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Communications

A General Stereocontrolled Strategy for the Heteroyohimbine Alkaloids: The Total Synthesis of (−)-Ajmalicine and (+)-19-Epiajmalicine

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Summary: A general approach is described for the total synthesis of enantiomerically pure 3-α-heteroyohimbine alkaloids based on the utilization of D-glucose as a chiral template for ring E. 19-Epiajmalicine was thus prepared from α-D-glucose pentaacetate in 23 steps (2.5% overall yield), averaging 85% yield per step.

The indole alkaloids[1] have attracted much interest over the years due to their important pharmacological properties.[2] Ajmalicine (raubasine)[3] (1) and 19-epiajmalicine (mayumbine)[4] (2) are the better known members of a general family of the heteroyohimbine alkaloids that also includes tetrahydroalstonine (3) and rauniticine (4). Ajmalicine is a potent peripheral and central vasodilating agent[5] with a clinically demonstrated effect in reducing platelet aggregation.[6] The pentacyclic structures of this facinating family of alkaloids[7] harbor indole, piperidine, and dihydropyran-type subunits, fused together through a set of contiguous and alternating stereogenic centers (Figure 1).

Since the original synthesis of *dl*-ajmalicine by van Tamelen and co-workers,[8] a number of elegant studies by Wenkert, Uskokovic, Takano, Martin, and others have led to the total synthesis of *dl*-ajmalicine,[9] *dl*-tetrahydroalstonine,[9-11] their enantiomerically pure natural isomers,[12-14] and (+)-19-epiajmalicine.[15] The synthesis of advanced intermediates[16] and semisynthesis from related alkaloids[17] have also been reported. In spite of this, efforts

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Scheme I

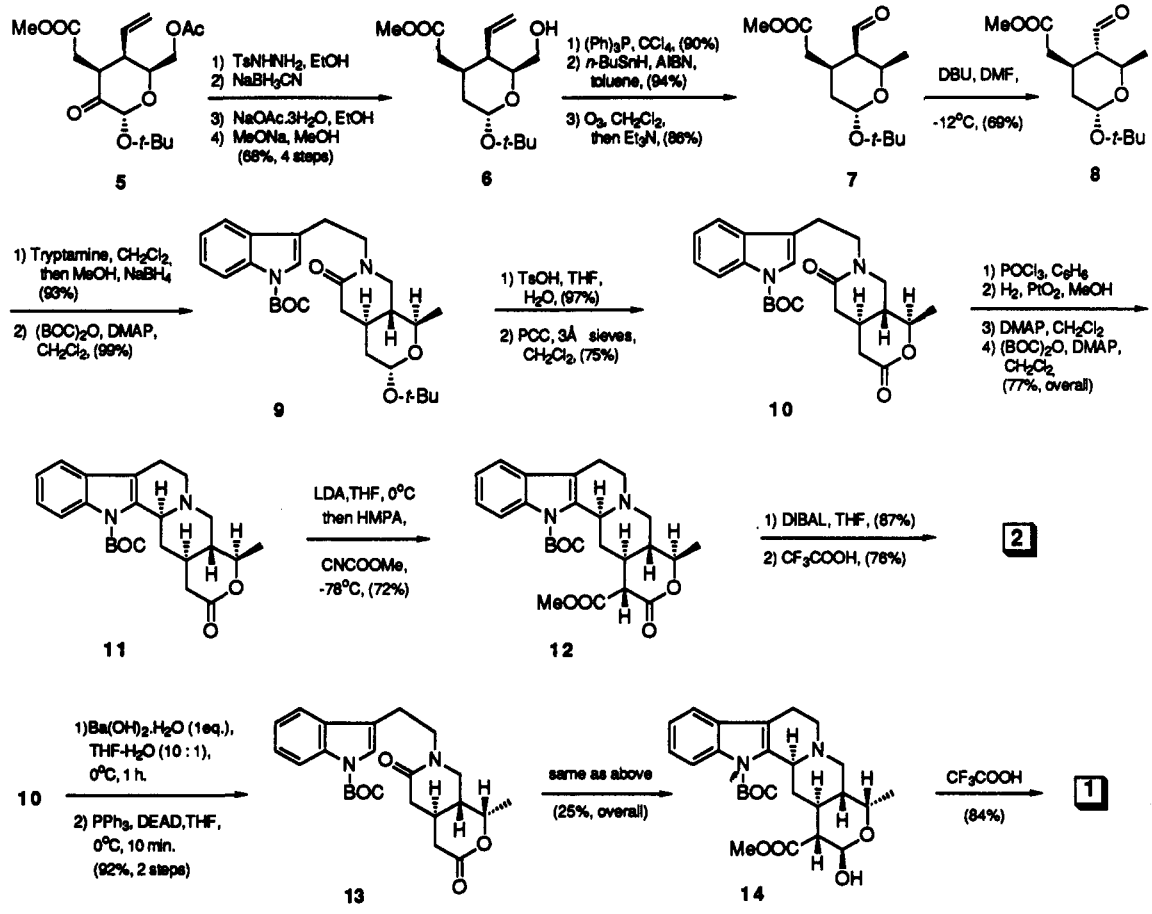

Figure 1.

to develop a general synthetic strategy that can lead to any one of the four isomeric 3-α-heteroyohimbines (Figure 1) through a common intermediate have been limited.[18]

We describe in this paper a general approach to this family of alkaloids as exemplified by the total synthesis of (−)-ajmalicine and (+)-19-epiajmalicine. The obvious skeletal overlap of the dihydropyran ring in all these alkaloids with a hexose-like structure instigated the search for an efficient and stereocontrolled C-functionalization at C-3/C-4 in D-glucose[19] with the aim of generating a common intermediate. Such a chiron could be further elaborated upon by functional and stereochemical adjustments en route to the respective targets.

Intermediate **5** (Scheme I), was readily prepared from D-glucose pentaacetate in six steps and in 30% overall yield by a series of sequential transformations previously reported from our laborabory.[20] With three contiguous stereogenic centers easily generated, we proceeded to test the feasibility of functionalizing the keto group in order to introduce the methoxycarbonyl group early in the synthesis. Such a structure would nearly converge with that of elenolic acid,[14,16,21] a known synthetic precursor of ajmalicine. Unfortunately, all attempts in this direction using phosphorus or sulfur ylids were unsuccessful, and we opted for a reductive deoxygenation of the keto group via the tosylhydrazone,[22] which afforded **6** after deacetylation (68%, four steps), $[\alpha]^{25}_D$ +142° (*c* 1.10, $CHCl_3$). Treatment of **6** with Ph_3P/CCl_4 gave the corresponding chloride, mp 30–31 °C, $[\alpha]^{25}_D$ +130° (*c* 1.55, $CHCl_3$), which when subjected to a radical-mediated dehalogenation[23] gave the corresponding deoxy derivative in 94% yield, $[\alpha]^{25}_D$ +152.3° (*c* 1.42, $CHCl_3$). At this juncture, our plan for synthesis in the heteroyohimbine series with a trans junction of rings D/E such as in ajmalicine (**1**) and the 19-epi isomer **2** called for an oxidative cleavage of the vinyl group and epimerization of the resulting aldehyde. Ozonolysis of the deoxy derivative gave the aldehyde **7**, $[\alpha]^{25}_D$ +136° (*c* 1.26, MeOH), which when treated with DBU, underwent smooth epimerization to aldehyde **8** (59%, two steps), mp 58–62 °C, $[\alpha]^{25}_D$ +97.1° (*c* 0,66, $CHCl_3$), containing a minor quantity of **7**.

Coupling of **8** with tryptamine under conditions used for reductive amination[24] led in excellent yield to **9**, mp

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188–9 °C, $[\alpha]^{25}_D$ +135.6° (c 0.84, $CHCl_3$), which was N-protected as the Boc derivative, $[\alpha]^{25}_D$ +104.2° (c 1.43, $CHCl_3$). At this stage, minor quantities of the cis-fused isomer derived from 7 could be easily separated by column chromatography. Acid hydrolysis of the glycosidic linkage followed by oxidation with PCC gave the lactone 10 (72%, two steps), $[\alpha]^{25}_D$ +63° (c 1.12, $CHCl_3$). We were now ready to effect the crucial Bischler–Napieralski reaction, which would give us the desired pentacyclic skeleton and the last stereogenic center at C-3 after catalytic reduction. The two-step sequence proceeded in excellent yield to give the desired product 11 (77% overall), mp 165–170 °C dec, $[\alpha]^{25}_D$ −144.5° (c 1.21, $CHCl_3$).[25]

Having assembled the immediate precursor to 19-epiajamalicine, we were faced with a number of choices for the methoxycarbonylation and functional adjustment of the lactone carbonyl group. Previously, van Tamelen and co-workers[8] had achieved this transformation via acylation of the lactone with methyl formate followed by an acid-catalyzed acyl–lactone rearrangement. More recently Uskokovic and co-workers[12] have used the Bredereck reagent in a bicyclic model lactone to obtain the α-(dimethylamino)methylidene derivative, which was then subjected to strong acid conditions in order to mediate the rearrangement. Although α-branching was successfully achieved in 11 under the same conditions, the subsequent acyl–lactone rearrangement failed and we resorted to an alterative approach. Thus, treatment of the 11 with LDA and Mander's reagent ($CNCO_2Me$)[26] as described by Leonard for a model lactone[16b] effected smooth methoxycarbonylation to give 12 as a single isomer, $[\alpha]^{25}_D$ −62.9° (c 0.7, $CHCl_3$). Treatment with DiBALH, followed by acid-catalyzed dehydration of the resulting lactol, gave crystalline 19-epiajmalicine (2), mp 205–206 °C dec, $[\alpha]^{25}_D$ +58.8° (c 0.17, $CHCl_3$); hydrochloride, mp 255–260 °C dec, $[\alpha]^{25}_D$ +84.5° (c 0.5, MeOH), identical in all respects with published data[15,17d] (^1H NMR, ^{13}C NMR, high-resolution mass, microanalysis).

Ajmalicine (1) was obtained from 10 via a ring-opening and inversion sequence through the intermediacy of the hydroxy acid. Thus, hydrolysis of 10 with barium hydroxide and careful acidification followed by intramolecular inversion of the resulting δ-hydroxy acid under Mitsunobu reaction conditions[27–29] gave the C-19 inverted lactone 13 $[\alpha]^{25}_D$ +12.3° (c 0.47, $CHCl_3$) and 10 (4:1). Application of the same sequence of reactions to 13 as for 10 gave the C-19 epimeric lactone corresponding to 13, $[\alpha]^{25}_D$ −130.4° (c 0.78, $CHCl_3$). Methoxycarbonylation with Mander's reagent followed by reduction with DiBALH gave *N*-Boc-ajmalicinine 14[30] as a 13:1 mixture of anomers. Dehydration of 14 led to ajmalicine isolated as the hydrochloride (21% overall from 10), mp and mixed mp 270–275 °C dec, $[\alpha]^{25}_D$ −12° (c 0.05, MeOH) (lit.[31] $[\alpha]^{25}_D$ −12.9° (c 0.24, MeOH).

We have described a strategy for the total synthesis of (−)-ajmalicine (1), (+)-19-epiajmalicine (2), and *N*-Boc-ajmalicinine (14) from a common progenitor. The general approach can be easily extended to tetrahydroalstonine (3) and rauniticine (4) as well as other 3-α-heteroyohimibines starting with the readily available chiron 7.[32,33]

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Supplementary Material Available: Selected spectra and physical constants of key compounds (37 pages). Ordering information is given on any current masthead page.

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(25) A portion of the product in which the *N*-Boc group was partially hydrolyzed during the reaction was transformed into 11 by treatment with Boc anhydride in CH_2Cl_2/DMAP.

(26) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 3425. *Aldrichimica Acta* **1987**, *20*, 53.

(27) A similar strategy was independently utilized by Leonard et al.[16b] to elaborate a synthesis of methyl elenolate.

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(31) Obtained from Fluka, A. G. See also: Höfle, G.; Heinstein, P.; Stöckigt, J.; Zenk, M. H. *Planta Medica* **1986**, *40*, 120.

(32) For example, 7 was easily converted to the corresponding lactone and lactam via reduction of aldehyde and lactonization, etc. (see supplementary material).

(33) All new compounds were satisfactorily characterized by chemical, physical, spectroscopic and microanalytical methods (see supplementary material).

On Deuterium-Labeling Studies for Probing Rhodium-Catalyzed Hydroboration Reactions

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Summary: Reactions of deuteriocatecholborane ($C_6H_4O_2BD$) with alkenes in the presence of rhodium(+1) complexes have been reinvestigated. Distributions of label in the products differ significantly from those reported previously, and alternative rationales for these observations are provided.

Deuterium-labeling studies were recently reported[1] to elucidate the mechanism of rhodium-catalyzed hydroborations (Scheme I). Our interest was aroused because the authors implied their results, particularly those depicted in eq 1, cast doubt upon a postulate one of us had used to explain substrate-controlled diastereoselectivities in catalyzed hydroborations of chiral, 1,1-disubstituted, acyclic alkenes.[2,3]

To explain the observed distribution of deuterium in the alcohol 2, the authors proposed,[1] "*The incorporation of deuterium α to the hydroxyl group of the product alcohol*

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