Synthesis of New Soluble Annelated Polypyridines

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A new octahydroacridine with a *tert*-butoxypropyl group in the 9-position was prepared and was used in the synthesis of new soluble annelated polypyridines. Quinquepyridine with 11 adjacent rings was prepared in 17–25% yield by condensation of an α-methylene ketone and an enolisable ketone in the presence of ammonium acetate under basic conditions.

Introduction

Since the work of Bell[1] and Thummel[2] on the synthesis of annelated polypyridines and other annelated polyaza structures, a wide variety of annelated pyridines capable of selectively binding charged or neutral organic molecules has been synthesised.[3] A useful approach to the synthesis of such molecules involves 1,5-diketone intermediates that, with a nitrogen-containing reagent, undergo ring closure to the corresponding pyridine. However, few methods have been developed for the preparation of soluble annelated polypyridines. The most important method for the construction of soluble annelated polypyridines was that employing a 9-substituted octahydroacridine, which was used in the synthesis of the "Torand"[1b] and the helicoidal polypyridine[1g,1f] (Figure 1).

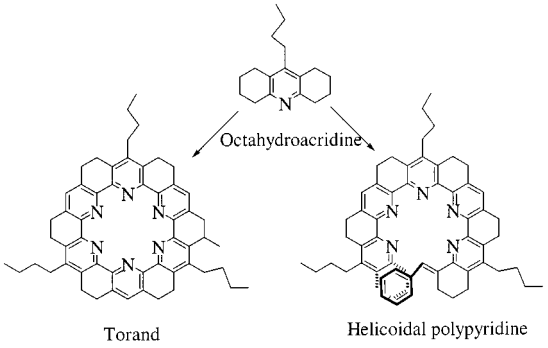

Figure 1. Synthesis of soluble annelated polypyridines from 9-butyloctahydroacridine

As part of a programme aimed at the use of annelated polypyridines in molecular recognition, and in order to extend the utility of such molecules,[4] we have synthesised soluble polypyridines by employing the Michael addition of an enolisable ketone to an α,β-unsaturated ketone followed by cyclisation of the 1,5-diketone intermediate in the presence of ammonium acetate.[5] In this paper we present the synthesis of a new substituted octahydroacridine and its application in the preparation of soluble annelated polypyridines. The present procedure is based on the condensation of α-methylene ketones with enolisable ketones under basic conditions.

Our strategy is based on the retrosynthetic analysis shown in Figure 2. The choice of *tert*-butyl as a protecting group for the 9-substituted octahydroacridine was made by considering its stability under harsh reaction conditions and its solubility in organic solvents. The protecting group was easy to remove under mild conditions[6] and the hydroxy group can then serve for immobilisation or conjugation of these molecules to solid supports or biomolecules.

As shown in Scheme 1, the synthesis began with the preparation of 4-*tert*-butoxybutanal (**3**). Starting from the readily available 3-chloropropan-1-ol (**1**), the aldehyde **3** was obtained in good yield in two steps. The transformation of **1** to 3-*tert*-butoxy-1-chloropropane (**2**) was carried out using a known procedure.[7] Conversion into the butanal **3** was achieved in 84% yield on a large scale by formylation of its corresponding Grignard reagent using *N*-formylpiperidine as a formylating agent.[8] 8-(3-*tert*-Butoxypropyl)-2-hydroxytricyclo[7.3.1.$0^{2,7}$]tridecan-13-one (**4**) was prepared in 87% yield by the aldol condensation of cyclohexanone with **3**.[9] The structure of **4** was confirmed by X-ray analysis and is shown in Figure 3.

The framework of the three fused rings of the hydroxytricyclotridecanone moiety is closely related to that reported for the 2-hydroxytricyclo[7.3.1.$0^{2,7}$]tridecan-13-one compounds $C_{14}H_{22}O_2$.[10] As observed in the methyl derivative, two hydrogen bonds [O(5)–H(5)···O(13′) and O(13)···H(5′)-O(5′)] link two enantiomers through an inversion centre. Conversion of **4** to 8-(3-*tert*-butoxypropyl)-1,2,3,4,5,6,7,8-octahydroacridine (**5**) was achieved by reaction with ammonium acetate and copper(II) acetate according to the literature procedure.[11]

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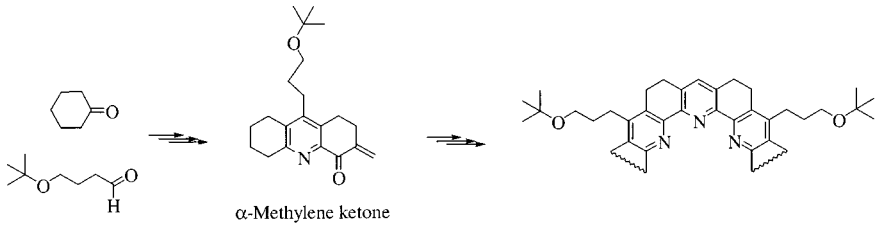
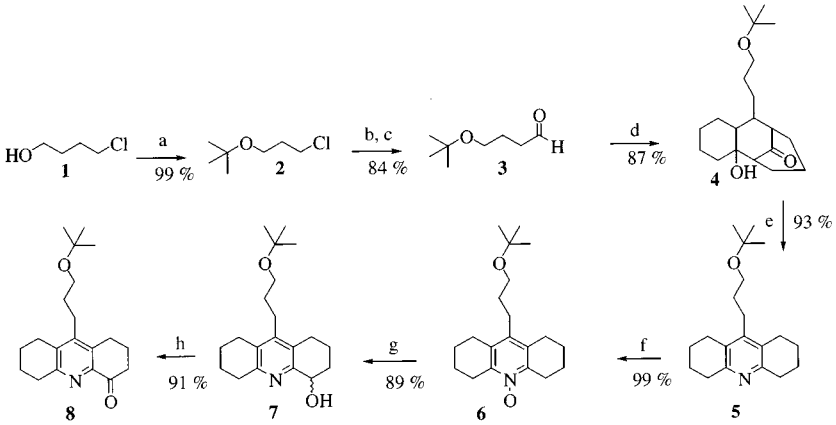


Figure 2. Synthetic strategy for the new annelated polypyridines



Scheme 1. (a) Isobutene, H_2SO_4 (cat.), CH_2Cl_2, –78 °C; (b) Mg, $(CH_2)_2Br_2$, THF, reflux; (c) *N*-formylpiperidine, THF, –20 °C, 3 N HCl; (d) cyclohexanone, EtONa/EtOH, reflux; (e) AcOH, $Cu(OAc)_2$, NH_4OAc; (f) *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C; (g) trifluoroacetic anhydride, CH_2Cl_2, room temp.; saponification with 2 M K_2CO_3 solution; (h) DMSO, oxalyl chloride, CH_2Cl_2, Et_3N, –78 °C

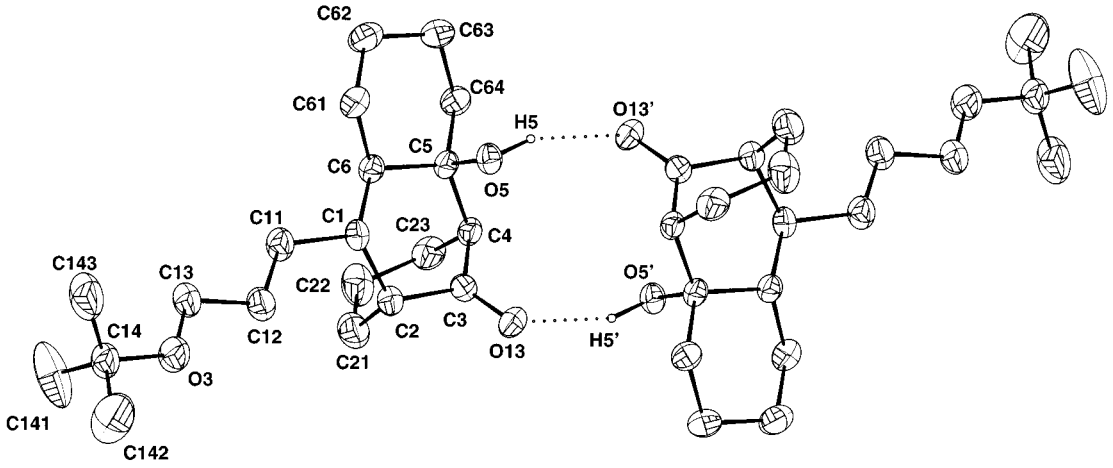
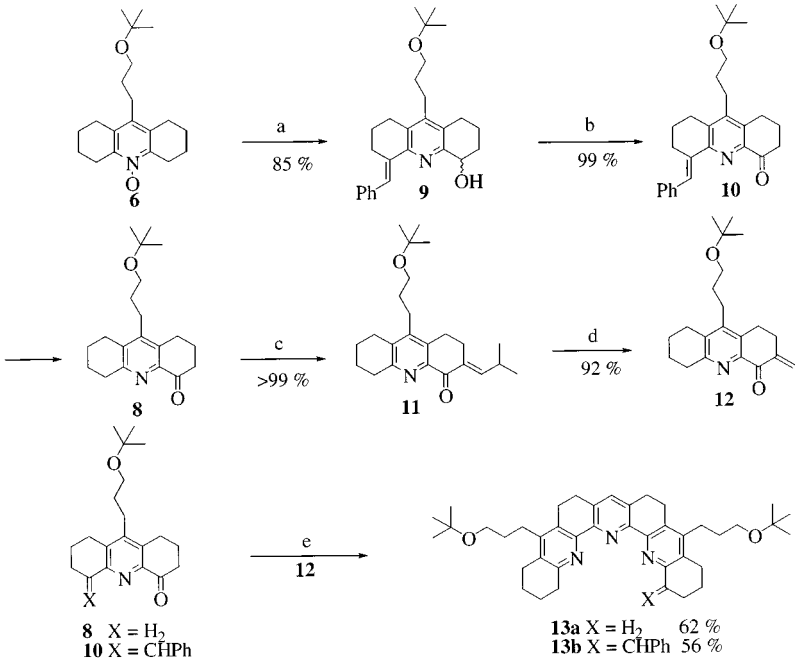


Figure 3. View of two enantiomers of **4** linked by hydrogen bonds with atom labelling scheme; ellipsoids are drawn at 30% probability

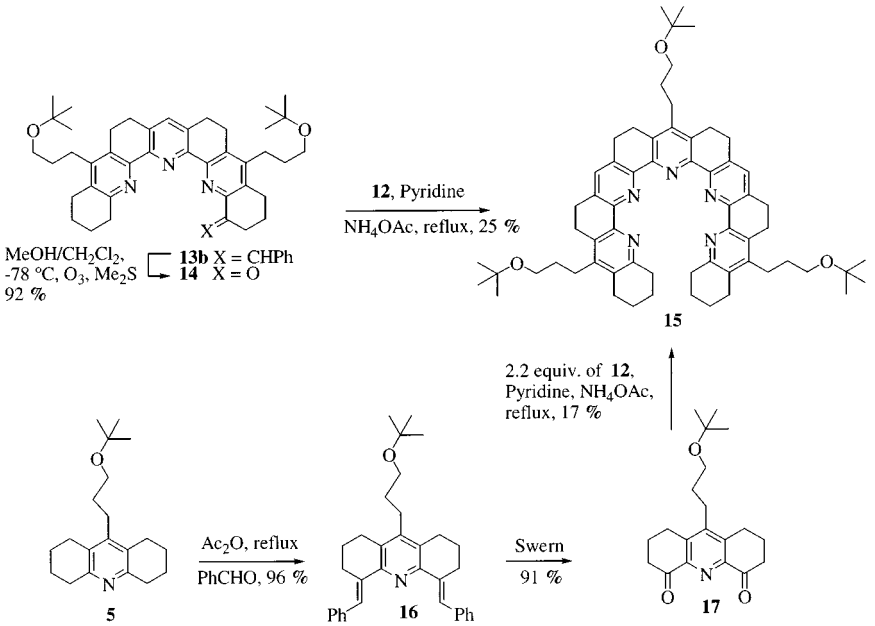
The transformation of octahydroacridine **5** into 8-(3-*tert*-butoxypropyl)-1*H*-2,3,5,6,7,8-hexahydroacridin-4-one (**8**) involves α-CH_2 oxidation, which may be effected by the "Boekelheide" rearrangement of an acetylated *N*-oxide.[12] Unfortunately, treatment of the *N*-oxide **6** with hot acetic anhydride and hydrolysis of the resulting acetate led to the alcohol **7** in only moderate yield (62%). An alternate procedure, using trifluoroacetic anhydride as a key acylating agent, proved more convenient. The treatment of *N*-oxide **6** with trifluoroacetic anhydride in dry dichloromethane, followed by saponification of the resulting trifluoroacetate, gave **7** in 89% yield.[13] Oxidation of this alcohol using modified Swern conditions[14] gave ketone **8** in 91% yield.

The formation of the heptacyclic terpyridine **13** requires the coupling of two ketones to create the central pyridine ring. Different methods have been reported for the preparation of such annelated polypyridines.[15] We concentrated on the Michael addition of an enolisable ketone to an enone because it offers access to unsymmetrical terpyridyls from two different ketones. Consequently, the benzylidene ketone **10** and the enone **12** were prepared. Ketone **10** was obtained in a two step procedure starting from *N*-oxide **6**.[16] A mixture of **6** in acetic anhydride and benzaldehyde was heated under reflux and subsequent in situ alkaline saponification of the resulting acetate gave the benzylidene alcohol **9** in 85% yield. This alcohol was then oxidised to the

benzylidene ketone **10** in 99% yield. For the preparation of the α-methylene ketone **12**, two different methods were examined: a method employing the Mannich base of **8** and a method based on the reduction of enaminone **11**. For the preparation of **12** via the Mannich base, ketone **8** was treated with *N*,*N*-dimethyl(methylene)immonium chloride in anhydrous acetonitrile at room temperature.[17] This method led, in all cases, to the Mannich base in low yield and was therefore not used for the preparation of **12**. As an alternative for the preparation of **12**, ketone **8** was first converted into enaminone **11** in quantitative yield by reaction with *tert*-butoxybis(dimethylamino)methane.[18] Treatment of **11** with diisobutylaluminium hydride gave the enone **12** in 85% yield.[19] The preparation of **13a** by the reaction of **8** with **12** (Scheme 2) in hot (90 °C) anhydrous DMSO[20] led to **13a** in 49% yield, while a 45% yield of **13a** was obtained in TMU[21] at 90 °C. It is important to point out that in both DMSO and TMU the addition of oxidising agent did not improve the yield of **13a**. However, the reaction of **8** and **12** in anhydrous pyridine at 90 °C gave the heptacyclic terpyridine **13a** in 62% yield. The unsymmetrical, homologous compound **13b** was obtained in 56%



Scheme 2. (a) Ac_2O/PhCHO 2:1, 170 °C; saponification with 2 M K_2CO_3 solution; (b) DMSO, oxalyl chloride, CH_2Cl_2, Et_3N, –78 °C; (c) *tert*-butoxybis(dimethylaminomethane), 45 °C, 3 h; (d) diisobutylaluminium hydride, THF, –78 °C, 2 h, NH_4Cl; (e) pyridine, NH_4OAc, 90 °C



Scheme 3. Synthesis of the annelated quinquepyridine **15** with 11 adjacent rings

yield by condensation of **12** with the benzylidene ketone **10** under the same conditions.

This strategy was also used for the preparation of larger annelated polypyridines such as **15**, which is a quinquepyridine with 11 adjacent rings. As shown in Scheme 3, two routes based on coupling of an enone with an enolisable ketone were used. The first approach was the condensation of the heptacyclic ketone of **13b** with the enone **12**. Consequently, ozonolysis of **13b** gave **14** in 92% yield. The reaction of ketone **14** with **12** and excess ammonium acetate in anhydrous pyridine gave **15** in 25% yield. ^{1}H-NMR and ^{13}C-NMR spectra of the product are consistent with the C_2-symmetric structure. A second approach to the preparation of **15** involved coupling of **12** with diketone **17**. This diketone was prepared in good yield by reaction of **5** with benzaldehyde to provide its dibenzylidene derivative **16**, which was then ozonolysed to diketone **17**.[2d] The condensation of **17** with 2 equivalents of **12**, under the same conditions as for **14**, provided **15** in <5% yield. The slow addition of **12** to a mixture of **17** and NH_4OAc in hot pyridine led to **15** in 10% yield. The best yield (17%) was obtained when the diketone **17** was preheated with NH_4OAc in pyridine before the addition of **12**. In this case, dienamine or a mixture of mono- and dienamine of **17** is apparently formed and reacts efficiently with the enone **12** as previously suggested by Bell.[1h]

In this work we have described the synthesis of a new octahydroacridine and its application in the preparation of soluble annelated polypyridines employing a two-step procedure based on the Michael addition of an α-methylene ketone and an enolisable ketone. Annelated polypyridines such as pentadentate **18** (Figure 4) are useful hosts for complexation of alkali metals (Na^+, K^+).[1h] Our octahydroacridine, which contains a protected hydroxy group on the side chain, can lead to hosts suitable for polymer immobilisation or incorporation into a dendrimer.

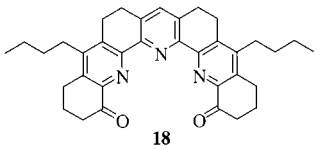


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Figure 4. Annelated polypyridine for the selective complexation of sodium and potassium

Experimental Section

All reactions were carried out under argon. Nuclear magnetic resonance spectra were recorded with Bruker AM-250 (250 MHz) and AC-200 (200 MHz) spectrometers for ^{1}H, and chemical shifts are reported in ppm downfield from Me_4Si. These instruments were also used for ^{13}C spectra. IR spectra were obtained with a Perkin–Elmer 883 or FT-1725X spectrophotometer. CI mass spectra and FAB mass spectra (*m*-nitrobenzyl alcohol matrix) were recorded with a quadripolar Nermag R10-10H instrument. GC mass spectra were recorded with a Hewlett-Packard HP MSD 7590. C, H, N and O elemental analyses were performed by the LCC (Laboratoire de Chimie de Coordination) Microanalytical Service. Column chromatography was performed with Merck alumina (70–230 mesh ASTM), deactivated with 8% of water. Preparative flash chromatography was performed on Merck Kieselgel.

3-*tert*-Butoxy-1-chloropropane (2): A solution of 95 g (1 mol) of 3-chloropropan-1-ol in 400 mL of anhydrous dichloromethane and 5 mL of concentrated sulfuric acid was added to 90 g (1.60 mol) of isobutene at –78 °C. The mixture was stirred at room temperature overnight and neutralised by the required amount of saturated sodium bicarbonate. The aqueous layer was extracted twice with dichloromethane. The combined organic phases were washed with water and with saturated sodium chloride, dried with $MgSO_4$ and concentrated under reduced pressure to afford an oil, which was distilled to yield 150 g (99%) of colourless, odorous liquid 3-*tert*-butoxy-1-chloropropane (**2**); b.p. 52 °C, 15 Torr. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.65 (t, 2 H, *J* = 6.4 Hz), 3.50 (t, 2 H, *J* = 5.8 Hz), 1.98 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 72.7, 57.8, 42.2, 33.4, 27.5. – $C_7H_{15}ClO$ (150.65): calcd. C 55.97, H 10.07, O 10.65; found C 55.76, H 10.20, O 10.70. – MS (CI, NH_3); *m*/*z* (%): 151 (100) [MH^+].

4-*tert*-Butoxybutanal (3): To a cooled (–20 °C) solution of 9.93 g (100 mmol) of *N*-formylpiperidine in 100 mL of anhydrous tetrahydrofuran was added, over 30 min, 250 mL (125 mmol, 1.25 equiv.) of a 0.5 M solution of 3-(*tert*-butoxypropyl)magnesium chloride. The reaction mixture was then left to reach room temperature overnight. The mixture was hydrolysed using 30 mL of 3 M hydrochloric acid. After decantation, the aqueous layer was extracted with diethyl ether (3 × 150 mL). The organic layers were combined and neutralised with saturated aqueous sodium hydrogencarbonate solution, washed with water and saturated aqueous sodium chloride solution. After drying ($MgSO_4$), the solution was concentrated under reduced pressure to afford a yellow oil, which gave after distillation 10.2 g (84%) of a colourless odorous liquid **3**; b.p. 54 °C, 5 Torr. – IR (nujol): $\tilde{\nu}$ = 2723, 1728 (CO) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 9.75 (m, 1 H), 3.40 (t, 2 H, *J* = 6.1 Hz), 2.50 (m, 2 H), 1.85 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 202.7, 72.8, 60.3, 41.1, 27.4, 23.4. – $C_8H_{16}O_2$ (144.21): calcd. C 66.63, H 11.18, O 22.19; found C 66.33, H 11.13, O 22.54. – MS (CI, NH_3); *m*/*z* (%): 145 (100) [MH^+].

8-(3-*tert*-Butoxypropyl)-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one (4): A solution of 0.5 g of potassium hydroxide in 50 mL of absolute ethanol was added in one portion to 120 mL of heated cyclohexanone at 75 °C. A solution of 20.59 g (143 mmol) of **3** in 100 mL of absolute ethanol was then added very slowly (6 h). The mixture was refluxed for 24 h. Removal of the solvent and cyclohexanone under reduced pressure gave an oil, which precipitated in hexane to give 39.77 g (87%) of **4** as a white microcrystalline powder; m.p. 129–130 °C. – IR (KBr): $\tilde{\nu}$ = 3382 (OH), 1714 (CO) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.30 (t, 2 H, *J* = 6.2 Hz), 2.40 (m, 2 H), 2.00–1.22 (m, 21 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 220.6, 72.4, 61.4, 59.6, 48.3, 45.0, 42.1, 36.5, 29.3, 28.7, 27.7, 27.5, 26.2, 25.4, 25.3, 21.1, 20.3. – $C_{20}H_{34}O_3$ (322.25): calcd. C 74.49, H 10.63, O 14.88; found C 74.80, H 10.85, O 15.17. – MS (CI, NH_3); *m*/*z* (%): 323 (100) [MH^+].

9-(3-*tert*-Butoxypropyl)-1,2,3,4,5,6,7,8-octahydroacridine (5): A mixture of 4.5 g (146 mmol, 1.25 equiv.) of ammonium acetate, 15.8 g (200 mmol, 1.7 equiv.) of copper(II) acetate and 150 mL of glacial acetic acid was heated at 100 °C for 15 min. After cooling, 15 g (117 mmol) of **4** was added in small portions and the resulting suspension was heated at 100 °C for 4 h. The solution was cooled to room temperature, filtered, concentrated and diluted with water (50 mL) and made basic with concentrated sodium hydroxide at 0 °C. The mixture was extracted with dichloromethane (3 × 100 mL).

The combined organic layers were washed successively with ammonia, water and brine, dried with ($MgSO_4$) and concentrated to yield a brown oil, which was chromatographed on alumina (ethyl acetate/pentane, 15:85) to afford 13.18 g (93%) of a beige crystalline solid **5**; m.p. 88–89 °C. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.40 (t, 2 H, *J* = 6.05 Hz), 2.90 (m, 4 H), 2.70 (m, 4 H), 2.60 (m, 2 H), 1.80 (m, 8 H), 1.60 (m, 2 H), 1.2 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 153.7, 148.1, 127.6, 72.7, 61.5, 33.2, 29.3, 27.7, 25.5, 24.8, 23.3, 23.1. – $C_{20}H_{31}NO$ (301.47): calcd. C 79.68, H 10.36, N 4.65, O 5.31; found C 79.30, H 10.49, N 4.66, O 5.54. – MS (CI, NH_3); *m*/*z* (%): 302 (100) [MH^+].

9-(3-*tert*-Butoxypropyl)-1,2,3,4,5,6,7,8-octahydroacridine *N*-Oxide (6): To a solution of 29.6 g (98 mmol) of **5** in 100 mL of dichloromethane was added dropwise a solution of 50.38 g (196 mmol, 2 equiv.) of 67% *m*CPBA. After 2 h of stirring at room temperature, the mixture was made basic with 15% aqueous sodium hydroxide. The organic layer was washed with water and dried ($MgSO_4$). After concentration under reduced pressure, 30.75 g (99%) of **6** was obtained as a pale yellow solid that slowly crystallised; m.p. 84–85 °C. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.40 (t, 2 H, *J* = 6.15 Hz), 2.90 (m, 4 H), 2.80 (m, 4 H), 2.60 (m, 2 H), 1.80 (m, 8 H), 1.60 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 145.4, 137.5, 130.3, 72.8, 61.1, 29.6, 27.6, 26.5, 25.7, 25.6, 24.5, 22.3, 21.9. – $C_{20}H_{31}NO_2$ (317.47): calcd. C 75.67, H 9.84, N 4.41, O 10.08; found C 75.72%, H 9.63, N 4.18, O 9.86. – MS (CI, NH_3); *m*/*z* (%): 318 (100) [MH^+], 335 (12) [MNH_4^+].

9-(3-*tert*-Butoxypropyl)-1,2,3,4,5,6,7,8-octahydroacridin-4-ol (7): To a solution of 22.42 g (70.4 mmol) of **6** in 400 mL of dry dichloromethane was added slowly 25 mL (177 mmol, 2.5 equiv.) of trifluoroacetic anhydride. After stirring for 2 h, the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in 100 mL of dichloromethane and saponified with 300 mL of 2 M aqueous potassium carbonate. The biphasic mixture was vigorously stirred for 3 h, decanted and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure to give 21.38 g of pale yellow crystals, which upon washing with hexane afforded 19.85 g (89%) of analytically pure **7** as beige crystals; m.p. 98–99 °C. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.60 (m, 1 H), 4.37 (s, 1 H, O*H*), 3.41 (t, 2 H, *J* = 6.2 Hz), 2.88 (m, 2 H), 2.71 (m, 2 H), 2.60 (m, 4 H), 2.27 (m, 1 H), 2.04 (m, 1 H), 1.85–1.66 (m, 8 H), 1.22 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 154.4, 148.9, 129.3, 126.9, 69.0, 61.4, 32.8, 30.5, 29.2, 27.7, 25.6, 25.5, 25.1, 23.2, 22.8, 19.7. – $C_{20}H_{31}NO_2$ (317.47): calcd. C 75.67, H 9.84, N 4.41, O 10.08; found C 75.72, H 9.63, N 4.18, O 9.80. – MS (CI, NH_3); *m*/*z* (%): 318 (100) [MH^+].

9-(3-*tert*-Butoxypropyl)-1*H*-2,3,5,6,7,8-hexahydroacridin-4-one (8): A solution of 1.6 mL (19.5 mmol, 1.5 equiv.) of oxalyl chloride in 50 mL of dry dichloromethane was cooled to –78 °C. To the above solution was added dropwise 1.8 mL (26 mmol, 2 equiv.) of dimethyl sulfoxide. After reaching thermal equilibrium, a solution of 4.13 g (13.0 mmol) of **7** in 50 mL of dry dichloromethane was added and the mixture was stirred at –78 °C for 35 min. 7 mL (52.0 mmol, 4 equiv.) of anhydrous triethylamine was then added. After a rapid return to room temperature the mixture was diluted with 500 mL of ether, washed with water (50 mL), 30 mL of brine and dried ($MgSO_4$). After filtration and concentration under reduced pressure 4.23 g of a light brown oil was obtained. This crude material was chromatographed on alumina (ethyl acetate/pentane, 15:85) to give 3.7 g (91%) of **8** as a white powder; m.p. 85–86 °C. – IR (KBr): $\tilde{\nu}$ = 1694 (CO) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.40 (t, 2 H, *J* = 6.07 Hz), 3.00 (m, 4 H), 2.80 (m, 6 H), 2.20 (m, 2 H), 1.80 (m, 4 H), 1.60 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 198.2, 156.8, 148.7, 136.7, 135.1, 72.8, 61.0, 39.4, 33.5, 29.3, 27.6, 26.5, 25.6, 25.1, 22.8, 22.6. – $C_{20}H_{29}NO_2$ (315.46): calcd. C 76.15, H 9.27, N 4.40, O 10.14; found C 75.86, H 9.35, N 4.20, O 10.39. – GC/MS; *m*/*z* (%): 315 (3%) [M^+], 215 (100%).

9-(3-*tert*-Butoxypropyl)-1,2,3,4,6,7,8-octahydro-5-(phenylmethylene)acridin-4-ol (9): A mixture of 7.11 g (22.4 mmol) of the *N*-oxide **6**, 20 mL of benzaldehyde (9.3 equiv.) and 40 mL of acetic anhydride was heated at 160 °C for 7 h. After concentration under vacuum, the resulting oil was dissolved in 250 mL of absolute ethanol. Solid sodium disulfide was added until saturation was achieved and the suspension was stirred for 1 h. The white precipitate was filtered off and the mother liquor was concentrated. The residue was then dissolved in diethyl ether, washed with saturated sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and concentrated to yield an oil, which was filtered (alumina, pentane/ethyl acetate, 95:5). The resulting residue was dissolved in 300 mL of methanol and was saponified overnight with 100 mL of 2 M potassium carbonate solution. After removal of methanol, 100 mL of water was added and the solution was extracted with dichloromethane (3 × 200 mL). The organic layers were washed with 100 mL of brine and dried with magnesium sulfate to yield, after concentration under reduced pressure, 7.71 g (85%) of **9** as a white solid; m.p. 114–115 °C. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.94 (s, 1 H), 7.38 (m, 4 H), 7.23 (m, 1 H), 4.70 (m, 1 H), 4.60 (s, 1 OH), 3.41 (t, 2 H, *J* = 6.15 Hz), 2.82 (m, 6 H), 2.65 (m, 2 H), 2.35 (m, 1 H), 2.05 (m, 1 H), 1.84 (m, 2 H), 1.72 (m, 2 H), 1.65 (m, 2 H), 1.22 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 155.0, 149.1, 148.5, 138.0, 135.8, 129.7, 129.6, 128.0, 127.9, 126.6, 126.1, 72.7, 69.5, 61.1, 30.4, 29.2, 27.6, 26.0, 25.6, 25.2, 23.0, 19.7. – $C_{27}H_{35}NO_2$ (405.58): calcd. C 79.96, H 8.70, N 3.46, O 7.89; found C 79.76, H 8.46, N 3.26, O 7.52. – MS (CI, NH_3); *m*/*z* (%): 406 (100) [MH^+].

9-(3-*tert*-Butoxypropyl)-1*H*-2,3,6,7,8-hexahydro-5-(phenylmethylene)acridine-4-one (10): The same procedure as described for compound **8** was used with 3.0 g (7.4 mmol) of **9**, 1.0 mL of oxalyl chloride, 1.1 mL of dimethyl sulfoxide and 4.8 mL of triethylamine. 2.96 g (99%) of **10** was obtained as a pale yellow solid that could be recrystallised from ether; m.p. 119–120 °C. – IR (KBr): $\tilde{\nu}$ = 1696 (CO), 1614 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.10 (s, 1 H), 7.41 (m, 4 H), 7.28 (m, 1 H), 3.44 (t, 2 H, *J* = 6.21 Hz), 3.04 (m, 2 H), 2.92 (m, 2 H), 2.88 (m, 2 H), 2.78 (m, 2 H), 2.74 (m, 2 H), 2.20 (m, 2 H), 1.84 (m, 2 H), 1.68 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 197.2, 152.0, 148.5, 145.6, 137.8, 137.0, 135.3, 134.8, 129.6, 128.2, 127.8, 126.5, 72.6, 60.8, 39.4, 29.3, 27.5, 26.6, 25.7, 25.1, 22.5, 22.3. – $C_{27}H_{33}NO_2$ (403.56): calcd. C 80.35, H 8.24, N 3.47, O 7.93; found C 80.09, H 8.52, N 3.53, O 7.86. – MS (CI, NH_3); *m*/*z* (%): 404 (100) [MH^+].

9-(3-*tert*-Butoxypropyl)-3-(dimethylaminomethylene)-1*H*-2,5,6,7,8-hexahydroacridin-4-one (11): To 3.55 g (11.3 mmol) of **8** was added 4.65 mL (22.6 mmol, 2 equiv.) of *tert*-butoxybis(dimethylamino)-methane. The mixture was heated at 45 °C for 3 h under nitrogen. The reaction was monitored by IR and, after confirming the absence of **8**, the solution was concentrated under reduced pressure to yield 4.70 g (>99%) of a brown amorphous, hygroscopic solid **11**. – IR (KBr): $\tilde{\nu}$ = 1573, 1652 (CO) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.70 (s, 1 H), 3.4 (t, 2 H), 3.10 (s, 6 H), 2.40 (s, 2 H), 2.90–2.60 (m, 6 H), 1.80 (m, 4 H), 1.60 (m, 4 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 184.8, 155.2, 149.5, 147.9, 146.1, 132.9, 132.0, 103.6, 72.0, 60.4, 42.9, 32.9, 29.2, 27.0, 25.6, 24.2, 24.1, 23.1, 22.4, 22.2. – $C_{23}H_{34}N_2O_2$ (370.53): calcd. C 74.56, H 9.25, N 7.56, O 8.64; found C 74.29, H 8.92, N 7.53, O 8.86. – MS (CI, NH_3); *m*/*z* (%): 371 (100) [MH^+], 388 (25) [MNH_4^+].

9-(3-*tert*-Butoxypropyl)-1*H*-2,3,5,6,7,8-hexahydro-3-methyleneacridin-4-one (12): A solution of 4.84 g (13.1 mmol) of **11** in 100 mL of dry THF was cooled to –78 °C and 1 M diisobutylaluminium hydride (15.7 mL, 1.2 equiv.) was added. The mixture was allowed to warm up to room temperature (2 h) and was saturated with solid NH_4Cl and stirred for a further 16 h. The solution was diluted with water (100 mL) and decanted. The aqueous phase was extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 4.85 g of a brown oil. This crude product was purified by flash column chromatography on silica gel (EtOAc) to give 3.92 g (92%) of a yellow oil. – IR (nujol): $\tilde{\nu}$ = 1684, 1616 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 6.38 (s, 1 H), 5.47 (m, 1 H), 3.41 (t, 2 H, *J* = 6.08 Hz), 3.06–3.02 (m, 4 H), 2.83–2.82 (m, 4 H), 2.71 (m, 2 H), 1.85 (m, 4 H), 1.66 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 187.1, 157.3, 148.3, 146.0, 144.3, 136.3, 135.0, 121.8, 72.8, 60.9, 33.6, 31.1, 29.5, 28.6, 26.5, 25.0, 22.8, 22.6. – $C_{21}H_{29}NO_2$ (327.47): calcd. C 77.02, H 8.93, N 4.28, O 9.77; found C 77.32, H 9.23, N 3.95, O 9.54. – MS (CI, NH_3); *m/z* (%): 328 (100) [MH^+].

Heptacyclic Annelated Terpyridine 13a: A mixture of 0.512 g (1.56 mmol) of **12**, 0.50 g (1.6 mmol) of **8**, 0.96 g (16.0 mmol) of ammonium acetate and 16 mL of anhydrous pyridine was heated at 90 °C for 6 h. After cooling to room temperature the solution was diluted with dichloromethane (20 mL) and washed with water (3 × 20 mL). The aqueous phases were combined and extracted with dichloromethane (2 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on alumina (ethyl acetate) to give 0.600 g (62%) of **13a** as beige crystals; m.p. 140–141 °C. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.35 (s, 1 H), 5.12 (s, 2 H, H_2O), 3.41 (m, 4 H), 3.20 (m, 4 H), 2.93 (m, 8 H), 2.72 (m, 8 H), 1.84 (m, 8 H), 1.68 (m, 4 H), 1.22 (s, 18 H). – ^{13}C NMR ($CDCl_3$): δ = 155.7, 150.8, 148.5, 147.2, 134.5, 133.0, 130.7, 129.4, 72.7, 61.0, 32.4, 29.8, 27.6, 26.1, 25.0, 23.4, 23.1, 22.7. – $C_{41}H_{55}N_3O_2.H_2O$ (639.92): calcd. C 76.95, H 8.98, N 6.57, O 7.50; found C 76.77, H 8.84, N 6.53, O 7.22. – MS (CI, NH_3) *m/z* (%): 622 (100) [MH^+], 639 (25) [MNH_4^+].

Annelated Terpyridine 13b: This unsymmetrical heptacyclic annelated terpyridine was prepared by using the procedure described for **13a**. Reaction of 1.65 g (5.10 mmol) of **12** with 2.03 g (5.9 mmol) of **10** under these experimental conditions gave, after workup and purification by chromatography on alumina (ethyl acetate), 1.96 g (56%) of **13b** as a yellow powder; m.p. 135–137 °C. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 8.36 (s, 1 H), 7.57 (m, 2 H), 7.36 (m, 3 H), 7.20 (m, 2 H), 3.43 (m, 2 H), 3.41 (m, 2 H), 3.15 (m, 2 H), 2.95 (m, 10 H), 2.74 (m, 6 H), 1.87 (m, 6 H), 1.71 (m, 4 H), 1.23 (s, 9 H), 1.22 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 151.5, 149.2, 148.9, 146.2, 138.9, 135.3, 134.2, 132.7, 130.6, 130.1, 129.9, 129.1, 127.8, 127.6, 125.9, 72.6, 61.0, 60.9, 33.2, 30.0, 29.9, 27.7, 27.5, 26.5, 26.0, 25.1, 24.8, 23.9, 23.5, 23.2, 23.0, 22.9. – $C_{48}H_{58}N_3O_2$ (709.01): calcd. C 81.31, H 8.25, N 5.93, O 4.51; found C 81.38, H 8.52, N 6.03, O 4.21. – FAB (NBA); *m/z* (%): 710 (79) [MH^+], 732 (100) [MNa^+].

Heptacyclic Ketone 14: A solution of 3.10 g (4.4 mmol) of **13b** in 50 mL of CH_2Cl_2/methanol (1:1, v/v) was cooled to –78 °C. An ozone/oxygen mixture was bubbled through the solution for 3 h and then the solution was purged of ozone by bubbling with oxygen and argon for 1 h. Dimethyl sulfide (1 mL) was added and the resulting mixture was stored at room temperature overnight. The mixture was concentrated under reduced pressure (0.1 Torr). The crude product was chromatographed on alumina, eluting with ethyl acetate/methanol (9:1, v/v), yielding 2.60 g (92%) of **14** as a yellow powder; m.p. 140–143 °C. – IR (KBr): $\tilde{\nu}$ = 1699 (CO) cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.41 (s, 1 H), 5.35 (s, 2 H, br, H_2O), 3.42 (m, 4 H), 3.20 (m, 2 H), 3.00 (m, 8 H), 2.78 (m, 8 H), 2.18 (m, 4 H), 1.82 (s, 4 H), 1.70 (m, 4 H), 1.23 (s, 9 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 195.8, 156.0, 151.2, 150.4, 148.3, 147.3, 147.0, 146.3, 138.3, 135.8, 134.1, 133.5, 132.9, 130.3, 129.4, 128.2, 72.6, 72.5, 39.0, 32.6, 29.7, 27.6, 27.4, 27.0, 26.0, 25.9, 25.1, 24.8, 24.3, 23.2, 23.0, 22.6, 22.1. – $C_{41}H_{53}N_3O_3\ H_2O$ (653.89): calcd. C 75.31, H 8.48, N 6.43, O 9.79; found C 75.15, H 8.28, N 6.41, O 9.86. – MS (CI, NH_3); *m/z* (%): 636 (100) [MH^+].

Annelated Quinquepyridine 15. – Method A: A mixture of 0.43 g (1.3 mmol) of **12**, 0.83 g (1.3 mmol) of **14** and 0.50 g (6.5 mmol) of ammonium acetate was refluxed for 8 h. The solution was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with water (2 × 30 mL). The aqueous layers were combined and then extracted with dichloromethane (2 × 25 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogencarbonate, filtered on phase separator paper and concentrated. The crude product was chromatographed on deactivated alumina (AcOEt/MeOH, 90:10) and gave a high *Rf* fraction, which was identified as a mixture of by-products, and a low *Rf* fraction containing the desired product **15**. The second fraction was chromatographed on deactivated alumina (AcOEt/*i*PrOH/Et_3N, 30:5:0.5) to give 0.265 g (25% yield) of the desired product as a yellow oil, which was triturated with ethyl acetate/dichloromethane to afford a yellow solid. Recrystallisation of this material by slow evaporation of a 1:1 dichloromethane/diethyl ether solution afforded fine yellow needles; m.p. 114–133 °C.

Method B: A mixture of 1.5 g (4.55 mmol) of **17**, 1.4 g (18.20 mmol) of ammonium acetate and 50 mL of anhydrous pyridine was heated at 40 °C for 1 h. A solution of 3.24 g (10.01 mmol) of α-methylene ketone **12** in 10 mL of pyridine was added to the preheated reaction mixture, and heating was continued at reflux for an additional 4 h. The solution was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and washed with water (2 × 70 mL). The aqueous layers were combined and then extracted with dichloromethane (2 × 50 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogencarbonate, filtered on phase separator paper and concentrated. The crude product was chromatographed on deactivated alumina (AcOEt/MeOH, 90:10) to give a high *Rf* fraction, which was identified as a mixture of by-products, and a low *Rf* fraction containing the desired product **15**. The second fraction was chromatographed as described above to give 0.730 g (17% yield) of the desired product as a yellow oil, which was triturated with ethyl acetate/dichloromethane to afford a yellow solid. Recrystallisation of this material by slow evaporation of a 1:1 dichloromethane/diethyl ether solution afforded fine yellow needles; m.p. 113–133 °C. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.65 (s, 2 H), 3.45 (m, 4 H), 3.10–2.40 (m, 30 H), 1.90–1.40 (m, 14 H), 1.22 (s, 27 H). – ^{13}C NMR ($CDCl_3$): δ = 154.9, 151.6, 149.7, 149.5, 148.7, 148.4, 147.0, 136.1, 134.4, 134.3, 133.8, 131.3, 129.6, 73.0, 72.9, 60.9, 60.6, 31.7, 30.1, 29.7, 27.6, 26.6, 26.3, 25.6, 25.2, 24.2, 22.5, 22.4, 22.1. – $C_{62}H_{79}N_5O_3$ (942.35): calcd. C 79.02, H 8.45, N 7.43, O 5.09; found C 79.35, H 8.68, N 7.27, O 5.41. – FAB (NBA); *m/z* (%): 964 (100) [MNa^+], 980 (7) [MK^+].

9-(3-*tert*-Butoxypropyl)-1,2,3,4,4,6,7,8-octahydro-4,5-bis-(phenylmethylene)acridine (16): A mixture of 18.04 g (60 mmol) of **5**, 54.4 mL (538 mmol) of freshly distilled benzaldehyde and 24 mL

Table 1. Crystal data and structure refinement

Compound	**4**
Empirical formula	$C_{20}H_{34}O_3$
Formula mass	322.47
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 13.033(2) Å b = 12.9530(14) Å c = 11.3633(18) Å β = 95.075(19)°
Volume	1910.8(5) Å^3
Z	4
Density (calculated)	1.121 Mg/m^3
Absorption coefficient	0.073 mm^{-1}
F(000)	712
Crystal size	0.40 × 0.30 × 0.12 mm
Theta range for data collection	2.22–24.32
Index ranges	$-15 \le h \le 15, -14 \le k \le 14, -13 \le l \le 13$
Reflections collected	15013
Independent reflections	3053 [R(int) = 0.1261]
Absorption correction	None
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	3053/0/212
Goodness-of-fit on F^2	1.119
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0860, $wR2$ = 0.1854
R indices (all data)	$R1$ = 0.1711, $wR2$ = 0.2181
Largest diff. peak and hole	0.217 and –0.158 e·Å^{-3}

(254 mmol) of distilled Ac_2O was refluxed for 16 h. The solution was cooled and concentrated under reduced pressure (0.1–1 Torr). The residue was dissolved in Et_2O and cooled to –20 °C. The precipitate was collected and washed with cooled Et_2O to give 27.48 g (96%) of **16** as white powder; m.p. 90–91 °C. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.13 (s, 2 H), 7.40 (m, 8 H), 7.28 (m, 2 H), 3.41 (t, 2 H, J = 6.1 Hz), 2.85 (m, 8 H), 2.68 (t, 2 H, J = 5.9 Hz), 1.95 (m, 4 H), 1.78 (m, 2 H), 1.23 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 149.4, 147.8, 138.4, 136.7, 129.6, 128.0, 126.4, 126.0, 72.7, 61.1, 29.4, 27.7, 27.6, 26.2, 25.0, 23.0. – $C_{34}H_{39}NO$ (477.68): calcd. C 85.49, H 8.23, N 2.93, O 3.35; found C 85.53, H 8.16, N 3.02, O 3.40. – MS (CI, NH_3); m/z (%): 479 (100%) [MH^+].

9-(3-*tert*-Butoxypropyl)-1,2,3,6,7,8-hexahydroacridine-4,5-dione (17): A solution of 9.57 g (20 mmol) of **16** in 400 mL of CH_2Cl_2/methanol (1:1, v/v) was cooled to –78 °C. An ozone/oxygen mixture was bubbled through the solution for 4 h and then the solution was purged of ozone by bubbling with oxygen and argon for 2 h. Dimethyl sulfide (4 mL) was added and the resulting mixture was stored at 0 °C overnight. The mixture was concentrated under reduced pressure (0.1 Torr) by heating on a steam bath (60–70 °C). The residue was dissolved in CH_2Cl_2 (200 mL), washed with water (2 × 50 mL) and dried ($MgSO_4$). Removal of the solvent and drying under vacuum gave a coloured solid, which was chromatographed on alumina eluting with Ac_2O/pentane (15:85, v/v), to give 5.96 g (91%) of **17** as a yellow powder; m.p. 114–115 °C. – IR (KBr): $\tilde{\nu}$ = 1705 (CO) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.42 (t, 2 H, J = 6.15 Hz), 3.08 (t, 2 H, J = 6.35 Hz), 2.80 (m, 4 H), 2.79 (m, 4 H), 2.18 (m, 4 H), 1.69 (m, 2 H), 1.20 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 195.7, 150.3, 147.2, 141.5, 72.8, 60.5, 39.1, 29.2, 27.5, 26.1, 25.4, 21.9. – $C_{20}H_{27}NO_3$ (329.44): calcd. C 72.92, H 8.26, N 4.25, O 14.57; found C 73.04, H 8.28, N 4.22, O 14.46. – MS (CI, NH_3); m/z (%): 330 (100) [MH^+].

X-ray Crystallographic Study: Data for **4** were collected with a Stoe IPDS diffractometer. The final unit cell parameters were obtained by the least-squares refinement of 5000 reflections. Only statistical fluctuations were observed in the intensity monitors over the course of the data collections.

The structure was solved by direct methods (SIR92[22]) and refined by least-squares procedures on F^2. All H atoms attached to carbon were introduced in calculations in idealised positions [d(CH) = 0.96 Å] and treated as riding models with isotropic thermal parameters 20% higher than those of the carbon to which they are attached. Least-squares refinements were carried out by minimising the function $\Sigma w(F_o^2 - F_c^2)^2$, where F_o and F_c are the observed and calculated structure factors. The weighting scheme used in the last refinement cycles was $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$. Models reached convergence with $R = \Sigma(||F_o| - |F_c||)/\Sigma(|F_o|)$ and $wR2 = \{\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2\}^{1/2}$, having values listed in Table 1.

The calculations were carried out with the SHELXL-97 program[23] running on a PC. The molecular view was obtained with the help of CAMERON.[24] Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-125052. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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