Bischler-Napieralski Synthesis of Some New Pyrazole-Fused β-Carbolines

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Bischler-Napieralski Reaction, Directed Cyclization, Pyrazolopyridoindoles

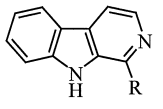
3-(4-Acylaminopyrazol-5-yl)-4-methylindoles (**13a,b**), under Bischler-Napieralski reaction conditions, undergo cyclization at the pyrrolic carbon-2 with ultimate formation of the corresponding pyrazolo[3,4:5′,6′]pyrido[3,4-*b*]indoles (**14a,b**) as evidenced by crystal structure analysis of **14a**.

Introduction

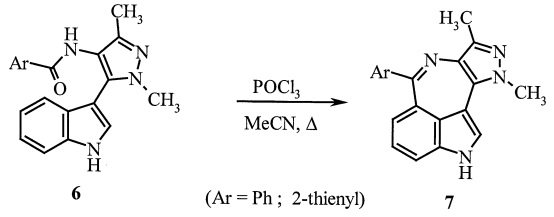
The β-carboline ring system is among the most commonly encountered alkaloid frameworks in the terrestrial environment [1, 2], and also occurs in compounds derived from a variety of marine species. [2, 3]. The Harmala alkaloids **1a,b** were the first marine derived β-carbolines to be reported in 1980 from *Noctiluca miliaris* [4]. Recently, several manzamines **2**, exhibiting antitumor activity, have been reported from different marine sponge genera [3, 5].

Currently, there is a wealth of research work oriented toward the synthesis and bioassay of various β-carboline derivatives [6]. We became interested in pyrazole-fused carbolines for which limited data were cited in the literature [7–9]. Examples of these condensed tetracyclic aza-heterocycles (pyrazolopyridoindoles) are confined to compounds **3** possessing pepsin-inhibiting and antiulcerogenic activity [7], the δ-carboline **4**, showing *in vitro* anxiolytic activity [8], and γ-carboline **5** [9].

Quite recently we have reported that 3-(4-acylamino-1,3-dimethylpyrazol-5-yl)indoles **6**, under Bischler-Napieralski reaction conditions, underwent regioselective cyclization at C-4 of the indole nucleus to deliver the corresponding pyrazolo-[3′,4′:6,7]azepino[5,4,3-*cd*]indoles (**7**) (Scheme 1) [10].

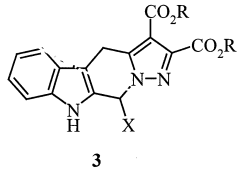


1a (R = H): norharman; **1b** (R = Me): harman
2 [R = intricate aza-(poly)cyclyl units] : manzamines

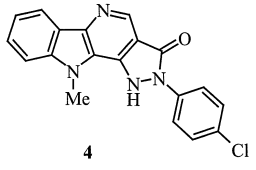


6 **7**

Scheme 1.



3
(X= alkyl, aryl ; R= H, Me)



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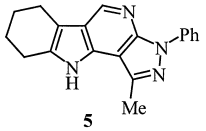

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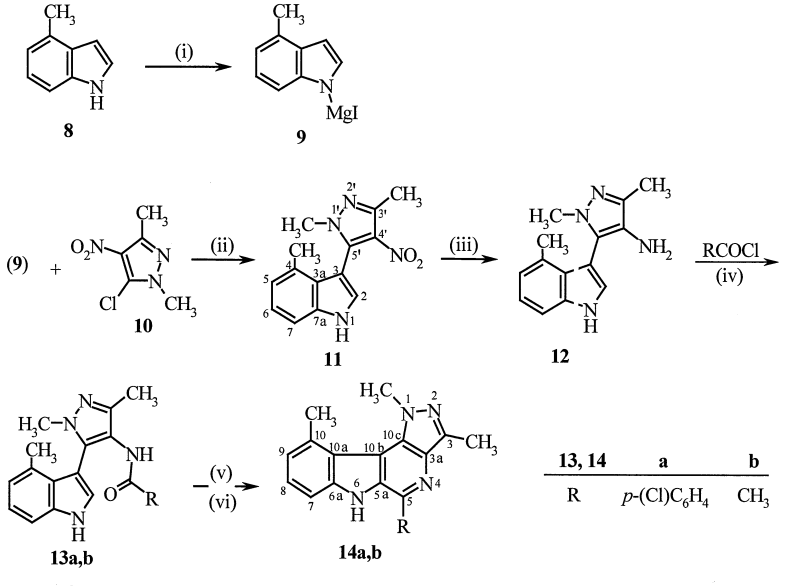
In this context, we wish to report herein on the use of 4-methylindole (**8**) in the synthesis of the new model 1,3,10-trimethylpyrazolo[3′,4′:5,6]pyrido[3,4-*b*]indoles **14a,b** (Scheme 2) *via* the Bischler-Napieralski route.

Results and Discussion

In the present study, we have utilized 3-[(4-(*N*-acetyl)amino-1,3-dimethylpyrazol-5-yl]-4-methylindoles **13a,b** (Scheme 2) as substrates in the cyclization step under Bischler-Napieralski reaction conditions. We envisaged that incorporation of a substituent, such as a methyl group, at C-4 of the indole nucleus would act as a blockage therein, and thence would direct ring closure solely at C-2 of the pyrrole ring. This anticipation has been realized with ultimate production of the corresponding pyrazolo-β-carbolines **14a,b** (Scheme 2).

Compounds **13a,b** were obtained by direct acylation of 3-(4-amino-1,3-dimethylpyrazol-5-yl)-4-methylindole (**12**) with the respective acid chloride in the presence of triethylamine. The synthon **12** was produced by reduction, using tin and HCl in the conventional manner, of 3-(1,3-dimethyl-4-nitropyrazol-5-yl)-4-methylindole (**11**). The latter precursor was, in turn, prepared by the reaction of 5-chloro-1,3-dimethyl-4-nitropyrazole (**10**) with 4-methylindolylmagnesium chloride (**9**) [11], prepared *in situ* from methylmagnesium iodide and 4-methylindole (**8**).

The spectral (MS, NMR) and microanalytical data are in conformity with the assigned structures **11**–**14**, and are given in the Experimental Part. Thus, their MS spectra display the correct M^+ for which the measured HRMS data are in good agreement with the calculated values. Assignments of the ^{1}H NMR signals to the different protons are straightforward, and ^{13}C-signal assignments are based on DEPT and 2D (COSY, HMBC, HMQC) experiments; these experiments showed different correlations that helped in the full assignments of hydrogens and carbons. It is worth noting that the doublet, belonging to 2-H of the indole ring in the ^{1}H NMR spectra of **13a,b**, is absent in the ^{1}H NMR spectra of **14a,b**. Furthermore, C-2 in **13a,b** is identified as tertiary in the ^{13}C NMR (DEPT) spectra, while it is quaternary (C-5a) in **14a**,**b**, indicating that ring closure has taken place at C-2 of the indole nucleus. Eventually, the spectral data of the target compounds **14a,b** are compatible with the pyrazolo-ß-carboline structure as determined for **14a** by X-ray crystal structure measurements.



Scheme 2.

X-Ray Crystal Structure Determination of 14a

An X-ray crystal structure of **14a** has been performed. The molecular structure of **14a** is shown in Fig. 1 and selected bond lengths and angles are given in Table 1. The crystallographic data confirm the proposed pyrazolo-β-carboline structure for **14a**.

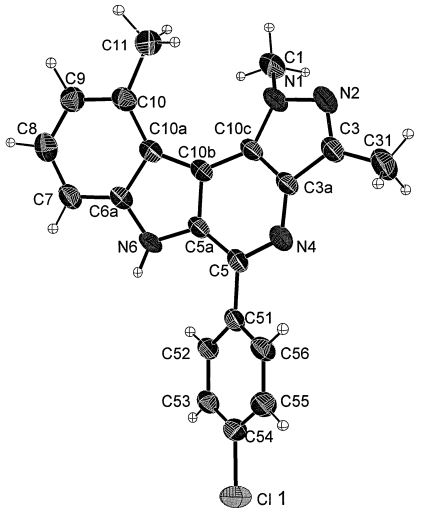


Fig. 1. ORTEP Plot (50% probability level for ellipsoids of thermal vibrations) of the molecular structure of **14a**.

Table 1. Selected bond lengths (Å) and angles (°) for **14a**.

N(1)–N(2)	1.386 (3)	N(1)–C(10c)–C(10b)	135.2 (2)
N(1)–C(10c)	1.374 (3)	C(10a)–C(10b)–C(10c)	139.6 (2)
N(2)–C(3)	1.314 (3)	C(10)–C(10a)–C(10b)	136.5 (2)
C(3)–C(3a)	1.424 (3)	N(1)–C(10c)–C(3a)	106.2 (2)
C(3a)–C(10c)	1.404 (3)	N(1)–N(2)–C(3)	107.9 (2)
N(4)–C(3a)	1.359 (3)	N(2)–C(3)–C(3a)	109.8 (2)
N(4)–C(5)	1.335 (3)	C(3)–C(3a)–C(10c)	106.1 (2)
C(5a)–C(5)	1.421 (3)	N(4)–C(3a)–C(3)	127.7 (2)
C(5a)–C(10b)	1.419 (3)	N(4)–C(5)–C(5a)	120.0 (2)
C(10b)–C(10c)	1.421 (3)	N(6)–C(5a)–C(5)	127.4 (2)
N(6)–C(5a)	1.382 (3)	C(5)–N(4)–C(3a)	116.7 (2)

Experimental Section

5-Chloro-1,3-dimethyl-4-nitropyrazole was purchased from Maybridge, U. K. 4-Methylindole (**8**) and phosphorous oxychloride were purchased from Acros. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker WM-400 or a Bruker DPX-300 spectrometer using TMS as internal reference. Mass spectra (EI) and high resolution data (HRMS) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. Microanalyses were performed at the Microanalytical Laboratory of the Inorganic Chemistry Institute, Tübingen University.

3-(1,3-Dimethyl-4-nitropyrazol-5-yl)-4-methylindole (**11**)

A solution of 4-methylindole (**8**) (3.00 g, 23 mmol) in dry diethyl ether (20 ml) was stirred with magnesium (0.61 g, 25 mmol) and methyl iodide (3.55 g, 25 mmol) at 22° C for 20 min. To the resultant solution of 4-methylindolylmagnesium iodide (**9**) was added dropwise a solution of 5-chloro-1,3-dimethyl-4-nitropyrazole (**10**) (1.34 g, 7.6 mmol) in dry diethyl ether (30 ml). The resulting reaction mixture was stirred for 4 h and then treated with water (100 ml). The ether layer was separated and the aqueous layer extracted with ether (2 × 100 ml). The combined organic extracts were dried (anhydrous Na_2SO_4) and the solvent was evaporated; the residue was dissolved in CH_2Cl_2 and precipitated using petroleum ether to give a yellowish solid which was soaked in petroleum ether to remove unreacted 4-methylindole. Yield of **11**: 1.65 g (80%), m.p. 178–179° C. – MS: *m/z* (%) = 270 (94) [M^+], 253 (87), 239 (100), 208 (76), 170 (63), 152 (76), 139 (26). – HRMS: calcd. for $C_{14}H_{14}N_4O_2$: 270.11165, found 270.11450. – ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.12 (s, 3H, 4-CH_3), 2.64 (s, 3H, 3′-CH_3), 3.61 (s, 3H, N–CH_3), 6.94 (d, J = 7.7 Hz, 1H, 5-H), 7.18 (dd, J = 7.7, 8.1 Hz, 1H, 6-H), 7.24 (d, J = 2.7 Hz, 1H, 2-H), 7.30 (d, J = 8.1 Hz, 1H, 7-H), 8.58 (s , 1H, N–H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.3 (3′-CH$_3$), 18.4 (4-CH$_3$), 37.3 (N–CH$_3$), 102.4 (C-3), 109.6 (C-7), 122.4 (C-5), 123.3 (C-6), 125.1 (C-2), 125.4 (C-3a), 130.0 (C-3′), 132.7 (C-4), 136.1 (C-7a), 138.9 (C-5′), 146.2 (C-4′). – $C_{14}H_{14}N_4O_2$ (270.29): calcd. C 62.21, H 5.22, N 20.73; found C 62.10, H 5.35, N 20.51.

3-(4-Amino-1,3-dimethylpyrazol-5-yl)-4-methylindole (**12**)

A mixture of 3-(1,3-dimethyl-4-nitropyrazol-5-yl)-4-methylindole (**11**) (1.35 g, 5.0 mmol), tin granules (3.0 g) in ethanol (10 ml) and conc. HCl (20 ml) was refluxed (water bath) for 2 h. The resulting acidic solution was cooled and basified with 40% aqueous NaOH. This cold basic solution was extracted with CH_2Cl_2 (3 × 50 ml). The combined dichloromethane extracts were dried (anhydrous Na_2SO_4), and the solvent was removed *in vacuo*. The resulting solid was recrystallized from

CH_2Cl_2–petroleum ether (b.p. 40–60° C) to afford a white solid. Yield of **7**: 1.06 g (88%), m.p. 219–220° C. – MS: *m/z* (%) = 240 (100) [M^+], 208 (6), 198 (11), 171 (12), 157 (41), 130(10). – HRMS: calcd. for $C_{14}H_{16}N_4$: 240.13750, found 240.13657. – ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.22 (s, 3H, 3′-CH_3), 2.27 (s, 3H, 4-CH_3), 2.55 (br s, 2H, NH_2), 3.55 (s, 3H, N–CH_3), 6.92 (d, J = 7.3 Hz, 1H, 5-H), 7.17 (dd, J = 7.3, 8.2 Hz, 1H, 6-H), 7.21 (d, J = 2.6 Hz, 1H, 2-H), 7.31 (d, J = 8.2 Hz, 1H, 7-H), 8.64 (br s , 1H, N–H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.1 (3′-CH$_3$), 18.1 (4-CH$_3$), 36.6 (N–CH$_3$), 104.5 (C-3), 109.2 (C-7), 121.8 (C-5), 122.9 (C-6), 125.0 (C-3′), 125.1 (C-2), 126.2 (C-5′), 126.3 (C-3a), 131.0 (C-4), 136.4 (C-7a), 137.0 (C-4′). – $C_{14}H_{16}N_4$ (240.29): calcd. C 69.97, H 6.71, N 23.31; found C 69.58, H 6.67, N 23.07.

3-[4-(4′-Chlorobenzoyl)amino-1,3-dimethylpyrazol-5-yl]-4-methylindole (**13a**)

p-Chlorobenzoyl chloride (0.24 g, 1.37 mmol) was added to a solution of **12** (0.29 g, 1.26 mmol) in dry benzene (20 ml),followed by addition of triethylamine (2 ml). The resulting mixture was refluxed (oil bath, 90 °C) for 4 h. The solvent was then evaporated *in vacuo*, and the solid residue soaked in water (40 ml), filtered and finally washed with petroleum ether to give a white solid. Yield of **13a**: 0.40 g (86%), m.p. 205–207° C. – MS: *m/z* (%) = 378 (90) [M^+], 239 (100), 224 (24), 222 (60), 208 (19), 156 (17), 155 (38), 139 (56), 111 (27). – HRMS: calcd. for $C_{21}H_{19}ClN_4O$: 378.12474, found 378.12942. – ^{1}H NMR (400.14 MHz, DMSO-d_6): δ = 2.07 (s, 3H, 3′-CH_3), 2.12 (s, 3H, 4-CH_3), 3.44 (s, 3H, N–CH_3), 6.76 (d, J = 7.5 Hz, 1H, 5-H), 6.99 (dd, J = 7.5, 8.0 Hz, 1H, 6-H), 7.24 (d, J = 8.0 Hz, 1H, 7-H), 7.28 (br s, 1H, 2-H), 7.51 (d, J = 8.5 Hz, 2H, 3″-H/5″-H), 7.87 (d, J = 8.5 Hz, 2H, 2″-H/6″-H), 9.47 (s , 1H, N–H), 11.37 (s, 1H, NHCO). – ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 11.5 (3′-CH$_3$), 18.0 (4-CH$_3$), 36.5 (N–CH$_3$), 102.2 (C-3), 109.7 (C-7), 117.2 (C-4′), 120.7 (C-5), 121.6 (C-6), 125.7 (C-3a), 126.1 (C-2), 128.3 (C-3″/C-5″), 128.9 (C-5′), 129.3 (C-4), 129.4 (C-2″/C-6″), 132.9 (C-1″), 135.2 (C-7a), 136.1(C-4″), 143.1 (C-3′), 165.3 (NHCO). – $C_{21}H_{19}ClN_4O$ (378.88): calcd. C 66.58, H 5.05, Cl 9.36, N 14.79; found C 66.71, H 5.06, Cl 9.24, N 14.59.

3-[4-(N-Acetyl)amino-1,3-dimethylpyrazol-5-yl]-4-methylindole (**13b**)

This compound was prepared from acetyl chloride (0.24 g, 3.1 mmol) and **12** (0.72 g, 3.0 mmol), following the same procedure and experimental conditions describrd above for **13a**. Yield of **13b**: 0.57 g (67%), m.p. 214–215 °C (dec.). – MS: *m/z* (%) = 282 (100) [M^+], 240 (82), 222 (21), 208 (12), 155 (28), 115 (7). – HRMS: calcd. for $C_{16}H_{18}N_4O$: 282.14806, found 282.14862. – ^{1}H NMR (400.14 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3CO), 2.04 (s, 3H, 3′-CH_3), 2.11 (s, 3H, 4-CH_3), 3.40 (s, 3H, N–CH_3), 6.76 (d, J = 7.5 Hz, 1H, 5-H), 7.02 (dd, J = 7.5, 8.0 Hz, 1H, 6-H), 7.24 (d, J = 2.5 Hz, 1H, 2-H), 7.27 (d, J = 8.0 Hz , 1H, 7-H), 8.83 (s , 1H, N–H), 11.40 (s, 1H, NHCO). – ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 11.7 (3′-CH$_3$), 18.0 (4-CH$_3$), 22.5 (CH$_3$CO), 36.4 (N–CH$_3$), 102.3 (C-3), 109.7 (C-7), 117.7 (C-4′), 120.7 (C-5), 121.7 (C-6), 125.8 (C-3a), 126.1 (C-2), 129.4 (C-4), 134.4 (C-5′), 136.2 (C-7a), 143.0 (C-3′), 168.9 (NHCO). – $C_{16}H_{18}N_4O$ (282.35): calcd. C 68.06, H 6.43, N 19.84; found C 68.13, H 6.29, N 19.79.

5-(4-Chlorophenyl)-1,3,10-trimethyl-1H,6H-pyrazolo[3′,4′:5,6]pyrido[3,4-b]indole (**14a**)

This compound was prepared by heating at reflux (oil bath) a solution of **13a** (0.3 g, 0.8 mmol) and $POCl_3$ (3 ml) in dry acetonitrile (20 ml) for 3 h. The resulting mixture was subjected to vacuum distillation to remove excess acetonitrile and $POCl_3$. The residue was cooled, basified with 5% aqueous NaOH, then extracted with CH_2Cl_2 (3 × 50 ml) to give a yellowish-green solid. Yield of **14a**: 0.18 g (63%). The crude product was purified on silica gel plates, eluting with MeOH:$CHCl_3$ (2:98 v/v) to furnish the title compound as a yellowish solid, m.p. 239–240° C. – MS: *m/z* (%) = 360 (100) [M^+], 345 (6), 304 (6), 268 (9), 180 (10), 162 (15), 134 (7). – HRMS: calcd. for $C_{21}H_{17}$ Cl N_4: 360.11417, found 360.11752 . – ^{1}H NMR (400.14 MHz, $CDCl_3$): δ = 2.75 (s, 3H, 10-CH_3), 3.08 (s, 3H, 3-CH_3), 4.15 (s, 3H, N–CH_3), 7.19 (d, J = 7.0 Hz, 1H, 9-H), 7.40 (d, J = 7.7 Hz, 1H, 7-H), 7.47 (dd, J = 7.0, 7.7 Hz, 1H, 8-H), 7.53 (d, J = 8.5 Hz, 2H, 3″-H/5″-H), 7.85 (d, J = 8.5 Hz, 2H, 2″-H/6″-H), 8.88 (s, 1H, N–H). – ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 11.5 (3-CH$_3$), 25.5 (10-CH$_3$), 41.4 (N–CH$_3$), 109.0 (C-7), 112.7 (C-10b), 121.0 (C-10a), 123.1 (C-9), 127.4 (C-8), 129.5 (C-3″/C-5″), 129.8 (C-2″/C-6″), 133.5 (C-10), 134.0 (C-10c), 134.8 (C-3), 134.9 (C-4″), 135.7 (C-5a), 136.9 (C-1″), 139.9 (C-6a), 140.0 (C-5), 146.0 (C-3a). – $C_{21}H_{17}$ Cl N_4 (360.85): calcd. C 69.90, H 4.75, Cl 9.82, N 15.53; found C 69.73, H 4.52, Cl 9.73, N 1544.

1,3,5,10-Tetramethyl-1H, 6H-pyrazolo[3′,4′:5,6]-pyrido[3,4-b]indole (**14b**)

This compound was prepared from compound **13b** (0.43 g, 1.5 mmol) and phosphorous oxychloride (4 ml) in acetonitrile (30 ml), following the same procedure and experimental conditions described above for **14a**. Yield of **14b**: 0.22 g (crude) (56%), m.p. 211–213° C (dec.). – MS: *m/z* (%) = 264 (100) [M^+], 222 (15), 208 (11), 182 (18), 132 (12). – HRMS: calcd. for $C_{16}H_{16}N_4$: 264.13750, found 264.13625. – ^{1}H NMR (400.14 MHz, DMSO-d_6): δ = 2.53 (s, 3H, 10-CH_3), 2.82 (s, 3H, 5-CH_3), 2.96 (s, 3H, 3-CH_3), 4.00 (s, 3H, N–CH_3), 7.09 (d, J = 7.0 Hz, 1H, 9-H), 7.43 (dd, J = 7.0, 8.0 Hz, 1H, 8-H), 7.51(d, J = 8.0 Hz, 1H, 7-H), 12.02 (s, 1H, N–H). – ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 11.1 (3-CH$_3$), 20.7 (5-CH$_3$), 22.6 (10-CH$_3$), 41.3 (N–CH$_3$), 109.6 (C-7), 109.8 (C-10b), 120.0 (C-10a), 122.0 (C-9), 126.6 (C-8), 132.5 (C-10), 133.0 (C-10c), 133.5 (C-3), 133.6 (C-5a), 139.9 (C-6a), 140.0 (C-5), 144.1 (C-3a). – $C_{16}H_{16}N_4$ (264.33): calcd. C 72.70, H 6.10, N 21.20; found C 72.52, H 6.21, N 21.35.

Crystal structure determination of **14a**

Crystals (light yellow needles) were obtained by allowing a hot solution of **14a** in ethanol/water (4:1, v/v) to stand at ambient temperature for 60 h; crystal dimensions: 0.28 × 0.12 × 0.24 mm. Crystal data for $C_{21}H_{17}ClN_4$: FW = 360.84; triclinic; space group $P\bar{1}$, with a = 1230.46 (8), b = 1257.60 (8), c = 1262.60 (9) pm, α = 85.819 (8)°, β = 64.807 (8)°, γ = 87.510 (8)°, V = 1.7631 (2) nm^3, Z = 2, D_{calc} = 1.359 g/cm^3. Data collection was made at 20 °C, on a STOE-IPDS diffractometer. 10867 Reflections were collected within the scan range θ = 3.25–22.98° using Mo-K_α radiation (λ = 71.073 pm). The unit cell parameters for the data collection were obtained using the setting angles of 7837 (θ = 55°) reflections. The structure was solved by direct methods using the program SHELXS-97 [12]. All non-hydrogen atoms were refined anisotropically by a full-matrix least-squares procedure based on F^2 using all unique data with SHELXL-97 [13]. The hydrogen atoms have been found in the difference Fourier map and were refined isotropically. This resulted in R values R_1/wR_2 = 0.0619/0.0655 for all data and 0.0299/0.0590 for reflections with $I > \sigma$ [R_{int} = 0.038] and 605 variable parameters; GOF = 1.003, largest peak and hole in final Fourier difference map were 0.17 and –0.13 e/Å^3, respectively.

Supplementary material

Further information on the crystal structure determination and X-ray data of compound **14a** can be ordered from the Cambridge Crystallographic Data Center (E-mail: deposit@ccdc.cam.au.uk) under the depository number CCDC 163856.

Acknowledgements

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