COMMUNICATION

An operationally simple and fully regiocontrolled formal total synthesis of the montanine-type *Amaryllidaceae* alkaloid (±)-pancracine

Martin G. Banwell,* Alison J. Edwards, Katrina A. Jolliffe and Michael Kemmler

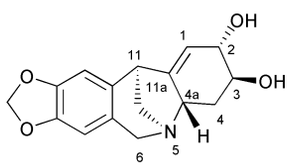
Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

Received (in Cambridge, UK) 7th March 2001, Accepted 30th April 2001
First published as an Advance Article on the web 29th May 2001

Reaction of β-nitrostyrene 4 with cyclohexane-1,3-dione (5) in the presence of DBU affords the Michael-addition product 6, which is readily elaborated, using straightforward chemistry, to the 5,11-methanomorphanthridine 2, acquisition of which constitutes a formal total synthesis of the racemic modification of the montanine alkaloid pancracine (1).

(−)-Pancracine (**1**) is a minor metabolite of the North American native plant *Rhodophiala bifida*[1] and a representative member of the montanine-class of *Amaryllidaceae* alkaloid. Such compounds embody the 5,11-methanomorphanthridine framework **2** and only vary in the nature and stereochemistry of the oxygen-based substituents (generally hydroxy and/or methoxy) attached at C2 and C3.[2] At least one member of the class which incorporates the enantiomeric framework, *viz*. *ent*-**2**, has been observed.[3] Some modest biological activities, including hypotensive and convulsive actions in dogs, have been ascribed to these natural products.[4] Such features, combined with the presence of a structurally novel pentacyclic framework, have prompted a number of synthetic studies.[5–10] Thus far total syntheses of the montanine alkaloids have been reported by Overman [(±)- and (−)-pancracine],[6] Hoshino [(±)-montanine, (±)-coccinine, (±)-pancracine, (±)-brunsvigine and (±)-*O*-acetylmontanine],[7] Weinreb [(−)-coccinine and (−)-pancracine],[8] Pearson [(+)-coccinine][9] and Ikeda [(+)-pancracine].[10] A popular, although not universal, strategy has been to construct an appropriate 3-arylperhydroindole and then apply a Pictet–Spengler reaction so as to install the C6 methylene group associated with the target framework. Subsequent manipulations, often of a C1 or C2 carbonyl group, have been employed to establish the $\Delta^{1,11a}$-double-bond and thereby provide compounds such as **2**, an advanced intermediate in the original Overman synthesis[6] of (±)-pancracine. Analysis of the total synthesis studies undertaken thus far reveals that installation of this double-bond is distinctly problematic so providing a means for doing this in a completely regiocontrolled manner would be an important step forward in developing more effective routes to the montanine alkaloids. Consequently, we now report an operationally simple and fully regiocontrolled synthesis of the racemic modification of compound **2**. Key features of our approach include the early stage and completely specific introduction of the pivotal $\Delta^{1,11a}$-double-bond and a Mitsunobu-promoted and intramolecular nucleophilic displacement of an allylic alcohol by a tethered sulfonamide[11] as the means of constructing 3-arylhexahydroindole precursor **3**. The straightforward manipulations of readily available substrates using conventional reagents allow an operationally simple and concise entry into the montanine alkaloid framework that should ensure greater access to this interesting class of compound.

The pivotal early stages of the synthetic sequence leading to the racemic modification of compound **2** are shown in Scheme 1. Thus, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted Michael addition of cyclohexane-1,3-dione (**5**) to the readily available β-nitrostyrene **4**[12] affords the adduct **6**† in quantitative yield.[13] In keeping with observations made by others on related compounds,[14] this adduct readily engages in a cyclodehydration reaction to give the *N*-hydroxyimidate **7** (mp 169–173 °C) the structure of which was secured by single-crystal X-ray analysis.‡ In order to avoid the unwanted conversion of **6**⟶**7** and to also facilitate a subsequent deoxygenation, the former compound was subject to standard acetylation conditions with the result that the *O*-acetyl derivative **8** (74%, mp 99–100 °C) was obtained. Reaction of compound **8** under Luche conditions[15] followed by treatment of the resulting allylic alcohol with methanolic potassium carbonate then afforded the enone **9** (mp 97–98 °C) in 67% yield. Luche reduction of this last compound delivered a chromatographically separable mixture of the expected 1,2-reduction products **10** (46%) and **11** (47%), the assigned stereochemistries of which follow from the synthetic and crystallographic studies outlined below. Chemoselective reduction of the nitro group within the former product was achieved using a mixture of nickel boride and hydrazine[16] and the resulting primary amine was immediately converted, by standard methods, into the corresponding toluene-*p*-sulfonamide **12** (84%, mp 58–60 °C). Subjection of this latter compound to reaction with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in dichloromethane at 0–18 °C afforded a chromatographically separable and *ca*. 85 : 15 mixture of the 3-arylhexahydroindoles **14** (71%, mp 41–43 °C) and **15** (12%, mp 178–180 °C). The structure of the latter product was established by X-ray crystallographic analysis.‡ Analogous chemistry was employed to convert the nitro alcohol **11**, *via* the open-chain sulfonamide **13** (87%, mp 127–129 °C), into a *ca*. 5 : 95 mixture of compounds **14** (4%) and **15** (85%). The outcomes of these Mitsunobu-type cyclodehydration reactions suggest they proceed *via* an almost strictly S_N2 pathway.[17]



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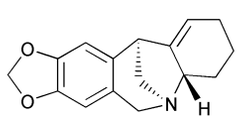

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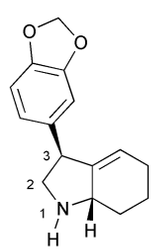

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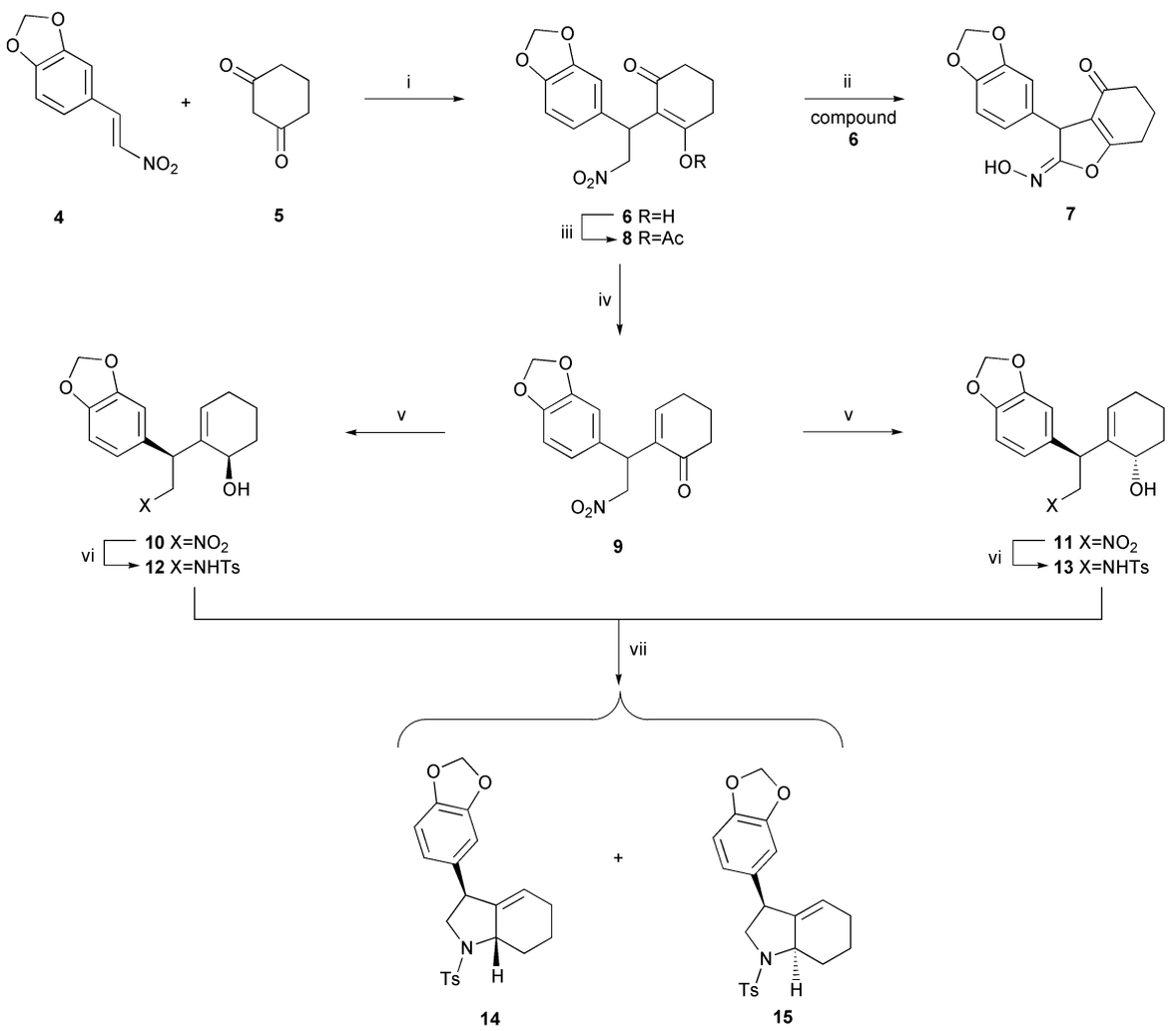
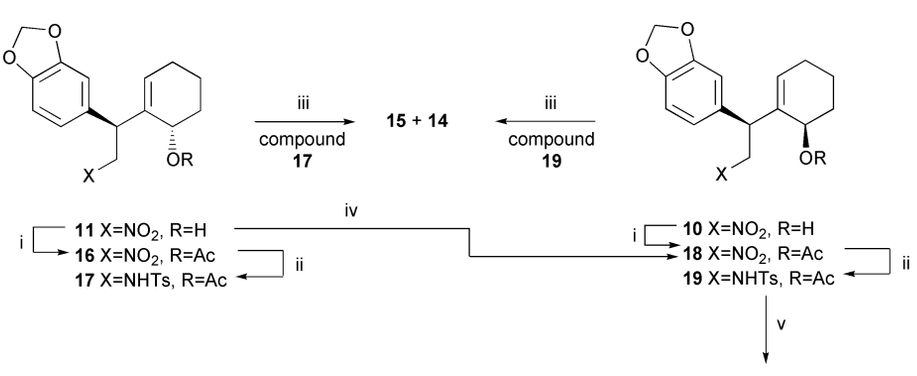
DOI: 10.1039/b102252k

Since the cyclisation product **14** (but not isomer **15**) embodies the stereochemical characteristics required in target **2**, various methods for effecting the stereocontrolled reduction of enone **9** to alcohol **10** (the precursor to **14**) were investigated. However, no useful levels of 1,3-stereoinduction could be achieved in this reaction and a close to 1 : 1 mixture of alcohols **10** and **11** was always obtained. As a consequence, methods for effecting the high-yield conversion of alcohol **11** into hexahydroindole **14** were pursued. To these ends (Scheme 2), the readily available acetate derivative, **16** (82%), of alcohol **11** was converted, using the methods described above, into the sulfonamide **17** (62%, mp 169–170 °C), the structure of which follows from an X-ray analysis.‡ This last compound was then subjected to reaction with 2.5% $Pd_2(dba)_3{\cdot}CHCl_3$,[18] triethylamine and triphenylphosphine in the expectation that the ensuing η^3-allylpalladium species would be attacked by the pendant sulfonamide residue,



Scheme 1 *Reagents and conditions*: (i) DBU (1 mole equiv.), CH_2Cl_2, 18 °C, 2 h; (ii) store in solid state, 18 °C, 24 h; (iii) Ac_2O (1 mole equiv.), DMAP (cat.), pyridine, 18 °C, 2.5 h; (iv) $NaBH_4$ (1 mole equiv.), $CeCl_3{\cdot}7H_2O$ (1 mole equiv.), MeOH, −10–18 °C, 0.25 h then K_2CO_3 (1.5 mole equiv.), MeOH, 18 °C, 3 h; (v) $NaBH_4$ (1.1 mole equiv.), $CeCl_3{\cdot}7H_2O$ (1.1 mole equiv.), MeOH, 0–18 °C, 0.20 h; (vi) NiB_2 (2.5 mole equiv.), 80% aq. hydrazine (10 mole equiv.), EtOH, 78 °C, 0.5 h then *p*-TsCl (1 mole equiv.), DMAP (cat.), pyridine (3 mole equiv.), CH_2Cl_2, 18 °C, 15 h; (vii) DIAD (1.25 mole equiv.), PPh_3 (1.25 mole equiv.), CH_2Cl_2, 0–18 °C, 4.5 h. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

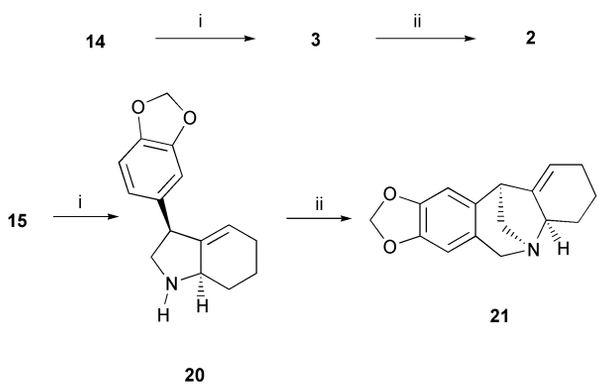


Scheme 2 *Reagents and conditions*: (i) Ac_2O (1.2 mole equiv.), pyridine (1.2 mole equiv.), DMAP (cat.), CH_2Cl_2, 18 °C, 18 h; (ii) NiB_2 (2.5 mole equiv.), 80% aq. hydrazine (10 mole equiv.), EtOH, 78 °C, 0.5 h then *p*-TsCl (1 mole equiv.), DMAP (cat.), pyridine (3 mole equiv.), CH_2Cl_2, 18 °C, 15 h; (iii) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mole%), PPh_3 (5 mole%), Et_3N (2 mole equiv.), MeCN, 75 °C, 18 h; (iv) DIAD (3 mole equiv.), PPh_3 (3 mole equiv.), AcOH (3 mole equiv.), C_6H_6, 0–18 °C, 25 h; (v) K_2CO_3 (2 mole equiv.), MeOH, 18 °C, 4 h.

such that overall retention of configuration would occur in what would be a nett displacement of the original acetate group by the tethered sulfonamide residue. In the event, however, essentially only the wrong hexahydroindole, namely compound **15** (75%), was obtained. Interestingly, under the same conditions the isomeric sulfonamide/acetate **19** [61%, prepared from compound **10** *via* intermediate **18** (84%)] afforded a *ca*. 1 : 3 mixture of hexahydroindoles **14** and **15** (86% yield at 20% conversion). The varying outcomes of these Pd[0]-catalysed reactions could be attributed to differing diastereofacial selectivities associated with formation of the two possible η^3-allylpalladium species arising from allylic acetates **16** and **17** as well as the differing modes of cyclisation available to such species.[19] Studies aimed at fully understanding these observations are now underway.

To date the most effective means of exploiting alcohol **11** in the synthesis of the desired hexahydroindole **14** has involved subjecting the former compound to a Mitsunobu reaction in which acetic acid is used as the nucleophilic species. The ensuing acetate **18** (38%) was then converted into sulfonamide **19** (62%) under the conditions described above. This last compound could be saponified with methanolic potassium carbonate thereby producing alcohol **12** (90%), a proven (*vide supra*) precursor to compound **14**.

Completion of the synthesis of target **2** (Scheme 3) was



Scheme 3 *Reagents and conditions*: (i) $C_{10}H_8Na$ (37 mole equiv.), DME, −78 °C, 0.15 h; (ii) paraformaldehyde (6 mole equiv.), HCO_2H, 80 °C, 14 h.

achieved by reductive cleavage of the sulfonamide group within compound **14** using sodium naphthalenide[20] and immediately subjecting the resulting deprotected and C3-arylated hexahydroindole **3** to reaction with formic acid–paraformaldehyde. The product of the ensuing Pictet–Spengler reaction,[21] 5,11-methanomorphanthridine **2** (59% from **14**, mp 101–103 °C, lit.[6] mp 101–103 °C), proved identical, as judged by appropriate spectroscopic comparisons, with the material Overman[6] obtained during his synthesis of (±)-pancracine. Overman was able to elaborate compound **2** to (±)-pancracine (**1**) using a series of five simple oxidation and reduction steps. Interestingly, compound **15** can also be carried forward in the same way as congener **14** and by this means, and *via* hexahydroindole **20**, compound **21** (56% from **15**, mp 98–100 °C), the C4a-epimer of 5,11-methanomorphanthridine **2**, was obtained and its structure confirmed by single-crystal X-ray analysis (Fig. 1). ‡

Experimental

Compound 12

$NaBH_4$ (57 mg, 1.5 mmol) was added, portionwise, to a solution of $NiCl_2 \cdot 6H_2O$ (890 mg, 3.7 mmol) in EtOH (7.5 mL). The resulting black mixture was stirred for 0.5 h at 18 °C and then diluted with H_2O (7.5 mL). The mixture was filtered and the ensuing black precipitate (NiB_2) was washed sequentially with H_2O (1 × 7.5 mL) and EtOH (3 × 7.5 mL), then added to a solution of compound **10** (440 mg, 1.5 mmol) in EtOH (15 mL). The resulting mixture was heated to reflux, then N_2H_4 (15 mmol of an 80% solution in H_2O) added, followed, after 0.5 h, by

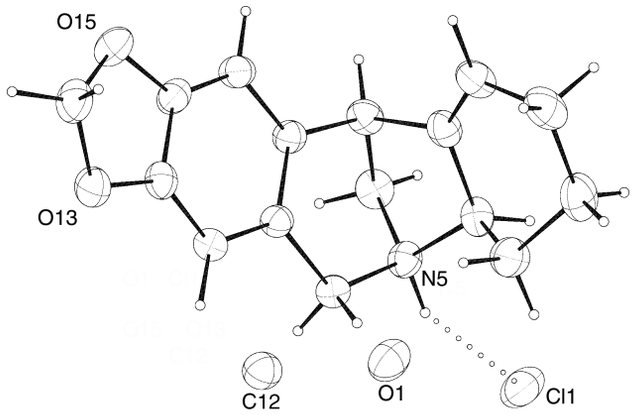


Fig. 1 A crystallographic formula unit (with 50% probability ellipsoids) of compound **21** derived from X-ray crystallographic data.[26]

NEt_3 (6 mmol).[22] The mixture was filtered, whilst still hot, through a plug of Celite™ which was washed with a solution of $CHCl_3$–MeOH–aq. NH_3 (80 : 19 : 1 v/v/v) (2 × 15 mL). The combined filtrates were concentrated under reduced pressure and the oily yellow residue dissolved in CH_2Cl_2 (3.75 mL), then pyridine (4.5 mmol), DMAP (7.5 mg) and *p*-TsCl (1.5 mmol) were added and the ensuing mixture stirred at 18 °C for 15 h. The mixture was partitioned between CH_2Cl_2 (45 mL) and saturated aq. NH_4Cl and the organic phase was washed with H_2O (45 mL) and brine (45 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography on silica gel (1 : 1 EtOAc–hexane elution) gave, after concentration of the appropriate fractions (R_f 0.4), the *title sulfonamide* **12** (520 mg, 84%) as a colourless and microcrystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.71–6.50 (complex m, 3H), 5.92 (s, 2H), 5.56 (t, J = 3.8 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.74 (br s, 1H), 3.56 (dd, J = 7.5 and 7.2 Hz, 1H), 3.28 (m, 1H), 3.13 (m, 1H), 2.42 (s, 3H), 2.15–1.43 (complex m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 146.6, 143.4, 138.5, 136.5, 134.4, 129.7, 127.2, 125.8, 121.4, 108.4, 108.0, 101.0, 65.6, 46.9, 46.4, 31.8, 25.4, 21.6, 17.2; IR (CH_2Cl_2 solution, NaCl cell) 3533, 3282, 2927, 1503, 1486, 1324, 1245, 1158 cm^{-1}; MS (EI) *m*/*z* 415.1456 (415.1453 calcd for $C_{22}H_{25}NO_5S$, $M^{+\bullet}$, 1%), 397 (1), 91 (100). Anal. calcd for $C_{22}H_{25}NO_5S$: C, 63.6; H, 6.1; N, 3.4. Found: C, 63.2; H, 6.1; N 3.2%.

Compounds 14 and 15

DIAD (260 μL, 1.3 mmol) was added dropwise and *via* syringe to a chilled (0 °C) solution of PPh_3 (340 mg, 1.3 mmol) and compound **12** (450 mg, 1.1 mmol) in dry CH_2Cl_2 (3 mL). The resulting mixture was warmed to 18 °C and stirred for a further 4 h. The solvent was then removed under reduced pressure and the residue subjected to flash chromatography on silica gel (3 : 1 hexane–Et_2O elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.15) afforded *hexahydroindole* **14** (300 mg, 71%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.4 Hz, 1H), 6.34 (dd, J = 8.4 and 1.6 Hz, 1H), 6.25 (d, J = 1.6 Hz, 1H), 5.88 (s, 2H), 5.60 (br s, 1H), 3.84 (dd, J = 10.5 and 7.2 Hz, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 3.29 (dd, J = 10.5 and 3.9 Hz, 1H), 2.64–2.55 (complex m, 1H), 2.40 (s, 3H), 2.07 (m, 2H), 1.93–1.84 (complex m, 1H), 1.55–1.42 (complex m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 146.0 (C), 143.3 (C), 140.0 (C), 136.1 (C), 133.6 (C), 129.7 (CH), 127.5 (CH), 124.0 (CH), 120.0 (CH), 108.1 (CH), 107.2 (CH), 100.9 (CH_2), 59.0 (CH), 55.7 (CH_2), 46.6 (CH), 29.9 (CH_2), 24.4 (CH_2), 21.5 (CH_3), 20.1 (CH_2); IR (CH_2Cl_2 solution, NaCl cell) 1503, 1488, 1442, 1345, 1249, 1233, 1161, 1092, 1039 cm^{-1}; MS (EI) *m*/*z* 397.1346 (397.1348 calcd for $C_{22}H_{23}NO_4S$, $M^{+\bullet}$, 46%), 369 (21), 242 (53), 214 (66), 91 (100). Anal. calcd for $C_{22}H_{23}NO_4S$: C, 66.5; H, 5.8; N, 3.5. Found: C, 66.5; H, 5.5; N, 3.4%.

Concentration of fraction B (R_f 0.2) afforded *hexahydroindole* **15** (51 mg, 12%) as colourless needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 1.5 Hz, 1H), 6.52 (dd, J = 7.8 and 1.5 Hz, 1H), 5.94 (s, 2H), 5.04 (br s, 1H), 3.80 (br s, 1H), 3.75 (dd, J = 10.5 and 8.7 Hz, 1H), 3.30 (app t, J = 10.5 Hz, 1H), 3.14 (br s, 1H), 2.58–2.50 (complex m, 1H), 2.45 (s, 3H), 2.04–1.92 (complex m, 2H), 1.90–1.82 (complex m, 1H), 1.60–1.45 (complex m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 (C), 146.6 (C), 143.5 (C), 141.7 (C), 134.7 (C), 132.0 (C), 129.8 (CH), 127.6 (CH), 121.9 (CH), 121.8 (CH), 108.6 (CH), 108.2 (CH), 101.0 (CH_2), 59.6 (CH), 54.7 (CH_2), 46.8 (CH), 30.1 (CH_2), 24.1 (CH_2), 21.6 (CH_3), 20.1 (CH_2); IR (CH_2Cl_2 solution, NaCl cell) 1503, 1488, 1443, 1346, 1249, 1161, 1092, 1040, 758 cm^{-1}; MS (EI) *m/z* 397.1349 (397.1348 calcd for $C_{22}H_{23}NO_4S$, $M^{+\bullet}$, 61%), 369 (23), 242 (57), 214 (86), 91 (100). Anal. calcd for $C_{22}H_{23}NO_4S{\cdot}0.5H_2O$: C, 65.0; H, 6.0; N, 3.4. Found: C, 64.9; H, 5.8; N, 3.2%.

Compound 2

A solution of sodium naphthalenide was prepared by adding sodium (400 mg, 17 mmol), in small pieces, to a solution of naphthalene (2.1 g, 16 mmol) in deoxygenated DME (10 mL) and by stirring the resulting green mixture at 18 °C for 2 h. This solution was then added, dropwise and *via* cannula, to a magnetically stirred solution of compound **14** (170 mg, 0.43 mmol) in DME (4.5 mL), maintained at –78 °C under a nitrogen atmosphere, until a light-green colour persisted. Saturated aq. NH_4Cl (10 mL) was added to the reaction mixture, which was then extracted with EtOAc (3 × 25 mL). The organic phases were combined and extracted with 1 M HCl (3 × 25 mL), then the combined aqueous phases were basified to pH 10 by the addition of solid NaOH. The resulting mixture was extracted with EtOAc (3 × 25 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was treated with formic acid (2 mL) then paraformaldehyde (700 mg, 2.4 mmol) and the resulting mixture heated at 80 °C for 14 h. The cooled reaction mixture was partitioned between H_2O (10 mL) and Et_2O (20 mL). The separated aqueous phase was washed with Et_2O (20 mL) then basified to pH 10 by the addition of saturated aq. K_2CO_3. The basic solution was extracted with EtOAc (3 × 20 mL) and the combined organic phases dried ($MgSO_4$) filtered and concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography on silica gel (80 : 19 : 1 v/v/v $CHCl_3$–MeOH–aq. NH_3 elution) and concentration of the appropriate fractions (R_f 0.6) yielded compound **2** (66 mg, 59%), as a colourless solid, which had spectroscopic properties identical to those reported[6] previously.

Acknowledgements

We thank the Institute of Advanced Studies for financial support including the provision of a IAS post-Doctoral Fellowship to KAJ. Professor Wolfgang Steglich (LMU—München) and his Department are thanked for allowing MK to carry out research work leading to the "Diplomhauptprüfung in Chemie" in the Research School of Chemistry, The Australian National University.

Notes and references

† All new and stable compounds had spectroscopic data (IR, NMR, mass spectrum) consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ Crystal data for **7**: $C_{15}H_{13}NO_5{\cdot}CH_3OH$, M = 319.31, T = 200(1) K, monoclinic, space group $P2_1/n$, Z = 4, a = 10.4370(6), b = 11.1112(6), c = 13.9707(6) Å, β = 108.346(3)°, V = 1537.80(14) Å^3, D_c = 1.379 g cm^{-3}, 14104 unique data ($2\theta_{max}$ = 46°), 1743 with $I > 3\sigma(I)$, R = 0.0415, R_w = 0.0450, S = 1.0581.

Crystal data for **15**: $C_{22}H_{23}NO_4S$, M = 397.49, T = 200(1) K, monoclinic, space group $P2_1/n$, Z = 4, a = 9.9458(2), b = 16.1368(4), c = 12.0708(3) Å, β = 94.2552(13)°, V = 1931.94(8) Å^3, D_c = 1.37 g cm^{-3}, 4414 unique data ($2\theta_{max}$ = 55°), 3733 with $I > 3\sigma(I)$, R = 0.0420, R_w = 0.0291, S = 1.0315.

Crystal data for **17**: $C_{24}H_{27}NO_6S$, M = 457.55, T = 200(1) K, monoclinic, space group $P2_1/c$, Z = 4, a = 9.51220(10), b = 24.4129(3), c = 9.93130(10) Å, β = 99.5571(6)°, V = 2274.24(4) Å^3, D_c = 1.336 g cm^{-3}, 5323 unique data ($2\theta_{max}$ = 55°), 3319 with $I > 3\sigma(I)$; R = 0.0688, R_w = 0.0746, S = 1.0311.

Crystal data for **21**: $C_{16}H_{17}NO_2{\cdot}HCl{\cdot}1.5H_2O$, M = 318.79, T = 200(1) K, monoclinic, space group $C2/c$, Z = 8, a = 20.0656(2), b = 13.9995(2), c = 13.3059(2) Å, β = 124.0651(7)°, V = 3096.35(7) Å^3, D_c = 1.368 g cm^{-3}, 4507 unique data ($2\theta_{max}$ = 60°), 1851 with $I > 3\sigma(I)$; R = 0.0360, R_w = 0.0230, S = 1.1222.

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[23] Structure solution was by direct methods (SIR92)[24] and refinement was by full matrix least-squares on F using the CRYSTALS program package.[25] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 160053–160056. See http://www.rsc.org/suppdata/p1/b1/b102252k/ for crystallographic files in .cif or other electronic format.

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