Formation of Dimers of Some 2-Substituted Indan-1-one Derivatives during Base-Mediated Cross-Aldol Condensation

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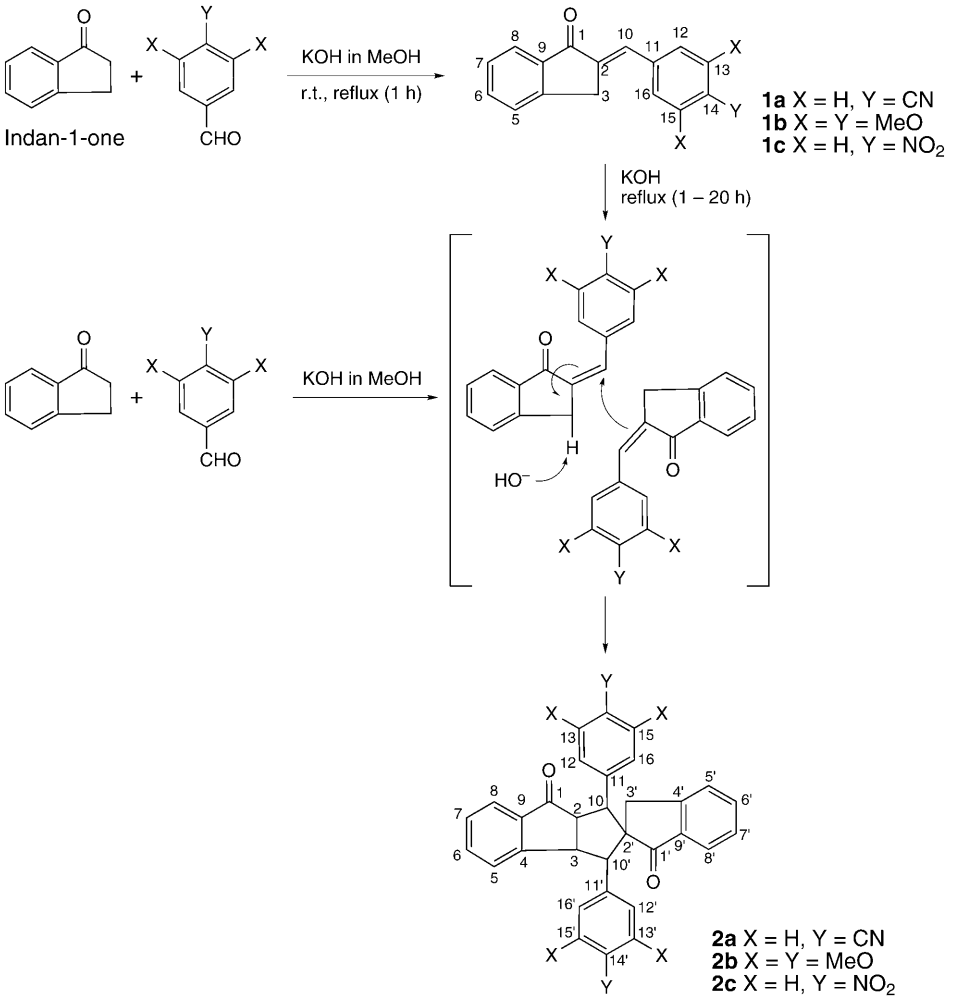
Dedicated to the memory of Professor *Dharam Paul Jindal*, who initiated the research described here

Unexpected dimers of some 2-substituted indan-1-one derivatives were isolated during aldol condensation of indan-1-one with various aldehydes in the presence of KOH (see *Scheme*). Monomeric products, usually expected from aldol condensation, further underwent a base-catalyzed nucleophilic addition reaction to their dimeric form in some cases. The structures of these dimers were characterized by using various spectral techniques and in one case, structural details were determined from a high-resolution crystallographic analysis.

Introduction. – Normally, aldol condensation of a ketone containing H-atoms in α-position with aromatic aldehydes in MeOH in the presence of a base, at room temperature or under reflux conditions, yields corresponding α-substituted monomeric aldol products [1–4]. This phenomenon holds true even on application of newer techniques like microwave irradiation [5] and ultrasound [6] for carrying out this reaction. *Hartmann et al.* [7] have also reported the formation of the normal aldol addition product on aldol condensation of indan-1-one with pyridine-4-carboxaldehyde in presence of piperidine/AcOH. However, while carrying out aldol condensation of indan-1-one with some aldehydes, we consistently obtained a novel dimeric form as a major product under various experimental conditions (*Scheme*).

Results and Discussion. – While working on the synthesis of some potential aromatase inhibitors, we treated indan-1-one (=2,3-dihydro-1*H*-inden-1-one) with various aldehydes such as pyridine-4-carboxaldehyde, 4-nitrobenzaldehyde, 4-cyanobenzaldehyde and 3,4,5-trimethoxybenzaldehyde in the presence of a strong base like KOH. Thereby, a major product different from the expected monomeric product was obtained (*Scheme*). The major products **2a**–**c** were isolated and purified by column chromatography and characterized by using various spectral techniques such as ^{1}H- and ^{13}C-NMR spectroscopy. Their structures were established to be novel dimeric forms of the expected products **1a**–**c**, in analogy with our earlier reported potential aromatase-

Scheme. *Formation of Monomers and Dimers of Indanone Derivatives under Various Reaction Conditions*[1])



inhibitory dimer obtained from pyridine-4-carboxaldehyde and indan-1-one [8]. The structure of dimer **2b** was also confirmed by X-ray crystallographic analysis (see below).

The ^{1}H-NMR spectra of **2a**–**c** exhibited an *AB* system for $CH_2(3')$[1]) in the range δ 2.95–3.00 ($J_{AB} \approx 17.0$ Hz). H–C(10′) and H–C(10) of the moiety connecting the two monomer units appeared as *d* at δ 3.80–3.88 ($J \approx 10.5$ Hz) and 4.05–4.11 ($J \approx 10.7$ Hz), respectively, for all the dimers. Except for the

[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*

^{1}H-signals of the connecting moiety, the integration of all signals was twice as much as expected for a monomer. Further confirmation of a dimeric structure came from the ^{13}C-NMR spectra, which showed two signals around δ 205 for two carbonyl C-atoms.

The formation of the dimers **2a**–**c** can be explained by the mechanism illustrated in the *Scheme*. The monomeric products **1** formed by aldol condensation of indan-1-one with some aldehydes further undergo base-catalyzed nucleophilic addition leading to their dimeric forms. The monomers **1a**–**c** formed from the aldehydes having electron-withdrawing substituents at the *para*-position facilitate the formation of dimers in the order (pyridine-4-carboxaldehyde) > 4-CN > 4-NO_2 > 3,4,5-$(MeO)_3$ as shown in the *Table*. Aldol condensation of indan-1-one with pyridine-4-carboxaldehyde has also been performed under milder conditions but in no case, a monomer has been formed [8]. However, with other aldehydes, we were also able to isolate monomeric products when the reaction was carried out at room temperature or for a short reflux time (see *Table*). This supports the proposed mechanism for the formation of the dimers. Also, the presence of electron-donating groups at the *meta*-position facilitate dimer formation as in case of the 3,4,5-trimethoxy derivative. The behavior of these aldol products can be explained on the basis of stabilization of carbanions formed in the intermediate state due to the presence of electron-withdrawing substituents at the *para*-position or electron-donating substituents, by their inductive effect, at the *meta*-position. No dimers were obtained when indanone was treated with aldehydes such as 4-isopropylbenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, or 3,4-dimethoxybenzaldehyde.

Table. *Reaction Conditions and Type of Products Formed*

Aldehyde	Reaction time [h]	Reaction temp. [°]	Type of compound formed	Yield [%]
1a 4-CN–C_6H_4–CHO	0.5	r.t.	monomer	49
1b 3,4,5-$(MeO)_3C_6H_2$–CHO	1	70	monomer	60
1c 4-NO_2–C_6H_4–CHO	1	70	monomer	54
2a 4-CN–C_6H_4–CHO	2.5	70	dimer	38
2b 3,4,5-$(MeO)_3C_6H_2$–CHO	20	70	dimer	36
2c 4-NO_2–C_6H_4–CHO	20	70	dimer	32

Conclusive evidence for the proposed nucleophilic-addition mechanism was obtained by the formation of these dimeric products **2a**–**c** from **1a**–**c** in refluxing MeOH in the presence of KOH, after 1–20 h. Thus, the synthesis of indanone derivatives by aldol condensation with aldehydes containing electron-withdrawing groups at the *para* position or electron-donating groups at the *meta*-positions with respect to the CHO group leads to the formation of novel compounds in the presence of a simple base such as KOH, compounds which may further find significance in various areas of therapeutic research.

Crystallographic Studies of **2b**. ORTEP/POV-Ray views of molecules *A* and *B* of **2b** are shown in the *Figure*, which also indicates the ring- and torsion-angle labels used in the following discussion. As expected, the two molecules *A* and *B* are very similar overall. Both bond lengths (±0.003 Å) and bond angles (±0.2°) compare well with those

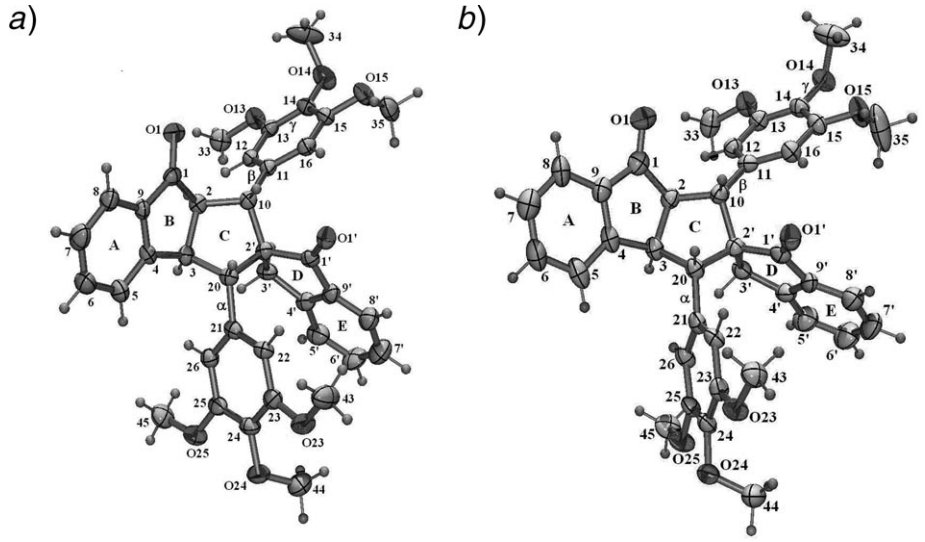


Figure. *ORTEP/Pov-Ray views of* a) *molecule* A *and* b) *molecule* B*, in the crystal structure of* **2b**. 50% Thermal motion ellipsoids, arbitrary atom numbering[1]). The bonds governing link torsion angles exhibiting most variation between molecules *A* and *B* are labeled α, β, and γ.

found in comparable organic compounds [9] and exhibit no unusual values and no significant differences between molecules *A* and *B*. The presence of two symmetry-independent molecules in the asymmetric unit of a crystal structure provides an ideal opportunity to look for variations in the molecular geometry, which in this case corresponds to differences in the ring puckerings and linkage torsion angles. The linkage torsion angles α and β (*Figure*) between the ring structures show some variation between molecules *A* and *B*. Linkage torsion angle α(C(3)−C(20)−C(21)−C(22))[1]) is -156.7° (2) in molecule *A* and -140.7° (2) in molecule *B*, while β(C(2)−C(10)−C(11)−C(12)) is -31.0° (3) in molecule *A* and -11.7° (3) in molecule *B*. The side-chain torsion angle γ(C(13)−C(14)-O(14)−C(34)) also differs significantly between the two molecules, being 81.3° (3) in molecule *A* and 112.9° (3) in *B*. Differences also occur in the fused-ring-system moieties. Rings A and E (*Figure*) are essentially planar in both molecules. Ring B adopts an envelope conformation in both molecules, the out-of plane atom being C(3) in molecule *A* and C(2) in molecule *B*. Ring C is a half-chair with C(2) as the apex in molecule *A*, and an envelope with C(2′) out-of-plane in molecule *B*. Ring D forms an envelope conformation in both molecules, with C(2′) out-of-plane in molecule *A* and C(9′) in molecule *B*. Of these fused rings, ring C in both molecules exhibits the largest degree of puckering.

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Experimental Part

General. Materials obtained from the commercial suppliers were used without further purification. Anh. Na_2SO_4 was used as a drying agent. The purity of the compounds was established by TLC and elemental analyses. TLC: plates (*E. Merck*, Darmstadt, Germany) were prepared according to *Stahl* (activated at 110° for 30 min); AcOEt as solvent; visualization by I_2 vapors. Column chromatography (CC): neutral alumina (*E. Merck*, Darmstadt, Germany). M.p.: *MP1-Veego* instrument (*Veego Instruments*, Mumbai, India); uncorrected. IR Spectra: *Perkin-Elmer-882* spectrophotometer (*Perkin Elmer Ltd*., Beaconsfield, England); KBr pellets; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AC-300F* (300 MHz) instrument (*Bruker AG*, Fällanden, Switzerland); Me_4Si as internal standard; chemical shifts δ in ppm, J in Hz. MS: *Vg-11-250J-70-S* spectrometer (*VG Analytical Ltd*., Manchester, England); in *m*/*z* (rel. %). Elemental analyses (C, H, N): *Perkin-Elmer-2400* apparatus.

Monomers **1a**–**c**: The aldehyde (1.81 mmol) was added to a stirred soln. of indan-1-one (0.2 g, 1.51 mmol) in MeOH (25 ml). KOH (0.13 g, 2.27 mmol) was then added, and the mixture was further stirred or refluxed for a required period of time as specified in the *Table* (TLC monitoring). Excess MeOH was evaporated, crushed ice was added, and the mixture was allowed to stand overnight. The precipitate obtained was filtered, washed thoroughly with dist. H_2O, dried, and crystallized from MeOH; **1a**–**c**.

*4-[(2,3-Dihydro-1-oxo-1*H*-inden-2-ylidene)methyl]benzonitrile* (**1a**): Yield 0.182 g (49.05%). M.p. 208–212°. IR (KBr): 2980, 2210, 1705, 1630, 1610, 1250, 1100, 740. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 4.07 (*d*, *J*(3,10) = 1.0, 2 H–C(3)); 7.46 (*t*, J_o = 7.4, H–C(6)); 7.58 (*d*, J_o = 7.7, H–C(5)); 7.61–7.63 (*m*, H–C(7), H–C(10)); 7.75 (*s*, 4 arom. H (benzonitrile)); 7.93 (*d*, J_o = 7.6, H–C(8)). Anal. calc. for $C_{17}H_{11}NO$ (245.28): C 83.25, H 4.52, N 5.71; found: C 83.56, H 4.79, N 5.53.

*2,3-Dihydro-2-(3,4,5-trimethoxybenzylidene)-1*H*-inden-1-one* (**1b**): Yield 59.6%. M.p. 160–164°. IR (KBr): 3010, 2920, 1690, 1620, 1580, 1500, 1130, 1000, 730. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 3.92 (*s*, MeO–C(14)); 3.94 (*s*, MeO–C(13), MeO–C(15)); 4.03 (*d*, *J*(3,10) = 1.3, 2 H–C(3)); 6.91 (*s*, H–C(12), H–C(16)); 7.45 (*t*, J_o = 7.4, H–C(6)); 7.55–7.63 (*m*, H–C(5), H–C(7), H–C(10)); 7.91 (*d*, J_o = 7.7, H–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$)[1]): 194.06 (C(1)); 153.27 (C(9)); 149.31 (C(13), C(15)); 139.73 (C(2)); 137.9 (C(4)); 134.5 (C(10)); 134.0 (C(6)); 133.66 (C (11)); 130.76 (C(14)); 127.62 (C(7)); 126.08 (C(5)); 124.24 (C(8)); 108.08 (C(12), C(16)); 60.91 (*Me*O–C(14)); 56.15 (*Me*O–C(13), *Me*O–C(15)); 32.10 (C(3)). Anal. calc. for $C_{19}H_{18}O_4$ (310.35): C 73.53, H 5.85; found: C 73.86, H 5.61.

*2,3-Dihydro-2-(4-nitrobenzylidene)-1*H*-inden-1-one* (**1c**): Yield 60.1%. M.p. > 240°. IR (KBr): 3080, 2930, 1690, 1620, 1590, 1335, 1260, 1090, 740. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 4.10 (*d*, *J*(3,10) = 1.7, 2 H–C(3)); 7.47 (*t*, J_o = 7.3, H–C(6)); 7.59 (*d*, J_o = 7.2, H–C(5)); 7.64–7.69 (*m*, H–C(7), H–C(10)); 7.82 (*d*, H–C(13), H–C(15)); 7.94 (*d*, J_o = 7.7, H–C(8)); 8.32 (*m*, H–C(12), H–C(16)). Anal. calc. for $C_{16}H_{11}NO_3$ (265.15): C 72.5, H 4.15, N 5.28; found: C 72.39, H 3.99, N 5.49.

Dimers **2a**–**c**. To a stirred soln. of indan-1-one (0.2 g, 1.51 mmol) in MeOH (25 ml), the aldehyde (1.81 mmol) and KOH (0.13 g, 2.27 mmol) were added. The mixture was further refluxed for a required period of time as specified in the *Table* (TLC monitoring). Excess MeOH was evaporated, dist. H_2O added, and the suspension allowed to stand overnight. The obtained precipitate was filtered, washed thoroughly with dist. H_2O, and air-dried. The crude product was subjected to CC (neutral alumina (25 g), CH_2Cl_2): crystalline **2a**–**c**.

*4,4′-{1′,3,3′,3a,8,8a-Hexahydro-1′,8-dioxospiro[cyclopent[*a*]indene-2(1*H*),2′-[2*H*]-indene]-1,3-diyl}-bis[benzonitrile]* (**2a**): Yield 0.28 g (37.7%). M.p. 158–162°. IR (KBr): 3040, 2925, 2245, 1715, 1610, 1480, 1305, 1110, 1035, 780. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 2.92 (*d*, J_{AB} = 17.3, H_A–C(3′)); 3.03 (*d*, J_{AB} = 17.3, H_B–C(3′)); 3.88 (*d*, *J* = 10.5, H–C(10′)); 3.94 (*dd*, *J* = 8.4, 2.1, H–C(3)); 4.11 (*d*, *J* = 10.7, H–C(10)); 4.58 (*t*, *J* = 9.6, H–C(2)); 7.00 (*t*, 2 H, H–C(16,16′)); 7.32–7.52 (*m*, 12 arom. H); 7.78 (*d*, J_o = 7.0, 2 H, H–C(8,8′)). ^{13}C-NMR (75 MHz, $CDCl_3$)[1]): 206.24 (C(1) or C(1′)); 204.57 (C(1) or C(1′)); 154.69 (C(9) or C(9′)); 151.84 (C(9) or C(9′)); 141.92 (C(4) or C(4′)); 141.69 (C(4) or C(4′)); 136.57 (C(6) or C(6′)); 135.69 (C(6) or C(6′)); 134.96 (C(11,11′)); 132.22 (C(13,13′), C(15,15′)); 129.19 (C(12,12′), C(16,16′)); 125.89 (C(7,7′)); 124.17 (C(5,5′)); 123.67 (C(8,8′)); 118.36 (2 CN); 111.40 (C(14,14′)); 69.85 (C(2′)); 59.02 (C(2)); 58.85 (C(10)); 53.87 (C(10′)); 45.7 (C(3)); 29.3 (C(3′)). EI-MS: 490 (41, M^+), 245 (100, $[C_{17}H_{11}NO]^+$). Anal. calc. for $C_{34}H_{22}N_2O_2$ (490.56): C 83.25, H 4.52, N, 5.71; found: C 82.94, H 4.25, N 6.04.

*1,3,3a,8a-Tetrahydro-1,3-bis(3,4,5-trimethoxyphenyl)spiro[cyclopent[*a*]indene-2(8*H*),2′-[2*H*]indene]-1′,8(3′*H*)-dione* (**2b**): Yield 36.3%. M.p. 205–209°. IR (KBr): 3000, 2930, 2835, 1710, 1590, 1570, 1430, 1240, 1120, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 2.98 (*d*, J_{AB}=17.0, H_A–C(3′)); 3.03 (*d*, J_{AB}=17.0, H_B–C(3′)); 3.66 (*s*, 6 H, MeO–C(14,14′)); 3.72 (*s*, 6 H, MeO–C(15,15′)); 3.74 (*s*, 6 H, MeO–C(13,13′)); 3.76–3.87 (*m*, 2 H, H–C(10′), H–C(3)); 4.06 (*d*, *J*=10.7, H–C(10)); 4.49 (*t*, *J*=9.6, H–C(2)); 6.46 (*s*, 2 H, H–C(16,16′)); 6.48 (*s*, 2 H, H–C(12,12′)); 7.06 (*d*, J_o=7.5, H–C(5) or H–C(5′)); 7.16–7.23 (*m*, H–C(5) or H–C(5′), H–C(7) or H–C(7′)); 7.33 (*t*, J_o=7.4, H–C(7) or H–C(7′)), 7.43 (*t*, J_o=7.2, H–C(6) or H–C(6′)); 7.51 (*t*, J_o=7.4, H–C(6) or H–C(6′)); 7.59 (*d*, J_o=7.5, H–C(8) or H–C(8′)); 7.80 (*d*, J_o=7.4, H–C(8) or H–C(8′)). ^{13}C-NMR (75 MHz, $CDCl_3$)[1]): 208.41 (C(1) or C(1′)); 205.79 (C(1) or C(1′)); 155.61 (C(9) or C(9′)); 153.38 (C(9) or C(9′)); 152.85 (C(13, 13′)); 152.7 (C(14,14′)); 137.49 (C(4) or C(4′)); 135.76 (C(4) or C(4′)); 135.42 (C(15) or C(15′)); 135.02 (C(15) or C(15′)); 132.72 (C(6) or C(6′)); 132.08 (C(6) or C(6′)); 128.47 (C(7) or C(7′)); 127.36 (C(7) or C(7′)); 126.24 (C(5) or C(5′)); 125.37 (C(5) or C(5′)); 124.59 (C(8) or C(8′)); 123.04 (C(8) or C(8′)); 105.66 (C(12,12′)); 105.31 (C(16,16′)); 70.08 (C(2′)); 60.72 (C(2)); 59.16 (C(10)); 56.18 (*Me*O–C(13,13′,15,15′)); 55.88 (*Me*O–C(14,14′)); 53.87 (C(10′)); 45.96 (C(3)); 30.38 (C(3′)). Anal. calc. for $C_{38}H_{36}O_8$ (620.69): C 73.53, H 5.85; found: C 73.26, H 6.03.

*1,3,3a,8a-Tetrahydro-1,3-bis(4-nitrophenyl)spiro[cyclopent[*a*]indene-2(8*H*),2′-[2*H*]indene]-1′,8-(3′*H*)-dione* (**2c**): Yield 25.3%. M.p. 202–206°. IR (KBr): 3070, 2920, 1705, 1610, 1570, 1470, 1310, 1250, 1035, 790. ^{1}H-NMR (75 MHz, $CDCl_3$)[1]): 3.00 (*d*, J_{AB}=17.4, H_A–C(3′)); 3.05 (*d*, J_{AB}=17.4, H_B–C(3′)); 3.78 (*d*, *J*=10.6, H–C(10′)); 4.14 (*d*, *J*=10.5, H–C(10)); 4.40–4.43 (*m*, H–C(3)); 4.65 (*t*, *J*=9.7, H–C(2)); 7.28–7.39 (*m*, 6 H, H–C(5,5′,6,6′,7,7′)); 7.82–7.97 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$)[1]): 207.85 (C(1) or C(1′)); 204.12 (C(1) or C(1′)); 151.26 (C(9) or C(9′)); 149.64 (C(9) or C(9′)); 143.02 (C(11) or C(11′)); 141.69 (C(11) or C(11′)); 136.48 (C(6) or C(6′)); 134.71 (C(6) or C(6′)); 133.42 (C(14,14′)); 131.66 (C(13,13′), C(15,15′)); 129.82 (C(12,12′), C(16,16′)); 124.69 (C(7,7′)); 124.21 (C(5,5′)); 123.67 (C(8,8′)); 71.62 (C(2′)); 58.06 (C(2)); 57.92 (C(10)); 54.48 (C(10′)); 45.88 (C(3)); 29.82 (C(3′)). Anal. calc. for $C_{32}H_{22}N_2O_6$ (530.53): C 72.45, H 4.18, N 5.28; found: C 72.17, H 3.90, N 5.73.

X-Ray Crystallographic Analysis of **2b**[2]). Seed crystals of **2b** ($C_{38}H_{36}O_8$, M_r 620.69) were grown by slow evaporation of a MeOH soln. Subsequent very slow evaporation of the seeded crystals at +4°, also from MeOH, after initial freezing at −20°, produced crystals suitable for X-ray diffraction. A crystal 0.30×0.20×0.20 mm^3 was selected, and intensity data were collected on an *Enraf-Nonius-CCD* diffractometer controlled with the COLLECT software [10], by using monochromated Mo*Kα* radiation, *λ* 0.71073 Å. The diffractometer was equipped with an *Oxford-Cryosystems* 'Cryostreams' cooler [11], enabling the data to be collected at 100 K. The crystals are triclinic, $P\bar{1}$, with unit-cell dimensions *a*=12.212(2) Å, *b*=12.906(3) Å, *c*=21.551(4) Å, *α*=75.85(3)°, *β*=73.97(3)°, *γ*=84.82(3)°, and cell volume=3164.5(11) Å^3. There are 4 molecules per unit cell (2 per asymmetric unit), giving a calculated density of 1.303 Mg/m^3, and a linear absorption coefficient of 0.091 mm^{-1}. In total 37631 integrated reflections were collected, of which 11086 were unique (R(int)=0.1286), completeness of data (to *θ*=25.06°) was 98.8%. The resolution range was 20.00–0.70 Å. The crystal showed no significant variation in intensity during the course of data collection. Data were processed using DENZO [12], correcting for *Lorentz* and polarization effects, and absorption effects were applied using the program SORTAV [13]. The structure was solved by direct methods with the program SHELXS-96 [14] and refined with SHELXL-97 [15] both implemented in the WinGX system of programs [16]. Non-H-atoms were refined anisotropically by full-matrix least-square methods. H-Atoms were added either using peaks in a difference electron density map or geometrically by using the program, and refined, in riding mode if in geometrical locations, and with isotropic temperature factors. Geometrical calculations were made with the programs PARST and PLATON [17] as implemented in WinGX. The programs ORTEP [18] and POV-RAY [19] also as implemented in WinGX were used to prepare *Fig. 2*,*a* and *b*. In the final refinement

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[2]) CCDC-280879 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

cycles, there were 11086 data to 839 parameters, resulting in a final goodness-of-fit on F^2 of 0.927 and final R indices ($I>2\sigma(I)$) of $R_1=0.0605$, $wR_2=0.1147$. The largest and smallest difference electron density regions were 0.335 and -0.267 e·Å^{-3}, respectively.

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