Synthesis of 6'- and 7'-(3-Furylmethyl) Derivatives of *endo*-1',2',3',4'-Tetrahydro-1',4'-ethano-2'-naphthylethanol with Potential Activity on Na^+,K^+-ATPase

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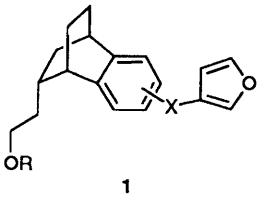
The 6'- and 7'-(3-furylmethyl) derivatives of *endo*-1',2',3',4'-tetrahydro-1',4'-ethano-2'-naphthylethanol **1** have been synthesized as simplified analogues of digitoxigenin. The skeleton was built starting from 3,4-dihydro-1,4-ethanonaphthalen-2(1*H*)-one **2**; the substituents were introduced by a Wittig–Horner reaction followed by a highly stereoselective hydrogenation to form the *endo* derivative **4** and successive acylation with 3-furoyl chloride to give the intermediates **8a** and **8b**. Tested compounds showed only moderate activity on the Na^+,K^+-ATPase, with IC_{50} values in the 10^{-4} mol dm^{-3} range.

Digitalis cardiac glycosides are well known drugs, clinically used for treatment of congestive heart failure.[1] Their action is mainly due to inhibition of Na^+,K^+-ATPase, an enzyme located in the cell membrane which promotes the outward transport of Na^+ and the inward transport of K^+.[2] Recently, the existence of endogenous digitalis-like factors that may be responsible for essential hypertension[3] has opened a new field in the study of compounds acting on the Na^+,K^+-ATPase.

The most potent inhibitors of Na^+,K^+-ATPase are natural products such as digoxin, digitoxin and ouabain; some of them, or their derivatives, are still widely used today for the treatment of congestive heart failure, despite their relative toxicity. The search for less toxic agents acting on Na^+,K^+-ATPase prompted much research on a variety of natural compounds. The above mentioned compounds (and their aglycones) have been modified with either the butenolide ring replaced by other heterocycles or the sugar residue replaced by various chains, and these derivatives were shown to be active on Na^+,K^+-ATPase.[4a] The steroidal skeleton was also replaced by simple structures such as deoxybenzoin,[5] stilbene,[6] flavone[7] and 1-benzoyl-2,3-dihydroindole,[8] which seem to have been chosen simply as spacers between the 3β-hydroxy function and the 17β-heterocyclic ring of aglycones. Some of these derivatives in fact inhibited the enzyme, albeit in a limited way.



1

X = CH_2, CHOH, C=O

R = H, CH_2CH_2N

In this paper we describe the synthesis of compounds with the general structure **1**. We expected them to be potential ligands of Na^+,K^+-ATPase since 1,2,3,4-tetrahydro-1,4-ethanonaphthalene, suitably substituted with an *endo* chain, can resemble the bent steroidal skeleton of the cardiac glycosides. For synthetic simplicity, the 3-furyl residue was chosen as a substitute for the butenolide ring (this substitution on digitoxigenin is known to maintain the inhibition potency on the Na^+,K^+-ATPase).[9] The computer generated superposition of selected conformations from the MM2-minimized † structures of the enantiomers of compound **12a** along with digitoxigenin, taken as the model template, showed that both the heterocycles and the hydroxy functions of the two molecules were very close, as shown in Fig. 1.

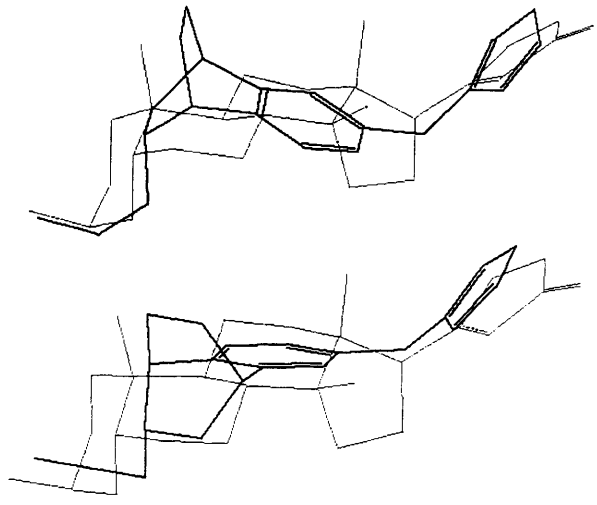


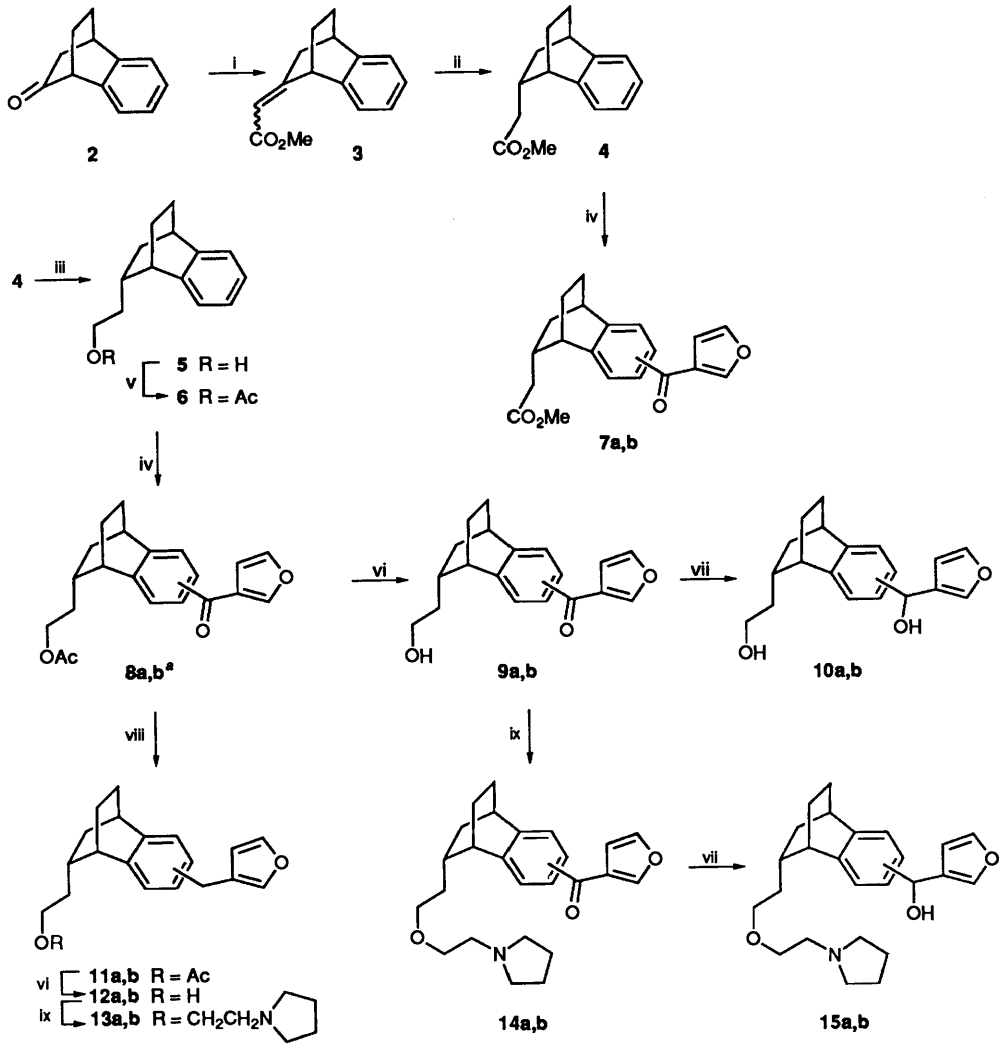
Fig. 1 Computer generated superposition of selected conformations of the enantiomers of compound **12a** and digitoxigenin

In order to enhance the binding to the enzyme, a basic function was also introduced by forming an ether of the hydroxy group using an aminoalkyl halide, since it has been reported that the C-3 binding region of the receptor contains carboxylic groups.[4b]

Results and Discussion

Synthesis.—Starting from the known ketone **2**,[10] the α,β-unsaturated ester **3** was obtained in a 1:1 *E*:*Z* mixture by a Wittig–Horner reaction. The subsequent atmospheric pressure hydrogenation of this mixture over PtO_2 in ethyl acetate at −30 °C gave the ester **4** with an *endo*:*exo* ratio of 97:3 and an overall yield of 90%. This was a large improvement compared to the 75:25 ratio obtained from the first attempted reduction over 5% Pd–charcoal at room temperature. Friedel–Crafts acylation on the ester **4** with 3-furoyl chloride and aluminium trichloride gave a 35:65 mixture of 2',6'- and 2',7'-disubstituted compounds **7a** and **7b** that we were not able to separate. The acylation was then performed on the ester **6**, obtained by lithium aluminium hydride reduction of the ester **4**, followed by esterification with

† MM2 minimizations were performed with the MM2(91) program implemented in the McMimic 2.0 molecular modelling software package and distributed by InStar Software, Ideon Research Park, S-223 70 Lund, Sweden.



Scheme 1 *Reagents and conditions:* i, NaOMe, $(MeO)_2POCH_2CO_2Me$, MeOH, room temp. to reflux; ii, H_2, PtO_2, AcOEt; iii, $LiAlH_4$, THF; iv, furoyl chloride, $AlCl_3$, $CHCl_3$; v, AcCl, pyridine, C_6H_6; vi, NaOH, MeOH; vii, $NaBH_4$, MeOH; viii, $NaBH_3CN$, ZnI_2, $ClCH_2CH_2Cl$, reflux; ix, *N*-(2-chloroethyl)pyrrolidine, NaH, THF, reflux. [a] The separation was performed on the mixture of compounds **8a** and **8b**; the successive reactions were carried out on the separate isomers.

acetyl chloride. A 45:55 mixture of 2′,6′-:2′,7′-disubstituted compounds **8a** and **8b** was obtained with only negligible amounts of the 2′,5′- and 2′,8′-disubstituted derivatives. This was in agreement with the strong β orientation of electrophilic aromatic substitution reactions of 1,2,3,4-tetrahydro-1,4-ethanonaphthalenes reported by Tanida *et al.*[11] Compounds **8a** and **8b** could only be separated using preparative HPLC and from this point on, the synthesis was performed on the separated 2′,6′- and 2′,7′-disubstituted *endo* isomers. The saponifications of the acetate groups of compounds **8a**, **8b**, **11a** and **11b** were accomplished using sodium hydroxide in methanol and the resulting alcohols **9a**, **9b**, **12a** and **12b** were alkylated under the Williamson condition. The reductions of the ketones of **9a**, **9b**, **14a** and **14b** to the corresponding alcohols **10a**, **10b**, **15a** and **15b** (mixture of diastereoisomers) were performed with sodium borohydride in methanol while the reductions of the ketones **8a** and **8b** to the corresponding methylene derivatives **11a** and **11b** were accomplished with the zinc iodide–sodium cyanoborohydride method.[12]

NMR Analysis; Structural and Stereochemical Assignments.— Pure samples of both the *Z* and *E* isomers of α,β-unsaturated ester **3** were separated by flash chromatography for analytical purposes. Their stereochemistry was straightforwardly assigned on the basis of simple chemical shift considerations. In fact, the 1′-H signal of the *Z* isomer is strongly deshielded (δ 5.30) by the *syn* ester function, in contrast to the corresponding signal in the *E* isomer (δ 3.65). Moreover, a strong nuclear Overhauser effect (NOE) observed on 1′-H (15% increase of intensity) after presaturation of the vinylic α-H confirmed the assignment of the *E* isomer.

The *endo*/*exo* relative configuration of compound **4** was determined on the basis of the following considerations. Due to the presence of a planar W arrangement[13] in 1,2,3,4-tetrahydro-1,4-ethanonaphthalene, the $3'\text{-}_{endo}$ and $10'\text{-}_{anti}$ hydrogens* at the end of this W exhibit a characteristic long-range coupling constant of 2.9 Hz. In our case (Fig. 2), the signal of the $3'\text{-}H_{endo}$ of compound **4** shows, besides the coupling constants with 2′-H and 4′-H, a ^4J long-range coupling of 2.9 Hz with $10'\text{-}H_{anti}$, in contrast with 2′-H which shows couplings to 1′-H, $3'\text{-}H_{endo}$, $3'\text{-}H_{exo}$ and $\alpha\text{-}CH_2$, but it is not coupled with 9′-H.

The 2′,6′- and 2′,7′-disubstituted constitutional isomers **8a** and **8b** were structurally identified by means of NOE experiments. Presaturation of bridgehead hydrogen 4′-H

* A group on the lowest numbered bridge which points towards the highest numbered bridge is termed *exo*, whilst that pointing away from it is called *endo*. However, a group on the highest numbered bridge pointing towards the lowest numbered bridge is called *syn* and that pointing away from it is called *anti*.

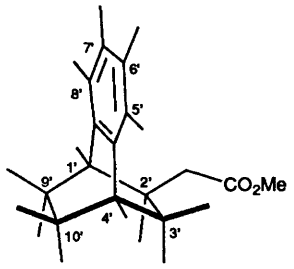


Fig. 2 Perspective view of molecule 4, showing the W arrangement of coupled $3'$-$_{endo}$ and $10'$-$_{anti}$ hydrogens

resulted in an intensity enhancement of the resonance of the corresponding opposite *peri* aromatic 5'-H, which was thus readily identified. On the basis of its characteristic coupling pattern ($J_{ortho\ 5'\text{-}H/6'\text{-}H}$ 8 Hz, in the 2',7'-disubstituted isomer or $J_{meta\ 5'\text{-}H/7'\text{-}H}$ 2 Hz in the 2',6'-analogue), the two isomers could be easily distinguished.

Biological Data.—Compounds **9**, **10**, **12–15** (**a** and **b**) were evaluated as racemic mixtures in the displacement of the specific ^{3}H-ouabain binding[14] and as inhibitors of the activity of Na^+,K^+-ATPase.[15] All showed moderate activity in both tests, with IC_{50} values in the 10^{-4} mol dm^{-3} range.

Experimental

Elemental analyses were performed by Redox, Cologno Monzese, Italy. IR spectra were measured as film using a Perkin-Elmer 1310 Infrared spectrophotometer. NMR spectra were obtained from deuteriochloroform solutions with a Bruker AC-300 spectrometer at 300.13 (^{1}H) or 75.48 (^{13}C) MHz. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as internal standard and coupling constants (J) are measured in Hz. ^{13}C NMR signals were attributed on the basis of the multiplicities obtained from DEPT experiments, in some cases through 2D NMR heteronuclear correlation spectroscopy and were checked for internal consistency. Mass spectral data were obtained with electron impact ionization technique at 70 eV from a Finnigan INCOS-50 mass spectrometer using the direct exposure probe (DEP). Preparative HPLC was performed on a Waters Delta Prep 3000 using PrepPak-500/Silica columns. All organic extracts were dried over Na_2SO_4 and samples were chromatographed on silica gel in all instances.

Methyl (E/Z)-1',2',3',4'-*Tetrahydro*-1',4'-*ethano*-2'-*naphthylideneacetate* **3**.—Sodium methoxide (18.8 g, 350 mmol) was dissolved in dry methanol (150 cm^3) under an atmosphere of nitrogen whilst being cooled in an ice-bath. After dissolution methyl *O*,*O*-dimethylphosphonoacetate (49.1 cm^3, 350 mmol) was then added dropwise to the mixture causing a white precipitate to form. A solution of compound **2** (15.0 g, 87 mmol) in dry methanol (100 cm^3) was added dropwise at room temperature to the mixture causing the white precipitate to dissolve and the colour of the solution to change to dark red and then green. After 0.5 h at room temperature, the solution was heated to reflux for 0.5 h. Glacial acetic acid (14.9 cm^3, 260 mmol) was added to the solution which was then concentrated under reduced pressure, diluted with ethyl acetate (500 cm^3), washed with water (200 cm^3 × 3), dried and finally evaporated to dryness. The residue was purified by chromatography (hexane–ethyl acetate, 9:1) to yield compound **3** (18.0 g, 90%; *E*/*Z* mixture 1:1) as a colourless oil, which was used directly in the next step. Pure samples of the (*Z*) and (*E*) isomers of **3** were obtained by flash chromatography (hexane–ethyl acetate, 95:5).

(*Z*)-Isomer **3**. Oil (Found: C, 78.7; H, 7.0. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.1%); δ_H 1.45–1.70 (2 H, m, $9'$-H_{anti} and $10'$-H_{anti}), 1.75–1.95 (2 H, m, $9'$-H_{syn} and $10'$-H_{syn}), 2.28 (1 H, dddd, *J* 16.9, 2.9, 2.7 and 2.5, $3'$-H_{endo}), 2.57 (1 H, dt, *J* 16.9 and 2.6, $3'$-H_{exo}), 3.20 (1 H, quintet, *J* 2.6, 4'-H), 3.72 (3 H, s, OMe), 5.30 (1 H, m, 1'-H), 5.63 (1 H, t, *J* 2.6, 2-H) and 7.1–7.35 (4 H, Ar-H).

(*E*)-Isomer **3**. Oil (Found: C, 78.6; H, 6.9%); δ_H 1.45–1.70 (2 H, m, $9'$-H_{anti} and $10'$-H_{anti}), 1.75–1.95 (2 H, m, $9'$-H_{syn} and $10'$-H_{syn}), 2.65 (1 H, dddd, *J* 18.7, 2.9, 2.7 and 2.5, $3'$-H_{endo}), 2.95 (1 H, dt, *J* 18.7 and 2.6, $3'$-H_{exo}), 3.30 (1 H, quintet, *J* 2.6, 4'-H), 3.64 (1 H, m, 1'-H), 3.66 (3 H, s, OMe), 5.85 (1 H, t, *J* 2.6, 2-H) and 7.10–7.35 (4 H, Ar-H).

Methyl endo-1',2',3',4'-*Tetrahydro*-1',4'-*ethano*-2'-*naphthylacetate* **4**.—A mixture of compound **3** (7.00 g, 30 mmol) and PtO_2 (0.35 g) in ethyl acetate (300 cm^3) was cooled to −20 °C and hydrogenated at atmospheric pressure for 8 h. The catalyst was filtered off and washed with ethyl acetate (100 cm^3). The combined filtrate and washings were evaporated to dryness to yield compound **4** (7.02 g, 99%; *endo*:*exo* 97:3) as a colourless oil, which was used for the next step without further purification. A sample was purified by flash chromatography (hexane–ethyl acetate, 95:5) for elemental analysis (Found: C, 78.0; H, 7.75. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.9%); ν_{max}/cm^{-1} 1736 (CO_2); δ_H 0.85–0.95 (1 H, ddt, J_{gem} 12.9, $J_{3'\text{-}endo,2'}$ 4.9, $J_{3'\text{-}endo,4'}$ 2.9, $J_{3'\text{-}endo,10'\text{-}anti}$ 2.9, $3'$-H_{endo}), 1.35–1.50 (2 H, m, $9'$-H_{anti} and $10'$-H_{anti}), 1.70–1.90 (2 H, m, $9'$-H_{syn} and $10'$-H_{syn}), 1.74 (1 H, dd, J_{gem} 15.4, $J_{CHH\text{-}CO,2'}$ 8.0, CH*H*CO), 1.97 (1 H, dd, J_{gem} 15.4, $J_{CHH\text{-}CO,2'}$ 7.2, C*H*HCO), 2.10 (1 H, ddd, J_{gem} 12.9, $J_{3'\text{-}exo,2'}$ 10.0, $J_{3'\text{-}exo,4'}$ 2.8, $3'$-H_{exo}), 2.42 (1 H, ddddd, $J_{2',3'\text{-}exo}$ 10.0, $J_{2',3'\text{-}endo}$ 4.9, $J_{2',1'}$ 2.2, J_{2',CH_2CO} 7.2 and 8.0, 2'-H), 2.83 (1 H, m, 1'-H), 2.98 (1 H, m, 4'-H), 3.65 (3 H, s, OMe) and 7.10–7.30 (4 H, m, ArH); δ_C 173.3 (CO), 143.8 (C-4'a), 140.8 (C-8'a), 126.2, 125.8, 125.5, 123.4 (Ar-C), 51.3 (OMe), 41.3 (C-2), 38.8 (C-1'), 34.2 (C-3' and C-4'), 33.8 (C-2'), 24.6 (C-9') and 26.5 (C-10').

2-(endo-1',2',3',4'-*Tetrahydro*-1',4'-*ethano*-2'-*naphthyl*)*ethanol* **5**.—A solution of the ester **4** (11.00 g, 43 mmol) in dry THF (100 cm^3) was added dropwise to a suspension of $LiAlH_4$ (21.00 g, 43 mmol) in dry THF (100 cm^3) under N_2. The mixture was stored at room temperature overnight and then quenched by the careful addition of water (21 cm^3), followed by 20% aq. NaOH (63 cm^3) and then water (21 cm^3). The organic phase was separated, dried and filtered and the precipitate was washed with ethyl acetate (100 cm^3). The combined filtrate and washings were evaporated to dryness to yield the alcohol **5** (8.50 g, 98%) as a colourless oil. A sample of this was purified by flash chromatography (hexane–ethyl acetate, 7:3) for elemental analysis (Found: C, 82.9; H, 8.7. $C_{14}H_{18}O$ requires C, 83.1; H, 9.0%); ν_{max}/cm^{-1} 3400 (OH); δ_H 0.80–1.00 (2 H, m, CH*H*–CH_2O and $3'$-H_{endo}), 1.10 (1 H, t, OH), 1.20–1.35 (1 H, m, C*H*H–CH_2O), 1.35–1.50 (2 H, m, $9'$-H_{anti} and $10'$-H_{anti}), 1.70–1.85 (2 H, m, $9'$-H_{syn} and $10'$-H_{syn}), 2.00–2.15 (2 H, m, 2'-H and $3'$-H_{exo}), 2.83 (1 H, m, 1'-H), 2.98 (1 H, m, 4'-H), 3.55–3.63 (2 H, m, CH_2OH) and 7.10–7.20 (4 H, m, Ar-H); δ_C 143.9 (C-4'a), 141.5 (C-8'a), 125.9, 125.6, 125.2, 123.3 (Ar-C), 60.7 (CH_2O), 40.2 (C-2), 39.0 (C-1'), 34.4 (C-3' and C-4'), 33.5 (C-2'), 25.2 (C-9') and 26.7 (C-10'); *m*/*z* 202 (M^+, 48.2%) and 130 (100).

2-(endo-1',2',3',4'-*Tetrahydro*-1',4'-*ethano*-2'-*naphthyl*)*ethyl Acetate* **6**.—A solution of acetyl chloride (2.35 cm^3, 33 mmol) in dry chloroform (10 cm^3) was added dropwise to a solution of the alcohol **5** (6.10 g, 30 mmol) and dry pyridine (2.66 cm^3, 33 mmol) in dry chloroform (90 cm^3) at 0 °C. After 1 h the mixture was poured into brine. The organic layer was separated, washed with 1 mol dm^{-3} HCl (100 cm^3 ×2) followed by water (100 cm^3), dried and then evaporated to dryness to give the ester **6** (7.20 g, 99%) as an oil that was used without further purification in the next preparation (Found: C, 78.45; H, 8.25. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%); ν_{max}/cm^{-1} 1730 (CO_2); δ_H 0.85–1.08 (2 H, m, CH*H*CH_2O and $3'$-H_{endo}), 1.30–1.50 (3 H,

m, C*H*HCH$_2$O, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.70–1.90 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 1.91–2.10 (2 H, m, 2′-H and 3′-H$_{exo}$), 2.05 (3 H, s, COMe), 2.83 (1 H, m, 1′-H), 3.00 (1 H, m, 4′-H), 3.95–4.10 (2 H, m, CH$_2$O) and 7.10–7.25 (4 H, m, Ar-H).

Methyl endo-6′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*ethano*-2′-*naphthylacetate* **7a** *and Methyl* endo-7′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′,*ethano*-2′-*naphthylacetate* **7b**.—Furoyl chloride[16] (1.68 g, 12.9 mmol) in chloroform (10 cm^3) was added dropwise to a stirred mixture of the methyl ester **4** (1.00 g, 4.3 mmol) and AlCl$_3$ (1.72 g, 12.9 mmol) in chloroform (40 cm^3). After 2 h the reaction mixture was poured into brine (50 cm^3) and extracted with chloroform (50 cm^3 × 2). The extract was washed with 5% aq. Na$_2$CO$_3$ (50 cm^3) and then with water (50 cm^3), dried and evaporated to dryness. Flash chromatography (CH$_2$Cl$_2$–diisopropyl ether, 99:1) afforded the acylated products **7a** and **7b** (1.22 g, 87%) in the ratio 35:65 as a pale yellow oil (Found: C, 73.8; H, 6.0. C$_{20}$H$_{20}$O$_4$ requires C, 74.1; H, 6.2%); *m*/*z* 324 (M$^+$, 54.6%), 95 (100).

7a: δ_H 0.85–0.95 (1 H, ddt, J_{gem} 12.9, $J_{3'\text{-}endo,2'}$ 4.9, $J_{3'\text{-}endo,4'}$ 2.9, $J_{3'\text{-}endo,10'\text{-}anti}$ 2.9, 3′-H$_{endo}$), 1.35–1.50 (2 H, m, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.70–1.90 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 1.74 (1 H, dd, J_{gem} 15.4, $J_{CHH\text{–}CO,2'}$ 8.0, CH*H*CO), 1.97 (1 H, dd, J_{gem} 15.4, $J_{CHH\text{–}CO,2'}$ 7.2, C*H*HCO), 2.10 (1 H, ddd, J_{gem} 12.9, $J_{3'\text{-}exo,2'}$ 10.0, $J_{3'\text{-}exo,4'}$ 2.8, 3′-H$_{exo}$), 2.42 (1 H, ddddd, $J_{2',3'\text{-}exo}$ 10.0, $J_{2',3'\text{-}endo}$ 4.9, $J_{2',1'}$ 2.2, J_{2',CH_2CO} 7.2 and 8.0, 2′-H), 2.83 (1 H, m, 1′-H), 2.98 (1 H, m, 4′-H), 3.65 (3 H, s, OMe), 6.91 (1 H, m, 4-H$_{fur}$), 7.22 (1 H, d, $J_{8',7'}$ 7.7, 8′-H), 7.51 (1 H, t, *J* 1.9, 5-H$_{fur}$), 7.65 (1 H, d, $J_{5',7'}$ 1.9, 5′-H), 7.71 (1 H, dd, $J_{7',8'}$ 7.7, $J_{7',5'}$ 1.9, 7′-H) and 7.96 (1 H, m, 2-H$_{fur}$); δ_C 189.5 (ArCO), 172.9 (CO$_2$), 148.3 (C-2$_{fur}$), 146.3 (C-8′a), 144.2 (C-4′a), 143.7 (C-5$_{fur}$), 137.1 (C-6′), 127.0, 125.5, 123.9 (C-5′, C-7′ and C-8′), 126.6 (C-3$_{fur}$), 110.4 (C-4$_{fur}$), 51.4 (OMe), 41.2 (C-2), 39.0 (C-1′), 34.3 (C-4′), 33.7 (C-2′), 33.9 (C-3′), 26.1 (C-10′) and 24.6 (C-9′).

7b: δ_H 0.85–0.95 (1 H, ddt, J_{gem} 12.9, $J_{3'\text{-}endo,2'}$ 4.9, $J_{3'\text{-}endo,4'}$ 2.9, $J_{3'\text{-}endo,10'\text{-}anti}$ 2.9, 3′-H$_{endo}$), 1.35–1.50 (2 H, m, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.70–1.90 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 1.74 (1 H, dd, J_{gem} 15.4, $J_{CHHCO,2'}$ 8.0, CH*H*CO), 1.97 (1 H, dd, J_{gem} 15.4, $J_{CHHCO,2'}$ 7.2, C*H*HCO), 2.10 (1 H, ddd, J_{gem} 12.9, $J_{3'\text{-}exo,2'}$ 10.0, $J_{3'\text{-}exo,4'}$ 2.8, 3′-H$_{exo}$), 2.42 (1 H, ddddd, $J_{2',3'\text{-}exo}$ 10.0, $J_{2',3'\text{-}endo}$ 4.9, $J_{2',1'}$ 2.2, J_{2',CH_2CO} 7.2 and 8.0, 2′-H), 2.83 (1 H, m, 1′-H), 2.98 (1 H, m, 4′-H), 3.65 (3 H, s, OMe), 6.93 (1 H, m, 4-H$_{fur}$), 7.26 (1 H, d, $J_{5',6'}$ 7.7, 5′-H), 7.51 (1 H, t, *J* 1.9, 5-H$_{fur}$), 7.65 (1 H, d, $J_{8',6'}$ 1.9, 8′-H), 7.74 (1 H, dd, $J_{6',5'}$ 7.7, $J_{6',8'}$ 1.9, 6′-H) and 7.98 (1 H, m, 2-H$_{fur}$); δ_C 189.6 (ArCO), 172.9 (CO$_2$), 149.5 (C-4′a), 148.4 (C-2$_{fur}$), 143.7 (C-5$_{fur}$), 141.0 (C-8′a), 136.6 (C-7′), 126.6 (C-3$_{fur}$), 127.6, 125.9, 123.6 (C-8′, C-6′ and C-5′), 110.4 (C-4$_{fur}$), 51.4 (OMe), 41.3 (C-2), 38.8 (C-1′), 34.4 (C-4′), 33.8 (C-3′), 33.7 (C-2′), 26.2 (C-9′) and 24.6 (C-10′).

2-[endo-6′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*ethano*-2′-*naphthyl*]*ethyl Acetate* **8a** *and* 2-[endo-7′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*ethano*-2′-*naphthyl*]*ethyl Acetate* **8b**.—Furoyl chloride[16] (11.00 g, 84 mmol) in chloroform (140 cm^3) was added dropwise to a stirred mixture of the acetate **6** (6.80 g, 28 mmol) and AlCl$_3$ (11.15 g, 84 mmol) in chloroform (140 cm^3) at −20 °C. The temperature of the mixture was raised to −15 °C after which the mixture was allowed to warm to room temperature overnight. After this it was poured into a mixture of ice and 1 mol dm^{-3} HCl (100 cm^3). The aq. phase was extracted with chloroform (100 cm^3 × 3), and the combined extracts were washed with 5% aq. Na$_2$CO$_3$ (100 cm^3) and then with water (100 cm^3), dried and finally evaporated to dryness. The residue was purified by chromatography (hexane–ethyl acetate, 80:20) to give the acylated products **8a** and **8b** (8.50 g, 90%) in a 45:55 ratio as a pale yellow oil. The two isomers were separated by preparative HPLC (CH$_2$Cl$_2$–acetone, 99.5:0.5).

8a: oil (Found: C, 74.2; H, 6.3. C$_{21}$H$_{22}$O$_4$ requires C, 74.5; H, 6.55%); ν_{max}/cm^{-1} 1730 (CO$_2$) and 1620 (ArCO); δ_H 0.85–1.10 (2 H, m, CH*H*CH$_2$O and 3′-H$_{endo}$), 1.25–1.50 (3 H, m, C*H*HCH$_2$O, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.75–1.92 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 2.02–2.13 (2 H, m, 2′-H and 3′-H$_{syn}$), 2.06 (3 H, s, COMe), 2.95 (1 H, m, 1′-H), 3.10 (1 H, m, 4′-H), 4.04 (2 H, m, CH$_2$OCO), 6.93 (1 H, dd, $J_{4.2}$ 0.8, $J_{4.5}$ 1.9, 4-H$_{fur}$), 7.24 (1 H, d, $J_{8',7'}$ 7.3, 8′-H), 7.51 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.68 (1 H, d, $J_{5',7'}$ 1,9, 5′-H), 7.72 (1 H, dd, $J_{7',8'}$ 7.3, $J_{7',5'}$ 1.9, 7′-H) and 7.97 (1 H, m, 2-H$_{fur}$).

8b: oil (Found: C, 74.2; H, 6.25. C$_{21}$H$_{22}$O$_4$ requires C, 74.5; H, 6.55%); ν_{max}/cm^{-1} 1730 (CO$_2$) and 1640 (ArCO); δ_H 0.85–1.10 (2 H, m, CH*H*CH$_2$O and 3′-H$_{endo}$), 1.25–1.50 (3 H, m, C*H*HCH$_2$O, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.75–1.92 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 2.02–2.13 (2 H, m, 2′-H and 3′-H$_{syn}$), 2.06 (3 H, s, COMe), 2.95 (1 H, m, 1′-H), 3.10 (1 H, m, 4′-H), 4.04 (2 H, m, CH$_2$OCO), 6.92 (1 H, dd, $J_{4.2}$ 0.8, $J_{4.5}$ 1.9, 4-H$_{fur}$), 7.25 (1 H, d, $J_{5',6'}$ 7.3, 5′-H), 7.51 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.67 (1 H, d, $J_{8',6'}$ 1.9, 8′-H), 7.74 (1 H, dd, $J_{6',5'}$ 7.3, $J_{6',8'}$ 1.9, 6′-H) and 7.97 (1 H, m, 2-H$_{fur}$).

2-[endo-6′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*ethano*-2′-*naphthyl*]*ethanol* **9a**.—1 Mol dm^{-3} NaOH (3.3 cm^3) was added dropwise to a solution of the acetate **8a** (1.00 g, 3.0 mmol) in methanol (15 cm^3) whilst the temperature was kept constant. After 2 h the mixture was concentrated under reduced pressure, diluted with water (20 cm^3) and extracted with ethyl acetate (30 cm^3 × 3). The combined extracts were washed with water (10 cm^3 × 2), dried and evaporated to dryness to yield the alcohol **9a** (0.80 g, 90%) as a pale yellow oil (Found: C, 76.8; H, 6.5. C$_{19}$H$_{20}$O$_3$ requires C, 77.0; H, 6.8%); ν_{max}/cm^{-1} 3400 (OH) and 1630 (ArCO); δ_H 0.90–1.05 (2 H, m, CH*H*CH$_2$O and 3′-H$_{endo}$), 1.18 (1 H, br s, OH), 1.27–1.35 (2 H, m, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.44 (1 H, m, C*H*HCH$_2$O), 1.73–1.92 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 2.05–2.20 (2 H, m, 2′-H and 3′-H$_{exo}$), 2.95 (1 H, m, 1′-H), 3.10 (1 H, m, 4′-H), 3.62 (2 H, m, CH$_2$O), 6.92 (1 H, dd, $J_{4.2}$ 0.8, $J_{4.5}$ 1.9, 4-H$_{fur}$), 7.24 (1 H, d, $J_{8',7'}$ 7.3, 8′-H), 7.51 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.68 (1 H, m, 5′-H), 7.72 (1 H, dd, $J_{7',8'}$ 7.3, $J_{7',5'}$ 1.9, 7′-H) and 7.96 (1 H, m, 2-H$_{fur}$); δ_C 189.7 (ArCO), 148.3 (C-2$_{fur}$), 147.2 (C-8′a), 144.3 (C-4′a), 143.7 (C-5$_{fur}$), 136.8 (C-6′), 126.6 (C-3$_{fur}$), 126.9, 125.3, 123.8 (C-5′, C-7′ and C-8′), 110.4 (C-4$_{fur}$), 60.5 (CH$_2$OH), 40.1 (C-2), 39.3 (C-1′), 34.5 (C-4′), 34.2 (C-3′), 33.4 (C-2′), 26.4 (C-10′) and 24.9 (C-9′); *m*/*z* 296 (M$^+$, 100%) and 95 (75).

2-[endo-7′-(3-*Furoyl*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*ethano*-2′-*naphthyl*]*ethanol* **9b**.—From the acetate **8b** (1.00 g, 3.0 mol), using the same procedure described for the preparation of compound **9a**, compound **9b** (0.78 g, 89%) was obtained as a pale yellow oil (Found: C, 76.7; H, 6.6. C$_{19}$H$_{20}$O$_3$ requires C, 77.0; H, 6.8%); ν_{max}/cm^{-1} 3400 (OH) and 1630 (ArCO); δ_H 0.85–1.05 (2 H, m, CH*H*CH$_2$O and 3′-H$_{endo}$), 1.18 (1 H, br t, OH), 1.25–1.35 (2 H, m, 9′-H$_{anti}$ and 10′-H$_{anti}$), 1.45 (1 H, m, C*H*HCH$_2$O), 1.73–1.92 (2 H, m, 9′-H$_{syn}$ and 10′-H$_{syn}$), 2.05–2.20 (2 H, m, 2′-H and 3′-H$_{exo}$), 2.95 (1 H, m, 1′-H), 3.09 (1 H, m, 4′-H), 3.62 (2 H, m, CH$_2$O), 6.92 (1 H, dd, $J_{4.2}$ 0.8, $J_{4.5}$ 1.9, 4-H$_{fur}$), 7.25 (1 H, d, $J_{5',6'}$ 7.3, 5′-H), 7.51 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.66 (1 H, d, $J_{8',6'}$ 1.9, 8′-H), 7.74 (1 H, dd, $J_{6',5'}$ 7.3, $J_{6',8'}$ 1.9, 6′-H) and 7.95 (1 H, m, 2-H$_{fur}$); δ_C 189.6 (ArCO), 149.4 (C-4′a), 148.2 (C-2$_{fur}$), 143.7 (C-5$_{fur}$), 142.0 (C-8′a), 136.5 (C-7′), 126.7 (C-3$_{fur}$), 127.4, 125.7, 123.4 (C-8′, C-6′ and C-5′), 110.4 (C-4$_{fur}$), 60.5 (CH$_2$OH), 40.1 (C-2), 39.2 (C-1′), 34.6 (C-4′), 34.1 (C-3′), 33.4 (C-2′), 26.5 (C-10′) and 24.9 (C-9′); *m*/*z* 296 (M$^+$, 16%) and 95 (100).

2-[endo-6′-(3-*Furylhydroxymethyl*)-1′,2′,3′,4′-*tetrahydro*-1′,-4′-*ethano*-2′-*naphthyl*]*ethanol* **10a**.—To a solution of compound **9a** (300 mg, 1.0 mmol) in methanol (3 cm^3) cooled to 0 °C, sodium borohydride (41 mg, 1.1 mmol) was added. After 0.5 h acetic acid (0.057 cm^3, 1.0 mmol) was added to the mixture which was then poured into water (15 cm^3) and extracted with ethyl acetate (30 cm^3 × 2). The combined extracts were washed

with 5% aq. Na_2CO_3 (10 cm^3) and then with water (10 cm^3), dried and evaporated to dryness to yield the diol **10a** (240 mg, 80%, 1:1 mixture of diastereoisomers) as a white solid (Found: C, 76.4; H, 7.5. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); ν_{max}/cm^{-1} 3370 (OH); δ_H 0.80–1.0 (2 H, m, CH*H*CH_2O and 3'-H_{endo}), 1.10 (1 H, br t, OH), 1.20–1.40 (2 H, m, 9'-H_{anti} and 10'-H_{anti}), 1.45 (1 H, m, C*H*HCH_2O), 1.78–1.85 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.97–2.20 (3 H, m, 2'-H, 3'-H_{exo} and OH), 2.83 (1 H, m, 1'-H), 3.00 (1 H, m, 4'-H), 3.60 (2 H, m, CH_2O), 5.80 (1 H, s, C*H*OH), 6.38 (1 H, m, 4-H_{fur}), 7.11 (1 H, d, 8'-H), 7.20 (2 H, m, 5'-H and 7'-H), 7.35 (1 H, d, 2-H_{fur}) and 7.40 (1 H, t, 5-H_{fur}); δ_C 144.2 (C-4'a), 143.2 (C-5_{fur}), 141.4 (C-6'), 140.7 (C-8'a), 139.7 (C-2_{fur}), 129.2 (C-3_{fur}), 125.3, 123.7, 121.4 (C-8', C-7' and C-5'), 109.4 (C-4_{fur}), 69.9 (CHOH), 60.7 (CH_2OH), 40.1 (C-2), 38.8 (C-1'), 34.5 (C-4'), 34.3 (C-3'), 33.4 (C-2'), 26.6 (C-10') and 25.1 (C-9'); *m/z* 298 (M^+, 90%) and 97 (100).

2-[endo-7'-(3-*Furylhydroxymethyl*)-1',2',3',4'-*tetrahydro*-1',4'-*ethano*-2'-*naphthyl*]*ethanol* **10b**.—Starting from compound **9b** and using the same procedure described for the preparation of compound **10a**, compound **10b** was obtained (280 mg, 94%, as a 1:1 mixture of diastereoisomers) as a white solid (Found: C, 76.3; H, 7.5. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); ν_{max}/cm^{-1} 3370 (OH); δ_H 0.80–1.00 (2 H, m, CH*H*CH_2O and 3'-H_{endo}), 1.17 (1 H, br s, OH), 1.20–1.50 (2 H, m, 9'-H_{anti} and 10'-H_{anti}), 1.45 (1 H, m, C*H*HCH_2O), 1.70–1.90 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.98–2.18 (3 H, m, 2'-H, 3'-H_{exo} and OH), 2.80 (1 H, m, 1'-H), 3.00 (1 H, m, 4'-H), 3.60 (2 H, m, CH_2O), 5.80 (1 H, s, C*H*OH), 6.35 (1 H, dd, 4-H_{fur}), 7.11 (1 H, d, 5'-H), 7.20 (2 H, m, 6'-H and 8'-H), 7.35 (1 H, t, 5-H_{fur}) and 7.40 (1 H, d, 2-H_{fur}); δ_C 143.7 (C-4'a), 141.8 (C-8'a), 143.3 (C-5_{fur}), 139.8 (C-2_{fur}), 137.6 (C-7'), 129.2 (C-3_{fur}), 124.0, 123.4, 123.3 (C-5', C-6' and C-8'), 109.3 (C-4_{fur}), 69.8 (CHOH), 60.6 (CH_2OH), 40.2 (C-2), 39.2 (C-1'), 34.4 (C-3'), 34.2 (C-4'), 33.5 (C-2'), 26.7 (C-10') and 25.2 (C-9'); *m/z* 298 (M^+, 80%) and 97 (100).

2-[endo-6'-(3-*Furylmethyl*)-1',2',3',4'-*tetrahydro*-1',4'-*ethano*-2'-*naphthyl*]*ethyl Acetate* **11a**.—A mixture of compound **8a** (1.14 g, 3.0 mmol), zinc iodide (1.44 g, 4.5 mmol) and sodium cyanoborohydride (85%; 1.66 g, 22.5 mmol) in 1,2-dichloroethane (25 cm^3) was refluxed for 0.5 h. The mixture was then cooled, filtered through Celite and washed with dichloromethane. The filtrate was evaporated to dryness to yield the reduced product **11a** (0.92 g, 95%) as a colourless oil that was used without further purification in the next preparation (Found: C, 77.45; H, 7.3. $C_{21}H_{24}O_3$ requires C, 77.75; H, 7.5%); ν_{max}/cm^{-1} 1730 (CO_2); δ_H 0.88 (1 H, m, CH*H*CH_2O), 1.02 (1 H, m, 3'-H_{endo}), 1.25–1.50 (3 H, m, C*H*HCH_2O, 9'-H_{anti} and 10'-H_{anti}), 1.65–1.85 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.90–2.10 (2 H, m, 2'-H and 3'-H_{exo}), 2.06 (3 H, s, COMe), 2.80 (1 H, m, 1'-H), 2.93 (1 H, m, 4'-H), 3.77 (2 H, s, C*H*$_2$-fur), 4.01 (2 H, m, CH_2OCO), 6.28 (1 H, m, 4-H_{fur}), 6.98 (1 H, s, 5'-H), 7.03 (2 H, s, 7'-H and 8'-H), 7.22 (1 H, m, 2-H_{fur}) and 7.35 (1 H, t, *J* 1.7, 5-H_{fur}).

2-[endo-7'-(3-*Furylmethyl*)-1',2',3',4'-*tetrahydro*-1',4'-*ethano*-2'-*naphthyl*]*ethyl Acetate* **11b**.—Starting from compound **8b** (1.14 g, 3.0 mmol), using the same procedure as described for the preparation of compound **11a**, the reduced product **11b** (0.90 g, 92%) was obtained as a colourless oil that was used without further purification in the next preparation (Found: C, 77.5; H, 7.3. $C_{21}H_{24}O_3$ requires C, 77.75; H, 7.5%); ν_{max}/cm^{-1} 1730 (CO_2); δ_H 0.90 (1 H, m, CH*H*CH_2O), 1.00 (1 H, m, 3'-H_{endo}), 1.25–1.50 (3 H, m, C*H*HCH_2O, 9'-H_{anti} and 10'-H_{anti}), 1.65–1.85 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.95–2.10 (2 H, m, 2'-H, 3'-H_{exo}), 2.06 (3 H, s, COMe), 2.80 (1 H, m, 1'-H), 2.95 (1 H, m, 4'-H), 3.75 (2 H, s, C*H*$_2$-fur), 4.00 (2 H, m, CH_2OCO), 6.28 (1 H, m, 4-H_{fur}), 6.97 (1 H, s, 8'-H), 7.02 (2 H, s, 5'-H and 6'-H), 7.22 (1 H, m, 2-H_{fur}) and 7.37 (1 H, t, *J* 1.7, 5-H_{fur}).

2-[endo-6'-(3-*Furylmethyl*)-1',2',3',4'-*tetrahydro*-1',4'-*ethano*-2'-*naphthyl*]*ethanol* **12a**.—1 Mol dm^{-3} NaOH (3.3 cm^3) was added to a solution of the acetate **11a** (0.90 g, 2.8 mmol) in methanol (15 cm^3). After 1 h, the solution was diluted with water (60 cm^3) and extracted with ethyl acetate (40 cm^3 × 2). The combined extracts were washed with water, dried and evaporated to dryness to yield the alcohol **12a** (0.63 g, 80%) as a colourless oil (Found: C, 80.5; H, 8.0. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%); ν_{max}/cm^{-1} 3350 (OH); δ_H 0.85–1.05 (2 H, m, CH*H*CH_2O and 3'-H_{endo}), 1.12 (1 H, br t, OH), 1.20–1.50 (3 H, m, C*H*HCH_2O, 9'-H_{anti} and 10'-H_{anti}), 1.65–1.85 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.90–2.10 (2 H, m, 2'-H and 3'-H_{exo}), 2.80 (1 H, m, 1'-H), 2.93 (1 H, m, 4'-H), 3.60 (2 H, m, CH_2O), 3.77 (2 H, s, C*H*$_2$-fur), 6.30 (1 H, m, 4-H_{fur}), 6.98 (1 H, s, 5'-H), 7.05 (2 H, s, 7'-H and 8'-H), 7.22 (1 H, m, 2-H_{fur}) and 7.35 (1 H, t, *J* 1.7, 5-H_{fur}); δ_C 144.0 (C-4'a), 142.9 (C-5_{fur}), 139.6 (C-2_{fur}), 139.3 (C-8'a), 137.9 (C-6'), 125.6, 125.2 (C-7' and C-8'), 124.6 (C-3_{fur}), 123.5 (C-5'), 111.4 (C-4_{fur}), 60.7 (CH_2O), 40.2 (C-2), 38.6 (C-1'), 34.5 (C-3'), 34.4 (C-4'), 33.5 (C-2'), 31.1 (CH_2-fur), 26.8 (C-10') and 25.2 (C-9'); *m/z* 282 (M^+, 48%) and 81 (100).

2-[endo-7'-(3-*Furylmethyl*)-1',2',3',4'-*tetrahydro*-1',4'-*ethano*-2'-*naphthyl*]*ethanol* **12b**.—Starting from the acetate **11b** and using the same procedure as described for the preparation of compound **12a**, the alcohol **12b** was isolated (0.60 g, 78%) as an oil (Found: C, 81.0; H, 7.9. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%); ν_{max}/cm^{-1} 3350 (OH); δ_H 0.85–1.20 (2 H, m, CH*H*CH_2O and 3'-H_{endo}), 1.15 (1 H, br t, OH), 1.20–1.50 (3 H, m, C*H*HCH_2O, 9'-H_{anti} and 10'-H_{anti}), 1.65–1.85 (2 H, m, 9'-H_{syn} and 10'-H_{syn}), 1.95–2.10 (2 H, m, 2'-H and 3'-H_{exo}), 2.78 (1 H, m, 1'-H), 2.95 (1 H, m, 4'-H), 3.60 (2 H, m, C*H*$_2$OH), 3.75 (2 H, s, C*H*$_2$-fur), 6.28 (1 H, m, 4-H_{fur}), 6.97 (1 H, m, 8'-H), 7.02 (2 H, s, 5'-H and 6'-H), 7.20 (1 H, m, 2-H_{fur}) and 7.35 (1 H, t, *J* 1.7, 5-H_{fur}); δ_C 142.9 (C-5_{fur}), 141.7, 141.4 (C-4'a and C-8'a), 139.5 (C-2_{fur}), 137.6 (C-7'), 126.0, 125.7 (C-5' and C-6'), 124.7 (C-3_{fur}), 123.2 (C-8'), 111.3 (C-4_{fur}), 60.3 (CH_2O), 40.0 (C-2), 39.0 (C-1'), 34.5 (C-3'), 33.9 (C-4'), 33.8 (C-2'), 31.1 (CH_2-fur), 26.7 (C-10') and 25.2 (C-9'); *m/z* 282 (M^+, 100%) and 210 (90).

General Procedure for the Synthesis of the 2-(*Pyrrolidin*-1-*yl*)-*ethyl Ethers* **13a**, **13b**, **14a**, **14b**.—The alcohols **9a**, **9b**, **12a** and **12b** (2.5 mmol), NaH (60% in oil; 4.5 mmol) and 1-(2-chloroethyl)pyrrolidine (4.5 mmol) were dissolved in anhydrous tetrahydrofuran (10 cm^3) under N_2 and the solution refluxed for 4 h. The cooled mixture was then poured into water (30 cm^3) and extracted with ethyl acetate (25 cm^3 × 2). The combined extracts were washed with water, dried and evaporated to dryness. The title compounds were purified by flash chromatography (chloroform–methanol, 90:10). Yields and physical data for each compound are listed here below.

endo-6-(3-*Furylmethyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **13a**.—(40% yield); oil (Found: C, 78.8; H, 8.9; N, 3.45. $C_{25}H_{33}NO_2$ requires C, 79.1; H, 8.8; N, 3.7%); δ_H 0.80–1.00 (2 H, m, CHCH*H*CH_2O and 3-H_{endo}), 1.20–1.50 (3 H, m, CHC*H*HCH_2O, 9-H_{anti} and 10-H_{anti}), 1.60–1.80 (6 H, m, 9-H_{syn}, 10-H_{syn} and β-CH_{2pyr}), 1.90–2.10 (2 H, m, 2-H and 3-H_{exo}), 2.54 (4 H, m, α-CH_{2pyr}), 2.68 (2 H, t, *J* 6.2, OCH_2CH_2N), 2.80 (1 H, m, 1-H), 2.91 (1 H, m, 4-H), 3.40 (2 H, m, $CHCH_2CH_2O$), 3.52 (2 H, t, *J* 6.2, OCH_2CH_2N), 3.75 (2 H, s, C*H*$_2$-fur), 6.28 (1 H, m, 4-H_{fur}), 6.95 (1 H, s, 5-H), 7.01 (2 H, s, 7-H and 8-H), 7.22 (1 H, m, 2-H_{fur}) and 7.36 (1 H, t, *J* 1.7, 5-H_{fur}); δ_C 144.0 (C-4a), 142.8 (C-5_{fur}), 139.5 (C-2_{fur}), 139.4 (C-8a), 137.8 (C-6), 125.6 and 125.2 (C-7 and C-8), 124.6 (C-3_{fur}), 123.5 (C-5), 111.4 (C-4_{fur}), 69.8 and 69.0 (COC), 55.6 (OC*C*N), 54.6 (α-C_{pyr}), 38.6 (C-1), 36.9 ($CHCH_2CH_2O$), 34.5 (C-3), 34.5 (C-4), 33.8 (C-2), 31.1 (CH_2-fur), 26.8 (C-10), 25.3 (C-9) and 23.4 (β-C_{pyr}); *m/z* 379 (M^+, 45%) and 84 (100).

endo-7-(3-*Furylmethyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **13b**.—(47% yield); oil (Found: C, 78.75; H, 8.7; N, 3.4. $C_{25}H_{33}NO_2$ requires C, 79.1; H, 8.8; N, 3.7%); δ_H 0.80–1.00 (2 H, m, CHCH*H*CH$_2$O and 3-H$_{endo}$), 1.20–1.45 (3 H, m, CHC*H*HCH$_2$O, 9-H$_{anti}$ and 10-H$_{anti}$), 1.60–1.80 (6 H, m, 9-H$_{syn}$, 10-H$_{syn}$ and β-CH$_{2pyr}$), 1.95–2.05 (2 H, m, 2-H and 3-H$_{exo}$), 2.63 (4 H, m, α-CH$_{2pyr}$), 2.72 (2 H, t, *J* 6.2, OCH$_2$C*H*$_2$N), 2.77 (1 H, m, 1-H), 2.93 (1 H, m, 4-H), 3.40 (2 H, m, CHCH$_2$C*H*$_2$O), 3.55 (2 H, t, *J* 6.2, OC*H*$_2$CH$_2$N), 3.75 (2 H, s, CH$_2$-fur), 6.28 (1 H, m, 4-H$_{fur}$), 6.95 (1 H, s, 8-H), 7.02 (2 H, s, 5-H and 6-H), 7.20 (1 H, m, 2-H$_{fur}$) and 7.35 (1 H, t, *J* 1.7, 5-H$_{fur}$); δ_C 142.8 (C-5$_{fur}$), 141.7, 141.8 (C-4a and C-8a), 139.5 (C-2$_{fur}$), 137.4 (C-7), 125.9, 125.6 (C-5 and C-6), 124.7 (C-3$_{fur}$), 123.2 (C-8), 111.4 (C-4$_{fur}$), 69.2 and 69.0 (COC), 55.5 (OC*C*N), 54.6 (α-C$_{pyr}$), 39.1 (C-1), 36.9 (CH*C*H$_2$CH$_2$O), 34.6 (C-3), 34.0 (C-4), 33.8 (C-2), 31.1 (CH$_2$-fur), 26.7 (C-10), 25.6 (C-9) and 23.4 (β-C$_{pyr}$); *m*/*z* 379 (M$^+$, 32%) and 84 (100).

endo-6-(3-*Furoyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **14a**.—(30% yield); oil (Found: C, 76.0; H, 7.7; N, 3.4. $C_{25}H_{31}NO_3$ requires C, 76.3; H, 7.9; N, 3.6%); ν_{max}/cm^{-1} 1640 (ArCO); δ_H 0.85–1.05 (2 H, m, CHCH*H*CH$_2$O and 3-H$_{endo}$), 1.20–1.50 (3 H, m, CHC*H*HCH$_2$O, 9-H$_{anti}$ and 10-H$_{anti}$), 1.70–1.90 (6 H, m, 9-H$_{syn}$, 10-H$_{syn}$ and β-CH$_{2pyr}$), 2.00–2.10 (2 H, 2-H and 3-H$_{exo}$), 2.55 (4 H, m, α-CH$_{2pyr}$), 2.70 (2 H, t, *J* 6.2, OCH$_2$C*H*$_2$N), 2.95 (1 H, m, 1-H), 3.07 (1 H, m, 4-H), 3.40 (2 H, m, CHCH$_2$C*H*$_2$O), 3.55 (2 H, t, *J* 6.2, OC*H*$_2$CH$_2$N), 6.90 (1 H, m, 4-H$_{fur}$), 7.22 (1 H, d, 8-H), 7.50 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.65 (1 H, m, 5-H), 7.70 (1 H, dd, $J_{7.8}$ 7.7, $J_{7.5}$ 1.9, 7-H) and 7.95 (1 H, m, 2-H$_{fur}$); δ_C 189.5 (ArCO), 148.3 (C-2$_{fur}$), 147.2 (C-8a), 144.3 (C-4a), 143.7 (C-5$_{fur}$), 137.0 (C-6), 126.6 (C-3$_{fur}$), 126.9, 125.3 and 123.8 (C-5, C-7 and C-8), 110.4 (C-4$_{fur}$), 68.9 (COC), 55.4 (OC*C*N), 54.6 (α-C$_{pyr}$), 39.3 (C-1), 36.9 (CH*C*H$_2$CH$_2$O), 34.5 (C-4), 34.2 (C-3), 33.7 (C-2), 26.3 (C-10), 24.9 (C-9) and 23.4 (β-C$_{pyr}$); *m*/*z* 393 (M$^+$, 20%) and 84 (100).

endo-7-(3-*Furoyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **14b**.—(50% yield); oil (Found: C, 75.95; H, 8.0; N, 3.3. $C_{25}H_{31}NO_3$ requires C, 76.3; H, 7.9; N, 3.6%); ν_{max}/cm^{-1} 1640 (ArCO); δ_H 0.85–1.05 (2 H, m, CHCH*H*CH$_2$O and 3-H$_{endo}$), 1.20–1.50 (3 H, m, CHC*H*HCH$_2$O, 9-H$_{anti}$ and 10-H$_{anti}$), 1.70–1.90 (6 H, m, 9-H$_{syn}$, 10-H$_{syn}$ and β-CH$_{2pyr}$), 2.00–2.10 (2 H, 2-H and 3-H$_{exo}$), 2.60 (4 H, m, α-CH$_{2pyr}$), 2.70 (2 H, t, *J* 6.2, OCH$_2$C*H*$_2$N), 2.93 (1 H, m, 1-H), 3.07 (1 H, m, 4-H), 3.40 (2 H, m, CHCH$_2$C*H*$_2$O), 3.55 (2 H, t, *J* 6.2, OC*H*$_2$CH$_2$N), 6.90 (1 H, m, 4-H$_{fur}$), 7.22 (1 H, d, $J_{8.6}$ 1.9, 8-H), 7.50 (1 H, t, *J* 1.7, 5-H$_{fur}$), 7.65 (1 H, m, 5-H), 7.72 (1 H, dd, $J_{6.5}$ 7.7, $J_{6.8}$ 1.9, 6-H) and 7.95 (1 H, m, 2-H$_{fur}$); δ_C 189.7 (ArCO), 149.5 (C-4a), 148.3 (C-2$_{fur}$), 143.7 (C-5$_{fur}$), 142.0 (C-8a), 136.5 (C-7), 126.7 (C-3$_{fur}$), 127.3, 125.7, 123.4 (C-5, C-6 and C-8), 110.4 (C-4$_{fur}$), 69.0, 68.8 (COC), 55.4 (OC*C*N), 54.5 (α-C$_{pyr}$), 39.1 (C-1), 36.9 (CH*C*H$_2$CH$_2$O), 34.6 (C-4), 34.3 (C-3), 33.8 (C-2), 26.4 (C-10), 24.9 (C-9) and 23.4 (β-C$_{pyr}$); *m*/*z* 393 (M$^+$, 1.87%) and 84 (100).

endo-6-(3-*Furylhydroxymethyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **15a**.—To a solution of the ketone **14a** (100 mg, 0.25 mmol) in methanol (1.0 cm^3), sodium borohydride (19 mg, 0.5 mmol) was added and the reaction mixture was stirred at room temperature overnight. It was then diluted with water (10 cm^3) and extracted with chloroform (20 cm^3 × 2). The combined extracts were washed with water (10 cm^3), dried and evaporated to yield the secondary alcohol **15a** (50 mg, 50%, as a 1:1 mixture of diastereoisomers) as a pale yellow oil (Found: C, 75.6; H, 8.3; N, 3.3. $C_{25}H_{33}NO_3$ requires C, 75.9; H, 8.4; N, 3.5%); ν_{max}/cm^{-1} 3400 (OH); δ_H 0.80–1.05 (2 H, m, CHCH*H*CH$_2$O and 3-H$_{endo}$), 1.20–1.50 (3 H, m, CHC*H*HCH$_2$O, 9-H$_{anti}$ and 10-H$_{anti}$), 1.70–2.15 (8 H, m, 9-H$_{syn}$, 10-H$_{syn}$, 2-H, 3-H$_{exo}$ and β-CH$_{2pyr}$), 2.55 (4 H, m, α-CH$_{2pyr}$), 2.65 (2 H, t, *J* 6.2, OCH$_2$C*H*$_2$N), 2.80 (1 H, m, 1-H), 2.98 (1 H, m, 4-H), 3.40 (2 H, t, *J* 6.6, CHCH$_2$C*H*$_2$O), 3.51 (2 H, m, OC*H*$_2$CH$_2$N), 5.78 (1 H, s, C*H*OH), 6.38 (1 H, m, 4-H$_{fur}$), 7.10 (1 H, d, $J_{8.7}$ 7.7, H-8), 7.20 (2 H, m, H-5 and H-7), 7.33 (1 H, m, 2-H$_{fur}$) and 7.40 (1 H, t, *J* 1.7, 5-H$_{fur}$); δ_C 144.2 (C-4a), 143.2 (C-5$_{fur}$), 141.4 (C-6), 140.7 (C-8a), 139.7 (C-2$_{fur}$), 129.1 (C-3$_{fur}$), 121.4 (C-5), 125.3 (C-8), 123.7 (C-7), 109.4 (C-4$_{fur}$), 69.9 (CHOH), 69.9 and 69.7 (COC), 55.6 (OC*C*N), 54.6 (α-C$_{pyr}$), 38.7 (C-1), 36.9 (CH*C*H$_2$CH$_2$O), 34.5 (C-4), 34.4 (C-3), 33.8 (C-2), 26.6 (C-10), 25.2 (C-9) and 23.4 (β-C$_{pyr}$); *m*/*z* 395 (M$^+$, 12%) and 84 (100).

endo-7-(3-*Furylhydroxymethyl*)-2-[2-(*pyrrolidin*-1-*yl*)*ethoxy*]*ethyl*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene* **15b**.—Starting from the ketone **14b** (100 mg, 0.25 mmol) and following the same procedure as described for compound **15a**, the secondary alcohol **15b** was obtained (50 mg, 50%, as a 1:1 mixture of diastereoisomers) as a pale yellow oil (Found: C, 75.55; H, 8.2; N, 3.4. $C_{25}H_{33}NO_3$ requires C, 75.9; H, 8.4; N, 3.5%); ν_{max}/cm^{-1} 3400 (OH); δ_H 0.80–1.05 (2 H, m, CHCH*H*CH$_2$O and 3-H$_{endo}$), 1.15–1.45 (3 H, m, CHC*H*HCH$_2$O, 9-H$_{anti}$ and 10-H$_{anti}$), 1.70–2.10 (8 H, m, 9-H$_{syn}$, 10-H$_{syn}$, 2-H, 3-H$_{exo}$ and β-CH$_{2pyr}$), 2.55 (4 H, m, α-CH$_{2pyr}$), 2.65 (2 H, m, OCH$_2$C*H*$_2$N), 2.83 (1 H, m, 1-H), 2.98 (1 H, m, 4-H), 3.40 (2 H, t, *J* 6.2, CHCH$_2$C*H*$_2$O), 3.52 (2 H, m, OC*H*$_2$CH$_2$N), 5.75 (1 H, s, C*H*OH), 6.35 (1 H, m, 4-H$_{fur}$), 7.11 (1 H, d, 5-H), 7.20 (2 H, m, 6-H and 8-H) and 7.30–7.40 (2 H, m, 2-H$_{fur}$ and 5-H$_{fur}$); δ_C 143.7 (C-7), 143.2 (C-5$_{fur}$), 141.9, 140.5 (C-4a and C-8a), 139.8 (C-2$_{fur}$), 129.3 (C-3$_{fur}$), 124.0, 123.4, 123.3 (C-5, C-6 and C-8), 109.4 (C-4$_{fur}$), 69.9, 69.7 (COC), 69.8 (CHOH), 55.6 (OC*C*N), 54.6 (α-C$_{pyr}$), 39.0 (C-1), 36.8 (CH*C*H$_2$CH$_2$O), 34.5 (C-3), 34.2 (C-4), 33.9 (C-2), 26.6 (C-10), 25.2 (C-9) and 23.4 (β-C$_{pyr}$); *m*/*z* 395 (M$^+$, 2%) and 84 (100).

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