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Synthesis of the Analogs of Triptolide: 7, 8-Deoxytriptolide, 7α, 8α-Epoxytriptolide and Related Ketones

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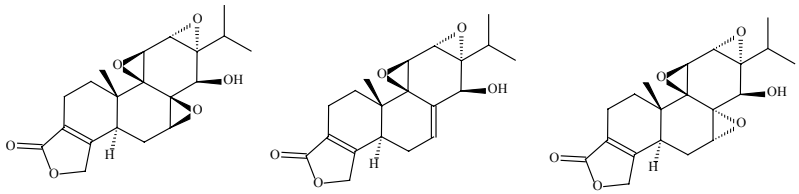
Abstrat: Two novel analogues of triptolide were synthesized using triptolide as the starting material through reductive opening of epoxy ring, hydration and olefin epoxidation, and related ketones have also been afforded by oxidation of them with IBX or Jone's reagent.

Keywords: Triptolide, analogue, dehydration, epoxide.

A diterpenoid triepoxide containing the 18 (4→3) *abeo*-abietane skeleton, triptolide **1**, was isolated from *Tripterygium wilfordii* Hook F by Kupchan and co-workers in 1972, possessing potent antileukemic activity[1]. Advanced researches indicated that it also possesses potential antiimflammatory and immunosuppressive activity[2-3], and its triepoxide portion and the stereochemistry of epoxy group are very important for its immunosuppressive activities[4]. In order to further elaborate the effects of 7,8-epoxide on biological activities, a synthetic route to novel triptolide analogues has been developed as a part of our study on its structure-activity relationship and analogues with 7α,8α-epoxide and 7,8-olefinic group have been synthesized successfully.

Owing to its unusual chemical structure and specific activity, a lot of efforts were made on the total synthesis and modification, and several approaches to triptolide have been disclosed separately by van Tamelen[5], Berchtold[6] and Yang[7] group. Since 7β,8β-epoxide was always established in the early stage of their synthetic routes, it seemed unfeasible to synthesize our desired analogues by the total synthesis. Recently,

Figure 1 Structures of compounds **1-3**



1 **2** **3**

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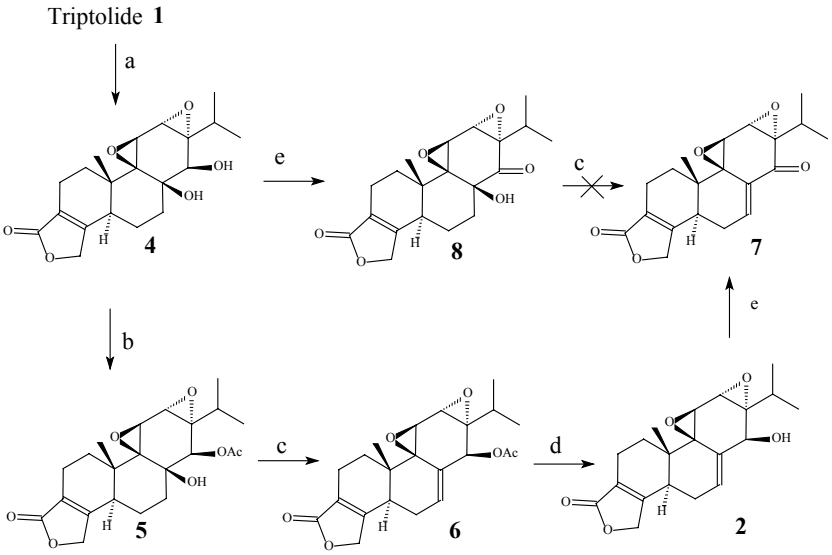
Jung and co-workers reported that treatment of triptolide with $LiBH_4$ and $BF_3 \cdot Et_2O$ in THF leads to reductive opening of 7β, 8β-epoxide [8], which provided a proper opportunity for synthesis from triptolide to the related analogues.

The synthetic route was list in **Scheme 1**. As demonstrated, our starting material was triptolide **1**, 7β, 8β-epoxide was opened by reacting with $LiBH_4$ and $BF_3 \cdot Et_2O$ to give **4** in 75% yield. Then 14-hydroxyl of **4** was selectively protected as acetate to produce **5** in 95% yield, and **5** was treated with a large excess of trifluoroacetic anhydride and pyridine in dichloromethane that led to the elimination of a molecule of water to afford **6** in 62% yield, which was subsequently hydrolyzed with hydrazine monohydrate in methanol to produce allylic alcohol **2**[9]. Compared with the parental triptolide **1**, **2** could be considered to be achieved through substituting the former epoxide with olefinic group. As **2** was oxidized under acid condition with Jone's reagent, IBX(1-hydroxyl-1, 2-benziodoxol-3(1H)-one 1-oxide) was selected to react with **2** in dimethylsulfone at 40℃ to afford ketone **7** in 95% yield.

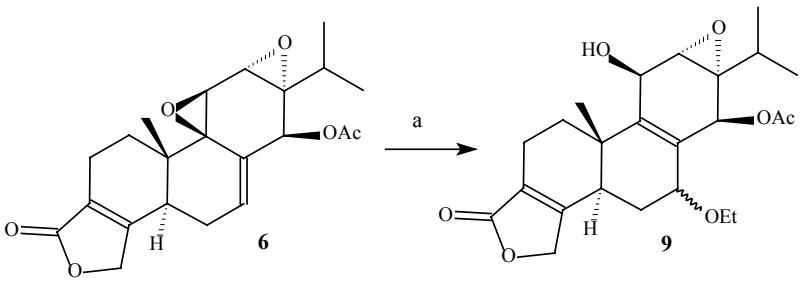
We have ever attempted to synthesize ketone **7** through dehydation of α-hydroxyl ketone **8**, which was obtained by oxidation of **4** with IBX in dimethylsulfone. But it failed to produce unsaturated ketone **7** under the same reaction condition as that in the dehydation of **5** and **8** remained unchanged. We believed that the existence of ketone in C-14 caused molecular conformation to be unfavorable for forming transient state required for elimination reaction that led to no reaction, which has also been confirmed by the result that treatment of **5** with trifluoroacetic anhydride readily led to dehydration reaction to give the corresponding olefin **6**.

Scheme 1 The synthesis of analogue **2** and related ketone **7**



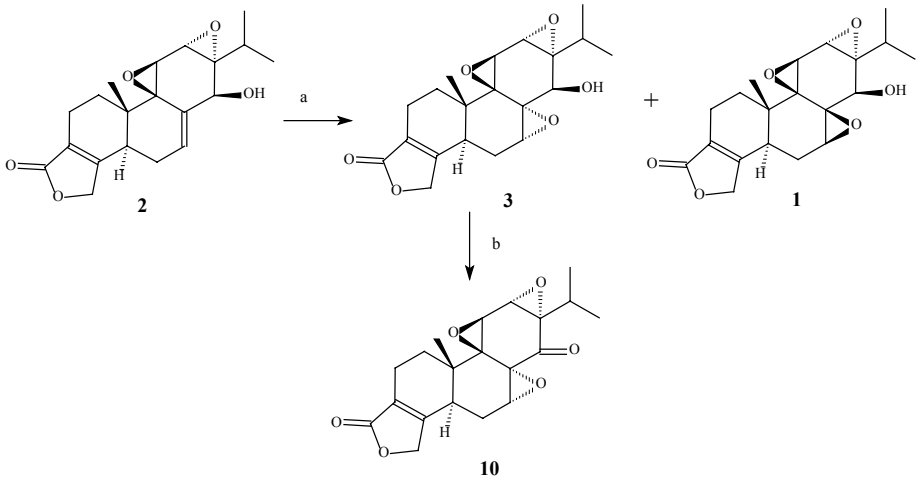
Reaction Condition: (a) $LiBH_4$, BF_3-OEt_2, THF (b) Ac_2O, Py (c) TFFA, Py,CH_2Cl_2 (d) NH_2NH_2 H_2O, CH_3OH (e) IBX, DMSO

Scheme 2



Reaction condition: (a) SeO_2, 95% EtOH , reflux

Scheme 3 The synthesis of analogue **3** and related ketone **10**



Reaction Condition: (a) mCPBA, Na_2HPO_4, benzene (b) Jone's reagent, acetone

To explore the possibility of chemical modification at C-6 of triptolide, we hoped to oxidize allylic hydrogen at C-6 into hydroxyl, but reaction of **6** with selenium dioxide in 95% ethanol under reflux afforded unexpected **9** in 50% yield (**Scheme 2**). Because selenium dioxide formed selenious acid (H_2SeO_3) in the presence of water, 9,11-epoxide of **6** was opened and the double bond moved to C-8 and C-9 spontaneously under attack of hydroxyl of ethanol on C-7 to give ethyl ether **9**. To avoid this transformation, we selected to react 6 with selenium dioxide in ethanol-pyridine, but there was also no product with hydroxyl at C-6.

With **2** in hand, we subsequently proceeded to the introduction of 7, 8-epoxide (**Scheme 3**). Since the epoxidation of **2** under Sharpless condition was not effective, this task was accomplished by exposure of **2** to MCPBA-Na_2HPO_4 for 48 hours in benzene to provide the 7α, 8α-epoxide **3**[10] in 30% yield as major product with small amount of triptolide **1** with 7β, 8β-epoxide in 4% yield, and the assignment of epoxide stereo-chemistry in **3** was based on NOESY, in which there is correlation observed between

methyl proton at C-10 and proton at C-7. It is conceivable that the angular methyl group at C-10 and 9β, 11β-epoxide in **2** directed the epoxidation to mainly take place on the αsurface of olefin, and the ratio of **3** and triptolide showed that their steric effect obviously outweighs the syn-directing effect of 14-hydroxyl introducing epoxide from β side. However, this steric hindrance might just be the reason of the low yield of epoxide and long reaction time. The oxidation of **3** with Jone's reagent afforded the ketone **10** with 95% yield.

Thus two novel triptolide analogues with related ketones was successfully prepared for the first time from triptolide. The reaction condition is simple and mild, and analogues **2** and **3** were obtained in only four to five steps with inexpensive reagents, and biological evaluation of **2**, **3**, **7** and **10** are in progress.

References and Notes

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9. The spectrum data for compound **2**: m.p. 199-201℃; $[\alpha]_D^{25}$ -195.4(c 0.13, acetone); ^{1}HNMR (400M Hz, $CDCl_3$, δ ppm): 6.06(dd, 1H, J=1.9, 5.5Hz), 4.70(m, 2H), 4.34(d, 1H, J=11.7Hz), 3.83(d, 1H, J=3.2Hz), 3.52(dd,1H,J=1.0, 3.2Hz),2.90(d, 1H, J=11.7Hz), 2.82-2.79(m, 1H), 2.41-2.35(m, 1H), 2.31(sept, 1H, J=6.9Hz), 2.30-2.24(m, 1H),2.22-2.11(m, 2H), 1.63-1.58(m, 1H), 1.34-1.27(m, 1H), 1.04(d, 3H, J=6.9Hz), 0.97(s, 3H), 0.88(d, 3H, J=6.9Hz); ^{13}CNMR (100M Hz, $CDCl_3$, δ ppm): 173.2, 160.4, 133.7, 130.8, 125.4, 73.5, 70.2, 67.3, 66.0, 58.2, 56.2, 39.9, 34.5, 28.5, 28.3, 24.7, 18.1, 17.5, 17.3, 14.1; IR(KBr): 3518, 2939, 1761, 1380, 1022 cm^{-1}; MS(EI, 70 eV) *m/z* 344 (M^+, 5), 329 (11), 311(68), 301(100), 231(79), 91(37); HRMS(EI) calcd. for$[C_{20}H_{24}O_5]^+$ 344.1624, found 344.1614.
10. The spectrum data for compound **3**: m.p.211-213℃; $[\alpha]_D^{25}$ -91.9(c 0.14, acetone); ^{1}H NMR (400M Hz,$CDCl_3$, δ ppm):4.69(m, 2H), 3.86(d, 1H, J=3.1Hz), 3.59(d, 1H, J=3.1Hz), 3.44(d, 1H, J=12.8Hz), 3.43(d, 1H, J=2.4Hz), 3.00-2.97(m, 1H), 2.92(d, 1H, J=12.8Hz), 2.38-2.32(m, 1H), 2.20-2.04(m, 3H), 2.01-1.94(m, 1H), 1.47-1.42(m, 1H), 1.35-1.28(m, 1H), 1.03(d, 3H, J=6.9Hz), 0.91 (d, 3H, J=6.9Hz), 0.86(s, 3H); ^{13}CNMR(100M Hz, $CDCl_3$, δ ppm): 173.3, 161.0,125.3, 73.6, 70.1, 65.5, 64.0, 58.2, 57.4, 56.4, 55.6,34.1, 32.6, 28.6, 28.4, 24.0, 17.9, 17.2, 16.9, 15.9; IR(KBr)3525, 2924, 1759, 1389, 1018, 895 cm^{-1}; MS(EI,70eV) *m/z* 361 ($[M+1]^+$, 5), 345(18), 327(26), 29(66), 271(100), 71(87); HRMS(EI) calcd. for $[C_{20}H_{24}O_6]^+$ 360.1573, found 360.1584.

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