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APPLICATIONS OF INTRAMOLECULAR DIELS-ALDER REACTIONS OF HETERODIENES. FACILE SYNTHESES OF THE HETEROYOHIMBINE ALKALOIDS TETRAHYDROALSTONINE AND AKUAMMIGINE.

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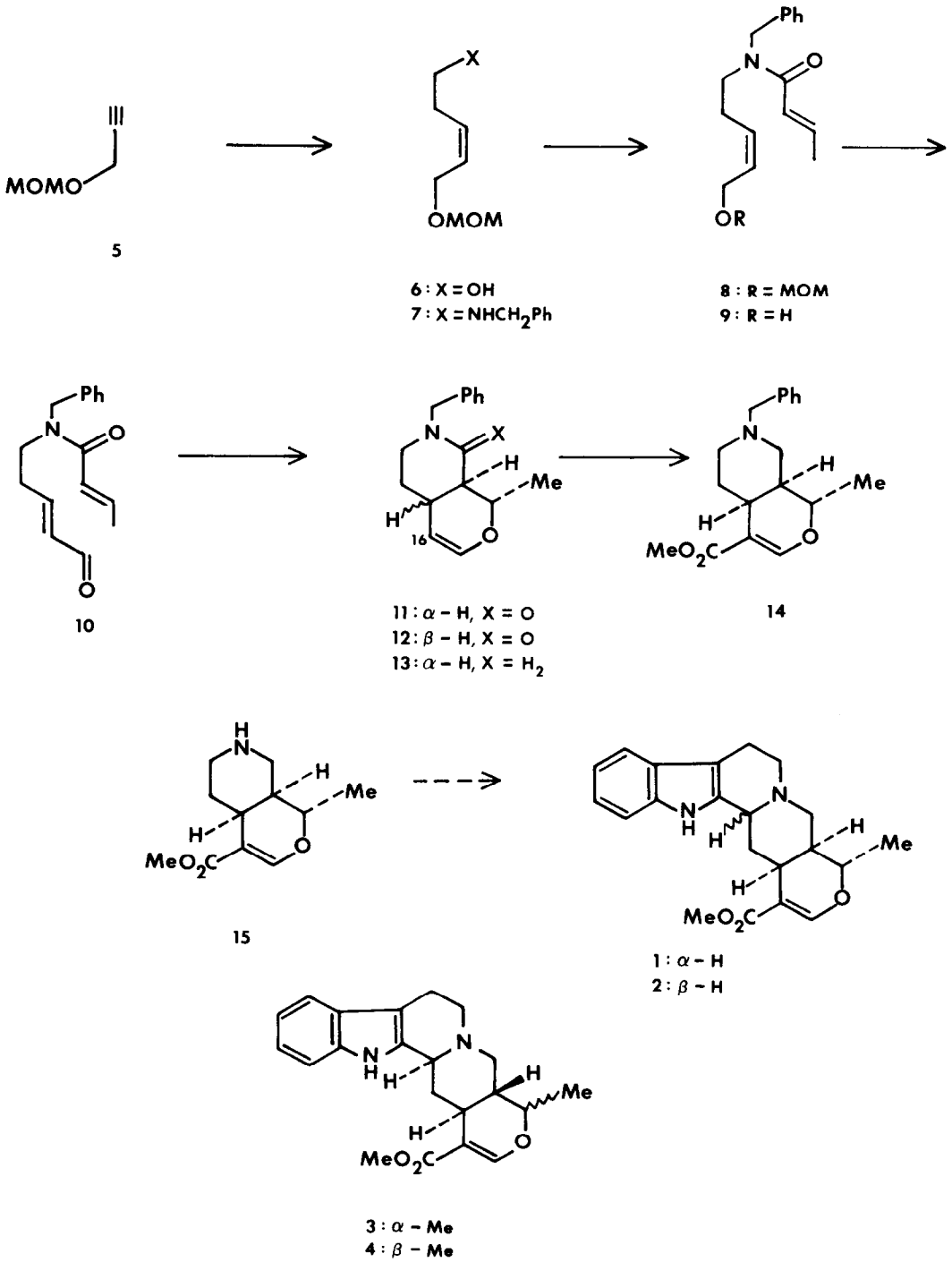
Abstract. A facile, formal synthesis of the heteroyohimbine alkaloids tetrahydroalstonine (1) and akuammigine (2) has been completed in which the D/E ring system is constructed by the novel cyclization of the triene 10, a process which involves the intramolecular [4+2] cycloaddition of a heterodiene with an α,β-unsaturated amide.

The heteroyohimbine alkaloids constitute an important class of natural products which have elicited the interest of numerous synthetic groups over the years.[2] Representative alkaloids of this family include tetrahydroalstonine (1), akuammigine (2), ajmalicine (3), and 19-epiajmalicine (4).[3] As part of a general program directed toward the development of practical and general strategies for alkaloid synthesis, we have explored the feasibility of exploiting intramolecular Diels-Alder reactions for the elaboration of heterocyclic ring systems common to various classes of alkaloids.[4,5] Within the context of addressing the synthetic challenge posed by the heteroyohimbine alkaloids, it was of particular interest to ascertain whether a hetero-Diels-Alder reaction[6,7] might be exploited for the facile construction of the D/E ring system of these alkaloids. The reduction of this strategy to practice has resulted in a concise synthesis of the heterocycle 15 (Scheme 1), which has been previously converted in two simple steps to tetrahydroalstonine (1) and akuammigine (2).[3c,h,i]

The task of preparing the requisite triene 10 was accomplished in a straightforward fashion. Thus, the two carbon chain extension of the protected propargyl alcohol derivative 5, which was prepared from propargyl alcohol [$MeOCH_2Br$ (1.2 equiv), $PhNEt_2$ (1.5 equiv), CH_2Cl_2, 0 °C→RT; 96%], to give 6 was readily achieved [a. BuLi (1.1 equiv), THF, -78 °C; b. $CH_2(OCH_2)_2$ (4.1 equiv), -78 °C→RT; c. H_2 (3 atm), 5% Pd-$CaCO_3$-PbO, EtOAc] in 78% overall yield. Subsequent conversion of the 6 to the secondary benzylamine 7 was smoothly effected by initial formation of the corresponding tosylate [TsCl (1.05 equiv), Py (1.2 equiv), CH_2Cl_2, -60→0 °C; 90%] followed by ammonolysis [$PhCH_2NH_2$ (2 equiv), cat. NaI, DMSO, RT; 88%].[8] Acylation of 7 (CH_2Cl_2, -78 °C→RT) with the mixed anhydride (1.2 equiv) derived from crotonic acid and ethyl chloroformate, which was prepared *in situ*, in the presence of triethylamine (2 equiv) provided the protected amide 8 in 85% yield. Sequential removal (MeOH, cat. H_2SO_4, reflux)[9] of the methoxymethyl protecting group from 8, Swern oxidation [$(COCl)_2$ (2 equiv), DMSO (5 equiv), Et_3N (10 equiv), CH_2Cl_2, -60 °C→RT] of the resulting allylic alcohol 9, and acid-catalyzed

SCHEME 1


MOMO
5
X
OMOM
6 : X = OH
7 : X = NHCH2Ph
Ph
N
O
OR
8 : R = MOM
9 : R = H
10
16
H
Me
MeO2C
11 : α - H, X = O
12 : β - H, X = O
13 : α - H, X = H2
14
15
1 : α - H
2 : β - H
3 : α - Me
4 : β - Me

isomerization (Et_3NHCl, CH_2Cl_2, reflux, 10 h) of the intermediate Z-α,β-unsaturated aldehyde afforded the E-α,β-unsaturated aldehyde 10 in 75% overall yield. The stage was then set for an examination of the key intramolecular hetero-Diels-Alder reaction.

In the event, thermolysis (0.5% in xylene, 190 °C, 14 h) of the triene 10 produced a 4.5:1 mixture of the cis- and trans-cycloadducts 11 and 12, respectively, which could be conveniently separated by column chromatography to provide the cis-lactam 11 in 73% yield. Thus, the feasibility of executing intramolecular [4+2] cycloadditions of heterodienes as a unique and expeditious entry to the cis-D/E ring system possessed by certain heteroyohimbane alkaloids was securely established. Subsequent hydride reduction [AlH_3 (3 equiv), THF, RT; 90%] of the lactam 11 proceeded smoothly to give the tertiary amine 13. Introduction of the requisite carbomethoxy function at C(16) of 13 was then easily effected to give 14 in 81% overall yield by acylation of 13 with neat trichloroacetyl chloride (60 °C, 2.5 h) followed by a haloform cleavage (MeOH, Et_3N, 55 °C, 1.5 h) of the intermediate trichloromethyl carbonyl compound.[10] Finally, hydrogenolysis [H_2 (1 atm), 20% $Pd(OH)_2$-C,[11] AcOH; 90%] of the benzylic amino protecting group provided the bicyclic amine 15, which was spectroscopically identical with material previously synthesized by Uskokovic.[12] Since 15 has been previously converted to a mixture of tetrahydroalstonine (1) and akuammigine (2) in two facile steps,[3c,h,i] its preparation constitutes a formal total synthesis of these two alkaloids.

The general strategy outlined in Scheme 1 for the synthesis of 1 and 2 is also eminently suited for modification and application to the syntheses of other heteroyohimbine and related alkaloids. For example, the trans-cycloadduct 12 might be converted into 19-epiajmalicine (4) by a sequence of reactions similar to that executed on 11. Furthermore, the use of a cis-dienophile would allow access to those alkaloids such as ajmalicine (3), which have a syn relationship of hydrogens at C(19) and C(20). Such conversions are the object of active investigations, the results of which will be recorded in due course.

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