Controlled Generation of Three Contiguous Stereocentres in the Michael Addition of 1-Pyrrolidinocyclohexene to (*E*)-(1-Methyl-2-oxoindolin-3-ylidene)acetophenone

Pilar López-Alvarado,[a] Santiago García-Granda,[b] Carmen Álvarez-Rúa,[b] and Carmen Avendaño*[a]

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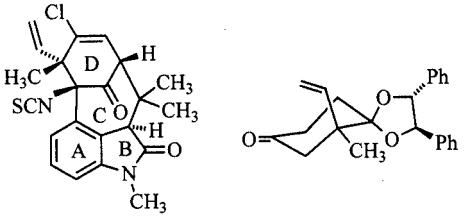
Addition of 1-pyrrolidinocyclohexene to (*E*)-(1-methyl-2-oxoindolin-3-ylidene)acetophenone followed by acid hydrolysis was diastereoselectively controlled to give (±)-**7a** (3*R**,1′*S**,2′*S**) or (±)-**7b** (3*S**,1′*R**,2′*S**), the structures of which were supported by ^{1}H NMR spectroscopic data and corroborated by X-ray diffraction analysis. The change in configuration at the C-2′ centre greatly affected the geometries of the two diastereomers, both in solid and in solution. An explanation of the observed diastereoselectivity is provided. An approach to the *N*-methylwelwitindolinone C skeleton from **7b** as a starting material, by insertion of a rhodium carbenoid into the C(4)–H indole position, was abandoned because of the initial experimental results, which are also described.

Introduction

Certain indole alkaloid natural products and analogous fully synthetic compounds are very active agents for reversal of multiple drug resistance (MDR) in cancer chemotherapy, a problem frequently related to overexpression of P-glycoprotein (P-170), which makes tumour cells resistant not only to the initial chemotherapeutic agent, but also to other clinically useful drugs.[1,2] One of these natural MDR reversal agents, isolated from a variety of blue-green algae, is *N*-methylwelwitindolinone C isothiocyanate (welwistatin, **1**),[3] which has an unusual indole ring-containing structure. It reverses resistance towards vinblastine, taxol, actinomycin D, daunomycin and colchicine at concentrations of about 10^{-7} M, far below its cytotoxicity values.[4]

Among the few published reports of attempted syntheses of welwistatin, formation of the seven-membered *C*-ring spanning C-3 and C-4 of the oxindole system has been envisaged by preparation of the cyclohexanone intermediate **2**, with the desired absolute stereochemistry, through the use of (*R*,*R*)-hydrobenzoin as a chiral auxiliary (Figure 1).[5,6]



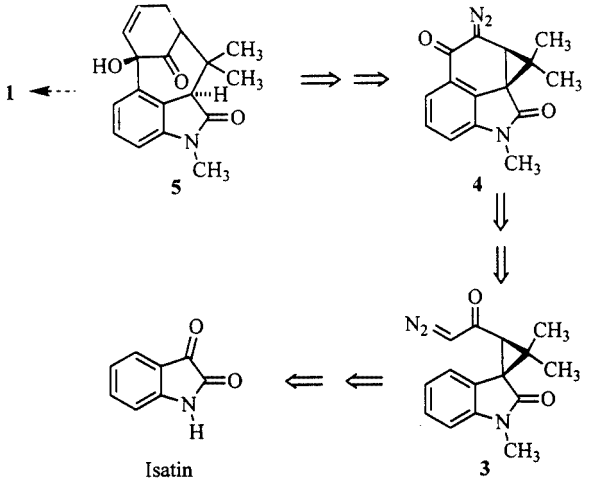
1 **2**

Figure 1. Welwistatin (**1**) and a synthetic intermediate (**2**)

Other approaches have focused on insertion of the chloroolefin and isothiocyanate functions in the final steps, and have established the utility of rhodium carbenoids derived from diazomethyl ketones to achieve the insertion of the methylene carbon atom into the C(4)−H indole position.[7] This methodology was applied to **3** by the use of $Rh_2(TFA)_4$ and Montmorillonite K10 as catalyst to give **4** after oxidation to an α-diketone and regioselective diazotization. Subsequent coupling of the corresponding rhodium carbenoid with allylic alcohols and further manipulation gave the welwistatin skeleton precursor **5** (Scheme 1).[8] Other intramolecular cyclizations of a C(3)-side chain of indole derivatives onto the C(4)-position to make a cyclohepta[*c*,*d*]indole system are also known.[9]

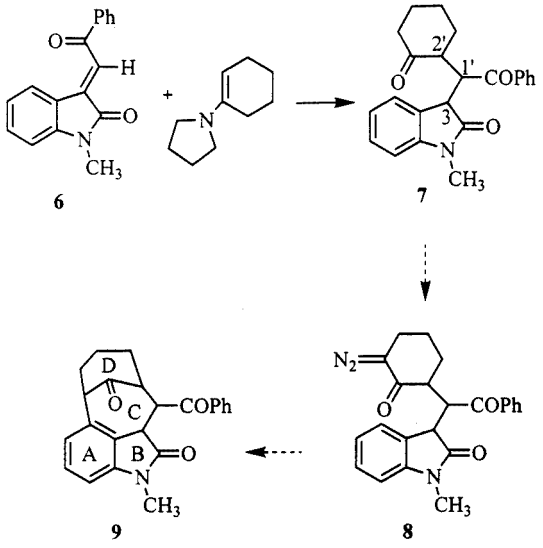
In this context, we planned the synthesis of the indole derivative **7** as a model compound with which to study the accessibility of compound **8** through a diazo transfer reaction on the 4′-formyl or 4′-benzoyl β-diketones. This diazo ketone could enable direct introduction of welwistatin C-D

[a] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense
28040 Madrid, Spain
Fax: (internat.) + 34−91/394 18 22
E-mail: avendano@farm.ucm.es
[b] Departamento de Química Física y Analítica. Facultad de Química. Universidad de Oviedo
33006 Oviedo, Spain



Scheme 1

rings under dirhodium tetraacetate catalysis conditions to give **9** (Scheme 2). Here we report the synthesis of **7** through conjugate addition of 1-pyrrolidinocyclohexene to (*E*)-(1-methyl-2-oxoindolin-3-ylidene)acetophenone (**6**), the geometry of the stereogenic centres thus formed, and initial attempts to obtain **8** by activation of the cyclohexanone α-position.



Scheme 2

Results and Discussion

The addition of 1-pyrrolidinocyclopentene to compound **6**[10] and the hydrolytic cleavage of the reaction products was reported by Tacconi, without attention being paid to the stereochemistry.[11] In that case, "at least two isomers", assumed to be the more and the less substituted enamine, were formed in the first step and, after acid hydrolysis, gave a 1.7:1 mixture of two cyclopentanone "isomers". The only basis for the identification of the two isomers in both enamines and ketones were the differences found in some ^{1}H NMR signals in the crude adducts (enamines recorded at low temperature) and ketones.

When the synthesis of compound **7** was planned, we expected some diastereoselective control in the formation of the stereogenic centres at C-3, C-1′, and C-2′, given the rigidity imposed by the intramolecular stabilization of the zwitterion intermediate **I**.[11] Addition of 1-pyrrolidino-1-cyclohexene to a cooled suspension of **6**[12] in light petroleum ether took place with a change from the original red colour to yellow. After a preliminary study, we found that if this suspension was maintained at 0 °C for 17 hours and the pale yellow precipitate (**IIa**)[13] was filtered and hydrolysed, we obtained a single product (**7a**, 55%) that was different to the one obtained if the suspension was kept for the same time at 25 °C and the dark yellow filtrate (**IIb**)[13] was similarly hydrolysed (room temperature, H_2O/HOAc) (**7b**, 64%).

Spectroscopic studies (^{1}H NMR, $CDCl_3$) showed that the H(2′)-proton in (±)-**7a** was deshielded relative to the same proton in (±)-**7b**, and comparison of the $J_{3\text{-}1'}$ values in the two isomers showed that the torsion angle H(3)−C(3)−C(1′)−H(1′) had to be close to 90° in **7b** (Figure 2). Furthermore, NOE experiments showed that the cyclohexane ring approached the indole system in **7b** (cf. the NOE between the H(4) and the H(2′)-protons), while this position was adopted by the phenyl ring in **7a** [cf. the NOE between the H(4) and the H(2′′)-protons]. This geometry explained the chemical shift of the H(2′)-proton in **7a**, because of the anisotropic effect of the close C(2)=O carbonyl group. All ^{1}H NMR spectroscopic data supported an *unlike* (*u*) stereochemistry for the C(3) and C(1′)-stereocentres in both diastereoisomers, but a *like* (*l*) stereochemistry for the C(1′) and C(2′)-stereocentres in **7a**, which was *unlike* (*u*) in **7b**.

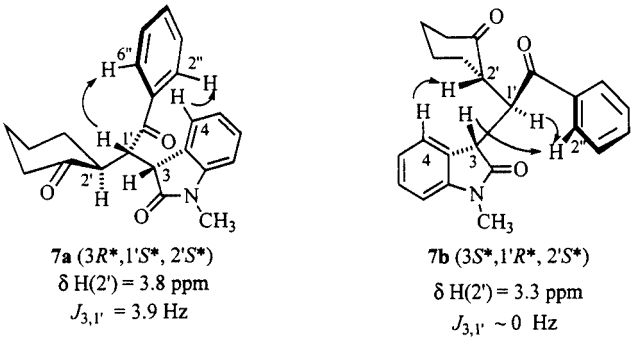


Figure 2. Selected NOEs of compounds **7a** and **7b**

X-ray diffraction analysis of crystals of (±)-**7a** (methanol) and (±)-**7b** (diethyl ether) confirmed the (3*R**,1′*S**,2′*S**) configuration for **7a** and the (3*S**,1′*R**,2′*S**) configuration in **7b** (Figures 3 and 4)[14].

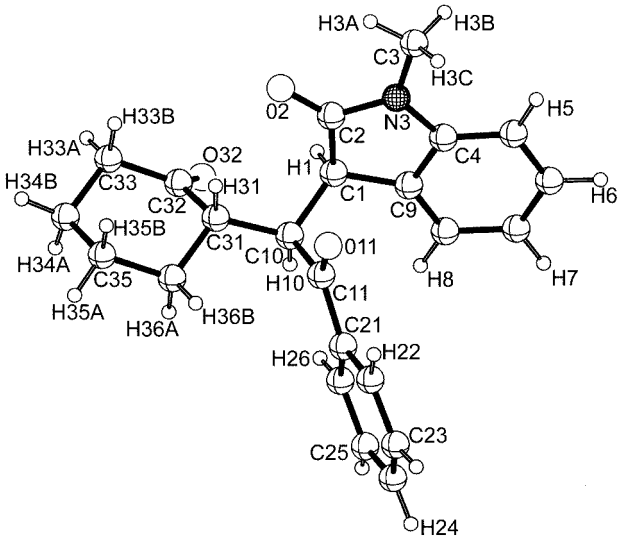


Figure 3. Perspective view of (±)-**7a** with crystallographic numbering

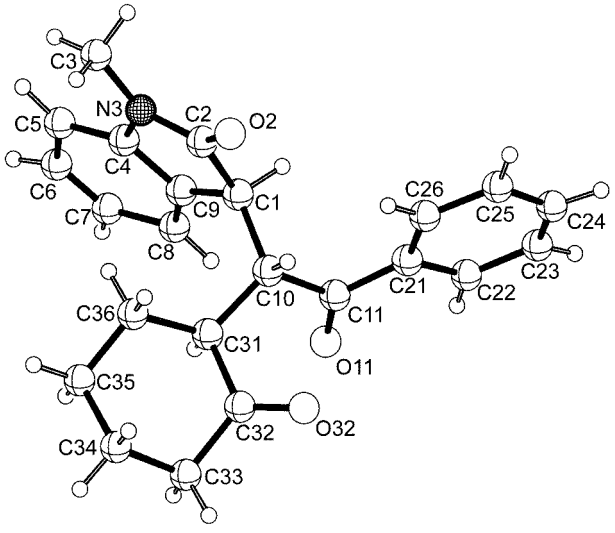
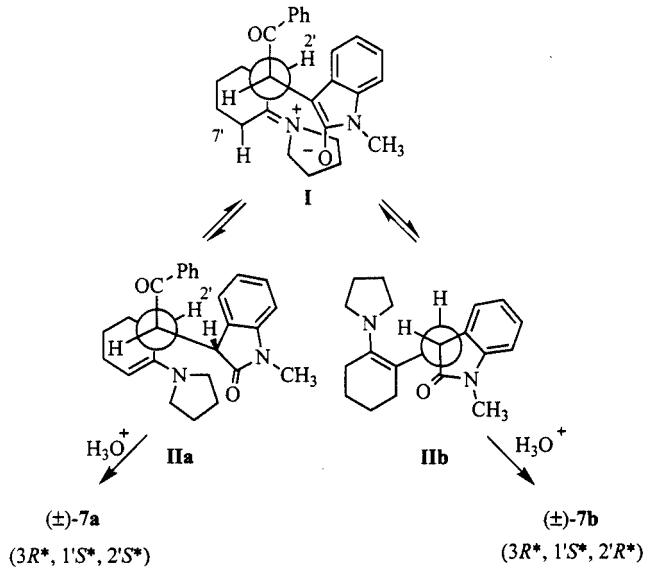


Figure 4. Perspective view of (±)-**7b** with crystallographic numbering

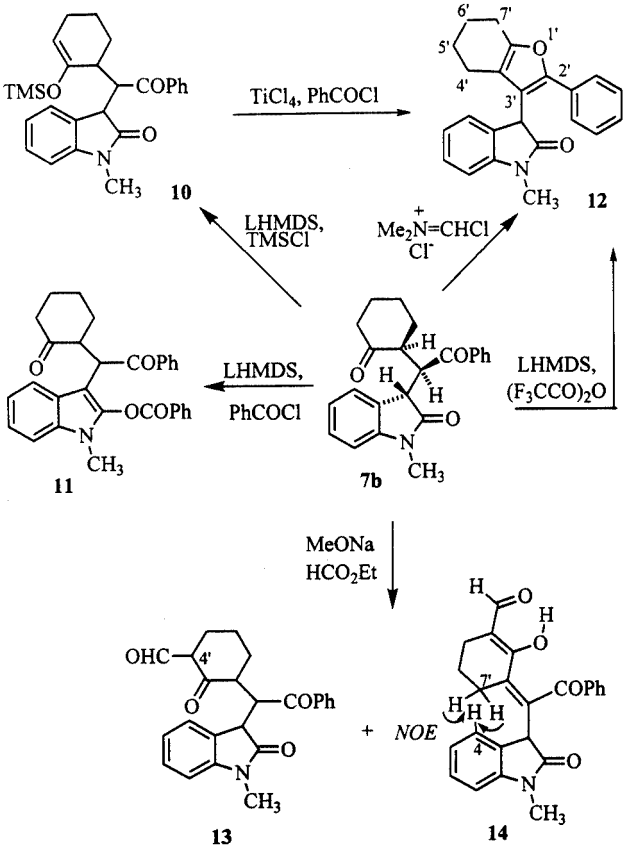
It seems reasonable that a *like* stereochemistry in the C-1′ and C-2′ stereocentres of the zwitterionic intermediate **I**[15] should permit its intramolecular stabilization, with less steric interaction than with the *unlike* stereochemistry (Scheme 3). At low temperature, this intermediate should give enamine **IIa** through elimination of the less hindered H(7′)-proton. In consequence, the hydrolysis product **7a** should have the same relative configuration as zwitterion **I**. At 25 °C, **I** would give the more substituted enamine **IIb** through elimination of the H(2′)-proton, and the stereochemistry of the hydrolysis here would be controlled to give the all *unlike* product **7b**.

Compound **7b** seemed more suitable than **7a** as a precursor of **9** through formation of the C(4)−C(4′) bond, as shown in Scheme 2. Activation of **7b** to obtain its diazo



Scheme 3

derivative **8** through the regioselective acylation of the C(4′)-position[16−18] seemed possible because, in a preliminary experiment, the desired enolate could be trapped as the trimethylsilyl derivative **10**. However, attempts at acylation revealed many difficulties due to the reactivity of the H-1′, H-2′, and H-3 protons (Scheme 4). For instance, the attempted benzoylation of **7b** (LHMDS, benzoyl chloride)



Scheme 4

gave the *O*-acyl derivative **11**, while treatment of **10** with benzoyl chloride in the presence of $TiCl_4$[19] produced dehydration to give **12** through a Paal−Knorr-type condensation. Compound **12** was also formed on attempted activation of the ketone of **7b** with a trifluoroacetyl group [LHMDS, $(F_3CCO)_2O$][20] or with a formyl group under Vilsmeier−Haack conditions.[21] Formylation under basic conditions (NaOMe, HCO_2Et)[22] required large excess of base (up to 8 equivalents)[23] to give the desired 4′-formyl derivative **13** (mixture of tautomers[24]) in low yield. The major product of this reaction (up to 50% after prolonged reaction time) was **14**, which must have been formed through oxidation of the enol tautomer of **13** to give more extended conjugation. NOE experiments on compound **14**, especially the observed enhancement of the H(4)-proton after irradiation of H(7′)-protons, showed that the C(1′)=C(2′) bond had *Z* stereochemistry. At this point, further manipulation of **7b** or **14** to obtain their 4′-diazo derivatives was abandoned.

Conclusion

In conclusion, we have shown that three stereocentres can be generated in a stereocontrolled fashion and, although our synthetic approach to the skeleton of *N*-methylwelwitindolinone C through formation of a bond between the cyclohexanone C(3′)-position into the indole C(4)-position failed, these results are significant in the chemistry of 2-oxo-1,3-dihydroindole compounds.

Experimental Section

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS) were dried and purified by standard techniques. "Petroleum ether" refers to the fraction boiling at 40−60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey−Nagel Alugram Sil G/UV_{254}). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230−40 mesh). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin−Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined in KBr pellets or as films on a NaCl disk. NMR spectra were obtained on Varian Unity 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C), Bruker AC 250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Bruker AC 500 (500 MHz for ^{1}H) spectrometers (Servicio de RMN, Universidad Complutense), with $CDCl_3$ as solvent. Exchangeable assignments are marked with the symbols * and **. Mass spectra were obtained by the Servicio de Espectroscopia, Universidad Complutense. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense. Crystal structures were solved by Direct Methods, using the SHELXS-97 program (Sheldrick, 1990). Anisotropic least-squares refinement was carried out with SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were geometrically placed and refined riding on their parent atoms for **7a**. Hydrogen atoms were located in a difference Fourier map for **7b**. Geometrical calculations were made with PARST (Nardelli, 1983). The crystallographic plots were made with PLATON (Spek, 2001). All calculations were performed at the University of Oviedo on the computers of the Scientific Computer Centre and the X-ray group.

Treatment of (*E*)-(1-Methyl-2-oxoindolin-3-ylidene)acetophenone (6) with 1-Pyrrolidinocyclohexene: 1-Pyrrolidino-1-cyclohexene (1.22 mL, 7.60 mmol, 2equiv.) was added to a cooled, stirred suspension of **6**[11] (1 g, 3.80 mmol) in petroleum ether (25 mL). Cooling and stirring were maintained until the starting material had disappeared and a pale yellow precipitate had formed (30 min). This suspension was maintained at 0 °C for 17 h, and the pale yellow precipitate was filtered off and washed with cold petroleum ether (15 mL) to give 1.110 g (70%) of enamine **IIa**. When the initial pale yellow mixture was maintained at 25 °C for 17 h, a dark yellow precipitate was formed. The solid was filtered off and washed with cold petroleum ether (15 mL) to give 1.237 g (79%) of enamine **IIb.**

Hydrolytic Cleavage of Enamines IIa and IIb: The solid enamines **IIa** or **IIb** were slowly added to a cooled and stirred mixture of acetic acid (6 mL) and water (1 mL). The resulting brown solutions were stirred at 0 °C for 30 min and then for 10 min at room temperature. A further 10 mL of water was added, and the solution was extracted with dichloromethane (3 × 25 mL). Solid sodium hydrogen carbonate was cautiously added, with stirring, to the aqueous fractions until neutralization was achieved, and they were again extracted with CH_2Cl_2 (25 mL). The combined organic layers were stirred with more solid sodium hydrogen carbonate for 30 min, dried (Na_2SO_4), filtered, evaporated under reduced pressure, and washed with diethyl ether (10 mL), yielding 0.750 g (78% from enamine **IIa**, 55% from **6**) of pure compound (±)-(3*R**,1′*S**,2′*S**)-**7a** or 0.873 g (81% from enamine **IIb**, 64% from **6**) of pure compound (±)-(3*S**,1′*R**,2′*S**)-**7b**, as white solids.

Data for 7a: $C_{23}H_{23}NO_3$ (361.4): calcd. C 76.43, H 6.41, N 3.87, found C 76.13, H 6.14, N 4.04; m.p. 164−165 °C (methanol); IR (KBr): $\tilde{\nu}$ = 1708, 1678, 1612 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 7.90 (dd, *J* = 7.1, 1.5 Hz, 2 H, H$^{2'',6''}$), 7.51 (t, *J* = 7.3 Hz, 1 H, H$^{4''}$), 7.39 (t, *J* = 7.1 Hz, 2 H, H$^{3'',5''}$), 7.22 (d, *J* = 7.4 Hz, 1 H, H^4), 7.12 (t, *J* = 7.8 Hz, 1 H, H^6), 6.82 (m, 1 H, H^5), 6.70 (d, *J* = 7.8 Hz, 1 H, H^7), 4.72 (dd, *J* = 10.0, 3.9 Hz, 1 H, H$^{1'}$), 3.88−3.77 (m, 1 H, H$^{2'}$), 3.81 (d, *J* = 3.9 Hz, 1 H, H^3), 3.24 (s, 3 H, *N*-CH_3), 2.45−2.29 (m, 2 H, H$^{4'}$), 2.08−2.03 (m, 1 H, H$^{5'ax}$), 1.85−1.78 (m, 1 H, H$^{7'ax}$), 1.68−1.55 (m, 3 H, H$^{5'eq,6'}$), 1.34−1.18 (m, 1 H, H$^{7'eq}$); δ_C ($CDCl_3$, 63 MHz): 212.25 (C$^{3'}$), 201.05 (*C*O-Ph), 177.01 (C^2), 144.52 (C^{7a}), 137.50 (C$^{1''}$), 133.32 (C$^{4''}$), 128.63 (C$^{3'',5''}$), 128.31 (C$^{2'',6''}$), 127.89 (C^6), 126.38 (C^{3a}), 123.75 (C^4), 121.61 (C^5), 107.83 (C^7), 49.34 (C$^{2'}$), 45.61 (C$^{1'}$), 44.37 (C^3), 42.42 (C$^{4'}$), 33.97 (C$^{7'}$), 28.78 (C$^{5'}$), 26.10 (CH_3), 25.33 (C$^{6'}$).

Data for 7b: . $C_{23}H_{23}NO_3$ (361.4): calcd. C 76.43, H 6.41, N 3.87; found C 76.24, H 6.64, N 3.83; m.p. 171−172 °C (diethyl ether); IR (KBr): $\tilde{\nu}$ = 1711, 1682, 1612 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 8.14 (dd, *J* = 8.4, 1.3 Hz, 2 H, H$^{2'',6''}$), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1 H, H$^{4''}$), 7.46 (tt, *J* = 8.4, 1.8 Hz, 2 H, H$^{3'',5''}$), 7.33 (d, *J* = 7.6 Hz, 1 H, H^4), 7.26 (m 1 H, H^6), 6.98 (td, 1 H, *J* = 7.6, 0.9 Hz, H^5), 6.80 (d, *J* = 7.8 Hz, 1 H, H^7), 4.56 (dd, *J* = 10.6, 2.0 Hz, 1 H, H$^{1'}$), 3.58 (br. s, 1 H, H^3), 3.40−3.24 (m, 1 H, H$^{2'}$), 3.21 (s, 3 H, *N*-CH_3), 2.30−2.26 (m, 2 H, H$^{4'}$), 2.10−1.90 (m, 1 H, H$^{5'ax}$), 1.66−1.61 (m, 1 H, H$^{6'}$), 1.57−1.41 (m, 1 H, H$^{5'eq}$), 1.37−1.21 (m, 3 H, H$^{6',7'ax,7'eq}$); δ_C ($CDCl_3$, 63 MHz): 211.34 (C$^{3'}$), 201.05 (*C*O-Ph), 175.79 (C^2), 143.72 (C^{7a}), 135.71 (C$^{1''}$), 132.90

($C^{4''}$), 128.63 and 128.61 ($C^{2'',6''}$ and $C^{3'',5''}$), 128.29 (C^6), 124.99 (C^4), 124.78 (C^{3a}), 122.50 (C^5), 108.08 (C^7), 50.46 ($C^{2'}$), 44.72 ($C^{1'}$), 43.99 (C^3), 41.90 ($C^{4'}$), 30.45 ($C^{7'}$), 27.82 ($C^{5'}$), 26.40 (CH_3), 25.07 ($C^{6'}$).

X-Ray Experimental and Crystal Data for 7a and 7b[25−28]

Data for 7a: $C_{23}H_{23}NO_3$, monoclinic, space group $P2_1/n$, a = 10.858(7), b = 16.39(1), c = 11.097(6) Å, β = 103.17(6) °, V = 1923(2) Å^3, Z = 4, Dx = 1.248 Mg·m^{-3}, μ (Mo-$K\alpha$) = 0.082 mm^{-1}. Crystal dimensions 0.25 × 0.20 × 0.15 mm. λ = 0.71073 Å (Mo-$K\alpha$ radiation, Nonius CAD-4 single crystal diffractometer). Data collection at 293 K, ω-2θ scan mode, 2.2 < 2θ < 26°, h 0 → 13, k 0 → 20, l −13 → 13. Multiple observations were averaged, R_{merge}= 0.1887, resulting in 3772 unique reflections of which 827 were observed with $I > 2\sigma(I)$. The final cycle of full-matrix, least-squares refinement based on 3772 reflections and 220 parameters converged to a final value of $R1[F^2>2\sigma(F^2)]$ = 0.1294, $wR2$ $[F^2>2\sigma(F^2)]$ = 0.4114, $R1(F^2)$ = 0.4076, $wR2(F^2)$ = 0.5027. Final difference Fourier maps showed no peaks higher than 0.523 e·Å^{-3} nor deeper than −0.337 e·Å^{-3}.

Data for 7b: $C_{23}H_{23}NO_3$, monoclinic, space group $P2_1/n$, a = 10.5644(1), b = 11.7887(1), c = 15.1836(1) Å, β = 95.8795(7) °, V = 1881.03(3) Å^3, Z = 4, Dx = 1.276 Mg·m^{-3}, μ(Cu-K_α) = 0.674 mm^{-1}. Crystal dimensions 0.35 × 0.35 × 0.25 mm. λ = 1.5418 Å (Cu-K_α radiation, Nonius KappaCCD single crystal diffractometer). Data collection at 200 K, φ and ω scans, 4.8 < 2θ < 69.8°, h −12 → 12, k −14 → 14, l −18 → 18. Multiple observations were averaged, R_{merge}= 0.047, resulting in 3516 unique reflections of which 3527 were observed with $I > 2\sigma(I)$. Final mosaicity was 0.504°. All data completeness was 94%. Intensity − error ratio for all reflections was 244.5:5.5. The final cycle of full-matrix, least-squares refinement based on 3516 reflections and 336 parameters converged to a final value of $R1[F^2>2\sigma(F^2)]$ = 0.0408, $wR2$ $[F^2>2\sigma(F^2)]$ = 0.1072, $R1(F^2)$ = 0.0431, $wR2(F^2)$ = 0.1090. Final difference Fourier maps showed no peaks higher than 0.156 e·Å^{-3} nor deeper than −0.171 e Å^{-3}.

Preparation of the Trimethylsilyl Derivative 10: A solution of LHMDS (1 M, 10 mL, 10 mmol, 3.6 equiv.) in THF was added dropwise by cannula at −20 °C, under an argon atmosphere, to a solution of **7b** (1 g, 2.77 mmol) in dry THF (20 mL). The solution was stirred for 2 min, and a centrifuged mixture of TMSCl/triethylamine (3.7 mL, 29.1 mmol, 10.5 equiv. of TMSCl and 5.4 mL, 38.8 mmol, 14 equiv. of triethylamine) was added. After 1 h, the reaction mixture was quenched with water (100 mL), extracted with diethyl ether (3 × 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a viscous solid. Petroleum ether (25 mL) was added, and stirring gradually changed the oily precipitate into a crystalline solid, which was filtered off to yield 1.152 g (96%) of the trimethylsilyl enol ether **10** as a white solid. $C_{26}H_{31}NO_3Si$ (433.6): calcd. C 72.05, H 7.21, N 3.23, found 72.11, H 7.40, N 3.51; m.p. 116−118 °C; IR (KBr): ṽ = 1714, 1685, 1612 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 7.88 (d, J = 7.3 Hz, 2 H, $H^{2'',6''}$), 7.48−7.32 (m, 4 H, $H^{4,3'',4'',5''}$), 7.18 (t, J = 7.8 Hz, 1 H, H^6), 6.88 (m, 1 H, H^5), 6.73 (d, J = 7.8 Hz, 1 H, H^7), 4.75 (m, 1 H, $H^{4'}$), 4.35 (dd, J = 10.0, 2.5 Hz, 1 H, $H^{1'}$), 3.54 (br. s, 1 H, H^3), 3.20 (s, 3 H, N-CH_3), 3.20−3.00 (m, 1 H, $H^{2'}$), 2.00−1.85 (m, 2 H, $H^{5'}$), 2.65−1.30 (m, 4 H, $H^{6',7'}$), −0.13 (s, 9 H, TMS); δ_C ($CDCl_3$, 63 MHz): 200.75 (*C*O-Ph), 176.19 (C^2), 151.14 ($C^{3'}$), 144.06 (C^{7a}), 137.27 ($C^{1''}$), 132.27 ($C^{4''}$), 128.46 and 128.11 ($C^{2'',6''}$ and $C^{3'',5''}$), 127.81 (C^6), 126.31 (C^{3a}), 124.80 (C^4), 121.95 (C^5), 107.66 (C^7), 104.33 ($C^{4'}$), 48.74, 44.57, 39.41, 26.26, 23.98, 21.36 ($C^{1'}$, $C^{2'}$, C^3, $C^{5'}$, $C^{6'}$, $C^{7'}$), 26.20 (CH_3), −0.36 [Si(*C*H$_3$)].

Activation of 7b by Benzoylation or Formylation

Treatment of 7b with LHMDS and Benzoyl Chloride. Synthesis of 11: A solution of LHMDS (1 M, 0.41 mL, 0.41 mmol, 1.5 equiv.) in THF was added dropwise by cannula at −20 °C, under an argon atmosphere, to a solution of **7b** (0.1 g, 0.277 mmol) in dry THF (2 mL). After the mixture had been stirred for 2 min and cooled to −78 °C, benzoyl chloride (0.035 mL, 0.304 mmol, 1.1 equiv.) was added. After 10 min at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), extracted with diethyl ether (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an orange oil. Chromatography (90% petroleum ether/Et_2O) yielded 0.112 g (87%) of compound **11** as a white solid. $C_{30}H_{27}NO_4$ (465.5): calcd. C 77.40, H 5.85, N 3.01, found C 77.23, H 5.64, N 2.99; m.p. 162−164 °C. IR (KBr): ṽ = 1753, 1707, 1683 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 8.25 (dd, J = 7.2, 1.3 Hz, 2 H, $H^{2'',6''}$), 8.00 (d, J = 7.2 Hz, 2 H, $H^{2,6}$-PhCOO-), 7.75 (t, J = 7.9 Hz, 2 H, $H^{3'',5''}$), 7.61 (t, J = 7.2 Hz, 2 H, $H^{3,5}$-PhCOO-), 7.43 (tt, J = 7.4, 2.2 Hz, 1 H, H^4-PhCOO-), 7.35−7.29 (m, 2 H, H^4 and $H^{4''}$), 7.22−7.12 (m, 3 H, H^5, H^6 and H^7), 4.92 (d, J = 10.6 Hz, 1 H, $H^{1'}$), 3.90−3.60 (m, 1 H, $H^{2'}$), 3.47 (s, 3 H, N-CH_3), 2.52−2.25 (m, 2 H, $H^{4'}$), 2.09−2.07 (m, 1 H, $H^{5'ax}$), 1.92−1.87 (m, 1 H, $H^{7'ax}$), 1.80−1.72 (m, 1 H, $H^{5'eq}$), 1.70−1.50 (m, 3 H, $H^{6',7'eq}$); δ_C ($CDCl_3$, 63 MHz): 212.73 ($C^{3'}$), 197.46 (*C*O-Ph), 164.20 (C^2-Ph*C*OO-), 140.46 (C^{7a}), 136.66* (C^1-PhCOO-), 134.58 (C^4-PhCOO-), 133.10* ($C^{1''}$), 132.29 ($C^{4''}$), 130.51 ($C^{2,6}$-Ph*C*OO-), 128.93, 128.46, and 128.12 ($C^{2'',6''}$, $C^{3'',5''}$, and $C^{3,5}$-PhCOO-), 127.52 (C^{3a}), 121.58 (C^4), 120.14 (C^5), 109.07 (C^7), 95.39 (C^3), 51.54 ($C^{2'}$), 42.90 ($C^{1'}$), 42.19 ($C^{4'}$), 32.02 ($C^{7'}$), 28.57 (CH_3), 28.33 ($C^{5'}$), 25.45 ($C^{6'}$). The signals due to C^2 and C^6 could not be detected.

Treatment of 10 with Benzoyl Chloride and Titanium (IV) Chloride. Synthesis of 12: A solution of titanium (IV) chloride in dry dichloromethane (0.138 mL, 0.138 mmol, 1 equiv.) was added under an argon atmosphere to cooled benzoyl chloride (0.023 g, 0.166 mmol, 1.2 equiv.), followed shortly by the dropwise addition of trimethylsilyl enol ether **10** (0.060 g, 0.138 mmol) in dry dichloromethane (0.15 mL). After having been stirred for 1 h at 0 °C, the reaction mixture was quenched with water (10 mL), extracted with dichloromethane (3 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 45 mg (95%) of furan **12**. $C_{23}H_{21}NO_2Si$ (371.5): calcd. C 80.44, H 6.16, N 4.08, found C 80.12, H 6.17, N 4.00; m.p. 146−147 °C. IR (KBr): ṽ = 1716, 1611 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 7.73 (br. s, 2 H, $H^{2'',6''}$), 7.40 (t, J = 7.2 Hz, 2 H, $H^{3'',5''}$), 7.32−7.24 (m, 2 H, $H^{4'',6}$), 7.12 (d, J = 7.3 Hz, 1 H, H^4), 7.01 (t, J = 7.3 Hz, 1 H, H^5), 6.85 (d, J = 7.7 Hz, 1 H, H^7), 4.88 (s, 1 H, H^3), 3.27 (s, 3 H, N-CH_3), 2.59−2.54 (m, 2 H, $H^{7'}$), 1.77−1.66 and 1.50−1.35 (2 m, 6 H, $H^{4'}$, $H^{5'}$, $H^{6'}$); δ_C ($CDCl_3$, 63 MHz): 175.94 (C^2), 150.62 ($C^{2'}$), 144.02 (C^{7a}), 131.18 ($C^{1''}$), 128.55 ($C^{3'',5''}$), 128.34 (C^{3a}), 128.20** ($C^{4''}$), 127.42** (C^6), 126.48 ($C^{2'',6''}$), 124.48 (C^4), 122.63 (C^5), 117.88* ($C^{3'}$), 114.79* ($C^{3a'}$), 107.91 (C^7), 43.24 (C^3), 26.36 (CH_3), 23.09, 22.52, 22.48, and 20.22 ($C^{4'}$, $C^{5'}$, $C^{6'}$, $C^{7'}$). The signal due to $C^{7a'}$ could not be detected. MS (EI): 343 [M$^+$].

Attempted Formylation under Vilsmeier−Haack Conditions. Synthesis of 12: A solution of (chloromethylene)dimethylammonium chloride (39 mg, 0.347 mmol, 1.25 equiv.) in dry dichloromethane (1 mL), was added dropwise by cannula at room temperature, under an argon atmosphere, to a solution of **7b** (0.1 g, 0.277 mmol) in dry dichloromethane (2 mL). The solution was stirred for 5 h and was then quenched with saturated aqueous sodium hydrogen carbonate (10 mL), extracted with dichloromethane (3 × 50 mL),

dried (Na_2SO_4), and concentrated under reduced pressure to yield 95 mg (100%) of furan **12**.

Attempted Activation with a Trifluoroacetyl Group (LHMDS, $(F_3CCO)_2O$). Synthesis of 12: A solution of LHMDS (1 M, 1 mL, 1 mmol, 3.7 equiv.) in THF was added dropwise by cannula at −20 °C, under an argon atmosphere, to a solution of **7b** (0.1 g, 0.277 mmol) in dry THF (1 mL). After the mixture had been stirred for 2 min and cooled to −78 °C, trifluoroacetyl anhydride (0.156 mL, 1.108 mmol, 4 equiv.) was added. After 10 min at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), extracted with diethyl ether (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an orange oil. Chromatography (90% petroleum ether/Et_2O) yielded 0.027 g (28%) of **12** and 0.043 g (43%) of recovered starting material.

Formylation under Basic Conditions (MeONa, HCO_2Et). Synthesis of 13 and 14: A solution of **7b** (75 mg, 0.208 mmol) in anhydrous benzene (3 mL) was added dropwise by cannula at room temperature, under an argon atmosphere, to a suspension of sodium methoxide (96 mg, 1.77 mmol, 8.5 equiv.) in the same solvent (1 mL). The reaction mixture turned dark red and was cooled to 0 °C. After 10 min, ethyl formate (127 mg, 1.72 mmol, 8.3 equiv.) was introduced, and stirring was maintained at room temperature for 4 h. Diethyl ether (50 mL) was then added, and the suspension was washed with water (2 × 25 mL). The ethereal solution was dried (Na_2SO_4), and concentrated under reduced pressure to yield 15 mg (18%) of **13** and 40 mg (50%) of **14**. Data for **13** (major tautomer): NMR: δ_H ($CDCl_3$, 250 MHz): 13.95 (d, J = 9.8 Hz, 1 H, CHO), 7.94 (d, J = 7.2 Hz, 2 H, $H^{2'',6''}$), 7.23−7.15 (m, 4 H, $H^{3'',5''}$, $H^{4''}$, H^6), 7.02−6.69 (m, 3 H, H^4, H^5, H^7), 4.77 (dd, J = 10.0, 2.4 Hz, 1 H, $H^{1'}$), 4.17 (d, J = 1 0.0 Hz, 1 H, H^3), 3.45−3.35 (m, 1 H, $H^{2'}$), 3.07 (s, 3 H, N-CH_3), 2.74−2.49, 2.33−2.14, 2.01−1.65, 1.51−1.13 (4 m, 6 H, $H^{5',6',7'}$). The $H^{4'}$-signal could not be clearly assigned. Data for **14**: $C_{24}H_{21}NO_4$ (387.4): calcd. C 74.40, H 5.46, N 3.61, found C 74.61, H 5.58, N 3.53; m.p. 190−192 °C. IR (KBr): $\tilde{\nu}$ = 3353, 1725, 1627 cm^{-1}; NMR: δ_H ($CDCl_3$, 250 MHz): 10.10 (s, 1 H, CHO), 7.61−7.57 (m, 2 H, $H^{2'',6''}$), 7.50−7.39 (m, 3 H, $H^{3'',5''}$ and $H^{4''}$), 7.30 (m, 1 H, H^6), 6.99 (m, 1 H, H^5), 6.83 (d, J = 7.8 Hz, 1 H, H^7), 6.64 (d, J = 7.5 Hz, 1 H, H^4), 6.47 (br. s, 1 H, OH), 4.16 (s, 1 H, H^3), 3.24 (s, 3 H, N-CH_3), 2.40−2.19 (m, 2 H, $H^{5'}$), 1.74−1.70 (m, 2 H, $H^{7'}$), 1.55−1.50 (m, 2 H, $H^{6'}$); δ_C ($CDCl_3$, 63 MHz): 188.09 (CHO), 175.24 (C^2, $C^{3'}$), 168.35 (*C*O-Ph), 143.82 (C^{7a}), 138.86* ($C^{4'}$), 137.85* ($C^{2'}$), 132.61 ($C^{1''}$), 129.31 ($C^{4''}$), 128.99 (C^6), 128.57 ($C^{3'',5''}$), 125.92 ($C^{2'',6''}$), 125.20 (C^{3a}), 124.37 (C^4), 123.30 (C^5), 113.55** ($C^{1'}$), 110.60** ($C^{3'}$), 108.80 (C^7), 43.99 (C^3), 26.71 (CH_3), 22.35 ($C^{7'}$), 21.39 ($C^{6'}$), 19.41 ($C^{5'}$). MS (EI): 387 [M^+].

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