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Flexible Synthetic Approaches to Monoterpene Indole Alkaloids

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Abstract: Preliminary model studies have demonstrated that our novel synthetic approaches to the *Iboga*- and seco-*Yohimbine* alkaloid families represent viable concepts for flexible strategies towards these alkaloid classes. The key step in the iboga case consists of an intramolecular nitrone-olefin 1,3-dipolar cycloaddition reaction of a monocyclic intermediate to yield a tricyclic isoxazolidine derivative that contains all of the stereochemical information of the envisaged final targets. The novel approach to seco-yohimbines involves a Cope-rearrangement of an appropriately functionalized azacyclodeca-3,7-diene precursor to establish ring D of the alkaloid target. Mild thermal treatment of an (*E,E*)-model compound gave the expected *trans*-3,4-divinylpiperidine derivative in 83% yield as the only detectable representative out of four possible diastereoisomers.

In the context of an envisaged biomimetic synthesis of the hexacyclic *Aristotelia* alkaloid aristone, the feasibility of thermally induced oxy-ene and of anionic oxy-ene reactions was investigated employing a variety of model compounds. As it turned out, such transformations can be performed under various reaction conditions in mostly good yields and with excellent diastereoselectivity.

Keywords: Anionic oxy-ene reaction · Cope rearrangement · Intramolecular nitrone-olefin cycloaddition · Thermal oxy-ene reaction

1. Introduction

Our aim is to synthesise moderately complex, pharmacologically interesting monoterpene indole alkaloids using flexible strategies that allow access to many members of the target family with only minor changes in the individual synthetic planning. This approach proved fruitful in the *Aristotelia* alkaloid family which contains several representatives that are very scarce in nature. Our efforts in this area now allow a more ready access to certain alkaloids by total synthesis than by extraction from natural sources where these alkaloids are present only in ppm amounts (for reviews, see [1]). In the present paper recent developments towards equally flexible synthetic approaches to other alkaloid families are described briefly.

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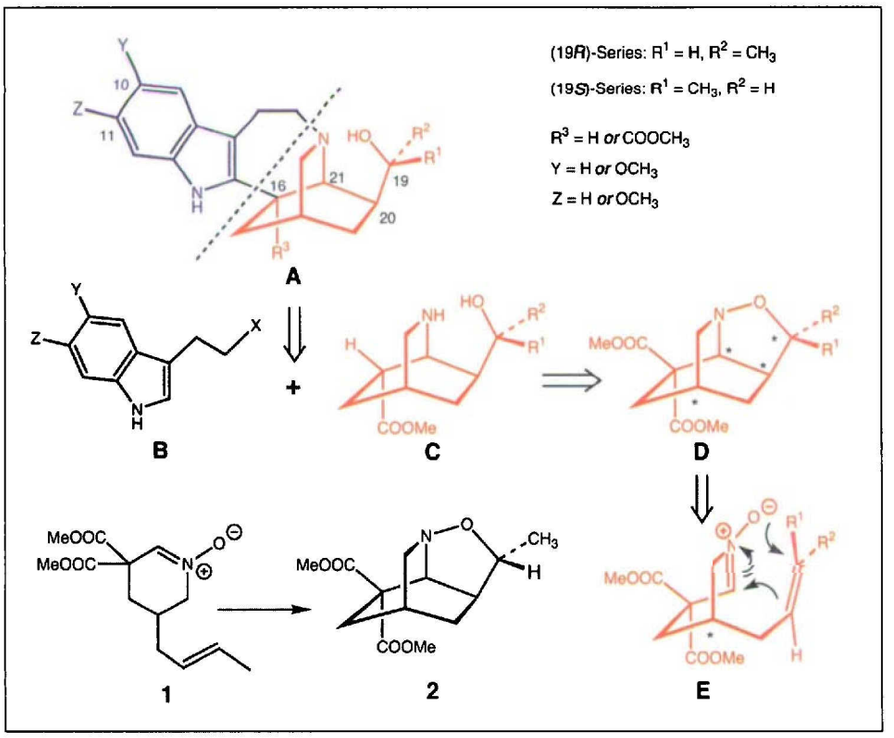
2. A Novel Approach to the *Iboga* Alkaloid Family

The *Iboga*-alkaloid family presently comprises some 60, structurally closely related representatives (for reviews, see [2]). Some of them display quite spectacular pharmacological, as well as ethnochemical and drug-addiction curing properties (for leading references, see [3]). An analysis of the naturally occurring substitution patterns within this alkaloid class (see **A**, Scheme 1) led us to develop the retrosynthetic approach detailed in Scheme 1 [3]. A disconnection of target **A** along the dashed line leads to the appropriately substituted tryptamine unit **B** and to the isoquinuclidine building block **C**. The latter can be obtained through reduction of the tricyclic isoxazole derivative **D** which is available *via* an intramolecular nitrone-olefin 1,3-dipolar cycloaddition reaction of a suitable precursor **E**. In this reaction the only chiral centre present in the latter determines the configuration of the three additional asymmetric centres of intermediate **D** which contains all of the stereochemical information of the envisaged alkaloid targets. Therefore, the chosen approach allows to determine in advance the relative configuration at C(19) by choosing the appropriate geometry of the C=C double bond in **E**.

Up to now, the reactivity of the (*E*)-isomer **1** has been investigated, which was shown to undergo a facile and high-yielding cycloaddition reaction to **2** as the single reaction product [3]. The relative configuration at C(19) was determined through an analysis of the relevant ^{1}H-NMR coupling constants of this compound. The reductive cleavage of the N–O bond in **2** was effected with Zn/AcOH in virtually quantitative yield. Presently, alternative approaches to **1** and the completion of the synthesis are being investigated in our laboratory.

3. A Novel Approach to the seco-*Yohimbine* Alkaloid Family

The heteroyohimbine alkaloids (type **F**, Scheme 2) and their closely related precursors of type **G** are wide-spread natural products, again with interesting pharmacological properties (for reviews, see [4][5]). For biogenetic reasons the absolute configuration at C(15) is invari-

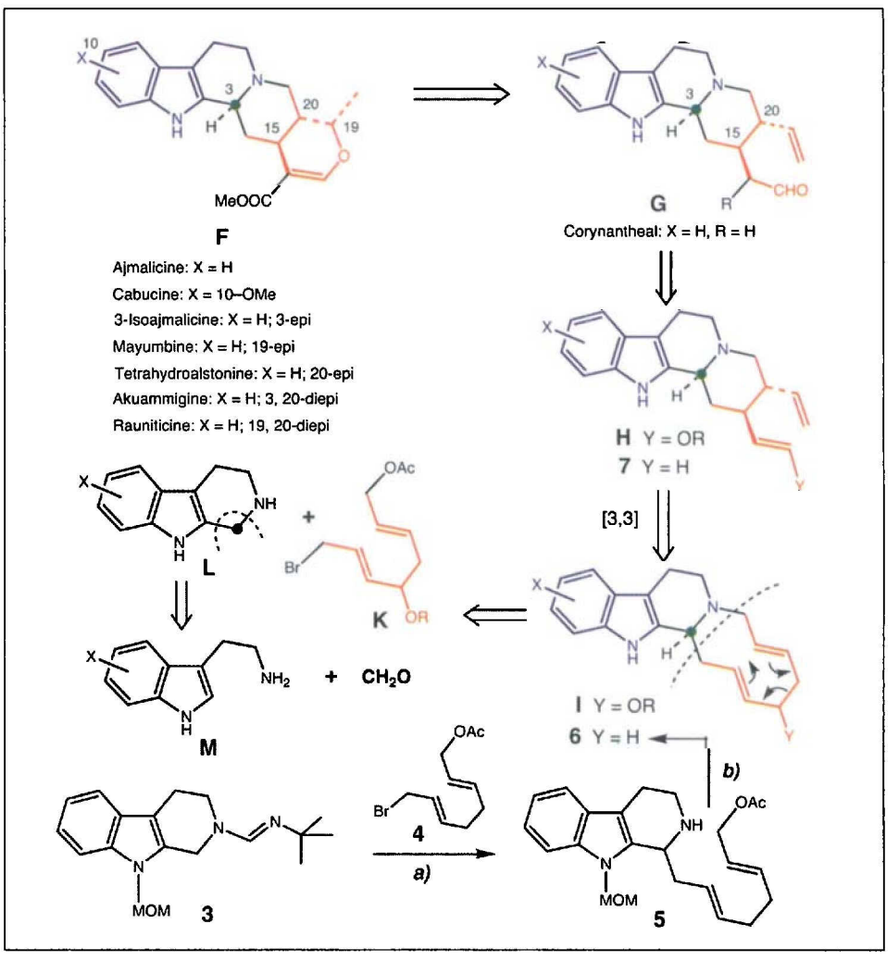


Scheme 1.

ably (*S*), while the configurations at C(3), C(19), and C(20) vary. Actually, representatives of all possible stereochemical combinations can be found in nature. Therefore, a flexible synthetic strategy should allow stereoselective access to all diastereoisomers. The chosen approach involves a Cope rearrangement [6] of a substituted azacyclodeca-3,7-diene **I** to give the substituted 3,4-divinylpiperidine **H**. Conceivably, the geometry of the olefinic double bonds in the medium-ring precursor **I** will determine the configurational relationship between the three stereocentres in **H** (for precedents, see [7]). Intermediate **I** can be degraded retrosynthetically into an acyclic precursor **K** and a tetrahydrocarboline unit **L** that is derived from a (substituted) tryptamine **M** and formaldehyde.

In the realm of a first model study to test the selected strategy, the readily available bromoacetate **4** was grafted onto the tetrahydrocarbazole derivative **3** to furnish **5** using Meyers's method [8]. Under the reaction conditions employed to close the 10-membered ring ($Pd(PPh_3)_4$

Scheme 2. *a)* 1. *t*-BuLi, THF, –70 °C, **4**, 1 h, –70 °C; 2. $NH_2NH_2 \cdot H_2O$, EtOH, AcOH, 1 h, 55 °C; *b)* $Pd(PPh_3)_4$, PPh_3, 1,2,2,6,6-pentamethylpiperidine, THF, 20 h, 50 °C.

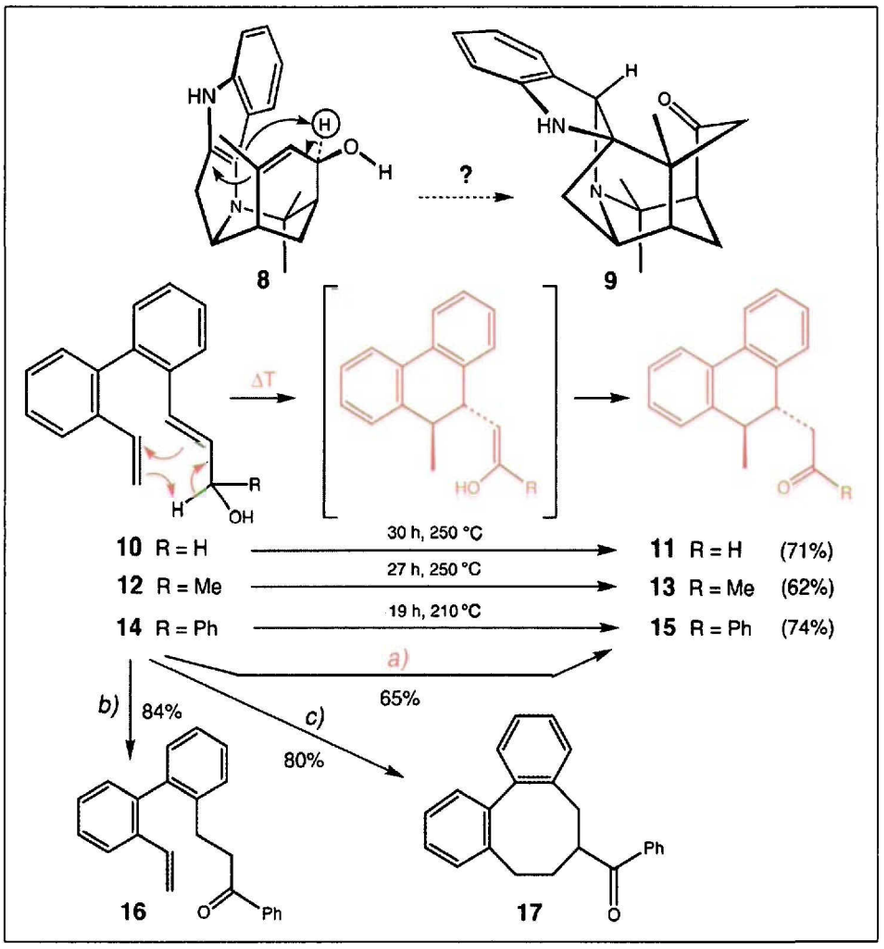


in refluxing toluene [9]) the putative intermediate **6** underwent the envisaged Cope rearrangement to give **7** as the only detectable product in 84% yield [5]. A spectroscopic analysis of the isolated product showed unambiguously that it belongs to the *normal* series, *i.e.* (3*S**, 15*S**, 20*R**). Work is in progress towards the analogue **H** with clearly differentiated vinyl groups which should yield corynantheal (**G**, X=R=H) upon simple acidic hydrolysis. In addition, the stereochemical outcome of the Cope rearrangement of geometrical olefin isomers of **4** will be investigated.

4. Thermally Induced and Anionic Oxy-Ene Reactions

The starting point for the studies described in this section were speculations that the hexacyclic *Aristotelia* alkaloid aristone (**9**) (Scheme 3) might arise from the putative precursor **8** *via* an intramolecular oxy-ene reaction [1d]. As there was seemingly no precedent for this transformation, several model systems were designed and investigated, for instance the *o,o'*-divinylbiphenyl derivatives **10**, **12** and **14** [10]. In all three cases thermally induced rearrangements to the dibenzocyclohexenes **11**, **13**, and **15**, respectively, were shown to proceed in decent yields and with high diastereoselectivity (usually *ca.* 96:4 in favour of the *trans*-substituted products [10a]) (Scheme 3).

Since concurring β-elimination of the starting allylic alcohol can present serious problems in the required temperature range, the behaviour of the above model compounds under basic conditions was also investigated [10b]. Interestingly, treatment of the same substrate **14** under various basic conditions led to entirely different products: *t*-BuOK at 25 °C for 2 h led to the isomerized ketone **16** in 85% yield, whereas Schwesinger's phosphazene base P_4-(*t*-Bu) furnished the dibenzocyclooctene derivative **17** in similar yield. In the case of **14** only the Li salt could be successfully transformed into the oxy-ene product **15**. Though the yield was somewhat lower than in the purely thermal rearrangement of **14** (65% as compared to 74%), the conditions of the anionic transformation for a comparable turnover were significantly milder (5 h at 200 °C, compared to 19 h at 210 °C). These and additional results not disclosed herein [10] bode well for the success of a future biomimetic synthesis of aristone (**9**) through intermediate **8**.



Scheme 3. *a)* 1. $LiN(Me_3Si)_2$, benzene; 2.5 h, 200 °C; *b)* ^{t}BuOK, toluene, 2 h, 25 °C; *c)* P4-(*t*-Bu), toluene, 1 h, 25 °C.

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