Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6865-6868, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01581-5

Studies on Triepoxide Analogs of Triptolide

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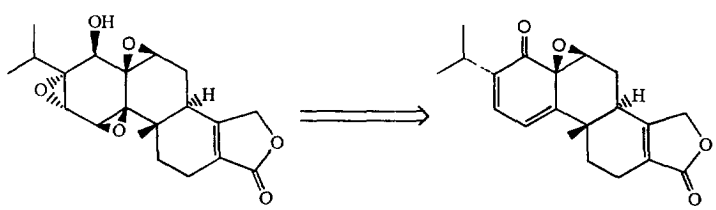
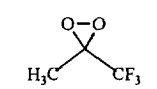
Abstract: Several triepoxide analogs of triptolide were synthesized efficiently using *in situ* generated dioxiranes and basic hydrogen peroxide. Two of them were found to be cytotoxic.

Triptolide is a natural product isolated from the poisonous plant *Tripterygium wilfordii* Hook F or Lei Gong Teng by Kupchan in 1972.[1] It contains an unusual triepoxide moiety and an α,β-unsaturated γ-lactone in the diterpene skeleton, and it has potent antileukemic[1] and immunosuppressive activities.[2] While triptolide's actions on cells remain elusive,[3] studies showed that the triepoxide portion of triptolide is important for its immunosuppressive activity.[4] As a part of our program on chemistry and biology of triptolide, an efficient synthetic route to the triepoxide analogs of triptolide has been developed and preliminary biological assays on those analogs have been carried out.

Previous efforts by both van Tamelen[5a] and Berchtold[5b, 5c] on the total syntheses of triptolide encountered difficulty in epoxidation of a dienone precursor (low yields and stereoselectivity). As the C=C double bonds in the dienone system are strongly electron-deficient, a more powerful oxidant is apparently required.



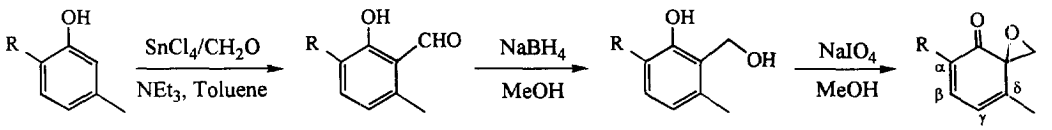
Triptolide Dienone precursor



Methyl(trifluoromethyl)-dioxirane (**1a**)

Since dioxiranes are highly efficient oxidants towards electron-deficient olefins under mild and neutral conditions,[6] we reasoned that dioxirane epoxidation could be effective for triptolide triepoxide synthesis. Two

dienone model compounds **2** and **3** were prepared in three steps starting from the commercially available phenols **2a** and **3a** (Scheme 1).[7]



2a R = Me
3a R = *i*-Pr

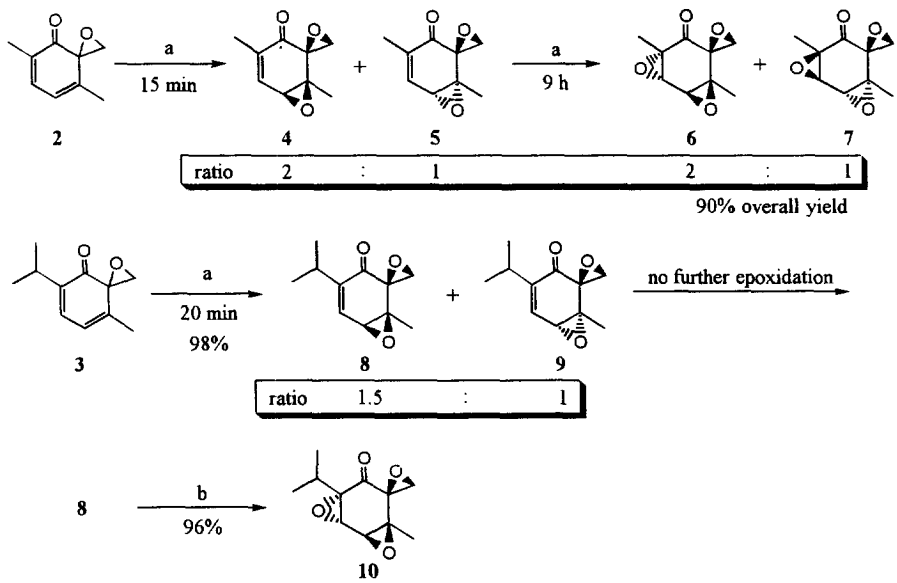
2b R = Me; 33%
3b R = *i*-Pr; 45%

2c R = Me; 75%
3c R = *i*-Pr; 77%

2 R = Me; 67%
3 R = *i*-Pr; 73%

Scheme 1.

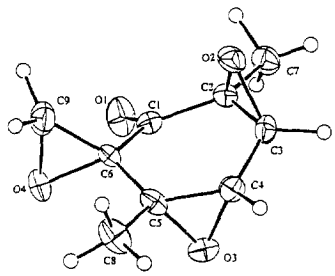
Dienone **2** was subjected to the epoxidation conditions using methyl(trifluoromethyl)dioxirane (**1a**) generated *in situ* (1,1,1-trifluoroacetone (**1**), Oxone/$NaHCO_3$, CH_3CN/H_2O, 0–1 °C) (Scheme 2).[6a] Two diepoxides (*cis*-**4** and *trans*-**5**) were formed in 15 min. When excess amounts of the epoxidizing reagents were added, triepoxides **6** and 7 were isolated in a 2 : 1 ratio after 9 h (90% overall yield).

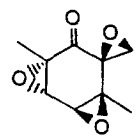


Reagents and conditions: (a) CF_3COCH_3 (**1**), Oxone/$NaHCO_3$, CH_3CN/H_2O, 0-1 °C, pH 7-7.5.
(b) Isopropyl pyruvate, Oxone/$NaHCO_3$, CH_3CN/H_2O, rt, 24 h, pH 7-7.5.

Scheme 2.

The stereochemistry of triepoxide **6** was established by X-ray crystallographic analysis.



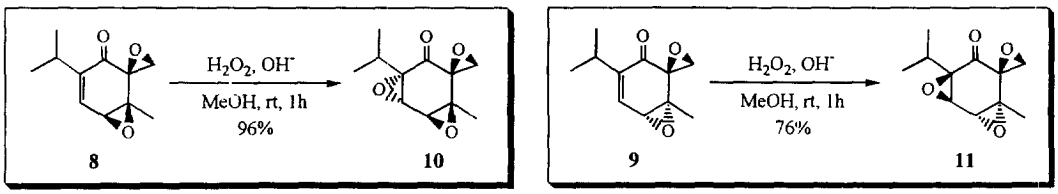


triepoxide **6**

Studies by both van Tamelen and Berchtold revealed that the last epoxidation was completely stereoselective, i.e., the epoxide at α,β position was anti to that at γ,δ position.[5] Therefore, we reasoned that triepoxide **6** came from epoxidation of *cis*-diepoxide **4** whereas triepoxide **7** was from *trans*-diepoxide **5**.

The same epoxidation protocol was applied to *iso*-propyl dienone **3** (Scheme 2). In 20 min, diepoxide **8** and **9** were formed, and their structures were determined by comparison of ^{1}H NMR spectra with those of *cis*-diepoxide **4** and *trans*-diepoxide **5**. However, no triepoxide could be obtained in a one-pot epoxidation of *iso*-propyl dienone **3**. The steric hindrance of the *iso*-propyl group may prevent further epoxidation of **8** and **9** at the α,β position.

Isopropyl pyruvate was used to further epoxidize **8** as it was found to have good catalytic activity toward sterically hindered and electron-deficient olefins.[8] Only a single product **10** was isolated (96% yield) (Scheme 2). As **10** had similar ^{1}H NMR spectra as triepoxide **6**, its structure was assigned accordingly. Besides, basic hydrogen peroxide was found to be effective for epoxidation of **8** and **9** to give triepoxides **10** and **11**, respectively, within 1 h (Scheme 3).



Scheme 3.

In summary, using our *in situ* epoxidation method, several monocyclic epoxide analogs of triptolide (**4**–**11**) have been synthesized in high yields.[9] Among them, compounds **8** and **9** were found to be cytotoxic to human leukemia HL-60 cells (IC_{50} 16 μM for both) and human lymphoma Jurkat cells (IC_{50} 31 μM and 36 μM, respectively).[10] The electrophilic α,β-enone groups, present in both compounds **8** and **9**, may be

responsible for their similar biological activities. Syntheses and biological evaluation of other triptolide analogs are in progress.

Acknowledgement: This work was supported by The University of Hong Kong, Leung Kau Kui/Run Run Shaw Research and Teaching Endowment Funds, Hong Kong Research Grants Council, and The Hong Kong University of Science and Technology.

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8. Unpublished results.
9. Selected analytical data for compounds **6** – **11**:
   6: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.87 (d, J = 2.4 Hz, 1H), 3.69 (d, J = 2.7 Hz, 1H), 2.98 (d, J = 5.4 Hz, 1H), 2.78 (d, J = 5.4 Hz, 1H), 1.48 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 198.0, 63.3, 61.6, 59.8, 59.5, 58.4, 50.8, 14.8, 14.6; IR (CCl_4) 1740 cm^{-1}; HRMS for $C_9H_{10}O_4$ (M^+), calcd 182.0579, found 182.0579; EIMS (20 eV) *m/z* 182 (25), 153 (20), 139 (30), 111 (35); Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.47; H, 5.55.
   7: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.83 (d, J = 2.7 Hz, 1H), 3.64 (d, J = 2.7 Hz, 1H), 3.42 (d, J = 5.4 Hz, 1H), 3.01 (d, J = 5.4 Hz, 1H), 1.46 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 198.2, 62.5, 60.6, 58.7, 55.8, 53.4, 47.1, 15.4, 15.1; IR (CCl_4) 1730 cm^{-1}; HRMS for $C_9H_{10}O_4$ (M^+), calcd 182.0579, found 182.0576.
   8: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.96 (d, J = 4.6 Hz, 1H), 3.56 (d, J = 4.6 Hz, 1H), 3.02 (d, J = 6.1Hz, 1H), 2.94 (d, J = 6.1 Hz, 1H), 2.92 – 2.84 (m, 1H), 1.40 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 191.05, 150.11, 136.24, 59.39, 57.73, 4.35, 52.46, 27.26, 21.45, 21.32, 15.39; IR (CCl_4) 1693 cm^{-1}; HRMS for $C_{11}H_{14}O_3$ (M^+), calcd 194.0943, found 194.0952; EIMS (20 eV) *m/z* 194 (1), 179 (26), 166 (30), 151 (100), 137 (96).
   9: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.00 (d, J = 4.6 Hz, 1H), 3.51 (d, J = 4.6 Hz, 1H), 3.48 (d, J = 6.4 Hz, 1H), 3.16 (d, J = 6.4 Hz, 1H), 2.91 (septet, J = 6.8 Hz, 1H), 1.38 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 190.78, 149.46, 136.82, 61.22, 55.46, 54.25, 49.95, 27.16, 21.39, 15.90; IR (CCl_4) 1683 cm^{-1}; HRMS for $C_{11}H_{14}O_3$ (M^+), calcd 194.0943, found 194.0947.
   10: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.87 (d, J = 2.7 Hz, 1H), 3.69 (d, J = 2.7 Hz, 1H), 2.96 (d, J = 5.1 Hz, 1H), 2.76 (d, J = 5.1 Hz, 1H), 2.43 (septet, J = 6.8 Hz, 1H), 1.25 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 197.48, 67.06, 60.17, 59.36, 58.26, 50.52, 25.59, 17.94, 16.47, 14.56; IR (CCl_4) 1739 cm^{-1}; HRMS for $C_{11}H_{14}O_4$ (M^+), calcd 210.0892, found 210.0900; EIMS (20 eV) *m/z* 210 (20), 181 (28), 163 (89), 151 (100), 111 (79); Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.72; H, 6.68.
   11: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.82 (d, J = 2.7 Hz, 1H), 3.63 (d, J = 2.7 Hz, 1H), 3.39 (d, J = 5.1 Hz, 1H), 2.90 (d, J = 5.1 Hz, 1H), 2.40 (septet, J = 6.8 Hz, 1H), 1.24 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 197.83, 65.96, 59.01, 58.54, 58.31, 56.40, 47.23, 25.85, 18.05, 16.18, 15.42; IR (CCl_4) 1729 cm^{-1}; HRMS for $C_{11}H_{14}O_4$ (M^+), calcd 210.0892, found 210.0884.
10. The viabilities of HL-60 and Jurkat cells were tested by the XTT assay after exposure of cultured cells to each analogs for 48 hours. The IC_{50} values are the concentrations at which 50% of inhibition of cell growth are observed.

(*Received in China* 28 *May* 1997; *accepted* 18 *July* 1997)