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TOTAL SYNTHESES OF (-)-2-DEOXYFORTAMINES

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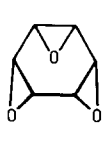
Starting from the now readily available dianhydro-deoxy(epi)inositol (2) an efficient access to suitably protected (-)-2-deoxy-fortamines (10/11) has been worked out, in which the racemic epoxide intermediates (6) are cleanly separated via their R-(+)-1-phenylethylamine-adducts (8/9).

In connection with our activities concerning the cis-trioxa-tris-σ-homobenzene 1 (tris-anhydro-cis-inositol) efficient procedures - starting from benzene - have also been developed for dianhydro-(deoxy)inositols, e.g. 2/3. With these thus readily available epoxides highly stereoselective pathways have been opened up towards a variety of biologically interesting cis-1,3(1,4)-(deoxy)inosadiamines [1,2]. A very recent example is the application of 3 for the synthesis of (-)-3-de-O-methyl-fortamine (4)[3]. Like 4 the 2-deoxy-fortamine 11c and its 3-de-O-methyl-derivative 11a (scheme, in addition to the "inositol"-numbering as used in the scheme the "fortimicine"-numbering (4) is given) are components of some new aminoglycoside antibiotics (sannamycine [4], istamycine [5]).



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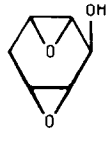

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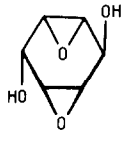

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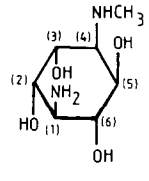


4

Following the strategy described for 4 we now used 2 as educt for a similarly attractive route to enantiomerically pure 11a/11c and to suitably protected (for glycosidation) [6] equivalents. Noticeable features of this approach are again availability of starting material [7], regioselectivity (specificity) in the two epoxide opening steps and efficiency in the separation of the diastereomeric R(+)-1-phenylethylamine-adducts [3,6].

The urethane 5 [8], obtained from 2 and methyl isocyanate (dioxane, 100°C, 5h) in practically quantitative yield (m.p. 138°C), in the presence of a strong, weakly nucleophilic base (preferably tris(dimethylamino)N-methyl-phosphineimine [9,10], acetonitrile, 20°C, 24h) cyclises regiospecifically at C-2(4) (more than 2% competition by attack at C-1(5) would have been detected). The carbamate rac-6a (m.p. 97°C, ^{1}H-nmr (250 MHz, CD_3OD) : δ = 4.98(3-H), 3.86(5-H), 3.68(4-H), 3.39(1-H), 3.27(2-H), 2.89(CH_3), 2.22(6α-H), 2.03(6β-H); $J_{1,2}$=3.8, $J_{2,3}\simeq 1$, $J_{3,4}$ = 7.5, $J_{4,5}$ = 5.0, $J_{5,6\alpha}\simeq 5$, $J_{5,6\beta}$ = 6.0, $J_{6\alpha,6\beta}$ = 16.5, $J_{6\alpha,1}$ = 3.0, $J_{6\beta,1}$ = 2.5 Hz) in aprotic solvents, e.g. $CDCl_3$, adopts a half-chair like conformation with a H-bridge between the quasi-axial 5-OH and the epoxide oxygen ($J_{5,OH}$=11 Hz), the conventionally prepared acetate 6b (95%, m.p.115°C) and ethers 6c,d (90-95%, m.p.56(82)°C) the half-chair with the group at C-5 quasi-equatorial. Independent of the nature of the R-rest the epoxide in 6a,c,d is opened by $N_3^{\ominus}$ (refl. methanol, $MgSO_4$, 4h, 94-97%) - as well as by other nucleophiles - exclusively (^{1}H-nmr, DC) at C-1 to give 7a (m.p.92°C), 7c (m.p.156°C) and 7d (m.p.134°C) [11]. The same stereospecificity is observed in the reactions of 6a/c with R-(+)-1-phenylethylamine (refl. n-propanol, 3h, quantitative). From ca. 1 M methanolic solutions of the diastereomers 8a/9a ca. 30% 8a crystallise; after "flash"-chromatography[12] of the mother liquor (in 8 g batches) 45% of each diastereomer are reproducibly obtained. The mixture 8c/9c is separated directly by chromatography (8 g batches, 46% each). In the 250 ^{1}H-nmr spectra (Tab.) the diastereomers 8a/9a, 8c/9c and 8d/9d are clearly distinguishable by shift differences for 5α-H, 5β-H and 6-H. Clean hydrogenolysis of 8a,c/9a,c to 10a,e and ent-10a,e is achieved with 10% Pd/C in pure[13] methanol/0.3 equiv. HCl (1bar H_2, 20°C, 24h). 10a(ent-10a) are characterised as hydrochlorides 10b(ent-10b) (^{1}H-nmr), as triacetates 10c(ent-10c) (m.p.

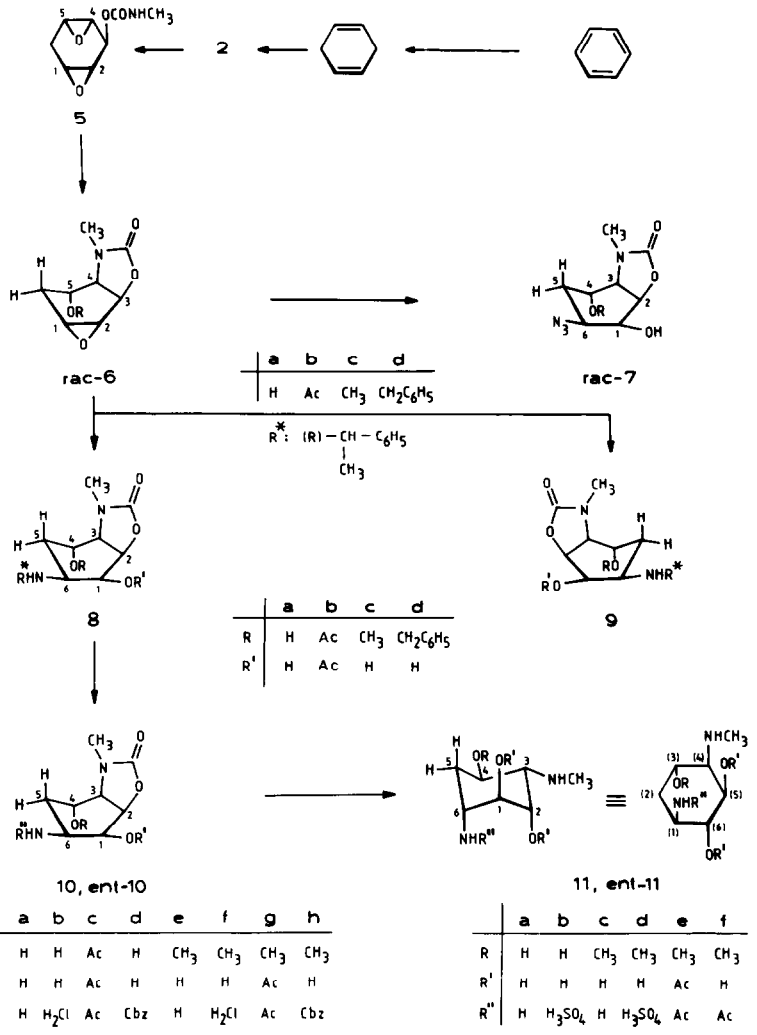
Tab. ^{1}H-nmr data (250 MHz, J(Hz)) for 7a, 8a/c, 9a/c, 10b/f and 11b/d

	1-H	2-H	3-H	4-H	5α-H	5β-H	6-H	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5\alpha(\beta)}$	$J_{5\alpha,5\beta}$	$J_{5\alpha(\beta),6}$	$J_{6,1}$
7a*	3.56	4.48	3.79	4.19	2.01	1.62	3.72	7.5	7.5	3.0	5.0(3.0)	13.0	5.0(10.0)	
8a*	3.51	4.46	3.69	4.04	1.77	1.31	2.97	8.0	8.0	4.0	5.5(3.5)	14.0	5.0(9.5)	9.5
9a*	3.52	4.30	3.61	4.07	1.87	1.59	2.56	8.0	8.0	4.5	5.5(3.5)	14.0	5.0(9.5)	10.5
8c**	3.5	4.41	3.66	3.6	1.68	1.24	2.79	7.5	7.5	3.5	4.5(3.0)	14.0	4.5(10.5)	10.5
9c**	3.55	4.29	3.6	3.6	2.12	1.42	2.55	7.5	7.5		4.5(3.0)	13.5	4.5(10.0)	10.0
10b*	3.63	4.48	3.78	4.23	2.06	1.75	3.32	7.5	7.5	4.0	4.0(4.0)	14.0	4.0(10.5)	10.5
10f*	3.57	4.43	3.86-3.96		2.29	1.73	3.23	7.5	7.5	3.0	4.0(3.0)	14.0	4.0(11.5)	11.5
11b***	3.89	4.17	3.14	4.08	1.9	-2.05	3.45	5	5	9.0	5 (9)		5 (5)	5
11d***	4.10	4.35	3.41	3.95	2.08	2.42	3.66	3.8	3.8	9.0	10.5(4.5)	15.0	4.5(4.5)	4

*) : CD_3OD **) : $CDCl_3$ ***) : D_2O

210°C, $[\alpha]_D$=+111°(-104°), c=1, $CHCl_3$) and carbamates 10d (ent-10d) (m.p.222-225°C, $[\alpha]_D$ = 44° (+43.6°), c=1, CH_3OH), 10e (ent-10e) as hydrochlorides 10f (ent-10f) (m.p.240-245°C, $[\alpha]_D$= -62.4°(+62.5°), c=1, CH_3OH) and diacetates 10g (ent-10g) (m.p.202-204°C, $[\alpha]_D$=84.7°(+82.4°), c=1, $CHCl_3$). After N-specific benzyloxycarbonylation of 10e (benzyl chloroformate, acetone/water 1:1, sodium carbonate, 3h, 95%) in 10h ($[\alpha]_D$= +43.5°, c=1, $CHCl_3$) the OH-function is set up

Scheme



for glycosidation. After alkaline hydrolysis of 10a (ent-10a) and of 10e (ent-10e) (barium-hydroxide, water, 100°C, 3h, 97%) the diaminotriols 11a (ent-11a) and the known 11c (ent-11c)[4] ($[\alpha]_D$= -37°(lit. -44°)[4] (+37°), c=1, H_2O) are transformed into their crystalline bis-ammonio-hydrogensulfate salts 11b (ent-11b/11d (ent-11d) and the acetates 11f (ent-11f), resp. ($[\alpha]_D$= +90° (lit. +108°) (-90°), c=1, H_2O). The assignment of the diastereomers 8a/9a is based on the correlation with 8c/9c by methylation of 8a to 8c.

The procedure, in which R(+)-1-phenylethylamine is used for the introduction of an amino function and for the separation of diastereomers, allows also an efficient synthesis of the sporamine enantiomers from rac-6c [7].

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6) For a new and versatile total synthesis of suitably protected purpurosamine C portions s. B. Schwesinger, R. Schwesinger, H. Prinzbach, Tetrahedron Lett., in press.

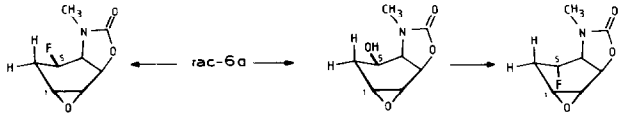
7) A recently published synthesis of rac-2-deoxy-fortamine starts from 1,3-cyclohexadiene and features rac-6c as intermediate, into which the second amino-function is introduced by the regiospecific $N_3^{\ominus}$-addition (rac-7c): S. Knapp, M.J. Sebastian, H. Ramanathan, J. Org. Chem. 48 (1983) 4786; cf. S. Knapp, D.V. Patel, J. Am. Chem. Soc. 105 (1983) 6985 (± sporamine).

8) The new compounds are fully analysed (elemental analysis, IR, ^{1}H-, ^{13}C-nmr).

9) R. Schwesinger, unpublished.

10) Using e.g. R-(+)-1,1,3,3-tetramethyl-4-(1-phenylethyl)-guanidine as a chiral base no appreciable enantioselectivity in the formation of 6 was achieved.

11) In preliminary experiments (B. Seitz, Diplomarbeit, Univ. Freiburg, 1984) with rac-6a and the DAST-reagent rac-12 is obtained in only moderate yields; in the epimeric alcohol rac-13, however, a rather uniform S_N2-substitution (rac-14) occurs (cf. T. Tsuchiya, T. Torii, Y. Susuki, S. Umezawa, Carbohydr. Res. 116 (1983) 277; T. Torii, T. Tsuchiya, S. Umezawa, ibid. 116 (1983) 289, cit. lit.).



rac-12 rac-13 rac-14

12) W. C. Still, M. Kahn, A. Mitra, J. Org. Chem. 43 (1978) 2923.

13) In methanol containing some acetone (techn. grade) 10a is accompanied by its 6-N-isopropyl-derivative.

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