Addition Reactions of Allyl Stannanes to an Indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline Imminium Salt

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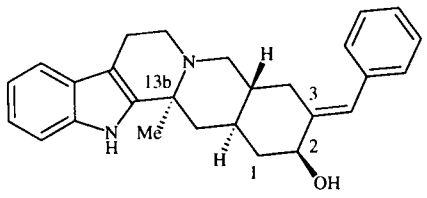
Received October 8, 1999

The addition of organometallic reagents to the 13b-position of the indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline imminium salt **4** is described. Reaction of **4** with tetraallyl tin in 2-methoxyethanol gave the allyl adduct **7** in moderate yield. Further elaboration of **7** yielded the pentacyclic benzylidene alcohols **13** and **14**. Structure elucidation of the compounds prepared was achieved by a combination of ^{1}H nmr spectroscopy and X-ray crystallography.

J. Heterocyclic Chem., **37**, 1081 (2000).

Derivatives of the natural product yohimbine have been of wide interest both for their variety of medicinal properties and the synthetic challenges inherent in their preparation [1,2]. Earlier work in the Warner-Lambert laboratories [3] identified the yohimban [4] derivative **1** as a compound of biological interest. This compound was originally prepared as part of a project to investigate substitution at the 13b-position of the fused pentacycle [5]. The original synthetic method involved the addition of organolithium reagents to various imminium salts [6,7]. This



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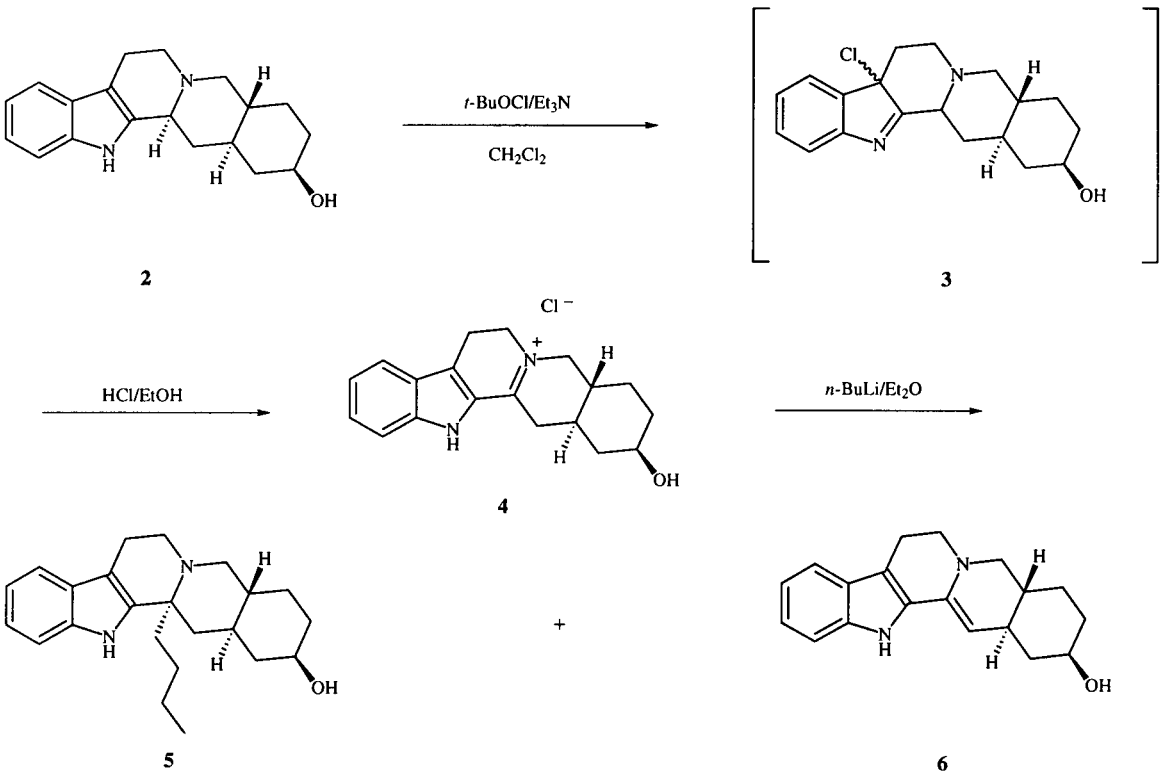
reaction was usually accompanied by the generation of substantial quantities of unsaturated side products due to proton abstraction by the lithium reagent rather than the desired addition to the imminium moiety. We reinvestigated this addition reaction in order to prepare additional 13b-substituted analogs of **1** for biological testing. We began by examining the addition of *n*-butyl lithium to the indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline imminium salt **4** (Scheme 1). Compound **4** [5] was prepared in moderate yield by chlorination of the carbinol **2** [8] followed by acid treatment of the resulting chloro intermediate **3**. Reaction of **4** with an excess of *n*-butyl lithium under a variety of reaction conditions gave the 13b-butyl adduct **5** in only 15-20% yield, accompanied by the dehydro derivative **6** [5] as the main product. Similar results were observed for the addition of methyl lithium in diethyl ether to **4**, while the reaction in tetrahydrofuran as the solvent gave **6** as the exclusive product. Addition of ethyl magnesium bromide to **4**, with or without added cerium chloride [9], gave no reaction.

With the addition of organolithium or Grignard reagents to **4** found to be unsatisfactory for our requirements, we investigated other methods for the introduction of a 13b-position substituent on the pentacyclic nucleus. Imminium salts derived from isoquinolines [10] and 3,4-dihydro-β-carbolines [11] have been shown to react with allyl stannanes by addition to the C=N bond. These β-carboline adducts have been subsequently transformed into yohimban systems by Diels-Alder cyclizations [12,13]. To our knowledge, the addition of allyl stannanes to a pre-formed yohimban imminium salt has not been previously described. We observed that reaction of **4** with allyltributyl tin in methanol/chloroform at reflux gave the desired 13b-allyl adduct **7** in 20% yield (Scheme 2). However, reaction of **4** with tetraallyl tin in 2-methoxyethanol at reflux raised the yield of **7** to 58%. A similar reaction of **4** with tetravinyl tin gave **2** as the only isolated product. Attempted addition to **4** of other nucleophiles, such as sodium azide, potassium cyanide, cyanoacetic acid, or diethyl malonate, did not yield useful products.

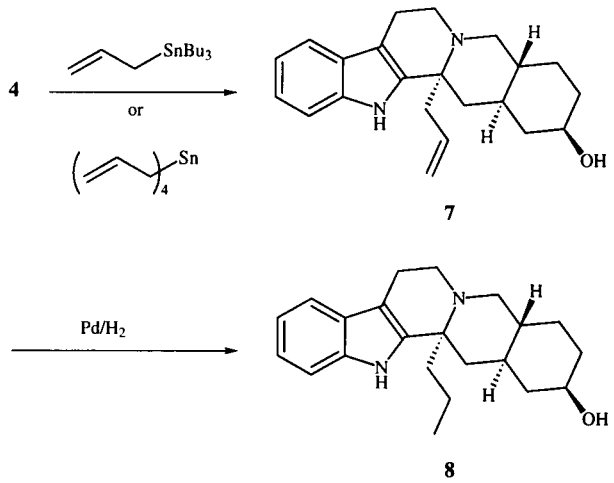
The 13b-allyl adduct **7** was further elaborated in order to prepare direct analogs of **1** (Scheme 3). Catalytic reduction of the 13b-allyl substituent of **7** gave the 13b-propyl alcohol **8**. A Swern oxidation of **7** and **8** yielded the ketones **9** and **10**. Aldol condensation on **9** and **10** with benzaldehyde gave the benzylidene ketones **11** and **12** as semi-pure intermediates suitable for further reaction. Reduction of the keto group of **11** with sodium borohydride provided the benzylidene alcohol **13**, the 13b-allyl analog of **1**, as a single isomer. Similar reduction of **12** yielded stereoselectively the benzylidene alcohol **14**, the 13b-propyl analog of **1**.

Scheme 1



2 3 4 5 6

Scheme 2



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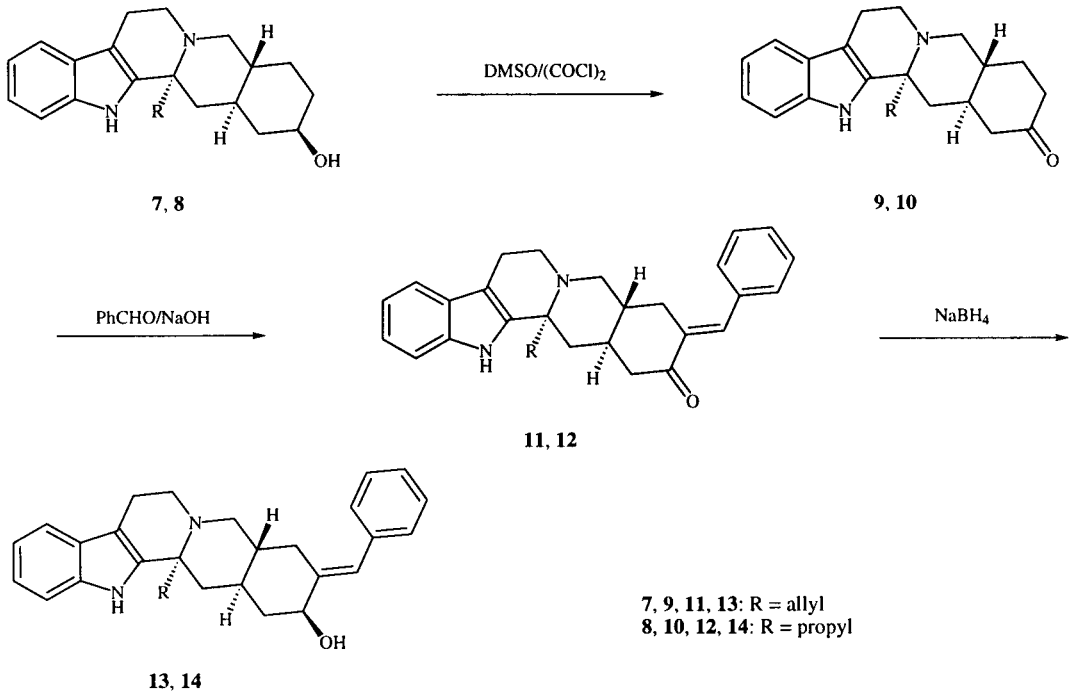
In the ^{1}H nmr spectra of **5-8**, the resonance for the 2-position axial (α) ring proton in these compounds appears as a clearly discernable multiplet between δ 3.4-3.6 ppm, in agreement with that of structurally similar systems [14,15]. Decoupling experiments indicated a representative coupling constant of approximately 11 Hz for the coupling of this proton with the adjacent 1-position axial ring proton. This value is consistent with that generally observed for axial-axial coupling of protons on adjacent carbons in a cyclohexane ring [16]. The 2-position equatorial (β) hydroxyl proton resonance in these four compounds is observed as a doublet between δ 4.4-4.6 ppm. However, in the ^{1}H nmr spectra of **13** and **14**, the 2-position ring proton resonance has been shifted to δ 4.13 and 4.11 ppm, respectively, while the corresponding hydroxyl resonances are observed at δ 5.10 and 5.09 ppm, apparently due to the influence of the benzylidene moiety. In order to unambiguously establish the regiochemistry of the 13b- and 2-positions and the benzylidene double bond of **14** (and by analogy, that of **13**), a X-ray crystallography analysis was performed on **14**. The observed X-ray structure of **14** complexed with one equivalent of diethyl ether is illustrated as an ORTEP diagram in Figure 1. The X-ray structure confirms the axial (α) orientation of the 13b-position propyl substituent as well as that of the 2-position ring

Scheme 3



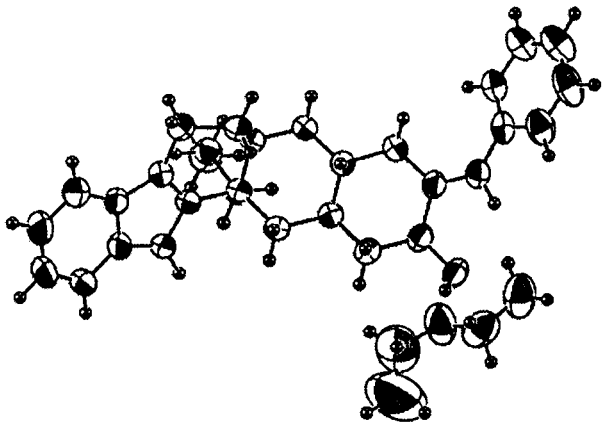


Figure 1. ORTEP plot of compound **14**.

proton. The *E* orientation of the benzylidene moiety minimizes steric interaction with the 2-position hydroxyl. Crystal and refinement parameters for compound **14** as well as positional parameters and their estimated standard deviations are shown in Tables 1 and 2, respectively. Bond distances and angles for **14** are listed in Tables 3 and 4. A similar X-ray analysis of compound **5** confirmed the axial orientation of the 13b-butyl substituent and the 2-position ring proton.

Table 1

Crystal and Refinement Data for **14**

Formula	$C_{33}H_{44}N_2O_2$ (including Et_2O)
Formula weight	500.72
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (#19)
a, Å	9.414(1)
b, Å	11.522(1)
c, Å	27.097(2)
V, Å^3	2939.0(3)
Z	4
F(000)	1088
Density (calc), g/cm^3	1.13
Crystal size (mm)	0.1 x 0.1 x 0.3
Absorbtion coef., cm^{-1}	5.1
2 θ (max), deg.	148.7
Reflections collected	3427
Independent reflections	3397
Parameters refined	335
Final R indices	R1 = 0.049, wR2 = 0.078
Largest diff. peak, e/Å^3	0.16

Table 2

Positional Parameters for **14** [a]

Atom	x	y	z	B(A2)
O1	0.6331(2)	0.3250(2)	0.67923(6)	5.29(4)
O2	0.8439(4)	0.1832(2)	0.6411(1)	9.00(8)
N1	0.6444(2)	0.1983(2)	0.91599(7)	3.96(4)
N2	0.5540(3)	-0.1156(2)	0.90102(7)	4.13(4)
C1	0.7939(5)	-0.3329(3)	0.9884(1)	6.57(8)
C2	0.8080(4)	-0.2132(3)	0.9899(1)	5.60(7)
C3	0.7225(3)	-0.1461(2)	0.95901(9)	4.34(5)
C4	0.7125(3)	-0.0236(2)	0.94913(9)	4.14(5)
C5	0.7970(3)	0.0771(3)	0.9680(1)	4.86(6)
C6	0.7930(3)	0.1710(3)	0.9290(1)	4.60(5)
C7	0.6276(3)	0.3086(2)	0.89057(9)	4.38(5)
C8	0.6680(3)	0.3081(2)	0.83599(9)	4.07(5)
C9	0.6443(3)	0.4280(2)	0.8127(1)	4.58(6)
C10	0.6705(3)	0.4290(2)	0.75732(9)	4.17(5)
C11	0.6024(3)	0.3281(2)	0.73038(9)	4.49(5)
C12	0.6318(3)	0.2113(2)	0.75506(9)	4.39(5)
C13	0.5854(3)	0.2146(2)	0.80896(9)	3.93(5)
C14	0.6036(3)	0.0984(2)	0.83480(9)	4.00(5)
C15	0.5658(3)	0.1030(2)	0.89033(9)	3.77(4)
C16	0.6097(3)	-0.0086(2)	0.91429(9)	3.85(5)
C17	0.6232(3)	-0.2007(2)	0.92780(9)	4.36(5)
C18	0.6084(4)	-0.3204(3)	0.9265(1)	5.61(7)
C19	0.6947(5)	-0.3843(3)	0.9571(1)	6.75(9)
C20	0.4050(3)	0.1214(2)	0.8974(1)	4.24(5)
C21	0.3561(3)	0.1459(3)	0.9499(1)	4.68(6)
C22	0.1989(4)	0.1563(3)	0.9540(1)	5.81(7)
C23	0.7351(3)	0.5130(3)	0.7324(1)	4.70(6)
C24	0.7930(3)	0.6261(2)	0.7480(1)	4.75(5)
C25	0.8944(4)	0.6788(3)	0.7184(1)	6.28(7)
C26	0.9440(5)	0.7900(3)	0.7297(2)	7.9(1)
C27	0.8981(5)	0.8501(3)	0.7689(2)	7.19(9)
C28	0.7971(4)	0.8000(3)	0.7992(1)	6.05(8)
C29	0.7441(3)	0.6887(3)	0.7885(1)	5.21(6)
C30	0.9168(6)	0.3567(5)	0.6049(2)	8.9(1)
C31	0.9369(5)	0.2305(4)	0.6060(2)	8.1(1)
C32	0.8626(8)	0.0626(5)	0.6528(2)	12.5(2)
C33	0.802(1)	-0.0108(6)	0.6198(4)	19.3(4)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3

Bond Distances (A^0) for **14** [a]

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C11	1.416(3)	C10	C23	1.328(4)
O2	C31	1.401(6)	C11	C12	1.528(4)
O2	C32	1.436(6)	C12	C13	1.525(4)
N1	C6	1.477(4)	C13	C14	1.521(4)
N1	C7	1.454(3)	C14	C15	1.547(3)
N1	C15	1.495(3)	C15	C16	1.499(3)
N2	C16	1.387(3)	C15	C20	1.540(4)
N2	C17	1.383(3)	C17	C18	1.387(4)
C1	C2	1.386(5)	C18	C19	1.374(5)
C1	C19	1.394(6)	C20	C21	1.520(4)
C2	C3	1.395(4)	C21	C22	1.489(5)

Table 3 (continued)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
C3	C4	1.440(4)	C23	C24	1.475(4)
C3	C17	1.409(4)	C24	C25	1.387(5)
C4	C5	1.497(4)	C24	C29	1.392(4)
C4	C16	1.363(4)	C25	C26	1.397(5)
C5	C6	1.512(4)	C26	C27	1.340(6)
C7	C8	1.527(4)	C27	C28	1.383(6)
C8	C9	1.536(4)	C28	C29	1.406(5)
C8	C13	1.517(4)	C30	C31	1.467(7)
C9	C10	1.520(4)	C3	C33	1.36(1)
C10	C11	1.515(4)			

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 4

Bond Angles (deg) for **14** [a]

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C31	O2	C32	116.7(4)	C11	C10	C23	120.5(2)
C6	N1	C7	113.7(2)	O1	C11	C10	113.9(2)
C6	N1	C15	115.1(2)	O1	C11	C12	111.7(2)
C7	N1	C15	111.6(2)	C10	C11	C12	112.8(2)
C16	N2	C17	108.4(2)	C11	C12	C13	110.2(2)
C2	C1	C19	120.3(3)	C8	C13	C12	109.5(2)
C1	C2	C3	118.6(3)	C8	C13	C14	110.2(2)
C2	C3	C4	133.8(3)	C12	C13	C14	112.7(2)
C2	C3	C17	119.7(3)	C13	C14	C15	113.0(2)
C4	C3	C17	106.4(2)	N1	C15	C14	111.3(2)
C3	C4	C5	131.4(3)	N1	C15	C16	107.0(2)
C3	C4	C16	107.4(2)	N1	C15	C20	109.1(2)
C5	C4	C16	121.0(2)	C14	C15	C16	109.2(2)
C4	C5	C6	107.6(2)	C14	C15	C20	110.6(2)
N1	C6	C5	110.0(2)	C16	C15	C20	109.6(2)
N1	C7	C8	115.4(2)	N2	C16	C4	109.6(2)
C7	C8	C9	111.0(2)	N2	C16	C15	123.1(2)
C7	C8	C13	110.1(2)	C4	C16	C15	127.2(2)
C9	C8	C1	111.5(2)	N2	C17	C3	108.1(2)
C8	C9	C10	112.9(2)	N2	C17	C18	130.2(3)
C9	C10	C11	113.7(2)	C3	C17	C18	121.7(3)
C9	C10	C23	125.6(2)	C17	C18	C19	117.3(3)
C1	C19	C18	122.4(3)	C24	C25	C26	120.3(3)
C15	C20	C21	116.0(2)	C25	C26	C27	122.7(4)
C20	C21	C22	112.7(3)	C26	C27	C28	118.5(3)
C10	C23	C24	131.9(3)	C27	C28	C29	120.1(3)
C23	C24	C25	118.5(3)	C24	C29	C28	121.2(3)
C23	C24	C29	124.2(3)	O2	C31	C30	108.6(4)
C25	C24	C29	117.2(3	O2	C32	C33	113.9(6)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. (Madison, NJ). The ir spectra were recorded as potassium bromide disks on a Mattson Cygnus 100 FTIR spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian Unity 400 spectrometer with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a Micromass Platform II or Platform LC spectrometer operating at atmospheric pressure. Reactions were usually run under a nitrogen atmosphere, and solutions were concentrated at reduced pressure on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM. Since the sole previous publication of **4** and **6** [5] included only the ultraviolet spectra of these compounds, we have included their preparation here with full spectral characterization.

[2*R*-(2α,4aα,14aβ)]-2-Hydroxy-2,3,4,4a,5,7,8,13,14,14a-decahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolinium/chloride (**4**).

A suspension of **2** (8.0 g, 27 mmoles) and triethylamine (5.0 ml, 3.6 g, 35.6 mmoles) in 400 ml of dichloromethane was cooled to -5° in an ice/sodium chloride bath. A solution of *tert*-butyl hypochlorite (8.0 ml, 7.7 g, 70.7 mmoles) in 50 ml of dichloromethane was added dropwise, with the reaction mixture temperature maintained at -5 to -10°. The mixture was stirred as the ice bath slowly melted for 18 hours. The mixture was filtered, and the filtrate was washed several times with brine. The organic layer was dried (anhydrous sodium sulfate) and evaporated. The residue was dissolved in 80 ml of ethanol, and the solution was cooled in ice and treated with 20 ml of ethanol previously saturated with gaseous hydrogen chloride. The precipitated product was filtered and washed several times with ether to yield 4.9 g (55%) of salt **4**. An additional 1.0 g of product was obtained by treating the ethanol filtrate with ether. A sample recrystallized from methanol/2-propanol had mp 295°-dec. (lit [5] mp 298-301°); ir: 3326, 1625, 1546, 1333 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.98-1.26 (m, 3H), 1.66 (m, 2H), 1.78 (m, 1H), 1.92 (m, 1H), 2.03 (m, 1H), 2.79-2.91 (m, 1H), 3.26 (t, J = 8.4 Hz, 2H), 3.38-3.52 (m, 3H), 3.88 (m, 1H), 3.95-4.12 (m, 2H), 4.77 (d, J = 4.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.41-7.45 (m, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 12.36 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 20.2, 28.4, 32.6, 32.7, 34.7, 35.2, 36.9, 41.3, 53.9, 58.8, 70.0, 114.1, 122.5, 122.8, 123.5, 125.4, 127.6, 129.6, 142.6; ms: m/z 295 $(M-Cl)^+$.

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.98, H, 7.01; N, 8.47. Found: C, 68.74; H, 6.89; N, 8.43.

[2*R*-(2α, 4aα,13β,14aβ)]-13b-Butyl-1,2,3,4,4a,5,7,8,13,13b,14,-14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-ol (**5**).

A suspension of **4** (10.6 g, 32.0 mmoles) in 600 ml of ether was cooled in an ice bath while a solution of *n*-butyl lithium (100 ml, 160 mmoles of 1.6 *M* in hexane) was added dropwise. The mixture was stirred at room temperature for 18 hours, then at reflux for 6 hours. The mixture was again cooled in ice and treated dropwise with 200 ml of saturated aqueous ammonium chloride solution. The mixture was filtered, and the filtrate layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 200 ml), and the extracts were combined with the original organic layer. The insoluble material was digested twice with 200 ml of warm ethyl acetate. The mixture was filtered, and the filtrate was added to the original ethyl acetate extracts. The combined organic layers were washed several times with brine, dried (anhydrous sodium sulfate), and evaporated. Chromatography (2% triethylamine in ethyl acetate) of the residue gave 1.8 g (16%) of **5**. A sample recrystallized twice from aqueous 2-propanol had mp 235°-dec.; ir: 3314, 1453, 1322, 1035 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.63-0.79 (m, 4H), 0.82-1.15 (m, 2H), 1.17-1.28 (m, 5H), 1.35-1.52 (m, 3H), 1.61-1.72 (m, 3H), 1.87 (m, 1H), 2.13 (m, 1H), 2.55-2.76 (m, 4H), 2.87 (m, 1H), 3.09 (m, 1H), 3.46 (m, 1H), 4.49 (d, J = 4.6 Hz, 1H), 6.89-7.00 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 10.59 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.6, 22.7, 23.2, 26.5, 28.4, 32.6, 35.6, 36.0, 36.9, 38.8, 43.1, 47.4, 54.8, 57.4, 69.1, 106.7, 111.2, 117.8, 118.4, 120.5, 127.0, 136.3, 141.3; ms: m/z 353 $(M+1)^+$.

Anal. Calcd. for $C_{23}H_{32}N_2O$: C, 78.37; H, 9.15; N, 7.95. Found: C, 78.17; H, 9.22; N, 7.81

[2*R*-(2α,4aα,14aβ)]-1,2,3,4,4a,5,7,8,13,14a-Decahydroindolo-[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-ol (**6**).

A suspension of **4** (8.5 g, 25.7 mmoles) in 500 ml of tetrahydrofuran was treated dropwise at room temperature with 116 ml of 1.0 *M* methyl lithium in 10% tetrahydrofuran in cumene. The mixture was stirred at reflux for 21 hours, then cooled and poured over ice. The precipitated solid was filtered, washed with water, and dried to yield 5.0 g (66%) of **6**. A sample recrystallized from 95% ethanol/methanol/chloroform had mp 205-209° (lit [5] mp 212-215°); ir: 3205, 1650, 1447, 1326 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.82-1.12 (m, 2H) 1.15-1.30 (m, 1H), 1.35-1.48 (m, 1H), 1.67 (m, 1H), 1.84-2.05 (m, 3H), 2.67 (t, J = 11.0 Hz, 1H), 2.70-3.15 (m, 5H), 3.52 (m, 1H), 4.60 (d, J = 4.3 Hz, 1H), 4.96 (d, J = 1.4 Hz, 1H), 6.92-7.07 (m, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 10.92 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 21.1, 28.1, 35.5, 37.3, 38.6, 42.0, 50.3, 55.9, 68.9, 98.4, 108.4, 110.9, 118.0, 118.4, 121.6, 126.4, 130.5, 135.5, 136.7; ms: m/z 295 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.37; H, 7.55; N, 9.39.

[2*R*-(2α,4aα,13β,14aβ)]-13b-Allyl-1,2,3,4,4a,5,7,8,13,13b,14,-14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-ol (**7**).

A solution of **4** (1.0 g, 3.0 mmoles) in 15 ml of chloroform and 15 ml of methanol was treated with allyltributyltin (1.2 ml, 1.3 g, 3.9 mmoles). The mixture was stirred at reflux for 46 hours, then cooled and added to 300 ml of brine. The mixture was filtered and extracted with chloroform. The combined organic layers were washed with brine, dried (anhydrous sodium sulfate) and evaporated. Chromatography (0.75% triethylamine in ethyl acetate) of the residue gave 0.20 g (20%) of **7** as a foam. Recrystallization from aqueous 2-propanol gave crystals of mp 228-230°; ir: 3283, 1455, 1321, 1271 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.87-1.27 (m, 4H), 1.35-1.51 (m, 3H), 1.68 (m, 1H), 1.78-1.93 (m, 2H), 2.52-2.73 (m, 5H), 2.81-3.07 (m, 3H), 3.47 (m, 1H), 4.51 (d, J = 4.3 Hz, 1H), 4.81 (dd, J = 2.2, 8.2 Hz, 1H), 4.92 (dd, J = 2.2, 15.2 Hz, 1H), 5.52 (m, 1H), 6.89-7.01 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 10.60 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 22.5, 28.3, 35.2, 35.9, 36.3, 38.2, 38.9, 43.0, 47.3, 54.6, 57.5,

69.2, 106.6, 111.3, 116.2, 117.9, 118.5, 120.6, 126.9; 136.1, 136.4, 140.8; ms: m/z 337 $(M+1)^+$.

Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.28; H, 8.44; N, 8.15.

Alternate Preparation of **7**.

A suspension of **4** (11.2 g, 33.9 mmoles) and tetraallyltin (10.5 ml, 12.4 g, 43.7 mmoles) in 100 ml of 2-methoxyethanol was stirred at reflux for 4 hours. The cooled reaction mixture was added to 1.0 L of 5% aqueous sodium bicarbonate solution and 1.0 L of ethyl acetate. The mixture was filtered, and the filtrate layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 400 ml), and the extracts were combined with the original organic layer. The insoluble material was digested with warm ethyl acetate (3 x 200 ml). The mixture was filtered, and the filtrate was added to the original ethyl acetate extracts. The combined organic layers were washed several times with brine, dried (anhydrous sodium sulfate) and evaporated. Chromatography (0.75% triethylamine in ethyl acetate) of the residue gave 6.6 g (58%) of **7**, identical to the product obtained from the reaction of **4** and allyltributyltin in methanol and chloroform.

[2*R*-(2α,4aα,13β,14aβ)]-13b-Propyl-1,2,3,4,4a,5,7,8,13,13b,14,-14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-ol (**8**).

A solution of **7** (5.3 g, 15.8 mmoles) in 100 ml of 50% tetrahydrofuran/methanol was hydrogenated over 0.5 g of 10% palladium on carbon catalyst. The catalyst was filtered, and the filtrate was evaporated to yield 5.1 g (96%) of **8**. A sample chromatographed (10% methanol in dichloromethane) and recrystallized from ethyl acetate/hexane had mp 195°-dec.; ir: 3308, 1461, 1322, 1026 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.75-0.76 (m, 4H), 0.83-1.06 (m, 2H), 1.08-1.32 (m, 3H), 1.33-1.52 (m, 3H), 1.58-1.77 (m, 3H), 1.87 (m, 1H), 2.07 (m, 1H), 2.53-2.75 (m, 4H), 2.88 (m, 1H), 3.09 (m, 1H), 3.45 (m, 1H), 4.49 (d, J = 4.6 Hz, 1H), 6.89-7.00 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 10.59 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.9, 17.5, 22.7, 28.4, 35.0, 35.6, 35.9, 37.2, 38.8, 43.0, 47.4, 54.9, 57.5, 69.1, 106.7, 111.2, 117.8, 118.4, 120.5, 127.0, 136.3, 141.4; ms: m/z 339 $(M+1)^+$.

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.96; H, 9.06; N, 8.30.

[2*R*-(2α,4aα,13β,14aβ)]-13b-Allyl-3,4,4a,5,7,8,13,13b,14,14a-decahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-one (**9**).

A solution of oxalyl chloride (0.93 ml, 1.4 g, 10.7 mmoles) in 35 ml of dichloromethane was cooled to -78° while a solution of dimethyl sulfoxide (1.7 ml, 1.9 g, 24.0 mmoles) in 10 ml of dichloromethane was added dropwise. The mixture was stirred for 15 minutes, and a solution of **7** (2.9 g, 8.6 mmoles) in 40 ml of tetrahydrofuran was added dropwise. The mixture was stirred for 30 minutes, and *N,N*-diisopropylethylamine (7.5 ml, 5.6 g, 43.1 mmoles) was added dropwise. The cooling bath was removed, and the mixture was stirred as it warmed to room temperature for 16 hours. The reaction mixture was added to 800 g of ice and water, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous sodium sulfate), and evaporated. The residue was chromatographed (ethyl acetate/hexane/triethylamine; 50:50:1) to yield 2.2 g (76%) of **9**. A sample recrystallized from ethyl acetate/hexane had mp 220-223°; ir 3343, 1704, 1451, 1275 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30-1.38 (m, 1H), 1.48 (t, J = 13.0 Hz, 1H), 1.75-1.81 (m, 4H), 1.98-2.21 (m, 3H), 2.33-3.08 (m, 9H), 4.75 (dd, J = 2.2, 10.0 Hz, 1H), 4.87 (d, J = 17.3 Hz, 1H), 5.45 (m, 1H), 6.85-6.96 (m, 2H), 7.20 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 10.59 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 22.5, 29.6, 36.4, 36.6, 37.2, 38.9, 41.3, 47.3, 47.8, 53.9, 57.2, 106.7, 111.3, 116.3, 118.0, 118.5, 120.7, 126.9, 135.9, 136.4, 140.4; ms: m/z 335 $(M+1)^+$.

Anal. Calcd. for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 78.68; H, 7.74; N, 8.29.

[2*R*-(2α,4aα,13β,14aβ)]-13b-Propyl-3,4,4a,5,7,8,13,13b,14,14a-decahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-one (**10**).

Prepared from **8** (5.7 g, 16.8 mmoles), oxalyl chloride (1.8 ml, 2.6 g, 20.6 mmoles), dimethyl sulfoxide (3.4 ml, 3.7 g, 47.9 mmoles), and *N,N*-diisopropylethylamine (15.0 ml, 11.1 g, 86.1 mmoles) by the procedure described for the preparation of **9**. Chromatography of the crude product gave 4.3 g (75%) of **10**. A sample recrystallized from ethyl acetate/hexane had mp 255°-dec.; ir: 3316, 1700, 1470, 1321, cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.75-0.79 (m, 4H), 1.17-1.39 (m, 2H), 1.56-1.68 (m, 2H), 1.74-1.81 (m, 4H), 2.03-2.26 (m, 4H), 2.38-3.19 (m, 7H), 6.90-7.01 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 10.62 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.8, 17.4, 22.6, 29.7, 34.9, 35.7, 37.6, 38.8, 41.3, 47.3, 47.9, 54.0, 57.2, 106.8, 111.2, 117.8, 118.4, 120.6, 126.9, 136.3, 140.9; ms: m/z 337 $(M+1)^+$.

Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.23; H, 8.24; N, 8.52.

[2*S*-(2α,4aα,13β,14aβ)]-13b-Allyl-3-benzylidene-1,2,3,4,4a,5,-7,8,13,13b,14,14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-ol (**13**).

A solution of **9** (0.26 g, 0.78 mmoles) in 70 ml of methanol was treated with a solution of 10% aqueous sodium hydroxide (0.32 ml, 0.80 mmoles), and the mixture was heated to reflux. A solution of benzaldehyde (0.21 ml, 0.22 g, 2.1 mmoles) in 3.0 ml of methanol was added dropwise, and heating at reflux was continued for 4 hours. The cooled reaction mixture was evaporated, and the residue was partitioned between ethyl acetate and brine. The combined organic layers were dried (anhydrous sodium sulfate) and evaporated. The residue was chromatographed (ethyl acetate/hexane/triethylamine; 25:75:1) to yield 0.27 g (82%) of [4a*S*-(2*E*,4aα,13β,14aβ)]-13b-allyl-3-benzylidene-3,4,4a,5,7,8,-13,13b,14,14a-decahydro-1*H*-indolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-one (**11**) as a foam; ^1H nmr (DMSO-d_6): δ 1.14 (s, 1H), 1.50 (t, J = 12.0 Hz, 1H), 1.68-1.79 (m, 1H), 1.87-1.95 (m, 1H), 2.15 (t, J = 13.7 Hz, 2H), 2.37-2.73 (m, 4H), 2.80-3.01 (m, 5H), 3.03-3.12 (m, 1H), 4.83 (d, J = 10.3 Hz, 1H), 4.97 (d, J = 7.1 Hz, 1H), 5.53 (m, 1H), 6.92 (t, J = 7.3 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 7.20-7.55 (m, 8H), 10.67 (s, 1H); ms: m/z 423 $(M+1)^+$.

A solution of **11** (1.8 g, 4.3 mmoles) in 75 ml of methanol was cooled in an ice bath while sodium borohydride (0.73 g, 19.3 mmoles) was added slowly. The mixture was stirred at room temperature for 18 hours, and the solvent was evaporated. The residue was partitioned between ethyl acetate and ice water. The layers were separated, and the aqueous layer was extracted with fresh ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous sodium sulfate) and evaporated. The residue was chromatographed (ethyl acetate/hexane/tri-

ethylamine; 33:67:0.5) to yield 1.3 g (72%) of **13**. Recrystallization from ethyl acetate-hexane gave crystals of mp 211-213°; ir: 3396, 1637, 1446, 1318 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.09 (q, J = 11.5 Hz, 1H), 1.26-1.38 (m, 1H), 1.41 (t, J = 12.7 Hz, 1H), 1.64 (t, J = 12.9 Hz, 1H), 1.72-1.77 (m, 1H), 1.86-1.92 (m, 2H), 2.55-3.02 (m, 9H), 4.13 (m, 1H), 4.82 (d, J = 10.0 Hz, 1H), 4.96 (d, J = 17.8 Hz, 1H), 5.10 (d, J = 5.1 Hz, 1H), 5.51 (m, 1H), 6.57 (s, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.99 (t, J =7.4 Hz, 1H), 7.18-7.37 (m, 7H), 10.64 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 22.5, 31.6, 35.3, 36.5, 38.4, 39.4, 39.5, 40.6, 44.2, 47.2, 54.4, 57.5, 71.3, 106.6, 111.3, 116.3, 117.9, 118.5, 119.1, 120.6, 126.4, 126.9, 128.7, 129.2, 136.1, 136.4, 138.3, 140.6, 144.8; ms: m/z 425 $(M+1)^+$.

Anal. Calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 81.77; H, 7.48; N, 6.39.

[2*S*-(2α,4aα,13β,14aβ)]-3-Benzylidene-13b-propyl-1,2,3,4,4a,-5,7,8,13,13b,14,14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-*b*]-isoquinolin-2-ol (**14**).

Using the procedure described in the preparation of **11**, a mixture of **10** (1.0 g, 3.0 mmoles), benzaldehyde (0.80 ml, 0.84 g, 7.9 mmoles) and 10% aqueous sodium hydroxide solution (1.2 ml, 3.0 mmoles) was reacted to yield 0.9 g (71%) of [4a*S*-(2*E*,4aα, 13β,14aβ)]-3-benzylidene-13b-propyl-3,4,4a,5,7,8,13,13b,14,-14a-decahydro-1*H*-indolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-2-one (**12**) as a foam; ^1H nmr (DMSO-d_6): δ 0.71-0.88 (m, 4H), 1.21-1.36 (m, 1H), 1.58 (t, J = 12.3 Hz, 1H), 1.63-1.79 (m, 2H), 1.83 (m, 1H), 2.02-2.23 (m, 3H), 2.30-2.70 (m, 4H), 2.78-2.95 (m, 4H), 3.05-3.19 (m, 1H), 6.89-7.01 (m, 2H), 7.11-7.52 (m, 8H), 10.64 (s, 1H); ms: m/z 425 $(M+1)^+$.

Ketone **12** above (2.5 g, 5.0 mmoles) was reduced with sodium borohydride (1.0 g, 26.4 mmoles) in 100 ml of methanol by the procedure described in the preparation of **13**. Chromatography of the crude product gave 2.0 g (80%) of **14**. Recrystallization from ethanol/ether gave crystals of mp 224-226°; ir: 3401, 1469, 1319, 1065 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.76-0.77 (m, 4H), 1.08 (q, J = 11.7 Hz, 1H), 1.15-1.35 (m, 2H), 1.46 (t, J = 12.5 Hz, 1H), 1.52-1.92 (m, 5H), 2.07-2.20 (m, 1H), 2.52-2.91 (m, 6H), 2.99-3.11 (m, 1H), 4.11 (m, 1H), 5.09 (d, J = 4.2 Hz, 1H), 6.56 (s, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.17-7.36 (m, 7H), 10.62 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.9, 17.5, 22.6, 31.6, 35.1, 35.6, 38.4, 38.6, 40.6, 44.3, 47.3, 54.7, 57.5, 71.3, 87.7, 106.7, 111.2, 117.8, 118.4, 119.0, 120.5, 126.4, 127.0, 128.7, 129.2, 136.3, 138.3, 141.2, 144.9; ms: m/z 427 $(M+1)^+$.

Anal. Calcd. for $C_{29}H_{34}N_2O$: C, 81.65; H, 8.03; N, 6.57. Found: C, 81.42; H, 8.03; N, 6.43.

X-ray Structure Determination of **14**.

Compound **14** crystallized as colorless plates from ethanol solutions. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer using CuK radiation (λ = 1.54184 Å). The cell constants and an orientation matrix for data collection were determined from the centered angles of 25 reflections. X-ray diffraction data were collected at 23° using the omega scan technique with a variable omega scan rate from 2° to 20° per minute. The data were collected to a maximum 2θ of 148.7°. A total of 3427 reflections were collected, of which 3397 were unique and not systematically absent. Lorentz and polarization corrections were applied to the data as was an empirical absorption correction based on a series of psi scans. The crystal structure was determined by direct methods using SIR-92. A total of 273 reflections with E>1.63 were used to produce a phase set with an absolute figure of merit of 0.90. All 37 heavy atoms in the structure were located from the E map calculated using this phase set. Hydrogen atom positions were located in subsequent difference fouriers and added to the structure, but their positions were not refined. The heavy atom parameters including anisotropic temperature factors were refined by full matrix least squares using 2985 reflections with intensity greater than three times their standard deviation. The final unweighted R-factor is 0.049. The final difference fourier was essentially featureless. The highest peak in this map had a height of only 0.16 e/$Å^3$.

Acknowledgements.

We thank Dr. Gary McClusky and staff for spectral data, and Norman Colbry and Don R. Johnson for hydrogenation experiments.

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