_{H_{4-5}}$ <1H2) of the vicinal hydrogens.[19] Complete diastereofacial control in the amine addition is deduced from the fact that one ^{1}H-NMR absorption for the acetal proton is observed for adducts 1 whereas two absorptions (40:60 ratio) were found for the same protons in the two diastereoisomeric amine adducts that were obtained using a 40-60 mixture of diastereoisomers of 7 as starting material. This indicates a diastereomeric excess (d.e.) higher than 96% for all aminolactones 1 prepared sofar (table).

Reductions of 1 with lithiumaluminiumhydride in tetrahydrofuran affords (R)-2-amino-1,4-butanediols 3 in good yields (table). The chiral auxiliary l-menthol is readily recovered by distillation.[18]

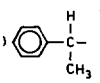
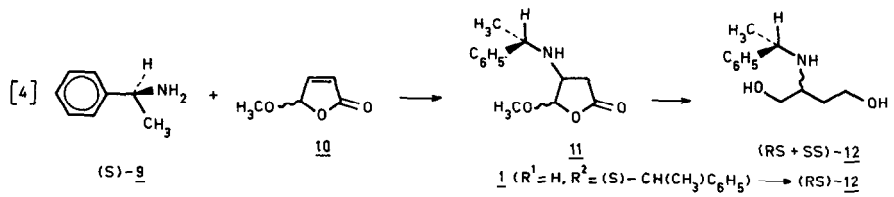
					1				3
entry	R_1	R_2	solvent	reaction time (hrs)	yield[a] (%)	isolated yield (%)	m.p. (°C)	$[\alpha]_D^{23}$ (°, c=1, $CHCl_3$)	isolated yield (%)	$[\alpha]_D^{23}$ (°, c=1, $CHCl_3$)
1	$(CH_2)_4$		CH_2Cl_2	0.5	100	76	134.6-134.8	-150.1	73	+ 2.1
2	$(CH_2)_5$		CH_2Cl_2	0.5	100	68	114.9-115.6	-149.0	76	+ 1.9
3	$(CH_2)_2O(CH_2)_2$		DMF	1	100	73	109.4-110.2	-142.2	39	+ 2.0
4	C_2H_5	C_2H_5	DMF	2[b]	100	95	oil	-148.1	62	+ 5.3
5	H	n-C_4H_9	DMF	1	100	90	semi-solid	-134.1	58	+12.2
6	H		DMF	8	>95	50	100.6-102.7	-100.7	63	+24.4
7	H	(l-) 	DMF	8	>95	90	oil	-109.0	69	-11.8

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

In order to determine the enantiomeric excess of aminoalcohols 3 independently and to exclude possible racemization during the reduction of the sensitive aminolactones, the (l)-α-methyl-benzylamine adducts of racemic methoxylactone 10 and optically pure menthoxylactone 7 (table, entry 7 and eq. 4) were compared in the reductive conversion.

In accordance with expectation a 50:50 mixture of RS and SS diastereoisomers of 12 was obtained from racemic 10 which showed well separated C_2 and methyl-proton absorptions in the ^{1}H-NMR spectra for the two diastereoisomers. In contrast herewith reduction of 1



(R_1=H R_2=(S)-$CH(CH_3)C_6H_5$) resulted exclusively in the formation of the RS diastereoisomer of 12 indicating a diastereomeric excess >96%. Finally it was shown that the S-enantiomers of aminodiols 3 are accessible following the same two step procedure starting with (d)-(5)-menthyloxy)-2-[5H]-furanone ($[\alpha]_D^{20}$ + 139.7° (c=1, 95% ethanol; mp- 74.2-74.4°C) e.g. pyrrolidine adduct 1 (mp 133.8-134.6°C; $[\alpha]_D^{23}$+150.0°, c=1, $CHCl_3$) was obtained quantitatively.

In conclusion we have developed the first efficient asymmetric synthesis of β-aminolactones through conjugated addition of amines to α, β-unsaturated lactones.

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16. 7: $[\alpha]_D^{20}$ -136.4° (c=1, 95% ethanol); mp=70.5-70.7°C; a remarkable second order asymmetric transformation accompagnies the crystallization proces to afford enantiomerically pure 7.
17. B.L. Feringa, J.C. de Jong, J. Org. Chem., submitted.
18. Typical procedures: A equimolar mixture of 7 and the amine were stirred at room temperature in CH_2Cl_2 or DMF (table) for the appropriate reaction until addition was complete (^{1}H NMR). The solvent was removed under reduced pressure and the aminolactoned were obtained by crystallization or destillation. For the preparation of aminodiols the adducts 1 dissolved in THF were added to a solution of 2 molar excess of $LiAlH_4$ in THF at 0°C. After the appropriate reaction time the excess $LiAlH_4$ was destroyed with H_2O/10% aqueous KOH. Following extraction with THF, analytically pure aminodiols were obtained by distillation. All spectrocopic and analytical data were in agreement with the structures. The R-configuration at the acetal carbon in 7 was established via X-ray analysis of the 2,3-dimethylbutadiene Diels Alder product of 7. (J.C. de Jong, B.L. Feringa, unpublished results).
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