A Concise Total Synthesis of Triptolide

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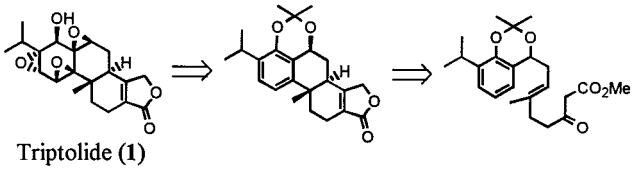
Triptolide **1**, a diterpenoid with a triepoxide structure, was isolated by Kupchan from the Chinese medicinal herb *Tripterygium wilfordii* Hook F (Lei Gong Teng) and found to have potent antileukemic and antitumor activities.[1] Subsequent studies showed that triptolide also inhibits lymphocyte proliferation and interleukin-2 production, which may account for the effectiveness of Lei Gong Teng crude extracts in the treatment of a number of immune disorders such as rheumatoid arthritis and systemic lupus erythematosus.[2] While epoxide alkylation was proposed to be the mode of action, triptolide's actions on cells remain unknown.[1b,3] To unravel triptolide's structural features that are responsible for its immnosuppressive activities, we have developed a concise total synthesis of triptolide and its analogues, which is reported herein.[4]

Our synthetic strategy for triptolide **1** is shown in Figure 1. The key steps involve (1) radical cyclization of an acyclic precursor mediated by $Mn(OAc)_3$[5] and (2) triepoxide construction using our previously reported method.[6]

As shown in Scheme 1, compound **2** was readily synthesized from commercially available 2-isopropylphenol in three steps.[7] Benzylic deprotonation of **2** and coupling of the derived higher order mixed cuprate with 2-methyl-2-vinyloxirane using the Lipshutz method[8] generated **3** in 72% yield. Allylic alcohol **3** was converted to bromide **4**, which upon treatment with methyl acetoacetate dianion furnished the acyclic precursor **5**.[9] Radical cyclization of compound **5** using the Snider method[5] gave two major products: **6** of *trans* ring juncture (40%) and **7** of *cis* ring juncture (8%).



Triptolide (1)

Figure 1.

Here, the radical cyclization was highly stereoselective, as four stereocenters were set up in one step. Construction of α,β-unsaturated γ-lactone **8** was carried out in three steps following the method developed by Crisp.[10] Vinyl triflate formation from β-keto ester **6** was followed by DIBAL-H reduction. Subsequent Pd-catalyzed carbonylation of the hydroxy vinyl triflate provided lactone **8**.

Acetonide deprotection of **8** gave a 1:1 mixture of diols **9** and **10**, the latter being formed as a result of epimerization under the hydrolysis condition. Diol **9** was converted to monoepoxide **11** using the Adler reaction.[11] A one-pot process involving acetonide removal and Adler reaction was found to give a moderate yield of monoepoxide **11** directly from **8**. When methyl(trifluoromethyl)dioxirane generated in situ was used,[12] the second epoxide was introduced as a single diastereomer. Further epoxidation with basic H_2O_2 provided triptonide **12**, another potent immunosuppressant isolated from Lei Gong Teng. Here the two epoxidation processes offered complete stereocontrol and high efficiency. Finally, reduction of triptonide **12** with $NaBH_4$ in MeOH in the presence of $Eu(fod)_3$ furnished triptolide **1** (47%) together with its α-hydroxyl epimer **13** (47%).[13]

Despite high stereoselectivity, radical cyclization of **5** suffered from side reactions such as hydrolysis of the acetonide group and benzylic elimination. Therefore, an alternative preparation of **9** was developed (Scheme 2). *Ortho*-directed metalation of MOM ether **14** with *n*-BuLi and alkylation with MeI was followed by another lithiation with *s*-BuLi and quenching with 4-bromo-2-methyl-2-butene to furnish olefin **15**.[14] Compound **15** was converted to its methyl ether, which was then oxidized to allylic alcohol **16**.[15] Acyclic precursor **17** was prepared in two steps from **16** by bromination and dianion displacement. Radical cyclization of **17** gave two major products **19a** (55%) and **20** (20%). In comparison, radical cyclization of α-chlorinated precusor **18** gave the desired *trans* product **21** in excellent yield (90%), and dechlorination of **21** afforded compound **19b** quantitatively.[16,17] **19a** and **19b** were converted to the known lactone **22** following the Crisp method.[10] Deprotection of **22** with BBr_3[18] furnished racemic triptophenolide **23**, an antiinflammatory agent also isolated from Lei Gong Teng.[19] Benzylic oxidation of **22** and subsequent demethylation and reduction provided β-alcohol **9**.[4f]

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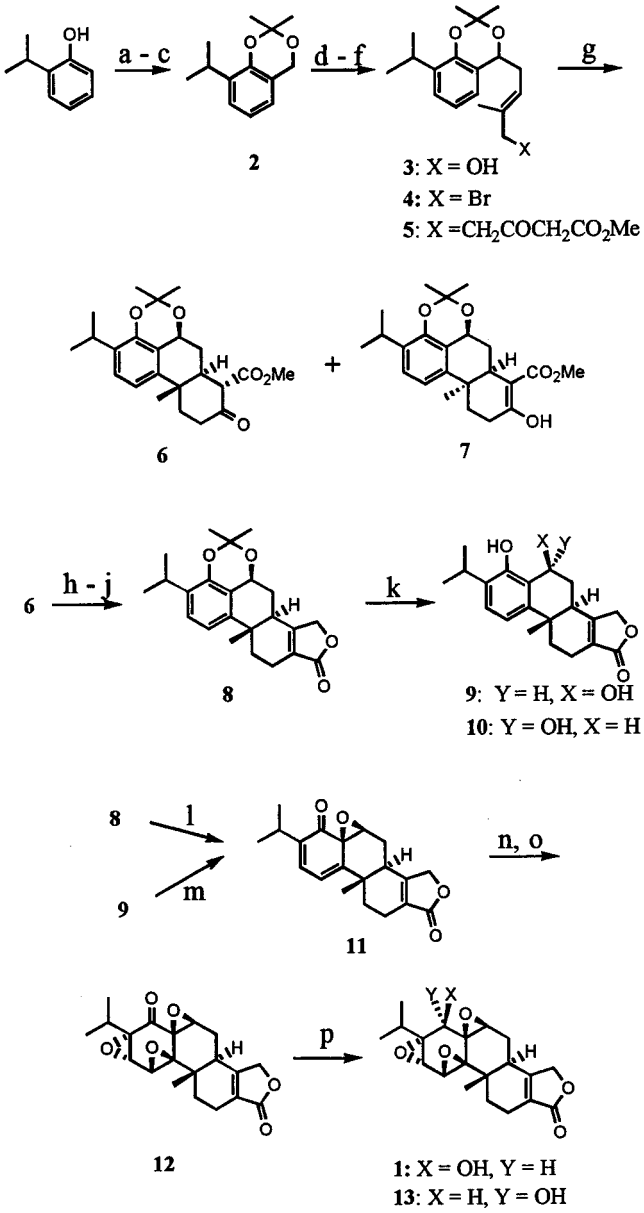
Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_2O)_n$, $SnCl_4$, 2,6-lutidine, toluene, 100 °C, 10 h, 82%; (b) $NaBH_4$, MeOH, 0 °C, 1 h, 96%; (c) $(CH_3)_2C(OCH_3)_2$, TsOH (cat.), CH_2Cl_2, reflux, 1 h, 80%; (d) *s*-BuLi, THF, −78 °C, 0.5 h; CuCN, 2-thienylithium, THF, −78 to +25 °C, 1 h; 2-methyl-2-vinyloxirane, −78 to 0 °C, 4 h, 72%; (e) PPh_3, CBr_4, CH_2Cl_2, 25 °C, 0.5 h, 88%; (f) $CH_3COCH_2COOCH_3$, NaH, *n*-BuLi, THF, 0 °C, 1 h, 84%; (g) $Mn(OAc)_3 \cdot 2H_2O$, HOAc, 70 °C, 1 h, 40% of **6** and 8% of **7**; (h) KHMDS, $PhNTf_2$, THF, −78 to +25 °C, 14 h, 98%; (i) DIBAL-H, THF, −78 to +25 °C, 8 h, 72%; (j) LiCl, *n*-Bu_3N, $Pd(PPh_3)_4$, CO (1 atm), THF, 65 °C, 12 h, 97%; (k) PPTS, CH_3CN/H_2O (1:1), 70 °C, 10 h, 40% of **11** and 40% of **12**; (l) $NaIO_4$, TsOH, CH_3CN/H_2O (3:1), 25 °C, 4 h, 52% (50% conversion); (m) $NaIO_4$, $MeOH/H_2O$ (3:1), 0−25 °C, 1 h, 96%; (n) CF_3COCH_3, Oxone, $NaHCO_3$, CH_3CN/H_2O (3:2), 25 °C, 4 h, 70%; (o) H_2O_2, NaOH, MeOH, 25 °C, 3 h, 96%; (p) Eu(fod)$_3$, $NaBH_4$, MeOH, −40 °C, 0.5 h, 47% of **1** and 47% of **16**. Abbreviations: KHMDS, potassium hexamethyldisilazide; PPTS, pyridinium *p*-toluenesulfonate.

The above scheme can be adapted to an enantioselective total synthesis by using acyclic precursors bearing chiral auxiliaries in the radical cyclization step.[20] More importantly, it will allow rapid access to various triptolide analogues designed to probe the cellular processes that triptolide interferes with.

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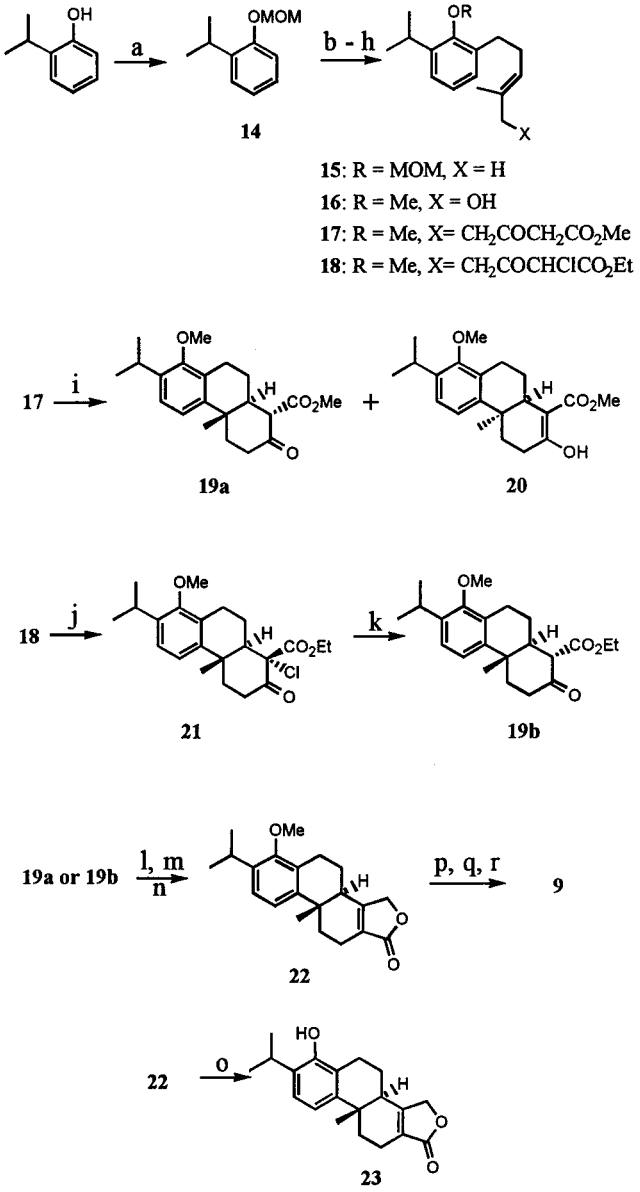
Scheme 2[a]



[a] Reagents and conditions: (a) MOMCl, NaH, THF, 65 °C, 2.5 h, 99%; (b) *n*-BuLi, THF, −40 to +20 °C, 2 h, then MeI, −78 °C, 1 h, 98%; (c) *s*-BuLi, THF, −78 to −30 °C, 2 h, then $(CH_3)_2C{=}CHCH_2Br$, −78 °C, 1 h, 98%; (d) TMSCl, $LiBF_4$, CH_3CN, −10 to +25 °C, 4 h, 97%; (e) Me_2SO_4, K_2CO_3, acetone, reflux, 2.5 h, 100%; (f) SeO_2, *t*-BuOOH (4.0 equiv), CH_2Cl_2, 0 °C, 8 h, then $NaBH_4$, MeOH, 73%; (g) MsCl, Et_3N, CH_2Cl_2, −40 to −20 °C, 1 h, then LiBr, THF, −20 to +25 °C, 2 h, 96%; (h) $CH_3COCH_2CO_2CH_3$, NaH, *n*-BuLi, THF, 0 °C, 1 h, 85% of **17**; or $CH_3COCHClCO_2Et$, NaH, *n*-BuLi, THF, −10 °C, 1 h, 84% of **18**; (i) HOAc, $Mn(OAc)_3 \cdot 2H_2O$, 70 °C, 1 h, 55% of **19a** and 20% of **20**; (j) HOAc, $Mn(OAc)_3 \cdot 2H_2O$, rt, 6 h, 90%; (k) Zn/HOAc, rt, 2 h, 100%; (l) KHMDS, $PhNTf_2$, THF, −78 to +25 °C, 14 h; (m) DIBAL-H, THF, −78 to +25 °C, 8 h; (n) LiCl, *n*-Bu_3N, $Pd(PPh_3)_4$, CO (1 atm), THF, 65 °C, 12 h, overall 64% (from **19a** or **19b**); (o) BBr_3, CH_2Cl_2, −40 to +25 °C, 12 h, 99%; (p) CrO_3, $HOAc/H_2O$ (9:1), 6 h; (q) BBr_3, CH_2Cl_2, −40 °C to +25 °C, 12 h; (r) $NaBH_4$, MeOH, 0 °C, 2 h, 44% from **22**. Abbreviations: MOM, methoxymethyl.

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Supporting Information Available: Determination of stereochemistry for compounds **6** and **7** (34 pages).

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