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Stereocontrolled Total Synthesis of Alkaloid G via the Oxy-anion Cope Rearrangement and Improved Total Synthesis of (+)-Ajmaline

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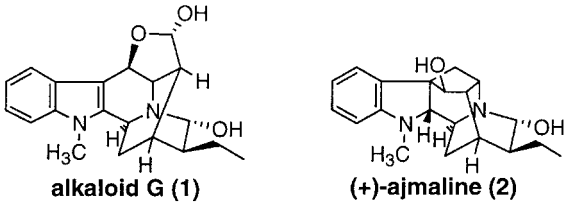
ABSTRACT



The oxy-anion Cope rearrangement followed by protonation of the enolate which resulted under conditions of kinetic control has been employed to generate the key asymmetric centers at C(15), C(16), and C(20) in alkaloid G (1) and (+)-ajmaline (2) in a highly stereocontrolled fashion. The aldehyde 7b from this process has been converted into alkaloid G (1) and (+)-ajmaline (2) in 36% and 13% overall yields (11 reaction vessels from 3), respectively.

Alkaloid G (**1**) was isolated from plant cell cultures of *Rauwolfia serpentina* Benth by Stöckigt et al.[1] after feeding experiments with (+)-ajmaline (**2**); the latter alkaloid was isolated from the roots of *R. serpentina* in 1931.[2] Alkaloid G (**1**) is of interest because of the novel C(6)-oxygen, C(17)-hemiacetal bond illustrated in Figure 1, while (+)-ajmaline

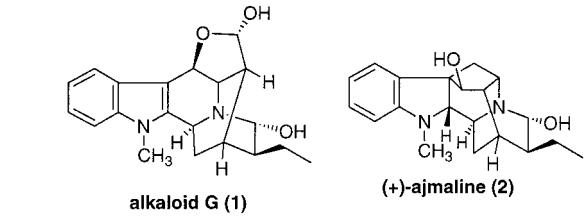


Figure 1.

(**2**) contains four heteroatoms, six rings, and nine asymmetric centers. It is a clinically important indole alkaloid[3−8] with historical significance[2,9] and is related to the sarpagine bases.[10,11] "The most prominent action of ajmaline is an

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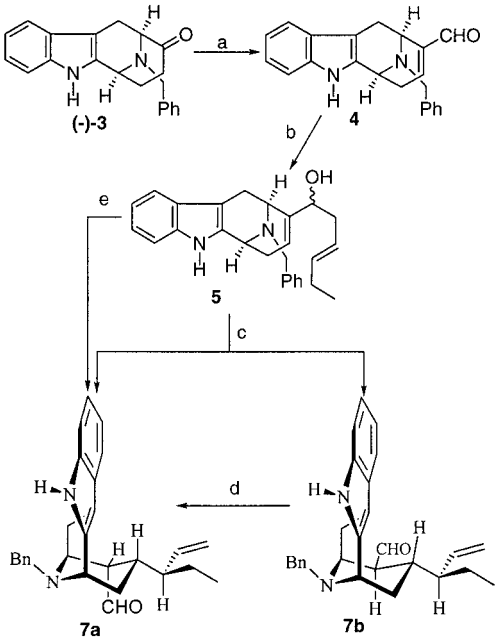
antiarrhythmic effect on the heart" as was reviewed by Creasey, "that is less pronounced than that of propranolol,[7] but is superior in terms of the ratio of the refractory phase over reduced conduction to that of procaine amide and quinidine".[7,12] Both alkaloid G (**1**) and (+)-ajmaline (**2**) are structurally related by the presence of the quinuclidine ring and the C(5)−C(16) bond linkage as well as the identical absolute configurations of the stereogenic centers at C(3), C(5), C(15), C(16), C(20), and C(21) as shown in Figure 1.

Three important reports on the synthesis of **2** have appeared previously,[13−16] and an enantiospecific total synthesis of (+)-**2** as well as alkaloid G (**1**) has recently been reported.[17,18] The chiral centers of C(15), C(16), and C(20) were established selectively in earlier work[17,18] based on a Barbier−Grignard process[17−19] (Mg metal) with a seven-carbon-atom pseudosymmetric carbanion, followed by an oxy-anion Cope rearrangement. This approach resulted in the formation of several diastereomers at C(20), the majority of which could be employed in the synthesis of (+)-**2**.[17,18] Recently, this seven-carbon fragment has been replaced with a five-carbon unit (*trans*-1-bromo-2-pentene) employing the barium chemistry of Yamamoto.[20,21] This provided a homoallylic alcohol which underwent the oxy-anion Cope rearrangement with high diastereoselectivity. Kinetic protonation of the enolate, which resulted, gave the desired intermediate with the asymmetric centers at C(15), C(16), and C(20) in high diastereoselectivity (43:1). This improvement provides the first facile entry into the desired absolute configuration of the ethyl group at C(20) of the ajmaline-related alkaloids and resulted in an enantiospecific total synthesis of alkaloid G (**1**) and an improved synthesis of (+)-**2**, the details of which follow below.

The starting (−)-N_a-H, N_b-benzyl tetracyclic ketone **3** has been synthesized via a two-pot process on multihundred gram scale in our laboratory.[17,18,22−25] Conversion of the carbonyl function of (−)-**3** into the α,β-unsaturated aldehyde moiety of **4** was achieved through the spirooxiranophenylsulfoxide[26,27] in 87% yield, as shown in Scheme 1. A key improvement in the synthesis of **2** came on conversion of aldehyde **4** into the allylic alcohol **5** employing a modification of the chemistry of Yamamoto.[20,21] When *trans*-1-bromo-2-pentene was stirred with barium metal under normal reaction conditions, none of the desired olefinic alcohol **5** was observed. However, when aldehyde **4** and *trans*-1-bromo-2-pentene were premixed and added to a solution of preformed barium metal at −78 °C, analogous to a Barbier−Grignard process, a 90% yield of the desired homoallylic alcohol **5** was obtained. Allylic rearrangement of the barium-stabilized carbanion did not occur at −78 °C.

Scheme 1[a]



[a] (a) $ClCH_2SOPh$, LDA/THF, −78 °C, KOH (aq), rt; $LiClO_4$/dioxane, reflux, 24 h, on 50 g scale, 87% overall yield; (b) Li/biphenyl/BaI_2/THF, −78 °C, **4** and *trans*-1-bromo-2-pentene, 90%; (c) KH/dioxane/18-crown-6, 100 °C, 14 h, 85%; (d) NaOMe/MeOH, 95%; (e) KH/dioxane/18-crown-6, 100 °C, 14 h; CH_3OH, 0 °C → rt, 4 h, 85%.

When the homoallylic alcohol **5** was heated to 100 °C under the conditions of the oxy-anion Cope rearrangement (KH, 18-crown-6, dioxane), the process took place from the α-face of the olefinic system to furnish the desired stereochemistry at C(15) and C(20) with high diastereoselectivity (>30:1). Only a trace of the epimeric diastereomer at C(15) was ever observed; moreover, the correct chirality of the ethyl function as 20(*S*) required for **1** and **2** had been established. The two epimers **7a** and **7b** at C(16), originally isolated as a 4:1 mixture, could be converted entirely into the sarpagine stereochemistry at C(16) on treatment with base.[24]

From examination of MM2[28] calculations and epimerization experiments, it was clear that epimer **7b** with the ajmaline aldehydic stereochemistry at C(16) was the thermodynamically less stable isomer. In earlier work, epimerization of the aldehydic group at C(16) from the *R* to the *S* (ajmaline) configuration was reported as 43:7 to 7:3,[13,14,16]

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with the desired 16(*S*) material as the minor component. A study of the structure of the enolate (see **6**, Figure 2) indicated

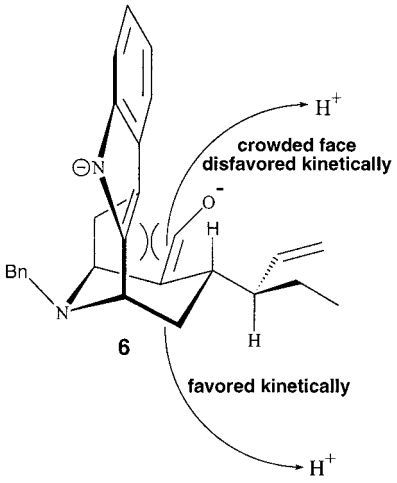


Figure 2.

that protonation from the less hindered (bottom) face (kinetic protonation) might provide the desired 16(*S*) stereochemistry directly in a one-pot fashion. Consequently, a number of experiments were carried out to study the effect of kinetic protonation in this system (see **6**). After many attempts, only a few of which are listed in Table 1, this kinetic protonation

Table 1. Kinetic Protonation versus Thermodynamic Protonation

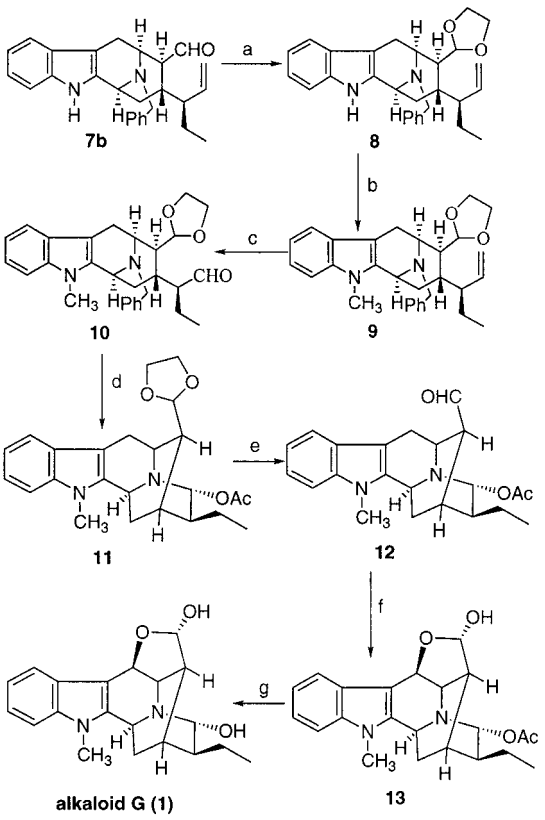
entry	solvent	temp, °C	reagent for quench	ratio (**7a**:**7b**)[a]
1	dioxane	0	CH_3OH; rt, 4 h	100:0
2	dioxane	0	CH_3OH	4:1
3	dioxane	0	2,6-diisopropylphenol	3:2
4	dioxane	0	1 N HCl (aq)	5:6
5	dioxane/THF	−78	1 N TFA (THF solution)	1:27
6	dioxane/THF	−100	1 N TFA (THF solution)	1:43

[a] The ratio was determined by integration of the ^{1}H NMR spectrum of the crude product.

was realized. When the enolate **6** was quenched under acidic conditions at lower temperature, the ratios of the desired **7b** (16*S*) to **7a** began to increase [compare entries 4 and 5, Table 1, to entry 1 (basic conditions)]. When the enolate was quenched by pouring it (**6**, THF/dioxane, −100 °C) into a (1 N) TFA/THF solution at −100 °C, the ratio of **7b** to **7a** improved dramatically to greater than 43:1. This one-pot conversion of **5** into **7b** can now be accomplished in high yield. This, for the first time, provided a highly stereocontrolled route to the key chiral centers at C(15), C(16), and C(20) of the ajmaline series.

The enantiospecific total synthesis of alkaloid G (**1**) (from **7b**) was completed as follows. The aldehydic group in **7b** was protected as the acetal with ethylene glycol/*p*-TSA with no epimerization at C(16). This provided a stable stereocenter at C(16) which permitted the conversion (NaH, CH_3I) of **8** into the N_a-methyl derivative **9** in 94% yield. This improvement resulted in the replacement of N_a-methyl-D-tryptophan with the cheaper D-(+)-tryptophan employed in the asymmetric Pictet−Spengler reaction.[29] Oxidative removal of the methylene group of the latent aldehyde in **9** with OsO_4/$NaIO_4$ furnished aldehyde **10** in 91% yield (see Scheme 2 for

Scheme 2[a]



[a] (a) ethylene glycol/*p*-TSA/benzene, Δ, 20 h, 92%; (b) NaH/THF, CH_3I, 94%; (c) OsO_4/py/THF, 0 °C, 16 h; $NaHSO_3$(aq), rt, 4 h; $NaIO_4$/CH_3OH/H_2O, 0 °C, 16 h, 91%; (d) Pd/C/H_2, DME, 2 d; Ac_2O/DMAP, 2 h, 91%; (e) *p*-TSA/acetone, rt, 12 h, 89%; (f) DDQ/THF/H_2O, rt, 94%; (g) CH_3OH, K_2CO_3 (5% aq), 0 °C, 2 h, 92%.

details). This was followed by catalytic removal of the benzyl function (Pd/C, H_2) and acetylation of the carbinolamine which resulted in a one-pot process to provide acetate **11**. The acetal moiety of **11** was removed under standard conditions to release the aldehyde **12**. This aldehyde was oxidized at C(16) employing the conditions of Yonemitsu[30,31] later modified in our laboratory (DDQ, aqueous THF)[32,33]

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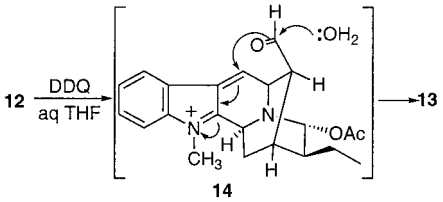
to provide the acetal **13**, stereospecifically (94%). A number of mechanisms for the generation of **13** are possible,[30−37] only one of which is depicted here (Scheme 3).

Scheme 3

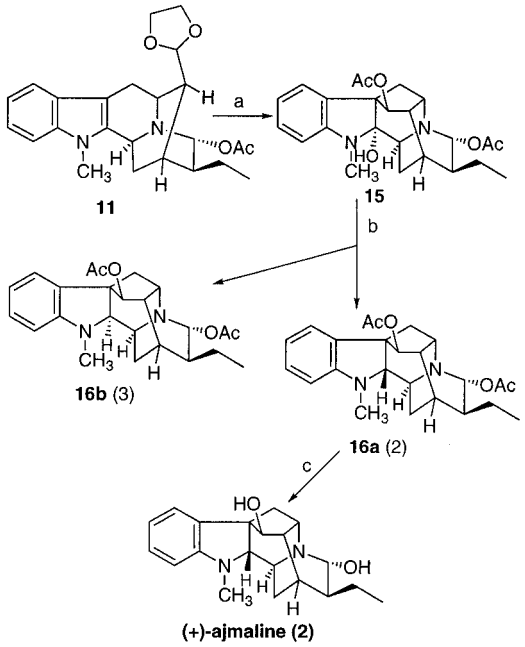


It has been proposed in the N_a-H indole system that indolenine/diene intermediates such as **14** are involved.[30−37] Although higher in energy, by analogy it is conceivable that the N_a-methyl-substituted indolenine **14** was involved which could only be attacked by the aldehyde from the top face of the olefinic system. This would provide the stereochemistry at C(6) illustrated in **14**. Other pathways or equilibrium processes might well be involved; however, if they proceed via **14**, the stereochemistry of the hydroxyl group at C(6) would be set as β. Hydrolysis of **13** under standard conditions provided **1** in enantiospecific fashion and in 36% overall yield (from **3**).

The readily available aldehyde **7b** was also converted via **11** (Scheme 2) into (+)-ajmaline **2** (Scheme 4) by following the chemistry of Li[17,18] earlier reported from our laboratory. This has now provided an enantiospecific route to (+)-**2** in 13% overall yield (from **3**, 8.9% overall yield from D-(+)-tryptophan methyl ester).

In summary, the oxy-anion Cope rearrangement of **5**, followed by quenching of the enolate under kinetically controlled conditions at −100 °C, has provided the C(15), C(16), and C(20) asymmetric centers in **7b** in a highly stereoselective manner. The homoallylic alcohol **5** was

Scheme 4[a]



[a] (a) HOAc/HCl(concd), 3 h; Ac_2O/HCl(g), 18 h, aq workup, 85%; (b) BF_3OEt_2, CH_2Cl_2, PtO_2, H_2, 14 h, 89% (**16a** + **16b**); (c) CH_3OH, 5% aq K_2CO_3, 93%.

prepared by a Barbier modification of the barium chemistry of Yamamoto[20,21] again in high yield. Because the DDQ (aqueous THF)[32,33] mediated oxidation at C(6) of aldehyde **12** provided the hemiacetal as the sole diastereomer, the route to **1** is highly efficient. This modification **5** → [**6**] → **7b** → → **10** now provides a route to (+)-ajmaline **2** (13% from **3**) in much higher overall yield (8.9% from D-(+)-tryptophan methyl ester) than previously reported and in fewer steps (11 reaction vessels).[13−18]

The combination of the cyclization reactions described above has permitted the use of D-(+)-tryptophan as both the chiral auxiliary and the starting material in the synthesis of **1** and (+)-**2** with extremely high stereocontrol.

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