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Concise Synthesis of (±) –*epi* –Chrysotricine

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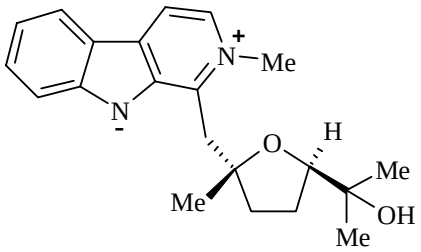
Abstract: (±)*epi*-Chrysotricine **6** was synthesized by a cascade stereoselective oxidative cyclization of 5-hydroxyalkene **3** using tert-butyl hydroperoxide(TBHP) catalyzed by $VO(acac)_2$.

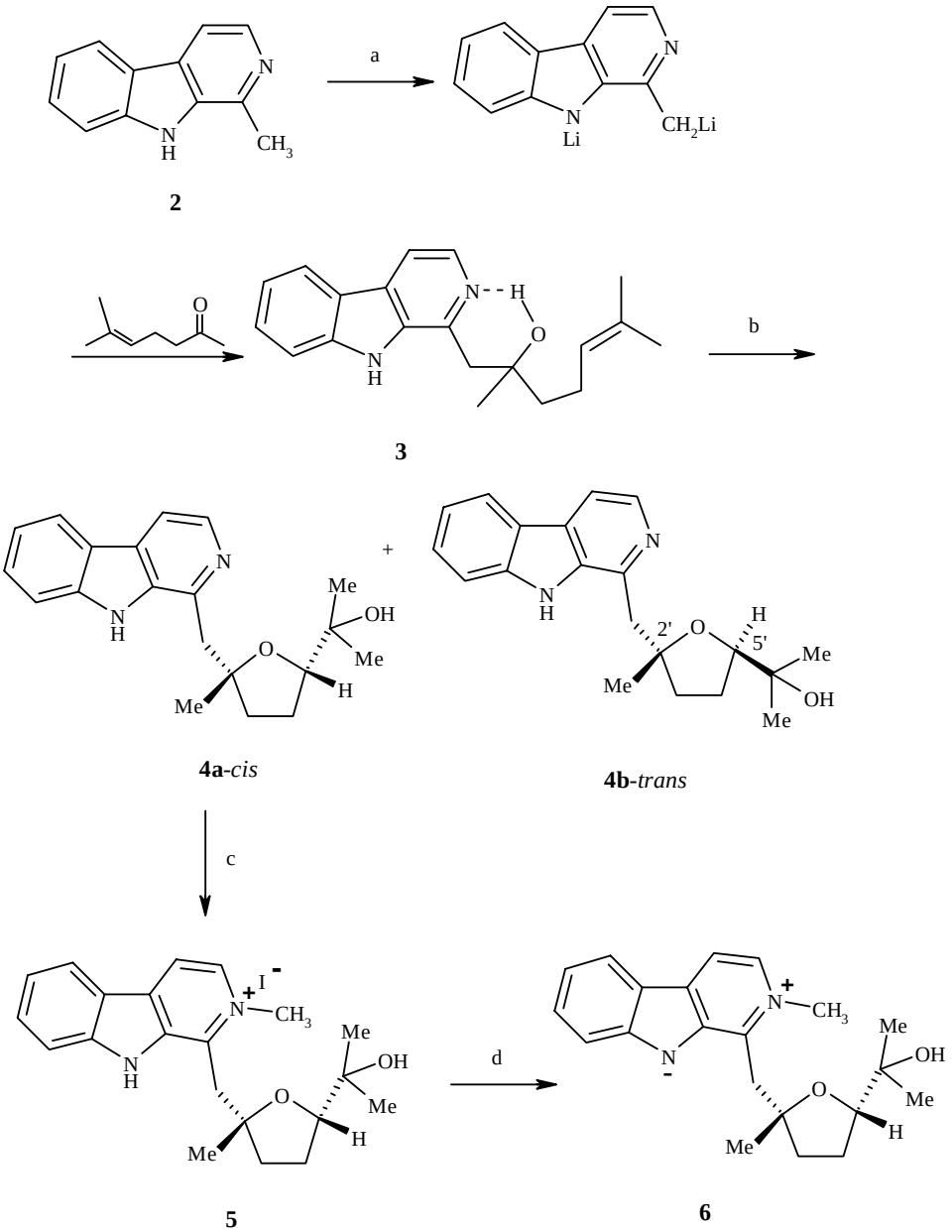
Keywords: (±)-*epi*-chrysotricine, dilithium salt of harman, $VO(acac)_2$, TBHP, oxidation

Chrysotricine **1** was isolated from the Chinese herb medicine *Hedyotis Chrysotricha* and was shown to possess antitumor activity[1]. Its structure has been elucidated as a novel zwitterionic β-carboline alkaloid containing a 2,2,5-trisubstituted tetrahydrofuranyl group. The β-carboline compounds have attracted considerable attraction in recent years because of their promising and intriguing biological activities[2]. Recently, we have established the absolute configuration of chrysotricine by the first total synthesis[3] of this compound. As an undergoing project and in order to further study the structure-activity relationship of chrysotricine, we were interested in the synthesis of alternate stereroisomers of chrysotricine. Herein, we wish to report a concise and stereoselective synthesis of (±)-*epi* –chrysotricine. The synthetic route to (±)-*epi*-chrysotricine was outlined in **Scheme 1**.



Chrysotricine 1

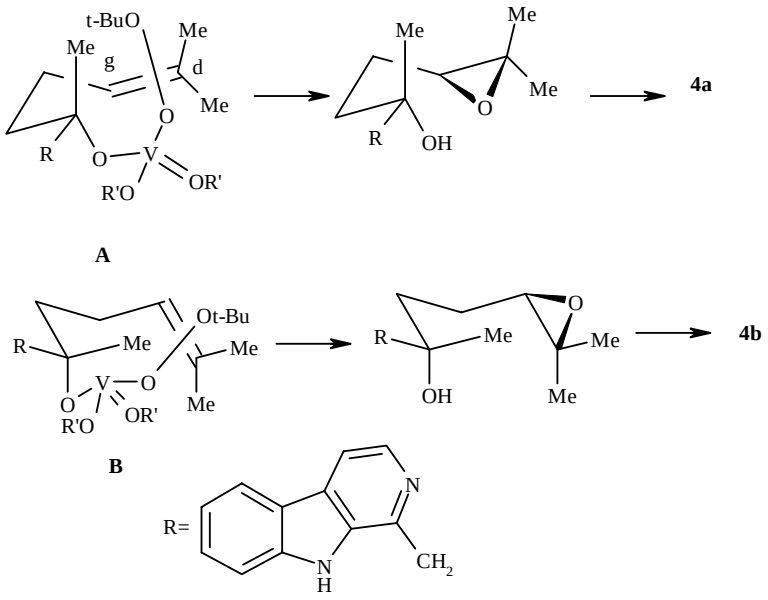
Scheme 1 The synthetic route to the title compound



Reagents and conditions: a) n-BuLi (2.1 eq), THF, r.t., 0.5 h, then 6-methyl-5-heptene-2-one (1.1eq), r.t., 30 min, 87% b) $Vo(acac)_2$ (5%), TBHP (2.5 M in CH_2Cl_2, 5 eq), CH_2Cl_2, 0°C to r.t., 4 h, then trace HOAc, r.t., 1h **4a**: 58% **4b**: 7% c) MeI (10 eq), EtOH, r.t., 93% d) 3N NaOH, reflux, 2 h, 92%

The 5-hydroxyalkene **3** was obtained in high yield by deprotonation of commercially available harman **2** using n-BuLi (2.1eq) and followed by the reaction of the resulting dilithium salt with 6-methyl-5-heptene-2-one. ^{1}HNMR and IR showed an intramolecular hydrogen bond between the hydroxy group and the *N*- atom of *β*-carboline in compound **3**. When compound **3** was oxidized with MCPBA, a mixture of **4a** and **4b** was obtained in a ratio of 2 to 3 in favor of the 2',5'-*trans* isomer[3a]. In 1990, Hanessian and coworkers[4] reported that oxidation of 5-hydroxyalkene using TBHP catalyzed by $VO(acac)_2$ can give predominantely one isomer according to the substitution pattern at the δ, γ-positions of the hydroxyalkene. Based on the proposed mechanism, we envisioned that when compound **3** was oxidized using the same reagent, two transition states **A** and **B** were formed, which ultimately gave products **4a** and **4b** respectively (**Scheme 2**).

Scheme 2

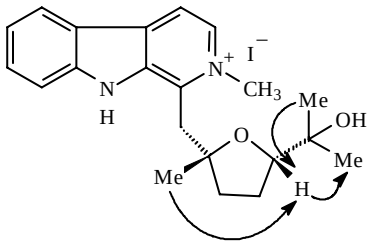


In contrast to the case of using MCPBA, transition state **B** formed using $Vo(acac)_2$ and TBHP is disfavored due to the steric compression between the vinylic methyl group (δ position) and the tertiary oxygen bound to the catalyst, while transition state **A** can minimize this interaction and thus give the major isomer with the desired stereochemistry. Indeed, when compound **3** was oxidized with TBHP/$VO(acac)_2$, an 8:1 mixture of compound **4a** and **4b** was obtained (as judged by ^{1}HNMR) from which the desired isomer **4a** was obtained in 58% yield after chromatography (EtOAc). Compound **4a** was then converted to its quaternary aminnium salt **5** by reaction with MeI in EtOH. The stereochemistry of compound **5** was further confirmed by NOE experiment as shown in the following. Compound **5**: pale yellow crystals. m.p. 264.5 ^{o}C (dec.) (EtOH). EI-MS (*m/z*): 309, 265, 196, 182, 142. ^{1}HNMR (DMSO-d_6, 500MHz): δ ppm: 8.67 (dt,

2H, J = 8.0/1.5Hz), 8.46 (d, J=8.0Hz), 7.8 (dd, J = 8.0/1.5Hz), 7.44 (dt, J = 8.0/1.5Hz), 4.5 (s, 3H), 3.73 (t, J = 5.5Hz), 3.74 (AB, 2H), 1.86 (m, 4H), 1.24 (s, 3H), 0.98 (s, 3H), 0.84 (s, 3H). Anal: $C_{21}H_{27}N_2O_2I$ Cacld. C 54.09% H 5.83% N 6.01% Found: C 53.98%, H 5.97%, N 6.13%. The pertinent NOE relationships were as shown:

Elimination of HI in compound **5** by refluxing in 3mol/L NaOH afforded the desired (±)-*epi*-chrysotricine[5] in 92% yield after recrystallization from water.

In summary, we have achieved the synthesis of (±) -*epi*-chrysotricine in a four step concise and convenient manner from the commercially available harman. This study will aid in further studies of chrysotricine analogs.



Acknowledgments

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References and note

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