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Enantiospecific synthesis of some bioactive amino alcohols and related compounds from cyclohexylideneglyceraldehyde

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Abstract

Two bioactive amino alcohols or related derivatives, 2-aminohexadecanol **I** and *erythro*-9-(2-hydroxy-3-nonyl)adenine hydrochloride (EHNA hydrochloride) **IIa**, have been synthesized from some enantiomerically pure 3-alkylglycerols. The required C-3 epimeric 3-alkylglycerols were, in turn, prepared by simple Grignard addition to cyclohexylideneglyceraldehyde **1** followed by column chromatography.

1. Introduction

Amino carbinols have assumed contemporary importance in medicinal chemistry due to their various biological profiles.[1] They may be categorized as adrenaline or ephedrine types, depending on the presence of the amino group at a primary or a secondary carbon atom. The former can be easily prepared by reduction of the corresponding cyanohydrins which again can be synthesized via various chemical and enzymatic routes.[2] However, synthesis of the latter class is not so straightforward, especially when the target contains a primary carbinol function. Very recently, we have shown[3] that addition of Grignard reagents to cyclohexylideneglyceraldehyde **1** provides easy access to the C-3 epimers of alkanetriol derivatives which are useful chirons for the synthesis of various classes of bioactive compounds. We envisaged that the products, 3-alkylglycerols, are tailor-made for the synthesis of the ephedrine type of amino carbinols or more complex related compounds. In this paper, we wish to report the synthesis of two such compounds, 2-aminohexadecanol **I** and *erythro*-9-(2-hydroxy-3-nonyl)-adenine (EHNA) **II**, from two 3-alkylglycerols. Compound **I** was very recently shown[4] to possess the minimum basic structural skeleton as a simpler analogue of the immunosuppressant, ISP1 and reported[5] to exhibit immunosuppressive activity comparable to that of FTY720. EHNA on the other hand, has been implicated as an important inhibitor for adenosine deaminase (ADA).[6] This synthetic inhibitor,

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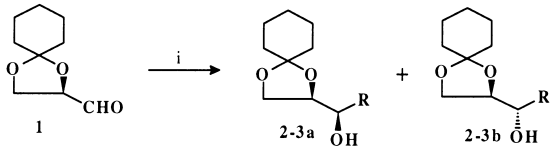
despite showing moderate biological activity might emerge as the most desirable co-drug for use against viruses and cancer in view of its low toxicity, reversible ADA binding and the capacity to prevent the deamination of chemotherapeutic agents containing adenine bases such as 8-azaadenosine.[7] In addition, ADA-inhibition leads[8] to increased levels of adenosine which in turn protects injured tissues in cerebral and myocardial ischemia.

2. Results and discussion

Given the above importance of the compounds **I** and **II**, we explored the Grignard addition approach to **1** for their synthesis (Scheme 1). Compared to the existing syntheses of **I**[5] and **II**,[9] the present method is far superior in terms of brevity, simplicity and overall efficiency. For compound **I**, since its (*R*)-antipode was most active, we prepared the eutomer, while for EHNA, we prepared its (2*R*,3*S*)-isomer as its hydrochloride **IIa**, although (2*S*,3*R*)-**II** is most active among its possible diastereomers. However, in all cases, the flexibility of the synthetic scheme would allow the preparation of any desired isomer with equal efficiency.



2: R = $CH_3(CH_2)_{13}$; 3: R = $CH_3(CH_2)_5$

i) $CH_3(CH_2)_{13}MgBr$ or $CH_3(CH_2)_5MgBr$/THF

Scheme 1.

The initial task was the preparation of the required alkylglycerol derivatives for which aldehyde **1** was reacted with suitable Grignard reagents viz. *n*-tetradecylmagnesium bromide for **I** and *n*-hexylmagnesium bromide for **II**, respectively (Scheme 1).

The diastereoselectivity of each of the reactions is shown in Table 1. The resultant *syn*-carbinols **2a** and **3a** and *anti*-carbinols **2b** and **3b** were were easily isolated in an enantiomerically pure form by column chromatography. Their *syn*- and *anti*-stereochemistry were confirmed by comparing the ^{1}H NMR resonances of the -CH_2O and -CHO groups with those reported in literature.[9a,b] In both cases, the high field (500 MHz) ^{1}H NMR spectra of the *syn*-compounds **2a** and **3a** showed three multiplets in the ratio of 1:1:2 protons between δ 3.5–4.20 while the same for the corresponding *anti*-compounds **2b** and **3b** contained four well separated multiplets (1:1:1:1) at δ 3.7–4.0 (1H). The C-3 epimeric carbinols were then used for the synthesis of **I** and **IIa**, respectively, as discussed below.

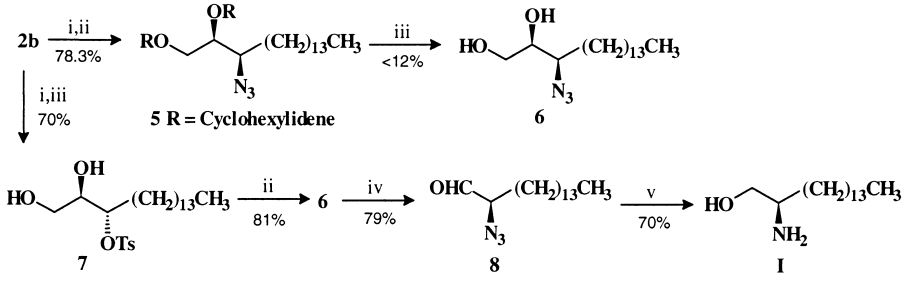
Table 1
Stereochemical course of Grignard addition to **1**

Grignard Reagent	Diast. Ratio[a]	% Yield (*syn*/*anti*)[b]
$CH_3(CH_2)_{13}MgBr$	5:7	63 (25.8/37.2)
$CH_3(CH_2)_5MgBr$	8:13	81.3 (29.7/51.6)

[a]Determined by GLC analysis on DB 5 capillary column.
[b]Based on isolated products.

2.1. Synthesis of **I**

The triol derivative **2b** was tosylated and subjected to azidation with inversion to give compound **5**. However, attempted acidic hydrolysis of its acetal function led to some undesired product along with a minor amount of **6**. Consequently, the tosylate of **2b** was directly deacetalized with trifluoroacetic acid (TFA) to give **7** which was converted to the azide **6**. Its $NaIO_4$ cleavage furnished the aldehyde **8** which on LAH reduction finally afforded the amino alcohol (*R*)-**I** (Scheme 2).

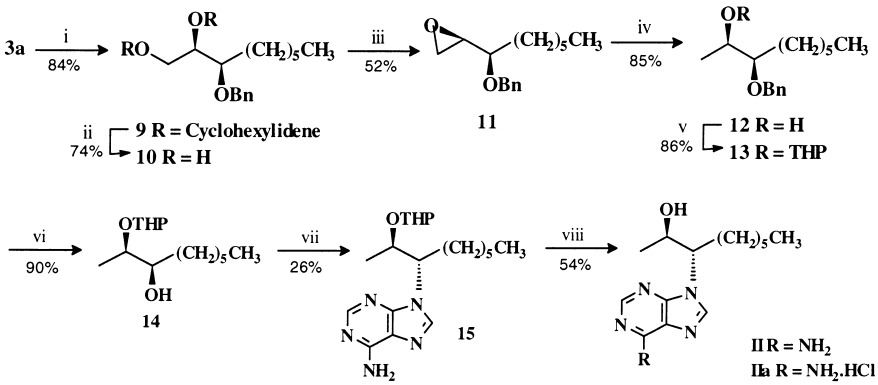


i) *p* - TsCl/py; ii) NaN_3/DMF/Δ; iii) TFA, iv) $NaIO_4/CH_3CN/H_2O$; v) LAH/ether.

Scheme 2.

2.2. Synthesis of **IIa**

For the synthesis (Scheme 3), the *syn*-carbinol **3a** was benzylated to give **9** which on deacetalization afforded compound **10**. Treatment of this compound with *p*-TsCl and NaH smoothly furnished epoxide **11** which was reduced to yield the diol derivative **12**. After protection of the hydroxyl function as a tetrahydropyranyl ether **13**, the benzyl group was removed by catalytic hydrogenation to give compound **14**. This was mesylated and reacted with sodium adenylate to afford compound **15**, which upon acid catalyzed deprotection gave the title compound **IIa**.



i) NaH/BnBr/Δ, ii) TFA, iii) NaH/*p* - TsCl, iv) LAH/ether, v) DHP/PPTS/CH_2Cl_2, vi) H_2/10% Pd - C/EtOH, vii) MsCl/py; NaH/Adenine/DMF - HMPA/Δ, viii) MeOH/HCl.

Scheme 3.

Thus, a simple synthetic approach for the syntheses of two different types of amino carbinols or related compounds has been formulated. The enantiomeric homogeneity of the starting chirons **2b** and **3a** used for the syntheses was established by ^1H NMR spectra. Based on this estimation, the synthetic

target compounds should also be enantiomerically pure. This is also corroborated by comparison of their chiroptical data with those reported in literature.[4,9b]

3. Experimental

The IR spectra were scanned as thin films with a Perkin–Elmer spectrophotometer model 837. The ^{1}H NMR were recorded with a Bruker AC-200 (200 MHz) instrument. The optical rotations were measured with a Jasco DIP 360 polarimeter. The GLC analyses were carried out with a Chemito instrument fitted with a DB 5 capillary column (15 M×0.25 mm) using He (1 ml/min) as the carrier gas and under temp. prog. 80–240°C @ 4°C/min. All anhydrous reactions were carried out under an Ar atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

*3.1. General method of preparation of **2a**, **2b**, **3a** and **3b***

To a stirred solution of the Grignard reagent [0.03 mol, prepared from the respective bromide (0.03 mol) and Mg turnings (0.864 g, 0.036 mol)] in THF (60 ml) was added **1** (1.7 g, 0.01 mol) in THF (20 ml). After stirring for 12 h at room temperature, the reaction was quenched with an aqueous saturated solution of NH_4Cl. The organic portion was separated, the aqueous part was extracted with ether and the combined organic extracts were washed with brine and dried. Removal of the solvent in vacuo and column chromatography (silica gel, 0–15% EtOAc/hexane) of the residue furnished the respective *syn*- and *anti*-products.

2a: Yield 0.95 g (25.8%); $[\alpha]_D^{22}$ +1.29 (c 0.9, $CHCl_3$); IR: 3440, 1480, 1380 cm^{-1}; ^{1}H NMR: δ 0.9 (dist. t, 3H), 1.32 (br. s, 26H), 1.68 (br. s, 10H), 2.7 (br. s, D_2O exchangeable, 1H), 3.48–3.59 (m, 1H), 3.75–3.87 (m, 1H), 4.04–4.24 (m, 2H). Anal. calcd for $C_{23}H_{44}O_3$: C 74.94, H 12.03; found: C 75.12; H 11.88. **2b**: Yield 1.37 g (37.2%); $[\alpha]_D^{22}$ +5.2 (c 0.84, $CHCl_3$); IR: 3380, 1470, 1380 cm^{-1}; ^{1}H NMR: δ 0.9 (dist. t, 3H), 1.3 (br. s, 26H), 1.68 (br. s, 10H), 1.9 (br. s, D_2O exchangeable, 1H), 3.71–3.78 (m, 1H), 3.82–3.86 (m, 1H), 3.90–3.94 (m, 1H), 3.97–4.02 (m, 1H). Anal. calcd for $C_{23}H_{44}O_3$: C 74.94; H 12.03; found: C 74.68; H 11.78.

3a: Yield 0.76 g (29.7%); $[\alpha]_D^{22}$ +5.31 (c 0.5, $CHCl_3$); IR: 3440, 1480, 1380 cm^{-1}; ^{1}H NMR: δ 0.88 (dist. t, 3H), 1.3–1.6 (m, 10H), 1.68 (br. s, 10H), 1.8 (br. s, D_2O exchangeable, 1H), 3.51–3.60 (m, 1H), 3.82–3.90 (m, 1H), 4.0–4.2 (m, 2H). Anal. calcd for $C_{15}H_{28}O_3$: C 70.27; H 11.01; found: C 70.43; H 11.20. **3b**: Yield 1.32 g (51.6%); $[\alpha]_D^{22}$ +8.53 (c 1.5, $CHCl_3$); IR: 3380, 1470, 1380 cm^{-1}; ^{1}H NMR: δ 0.88 (dist. t, 3H), 1.3–1.6 (m, 10H), 1.68 (br. s, 10H), 2.7 (br. s, D_2O exchangeable, 1H), 3.77–3.83 (m, 1H), 3.86–3.89 (m, 1H), 3.93–3.96 (m, 1H), 3.98–4.04 (m, 1H). Anal. calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01; found: C 70.39; H 10.86.

*3.2. (2*R*,3*R*)-3-Azido-1,2-cyclohexylideneheptadecane **5***

To a cooled (0°C) and stirred solution of **2b** (1.37 g, 3.7 mmol) and pyridine (0.33 ml, 4.09 mmol) in CH_2Cl_2 (20 ml) was added *p*-TsCl (0.852 g, 4.47 mmol). After stirring for 2 h at the same temperature, the mixture was kept in the freezer for 12 h. It was poured into ice-water, the organic layer was separated and the aqueous part extracted with $CHCl_3$. The combined organic extract was washed with water and brine and then dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0–5% EtOAc/hexane) of the residue furnished the corresponding tosylate. Yield: 1.77 g (91%); IR: 3090, 3060,

1620, 1460, 1370, 1180 cm^{-1}; ^1H NMR: δ 0.86 (dist. t, 3H), 1.32 (br. s, 26H), 1.64 (br. s, 10H), 2.43 (s, 3H), 3.77–3.79 (m, 1H), 3.88–3.93 (m, 1H), 3.96–4.0 (m, 1H), 4.24–4.30 (m, 1H), 7.30 (d, *J*=8 Hz, 2H), 7.81 (d, *J*=8 Hz, 2H).

A mixture of the above compound (1.77 g, 3.39 mmol) and NaN_3 (0.663 g, 10.2 mmol) in DMF (20 ml) was gently heated at 80°C for 6 h. After cooling to room temperature, the mixture was poured into a large excess of cold water and extracted with ether. The ether layer was thoroughly washed with water and brine. After drying, the extract was concentrated and the crude product purified by column chromatography (silica gel, 0–5% EtOAc/hexane) to furnish pure **5**. Yield: 1.15 g (86%); IR: 2100, 1450, 1280 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, 3H), 1.28 (br. s, 26H), 1.64 (br. s, 10H), 3.5–3.54 (m, 1H), 3.81–3.86 (m, 1H), 3.88–4.11 (m, 2H).

*3.3. (2*R*,3*S*)-3-Tosyloxyheptadecane-1,2-diol **7***

A mixture of the tosylate of **2b** (1.5 g, 2.87 mmol) in TFA (10 ml) and H_2O (5 ml) was stirred for 48 h at 50°C. Most of the solvent was removed under reduced pressure, the residue was diluted with EtOAc and the organic layer washed with water and brine then dried and concentrated. The product was purified by column chromatography (silica gel, 0–5% $CHCl_3$/MeOH) to furnish pure **7**. Yield: 0.888 g (70%); IR: 3440, 3060, 1640, 1460, 1370, 1180 cm^{-1}; ^1H NMR: δ 0.90 (dist. t, 3H), 1.29 (br. s, 26H), 2.37 (s, 3H), 2.6 (br. s, D_2O exchangeable, 2H), 3.77–3.93 (m, 3H), 4.17–4.28 (m, 1H), 7.32 (d, *J*=8.4 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 2H).

*3.4. (2*R*,3*R*)-3-Azidoheptadecane-1,2-diol **6***

As described earlier, reaction of **7** (0.88, 1.99 mmol) and NaN_3 (0.388, 5.97 mmol) in DMF (20 ml) at 80°C gave **6** after work-up and purification by column chromatography (0–5% MeOH/$CHCl_3$). Yield: 0.504 g (81%); $[\alpha]_D^{22}$ +3.39 (c 1.3, $CHCl_3$); IR: 3380, 2100, 1450, 1280 cm^{-1}; ^1H NMR: δ 0.93 (dist. t, 3H), 1.32 (br. s, 26H), 2.15 (br. s, D_2O exchangeable, 2H), 3.53–3.57 (m, 1H), 3.78–3.84 (m, 1H), 3.86–4.08 (m, 2H). Anal. calcd for $C_{17}H_{35}O_2N_3$: C 65.13; H 11.25; N 13.41; found: C 65.34; H 11.12; N 13.18.

*3.5. (2*R*)-2-Azidohexadecanal **8***

To a cooled (0°C) and stirred solution of **6** (0.5 g, 1.59 mmol) in CH_3CN (30 ml) and H_2O (20 ml) was added $NaIO_4$ (0.684 g, 3.19 mmol) in portions. After stirring for 1 h at the same temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was taken in ether and the extract washed successively with water, aqueous $NaHSO_3$, water, aqueous $Na_2S_2O_3$, water, and brine. After drying, the solvent was removed in vacuo to give pure **8** which was used as such for the next step. Yield: 0.355 g (79%); IR: 2720, 2100, 1720, 1280 cm^{-1}; ^1H NMR: δ 0.89 (dist. t, 3H), 1.32 (br. s, 26H), 4.12–4.28 (m, 1H), 9.71 (d, *J*=1.5 Hz, 1H).

*3.6. (2*R*)-2-Aminohexadecan-1-ol **I***

To a cooled (0°C) and stirred suspension of LAH (0.15 g, 3.94 mmol) in ether (30 ml) was added compound **8** (0.545 g, 1.94 mmol). The reaction mixture was gently refluxed for 3 h, quenched with aqueous saturated Na_2SO_4, and the mixture filtered to get rid of the solid precipitate which was thoroughly washed with EtOAc. The organic extract was concentrated in vacuo and the residue

chromatographed over silica gel (0–20% EtOAc/hexane) to give **I**. Yield: 0.348 g (70%); $[\alpha]_D^{22}$ −3.9 (c 0.28, MeOH) (lit.[4] $[\alpha]_D^{22}$ −3.7 (c 0.4, MeOH)); IR: 3440, 3060, 3030 cm^{-1}; ^1H NMR: δ 0.89 (t, *J*=6 Hz, 3H), 1.3 (br. s, 24H), 1.51–1.72 (m, 3H), 3.05–3.14 (m, 1H), 3.55–3.68 (m, 2H), 4.87 (br. s, 2H). Anal. calcd for $C_{16}H_{35}ON$: C 74.64; H 13.70; N 5.44; found: C 74.48; H 13.52; N 5.61.

*3.7. (2*R*,3*R*)-3-Benzyloxy-1,2-cyclohexylidenenonane **9***

To a stirred suspension of NaH (0.737 g, 15.35 mmol, 50% suspension in oil) in THF (20 ml) compound **4a** (1.31 g, 5.12 mmol) in THF (10 ml) was added. After the brisk evolution of H_2 was over, the mixture was refluxed for 0.5 h, brought to room temperature and BnBr (1.05 g, 6.14 mmol) in THF (10 ml) added to it. The mixture was subsequently refluxed until the completion of the reaction (~2 h, cf. TLC). It was brought to room temperature, poured into ice-water, the organic layer separated and the aqueous portion extracted with ether. The combined organic extract was washed with water and brine and then dried. Removal of solvent followed by column chromatography (silica gel, 0–10% EtOAc/hexane) gave pure **9**. Yield: 1.49 g (84%); $[\alpha]_D^{22}$ +18.1 (c 0.46, $CHCl_3$); IR: 3090, 3030, 1610, 1450, 720 cm^{-1}; ^1H NMR: δ 0.88 (t, *J*=6 Hz, 3H), 1.21–1.38 (m, 10H), 1.48–1.83 (m, 10H), 3.48–3.56 (m, 1H), 3.78–3.84 (m, 1H), 3.88–3.96 (m, 2H), 4.55 (s, 1H), 4.62 (s, 1H), 7.35 (m, 5H). Anal. calcd for $C_{22}H_{34}O_3$: C 76.26; H 9.89; found: C 76.23; H 10.10.

*3.8. (2*R*,3*R*)-3-Benzyloxynonane-1,2-diol **10***

Compound **9** (1.77 g, 5.12 mmol) was deacetalized using TFA (10 ml) and H_2O (5 ml) in the same manner as for compound **7**. Identical isolation followed by chromatography of the crude product (silica gel, 0–5% MeOH/$CHCl_3$) gave pure **10**. Yield: 1.0 g (74%); $[\alpha]_D^{22}$+6.7 (c 0.8, $CHCl_3$); IR: 3440, 3090, 1620, 1090, 700 cm^{-1}; ^1H NMR: δ 0.90 (t, *J*=6 Hz, 3H), 1.29 (br. s, 10H), 2.44 (br. s, D_2O exchangeable, 2H), 3.51–3.59 (m, 2H), 3.65–3.81 (m, 1H), 4.14–4.61 (m, 3H), 7.35 (s, 5H). Anal. calcd for $C_{16}H_{26}O_3$: C 72.14; H 9.84; found: C 72.34; H 10.12.

*3.9. (2*R*,3*R*)-3-Benzyloxy-1-epoxynonane **11***

To a stirred suspension of NaH (0.294 g, 6.12 mmol, 50% suspension in oil) in THF (20 ml) was added compound **10** (0.74 g, 2.78 mmol) in THF (10 ml). After the initial reaction subsided, *p*-TsCl (0.636 g, 3.34 mmol) in THF (10 ml) was added and the mixture stirred for 4 h at room temperature. The mixture was poured into ice-water, the organic layer separated and the aqueous portion extracted with ether. The combined organic extract was washed with water and brine and then dried and concentrated in vacuo. The residue was chromatographed over silica gel (0–5% EtOAc/hexane) to give pure **11**. Yield: 0.360 g (52%); $[\alpha]_D^{22}$ +31.5 (c 0.42, $CHCl_3$); IR: 3090, 1370, 1215, 1190 cm^{-1}; ^1H NMR: δ 0.9 (t, *J*=6 Hz, 3H), 1.2–1.5 (m, 10H), 2.5–2.7 (m, 2H), 2.8–3.0 (m, 1H), 3.5–4.1 (m, 1H), 4.55 (s, 1H), 4.62 (s, 1H), 7.30 (m, 5H). Anal. calcd for $C_{16}H_{24}O_2$: C 77.37; H 9.74; found: C 77.18; H 9.96.

*3.10. (2*R*,3*R*)-3-Benzyloxynonan-2-ol **12***

To a cooled (0°C) and stirred suspension of LAH (0.165 g, 4.4 mmol) in ether (30 ml) was added compound **11** (0.72 g, 2.9 mmol). After stirring for 1 h, the reaction was quenched with aqueous saturated Na_2SO_4, and the mixture filtered to get rid of the solid precipitate. The organic extract was concentrated in vacuo and the residue chromatographed over silica gel (0–10% EtOAc/hexane) to give **12**. Yield: 0.620

g (85%); $[\alpha]_D^{22}$ +42.8 (c 0.28, $CHCl_3$); IR: 3430, 3090, 3030, 1460 cm^{-1}; ^1H NMR: δ 0.89 (t, *J*=6 Hz, 3H), 1.14 (d, *J*=6 Hz, 3H), 1.2–1.4 (m, 10H), 2.1 (br. s, D_2O exchangeable, 1H), 3.5–3.7 (m, 1H), 3.9–4.0 (m, 1H), 4.51 (s, 1H), 4.65 (s, 1H), 7.26 (m, 5H). Anal. calcd for $C_{16}H_{26}O_2$: C 76.75; H 10.47; found: C 76.78; H 10.61.

*3.11. (2*R*,3*R*)-3-Benzyloxy-2-tetrahydropyranyloxynonane **13***

A mixture of **12** (0.6 g, 2.4 mmol), DHP (0.242 g, 2.88 mmol) and PPTS (0.02 g) in CH_2Cl_2 (20 ml) was stirred at room temperature until completion of the reaction (~8 h). The reaction was quenched with 10% aqueous $NaHCO_3$, the organic layer separated and the aqueous portion extracted with $CHCl_3$. The organic extract was washed with water and brine and then dried. Removal of solvent followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) gave pure **13**. Yield: 0.689 g (86%); $[\alpha]_D^{22}$ +15.7 (c 0.78, $CHCl_3$); IR: 3090, 3065, 1450, 870, 810 cm^{-1}; ^1H NMR: δ 0.9 (t, *J*=6 Hz, 3H), 1.16 (d, *J*=6 Hz, 3H), 1.3–1.5 (m, 10H), 1.6–1.8 (m, 6H), 3.41–3.59 (m, 2H), 3.82–4.03 (m, 2H), 4.55 (br. s, 0.5H), 4.71 (br. s, 0.5H), 4.9 (s, 2H), 7.32 (m, 5H). Anal. calcd for $C_{21}H_{34}O_3$: C 75.40; H 10.25; found: C 75.24; H 10.37.

*3.12. (2*R*,3*R*)-3-Hydroxy-2-tetrahydropyranyloxynonane **14***

A mixture of **13** (0.68 g, 2.04 mmol) and 10% Pd–C (50 mg) in EtOH (20 ml) was stirred under a slight positive pressure of H_2 gas. After the required uptake of H_2, the mixture was diluted with ether and passed through a pad (2 in.) of silica gel and the eluent was concentrated in vacuo to give pure **14**. Yield: 0.45 g (90%); $[\alpha]_D^{22}$ +10.2 (c 0.68, $CHCl_3$); IR: 3440, 880, 810 cm^{-1}; ^1H NMR: δ 0.87 (t, *J*=6 Hz, 3H), 1.17 (d, *J*=6 Hz, 3H), 1.2–1.45 (m, 10H), 1.55–1.7 (m, 6H), 2.16 (br. s, D_2O exchangeable, 1H), 3.34–3.63 (m, 2H), 3.73–3.98 (m, 2H), 4.5 (br. s, 0.5H), 4.65 (br. s, 0.5H). Anal. calcd for $C_{14}H_{28}O_3$: C 68.81; H 11.55; found: C 68.74; H 11.43.

*3.13. (2*R*,3*S*)-3-(Adenin-9-yl)-2-nonanol hydrochloride **IIa***

To a stirred solution of **14** (0.45 g, 1.84 mmol) in dry pyridine (10 ml) was added methanesulphonyl chloride (0.235 g, 2.05 mmol). After stirring for 48 h at room temperature, the mixture was poured onto crushed ice and extracted with $CHCl_3$. The organic extract was washed with water and brine and then dried. Removal of the solvent gave the crude mesylate which was used as such for the next step in view of its instability. IR: 1350, 880, 810 cm^{-1}.

To a stirred suspension of pentane washed NaH (0.113 g, 2.36 mmol, 50% suspension in oil) in dry DMF (10 ml) was added adenine (0.316 g, 2.34 mmol). The mixture was stirred at room temperature for 24 h, HMPA (2 ml) added, followed by the above mesylate in DMF (2 ml), and stirring continued for 7 days at 50°C. It was cooled to room temperature, quenched with MeOH and concentrated in vacuo. Water was added to the residue which was then extracted with EtOAc. The organic extract was washed with half-saturated brine, brine and then dried. Solvent removal followed by preparative chromatography (silica gel, 10% MeOH/$CHCl_3$) gave **15**. Yield: 0.173 g (26%); $[\alpha]_D^{22}$ −61.5 (c 0.98, MeOH); IR: 1670, 1600, 870, 820 cm^{-1}; ^1H NMR: δ 0.89 (t, *J*=6 Hz, 3H), 1.22–1.54 (m, 7H), 1.62–2.17 (m, 12H), 3.57–3.72 (m, 3H), 4.45–4.65 (m, 2H), 7.96 (br. s, 2H), 8.42 (s, 1H), 8.72 (s, 1H).

A solution of **15** (0.170 g, 0.5 mmol) in MeOH (10 ml) containing one drop of HCl was stirred at room temperature for 12 h. Removal of the solvent under vacuum at 40°C gave a gummy product which was recrystallized from EtOH/ether to obtain **IIa**. Yield: 0.08 g (54%); $[\alpha]_D^{22}$ −30.8 (c 0.9, EtOH), (lit.[9b]

$[\alpha]_D^{17}$ −31.7 (c 0.5, EtOH)); IR: 3300, 1680, 1600 cm^{-1}; ^1H NMR (d_6-DMSO): δ 0.81 (t, *J*=6 Hz, 3H), 1.18–1.31 (m, 6H), 1.36 (d, *J*=6 Hz, 3H), 2.43–2.56 (m, 4H), 4.51–4.63 (m, 1H), 4.68–4.78 (m, 1H), 8.5 (br. s, 2H), 8.59 (s, 1H), 8.78 (s, 1H).

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