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A novel synthetic approach towards the AB-ring system of 9-azasteroids

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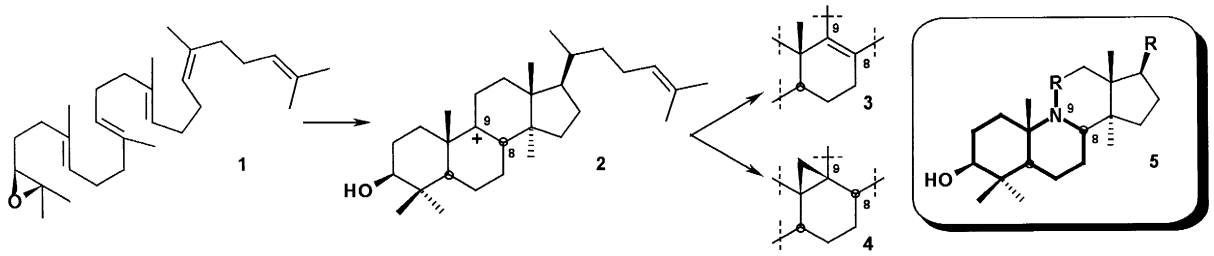
Abstract

Based on a high energy intermediate model for the inhibition of the ergosterol biosynthesis 9-azasteroids represent potential bioactive compounds as antimycotics. Herein, we describe a novel diastereoselective approach towards a substructure containing the AB-ring system bearing an angular methyl group. Utilizing Diels–Alder chemistry for the construction of the A-ring, the heterocyclic system (ring B) was constructed via a reductive cyclization methodology. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Diels–Alder reactions; aza compounds; biologically active compounds.

Placing a nitrogen atom at the position of carbocations in intermediates within the biosynthesis of ergosterol[1,2] is a general approach for the inhibition of the enzyme systems involved.[3] After the cyclization of squalene-oxide **1** and a migration sequence of methyl groups and hydrogens the intermediate **2** is formed (Scheme 1). This carbocation can react either via an elimination to lanosterol **3** in fungi or by cyclization to cycloartenol **4** in plants.[4] According to the above strategy 9-azasteroids **5** and partial structures thereof are promising candidates as inhibitors for this biochemical pathway with potential antimycotic and fungicidal activity.[5]



Scheme 1.

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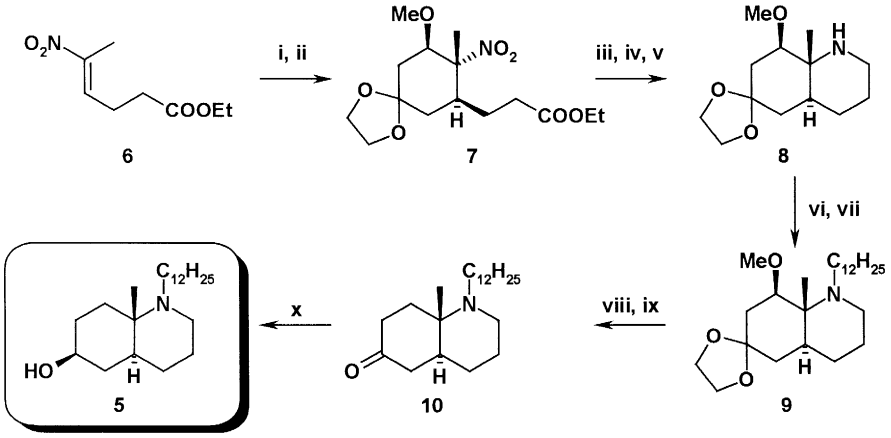
In a novel approach towards the total synthesis of compounds **5** we developed a diastereoselective route for a substructure containing the AB-ring system and the angular methyl group as well as the hydroxyl functionality as key structural elements (bold parts in **5**). In order to imitate the lipophilic properties of the CD-rings we placed a long side chain at the 9-position (R=$C_{12}H_{25}$) of our target molecule **5**.

The starting compound **6** was easily accessible by a procedure reported by us recently via addition of organometallic reagents to nitro-alkenes and transformation to the *E*-isomer utilizing solid supported triphenylphosphine.[6] Although the reactivity of 2-TMSO-butadiene proved to be insufficient, successful Diels–Alder cyclization was performed with Danishefsky's diene[7] to give product **7** in diastereomerically pure form after protection of the carbonyl group (Scheme 2).[8] The correct stereochemistry for the AB-ring system was already established at this point of the synthesis towards **5**.



Scheme 2. (i) Danishefsky's diene, benzene, reflux, 63%; (ii) $(CH_2OH)_2$, TSA, benzene, Dean–Stark separator, 98%; (iii) Al/Hg, THF/H_2O, 79%; (iv) $TiCl_3$, 75%; (v) Red-Al®, 75%; (vi) $C_{11}H_{23}COCl$, NEt_3, DMAP, 75%; (vii) Red-Al®, 88%; (viii) 6N HCl, 76%; (ix) H_2/Pd(C), 97%; (x) Red-Al®, 95%

Due to the strong sterical hindrance the nitro group was not susceptible to reduction to the amine functionality directly but rather gave the corresponding hydroxylamine upon treatment with Al/Hg. It is noteworthy that no cyclization towards the quinoline system was observed under the mild reaction conditions applied. By further reduction of this intermediate in the presence of $TiCl_3$[9] ring closure was accomplished. Subsequent reduction of the obtained amide with Red-Al® gave the heterocyclic compound **8**. Introduction of the lipophilic side chain was carried out by a straight forward strategy: conversion with dodecanoic acid chloride and reduction of the corresponding amide gave **9** in good overall yield.

Removal of the methoxy group at an earlier stage of the sequence proved difficult due to the formation of several by-products. However, elimination of methanol under acidic conditions starting with **9** smoothly afforded the expected enone. Compound **10** was obtained by subsequent catalytic hydrogenation. Treatment of this ketone with Red-Al® finally gave the target molecule **5** as the only diastereomer.[10] Further extension of this methodology towards the construction of rings C and D are presently in progress within our laboratory.

Acknowledgements

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8. The structure of **7** was confirmed by X-ray diffraction and the results will be published elsewhere.
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10. All new compounds were characterized by ^{1}H and ^{13}C NMR spectra and gave satisfactory elemental analyses. Product **5** was obtained as colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75–0.95 (m, 6H), 1.10–1.50 (m, 28H), 1.50–1.70 (m, 2H), 1.77–1.95 (m, 3H), 2.20–2.40 (m, 1H), 2.60–2.80 (m, 2H), 3.58–3.76 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.9 (q), 14.0 (q), 22.6 (t), 26.2 (t), 27.4 (t), 27.7 (t), 29.2 (t), 29.3 (t), 29.5 (t), 31.8 (t), 32.1 (t), 36.6 (t), 38.5 (t), 43.3 (d), 47.2 (t), 56.6 (s), 70.2 (d).