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1,6-Dihydro-3(2*H*)-pyridinones. III.[1] A Formal Synthesis of (±)-Catharanthine[2]

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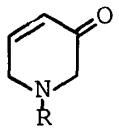
On treatment with ethyl vinyl ether containing mercuric acetate, the allylic alcohol (**5**) afforded the aldehyde (**7**), which was acetalized to **8**. Hydroboration-oxidation of **8** was followed by pyridinium chlorochromate (PCC) oxidation to yield two isomeric ketones (**11** and **12**), of which the former was subjected to acidic hydrolysis to afford the 2-azabicyclo-[2.2.2]octanone (**3b**) in excellent yield. On the other hand, the diketal (**22**) derived from **11** also gave the *N*-benzyloxycarbonyl analogue (**3c**) on acidic treatment. Ketalization of **3c** and subsequent oxidation provided the ketone (**27**), which was transformed into the amide (**29**) *via* the amine (**28**). Cyclization of **29** furnished the pentacyclic product (**30**), which has already been converted into (±)-catharanthine (**4**) and (±)-velbanamine (**31**).

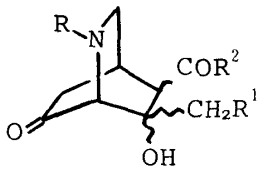
Keywords——dihydropyridinone; Claisen rearrangement; hydroboration-oxidation; 2-azabicyclo[2.2.2]octane; homoconjugation; intramolecular aldol reaction; catharanthine; velbanamine

In the previous papers of this series, we reported the synthesis for the first time of the *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1**), and the formation of the 2-azabicyclo[2.2.2]-octanes (**2**) by the reaction of **1** with some 1,3-dicarbonyl compounds in the presence of base.[1,3] The 2-azabicyclo[2.2.2]octane ring system is of great interest because it constitutes a partial structure of the Iboga alkaloids. The *N*-substituted 7-hydroxy-2-azabicyclo[2.2.2]octan-6-one (**3**) could serve as a potential key intermediate for synthesis of these alkaloids because **3** bears the requisite functionalities (hydroxy and ketonic groups), properly situated, for construction of new carbon-carbon bonds. Although the *N*-methanesulfonyl analogue (**3a**) was previously prepared *via* **2** (R=SO_2Me, R^1=H, R^2=OEt),[1] this route was found to be impractical for



1a : R = CO_2Et

1b : R = SO_2Me



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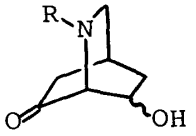

3a : R = SO_2Me

3b : R = CO_2Et

3c : R = Cbz

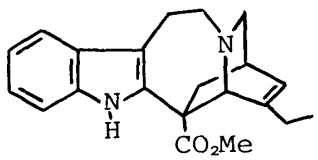

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Chart 1

synthesis of the Iboga alkaloids because of the extended sequence required and the limitation on exchange of the *N*-protecting group. This paper describes a novel and efficient synthesis of *N*-substituted 7-hydroxy-2-azabicyclo[2.2.2]octan-6-ones (**3**) and a formal synthesis of (±)-catharanthine (**4**), one of the Iboga alkaloids, from **3c**.

The allylic alcohol (**5**), the synthetic precursor of **1a**,[3,4] was treated with a large excess of ethyl vinyl ether in the presence of mercuric acetate[5] at 200°C for 48 h to give the labile aldehyde (**7**) *via* the Claisen rearrangement of the ether (**6**). The aldehyde (**7**) was derived into the acetal (**8**) in 69% overall yield from **5** in a usual manner. Hydroboration of **8** with diborane and subsequent oxidation with alkaline hydrogen peroxide[6] provided two regioisomeric alcohols (**9** and **10**) in 52 and 13% yields, respectively. These were oxidized to the corresponding ketones (**11** and **12**) with pyridinium chlorochromate (PCC) or by Jones oxidation. The structures of **11** and **12** were confirmed as follows. On reaction with vinylmagnesium bromide in tetrahydrofuran, the dihydropyridinone (**1a**) gave the 1,4-adduct (**13**; 23%) and the 1,2-adduct (**14**; 48%), of which the former was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid to afford the ketal (**15**) in 69% yield. Hydration of **15** by the hydroboration-oxidation process was followed by PCC oxidation to yield the desired aldehyde (**16**) in 59% yield along with a trace amount of the ketone (**17**). Acetalization of **16** with ethylene glycol afforded the diketal (**18**; 86%), which was found to be identical with the product obtained by ketalization of **11** in the usual way.

Upon treatment with 10% hydrochloric acid in boiling acetone, either **11** or **16** provided the same product, ethyl 7-hydroxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**3b**), in 98 or 70% yield, respectively. The formation of **3b** under the conditions employed can be

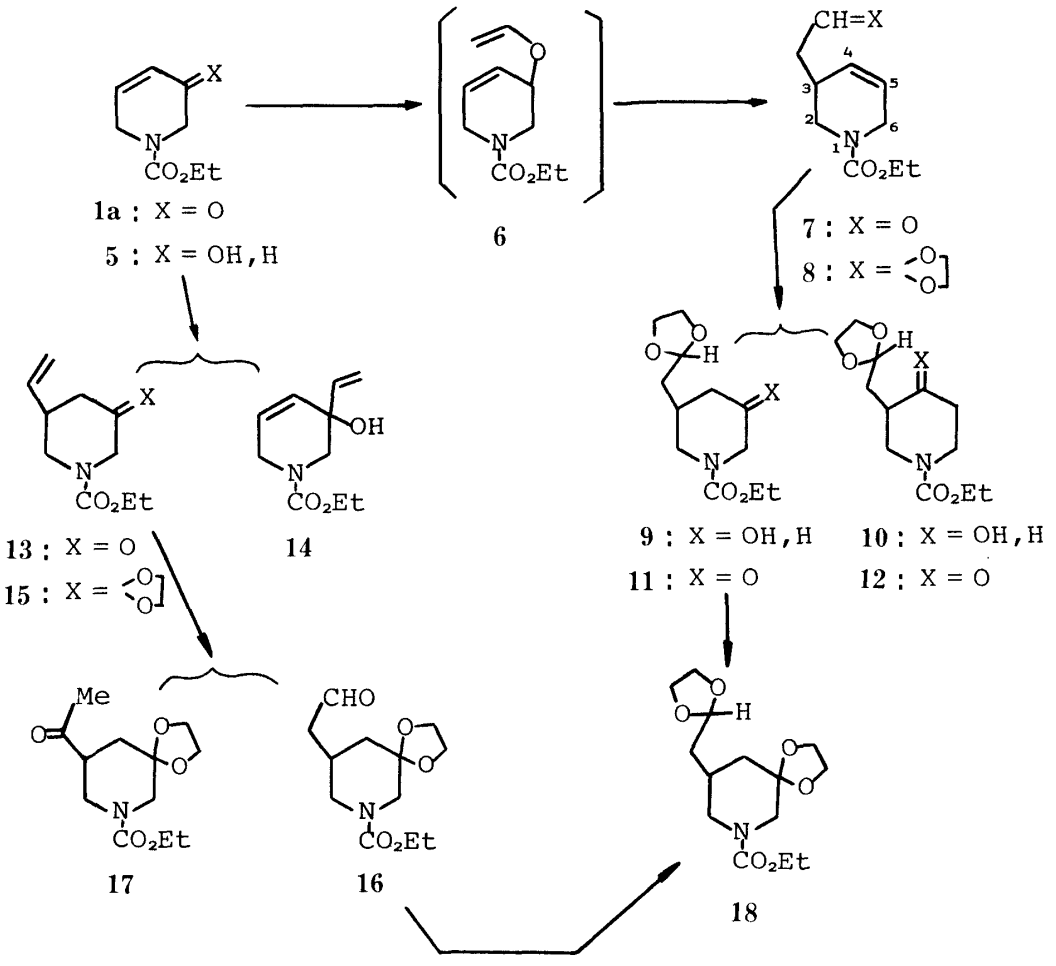

Chart 2

easily interpreted in terms of immediate cyclization of the initially formed intermediate (**19**) *via* an intramolecular aldol-type reaction even in the acidic medium.[7] The structure of **3b** was completely determined by spectral analysis of its benzoyl derivative (**20**), which was obtained from **3b** on treatment with benzoyl chloride in pyridine in 88% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **20** exhibited a broad signal at 4.58 ppm due to the C_1-proton and a doublet of doublets of doublets at 5.42 ppm (J=9, 4.5, and 3 Hz) attributable to the C_7-proton, and its infrared (IR) spectrum showed three carbonyl bands at 1738, 1715, and 1690 cm^{-1} owing to the ketone,[8] ester, and urethane, respectively. On the other hand, the diketal (**18**) was hydrolyzed with potassium hydroxide in boiling aqueous ethanol to give the amine (**21**) in 79% yield, and this was acylated with carbobenzoxy chloride to afford the benzyl urethane (**22**) in 94% yield. Acidic hydrolysis of **22** also provided the 2-azabicyclo[2.2.2]octanone (**3c**), mp 95—96.5°C, in 89% yield.

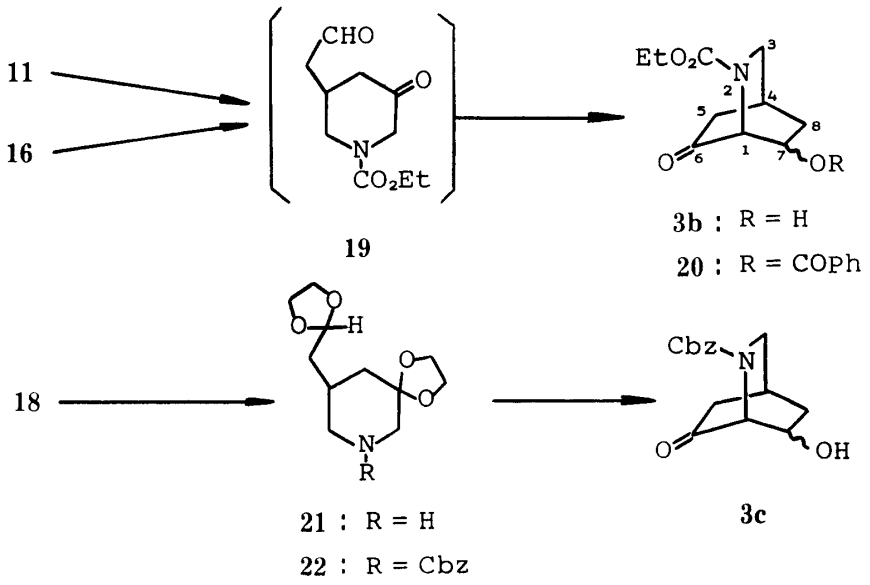

Chart 3

Thus, a new synthetic method for the 2-azabicyclo[2.2.2]octane ring system has been developed by utilizing an intramolecular aldol reaction as a key step. The present method seems to be of great value in that the produced azabicyclooctanone (**3**) bears the essential functional groups required for new carbon-carbon bond formation of the ring carbons and exchangeability of the *N*-substituent. As an application of this novel method to alkaloid syntheses, a formal synthesis of (±)-catharanthine (**4**) was investigated.

In order to prevent ring opening of the 2-azabicyclo[2.2.2]octane system *via* a retro-aldol process,[9] the alcohol (**3c**) was protected by acetylation to afford the ester (**23**) in 89% yield. On reaction with methyl orthoformate in methanol the ketone (**23**) was transformed into the dimethyl ketal (**24**), which was subjected to basic hydrolysis to give the alcohol (**25**) in 61% yield from **23**. Fortunately, direct ketalization of the ketol (**3c**) with methyl orthoformate gave the desired ketal (**25**) in 74% yield without any of the possible diketal(**26**). The successful formation of **25** can be attributed to the short reaction time (within 1 h). Oxidation of **25** with PCC in the presence of sodium acetate gave the ketone (**27**; 83%), the IR spectrum of which showed a ketone band at 1740 cm^{-1}. On hydrogenolysis over 5% palladium on carbon in methanol, the urethane (**27**) afforded the unstable amino ketone (**28**), which showed a carbonyl band at the rather lower frequency of 1720 cm^{-1} in the IR spectrum, probably owing to participation of the homoconjugation depicted in **28'**. On treatment with β-indolylacetyl chloride,[10] the amine (**28**) was converted into the amide (**29**) in 88% yield calculated from **27**.

According to the known method,[11] heating of **29** with *p*-toluenesulfonic acid in boiling benzene for a short time provided the pentacyclic compound, *rel*-(6*R*, 6a*S*, 9*R*)-6-methoxy-7,12-dioxo-6,6a,7,8,9,10,12,13-octahydro-6,9-methano-5*H*-pyrido[1′, 2′: 1, 2]azepino[4,5-*b*]indole (**30**), mp 281—282°C, in 69% yield. The product was proved by means of IR and ^{1}H-NMR spectroscopy to be identical with an authentic sample (**30**).[11] Since the conversion of **30** into (±)-catharanthine (**4**) and (±)-velbanamine (**31**) has already been reported,[11] our present synthesis of **30** represents a formal synthesis of **4** and **31**.

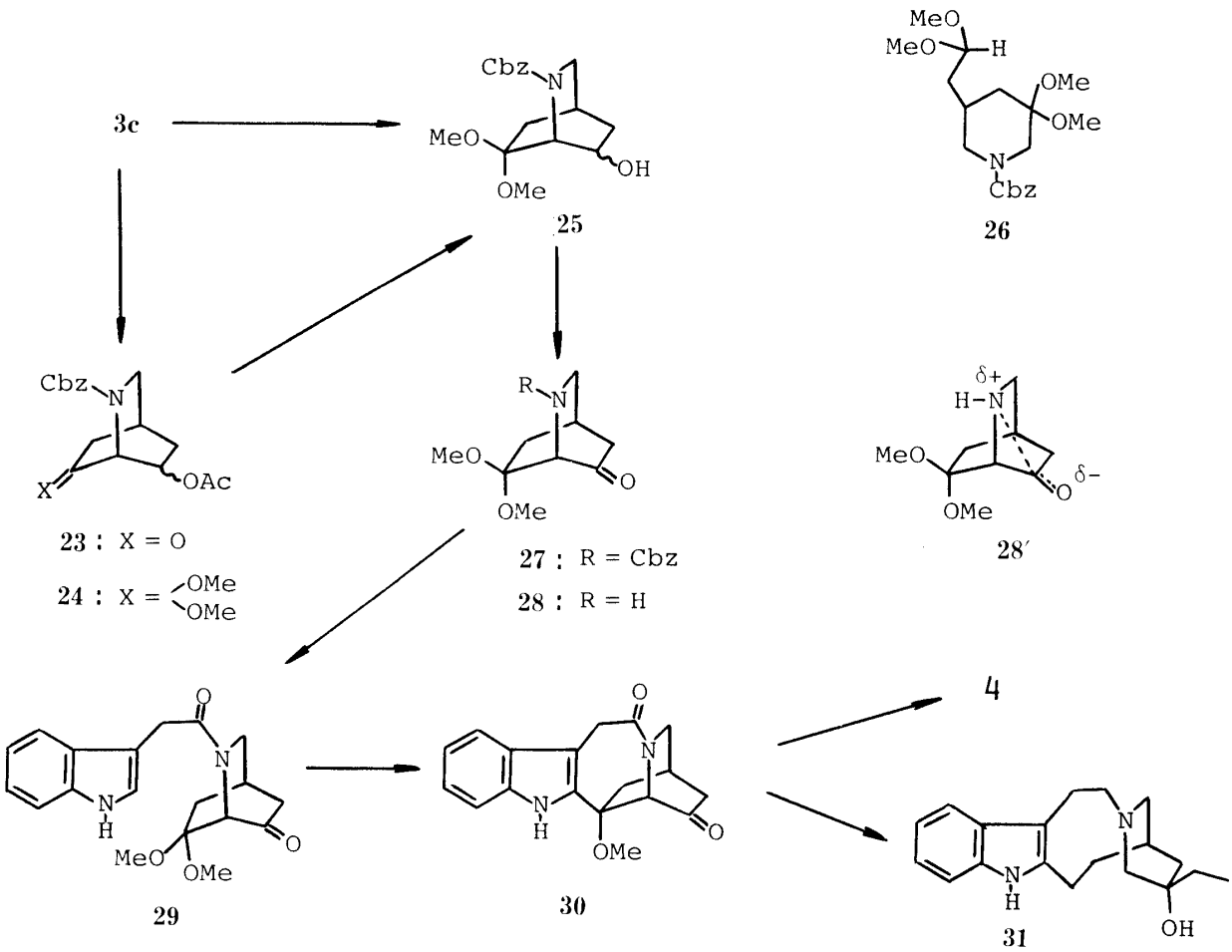

Chart 4

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 70 eV) and ultraviolet (UV) spectra with a Hitachi 323 spectrophotometer. NMR spectra were recorded with a JEOL PMX-60 or FX-100 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, ddd=doublet of doublets of doublets, br=broad, and m=multiplet. All organic extracts were dried over anhydrous sodium sulfate. Column chromatography was carried out with Kieselgel 60 (70—230 mesh, Merck) and Aluminiumoxid 90 (Aktivitätsstufe II—III, 70—230 mesh, Merck). Preparative thin-layer chromatography (TLC) was performed on Kieselgel 60 PF_{254} (Merck).

Ethyl 3-(2-Ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (8)——A mixture of the alcohol (**5**; 3.0 g), $Hg(OAc)_2$ (2.0 g), and ethyl vinyl ether (20 ml) was heated in a sealed tube at 200°C for 48 h. The solvent was removed *in vacuo* and the residue was taken up in C_6H_6 (200 ml). The organic solution was washed with H_2O, 10% HCl, and H_2O and concentrated *in vacuo* to 3/4 of the original volume. Ethylene

glycol (3 ml) and *p*-TsOH (100 mg) were added to the remainder. The resulting mixture was heated under reflux for 1 h while water was removed with the aid of a Dean-Stark apparatus. After cooling, the mixture was washed with sat. $NaHCO_3$ and brine, and dried. Evaporation of the solvent left an oily residue, which was chromatographed on alumina with C_6H_6 to afford 2.9 g (69%) of the acetal (**8**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700—1680 (CO), 1655 (C=C). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.63 (2H, dd, J=7, 5 Hz, $\overset{O}{\underset{O}{>}}$CH–C$\underline{H}_2$–CH), 2.40 (1H, m, C_3–H), 3.17 (1H, dd, J=13, 6 Hz, C_2–H), 3.65 (1H, dd, J=13, 4 Hz, C_2–H), 3.7—4.0 (6H, m, OCH_2CH_2O, C_6–H), 4.03 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.87 (1H, t, J=5 Hz, $CH\overset{O}{\underset{O}{<}}$), 5.62 (2H, m, C_4– and C_5–H). MS *m/e*: 241 (M^+), 153 (base). High resolution MS *m/e*: Calcd for $C_{12}H_{19}NO_4$: 241.131. Found: 241.134.

Ethyl 5-(2-Ethylenedioxyethyl)-3-hydroxypiperidine-1-carboxylate (9) and Ethyl 3-(2-Ethylenedioxyethyl)-4-hydroxypiperidine-1-carboxylate (10)——A solution of BF_3-etherate (44 mg) in abs. tetrahydrofuran (THF) (1 ml) was added dropwise to a stirred suspension of $NaBH_4$ (32 mg) in abs. THF (1 ml) under ice cooling. The mixture was stirred under cooling for 10 min, then a solution of the olefin (**8**; 110 mg) in abs. THF (1 ml) was added to the mixture and stirring was continued for another 3 h under cooling. Aq. 30% H_2O_2 (0.15 ml) and 3 N NaOH (0.3 ml) were added to the mixture and the resulting mixture was further stirred under cooling for 2 h. The organic solvent was removed *in vacuo* and the aqueous mixture was extracted with $CHCl_3$ (15 ml×3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$. The first fraction gave 15 mg (13%) of the C-4 hydroxy compound (**10**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (OH), 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.90 (4H, m, OCH_2CH_2O), 4.07 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.90 (1H, m, $CH\overset{O}{\underset{O}{<}}$). High resolution MS *m/e*: Calcd for $C_{12}H_{21}NO_5$: 259.142. Found: 259.140. The second fraction gave 61 mg (52%) of the C-3 hydroxy compound (**9**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.82 (4H, m, OCH_2CH_2O), 4.03 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.83 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{<}}$). High resolution MS *m/e*: Calcd for $C_{12}H_{21}NO_5$: 259.142. Found: 259.145.

Ethyl 5-(2-Ethylenedioxyethyl)-3-oxopiperidine-1-carboxylate (11)——a) Jones Oxidation: Jones oxidant[12] (8 N; 0.5 ml) was added dropwise to a stirred solution of the alcohol (**9**; 330 mg) in purified acetone (4 ml) under ice cooling over a period of 20 min. Stirring was continued for a further 3 h under cooling and the mixture was diluted with 10 ml of water. The resulting mixture was extracted with $CHCl_3$ (20 ml×3) and the extract was washed with brine and dried. Evaporation of the solvent left an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 260 mg (79%) of the ketone (**11**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.90 (4H, m, OCH_2-CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.87 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{<}}$). MS *m/e*: 257 ($M^+$), 185 (base). High resolution MS *m/e*: Calcd for $C_{12}H_{19}NO_5$: 257.126. Found: 257.125.

b) PCC Oxidation: A solution of **9** (50 mg) in CH_2Cl_2 (2 ml) was added to a stirred suspension of PCC[13] (60 mg) and NaOAc (20 mg) in CH_2Cl_2 (5 ml) and the mixture was stirred at room temperature for 24 h. The reaction mixture was passed through a short column packed with Florisil and the column was thoroughly washed with ether. The combined eluates were concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 45 mg (91%) of **11**.

Ethyl 3-(2-Ethylenedioxyethyl)-4-oxopiperidine-1-carboxylate (12)——A solution of the alcohol (**10**; 60 mg) in CH_2Cl_2 (2 ml) was added to a stirred suspension of PCC (80 mg) and NaOAc (25 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred at room temperature for 15 h. Work-up as usual gave 45 mg (75%) of the ketone (**12**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.85 (4H, m, OCH_2CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.90 (1H, t, J=4 Hz, $CH\overset{O}{\underset{O}{<}}$). MS *m/e*: 257 ($M^+$), 170 (base). High resolution MS *m/e*: Calcd for $C_{12}H_{19}NO_5$: 257.126. Found: 257.126.

Ethyl 9-(2-Ethylenedioxyethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (18)——a) From the Ketone (**11**): A mixture of the ketone (**11**; 470 mg), ethylene glycol (1.0 ml), *p*-TsOH (50 mg), and C_6H_6 (50 ml) was heated under reflux for 20 h while water was removed with the aid of a Dean-Stark apparatus. Work-up as usual gave an oily residue, which was chromatographed on alumina with C_6H_6 to afford 475 mg (86%) of **18** as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1690 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=7 Hz, OCH_2-$C\underline{H}_3$), 3.8—4.0 (8H, m, OCH_2CH_2O×2), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.88 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{<}}$). High resolution MS *m/e*: Calcd for $C_{14}H_{23}NO_6$: 301.152. Found: 301.153.

b) From the Dihydropyridinone (**1a**) through **15**: Cuprous chloride (30 mg) was added to a stirred solution of vinylmagnesium bromide in abs. THF [prepared from Mg (0.43 g) and vinyl bromide (1.3 ml) in abs. THF (30 ml) according to the literature[14]] at 0°C. The mixture was cooled to −50°C and a solution of the dihydropyridinone (**1a**; 880 mg) in abs. THF (20 ml) was added to the stirred mixture over a period of 30 min. Stirring was continued for another 30 min at −50°C. Excess reagent and the complex were decomposed with sat. NH_4Cl solution and the organic layer was separated. The aqueous layer was extracted

with ether (30 ml × 3). The combined organic layers were washed with brine and dried. Evaporation of the solvent *in vacuo* left an oily residue, which was chromatographed on silica gel with $CHCl_3$. The first fraction afforded 223 mg (23%) of the 1,4-adduct (**13**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.06 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.01 (1H, d, J=17 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{\underline{H}}$), 5.08 (1H, d, J=9 Hz, $^{H}\!>\!C\!=\!C\!<^{\underline{H}}_{H}$), 5.74 (1H, ddd, J=17, 9, 5 Hz, $^{\underline{H}}\!>\!C\!=\!C\!<^{H}_{H}$). The second fraction afforded 453 mg (48%) of the 1,2-adduct (**14**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.91 (1H, s, OH), 3.46 (2H, s, C_2–H), 3.89 (2H, s, C_6–H), 4.06 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.06 (1H, dd, J=10, 2 Hz, $^{H}\!>\!C\!=\!C\!<^{\underline{H}}_{H}$), 5.19 (1H, dd, J=18, 2 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{\underline{H}}$), 5.69 (2H, s, C_4- and C_5–H), 5.93 (1H, dd, J=18, 10 Hz, $^{\underline{H}}\!>\!C\!=\!C\!<^{H}_{H}$). A mixture of **13** (95 mg), ethylene glycol (1 ml), *p*-TsOH (trace), and C_6H_6 (30 ml) was treated as usual to afford an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 78 mg (69%) of the ketal (**15**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.26 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.98 (4H, s, OCH_2CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.02 (1H, d, J=10 Hz, $^{H}\!>\!C\!=\!C\!<^{\underline{H}}_{H}$), 5.05 (1H, d, J=18 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{\underline{H}}$) 5.71 (1H, ddd, J=18, 10, 7 Hz, $^{\underline{H}}\!>\!C\!=\!C\!<^{H}_{H}$). Treatment of the ketal (**15**; 122 mg) with a mixture of $NaBH_4$ (64 mg), BF_3-etherate (296 mg), and abs. THF (10 ml) was followed by oxidation with a mixture of 30% H_2O_2 (0.3 ml) and 10% NaOH (0.6 ml) in a usual manner to afford a crude hydroxy product, which was oxidized with PCC (150 mg) and NaOAc (45 mg) in CH_2Cl_2 (8 ml). Work-up as usual afforded an oily residue, which was chromatographed on silica gel with $CHCl_3$. The first fraction gave 5 mg (4%) of the ketone (**17**) as a colorless oil. ^{1}H-NMR δ ($CDCl_3$): 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.20 (3H, s, $COCH_3$), 4.01 (4H, s, OCH_2CH_2O), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). The second fraction gave 77 mg (59%) of the aldehyde (**16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2720 (CHO), 1720, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.98 (4H, s, OCH_2CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 9.76 (1H, s, CHO). A mixture of the aldehyde (**16**; 470 mg), ethylene glycol (1 ml), *p*-TsOH (50 mg), and C_6H_6 (30 ml) was heated under reflux for 20 h using a Dean-Stark apparatus. Work-up as usual afforded an oily residue, which was chromatographed on alumina with C_6H_6 to give 475 mg (86%) of **18**, which was identical with the sample obtained in a).

Ethyl 7-Hydroxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (3b)——a) From **11**: A mixture of **11** (260 mg), 10% HCl (1 ml), and acetone (20 ml) was heated under reflux for 45 min. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (40 ml). The organic layer was washed with brine, dried, and concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$–EtOH (20: 1) to afford 210 mg (98%) of **3b** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1735, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.38 (2H, br s, C_5–H), 3.28 (2H, br s, C_3–H), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). High resolution MS *m/e*: Calcd for $C_{10}H_{15}NO_4$: 213.100. Found: 213.099.

b) From **16**: A mixture of **16** (36 mg), 10% HCl (0.3 ml), and acetone (5 ml) was heated under reflux for 17 h. Work-up as usual gave 20 mg (70%) of **3b**.

Ethyl 7-Benzoyloxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (20)——A mixture of **3b** (55 mg), benzoyl chloride (50 mg), and dry pyridine (0.5 ml) was allowed to stand at room temperature overnight. The reaction mixture was diluted with ice water and neutralized with 10% HCl. The resulting mixture was extracted with $CHCl_3$ (15 ml × 3) and the extract was washed with water, dried, and concentrated *in vacuo*. The oily residue was chromatographed on silica gel with $CHCl_3$ to give 72 mg (88%) of **20** as a colorless viscous oil, which solidified on standing overnight. Recrystallization from hexane afforded colorless plates, mp 100—101°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738, 1715, 1690 (CO), 1600, 1582 (aromatic). ^{1}H-NMR δ ($CDCl_3$): 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.73 (1H, br d, J=14 Hz, C_8–H), 2.42 (1H, br dd, J=14, 9 Hz, C_8–H), 2.50 (3H, br s, C_4- and C_5–H), 3.42 (2H, br s, C_3–H), 4.17 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.58 (1H, br, C_1–H), 5.42 (1H, ddd, J=9, 4.5, 3 Hz, C_7–H), 7.3—7.7 (3H, m, Ar–H), 7.8—8.0 (2H, m, Ar–H). ^{13}C-NMR ($CDCl_3$): 14.6 (q, $OCH_2\underline{C}H_3$), 27.5 (d, C_4), 33.1 (t, C_8), 42.6 (t, C_5), 47.6 (t, C_3), 56.7 and 56.8[15] (each d, C_1), 62.0 (t, $O\underline{C}H_2$-CH_3), 69.3 (d, C_7), 128.4 (d, Ar), 129.2 (s, Ar), 129.6 (d, Ar), 133.4 (d, Ar), 155.1 (s, $Ph\underline{C}O$–O), 164.9 (s, $N\underline{C}O$–O), 203.6 (s, C_6). MS *m/e*: 317 (M^+), 105 (base). *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.05; H, 5.95; N, 4.62.

9-(2-Ethylenedioxyethyl)-1,4-dioxa-7-azaspiro[4.5]decane (21)——A mixture of the urethane (**18**; 1.63 g), KOH (2.1 g), EtOH (60 ml), and H_2O (20 ml) was heated under reflux for 36 h. Ethanol was removed *in vacuo* and the residue was extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated *in vacuo* to leave an oily residue, which was chromatographed on alumina. The fraction eluted with C_6H_6 afforded the unchanged starting material (197 mg; 12%) and that eluted with $CHCl_3$ gave 978 mg (79%; 90% based on the consumed starting material) of the amine (**21**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310 (NH). ^{1}H-NMR δ ($CDCl_3$): 3.7—4.1 (8H, m, OCH_2CH_2O × 2), 4.85 (1H, t, J=5 Hz, $CH\!<^{O}_{O}$). MS *m/e*: 229 (M^+), 73 (base).

Benzyl 9-(2-Ethylenedioxyethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (22)——A solution of

carbobenzoxy chloride (0.70 ml) and Et_3N (0.8 ml) in abs. ether (5 ml) was added dropwise to a stirred solution of the amine (**21**; 978 mg) in abs. ether (80 ml) under ice cooling. Stirring was continued for 1 h at room temperature. The reaction mixture was washed with brine, 2% HCl, and then brine again. The dried ethereal solution was concentrated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$ to afford 1.45 g (94%) of the urethane (**22**) as a colorless oil. On standing overnight, the product solidified and recrystallization from hexane afforded colorless prisms, mp 57—59°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.26 (2H, dd, J=6, 4.5 Hz, $C\underline{H}_2CH\langle^{O}_{O}$), 4.89 (1H, t, J=4.5 Hz, $CH\langle^{O}_{O}$), 5.05 and 5.20 (2H, AB-q, J=13 Hz, $C\underline{H}_2$-Ar), 7.33 (5H, s, Ar-H). *Anal.* Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.73; H, 6.93; N, 4.10.

Benzyl 7-Hydroxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**3c**)——A mixture of **22** (1.46 g), 10% HCl (18 ml), and THF (60 ml) was heated under reflux for 18 h. The organic solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$ (30 ml×3). The extract was washed with brine, dried, and concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$–MeOH (50: 1) to afford 978 mg (89%) of **3c** as a solid. Recrystallization from C_6H_6–hexane gave a white powder, mp 95—96.5°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1735, 1682 (CO). ^{1}H-NMR δ ($CDCl_3$): 4.20 (1H, m, C_7-H), 4.30 (1H, br s, C_1-H), 5.03 (2H, s, $C\underline{H}_2$-Ar), 7.20 (5H, s, Ar-H). *Anal.* Calcd for $C_{15}H_{17}NO_4\cdot 1/5H_2O$: C, 64.59; H, 6.29; N, 5.02. Found: C, 64.62; H, 6.14; N, 4.81.

Benzyl 7-Acetoxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**23**)——A mixture of **3c** (320 mg), Ac_2O (3 ml), and dry pyridine (5 ml) was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (60 ml). The $CHCl_3$ solution was washed with sat. $NaHCO_3$, brine, 10% HCl, and then brine again. Concentration of the dried solution *in vacuo* left an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 330 mg (89%) of **23** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1690 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.98 (3H, s, $COCH_3$), 4.44 (1H, d, J=4.5 Hz, C_1-H), 5.07 (2H, s, $C\underline{H}_2$-Ar), 7.23 (5H, s, Ar-H). MS *m/e*: 317 (M^+), 91 (base). High resolution MS *m/e*: Calcd for $C_{17}H_{19}NO_5$: 317.126. Found: 317.125.

Benzyl 7-Hydroxy-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (**25**)——a) From **23**: A mixture of **23** (469 mg), methyl orthoformate (0.4 ml), *p*-TsOH (trace), and abs. MeOH (30 ml) was heated under reflux for 15 h. The solvent was removed *in vacuo* and the residue was taken in $CHCl_3$ (60 ml). The organic layer was washed with sat. $NaHCO_3$ and brine, and dried. Evaporation of the solvent left 510 mg of crude product (**24**), which was used for the next step without further purification. A mixture of the crude product (510 mg), 5% aq. NaOH (1 ml), and MeOH (10 ml) was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (60 ml). The organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina with $CHCl_3$ to give 290 mg (61% from **23**) of **25** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 3.1—3.4 (6H, $OCH_3\times 2$), 3.69 and 3.75 (total 1H, each d, J=6.5 Hz, OH, disappeared with D_2O), 3.95 (1H, m, C_7-H), 4.21 and 4.35 (total 1H, each d, J=3.5 Hz, C_1-H), 5.15 (2H, s, $C\underline{H}_2$-Ar), 7.35 (5H, s, Ar-H). MS *m/e*: 321 (M^+).

b) From **3c**: A mixture of **3c** (978 mg), methyl orthoformate (1.3 ml), *p*-TsOH (trace), and abs. MeOH (20 ml) was heated under reflux for 50 min. Work-up as usual gave 840 mg (74%) of **25**.

Benzyl 7,7-Dimethoxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**27**)——A solution of **25** (190 mg) in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (200 mg) and NaOAc (70 mg) in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 14 h and passed through a short column packed with Florisil. The column was washed thoroughly with ether and the combined eluates were concentrated *in vacuo* to leave an oily residue, which was chromatographed on alumina with $CHCl_3$ to give 156 mg (83%) of **27** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1690 (CO). ^{1}H-NMR δ ($CDCl_3$): 3.19 (6H, s, $OCH_3\times 2$), 3.43 (2H, m, C_3-H), 4.54 (1H, br s, C_1-H), 5.14 and 5.17 (2H, AB-q, J=14 Hz, CH_2-Ar), 7.32 (5H, s, Ar-H). High resolution MS *m/e*: Calcd for $C_{17}H_{21}NO_5$: 319.142. Found: 319.143.

2-(β-Indolylacetyl)-7,7-dimethoxy-2-azabicyclo[2.2.2]octan-6-one (**29**)——The benzyl urethane (**27**; 114 mg) was hydrogenated in abs. MeOH (3 ml) over 5% Pd-C (100 mg) under 1 atm pressure of H_2 at room temperature for 4.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave the crude amino ketone (**28**), which was used for the next step without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO). A solution of β-indolylacetyl chloride[10] (80 mg) in CH_2Cl_2 (2 ml) was added to a stirred solution of the amino ketone (**28**) in CH_2Cl_2 (10 ml) under ice cooling. After being stirred for 2 min under cooling the mixture was treated with a solution of K_2CO_3 (150 mg) in H_2O (2 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml). The combined organic layers were washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 108 mg (88% from **27**) of **29** as a yellow oil. On standing overnight, the product solidified and recrystallization from C_6H_6–hexane afforded yellow prisms, mp 90—94°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1740, 1640 (CO). ^{1}H-NMR δ ($CDCl_3$): 3.18 (6H, br, $OCH_3\times 2$), 3.78 (2H, m, Ar-CH_2), 4.39 and 5.15 (total 1H, each br s, C_1-H), 6.9—7.3 (4H, m, Ar-H), 7.55 (1H, m, Ar-H), 8.05 (1H, br s, NH). MS *m/e*: 342 (M^+), 130 (base).

***rel*-(6*R*,6a*S*,9*R*)-6-Methoxy-7,12-dioxo-6,6a,7,8,9,10,12,13-octahydro-6,9-methano-5*H*-pyrido[1′,2′: 1,2]azepino[4,5-*b*]indole** (**30**)——According to the method of Büchi *et al.*,[11] a solution of **29** (14 mg) in dry C_6H_6

(2 ml) was added to a boiling solution of anhydrous *p*-TsOH (7 mg) in dry C_6H_6 (10 ml) all at once. The resulting mixture was heated under stirring at boiling point for 7 min while C_6H_6 distilled off very slowly. The mixture was cooled and then concentrated *in vacuo* at room temperature. The residue was chromatographed on alumina with $CHCl_3$ to give 9.0 mg (69%) of **30** as colorless plates, mp 281—282°C (from $CHCl_3$) (lit.[11] mp 283—284°C). IR ν_{max}^{Nujol} cm^{-1}: 3130 (NH), 1742, 1640 (CO). ^{1}H-NMR δ ($CDCl_3$): 3.05 (3H, s, OCH_3), 3.74 and 4.02 (2H, AB-q, $J=16$ Hz, Ar–CH_2), 4.79 (1H, s, C_{6a}–H), 7.00—7.60 (4H, m, Ar–H), 8.28 (1H, br s, NH). UV λ_{max}^{MeOH} nm (ε): 221.5 (34000), 283.5 (7500), 292.5 (6500). MS *m/e*: 310 (M^+), 170 (base).

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References and Notes

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