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Microwave-assisted total synthesis of tangutorine

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ABSTRACT

A novel microwave approach to the synthesis of tangutorine is described. The key steps comprise a diastereoselective aldol condensation of monoprotected glutaraldehyde and a microwave-assisted Pictet–Spengler reaction. The stereochemistry of the tangutorine diastereomers obtained was determined by means of NOE-experiments.

1. Introduction

The first total synthesis of tangutorine **1a**, isolated in 1999 as a racemic mixture from the leaves of *Nitraria tangutorum* by Duan et al.,[1] was published in our laboratory in 2001.[2] Since then, four other total syntheses leading to racemic tangutorine[3–6] as well as a formal synthesis[7] and some synthetic approaches[8,9] have been reported. It has been shown that tangutorine has cytotoxic activity against human colon cancer HT-29 cells.[10] The only enantioselective total synthesis of tangutorine has been performed by Hamada et al.[11] They also evaluated the cytotoxic activity of each enantiomer but no significant differences in activities between pure enantiomers and racemic tangutorine were observed.[11]

In the first total synthesis of tangutorine by Jokela et al. 7,8-dihydroquinoline-5(6*H*)-one and tryptophyl bromide were used as building blocks for the 5-ring heterocycle.[2] A detailed synthesis and enantioseparation of tangutorine by chiral HPLC was introduced in 2003 (3.4% overall yield).[3] A 19 step synthesis by Hsung et al. from a 2,3-disubstituted indole derivative and cyclohexane-1,3-dione using aza-[3+3] cycloaddition afforded the pentacycle in 5.5% overall yield.[4] In turn, Ho and Chen prepared the 5-ring framework from tryptamine and 3-(6-oxocyclohexenyl)propanal (five steps, 3.5% overall yield) using a Pictet–Spengler reaction.[5] The Pictet–Spengler reaction was utilized also in a biomimetic synthesis by Poupon et al.[6] (three steps, 2.6–4.3% overall yield) and Hamada et al.[11] (24 steps, 15.8% overall yield).

2. Results and discussion

In a previous article[12] we introduced the microwave-assisted selective protection of glutaraldehyde as monoacetal, which is an excellent compound to be used in our new improved total synthesis of tangutorine (Scheme 1).

Glutaraldehyde was protected as described in Ref. 12. At best, under acidic conditions and when proline based amide **6** was used as catalyst[13,14] the monoacetal protected glutaraldehyde **7** afforded aldol **5** in 72% yield (10:1 *syn*/*anti*). Since removal of the protecting groups in **5** turned out to be unsuccessful due to water elimination the hydroxyl group was protected with TBSCl. All protecting groups were removed successfully under the subsequent reaction conditions. Treating TBS-protected aldol **4** with *p*-TsOH in acetone/H_2O (1:1) for 15 min in a microwave reactor afforded **3a** and **3b** (5:6 dr) and hemiacetal **3c** (45% overall yield). Both **3a** and **3b** were in equilibrium with **3c**. Attempts to remove the protecting groups using conventional heating (*p*-TsOH, acetone/H_2O, rfx, 5.5 h) were unsuccessful.

We repeated the Pictet–Spengler reaction of Poupon et al. (CH_2Cl_2, AcOH, rt, 48 h) between aldehydes **3a** and **3b** and tryptamine (CH_2Cl_2, AcOH, rt, 66 h–6 days) but without success.[6] However, using microwave irradiation (30 min, CH_2Cl_2, TFA) compound **2** was formed as a mixture of diastereomers. No unreacted aldehydes **3a** or **3b** were found but the crude product still contained some hemiacetal **3c**. Only traces of other side products were formed. NMR data for **2** were congruent with the data of Poupon et al.[6] as well as our own previous data.[3] Chemical shifts for C-6 (22.4 ppm) and H-3 (3.57 ppm) are characteristic for products having *trans*-quinolizidine conformation.[3,20,21] Reduction of aldehyde **2** with $NaBH_4/CeCl_3$[6] finished the total synthesis of tangutorine, which was obtained as

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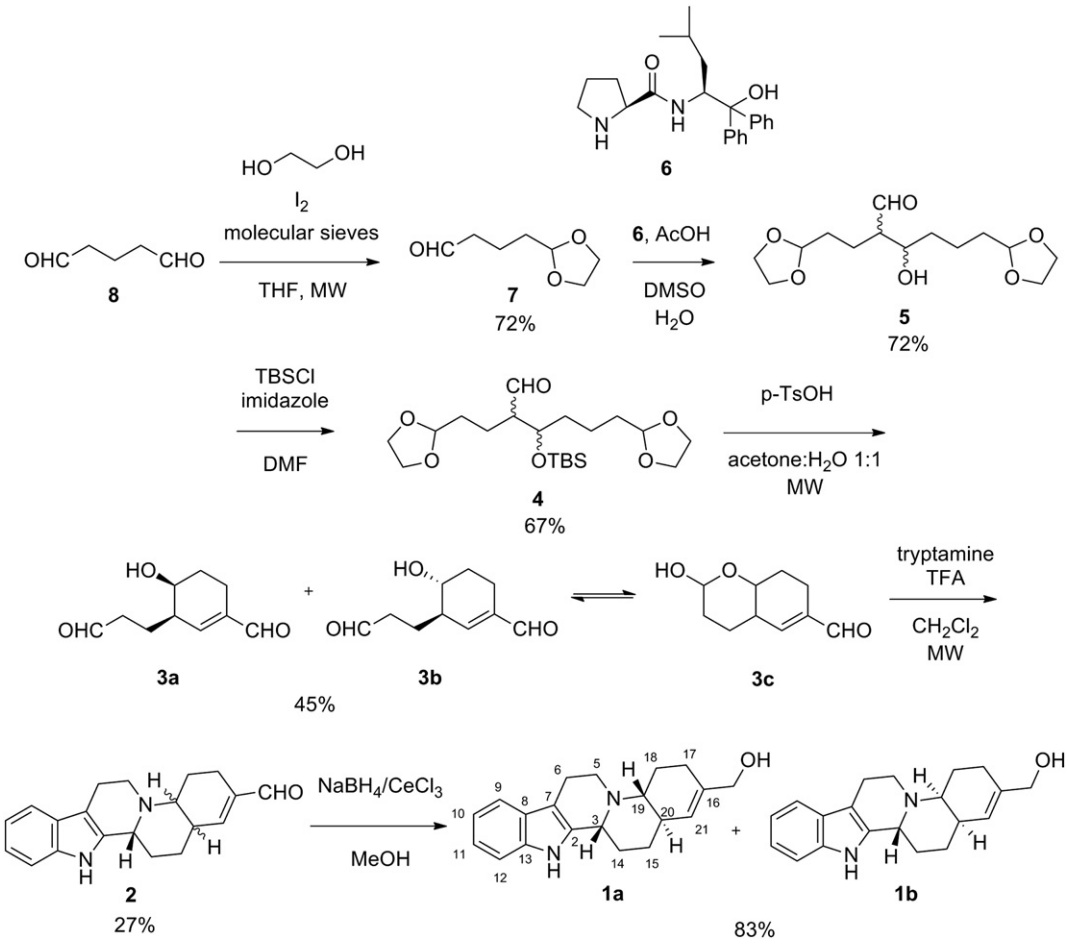

Scheme 1. Total synthesis of tangutorine diastereomers **1a** and **1b**.

a mixture of two diastereomers **1a** and **1b** (2:1 dr). The stereochemistry of the diastereomers was confirmed by NOE experiments. NOE effects in **1a** between H-5eq and H-18eq and H-20 and H-18ax and in **1b** between H-3 and H-18ax were obtained (Fig. 1). This proves that in **1b** H-19 and H-20 are cis.

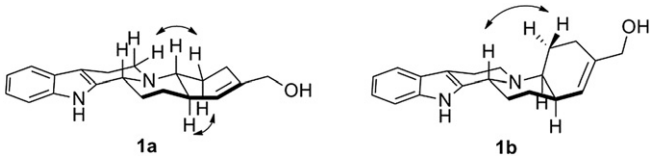

Fig. 1. NOE effects in **1a** and **1b**.

3. Conclusions

We have reported a fast, six step microwave-assisted diastereoselective total synthesis of tangutorine. The overall yield is 4.9% starting from protected glutaraldehyde **7**. In three of six steps microwaves were used. To the best of our knowledge, only few microwave-assisted Pictet–Spengler reactions for β-carboline syntheses have been performed.[15–19]

4. Experimental section

4.1. General

CH_2Cl_2 was obtained by passing deoxygenated solvent through activated alumina column (MBraun SPS-800 solvent purification system). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F_{254} (230–400 mesh) plates and analyzed by heating upon staining with $KMnO_4$ solution. Flash chromatography with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents were used unless otherwise noted. The microwave reactions were performed in an 80 mL microwave sealed vessel in a CEM Discover apparatus. ^1H (399.98 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ or MeOD. For ^1H NMR the chemical shifts are reported in parts per million relative to TMS (δ 0.00) and for ^{13}C NMR in ppm relative to $CDCl_3$ (δ 77.0) or MeOD (δ 49.0). IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer. High resolution mass spectrometric data were obtained using MicroMass LCT Premier spectrometer.

4.2. Synthesis of tangutorine

*4.2.1. (S)-N-((S)-1-Hydroxy-4-methyl-1,1-diphenylpental-2-yl)pyrrolidine-2-carboxamide (**6**).* Compound **6** was prepared as in Refs. 13 and 14.

*4.2.2. 4-(1,3-Dioxolan-2-yl)butanal (**7**).* Compound **7** was prepared as in Ref. 12.

*4.2.3. 2-(2-(1,3-Dioxolan-2-yl)ethyl)-6-(1,3-dioxolan-2-yl)-3-hydroxyhexanal (**5**).* Acetal protected glutaraldehyde **7** (1550 mg, 10.7 mmol) was dissolved in DMSO (10 mL) followed by the addition of water (0.20 mL), catalyst **6** (295 mg, 0.804 mmol) and acetic