Diastereoselective Synthesis of 3-Oxo-14,15-dihydroandranginine

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Synthesis of 3-oxo-14,15-dihydroandranginine (**3**) is detailed based on Diels−Alder reaction of 5-ethenyl-*N*-[[(*tert*-butyldimethylsilyl)oxy]ethyl]-3,4-dihydropyridin-2-one (**11b**) and methyl *N*-(*p*-methoxybenzensulfonyl)indole-2-(2-propenoate) (**9**). This represents the first synthesis of the skeleton of (±)-andranginine **1**.

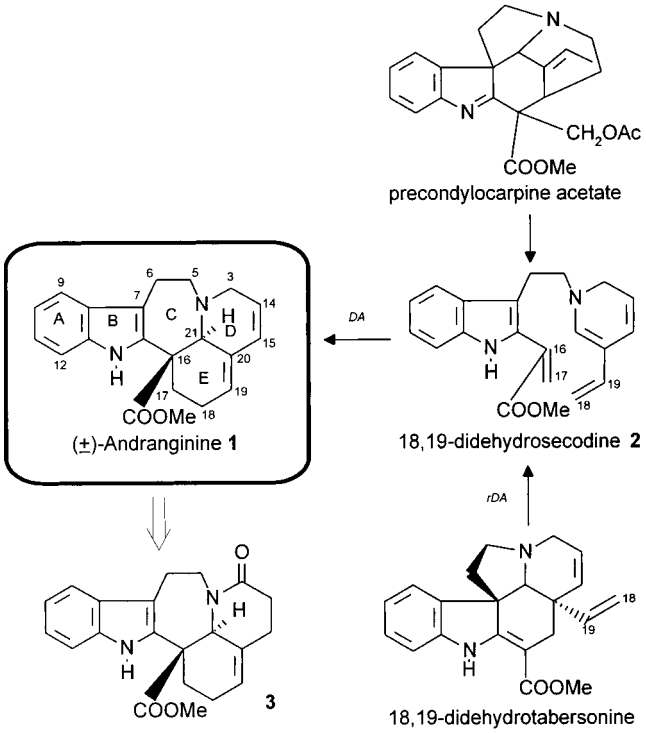
Introduction

(±)-Andranginine (**1**), isolated from *Craspidosperma verticillatum* in 1974,[1] is a unique indole alkaloid in that it possesses an unusual ring system that includes a tetrahydroazepine unit condensed with an hexahydroquinoline moiety in a *trans*−*trans* fashion.[2] It has been suggested[1] that andranginine is formed *in vivo* by the regioselective intramolecular [4 + 2]π cyclization of a didehydrosecodine **2** (Scheme 1) formally derived from precondilocarpine acetate, a key intermediate in the biosynthetic pathway of monoterpenoid indole alkaloids. The pivotal role of **2** in the formation of **1** was later confirmed by Langlois,[3] who converted 18,19-didehydrotabersonine into andranginine through a tandem thermally induced retro-Diels−Alder Diels−Alder sequence.

Probably due to the unique architecture of the tricyclic CDE substructure this alkaloid has, to date, remained synthetically inaccessible.[4] The structural uniqueness of andranginine in addition to its as yet unknown biological function make it an attractive target for synthesis.

In pursuing our interest in the total synthesis of indole alkaloids,[5] we have devised three strategies for the first construction of the andranginine skeleton. All these strategies have as target 3-oxo-14,15-dihydroandranginine and are based on a [4 + 2]π cyclization as the crucial step. The difference is the order of construction of rings C, D, and E. Our retrosynthetic analyses are reported in Scheme 2. In the first analysis (path a) it was logical to disconnect[6] the C16/C21 and C17/C18 bonds by an intramolecular Diels−Alder transformation, emulating the biogenetic hypothesis. The ene-diene intermediate **4** could derive from **5** by dehydrogenation. In the second approach (path b) we disconnected the N4/C3 and C14/C20 bonds by an aza-annulation involving the intermediate **6** that could be derived from **7** through imine formation. We envisioned that the protected indolylcyclohexenol **8**, whose preparation we recently described,[7] would serve as a suitable precursor of amino ketone **7** by way of nitroethylenation. In the third (path c) the C7/C6 bond was first disconnected, giving the indolylhydroquinoline **10**. We anticipated that **10** could then be assembled by an intermolecular Diels−Alder reaction involving an indole acrylate **9** and an *N*-substituted 5-ethenyldihydropyridinone **11**.[7] The synthetic approaches following the first and the second analyses were abandoned owing to the difficulty associated with the controlled elaboration of advanced intermediates to the final target. They are presented but discussed only briefly. The third approach was successfully developed to obtain **3**, and it is the main subject of this report.

Scheme 1



Results and Discussion

Strategy a. We recently reported the total synthesis of 3-oxovincadifformine ethyl ester **16** (Scheme 3) by

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Kan-Fan, C.; Massiot, G.; Ahond, A.; Das, B. C.; Husson, H.-P.; Potier, P.; Scott, A. I.; Wei, C.-C. *J. Chem. Soc., Chem. Commun.* **1974**, 164.

(2) The correct stereochemistry of **1** was elucidated in a second step after the first *cis*−*trans* assignment: (a) Massiot, G.; Kan, S. K.; Gonord, P.; Duret, C. *J. Am. Chem. Soc.* **1975**, *97*, 3277. (b) Riche, P. C.; Pascard-Billy, C. *Acta Crystallogr.* **1979**, *B35*, 666.

(3) Andriamialisoa, R. Z.; Diatta, L.; Rasoanaivo, P.; Langlois, N.; Potier, P. *Tetrahedron* **1975**, *31*, 2347.

(4) Saxton reported the total synthesis of 18,19-didehydrotabersonine also as a formal synthesis of andranginine: Blowers, J. W.; Saxton, J. E.; Swanson, A. G. *Tetrahedron* **1986**, *42*, 6071.

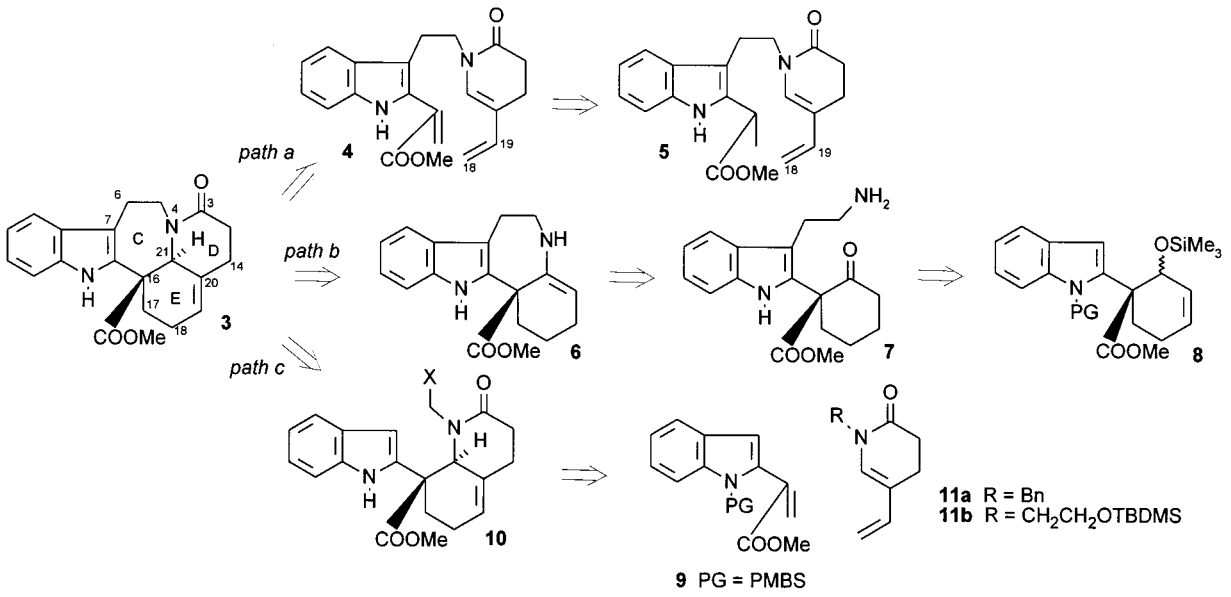
(5) (a) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Pyuskyulev, B.; Mai Ngoc, T. *J. Org. Chem.* **1994**, *59*, 5810. (b) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506. See also refs 8a,b,c.

(6) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; J. Wiley: New York, 1989

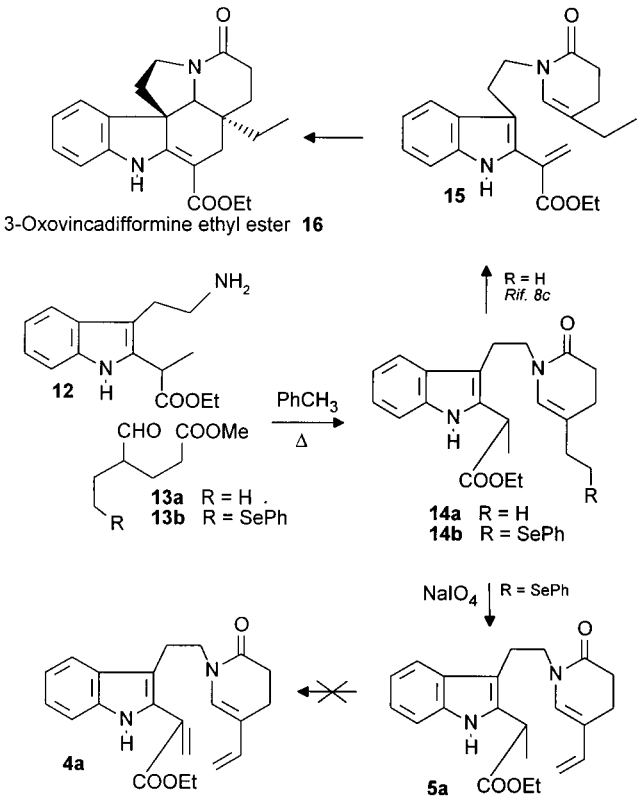
(7) Danieli, B.; Lesma, G.; Luzzani, M.; Passarella, D.; Silvani, A. *Tetrahedron* **1996**, *52*, 11291.

S0022-3263(97)00370-8 CCC: $14.00

Scheme 2. Retrosynthetic Analysis of the 3-Oxo-14,15-dihydroandranginine



Scheme 3



thermal cyclization of 3-oxosecodine **15**.[8c] We selected the less reactive ethoxycarbonyl and not the methoxycarbonyl function in order to inhibit spontaneous lactamization[9] of **12**. In the same manner we planned to prepare the secodine **4a**. Condensation of tryptamine derivative **12**[8c] and methyl selenophenyl formylhexanoate **13b**[10] afforded the lactam **14b** that was converted by conventional procedure to 3-oxo-16,17-dihydro-18,19-didehydrosecodine ethyl ester **5a**. Unfortunately reaction of **5a** with BSA[8] gave an unseparable mixture of unidentified products, determining our decision to abandon this strategy. The course of the oxidation reaction can be rationalized by taking into account the competition of C18−C19 double bond toward electrophilic species ($PhSe^+$).

Strategy b. In the second approach we wanted to construct first the C ring and then the D ring starting from compounds **8**[7] (Scheme 4). The mixture of derivatives **19** was obtained in a straightforward manner from **8**. Exposure of **19** to *N*,*N*-dimethyl-2-nitroethenamine in the presence of trifluoroacetic acid[11] allowed the introduction of the nitroethylene side-chain at C-7 to give derivatives **20**. $NaBH_4$ reduction, hydrolysis of acetate group by K_2CO_3, and PCC[12a] oxidation gave compound **23**. Disappointingly all attempts to obtain **7** proved unsuccessful. In particular the catalytic hydrogenation of **23** gave only an unseparable mixture in which amino ketone **7**, enamine **6**, and the corresponding 20,21-dihydro derivative could be detected by spectral analysis.

Strategy c. We reconsidered our strategy and focused our attention on constructing the C ring in the last step by formation of the C6/C7 bond. We recently reported[7] an approach to the tetracyclic ABDE substructure of andranginine by Diels−Alder reaction between methyl (*p*-methoxybenzenesulfonyl)indole-2-(2-propenoate) (**9**) and 5-ethenyl-*N*-benzylpyridinone (**11a**) (Scheme 2). In order to have a more direct access to the target structure, we studied the preparation of the diene **11b** that presents the N4 proper chain for the successive formation of C ring. The synthesis of **11b** was achieved starting from 3-butyn-2-one **25** that was subjected to reaction with amine **25** at 0 °C and subsequentely with acryloyl chloride to obtain the ketone **26**[13,14] (Scheme 5). Reduc-

(8) Benzeneseleninic anhydride (BSA) has been successfully used as selective oxidant for the synthesis and modification of indole alkaloids: (a) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909. (b) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 155. (c) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Silvani, A. *Tetrahedron* **1994**, *50*, 6941. (d) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347. (e) Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, 61, 7873.

(9) See also Mahbobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034.

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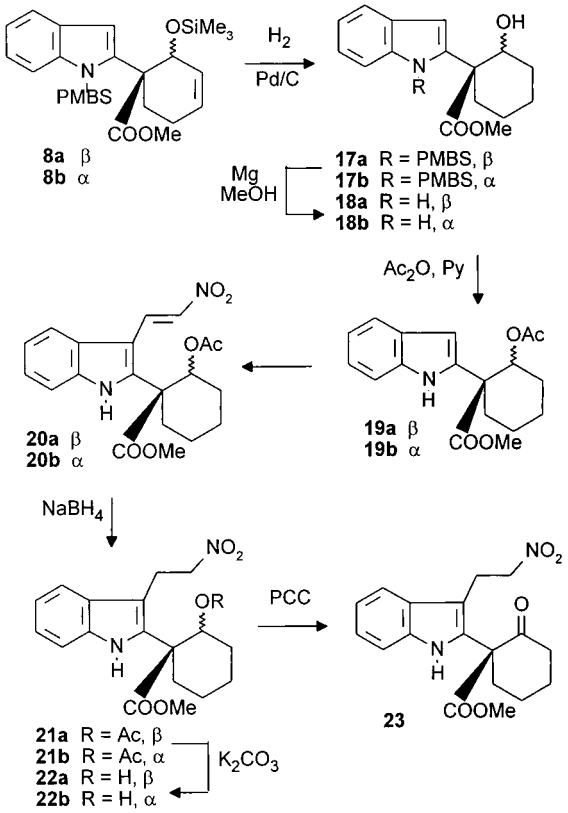
(11) Buchi, G.; Mak, C.-P. *J. Org. Chem.* **1977**, *50*, 1784

(12) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647. (b) Parikh, J. R.; Doering, W.von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

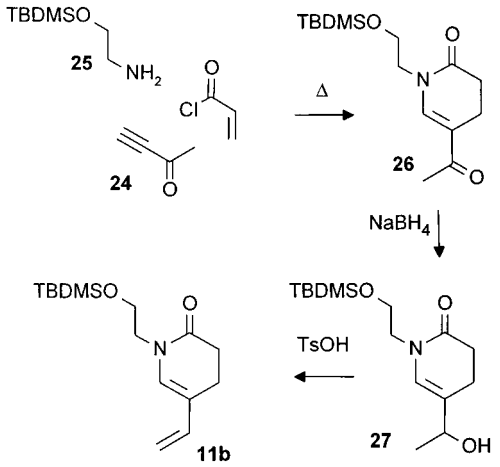
(13) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994,** *59*, 1613.

(14) Cook G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994,** *59*, 3575.

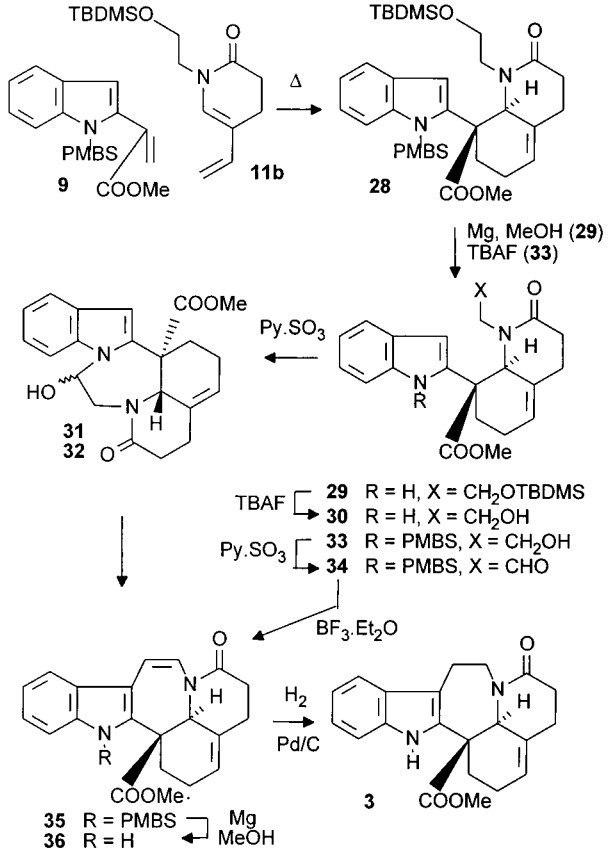
Scheme 4



Scheme 5



Scheme 6



tionof **26** with $NaBH_4$ gave the alchool **27** that spontaneously converted to the target diene. Complete conversion to **11b** was induced by heating in toluene in the presence of a catalytic amount of TsOH. Heating a solution of **9** and **11b** to reflux in toluene led to compound **28** through a regio- and diastereoselective [4 + 2]π cycloaddition (Scheme 6). Analysis of the NMR spectra ascertained the regiochemical outcome of the cyclization reaction; of particular interest is the signal at δ 5.25 (H-21), that appears as a broad singlet. Relevant is the downfield shift observed for the signal of H-7, that appears at δ 7.35, while it appeared at δ 6.50 in the starting compound **9**. The relative stereochemistry of hydrogen at C21 was established by NMR NOE experiments that showed interaction of the hydrogens at C21 (δ 5.25) and at C7 (δ 7.35). In the minimized structure[15] of **28** the medium distance between H-7 and H-21 is 2.1 Å, consistent with a NOE interaction, while in the minimized structure of the epimer at C21 the corresponding distance is 3.8 Å. The cycloadduct **28** possesses the relative stereochemistry and all the carbon units proper for the andranginine skeleton. Reaction of the tetracyclic compound **28** with Mg/MeOH[16] at 60 °C to give **29** and subsequent treatment with TBAF afforded the compound **30**. When **30** was submitted to oxidation with $Py.SO_3$, unexpected carbinolamines **31** and **32** were isolated. In the ^{1}H NMR spectrum of **31** and **32**, the aminalic proton H-6 appeared at δ 6.10 (J = 6 and <0.5 Hz) and 6.25 (J = 6 and <0.5 Hz), respectively. We repeated the oxidation maintaining the protective group at the indole nitrogen in order to avoid the formation of the aminalic compounds. $Py.SO_3$[12b] oxidation of **33** provided the rather unstable aldehyde **34**. The cyclization was obtained when **34** was allowed to react with excess $BF_3{\cdot}Et_2O$[17] at 65 °C for 40 min to afford enamide **35**. The ^{1}H NMR spectrum of **35** is in accordance with the structure but presents an unusual aromatic spin system: H-12 appears at δ 9.90 as a broad singlet while H-10 appears at δ 7.30 as a doublet (J = 8 Hz).[18] Removal of the *p*-methoxybenzensulfonyl (PMBS) group with Mg/MeOH resulted in compound **36** with a regular aromatic system in the ^{1}H NMR spectrum. This observation prompted us to consider the steric compression conferred on H-12 by the sulfonyl group as being responsible for its unusually irregular splitting in the

(15) Energy minimization was performed using the HyperChem program with MM+ force field.

(16) Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 7615.

(17) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987,** *52*, 3151

(18) The ^{1}H NMR spectrum of **35** was also consistent with the isomer where the nitrogen protecting group could be transposed from N4 to C12. In this manner the signals at δ 9.90 (bs), 7.80 (t), 7.72 (d), 8.05 (d) could be assigned to NH, H-9, H-10, H-11, respectively. ^{1}H−^{1}H-COSY and ^{13}C−^{1}H-COSY confirmed the structure indicated as **35**.

NMR spectrum of **35**. In the course of the recording of ^{13}C NMR spectra of compounds **31** and **32** with $CDCl_3$ as a solvent, we observed their spontaneous rearrangment to compound **36**. Catalytic hydrogenation (Pd/C), without affecting the C19/C20 double bond, gave 3-oxo-14,15-dihydroandranginine **3** in 82% yield. The first total synthesis of the skeleton of andranginine and, in particular, of its 3-oxo-14,15-dihydro derivative **3** was therefore accomplished in six steps and 11% overall yield from diene **11b**.

Attempts to introduce the PhSe group at C15 of the amide[19] **3** or to transform the amide into the thioamide[20] met with no success, thus preventing the access to the natural product andranginine **1**.

Experimental Section[7]

Indole derivatives were characterized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent.

5-Acetyl-*N*-[[(*tert*-butyldimethylsilyl)oxy]ethyl]-3,4-dihydropyridin-2-one (26). **25** (5 g, 29 mmol) was added to a solution of 3-butyn-2-one (**24**) (2.11 g, 31 mmol) at 0 °C. After the solution was warmed to rt, the mixture was stirred for 18 h. Acryloyl chloride (2.7 mL, 34.1 mmol) was added at rt. After being heated for 18 h at reflux, the solution was washed with a saturated aqueous $NaHCO_3$ and the organic layer extracted with Et_2O. The mixture was purified by chromatography (EtOAc/hexane 1:1) to give **26** (4 g, 48%): $R_f = 0.41$ (EtOAc/hexane 1:1); ^1H NMR ($CDCl_3$) δ 0.10 (6 H, s), 0.42 (9 H, s), 2.20 (3 H, s), 2.46−2.69 (4 H, m), 3.65−3.85 (4 H, m), 7.14 (1 H,s); ^{13}C NMR ($CDCl_3$) δ −5.1 (2C), 18.4, 24.3, 25.5 (3C), 30.4, 49.8, 61.5, 117.5, 143.1, 169.8, 194.8; MS *m/z* 297 (27), 240 (100). Anal. Calcd for $C_{15}H_{27}NO_3Si$: C, 60.56; H, 9.15; N, 4.71. Found: C, 60.65; H, 9.27; N, 4.84.

5-Ethenyl-*N*-[[(*tert*-butyldimethylsilyl)oxy]ethyl]-3,4-dihydropyridin-2-one (11b). To a solution of **26** (2 g, 7 mmol) in THF/MeOH 1:2 (60 mL) was added $NaBH_4$ (260 mg, 7 mmol) at 0 °C. After 2 h, the reaction mixture was poured into a 5% NH_4Cl solution and extracted with EtOAc. The crude mixture was directly dissolved in toluene, and TsOH (135 mg, 07 mmol) was added. The mixture was heated at 40 °C for 30 min and then washed with a saturated aqueous solution of $NaHCO_3$. Purification by chromatography (Et_2O) gave **11b** (1.89 g, 96%): $R_f = 0.56$ (Et_2O); ^1H NMR ($CDCl_3$) δ 0.01 (6 H, s), 0.89 (9 H, s), 2.38−2.65 (4 H, m), 3.60 (2 H, t, J = 5.6 Hz), 3.75 (2 H, t, J = 5.6 Hz), 4.97 (1 H, d, J = 10 Hz), 5.02 (1 H, d, J = 17 Hz), 6.31 (1 H, dd, J = 17, 10 Hz), 6.23 (1 H, s); ^{13}C NMR ($CDCl_3$) δ −4.9 (2C), 18.7 (3C), 20.3, 26.4, 31.4, 49.7, 62.4, 110.4, 117.5, 132.4, 135.3, 169.8; MS *m/z* 281 (9), 224 (100). Anal. Calcd for $C_{15}H_{27}NO_2Si$: C, 64.00; H, 9.67; N, 4.97. Found: C, 64.22; H, 9.82; N, 5.01.

8-Carbomethoxy-3,4,6,7,8,8a-hexahydro-8-[*N*-(*p*-methoxybenzenesulfonyl)indol-2-yl]-*N*-[2-*tert*-butyldimethylsilyl)oxy]ethyl]-1*H*)-quinolin-2-one (28). To a solution of **9** (2.5 g, 7 mmol) in toluene (8 mL) at reflux was added **11b** (2g, 6.8 mmol). The solution was mantained at reflux for 72 h. Evaporation of the solvent and purification by chromatography (EtOAc/CH_2Cl_2 1:2) gave **28** (2.08 g, 47%): $R_f = 0.43$ (EtOAc/CH_2Cl_2 1:2); ^1H NMR (d_6-DMSO, 60 °C) δ 0.09 (3 H, s) 0.11 (3 H, s), 0.90 (9 H, s), 1.70−1.82 (1 H, m), 2.05−2.19 (1 H, m), 2.30−2.53 (6 H, m), 2.98−3.10 (1 H, m), 3.45 (3 H, s), 3.61 (1 H, td, J = 16, 4 Hz), 3.69 (1 H, td, J = 16, 4 Hz), 3.88 (3 H, s), 3.91 (1 H, dt, J = 16, 4 Hz), 5.25 (1 H, bs), 6.00 (1 H, bs), 7.11 (2 H, AA′ part of AA′BB′ system), 7.19−7.29 (2 H, m), 7.35 (1 H, s), 7.49−7.56 (2 H, m), 7.68 (2 H, BB′ part of AA′BB′ system); ^{13}C NMR ($CDCl_3$) δ −4.9, 5.1, 18.7, 21.6, 26.4 (3C), 29.8, 32.9 (2C), 38.7, 46.8, 52.5, 56.2, 63.9, 64.2, 112.1, 114.8 (2C), 115.4, 121.3, 123.8, 125.3, 126.2, 128.2, 129.5 (2C), 132.4, 134.3, 138.1, 145.2, 163.9, 173.3, 173.9; HRMS for $C_{34}H_{44}N_2O_7SSi$ 652.2638. Found 652.2649.

8-Carbomethoxy-3,4,6,7,8,8a-hexahydro-8-(indol-2-yl)-*N*-[2-*[(tert*-butyldimethylsilyl)oxy]ethyl]-1*H*-quinolin-2-one (29). A mixture of **28** (200 mg, 0.28 mmol), NH_4Cl (400 mg), and Mg (400 mg) in methanol (20 mL) was stirred for 6 h. The reaction mixture was poured into water, and the pH was adjusted to 7 with 20% HCl. Extraction with EtOAc and chromatographic purification (Et_2O/hexane 3:1) gave **29** (128 mg, 95%) as a white foam: $R_f = 0.31$ (EtOAc/CH_2Cl_2 2:1); CAS red; ^1H NMR ($CDCl_3$) δ −0.10 (6 H, s), 0.80 (9 H, s), 1.40−1.62 (1 H, m), 2.30−2.68 (7 H, m), 3.20 (1 H, dt, J = 10, 2.5 Hz), 3.51−3.85 (3 H, m), 3.70 (3 H, s), 4.52−4.59 (1 H, s), 5.45−5.55 (1 H, s), 6.41 (1 H, s), 7.09 (1 H, t, J = 7.5 Hz), 7.17 (1 H, t, J = 7.5 Hz), 7.37 (1 H, d, J = 7.5 Hz), 7.58 (1 H, d, J = 7.5 Hz), 8.72 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ −5.7 (2C), 17.8, 23.5, 25.6 (3C), 29.6, 29.9, 33.1, 48.6, 50.8, 52.3, 61.2, 68.6, 99.6, 111.2, 120.0, 120.4, 121.6, 122.2, 127.9, 134.2, 135.8, 136.4, 172.5, 174.3; HRMS for $C_{27}H_{38}N_2O_4Si$ 482.2600. Found 482.2621; mp 194 °C.

8-Carbomethoxy-3,4,6,7,8,8a-hexahydro-8-(indol-2-yl)-*N*-(2-hydroxyethyl)-1*H*)-quinolin-2-one (30). To a cooled (0 °C) solution of the adduct **29** (128 mg, 0.24 mmol) in THF (15 mL) was added TBAF·$3H_2O$ (76 mg, 0.28 mmol). The resulting solution was maintained for 1 h, at which time it was poured into saturated aqueous NaCl and extracted with Et_2O. Purification by chromatography gave **30** (84 mg, 84%) as a white foam: $R_f = 0.14$ (EtOAc/MeOH 9:1); CAS orange; IR ($CHCl_3$) ν_{max}, 3430, 1745, 1648 cm^{-1}; ^1H NMR (d_6-DMSO) δ 1.34−1.53 (1 H, m), 2.25−2.45 (7 H, m), 2.55−2.70 (1 H, m), 3.10 (1 H, dt, J = 10.5, 6 Hz), 3.25 (1 H, dt, J = 10.5, 6 Hz), 3.41 (1 H, dt, J = 13.5, 6 Hz), 3.64 (3 H, s), 4.56 (1 H, t, J = 4.5 Hz), 4.66 (1 H, bs), 5.52 (1 H, bs), 6.24 (1 H, bs), 7.00 (1 H, t, J = 7.5 Hz), 7.10 (1 H, t, J = 7.5 Hz), 7.45 (1 H, d, J = 7.5 Hz), 7.52 (1 H, d, J = 7.5 Hz), 10.9 (1 H, bs); ^{13}C NMR (d_6-DMSO) δ 23.3, 29.5, 31.4, 33.24, 47.4, 51.5, 51.9, 57.8, 65.1, 100.1, 111.5, 119.2, 119.8, 120.9, 121.2, 127.4, 134.6, 136.2, 138.5, 171.5, 172.7; MS *m/z* 368 (10), 201 (100). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.60. Found: C, 68.33; H, 6.55; N, 7.53. mp 222 °C.

Oxidation of 30. To a solution of **30** (150 mg, 0.41 mmol) and TEA (0.68 mL) in DMSO (3 mL) was added $Py.SO_3$ (190 mg, 1.19 mmol). The resulting solution was stirred for 1 h at rt and then poured into a 5% NH_4Cl solution. Extraction with EtOAc and purification by chromatography (EtOAc/CH_2Cl_2 1:2) gave **31** (50 mg, 34%) and **32** (40 mg, 27%). **31**: $R_f = 0.14$ (EtOAc/CH_2Cl_2 1:2); CAS green; IR ($CHCl_3$) ν_{max}, 3200, 1780, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30−2.50 (5 H, m), 2.60−2.90 (4 H, m), 2.89 (1 H, d, J = 15 Hz), 3.51 (3 H, s), 4.29 (1 H, bs), 5.02 (1 H, dd, J = 15, 5 Hz), 5.64 (1 H, bs), 6.10 (1 H, d, J = 5 Hz), 6.71 (1 H, s), 7.10 (1 H, t, J = 7.5 Hz), 7.25 (1 H, t, J = 7.5 Hz), 7.40 (1 H, d, J = 7.5 Hz), 7.58 (1 H, d, J = 7.5 Hz); (d_6-DMSO) δ 2.00−2.60 (8 H, m), 2.74 (1 H, d, J = 13.7 Hz), 3.45 (3 H, s), 4.35 (1 H, bs), 5.09 (1 H, dd, J = 13.7, 5.1 Hz), 5.62 (1 H, bs), 5.94 (1 H, d, J = 3.5 Hz), 6.16 (1 H, dd, J = 5.1, 3.5 Hz), 6.72 (1 H, s), 7.05 (1 H, t, J = 7.5 Hz), 7.19 (1 H, t, J = 7.5 Hz), 7.50 (1 H, d, J = 7.5 Hz), 7.55 (1 H, d, J = 7.5 Hz); ^{13}C NMR (d_6-DMSO) δ 22.2, 29.7, 31.7, 33.8, 49.8, 50.1, 51.7, 63.7, 74.6, 103.1, 109.9, 119.4, 120.1, 121.1, 121.5, 126.2, 132.6, 136.4, 140.9, 170.4, 172.3; MS *m/z* 366 (15), 348 (47). **32**: $R_f = 0.21$ (EtOAc/CH_2Cl_2 1:2); CAS green; ^1H NMR ($CDCl_3$) δ 1.60−2.90 (8 H, m), 3.30 (1 H, d, J = 15 Hz), 3.61 (3 H, s), 5.01 (1 H, dd, J = 15, 6 Hz), 5.13 (1 H, bs), 5.61 (1 H, bs), 6.25 (1 H, d, J = 6 Hz), 6.68 (1 H, s), 7.10 - 7.30 (2 H, m), 7.43 (1 H, d, J = 7.5 Hz), 7.60 (1 H, d, J = 7.5 Hz).

8-Carbomethoxy-3,4,6,7,8,8a-hexahydro-8-[*N*-(*p*-methoxybenzenesulfonyl)indol-2-yl]-*N*-(2-hydroxyethyl)-1*H*-quinolin-2-one (33). To a cooled (0 °C) solution of the adduct **28** (200 mg, 0.3 mmol) in THF (12 mL), was added TBAF.$3H_2O$ (100 mg, 0.36 mmol). After 2 h the solution was poured into saturated aqueous NaCl and extracted with Et_2O. Purification by chromatography gave **33** (161 mg, 99%): $R_f = 0.14$ (EtOAc/MeOH 95:5); CAS red; ^1H NMR (d_6-DMSO, 60 °C) δ 1.55−1.70 (1 H, m), 1.75−1.90 (1 H, m), 2.05−2.53 (6 H, m), 2.90 (1 H, td, J = 15, 6 Hz), 3.37−3.55 (2 H, m), 3.90 (1 H, dt, J = 15,

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6 Hz), 3.41 (3 H, s) 3.82 (3 H, s), 4.59 (1 H, m), 5.20 (1 H, bs), 5.95 (1 H, bs), 7.11 (2 H, AA′ part of AA′BB′ system), 7.20−7.25 (2 H, m), 7.36 (1 H, s), 7.48−7.52 (1 H, m), 7.61−7.65 (1 H, m), 7.68 (2 H, BB′ part of AA′BB′ system); ^{13}C NMR ($CDCl_3$) δ 21.2, 23.9, 29.5, 32.6, 48.8, 51.9, 55.6, 58.7, 61.8, 63.3, 111.9, 114.3 (2C), 114.9, 120.9, 123.4, 124.1, 124.9, 127.6, 128.6 (2C), 131.6, 133.7, 137.7, 143.2, 163.4, 172.3, 175.1; FABMS *m*/*z* 539 (M + H). Anal. Calcd for $C_{28}H_{30}N_2O_7S$: C, 62.44; H, 5.61; N, 5.20. Found: C, 62.56; H, 5.85; N, 5.41.

8-Carbomethoxy-3,4,6,7,8,8a-hexahydro-8-[*N*-(*p*-methoxybenzenesulfonyl)indol-2-yl]-*N*-(formylmethyl)-1*H*)-quinolin-2-one (34). To a solution of **33** (200 mg, 0.36 mmol) and TEA (0.6 mL) in DMSO (3 mL), was added Py.SO_3 (172 mg, 1.12 mmol). The resulting solution was stirred for 1 h at rt and then poured into a 5% NH_4Cl solution. Extraction with EtOAc and purification by chromatography (EtOAc/MeOH 9:1) gave **34** (182 mg, 94%): R_f = 0.43 (EtOAc/MeOH 9:1); CAS yellow; ^{1}H NMR ($CDCl_3$) δ 1.91−2.02 (1 H, m), 2.20−2.32 (1 H, m), 2.40−2.59 (4 H, m), 2.61−2.78 (2 H, m), 3.52 (1 H d, *J* = 13 Hz), 3.65 (3 H, s), 3.81 (3 H, s), 4.50−4.71 (1 H, bs), 5.10 (1 H, s), 5.79 (1 H, bs), 6.61 (1 H, bs), 6.90 (AA′ part of AA′BB′ system), 7.19−7.24 (2 H, m), 7.45−7.49 (1 H, m), 7.65 (2 H, BB′ part of AA′BB′ system), 7.68−7.73 (1 H, m), 9.31 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 22.5 (2C), 29.6, 32.4, 52.1, 55.6, 56.1, 63.1, 111.0, 114.5 (2C), 115.2, 120.9, 123.8, 125.0, 125.3, 127.5, 128.7 (2C), 131.0, 133.1, 138.1, 143.2, 164.1, 172.1, 174.2, 203.7; HRMS for $C_{28}H_{28}N_2O_7S$ 536.16.17. Found 536.1623.

Methyl 1*H*,6*H*-6-Oxo-2,4,5,14,14b,14c-hexahydroindolo[3,2-*d*]pyrido[3,2,1-*jk*][1]benzazepine-14b-carboxylate (36). Method A. A mixture of **35** (90 mg, 0.26 mmol), NH_4Cl (200 mg), Mg (200 mg) in methanol (10 mL) was stirred for 6 h. The reaction mixture was poured into water, and the pH was adjusted to 7 with 20% HCl. Extraction with EtOAc and chromatographic purification (EtOAc/hexane 2:1) gave **36** (55 mg, 60%). **Method B.** A mixture of **31** and **32** (100 mg, 0.29 mmol) was dissolved in $CHCl_3$ and maintained for 70 h at room temperature. Chromatographic purification (EtOAc/hexane 2:1) gave **36** (80 mg, 88%): R_f = 0.35 (EtOAc/hexane 2:1); CAS green; ^{1}H NMR (d_6-DMSO) δ 2.01 (1 H, ddd, *J* = 15, 10, 7 Hz), 2.18−2.28 (2 H, m), 2.41−2.60 (4 H, m), 3.10 (1 H, dd, *J* = 15, 10 Hz), 3.61 (3 H, s), 4.42 (1 H, bs), 5.68 (1 H, bs), 6.22 (1 H, d, *J* = 10.5 Hz), 6.68 (1 H, d, *J* = 10.5 Hz), 7.04 (1 H, t, *J* = 8.5 Hz), 7.15 (1 H, t, *J* = 8.5 Hz), 7.38 (1 H, d, *J* = 8.5 Hz), 7.64 (1 H, d, *J* = 8.5 Hz), 11.20 (1 H, s); ^{13}C NMR (d_6-DMSO) δ 22.6, 29.7, 33.4, 33.6, 52.2, 52.4, 61.1, 104.8, 111.2, 115.0, 117.9, 119.1, 122.0, 122.7, 126.5, 129.1, 132.4, 133.9, 135.6, 170.9, 171.9; EIMS *m*/*z* 348 (100), 289 (77); Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.56; H, 5.93; N, 8.21.

Methyl 1*H*,6*H*-6-Oxo-2,4,5,8,9,14,14b,14c-octahydroindolo[3,2-*d*]pyrido[3,2,1-*jk*][1]benzazepine-14b-carboxylate (3). To a solution of **36** (60 mg, 0.17 mmol) in MeOH (5 mL) was added 5 mg of 5% Pd/C. The mixture was stirred under 1 atm of hydrogen for 4 h. Filtration through Celite and purification by flash chromatography (EtOAc) gave 49 mg (82%) of **3**: R_f = 0.44 (EtOAc); ^{1}H NMR (d_6-DMSO) δ 1.51−3.28 (9 H, m), 3.55 (3 H, s), 4.25−4.40 (1 H, m), 4.45−4.55 (2 H, m), 4.75 (1 H, bs), 5.61 (1 H, bs), 7.01 (1 H, t, *J* = 7.5 Hz), 7.08 (1 H, t, *J* = 7.5 Hz), 7.31−7.38 (1 H, m), 7.45−7.53 (1 H, m), 10.81 and 10.89 (1 H, bs); ^{13}C NMR (d_6-DMSO) δ 22.5, 22.8, 24.5, 32.3, 33.7, 47.9, 51.9, 55.8, 65.1, 111.1, 113.0, 117.5, 118.1, 118.6, 121.5, 127.5, 133.3, 133.5, 134.9, 167.9, 171.9; EIMS *m*/*z* 350 (100), 291 (40). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.03; H, 6.71; N, 8.03.

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Supporting Information Available: Experimental details for the preparation of **14b**, **5a**, **17a,b**, **18a,b**, **19a,b**, **20a,b** **22a,b**, **23**; ^{1}H and ^{13}C NMR spectra for compounds **14b**, **17a**, **17b**, **18b**, **19a**, **19b**, **20a**, **20b**, **21a**, **22b**, **23**, **26**, **11b**, **28**, **29**, **30**, **31**, **33**, **34**, **35**, **36**, **3**; ^{1}H NMR spectra for compounds **5a**, **18a**, **22a**, **32**; 2D COSY (^{1}H−^{1}H) of compound **35** (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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