

A variety of products from a “simple” reaction of [1-(6-acetyl-2-naphthyl)piperidin-4-yl]methyl 4-methylbenzenesulfonate with nucleophiles in DMF–K₂CO₃

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The course of the reaction between [1-(6-acetyl-2-naphthyl)piperidin-4-yl]methyl 4-methylbenzenesulfonate (**1**) and pyrrolidine, a model nucleophile, in DMF in the presence of anhydrous potassium carbonate at ambient and elevated temperatures is investigated. At elevated temperatures a 1-azabicyclo[2.2.1]heptane derivative is identified as the intermediate in the piperidine-to-pyrrolidine ring contraction process. The formation of formate, carbamate, and hydroxy derivatives, as a consequence of DMF and K₂CO₃ participating in the reaction, is documented.

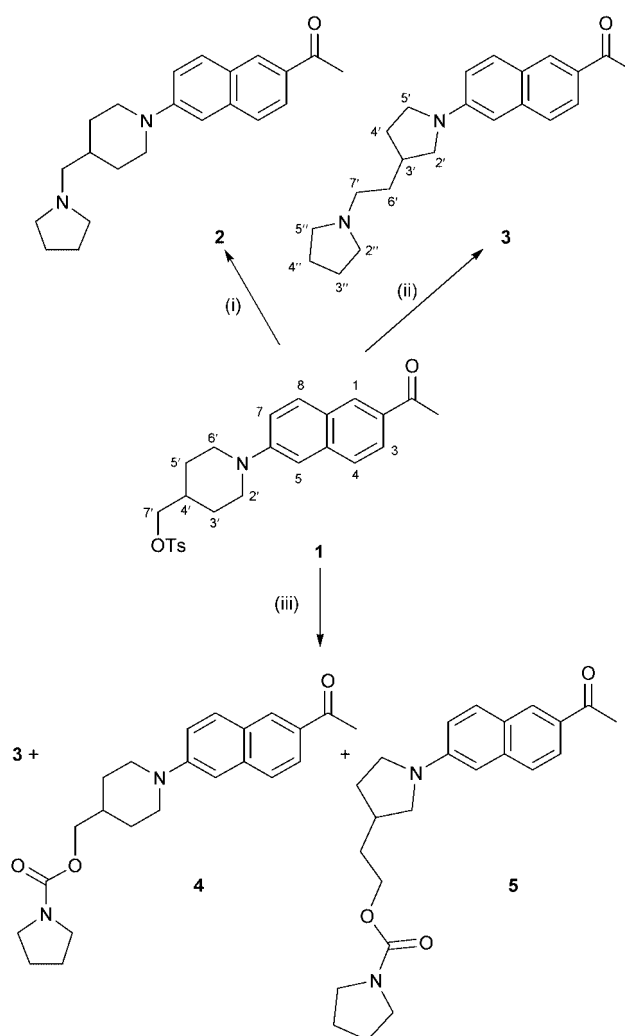
Introduction

In our work on the development of novel UV and visible wavelength fluorescent probes for biological research,¹ we explored whether fluorescent 2-(1,1-dicyanopropen-2-yl)-6-dimethylaminonaphthalene (DDNP)² can be structurally modified in a way to enable the attachment of a ligand of choice to the parent fluorophore. We have found that dimethylamine can be successfully replaced in the synthesis by bifunctional amines like piperazine,¹ 2-ethylaminoethanol,³ or piperidin-4-ylmethanol,³ leading to novel fluorescent reactive dyes. The synthesized reactive dyes were conjugated to spiperone ketal,⁴ a 4-imidazolinone derivative. Depending on the reaction temperature, the nucleophilic displacement of the tosyloxy group in [1-(6-acetyl-2-naphthyl)piperidin-4-yl]methyl 4-methylbenzenesulfonate (**1**) with spiperone ketal gave either a product with the piperidine skeleton intact^{3,5} or one containing a pyrrolidine moiety instead.⁵ To clarify the intriguing transformations, we decided to investigate the reaction of the compound **1** using pyrrolidine as a simple model nucleophile instead of a complex spiperone ketal.

Results and discussion

The tosyloxy group in the compound **1** was smoothly substituted with an excess of pyrrolidine in DMF in the presence of anhydrous K₂CO₃ at room temperature to give the product **2** (Scheme 1, path (i)). At 80 °C, however, a rearranged product **3** was formed (Scheme 1, path (ii)). The structures of the two isomeric compounds were elucidated on the basis of the ¹H NMR spectra. In the NMR spectrum of **2**, a characteristic subspectrum reflecting the symmetry of a substituted 4-methylpiperidine in a chair conformation was observed.⁶ The corresponding subspectrum of **3** reflected the arrangement of hydrogen atoms in a substituted 3-ethylpyrrolidine.

From the reaction of **1** with only one equivalent of pyrrolidine at an elevated temperature, the major rearranged product **3** and two highly fluorescent side products **4** and **5** were isolated (Scheme 1, path (iii)). Their respective MS spectra indicated the same molecular mass, 44 mass units higher than expected for **2** or **3**. ¹H NMR spectra indicated that the compounds **4** and **5** structurally resemble **2** and **3**, respectively. A significant downfield shift of the signals for 7'-CH₂ in **4** and **5** (4.02 and 4.21 ppm, respectively) in comparison to the corresponding signals in **2** and **3** (2.44 and 2.65 ppm, respectively), together with an

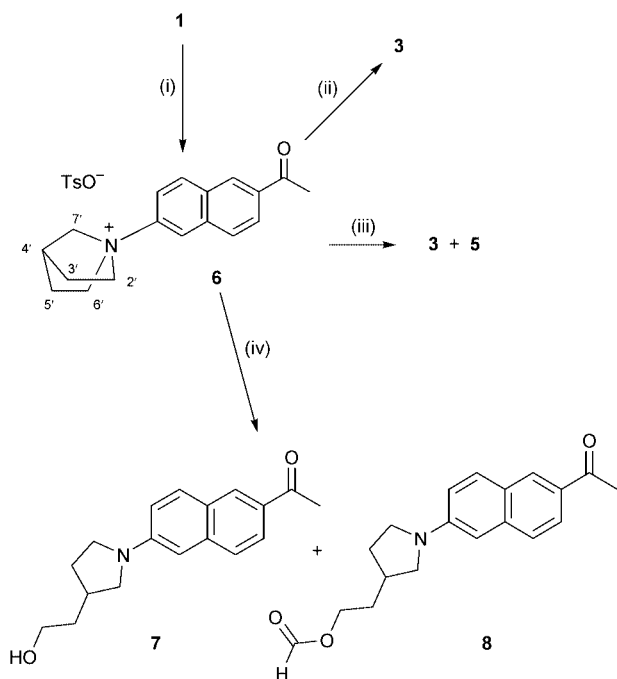


Scheme 1 Reagents and conditions: (i) pyrrolidine (an excess), room temperature, DMF–K₂CO₃; (ii) 1. Δ, DMF, 2. pyrrolidine (an excess), Δ, DMF; (iii) pyrrolidine (one equivalent), Δ, DMF–K₂CO₃.

additional signal in the ¹³C NMR spectrum of **5**, corresponding to a carboxy carbon, supported the proposed carbamate structures **4** and **5**. Carbamates are traditionally formed from amines

with reactive chloroformates.⁷ In the last decade formation of carbamates from amines, alkyl halides, and K_2CO_3 in the presence of a quaternary ammonium salt has been described.^{8,9} Alkyl esters of toluene-*p*-sulfonic acid instead of alkyl halides, and tetraethylammonium hydrogen carbonate instead of K_2CO_3 -quaternary ammonium salt can also be used to transform mainly primary amines into carbamates.¹⁰ Also, carbamates can be efficiently prepared from secondary amines, carbon dioxide and an alkyl halide.¹¹ The formation of carbamates **4** and **5** could not be explained solely on the basis of the similarity of compositions of the above and the reaction mixture in our hands. We needed to account for a quaternary ammonium salt in the reaction mixture and to explain the piperidine-to-pyrrolidine ring transformation.

To address both issues, we envisaged that at an elevated temperature the tosylate **1** first undergoes intramolecular nucleophilic substitution of the tosyloxy group by the ring nitrogen, leading to a quaternary 1-azabicyclo[2.2.1]heptane derivative **6** (Scheme 2). The transition of the piperidine ring from a more



Scheme 2 Reagents and conditions: (i) Δ , toluene; (ii) pyrrolidine (an excess), Δ , DMF; (iii) pyrrolidine (one equivalent), Δ , DMF- K_2CO_3 ; (iv) Δ , DMF- K_2CO_3 .

stable chair⁶ to a higher energy boat conformation is a prerequisite for such cyclization. This brings the two reacting centers in close enough proximity for the reaction to occur. Indeed, we isolated and characterized the intermediate **6** (Scheme 2, path (i)). Our findings are in agreement with the literature data on similar compounds.^{11–15} With the compound **6**, formed from **1** at elevated temperature, we can account for all required reagents for the formation of the carbamate **4**, although the mechanism of this transformation has not yet been elucidated.^{8,9}

It has been also shown before that quaternary ammonium salts can either undergo base catalyzed Hofmann degradation^{13,14} or can react as alkylating agent, especially in reactions with nitrogen nucleophiles,¹⁶ leading to a mixture of amines. Cyclic quaternary ammonium salt **6** predominantly underwent dealkylation because we did not isolate nor detect any alkene product formed as the result of the Hofmann degradation. The nucleophilic attack on **6** can take place at different positions leading to 1-azabicyclo[2.2.1]heptane ring opening:^{13,17} attack at the bridging methylene group ($7'$ - CH_2) would lead to the formation of a piperidine derivative, while attack at either $2'$ -

CH_2 or $6'$ - CH_2 would lead to a pyrrolidine derivative. In our hands, the ring opening reaction occurred exclusively at the two equivalent positions $2'$ and $6'$ in **6** giving 3-ethylpyrrolidine derivatives (Scheme 2). Statistically, 4-methylpiperidine and 3-ethylpyrrolidine derivatives should be formed in a 1:2 ratio. A thorough examination of molecular models and computer molecular modeling results¹⁸ revealed a difference in steric hindrance at $7'$ and $2'$ ($6'$) carbons. The methine proton at $4'$ -C hinders the attack of a nucleophile on the $7'$ -C methylene group while the approach to $2'$ -C (or $6'$ -C) is less hindered because the two ethylene bridges in **6** are fixed in an eclipsed conformation. It is generally impossible to predict product formation based only on steric hindrance differences, but the exclusive formation of 3-ethylpyrrolidine derivatives from **6** corroborates such an explanation. With an excess of pyrrolidine, the intermediate **6** was transformed into **3** (Scheme 2, path(ii)), while using one equivalent of pyrrolidine in DMF in the presence of K_2CO_3 resulted in a mixture of **3** and the rearranged carbamate **5** (Scheme 2, path (iii)). At a certain stage in the formation of both types of products, a nucleophilic attack at the quaternary ammonium salt **6** must take place. The nucleophile in the above transformations can be pyrrolidine, carbonate or its derivative. Carbonate can successfully compete in the reaction with a stronger nucleophile (*e.g.* pyrrolidine) only if the latter is not present in excess, which then leads to the formation of carbamate **5**. The same applies to the reaction of the tosylate **1** with one equivalent of pyrrolidine at an elevated temperature (Scheme 1, paths (ii) and (iii)).

To prove our assumption that K_2CO_3 reacts in the above transformations as a nucleophile and not just as a base, we subjected the ammonium salt **6** to its action in DMF (Scheme 2, path (iv)). We isolated two products, the alcohol **7** and the formate **8**. We tried our best to dry the reactants prior to reaction, so we can assume that **7** was not formed in a hydrolytic process. The formation of **7** can be explained by a nucleophilic attack of the carbonate ion, which is followed by decarboxylation and protonation upon workup. It is not clear how the formate **8** was formed, but DMF must have been the source of the formyl group.

Conclusion

We explored the reaction of [1-(6-acetyl-2-naphthyl)piperidin-4-yl]methyl 4-methylbenzenesulfonate with the model nucleophile pyrrolidine at room and elevated temperatures. We found that, at room temperature, a direct nucleophilic substitution of the tosyloxy group with the intended nucleophile took place leaving the 4-methylpiperidine moiety intact. At elevated temperatures, however, an intramolecular nucleophilic substitution proceeded faster than the intermolecular substitution leading to a 1-azabicyclo[2.2.1]heptane derivative. The latter underwent a ring opening reaction with nucleophiles, preferentially at the ethylene bridges, to give the products of formal 4-methylpiperidine to 3-ethylpyrrolidine moiety rearrangement during the nucleophilic substitution. Pyrrolidine reacted as an exclusive nucleophile if present in excess. With one equivalent of pyrrolidine in the reaction mixture, a competing reaction involving potassium carbonate led to the formation of carbamate side products. The role of potassium carbonate as a nucleophile in the ring opening reaction was proven through isolation of the alcohol and its formic acid ester.

Experimental

NMR spectra were recorded on a Bruker DPX 300 spectrometer. 1H and ^{13}C chemical shifts are quoted in parts per million (ppm) downfield from TMS as internal standard and coupling constants are given in Hz. Atom numbering as specified in Schemes 1 and 2 was used in reporting the spectral assignments, although in some cases the numbering according

to the IUPAC Nomenclature rules differs. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were determined at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana using a Perkin-Elmer 2400 CHN elemental analyzer. Mass spectra were recorded by Dr Bogdan Kralj at the Mass Spectrometry Center, Jožef Stefan Institute. Radial chromatography was performed using Chromatotron (Harrison Research, 840 Moana Court, Palo Alto, CA 94306). The rotors were prepared as recommended by Harrison Research using E. Merck Silica Gel (Cat. No. 7749-3), with 1 or 2 mm layer thickness. DMF was dried for several days over activated 3 Å molecular sieves before it was distilled under reduced pressure. It was stored over molecular sieves.

1-{6-[4-(Pyrrolidinomethyl)piperidino]-2-naphthyl}ethanone 2

A mixture of **1**³ (90 mg, 0.21 mmol), K₂CO₃ (600 mg), DMF (3 cm³) and pyrrolidine (2 cm³, 24 mmol) was stirred at RT for 2 h. The reaction mixture was concentrated to dryness and the residue was distributed between DCM and water. The organic layer was dried, concentrated and chromatographed by radial chromatography (2 mm silica, 3% MeOH in DCM) to yield compound **2** (55 mg, 79%), mp 113.3–115.0 °C (from chloroform–petroleum ether mixture) (Found C, 78.65; H, 8.15; N, 8.6. C₂₂H₂₈N₂O requires C, 78.5; H, 8.4; N, 8.3%); δ_H (300 MHz; CDCl₃) 1.41 (2 H, ddd, *J* 14.3, 13.0 and 4.0, 3'-a-H, 5'-a-H), 1.75 (1 H, m, 4'-H), 1.82 (4 H, br s, 3''-CH₂, 4''-CH₂), 1.97 (2 H, br d, *J* 14.3, 3'e-H, 5'e-H), 2.44 (2 H, d, *J* 6.4, 7'-CH₂), 2.58 (4 H, br s, 2''-CH₂, 5''-CH₂), 2.66 (3 H, s, CH₃), 2.86 (2 H, dd, *J* 13.0 and 12.5, 2'-a-H, 6'-a-H), 3.89 (2 H, dd, *J* 12.5 and 4.0, 2'e-H, 6'e-H), 7.08 (1 H, br s, 5-H), 7.30 (1 H, br d, *J* 9.3, 7-H), 7.65 (1 H, d, *J* 9.0, 4-H), 7.78 (1 H, d, *J* 9.3, 8-H), 7.93 (1 H, br d, 9.0, 3-H), 8.31 (1 H, br s, 1-H); *m/z* 336.2211 (M⁺), C₂₂H₂₈N₂O requires 336.2202.

1-{6-[3-(2-Pyrrolidinoethyl)pyrrolidino]-2-naphthyl}ethanone 3

Compound **1** (22 mg, 0.05 mmol) was first heated in DMF (0.5 ml) at 80 °C for 0.5 h, then pyrrolidine (0.6 cm³, 7.2 mmol) was added and heating continued for additional 1 h. The reaction mixture was concentrated to dryness and the residue was distributed between DCM and water. The organic layer was dried, concentrated and chromatographed by radial chromatography (1 mm silica, 2% MeOH in DCM) to yield compound **3** (13 mg, 77%), mp 102.1–102.8 °C (from benzene–hexane mixture) (Found C, 78.5; H, 8.6; N, 8.3. C₂₂H₂₈N₂O requires C, 78.5; H, 8.4; N, 8.3%); δ_H (300 MHz; CDCl₃) 1.70 (1 H, ddd, *J* 9.0, 8.6 and 2.9, 4'-H), 1.82 (4 H, m, 3''-CH₂, 4''-CH₂), 1.87 (2 H, m, 6'-CH₂), 2.25 (1 H, m, 4'-H), 2.40 (1 H, m, 3'-H), 2.63 (4 H, m, 2''-CH₂, 5''-CH₂), 2.65 (2 H, m, 7'-CH₂), 2.66 (3 H, s, CH₃), 3.08 (1 H, dd, *J* 8.9 and 7.5, 2'-H), 3.43 (1 H, ddd, *J* 9.0, 8.6 and 2.9, 5'-H), 3.53 (1 H, ddd, *J* 9.0, 8.6 and 2.9, 5'-H), 3.62 (1 H, dd, *J* 8.9 and 7.5, 2'-H), 6.70 (1 H, d, *J* 2.3, 5-H), 6.98 (1 H, dd, *J* 9.0 and 2.3, 7-H), 7.59 (1 H, d, *J* 8.7, 4-H), 7.78 (1 H, d, *J* 9.0, 8-H), 7.90 (1 H, dd, *J* 8.7 and 1.9, 3-H), 8.30 (1 H, d, *J* 1.9, 1-H); δ_C (75 MHz; CDCl₃) 23.49 (3''-C, 4''-C), 26.38 (CH₃), 31.82 (4'-C), 33.18 (6'-C), 37.32 (3'-C), 47.57 (5'-C), 53.59 (2'-C), 54.36 (2''-C, 5''-C), 55.27 (7'-C), 104.18 (5-C), 116.08 (7-C), 124.67 (3-C), 124.71 (8a-C), 125.77 (4-C), 130.27 (2-C), 130.68 (1-C), 130.91 (8-C), 137.94 (4a-C), 147.68 (6-C), 197.65 (C=O); *m/z* 336.2210 (M⁺), C₂₂H₂₈N₂O requires 336.2201.

Reaction of **1** with one equivalent of pyrrolidine. [1-(6-Acetyl-2-naphthyl)piperidin-4-yl]methyl pyrrolidine-1-carboxylate **4** and 2-[1-(6-acetyl-2-naphthyl)pyrrolidin-3-yl]ethyl pyrrolidine-1-carboxylate **5**

A mixture of **1** (42 mg, 0.1 mmol), K₂CO₃ (140 mg), DMF (2 cm³) and pyrrolidine (0.01 cm³, 0.1 mmol) was stirred at 80 °C

for 2.5 h. The reaction mixture was concentrated to dryness and the residue was distributed between DCM and water. The organic layer was dried, concentrated and chromatographed by radial chromatography (2 mm silica, DCM) to yield compounds **3** (19 mg, 59%), **4** (1 mg, 3%), and **5** (1 mg, 3%). Compound **4**: δ_H (300 MHz; CDCl₃) 1.49 (2 H, m, 3'-a-H, 5'-a-H), 1.87 (7 H, m, 3''-CH₂, 4''-CH₂, 4'-H, 3'e-H, 5'e-H), 2.66 (3 H, s, CH₃), 2.87 (2 H, ddd, *J* 12.3, 12.3 and 2.3, 2'-a-H, 6'-a-H), 3.38 (4 H, m, 2''-CH₂, 5''-CH₂), 3.92 (2 H, br d, *J* 12.3, 2'e-H, 6'e-H), 4.02 (2 H, d, *J* 5.7, O-CH₂-C), 7.09 (1 H, d, *J* 2.3, 5-H), 7.31 (1 H, dd, *J* 9.0 and 2.3, 7-H), 7.66 (1 H, d, *J* 8.7, 4-H), 7.8 (1 H, d, *J* 9.0, 8-H), 7.94 (1 H, dd, *J* 8.7 and 1.5, 3-H), 8.31 (1 H, d, *J* 1.5, 1-H); *m/z* 380.2110 (M⁺), C₂₃H₂₈N₂O₃ requires 380.2100. Compound **5**: δ_H (300 MHz; CDCl₃) 1.77 (1 H, br dd, *J* 9.2 and 3.0, 4'-H), 1.87 (2 H, m, 6'-CH₂), 1.88 (4 H, m, 3''-CH₂, 4''-CH₂), 2.27 (1 H, m, 4'-H), 2.46 (1 H, m, 3'-H), 2.66 (3 H, s, CH₃), 3.11 (1 H, dd, *J* 9.2 and 7.3, 2'-H), 3.39 (4 H, m, 2''-CH₂, 5''-CH₂), 3.45 (1 H, ddd, *J* 9.2, 8.3 and 3.0, 5'-H), 3.54 (1 H, ddd, *J* 9.2, 8.3 and 3.0, 5'-H), 3.65 (1 H, dd, *J* 9.2 and 7.3, 2'-H), 4.21 (2 H, m, 7'-CH₂), 6.7 (1 H, d, *J* 2.5, 5-H), 6.98 (1 H, dd, *J* 9.0 and 2.5, 7-H), 7.59 (1 H, d, *J* 9.0, 4-H), 7.78 (1 H, d, *J* 9.0, 8-H), 7.9 (1 H, dd, *J* 9.0 and 1.9, 3-H), 8.3 (1 H, d, *J* 1.9, 1-H); δ_C (75 MHz; CDCl₃) 26.99 and 25.81 (3''-C, 4''-C), 26.38 (CH₃), 31.73 (4'-C), 33.09 (6'-C), 36.17 (3'-C), 45.84 and 46.23 (2''-C, 5''-C), 47.49 (5'-C), 53.46 (2'-C), 63.77 (7'-C), 104.26 (5-C), 116.05 (7-C), 124.7 (3-C), 126.76 (8a-C), 125.79 (4-C), 130.35 (2-C), 130.67 (1-C), 130.95 (8-C), 137.94 (4a-C), 147.6 (6-C), 155.14 (C=O), 197.66 (C=O); *m/z* 380.2101 (M⁺), C₂₃H₂₈N₂O₃ requires 380.2100.

1-(6-Acetyl-2-naphthyl)-1-azoniabicyclo[2.2.1]heptane 4-methylbenzenesulfonate **6**

Compound **1** (54 mg, 0.12 mmol) was heated under argon in anhydrous toluene (4 cm³) at 80 °C. The reaction mixture was cooled at 12, 24, and 36 h; the white solid was filtered off; and the mother liquor was heated further. This procedure gave the salt **6** (35 mg, 65%), mp 142–143 °C (from toluene) (Found C, 67.3; H, 6.7; N, 3.1. C₂₅H₂₇NSO₄·0.5 H₂O requires C, 67.2; H, 6.3; N, 3.1%); δ_H (300 MHz; CDCl₃) 2.02 and 2.41 (2 H, m and 2H, m, 3'-CH₂, 5'-CH₂), 2.31 (3 H, s, tolyl-CH₃), 2.71 (3 H, s, CH₃), 3.11 (1 H, m, 4'-H), 3.72 and 4.73 (2 H, m and 2 H, m, 2'-CH₂, 6'-CH₂), 4.11 (2 H, s, 7'-CH₂), 7.08 (2 H, br d, *J* 8.0, tolyl 3-H, tolyl 5-H), 7.75 (2 H, d, *J* 8.0, tolyl 2-H, tolyl 6-H), 7.98 (1 H, dd, *J* 9.0 and 2.5, 7-H), 7.99 (1 H, d, *J* 8.7, 4-H), 8.03 (1 H, dd, *J* 8.7 and 1.3, 3-H), 8.04 (1 H, d, *J* 9.0, 8-H), 8.4 (2 H, br s, 1-H and 5-H).

Reaction of **6** with an excess of pyrrolidine

A mixture of **6** (18 mg, 0.04 mmol), pyrrolidine (0.6 cm³, 7.2 mmol) and DMF (0.5 cm³) was stirred and heated under argon at 80 °C for 5 h. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate (50 cm³) and washed with brine (3 × 25 cm³). The inorganic layer was further extracted with ethyl acetate (3 × 25 cm³); the organic layers were combined, dried, concentrated and chromatographed by radial chromatography (1 mm silica, 5% MeOH in DCM) to yield compound **3** (9 mg, 67%).

Reaction of **6** with one equivalent of pyrrolidine

A mixture of **6** (13 mg, 0.03 mmol), K₂CO₃ (28 mg) and pyrrolidine (0.003 cm³, 0.03 mmol) was stirred and heated in DMF (1 cm³) at 80 °C for 4 h. The reaction mixture was concentrated and the residue was suspended in DCM. The suspension was filtered and the filtrate was concentrated and applied to a 100 × 100 mm silica gel preparative TLC plate (2 mm layer thickness). The chromatogram was developed twice, first by DCM, followed by 1% MeOH in DCM. The usual isolation

procedure gave compounds **3** (3.7 mg, 37%) and **5** (0.5 mg, 4%).

Reaction of 6 with K₂CO₃ in DMF. 1-{6-[3-(2-Hydroxyethyl)-pyrrolidino]-2-naphthyl}ethanone **7 and 2-[1-(6-acetyl-2-naphthyl)pyrrolidin-3-yl]ethyl formate **8****

A mixture of **6** (21 mg, 0.05 mmol), K₂CO₃ (1 g, 7.2 mmol) and DMF (6 cm³) was heated at 80 °C for 4.5 h. The reaction mixture was concentrated to dryness and the residue was suspended in DCM. The suspension was filtered and the filtrate was concentrated and chromatographed by radial chromatography (1 mm silica, ether–petroleum ether = 1 : 1) to yield compounds **7** (2 mg, 15%) and **8** (4 mg, 27%). Compound **7**: mp 121–123 °C; δ_H (300 MHz; CDCl₃) 1.75 (1 H, m, 4'-H), 1.79 (2 H, m, 6'-CH₂), 2.27 (1 H, m, 4'-H), 2.50 (1 H, m, 3'-H), 2.66 (3 H, s, CH₃), 3.10 (1 H, dd, *J* 9.3 and 7.7, 2'-H), 3.43 (1 H, ddd, *J* 9.0, 7.2 and 3.0, 5'-H), 3.53 (1 H, ddd, *J* 9.0, 7.2 and 3.0, 5'-H), 3.64 (1 H, dd, *J* 9.3 and 7.7, 2'-H), 3.79 (2 H, t, *J* 6.4, 7'-CH₂), 6.71 (1 H, d, *J* 2.3, 5-H), 6.99 (1 H, dd, *J* 9.0 and 2.3, 7-H), 7.59 (1 H, d, *J* 8.8, 4-H), 7.78 (1 H, d, *J* 9.0, 8-H), 7.91 (1 H, dd, *J* 8.8 and 1.9, 3-H), 8.30 (1 H, d, *J* 1.9, 1-H); δ_C (75 MHz; CDCl₃) 26.36 (CH₃), 31.74 (4'-C), 35.85 (3'-C), 36.47 (6'-C), 47.48 (5'-C), 53.50 (2'-C), 61.74 (7'-C), 104.23 (5-C), 116.06 (7-C), 124.67 (3-C), 124.74 (8a-C), 125.77 (4-C), 130.31 (2-C), 130.66 (1-C), 130.92 (8-C), 137.91 (4a-C), 147.62 (6-C), 197.66 (C=O); *m/z* 283.1572 (M⁺), C₁₈H₂₁NO₂ requires 283.1580. Compound **8**: δ_H (300 MHz; CDCl₃) 1.77 (1 H, m, 4'-H), 1.90 (2 H, m, 6'-CH₂), 2.27 (1 H, m, 4'-H), 2.45 (1 H, m, 3'-H), 2.66 (3 H, s, CH₃), 3.11 (1 H, dd, *J* 9.0 and 7.5, 2'-H), 3.45 (1 H, ddd, *J* 8.9, 8.9 and 3.1, 5'-H), 3.55 (1 H, ddd, *J* 8.9, 8.9 and 3.1, 5'-H), 3.65 (1 H, dd, *J* 9.0 and 7.5, 2'-H), 4.30 (2 H, t, *J* 6.7, 7'-CH₂), 6.71 (1 H, d, *J* 2.3, 5-H), 6.99 (1 H, dd, *J* 9.0 and 2.3, 7-H), 7.61 (1 H, d, *J* 8.7, 4-H), 7.79 (1 H, d, *J* 9.0, 8-H), 7.91 (1 H, dd, *J* 8.7 and 1.5, 3-H), 8.10 (1 H, s, CHO), 8.31 (1 H, d, *J* 1.5, 1-H); δ_C (75 MHz; CDCl₃) 26.37 (CH₃), 31.55 (4'-C), 32.35 (3'-C), 35.89 (6'-C), 47.42 (5'-C), 53.27 (2'-C), 62.68 (7'-C), 104.36 (5-C), 116.01 (7-C), 124.71 (3-C), 124.84 (8a-C), 125.82 (4-C), 130.44 (2-C), 130.62 (1-C), 130.96 (8-C), 137.86 (4a-C), 147.48 (6-C), 160.97 (CHO), 197.62 (C=O); *m/z* 311.1531 (M⁺), C₁₉H₂₁NO₃ requires 311.1521.

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References and notes

- 1 A. Petrič, A. F. Jacobson and J. R. Barrio, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1455.
- 2 A. F. Jacobson, A. Petrič, A. Sinur and J. R. Barrio, *J. Am. Chem. Soc.*, 1996, **118**, 5572.
- 3 A. Petrič, T. Špes and J. R. Barrio, *Monatsh. Chem.*, 1998, **129**, 777.
- 4 W. G. Scharpf, USP 3 839 342/1974; (*Chem. Abstr.*, 1975, **82**, 43416); D. O. Kiesewetter, W. C. Eckelman, R. M. Cohen, R. D. Finn and S. M. Larson, *Appl. Radiat. Isot.*, 1986, **37**, 1181.
- 5 G. Ambrožič, S. Čeh and A. Petrič, *Magn. Reson. Chem.*, 1998, **36**, 873.
- 6 A. Petrič and J. R. Barrio, *J. Heterocycl. Chem.*, 1994, **31**, 545.
- 7 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn., John Wiley and Sons, Inc., New York, 1999, p. 494.
- 8 V. Gomez-Parra, F. Sanchez and T. Torres, *Synthesis*, 1985, 282.
- 9 V. Gomez-Parra, F. Sanchez and T. Torres, *J. Chem. Soc., Perkin Trans. 2*, 1987, 695.
- 10 A. Inesi, V. Mucciante and L. Rossi, *J. Org. Chem.*, 1998, **63**, 1337.
- 11 W. McGhee, D. Riley, K. Christ, Y. Pan and B. Parnas, *J. Org. Chem.*, 1995, **60**, 2820.
- 12 G. R. Clemons and V. Prelog, *J. Chem. Soc.*, 1938, 400.
- 13 R. Lukeš, M. Ferles and O. Štrouf, *Collect. Czech. Chem. Commun.*, 1959, **24**, 212.
- 14 H. Henecka, U. Hörlein and K.-H. Risse, *Angew. Chem.*, 1960, **72**, 960.
- 15 D. O. Spry and H. S. Aaron, *J. Org. Chem.*, 1969, 3674.
- 16 S. Hünig and W. Baron, *Chem. Ber.*, 1957, **90**, 395.
- 17 T. Morie, S. Kato, H. Harada, I. Fujiwara, K. Watanabe and J. Matsumoto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2565.
- 18 Molecular modeling was performed with Alchemy II software package (Tripos Associates, Inc.).

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