# Synthesis of Pyrano[3,2-*b*]indole Derivatives Based on Intramolecular Hetero-*Diels–Alder* of 2-Benzylidene-2,3-dihydro-1*H*-indol-3-ones

by **Yann Davion**[a]), **Benoît Joseph**[a])[1]), **Valérie Bénéteau**[a]), **Jean-Michel Léger**[b]), **Christian Jarry**[b]), and **Jean-Yves Mérour***[a])

[a]) Institut de Chimie Organique et Analytique, UMR-CNRS 6005, Université d'Orléans, BP 6759, F-45067 Orléans Cedex 2 (fax: (33)2-38-41-70-81; e-mail: jean-yves-merour@univ-orleans.fr)

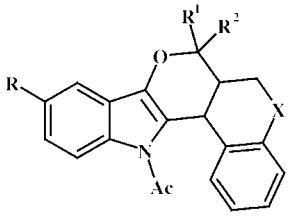
[b]) EA 2962, Pharmacochimie, Université Victor Segalen Bordeaux II, F-33076 Bordeaux Cedex

Pyrano[3,2-*b*]indole derivatives **2**–**6** were synthesized in good yields from 1-acetyl-2-benzylidene-2,3-dihydro-1*H*-indol-3-ones **8** and **13**–**15** by an intramolecular hetero-*Diels–Alder* reaction. The structures of compounds **2a**, **3a**, **4**, **5**, and **6** were unambiguously established by X-ray analysis. Compounds **4** and **5** were further aromatized to the corresponding derivatives **16** and **17**, respectively.

**1. Introduction.** – The hetero-*Diels–Alder* reaction has been developed in the last decade because of its elegant, economical, and stereocontrolled application in the synthesis of polycyclic skeletons of natural products [1]. Thus, *Tietze* and co-workers have performed hetero-*Diels–Alder* reactions of 1-oxa-1,3-butadiene as a powerful method for the synthesis of the pyran moiety [2]. By a similar approach, *Dehaen* and co-workers [3] have prepared in a diastereoselective manner polycyclic heterocycles with fused pyrano and thiopyrano rings. Under microwave irradiation conditions, *Raghunathan* and co-workers [4] have reported the synthesis of pyranoquinolinone by *Diels–Alder* methodology with a high degree of chemoselectivity. A limited number of benzylidenedihydroindol-2- or -3-ones have been reported to behave as dienophiles in *Diels–Alder* reactions. To the best of our knowledge, *Desimoni* and co-workers have described the preparation of pyrano[2,3-*b*]indole derivatives from benzylidenedihydroindol-2-one in good yields *via* this approach [5]. Among our research projects, the reactivity of 1-acetyl-2,3-dihydro-1*H*-indol-3-one (**1a**) was investigated in order to prepare new heterocyclic compounds through cycloaddition reactions [6]. Thus, we have already reported a convenient methodology for the preparation of pyrano[3,2-*b*]indole derivatives [7]. Following this preliminary communication, we herein describe the complete synthetic work with the corresponding structural analysis of the new pentacyclic derivatives **2**–**6**.

**Results and Discussion.** – First, we investigated the synthesis of pyrano[3,2-*b*]indole derivatives **2** and **3** (*Scheme 1*). Aldol condensation of 1-acetyl-2,3-dihydro-1*H*-indol-3-one (**1a**) or 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indol-3-one (**1b**) and 2-[(3-methylbut-2-enyl)oxy]benzaldehyde (**7a**) [8] or ethyl (*E*)-4-(2-formylphenoxy)but-2-enoate

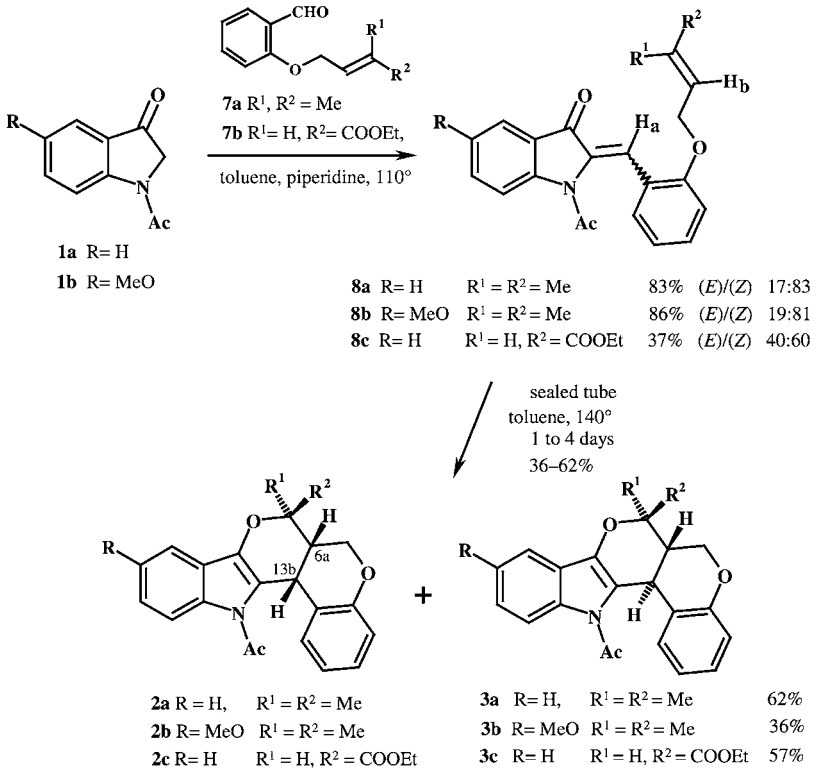
[1]) Present address: Laboratoire de Chimie Organique 1, Université Claude Bernard – Lyon 1, UMR-CNRS 5622, CPE - Bâtiment 308, 43 Boulevard du 11 Novembre 1918, F-69622 Villeurbanne Cedex



| | | | |
|---|---|---|---|
| **2, 3** | X= O | R = H, MeO | $R^1 = R^2$ = H, Me, COOEt |
| **4** | X= N-Piv | R = H | $R^1 = R^2$ = Me |
| **5** | X= $CH_2$ | R = H | $R^1 = R^2$ = Me |
| **6** | X= S | R = H | $R^1 = R^2$ = Me |

(**7b**) [9], respectively, gave compounds **8a**–**8c** in good yields (except **8c**) as (*E*)/(*Z*) diastereoisomer mixtures [10]. The intramolecular *Diels–Alder* reaction was first carried out with derivative **8a** ((*E*)/(*Z*) ratio 17:83). The reaction was performed in a sealed tube in toluene at 140° for 3 days to afford, after a chromatographic separation, the *cis*- and *trans*-pyrano[3,2-*b*]indole derivatives **2a** and **3a**, respectively, in 62% overall yield.

Scheme 1. *Synthesis of Compounds* **2** *and* **3**




The cyclization gave predominantly the *cis*-product (*cis*/*trans* ratio 76:24) [10]. The ratio did not exactly match the (*E*)/(*Z*) ratio of the starting heterodiene due to a partial isomerization of the mixture during the cyclization reaction. The *cis*-configuration of **2a** was supported by the coupling constant $J(6a,13b) = 4.4$ Hz (*trans*-isomer **3a**:

$J(6a,13b) = 12.0$ Hz) consistent with a *trans*-diaxal relationship and 2D-NOESY experiments (connectivities were observed between H–C(6a) and H–C(13b)). In addition, X-ray crystal-structure analyses of **2a** and **3a** were performed (*Figs. 1* and *2*), and the *cis*- and *trans*-configurations, respectively, were unambigously established.

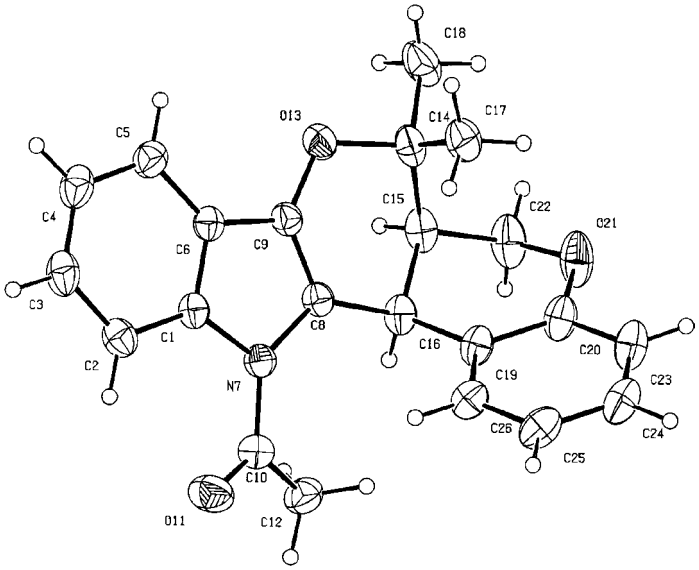



Fig. 1. *ORTEP Drawing of the crystal structure of compound* **2a** *with atom numbering* (ellipsoids at 50% probability)

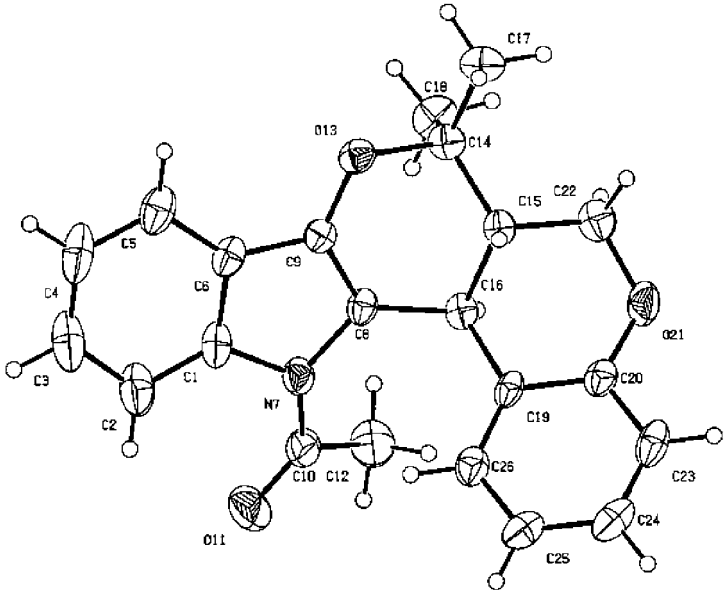


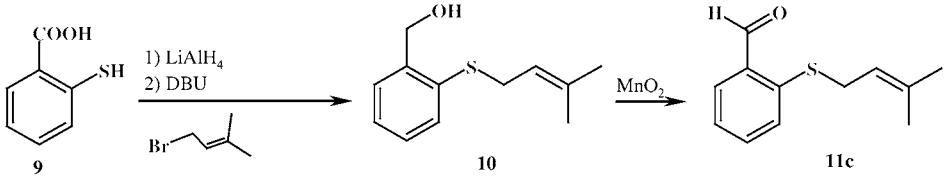

Fig. 2. *ORTEP Drawing of the crystal structure of compound* **3a** *with atom numbering* (ellipsoids at 50% probability)

All attempts to improve the yield of the intramolecular cyclization and the diastereoselectivity failed. Addition of a *Lewis* acid into the medium accelerates the reaction but decreases the yield (15–23%) by degradation of the starting material. In addition, no ene product was obtained in our different attempts at intramolecular cyclization.

The intramolecular-cyclization conditions (sealed tube, 140°, 3 days, toluene) were applied to the derivatives **8b** ((*E*)/(*Z*) ratio 19:81) and **8c** ((*E*)/(*Z*) ratio 40:60). The first one gave **2b** (*cis* isomer, $J$(6a,13b) = 5.4 Hz) and **3b** (*trans*-isomer, $J$(6a,13b) = 10.7 Hz) in moderate yield (36%) with a *cis*/*trans* diastereoisomer ratio of 69:31. Similarly from **8c**, compounds **2c** (*cis*-isomer, $J$(6a,13b) = 4.7 and $J$(6a,7) = 11.3 Hz) and **3c** (*trans*-isomer $J$(6a,13b) = 9.8 and $J$(6a,7) = 10.3 Hz) were obtained in 57% yield (*cis*/*trans* ratio 63:37). For the compounds **2c** and **3c**, the *trans*-configuration, observed in compound **8c** between the H-atoms $H_b$ and $H_c$, was also conserved *i.e.*, between H–C(6a) and H–C(7)).

On the basis of these successful results, we investigated the intramolecular hetero-*Diels–Alder* reaction of substituted 1-acetyl-2-benzylidene-2,3-dihydro-1*H*-indol-3-ones (**13**, **14**, and **15** obtained from **1a** and *tert*-butyl *N*-(2-formylphenyl)-*N*-(3-methylbut-2-enyl)carbamate (**11a**), 2-(4-methylpent-3-enyl)benzaldehyde (**11b**) [11], or 2-[(3-methylbut-2-enyl)sulfanyl]benzaldehyde (**11c**) [12], respectively, in the presence of piperidine in 78–80% yield as a mixture of diastereoisomers (**13**: (*E*)/(*Z*) 49:51; **14**: (*E*)/(*Z*) 7:93; **15**: (*E*)/(*Z*) 21:79). It should be noted that starting material **11c** was prepared from 2-sulfanylbenzoic acid (**9**) [13] by a reduction/alkylation sequence, followed by $MnO_2$ oxidation (*Scheme 2*). Alkylation [14][15] with 1-bromo-3-methylbut-2-ene must be performed on the 2-sulfanylbenzyl alcohol rather than 2-sulfanylbenzaldehyde in order to prevent dimerization.

Scheme 2. *Preparation of Sulfonyl-Substituted Benzaldehyde* **11c**

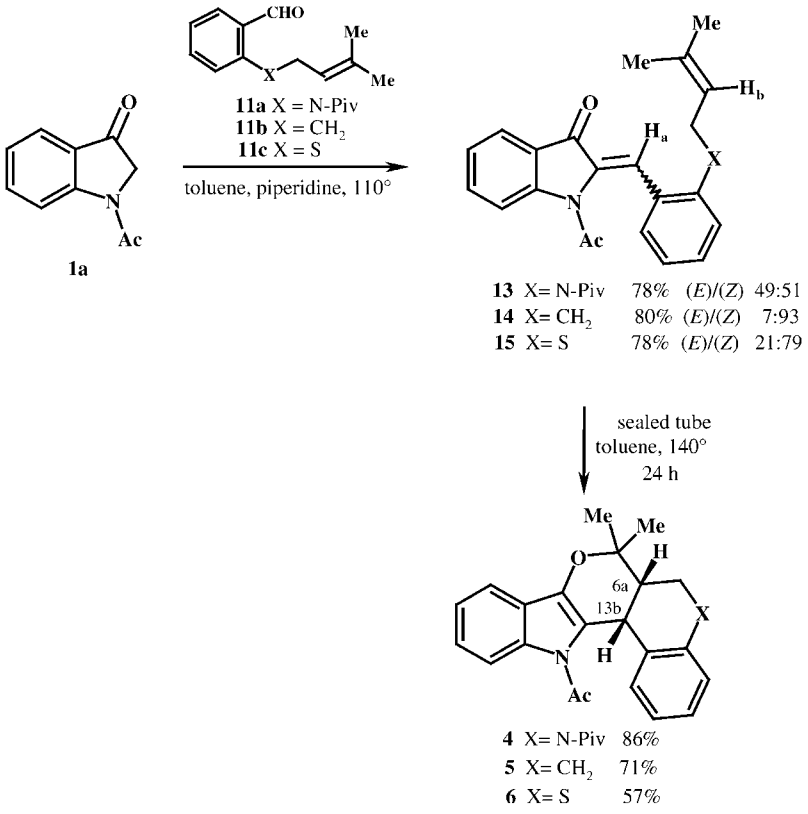



Hetero-*Diels–Alder* reactions were performed on **13–15** in a sealed tube (140°, 24 h) to afford exclusively the *cis*-diastereoisomers **4–6**, respectively, in 86, 71, and 57% yield (*Scheme 3*).

The structures were again deduced from the $^1$H-NMR coupling constants of the ring H-atoms H–C(6a) and H–C(13b) (**4**: $J$(6a,13b) = 7.0 and **5**: $J$(6a,13b) = 6.3 Hz) and 2D-NOESY experiments. X-Ray crystal-structure analyses were also performed for compounds **4–6** (see *Fig. 3* for compound **4**) indicating *inter alia* the *cis*-configuration.

In all cases studied, the *cis*-annelated products were predominantly or exclusively obtained from benzylidenedihydroindol-2-ones. As already described by *Tietze et al.* [12], under kinetic control, the *endo*-transition state **A**, leading to the *cis*-adduct, is energetically more favorable than the *exo*-transition state **B**. The presence of a heteroatom (X=O, N–Piv, S) instead of a $CH_2$ group in the chain adjacent to the aryl

Scheme 3. *Synthesis of Compounds* **4**–**6**



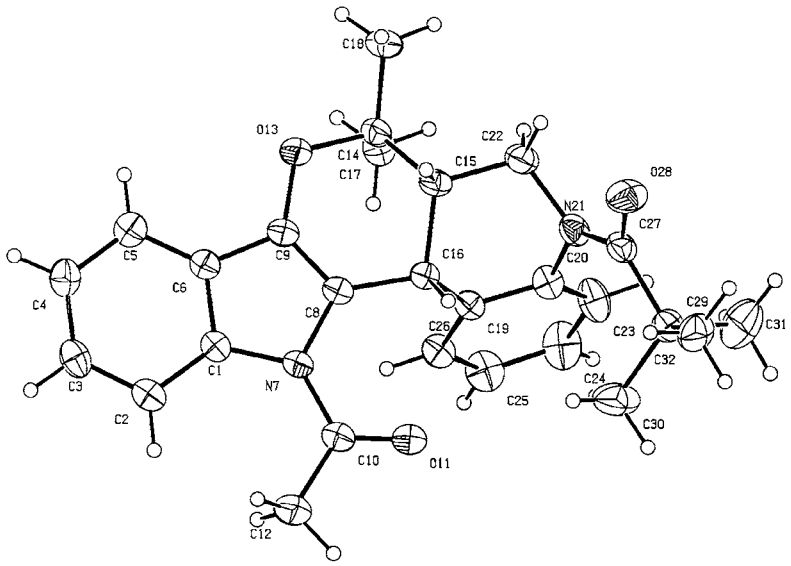




Fig. 3. *ORTEP Drawing of the crystal structure of compound* **4** *with atom numbering* (ellipsoids at 50% probability)

moiety has no product-determining influence on the conformation of the transition state (*Fig. 4*).

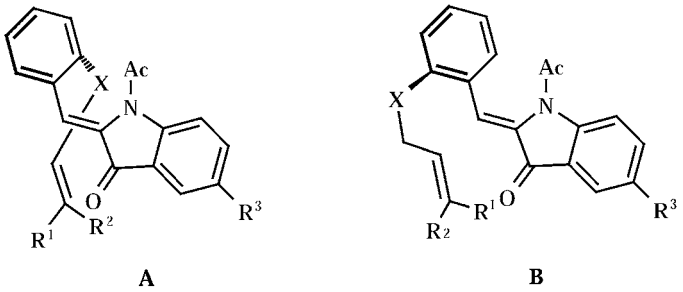
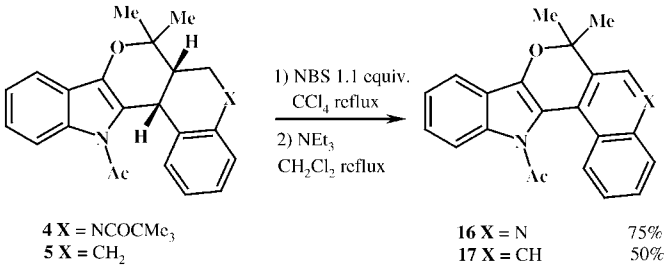



Fig. 4. endo- and exo-*Transition states* **A** *and* **B**, *respectively*

When compound **4** was treated with *N*-bromosuccinimide (NBS; 1.1 equiv.), followed by reflux in basic medium, a satisfying 75% yield of the corresponding aromatized derivative **16** was obtained. Similarly, the same conditions applied to **5** afforded derivative **17** in 50% yield (*Scheme 4*).

Scheme 4. *Aromatization*




In this study, new intramolecular *Diels–Alder* adducts **2**–**6** have been obtained from judiciously prepared substituted benzylidene-2,3-dihydro-1*H*-indol-3-ones. The method described is useful to synthesize polycyclic derivatives with potential pharmaceutical properties.

## Experimental Part

*General*. All reactions requiring anh. conditions were conducted in flame-dried apparatus. Petroleum ether (b.p. 40–60°) was used as chromatographic eluent. *2-[(3-methylbut-2-enyl)oxy]benzaldehyde* (**7a**) [8], *ethyl 4-(2-formylphenoxy)but-2-enoate* (**7b**) [9], and *2-(4-methylpent-3-enyl)benzaldehyde* (**11b**) [11] were prepared in good yields according to literature procedures. TLC: on precoated silica-gel plates (*Merck 60F*$_{254}$); visualization with an UV lamp. Flash chromatography (FC): on a column with flash silica gel *60 Merck* (40–63 μm) as the stationary phase. M.p.: *Büchi* capillary instrument; uncorrected. IR Spectra: *Perkin-Elmer FTIR paragon 1000* spectrometer. NMR Spectra: at 300 K in $CDCl_3$, with *Bruker Avance DPX-250* spectrometer; chemical shifts in ppm relative to $Me_4Si$ (TMS). MS: *Perkin-Elmer SCIEX API-300*; ion-spray methodology.

1. Diels–Alder *Reactions: Typical Procedure*. In a sealed tube, a soln. of **8** (1.0 mmol) or **13**–**15** (1.0 mmol) in toluene (10 ml) was stirred at 140° for 3 or 4 d for **8** and 24 h for **13**–**15**. After cooling, toluene was removed *in vacuo*, the crude residue was purified by CC (silica gel; AcOEt/petroleum ether 2:8) to give **2** and **3** except for **4**–**6** (AcOEt/petroleum ether 1:9). The diastereoisomers **2** and **3** were separated by CC.

*1-(6a,7,13,13b-Tetrahydro-7,7-dimethyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrano[3,2-*b*]indol-13-yl)ethan-1-one* (**2a** and **3a**) [7]. Time 3 d; 62% yield (*cis*/*trans* 76:24). *cis*-Isomer **2a**: m.p. 165–166° (AcOEt/hexane). *trans*-Isomer **3a**: m.p. 195–197° (AcOEt/hexane).

*1-(6a,7,13,13b-Tetrahydro-10-methoxy-7,7-dimethyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrano[3,2-*b*]indol-13-yl)ethan-1-one* (**2b** and **3b**). Time 4 d; 36% yield (*cis*/*trans* 69:31).

cis-*Isomer* **2b**: oil. IR (film): 3059, 2926, 1691, 1615, 1489, 1135, 1033, 757. $^1$H-NMR (250 MHz, $CDCl_3$): 7.77 (*d*, *J* = 9.1, 1 arom. H); 7.17 (*d*, *J* = 7.7, 1 arom. H); 7.09 (*t*, *J* = 7.7, 1 arom. H); 7.03 (*d*, *J* = 2.6, 1 arom. H); 6.95 (*dd*, *J* = 2.6, 9.1, 1 arom. H); 6.83 (*td*, *J* = 1.1, 7.7, 1 arom. H); 6.73 (*dd*, *J* = 1.1, 7.7, 1 arom. H); 5.03 (*d*, *J* = 5.4, H–C(13b)); 4.58 (*dd*, *J* = 5.0, 12.1, 1 H, $CH_2$); 4.42 (*dd*, *J* = 3.1, 12.1, 1 H, $CH_2$); 3.89 (*s*, Me); 2.78 (*s*, Me); 2.46–2.44 (*m*, H–C(6a)); 1.61 (*s*, Me); 1.12 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.3 (CO); 156.1 (C); 154.0 (C); 138.6 (C); 129.1 (CH); 129.0 (CH); 127.8 (CH); 124.9 (C); 123.0 (C); 120.9 (CH); 117.8 (C); 116.1 (CH); 115.9 (CH); 113.7 (CH); 100.3 (C); 78.7 (C); 66.1 ($CH_2$); 55.7 (Me), 40.6 (C(13b)); 33.4 (C(6a)); 28.2 (Me); 27.2 (Me); 23.0 (Me). MS: 378 ($[M+1]^+$). Anal. calc. for $C_{23}H_{23}NO_4$: C 73.19, H 6.14, N 3.71; found: C 72.81, H 5.98, N 3.91.

trans-*Isomer* **3b**: oil. IR (film): 3059, 2926, 1691, 1615, 1489, 1135, 1033, 757. $^1$H-NMR (250 MHz, $CDCl_3$): 8.08 (*d*, *J* = 9.0, 1 arom. H); 7.18–7.16 (*m*, 2 arom. H); 7.05 (*d*, *J* = 2.6, 1 arom. H); 7.00 (*dd*, *J* = 2.6, 9.0, 1 arom. H); 6.92 (*dd*, *J* = 1.1, 7.7, 1 arom. H); 6.87 (*t*, *J* = 7.7, 1 arom. H); 4.44 (*dd*, *J* = 6.3, 9.7, 1 H, $CH_2$); 4.42 (*d*, *J* = 10.7, H–C(13b)); 4.18 (*dd*, *J* = 9.7, 12.3, 1 H, $CH_2$); 3.90 (*s*, Me); 2.61 (*s*, Me); 2.27–2.21 (*m*, H–C(6a)); 1.52 (*s*, Me); 1.39 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.5 (CO); 156.3 (C); 153.8 (C); 140.4 (C); 129.7 (C); 128.8 (CH); 128.0 (CH); 124.7 (CH); 124.5 (C); 121.1 (CH); 117.1 (CH); 116.7 (CH); 115.3 (C); 114.2 (CH); 100.1 (C); 77.1 (C); 69.0 ($CH_2$); 55.8 (Me); 47.5 (C(13b)); 35.5 (C(6a)); 27.3 (Me); 26.4 (Me); 18.4 (Me). MS: 378 ($[M+1]^+$). Anal. calc. for $C_{23}H_{23}NO_4$: C 73.19, H 6.14, N 3.71; found: C 72.94, H 6.31, N 3.76.

*Ethyl 13-Acetyl-6a,7,13,13b-tetrahydro-6*H*-[1]benzopyrano[4′,3′:4,5]pyrano[3,2-*b*]indole-7-carboxylate* (**2c** and **3c**). Time 24 h; 57% yield (*cis*/*trans* 60:40).

cis-*Isomer* **2c**: M.p. 197–198° (AcOEt/hexane). IR (KBr): 2973, 2925, 1746, 1635, 1489, 1461, 1373, 1030, 755. $^1$H-NMR (250 MHz, $CDCl_3$): 7.81 (*d*, *J* = 8.3, 1 arom. H); 7.59 (*d*, *J* = 7.6, 1 arom. H); 7.40–7.25 (*m*, 2 arom. H); 7.14–7.08 (*m*, 2 arom. H); 6.86–6.79 (*m*, 2 arom. H); 5.24 (*d*, *J* = 4.7, H–C(13b)); 4.71 (*d*, *J* = 11.3, H–C(7)); 4.45–4.41 (*m*, $CH_2$); 4.39 (*q*, *J* = 7.1, $CH_2$); 2.88 (*s*, Me); 2.75–2.68 (*m*, H–C(6a)); 1.40 (*t*, *J* = 7.1, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.6 (CO); 169.5 (CO); 152.2 (C); 138.5 (C); 134.0 (C); 130.3 (CH); 128.3 (CH); 125.4 (CH); 123.4 (CH); 123.0 (C); 122.9 (C); 121.3 (CH); 118.9 (C); 118.4 (CH); 117.0 (CH); 115.0 (CH); 74.1 (C(7)); 65.9 ($CH_2$); 62.0 ($CH_2$); 34.0 (C(13b)); 33.8 (C(6a)); 27.8 (Me); 14.3 (Me). MS: 392 ($[M+1]^+$). Anal. calc. for $C_{23}H_{21}NO_5$: C 70.58, H 5.41, N 3.58; found: C 70.87, H 5.61, N 3.56.

trans-*Isomer* **3c**: M.p. 217–218° (AcOEt/hexane). IR (KBr): 2973, 2925, 1746, 1635, 1489, 1461, 1373, 1030, 755. $^1$H-NMR (250 MHz, $CDCl_3$): 8.13 (*d*, *J* = 8.3, 1 arom. H); 7.67 (*d*, *J* = 7.8, 1 arom. H); 7.41 (*t*, *J* = 7.8, 1 arom. H); 7.31 (*t*, *J* = 7.6, 1 arom. H); 7.16 (*t*, *J* = 7.6, 1 arom. H); 7.09 (*d*, *J* = 7.6, 1 arom. H); 6.93–6.84 (*m*, 2 arom. H); 4.58 (*d*, *J* = 9.8, H–C(13b)); 4.49 (*d*, *J* = 10.3, H–C(7)); 4.40–4.35 (*m*, 2 $CH_2$); 2.66 (*s*, Me); 2.55–2.48 (*m*, H–C(6a)); 1.37 (*t*, *J* = 7.1, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.9 (CO); 168.2 (CO); 154.3 (C); 141.7 (C); 134.8 (C); 128.5 (CH); 128.2 (C); 126.1 (CH); 124.1 (CH); 123.6 (CH); 122.5 (C); 121.5 (CH); 118.1 (CH); 117.4 (CH); 115.9 (C); 115.5 (CH); 76.6 (C(7)); 68.0 ($CH_2$); 62.2 ($CH_2$); 41.9 (C(6a)); 38.2 (C(13b)); 26.8 (Me); 14.3 (Me). MS: 392 ($[M+1]^+$). Anal. calc. for $C_{23}H_{21}NO_5$: C 70.58, H 5.41, N 3.58; found: C 70.25, H 5.45, N 3.43.

*1-(13-Acetyl-5,6,6a,7,13,13b-hexahydro-7,7-dimethylindolo[2′,3′:5,6]pyrano[3,4-*c*]quinolin-5-yl)-2,2-dimethylpropan-1-one* (**4**). According to the procedure for the synthesis of **2** and **3**, compound **4** was prepared from **13**. Time 24 h; 86% yield; *cis*-isomer exclusively; m.p. 225–226° ($CH_2Cl_2$/hexane).

*1-(5,6,6a,7,13,13b-Hexahydro-7,7-dimethylbenzo[5,6][2]benzopyrano[4,3-*b*]indol-13-yl)ethan-1-one* (**5**). According to the procedure for the synthesis of **2** and **3**, compound **5** was prepared from **14** in 24 h; yield 71%; *cis*-isomer exclusively. M.p. 173–175° (AcOEt/petroleum ether). IR (KBr): 3027, 2902, 1686, 1623, 1485, 1455, 1126, 753. $^1$H-NMR (250 MHz, $CDCl_3$): 8.13 (*d*, *J* = 8.2, 1 arom. H); 7.60 (br. *d*, *J* = 7.5, 1 arom. H); 7.39–7.24 (*m*, 2 arom. H); 7.16–7.00 (*m*, 4 arom. H); 4.39 (*d*, *J* = 7.0, H–C(13b)); 2.75–2.64 (*m*, $CH_2$, H–C(6a)); 2.55 (*s*, Me); 2.40–2.29 (*m*, 1 H, $CH_2$); 1.37 (*s*, Me); 1.23–1.07 (*m*, 1 H, $CH_2$); 0.66 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.3 (CO); 139.3 (C); 139.2 (C); 138.7 (C); 134.7 (C); 126.5 (CH); 126.4 (CH); 126.3 (2 CH); 125.2 (CH); 124.0 (C); 123.1 (CH); 117.7 (CH); 115.9 (CH); 115.8 (C); 80.0 (C); 41.4 (C(13b)); 36.6 (C(6a)); 28.4 ($CH_2$); 28.1 (Me); 26.6 (Me); 25.3 ($CH_2$); 19.8 (Me). MS: 346 ($[M+1]^+$). Anal. calc. for $C_{23}H_{23}NO_2$: C 79.97, H 6.71, N 4.05; found: C 79.75, H 6.89, N 3.91.

*1-(6a,7,13,13b-tetrahydro-7,7-dimethyl-6*H*[1]benzothiopyrano[4′,3′:4,5]pyrano[3,2-*b*]indol-13-yl)ethan-1-one* (**6**). According to the procedure for the synthesis of **2** and **3**, compound **6** was prepared from **15** ((*E*)/(*Z*)

mixture). Time 24 h; 57% yield; *cis*-isomer exclusively. Brown solid. M.p. 212°. IR (KBr): 3054, 2982, 2932, 1704, 1633, 1480, 1459, 1445, 1416, 1370. $^1$H-NMR (250 MHz, $CDCl_3$): 8.19 (*d*, *J* = 8.1, 1 arom. H); 7.61 (*d*, *J* = 7.1, 1 arom. H); 7.44 (*d*, *J* = 7.7, 1 arom. H); 7.37 (*t*, *J* = 8.1, 1 arom. H); 7.29 (*t*, *J* = 7.7, 1 arom. H); 7.21–7.05 (*m*, 3 arom. H); 4.50 (*d*, *J* = 6.3, H–C(13b)); 3.20–3.05 (*m*, $CH_2$); 2.41 (*s*, MeCO); 2.39–2.31 (*m*, H–C(6a)); 1.39 (*s*, Me); 0.81 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 169.1 (CO); 140.4 (C); 139.4 (C); 136.5 (C); 134.8 (C); 129.5 (CH); 127.6 (CH); 127.0 (CH); 126.5 (CH); 125.4 (CH); 123.4 (C); 123.1 (CH); 117.5 (CH); 116.0 (CH); 114.5 (C); 79.3 (C); 47.5 (CH); 39.1 (CH); 31.8 ($CH_2$); 28.3 (Me); 26.2 (Me); 19.9 (Me). MS: 364 ($[M+1]^+$). Anal. calc. for $C_{22}H_{21}NO_2S$: C 72.70, H 5.82, N 3.85; found: C 73.07, H 5.99, N 3.97.

2. *General Procedure for the Aldolization Reaction*. A soln. of **1** (1.0 mmol), **7** (1.5 mmol), and piperidine (0.25 ml) in toluene (25 ml) was stirred at 110° for a given time. After cooling and evaporation of toluene, the crude residue was purified by CC (silica gel; AcOEt/petroleum ether 1:9 for **8a** and **8b** and 2:8 for **8c**) to give **8**.

*1-Acetyl-2,3-dihydro-2-(1-{2-[(3-methylbut-2-enyl)oxy]phenyl}methylidene)-1*H-*indol-3-one* (**8a**). Time 1 h; yield 83% ((*Z*)/(*E*) 83:17). Oil.

*(Z)-Isomer:* IR (film): 3070, 2926, 1713, 1602, 1487, 1486, 1456, 1004, 755. $^1$H-NMR (250 MHz, $CDCl_3$): 8.32 (*d*, *J* = 8.4, 1 arom. H); 7.84 (*d*, *J* = 7.3, 1 arom. H); 7.63 (*d*, *J* = 7.3, 1 arom. H); 7.52 (*s*, $H_a$); 7.46 (*d*, *J* = 7.3, 1 arom. H); 7.38–7.24 (*m*, 2 arom. H); 7.01–6.93 (*m*, 2 arom. H); 5.45 (br. *t*, *J* = 6.5, $H_b$); 4.58 (*d*, *J* = 6.2, $CH_2$); 1.89 (*s*, Me); 1.74 (*s*, Me); 1.70 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 185.9 (CO); 170.4 (CO); 157.6 (C); 150.1 (C); 138.1 (C); 136.2 (CH); 134.9 (C); 131.5 (CH); 131.0 (NC=*C*H$C_6H_4$); 124.7 (CH); 124.2 (CH); 123.9 (C); 123.5 (C); 120.9 (CH); 119.4 ($Me_2C$=*C*); 118.7 (CH); 117.7 (CH); 112.5 (CH); 65.5 ($CH_2$); 25.8 (Me), 25.0 (Me), 18.4 (Me). MS: 348 ($[M+1]^+$). Anal. calc. for $C_{22}H_{21}NO_3$: C 76.06, H 6.09, N 4.03; found: C 75.82, H 5.91, N 3.85.

*1-Acetyl-2,3-dihydro-5-methoxy-2-(1-{2-[(3-methylbut-2-enyl)oxy]phenyl}methylidene)-1*H-*indol-3-one* (**8b**). Time 4.5 h; yield 86% ((*Z*)/(*E*) 81:19). Oil.

*(Z)-Isomer:* IR (film): 3078, 2931, 1687, 1629, 1486, 1132, 1027, 753. $^1$H-NMR (250 MHz, $CDCl_3$): 8.25 (*d*, *J* = 9.0, 1 arom. H); 7.52 (*s*, $H_a$); 7.47–7.17 (*m*, 5 arom. H); 7.04–6.89 (*m*, 1 arom. H); 5.45 (*t*, *J* = 6.4, $H_b$); 4.58 (*d*, *J* = 6.3, $CH_2$); 3.85 (*s*, Me); 1.87 (*s*, Me); 1.75 (*s*, Me); 1.71 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 186.0 (CO); 170.2 (CO); 157.7 (C); 157.1 (C); 144.8 (C); 138.1 (C); 135.5 (C); 131.6 (CH); 131.0 (NC=*C*H$C_6H_4$); 124.9 (C); 124.5 (CH); 123.6 (CH); 120.9 (CH); 119.4 (C); 119.2 (CH); 119.0 ($Me_2C$=C); 112.5 (CH); 105.8 (CH); 65.6 ($CH_2$); 56.0 (Me), 25.9 (Me); 24.9 (Me); 18.4 (Me). MS: 378 ($[M+1]^+$). Anal. calc. for $C_{23}H_{23}NO_4$: C 73.19, H 6.14, N 3.71; found: C 72.87, H 6.30, N 3.56.

*Ethyl (*E*)-4-{2-[(1-Acetyl-2,3-dihydro-3-oxo-1*H-*indol-2-ylidene)methyl]phenoxy)}but-2-enoate* (**8c**). Time 8 h; yield 37% ((*Z*)/(*E*) 60:40). Oil.

*(Z)-Isomer:* IR (film): 3078, 2931, 1704, 1487, 1462, 1031, 756. $^1$H-NMR (250 MHz, $CDCl_3$): 8.26 (*d*, *J* = 8.4, 1 arom. H); 7.83 (*d*, *J* = 7.5, 1 arom. H); 7.62 (*d*, *J* = 7.5, 1 arom. H); 7.51 (*s*, $H_a$); 7.47 (*d*, *J* = 8.5, 1 arom. H); 7.39–7.22 (*m*, 2 arom. H); 7.08–6.98 (*m*, 2 arom. H); 6.87–6.83 (*m*, $H_b$); 6.06 (*d*, *J* = 15.6, EtOCOC*H*); 4.75 (*m*, $CH_2$); 4.15 (*q*, *J* = 7.1, $CH_2$); 1.88 (*s*, Me); 1.25 (*t*, *J* = 7.1, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 182.8 (CO); 170.2 (CO); 165.9 (CO); 156.4 (C); 150.0 (C); 141.4 (CH); 137.9 (C); 136.4 (CH); 135.1 (C); 131.8 (CH); 131.1 (CH); 129.1 (CH); 124.8 (CH); 124.3 (CH); 122.7 (NC=*C*H$C_6H_4$); 122.5 (C); 121.7 (CH); 117.6 (CH); 112.2 (CH=*C*HCH$_2$); 67.0 ($CH_2$), 60.7 ($CH_2$), 24.9 (Me), 14.3 (Me). MS: 392 ($[M+1]^+$). Anal. calc. for $C_{23}H_{21}NO_5$: C 70.58, H 5.41, N 3.58; found: C 70.77, H 5.57, N 3.45.

N-*(2-Formylphenyl)-2,2-dimethyl*-N-*(3-methylbut-2-enyl)propanamide* (**11a**). To a soln. of *N*-(2-formylphenyl)-2,2-dimethylpropanamide (2.6 g, 12.5 mmol) in dry DMF (25 ml) was added portionwise NaH (607 mg, 15.4 mmol, 60% in dispersion) at 0°. Then, 2-methyl-4-bromobut-2-ene (2.8 g, 18.8 mmol) dissolved in DMF (25 ml) was added dropwise at 0°. The final mixture was stirred for 5 h at r.t. The mixture was poured into $H_2O$ (100 ml) and then extracted with AcOEt (2 × 40 ml). The org. layer was washed with brine, then dried ($MgSO_4$), and evaporated *in vacuo*. The crude residue was purified by CC (silica gel; petroleum ether/AcOEt 95:5) to afford **11a** (2.2 g, 65%). Oil. IR (film): 3088, 2994, 2870, 1688, 1638, 1597, 1394, 1356, 1172, 751. $^1$H-NMR (250 MHz, $CDCl_3$): 10.09 (*s*, CHO); 7.96 (*dd*, *J* = 1.6, 7.7, 1 arom. H); 7.63 (*dt*, *J* = 1.6, 7.7, 1 arom. H); 7.48 (*t*, *J* = 7.7, 1 arom. H); 7.24 (*d*, *J* = 7.7, 1 arom. H); 5.27 (*t*, *J* = 7.0, =CH); 4.33 (*dd*, *J* = 7.1, 13.9, 1 H, $CH_2$); 4.15 (*dd*, *J* = 8.1, 13.9, 1 H, $CH_2$); 1.61 (*s*, Me); 1.15 (*s*, Me); 1.03 (*s*, 3 Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 189.3 (CO); 177.2 (CO); 145.2 (C); 138.2 (C); 134.5 (CH); 133.6 (C); 131.1 (CH); 128.5 (CH); 128.4 (CH); 117.9 (CH); 50.8 ($CH_2$); 41.1 (C); 29.2 (3 Me); 25.4 (Me); 17.1 (Me). MS: 274 ($[M+1]^+$). Anal. calc. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.35, H 8.38, N 4.95.

N-*{2-[(1-Acetyl-2,3-dihydro-3-oxo-1*H-*indol-2-ylidene)methyl]penyl}-2,2-dimethyl*-N-*(3-methylbut-2-enyl)propanamide* (**13**). According to the procedure for the synthesis of **8**, **13** was prepared from **1a** and **11a**. Time 3 h; 78% yield ((*Z*)/(*E*) 51:49). Oil. IR (film): 3062, 2967, 1690, 1639, 1480, 1381, 1361, 1276, 757. $^1$H-NMR

(250 MHz, $CDCl_3$): (*E*)-Isomer: 8.21 (br. *d*, *J* = 8.3, 1 arom. H); 8.10–8.05 (*m*, 1 arom. H); 7.87 (*dd*, *J* = 1.0, 7.5, 1 arom. H); 7.72–7.68 (*m*, 1 arom. H, $H_a$); 7.43–7.40 (*m*, 2 arom. H); 7.35–7.24 (*m*, 1 arom. H); 7.23–7.19 (*m*, 1 arom. H); 5.36–5.23 (*m*, $H_b$); 4.66 (*dd*, *J* = 6.1, 14.3, 1 H, $CH_2$); 3.90–3.68 (*m*, 1 H, $CH_2$); 2.63 (*s*, Me); 1.66 (*s*, Me); 1.38 (*s*, Me); 1.13 (*s*, 3 Me). $^1$H-NMR (250 MHz, $CDCl_3$): (*Z*)-Isomer: 8.21 (br. *d*, *J* = 8.3, 1 arom. H); 8.07–8.05 (*m*, 1 arom. H); 7.76 (*dd*, *J* = 1.0, 7.5, 1 arom. H); 7.67–7.63 (*m*, 1 arom. H, $H_a$); 7.39–7.37 (*m*, 2 arom. H); 7.35–7.24 (*m*, 1 arom. H); 7.16–7.13 (*m*, 1 arom. H); 5.36–5.23 (*m*, $H_b$); 4.39 (*dd*, *J* = 6.1, 14.3, 1 H, $CH_2$); 3.90–3.68 (*m*, 1 H, $CH_2$); 2.12 (*s*, Me); 1.56 (*s*, Me); 1.23 (*s*, Me); 1.05 (*s*, 3 Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): (*E*)/(*Z*)-mixture: 185.5 (CO): 182.6 (CO); 178.0 (CO); 177.8 (CO); 169.9 (CO); 168.9 (CO); 150.1 (C); 148.3 (2 C); 144.3 (C); 142.7 (C); 136.4 (C); 136.3 (CH); 135.5 (C); 135.2 (C); 132.9 (C); 132.2 (CH); 130.9 (2 CH); 130.3 (CH); 130.2 (CH); 130.1 (CH); 128.0 (CH); 127.2 (CH); 126.0 (CH); 125.1 (CH); 124.7 (CH); 124.3 (2 CH); 124.0 (2 C); 119.0 (CH); 118.9 (CH); 117.7 (CH); 117.5 (CH); 117.3 (2 CH); 50.5 ($CH_2$); 41.2 (C); 41.0 (C); 29.2 (3 Me); 26.6 (Me); 25.8 (Me); 25.7 (Me); 25.2 (Me); 17.7 (Me); 17.5 (Me). MS: 431 ($[M+1]^+$). Anal. calc. for $C_{27}H_{30}N_2O_3$: C 75.32, H 7.02, N 6.51; found: C 75.15, H 7.20, N 6.50.

*1-Acetyl-2,3-dihydro-2-{[2-(4-methylpent-3-enyl)phenyl]methylidene}-1*H*-indol-3-one* (**14**). According to the procedure for the synthesis of **8**, **14** was prepared from **1a** and **11b** [11]. Time 9 h; yield 80% ((*Z*)/(*E*) 93:7). Oil.

*(*Z*)-Isomer:* IR (film): 3061, 2927, 1697, 1459, 1008, 758. $^1$H-NMR (250 MHz, $CDCl_3$): 8.31 (*d*, *J* = 8.2, 1 arom. H); 7.83 (*d*, *J* = 7.6, 1 arom. H); 7.63 (*t*, *J* = 8.2, 1 arom. H); 7.50 (*s*, $H_a$); 7.44 (*d*, *J* = 7.3, 1 arom. H); 7.31–7.18 (*m*, 4 arom. H); 5.19 (br. *t*, *J* = 6.1, $H_b$); 2.79 (*t*, *J* = 7.4, $CH_2$); 2.33 (*q*, *J* = 7.4, $CH_2$); 1.80 (*s*, MeCO); 1.69 (*s*, Me); 1.59 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): 185.5 (CO); 170.1 (CO); 150.1 (C); 142.5 (C); 136.3 (CH); 135.4 (C); 132.9 (C); 132.8 (C); 130.3 (CH); 129.8 (CH); 128.9 (CH); 126.6 (CH); 124.8 (CH); 124.1 (CH); 123.7 (C); 123.0 (CH); 120.4 (CH); 117.7 (CH); 33.8 ($CH_2$); 29.2 ($CH_2$); 25.7 (Me); 25.0 (Me); 17.7 (Me). MS: 346 ($[M+1]^+$). Anal. calc. for $C_{23}H_{23}NO_2$: C 79.97, H 6.71, N 4.05; found: C 80.18, H 6.67, N 4.19.

*1-Acetyl-2,3-dihydro-2-{2-[(3-methylbut-2-enyl)sulfanyl]benzylidene}-1*H*-indol-3-one* (**15**). According to the procedure for the synthesis of **8**, **15** was prepared from **1a** and **11c** [12][14] in 4 h; yield 78% ((*Z*)/(*E*) 79:21). Yellow oil. IR (film): 3056, 2974, 2930, 1694, 1634, 1459, 1365, 1311, 1277, 1188. $^1$H-NMR (250 MHz, $CDCl_3$): (*E*)-Isomer: 8.23 (*d*, *J* = 8.3, 1 arom. H); 7.84 (*d*, *J* = 7.6, 1 arom. H); 7.77 (*s*, $H_a$); 7.73 (*d*, *J* = 7.6, 1 arom. H); 7.63 (*t*, *J* = 7.1, 1 arom. H); 7.46–7.21 (*m*, 4 arom. H); 5.25 (br. *t*, *J* = 7.8, $H_b$); 3.50 (*d*, *J* = 7.8, $CH_2$); 2.68 (*s*, MeCO); 1.66 (*s*, Me); 1.54 (*s*, Me). $^1$H-NMR (250 MHz, $CDCl_3$): (*Z*)-Isomer: 8.30 (*d*, *J* = 8.3, 1 arom. H); 7.86 (*d*, *J* = 7.6, 1 arom. H); 7.65 (*t*, *J* = 7.9, 1 arom. H); 7.61 (*s*, $H_a$); 7.44–7.18 (*m*, 5 arom. H); 5.33 (br. *t*, *J* = 7.6, $H_b$); 3.63 (*d*, *J* = 7.6, $CH_2$); 1.80 (*s*, MeCO); 1.74 (*s*, Me); 1.69 (*s*, Me). $^{13}$C-NMR (62.90 MHz, $CDCl_3$): (*Z*)-Isomer: 185.4 (CO); 170.2 (CO); 150.0 (C); 139.1 (C); 137.5 (C); 136.3 (CH); 135.8 (C); 134.1 (C); 129.7 (CH); 129.1 (CH); 129.0 (CH); 126.0 (CH); 124.8 (CH); 124.1 (CH); 123.7 (C); 119.9 (CH); 118.2 (CH); 117.7 (CH); 31.8 ($CH_2$); 25.6 (Me); 24.8 (Me); 17.8 (Me). MS: 386.5 ($[M+Na]^+$). Anal. calc. for $C_{22}H_{21}NO_2S$: C 72.70, H 5.82, N 3.85; found: C 72.42, H 5.67, N 3.74.

*1-(7,13-Dihydro-7,7-dimethylindolo[2′,3′:5,6]pyrano[3,4-*c*]quinolin-13-yl)ethan-1-one* (**16**). To a soln. of **4** (133 mg, 0.31 mmol) in $CCl_4$ (10 ml) at reflux was added *N*-bromosuccinimide (NBS; 55 mg, 0.31 mmol). The final mixture was stirred for 45 min at reflux. After cooling, the solvent was removed *in vacuo*, and $CH_2Cl_2$ was added (10 ml). Then, $Et_3N$ (0.5 ml, 3.6 mmol) was added, and the soln. was stirred for 2 h at reflux. The latter was poured into $H_2O$ (10 ml). The medium was acidified with 37% HCl (1 ml) and extracted twice with $CH_2Cl_2$ (2 × 10 ml). The org. layer was washed with brine, then dried ($MgSO_4$), and evaporated *in vacuo*. The crude residue was purified by CC (silica gel; petroleum ether/AcOEt 8:2) to afford **16** (79 mg, 75%) as an oil [7].

*1-(7,13-Dihydro-7,7-dimethylbenzo[5,6][2]benzopyrano[4,3-*b*]indol-13-yl)ethan-1-one* (**17**). According to the procedure for the synthesis of **16**, **17** was prepared from **5** in 50% yield. Oil. IR (film): 3057, 2929, 1701, 1453, 1277, 1107, 751. $^1$H-NMR (250 MHz, $CDCl_3$): 8.45–8.39 (*m*, 2 arom. H); 7.80 (br. *d*, *J* = 7.8, 1 arom. H); 7.73 (*d*, *J* = 8.5, 1 arom. H); 7.65 (br. *d*, *J* = 7.0, 1 arom. H); 7.56–7.41 (*m*, 4 arom. H); 7.35 (*t*, *J* = 7.5, 1 arom. H); 2.16 (*s*, Me); 2.03 (*s*, Me); 1.66 (*s*, Me). $^{13}$C-NMR (62.9 MHz, $CDCl_3$): 172.7 (CO); 144.1 (C); 138.0 (C); 133.6 (C); 133.5 (C); 128.6 (CH); 127.4 (CH); 127.0 (CH); 126.9 (CH, C); 126.2 (CH); 125.1 (CH); 123.9 (CH); 122.5 (C); 122.4 (C); 121.8 (CH); 120.3 (C); 118.0 (CH); 116.3 (CH); 81.9 (C); 27.4 (Me); 27.3 (Me); 24.6 (Me). MS: 342 ($[M+1]^+$). Anal. calc. for $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10; found: C 81.27, H 5.43, N 3.95.

Crystallographic data for the structures **2a**, **3a**, and **4** (*Table*) have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No CCDC-203686, CCDC-203687, and CCDC-203688. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: ccdc.cam.ac.uk).

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Table 1. *Crystallographic Data of Compounds* **2a**, **3a**, *and* **4**

| Parameters | **2a** | **3a** | **4** |
|---|---|---|---|
| Empirical formula | $C_{22}H_{21}N_2O_3$ | $C_{22}H_{21}N_2O_3$ | $C_{27}H_{30}N_2O_3$ |
| Formula weight [g·mol$^{-1}$] | 347.40 | 347.40 | 450.53 |
| Temp. [K] | 296(2) | 296(2) | 296(2) |
| Crystal size [mm] | 0.50 × 0.37 × 0.25 | 0.37 × 0.10 × 0.05 | 0.30 × 0.15 × 0.10 |
| Wavelength [Å] | 1.54178 | 1.54178 | 1.54180 |
| Crystal system | monoclinic | monoclinic | triclinic |
| Space group | $P2_1/c$ | $P2_1/n$ | $P\bar{1}$ |
| Goodness-of-fit on $F^2$ | 1.049 | 1.049 | 1.035 |
| Unit-cell parameters | $a = 8.793(2)$ Å | $a = 10.523(3)$ Å | $a = 11.063(1)$ Å |
| | $b = 15.462(4)$ Å | $b = 17.839(2)$ Å | $b = 11.138(2)$ Å |
| | $c = 12.743(8)$ Å | $c = 10.586(3)$ Å | $c = 11.222(1)$ Å |
| | $\alpha = 90°$ | $\alpha = 90°$ | $\alpha = 103.88(1)°$ |
| | $\beta = 91.39(3)°$ | $\beta = 116.06(2)°$ | $\beta = 90.98(1)°$ |
| | $\gamma = 90°$ | $\gamma = 90°$ | $\gamma = 119.26(1)°$ |
| Volume [Å$^3$] | 1732.0(12) | 1785.2(7) | 1156.3(3) |
| $Z$, calc. density | 4, 1.332 mg/m$^3$ | 4, 1293 mg/m$^3$ | 2, 1237 mg/m$^3$ |
| Absorption coefficient | 0.711 mm$^{-1}$ | 0.689 mm$^{-1}$ | 0.641 mm$^{-1}$ |
| $F(000)$ | 736 | 736 | 460 |
| $\theta$ Range for data collection | 4.50 to 64.92° | 4.94 to 54.94° | 4.11 to 54.95° |
| Index ranges | $-10 \le h \le 10$ | $-11 \le h \le 10$ | $-11 \le h \le 11$ |
| | $0 \le k \le 18$ | $0 \le k \le 18$ | $-11 \le k \le 11$ |
| | $0 \le l \le 14$ | $0 \le l \le 11$ | $0 \le l \le 11$ |
| Reflections coll. | 2898 | 2230 | 2890 |
| Max. and min. transmission | 0.8424 and 0.7177 | 0.9663 and 0.7845 | 0.9387 and 0.8310 |
| Refinement method | full-matrix | full-matrix | full-matrix |
| | east-squares on $F^2$ | least-squares on $F^2$ | least-squares on $F^2$ |
| Data, restraints, parameters | 2898, 0, 248 | 2230, 3, 246 | 2890, 0, 302 |
| Final $R$ indices | $R_1 = 0.0570$, | $R_1 = 0.0535$, | $R_1 = 0.0433$, |
| | $wR_2 = 0.1420$ | $wR_2 = 0.1085$ | $wR_2 = 0.1000$ |
| $R$ Indices (all data) | $R_1 = 0.0906$, | $R_1 = 0.1046$, | $R_1 = 0.0776$, |
| | $wR_2 = 0.1691$ | $wR_2 = 0.1349$ | $wR_2 = 0.1196$ |
| Extinction coefficient | 0.0095(10) | 0.0039(4) | 0.0108(7) |
| Largest diff. peak and hole | 0.235 and −0.239 e·Å$^{-3}$ | 0.158 and −0.179 e·Å$^{-3}$ | 0.217 and −0.149 e·Å$^{-3}$ |

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