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REGIOCONTROL IN THE SYNTHESIS OF OPTICALLY ACTIVE AMINO-4-PENTENEDIOLS VIA EPOXY-4-PENTENOLS. NOVEL ACYCLIC ADENOSINE ANALOGUES[1]

Walter Hümmer, Tibor Gracza, and Volker Jäger*

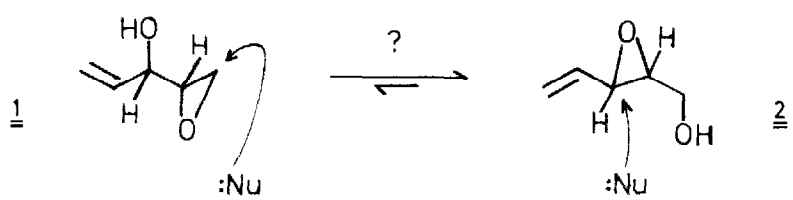
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg

Summary: *Regioisomeric erythro-1- and -3-amino-4-pentenediols are available from 1,2-epoxy-4-pentenol* **1** *by aminolysis of* **1** *or of the rearranged 2,3-epoxypentenol* **2**. *With adenine, D- and L-enantiomers of the nucleoside analogue* **10** *are obtained via the chloride* **9** *and the mesylate* **12**, *resp.*

The optically active epoxypentenol **1**, introduced in 1985/6,[2,3] has proven a versatile building block.[2-5] Starting from divinylcarbinol (DVC), this secondary epoxy alcohol can be obtained in both enantiomeric forms and high purity[2,4,6] – an inherent feature of the powerful Asymmetric Sharpless Epoxidation (A.S.E.).[7] In addition, **1** (erythro) with dilute alkali undergoes "epoxide migration" (Payne rearrangement[8]);[2,3,5] in the equilibrium mixture the regioisomer **2** (threo) predominates[5] (1/2 3:97) which makes **2** an equally attractive, complementary building block.[5,9]

Hydrolysis in slightly acidic medium, through attack at C-1 in **1** and at C-3 in **2**, respectively, has furnished opposite enantiomers of the corresponding pentenetriols[2,5,10] (stereocontrol at two levels[2]). Further, highly regioselective reductions of **1** and **2** have led to six out of eight 4-pentenediol isomers.[5]

It is tempting to extend this scheme of regio/stereocontrol and apply other nucleophiles. This is promising if the basicity of these nucleophiles does <u>not</u> induce equilibration of the epoxides as stated in the hydrolysis of **1** by strong alkali,[2] or as it has proven crucial to achieve substitution at C-1 of 'normal' 2,3-epoxyalcohols.[8b]

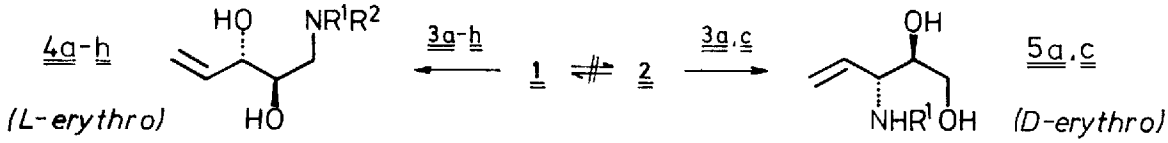


1 **2**

We now report that <u>amines</u> **3**[12-15] specifically open the epoxide ring of **1** at the terminal site, and that of **2** at the allylic position, without interfering rearrangement! A selection of experiments is summarized in Table 1.

These results show that a broad range of amino functions – from ammonia, primary and secondary aliphatic amines, and aniline as a typical aromatic amine – can be added to **1** to furnish

Table 1. Aminopentenediols 4 and 5 from epoxy-4-pentenols 1 and 2, respectively.



Entry/ Epoxide		Amine 3		Conditions	Product/ Yield [%]		Physical Data (b.p.[f] [°C/Torr] or m.p.[°C]; $[\alpha]_D^t$)
1	1	a	H_3N	a)	4a	quant.	120-150/0.008; $[\alpha]_D^{22}$ = -15.8 (c=2.217, MeOH)
2	1	b	H_2NCH_2Ph	b)	4b	83	38; $[\alpha]_D^{20}$ = +8.8 (c=1.750, $CHCl_3$)
3	1	c	$H_2NCHMePh$ (R)	b)	4c	96	40; $[\alpha]_D^{20}$ = +40.9 (c=1.370, $CHCl_3$)
4	1	d	$H_2NCH(CH_3)_2$	b)	4d	90	52-53; $[\alpha]_D^{22}$ = -3.3 (c=0.675, $CHCl_3$)
5	1	e	$H_2NC(CH_3)_3$	b)	4e	quant.	130-150/0.008; $[\alpha]_D^{22}$ = -2.0 (c=2.425, $CHCl_3$)
6	1	f	$HN(CH_3)_2$	b)	4f	96[e]	44[e]; $[\alpha]_D^{20}$ = -8.3[e] (c=1.535, $CHCl_3$)
7	1	g	$HN[CH(CH_3)_2]_2$	b)	4g	74	140-160/0.008; $[\alpha]_D^{22}$ = +13.9 (c=0.905, $CHCl_3$)
8	1	h	H_2NPh	b)	4h	90	50-52; $[\alpha]_D^{22}$ = +7.2 (c=1.245, MeOH)
9	2	a	H_3N	c)	5a	quant.	130-150/0.008; $[\alpha]_D^{22}$ = +19.5 (c=0.435, MeOH)
10	2	c	$H_2NCHMePh$ (R)	d)	5c	90	120-130/0.005; $[\alpha]_D^{20}$ = +41.8 (c=0.9765, $CHCl_3$)

a) With liquid ammonia, -78°C to room temp. over-night; similarly with conc. aqueous ammonia, room temp., 1 d. b) Room temp., 1 to 5 d; the epoxide **1** or **2** is dissolved in excess amine **3**; work-up by fractional distillation. c) Conc. aqueous ammonia, room temp., 3 d. d) 100°C, 27 h. e) Yield of crude **4f**, pure by NMR; data from material sublimed at 40°C/5 Torr, 52%. f) Kugelrohr.

1-amino-4-pentenediols 4. None of the regioisomers 5 expected from 2 could be detected in the crude products by NMR analysis. Likewise, when 2 was treated with ammonia 3a or phenethylamine 3c, the corresponding 3-aminodiols 5a,c were obtained in high yield and purity.[16] The aminodiols 4 and 5 constitute vinyl-substituted aminopropanediols, and should be of pharmaceutical interest when compared to the many well-known aryloxypropanolamines (β-blockers).[13]

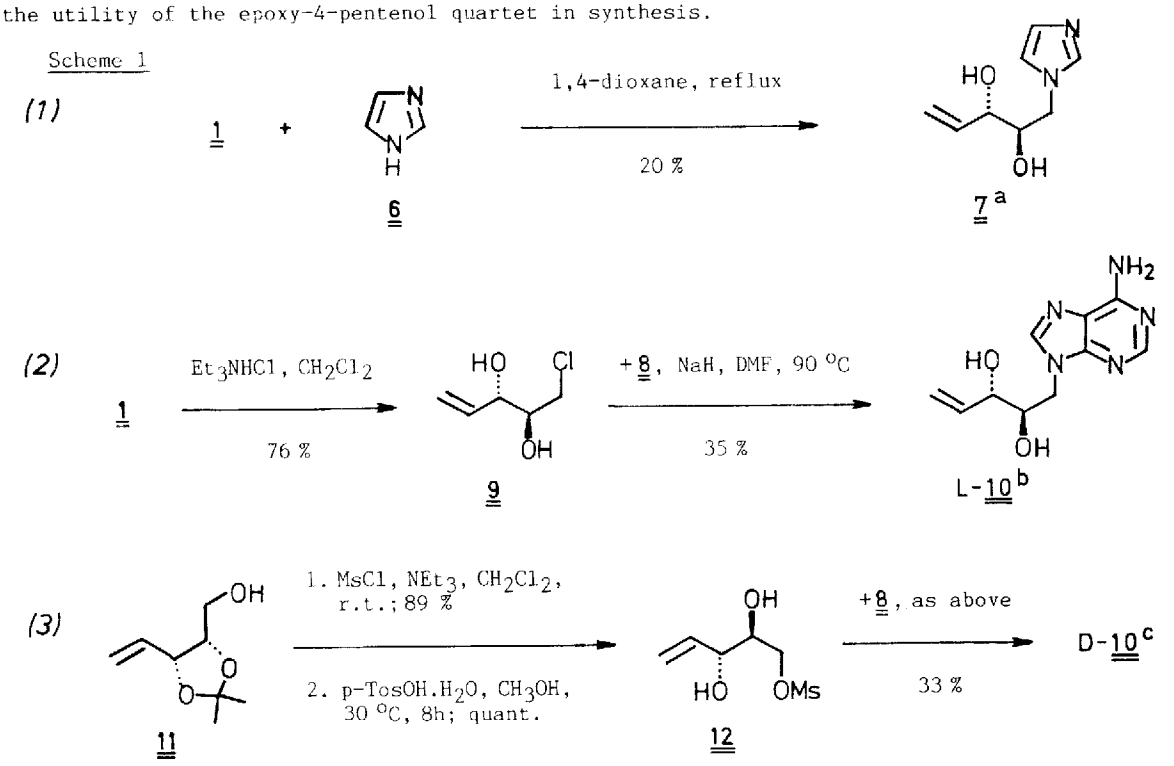
With respect to the enantiomeric purity of the new aminopentenediols, we note that this was not ascertained in most cases; we presume an e.r. of >96:4 for the 1-aminodiols 4, and of >93:7 for the 3-amino compounds 5 just as derived for the parent epoxides.[2,6] We have sought to verify this using (R)-α-phenethylamine 3c (e.r. > 97:3); the third stereogenic centre thus added in 4c and 5c would serve as an 'e.r. indicator'. Indeed, with 4c and 5c, some of the ^{13}C NMR signals showed a small neighbour peak of 3 to 6% intensity; these await identification (cp.[16]).

Next, the alkylation of less-reactive NH-heterocycles with 1 was explored, guided by results in the glycidol series.[13] With imidazole 6, slow reaction was encountered which necessitated heating in 1,4-dioxane[17a] to afford the diol 7 as an analytically pure oil in low yield, see Scheme 1, eq (1). Adenine (8) with sodium hydride in DMF at 100°C[17a] did react with 1 but led to a brown mixture of at least 5 compounds. The latter problem could be solved by recurring to an earlier observation when amine hydrochlorides were tested to effect the above aminolysis of 1: this had produced the (then undesired) 1-chloropentenediol 9. The sodium salt of

adenine 8,[17] prepared as above, with 9 at 90°C in DMF was converted to a near quantitative mixture of N^9-/N^3-substituted products (ca. 3:1 by NMR). Crystallization of this solid from ethanol gave the analytically pure adenosine analogue L-10,[18] see eq (2) in Scheme 1. The A.S.E. procedure would likewise be amenable to furnish the "natural" erythro compound D-10. In this case, however, we chose to rely on some of the ribonolactone chemistry we have developed recently,[2,19] since this would secure maximum optical purity.[6] Thus, the known triol acetonide 11[2,19] was transformed to the mono-mesylate 12 and this, as above, added to the sodium salt of adenine 8. Again (vide supra), a mixture of alkylation products was formed which provided pure D-10 on recrystallization. The adenine derivatives L-10 and D-10 of "natural" and "unnatural" configuration, readily prepared in 100 mg-quantity, represent novel acyclic nucleoside analogues to be tested for antiviral activity.

In conclusion, the protocol of stereo- and regiocontrol outlined should broaden considerably the utility of the epoxy-4-pentenol quartet in synthesis.

Scheme 1



a) **7**: pale-yellow oil, spectroscopically pure after chromatography; $[\alpha]_D^{20} = +3.0$ (c = 0.3535, MeOH).
b) L-**10**: colourless crystals, m.p. 216 - 218 °C (from ethanol); $[\alpha]_D^{20} = +2.8$ (c = 0.375, DMF).
c) D-**10**: colourless crystals, m.p. 218 - 220 °C; $[\alpha]_D^{20} = -3.33$ (c = 0.350, DMF).

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