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The total synthesis of chrysotricine

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Abstract

Geraniol was converted, using Sharpless oxidations as key steps, into the chiral *trans*-tri-substituted tetrahydrofuran **10**, from which chrysotricine was synthesized in 16 steps (1.1% overall yield).

Chrysotricine **14** was isolated from the Chinese herb medicine *Hedyotis chrysotricha*, and its structural characterization was first reported in 1997 as only a trace alkaloid (0.00001%) which exhibits an inhibitory activity against the growth of HL-60 cells in vitro.[1] The relative configuration was established by X-ray structure analysis. (±)-Chrysotricine has been synthesized by our group.[2] It possesses a rare *trans*-tri-substituted tetrahydrofuran unit as a crucial component.

2,5-Substituted tetrahydrofurans are commonly encountered in many natural products. There are numerous literature reports dealing with the synthesis of 2,5-di-substituted tetrahydrofurans,[3] but, to our knowledge, the enantioselective synthesis of 2,2,5-tri-substituted tetrahydrofurans is less established.[4] Scheme 1 illustrates a synthesis in which each stereogenic center of the tetrahydrofuran section of chrysotricine is controlled independently. Compound **1**, prepared from geraniol by a known procedure,[5] was protected by treatment with benzoyl chloride. After deprotecting the THP ether by PPTS, Sharpless asymmetric epoxidation using (−)DET provided the corresponding epoxy alcohol **3**.

The optical purity of **3** was judged to be 90% ee as determined by examination of its ^{1}H NMR spectrum in the presence of Eu(hfpc)$_3$.[6]

The hydroxyl group of the epoxide was then converted to the benzyl ether **4**. We attempted to use benzyl bromide and silver oxide in DMF, but the reaction was too slow to reach completion. So we protected the hydroxyl with NaH and benzyl bromide. In the absence of *n*-Bu$_4$NI, benzyl ether formation was also sluggish. Longer exposure of **3** to NaH was detrimental, and the yield decreased dramatically, probably due to the loss of the benzoyl-protecting group. By shortening this reaction time, we attained the benzyl ether in a reproducible yield of 64%.

After regioselective reduction by LiAlH$_4$, the desired diol **5** was obtained in satisfactory yield.

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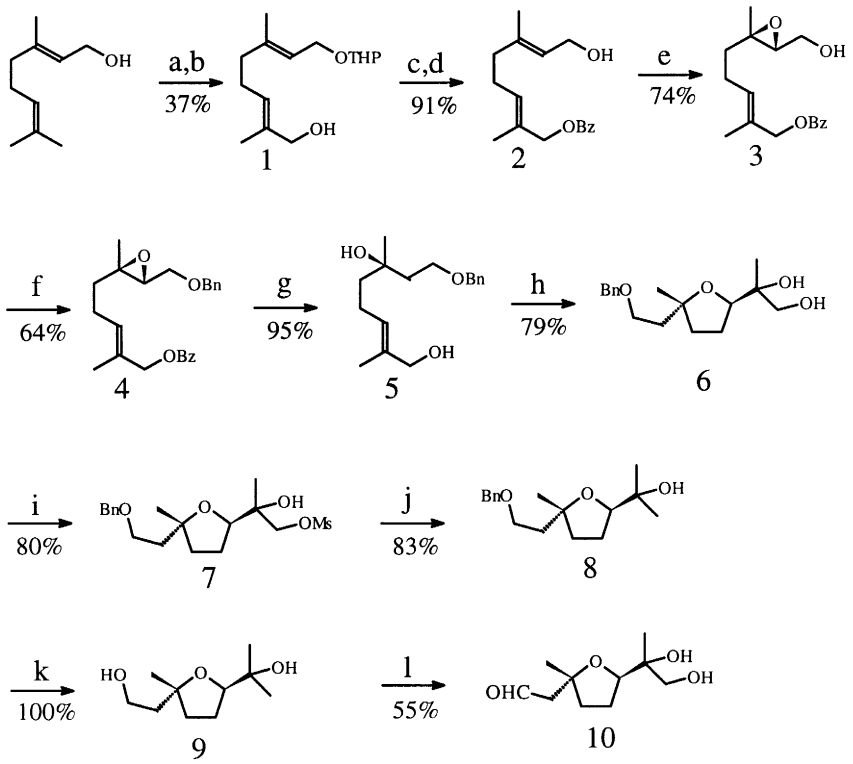


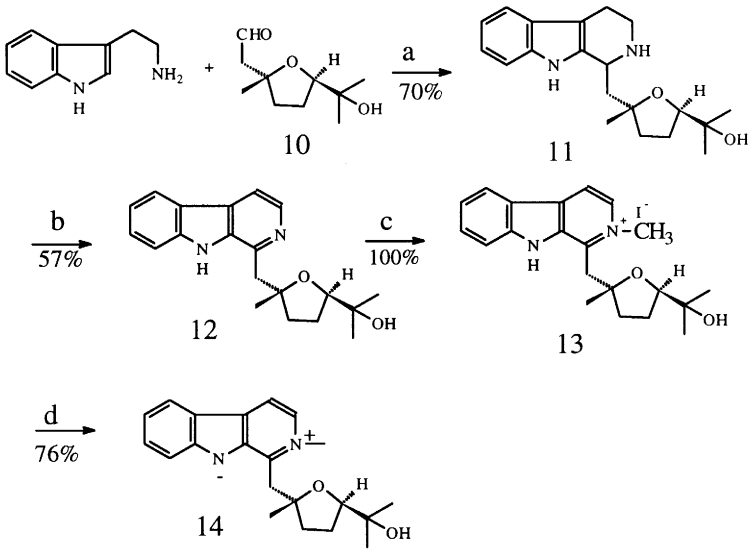
Scheme 1. (a) DHP, PPTS; (b) SeO_2/SiO_2, T BHP; (c) BzCl, pyridine; (d) PPTS, EtOH; (e) Ti(*i*OPr)$_4$, THBP, (−)DET; (f) BnBr, NaH, *n*-Bu_4NI; (g) $LiAlH_4$; (h) Ti(*i*OPr)$_4$, TBHP, (+)DET; (i) MsCl, Et_3N; (j) $LiAlH_4$; (k) Pd/C, H_2; (l) DMSO, $(COCl)_2$

Epoxidation of the double bond of **5** as well as the key ring-closure step was achieved in one step by a second Sharpless oxidation with (+)DET and gave **6**, with a de of 82%. The vicinal diol moiety of **6** was oxidized to the methyl ketone by HIO_4, to be treated with a methyl Grignard reagent to get alcohol **8**. Unfortunately, the methyl ketone was rather unstable even at a low temperature or under nitrogen. We, therefore, transformed the primary hydroxyl group into a mesylate followed by treatment of the intermediary mesylate with $LiAlH_4$ in THF to produce the required *tert*-hydroxyl compound **8** which was deprotected to give the alcohol **9**. By oxidizing the primary hydroxyl group of **9** into an aldehyde, we obtained the key intermediate **10**. The two Sharpless AEs defined the tetrahydrofuran core to be (2*R*,5*R*). To reach the natural product, we designed the route shown in Scheme 2.

A TFA-catalyzed Picter–Spengler reaction was utilized to form the tetrahydrocarboline **11**. On treatment with palladium black in boiling EtOH for 12 h, **11** produced the ring *C*-dehydrogenated product **12** in 57% yield. The structure assigned was supported by the MS and ^{1}H NMR spectra of **12** in $CDCl_3$. The crystalline quaternary iminium **13** was prepared smoothly by using CH_3I in acetone at 50°C for 2 h.[7]

Finally, treatment of **13** with aqueous NaOH in EtOH furnished the base **14**. The ^{1}H NMR data and $[\alpha]_D$ of **14** are in accordance with that of the literature.[1,7] Thus, we could confirm the absolute configuration of chrysotricine as (2*R*,5*R*).

In summary, a concise and straightforward synthesis of the natural compound chrysotricine has been developed. The total yield for the 16 steps was 1.1%. The strategy capitalized on the enantioselectivity of the Sharpless asymmetric epoxidation. The key synthon, the *trans*-tri-substituted tetrahydrofuran, was obtained in 11 steps and 8.2% yield.[8]



Scheme 2. (a) TFA, CH_2Cl_2; (b) Pd/C, EtOH, reflux; (c) CH_3I; (d) NaOH/EtOH

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7. All new compounds gave satisfactory spectroscopic data. Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$): 12.61 (s, 1H, NH), 8.17 (d, *J*=6.5, 1H), 8.13 (d, *J*=8.3, 1H), 8.12 (d, *J*=8.3, 1H), 8.11 (d, *J*=6.5, 1H), 7.70 (t, *J*=8.3, 1H), 7.38 (t, *J*=8.3, 1H), 4.58 (s, 3H), 4.07 (s, 2H), 3.52 (m, 1H), 2.46–1.67 (m, 4H), 1.39 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H). Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$): 8.16 (d, *J*=8.0, 1H), 8.06 (d, *J*=6.5, 1H), 8.00 (d, *J*=8.0, 1H), 7.58–7.56 (m, 2H), 7.19 (t, 1H, *J*=8.0), 4.43 (s, 3H), 4.18 (m, 1H), 3.83 (m, 1H), 3.10 (m, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.92 (m, 1H), 1.71 (m, 1H), 1.43 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H). $[\alpha]_D^{21}$=+30 (MeOH, *c* 0.049).
8. According to Ref. 1, in methanol the structure **14** is in equilibrium with structure **15**. The ^{1}H NMR data of **15** in methanol is in agreement with those reported in the literature.