Enantiospecific Total Synthesis of the Ajmaline Related Alkaloids (-)-Suaveoline, (-)-Raumacline, and (-)-N_b-Methylraumacline

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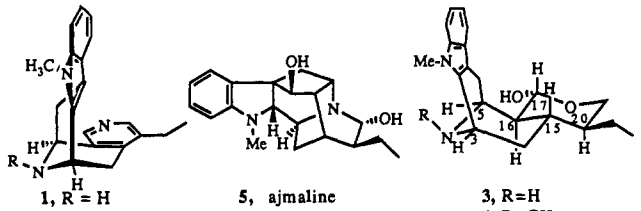
Suaveoline (**1**) was isolated from *Rauwolfia suaveolens* S. Moore in 1972[1] and from other species of *Rauwolfia*.[2] However, the alkaloid was reported to have no optical rotation, although the related N_b-methyl analog **2** was levorotatory. More recently, the natural products raumacline (**3**) and N_b-methylraumacline (**4**) were isolated from plant cell cultures of *Rauwolfia serpentina* Benth by Stöckigt, Sakai et al.[3] after feeding experiments with ajmaline.[3-5] From a biosynthetic perspective, both the suaveoline



1, R = H
2, R = CH_3

5, ajmaline

3, R=H
4, R=CH_3

and raumacline indole alkaloids appear to arise from the catabolism of the biologically important alkaloid ajmaline (**5**).[3,6,7] The absolute configurations of the stereogenic centers in **3** and **4** at C-3, C-5, C-15, C-16, and C-20 are identical to those found in ajmaline. Recently, the synthesis of the macroline/sarpagine base alstonerine was reported from this laboratory.[8] Extension of this strategy for the enantiospecific synthesis of the ajmaline related indole alkaloids suaveoline (**1**), raumacline (**3**), and N_b-methylraumacline (**4**) forms the subject of this report.

Optically active (-)-N_b-benzyl tetracyclic ketone **6** was prepared in enantiospecific fashion via a stereospecific Pictet-Spengler/Dieckmann protocol.[9-11a] Conversion of the carbonyl function of (-)-**6** into the α,β-unsaturated aldehyde moiety of **7** was accomplished[12,13] in 87% overall yield as illustrated in Scheme I.[8,14]

The α,β-unsaturated aldehyde (-)-**7** (>98% ee)[11] serves as the key intermediate for the total synthesis of alkaloids in both the sarpagine and ajmaline series.

Initial plans for the synthesis of (-)-suaveoline (**1**) called for the conversion of (-)-**7** into the allylic alcohol **9** followed by an anionic oxy-Cope rearrangement to functionalize C-15 of the tetracyclic framework (see **10**). Since the olefinic bond in **10** served as a latent aldehyde function, the pseudosymmetric secondary Grignard reagent **8b** available from 5-bromo-3-heptene[15] was employed. When (-)-**7** was treated with **8b** at 0 °C under Barbier-Grignard conditions,[16] the products of 1,2-addition (**9**) and 1,4-addition (**10a-c**)[17-19] were obtained in a combined yield of 90% in a ratio of 51(**9**):49(**10**). Alcohol **9** was easily separated from the mixture and underwent the anionic oxy-Cope rearrangement at 150 °C in 88% yield to provide the same C-15 functionalized tetracyclic systems **10a,b** and **10c** in a ratio of 3:2, all of which were employed for the preparation of (-)-**1**. The hindered nature of the N_b-benzyl azabicyclo[3.3.1] system **9** is evident for the rearrangement (KH, 150 °C) would not take place at temperatures normally required for this pericyclic process.[20,21] Nonetheless, the overall conversion of **7** into **10** required for the synthesis of **1** or **2** was greater than 80%.

The mixture of C-15 functionalized aldehydes **10** was converted into the oxime **11** in 95% yield. Oxidative cleavage[22,23] of the olefinic bond of **11** with osmium tetraoxide/sodium periodate (Scheme II) provided the 1,5-dialdehyde intermediate **12**, which cyclized in situ to **13** in 70% overall yield. When (-)-N_b-benzylsuaveoline (**13**) was subjected to catalytic debenzylation with excess Pd/C (10%) and hydrogen in methanol, a 98% yield of (-)-N_b-methylsuaveoline (**2**)[24] was realized in greater than 98% ee. Catalytic debenzylation [Pd/C (10%); H_2] of the hydrochloride salt of **13**[24] in ethanol provided a 96% yield of (-)-**1**, the optical rotation of which was found to be -9.3° (c = 0.30, $CHCl_3$)[24] rather than the 0° previously reported.[1] The spectral properties of both **1** and **2** are identical to those reported earlier by Potier.[1] This constitutes the first enantiospecific synthesis of **1** and **2**, and the seven-step route from (-)-**6** appears to be general.[8]

For the synthesis of (-)-**3** and (-)-**4**, execution of the chemistry in Scheme I provided a 64% overall conversion to (-)-**10a,b** (from (-)-**7**), epimeric about the C-20 ethyl moiety. The diastereomers **10a,b** were separated by flash chromatography. Since the absolute configurations of **10a,b** at C-3, C-5, C-15, and C-16 were identical to those of **3** and **4**, both diastereomers were employed (Scheme III). The aldehyde functions of **10a,b** were protected as the ethylene acetals (see **14a,b**) in 90% yield, and this was followed by oxidative cleavage (OsO_4; $NaIO_4$)[22,23] of the olefinic bond to provide two epimeric aldehydes **15a,b** in excellent yield. The

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(24) **1**: $[\alpha]_D^{25}$ = -9.33° (c = 0.30, $CHCl_3$), lit.[1] $[\alpha]_D$ = 0 ± 2° (c = 1.0, $CHCl_3$). **2**: $[\alpha]_D^{25}$ = -89.25° (c = 0.37, $CHCl_3$), lit.[1] $[\alpha]_D$ = -93° (c = 0.89, $CHCl_3$). **3**: $[\alpha]_D^{26}$ = -26.43° (c = 0.28, $CHCl_3$). **4**: $[\alpha]_D^{25}$ = -67.50° (c = 0.16, $CHCl_3$). **13**: $[\alpha]_D^{24}$ = -126.67° (c = 0.33, $CHCl_3$). **17**: $[\alpha]_D^{26}$ = -106.67° (c = 0.30, $CHCl_3$).

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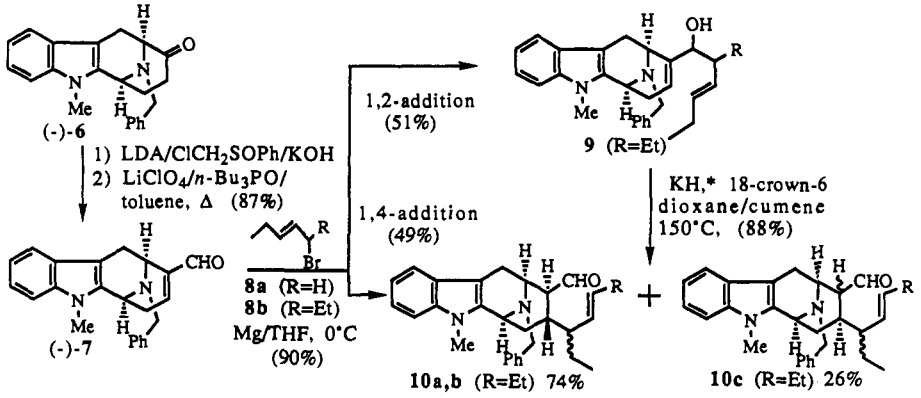
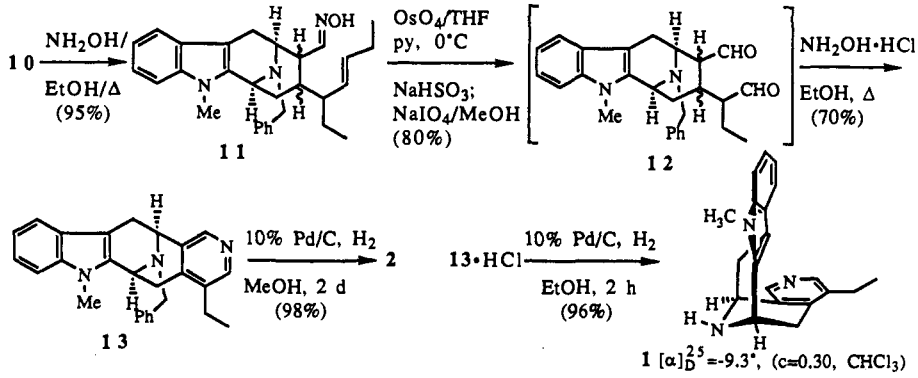
Scheme I

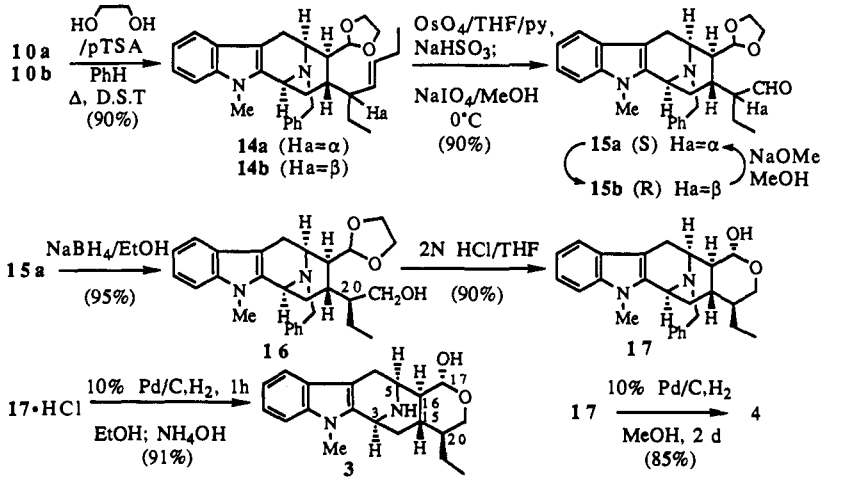


*Ratio of **10a,b** to **10c** from the anionic oxy-Cope rearrangement was 59:41.

Scheme II



Scheme III



desired (*S*)-aldehyde **15a** contains the required chirality for the preparation of **3**–**5**. For this reason, **15b** was treated with base and converted into an equilibrium mixture of **15a** and **15b** (1:1), which again was subjected to flash chromatography. In this manner, the conversion of **14a,b** into the required **15a** could be increased to greater than 85%.

The (−)-(*S*)-aldehyde **15a** was converted into the alcohol **16** in 95% yield with $NaBH_4$. Deprotection of the aldehyde function of **16** and cyclization to (−)-N_b-benzylraumacline (**17**)[24] were effected under acidic conditions in excellent yield. The conversion of **15a** into **17** is stereospecific providing only **17**, which contains the correct absolute configuration at all six chiral centers for the preparation of **3** and **4**.

Catalytic debenzylation (10% Pd/C, H_2) of the hydrochloride salt of **17** in ethanol provided (−)-raumacline (**3**)[24] in 91% yield. When (−)-**17** was subjected to catalytic debenzylation in methanol with excess Pd/C (10%) and hydrogen, an 85% yield of natural (−)-N_b-methylraumacline (**4**)[24] was realized. The ^1H and ^{13}C NMR spectra of (−)-**3** and (−)-**4** were identical to those reported for the natural products.[3] Moreover, since the Pictet–Spengler/Dieckmann approach to (−)-**6** is stereospecific,[11] all three ajmaline related alkaloids **1**, **3**, and **4** have been synthesized in greater than 98% ee.

The synthesis of (−)-**1**, (−)-**3**, and (−)-**4** described herein represents the first enantiospecific preparation of members of the ajmaline family of indole alkaloids and demonstrates that the strategy employed in the macroline related series[8] can be extended to other families.[25] The seven-step synthesis of (−)-suaveoline

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[from (-)-6] provided material in greater than 98% ee on which an accurate optical rotation could be obtained. The benzyl/methyl transfer reaction (excess Pd/C, MeOH, H_2) is noteworthy for it provides a simple procedure with which to convert the N_b-benzyl analogs into the natural N_b-methyl alkaloids (see **17** → **4**) and may be general (**13** → **2**).

Supplementary Material Available: Listing of NMR spectral data for **1**, **3**, **13**, and **17** (4 pages). Ordering information is given on any current masthead page.

Rhodium Geminal Dicarbonyl on TiO_2(110)

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Finely dispersed rhodium supported on oxide surfaces catalyzes a series of important industrial processes,[1] including the hydrogenation of carbon monoxide, the reduction of nitrogen monoxide, and the hydroformylation of olefins. The degree of dispersion has economic consequences and influences the activity and selectivity of the catalyst.[2] Consequently, there has been considerable effort in characterizing high area oxide supported rhodium using a variety of structural, spectroscopic, and chemical techniques on alumina,[3-17] silica,[6,16-18] and titania.[16,17,19-21] It appears that rhodium can be present as three-dimensional crystallites, two-dimensional rafts, and in the form of the so-called *gem*-dicarbonyl [$Rh(CO)_2$] species. Some considerable attention has been given to the generation of highly dispersed rhodium using organometallic precursors, in particular $[Rh(CO)_2Cl]_2$.[22-30] Interconversion of these phases is induced by chemisorbed CO[3,7-11,15,19,21,23,27] and can be accelerated by the presence of surface hydroxyl groups. In an effort to study the fundamental chemistry of the oxide supported *gem*-dicarbonyl, we have for the first time generated, and characterized, the species on a single crystal oxide surface under ultra high vacuum conditions. In order to avoid the more severe pressure conditions likely to be required to produce $Rh(CO)_2$ from the metal, we used the reactive adsorption of $[Rh(CO)_2Cl]_2$ at 300 K on TiO_2(110). Its adsorption and decomposition have been the subjects of an XPS and TPD investigation in the ultra high vacuum environment on amorphous alumina films grown on Al_2O_3.[31-33]

Experiments have been performed in a UHV system incorporating a 1-1000 amu quadrupole mass spectrometer, LEED, XPS,[34] and FT-RAIRS. A more detailed description of the apparatus will appear elsewhere.[35] The TiO_2(110) single crystal surface has been cleaned using cycles of Ar^+ bombardment, annealing at 1000 K, and oxygen treatment at 400 K following procedures described previously.[36] $[Rh(CO)_2Cl]_2$ has been prepared[37] and purified by vacuum sublimation and dosed into the UHV system using a doser situated 10 mm from the sample surface.

Exposure of the TiO_2(110) surface at 300 K to $[Rh(CO_2)Cl]_2$ results in the adsorption of a stable Rh surface species (E_{BE}-[$Rh(3d^{5/2})$] = 309.1 eV) which saturates at a Rh coverage of 0.35 ± 0.05 ML.[38] A concomitant adsorption of chlorine is observed with $E_{BE}[Cl(2p^{3/2})]$ = 198.5 eV. The Rh and Cl binding energies are shifted from the values associated with the physisorbed parent molecule obtained by adsorption at 200 K ($E_{BE}[Rh(3d^{5/2})]$ = 309.3 eV, $E_{BE}[Cl(2p^{3/2})]$ = 199.1 eV), in agreement with previous measurements.[1-3] XPS indicates that this surface species is stable to 450-500 K (the physisorbed species desorbs at lower temperature) when CO is desorbed, producing metallic rhodium.[35] The chlorine remains on the surface to 700 K and is associated with chemisorbed chlorine on TiO_2(100); no further change is observed in $E_{BE}[Cl(2p^{3/2})]$ during heating, particularly during the decomposition of the Rh species.

A series of FT-RAIRS spectra obtained while adsorbing $[Rh(CO)_2Cl]_2$ at 300 K is shown in Figure 1. Because of the transparency of titania in the IR, absorption of IR radiation in the adsorbed overlayer can give rise to both an increase (p) or decrease (s) in reflectivity for experiments carried out at angles more grazing than the Brewster angle.[35,39,40] A band is observed

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