Bio-Activities and Syntheses Developments of Triptolides

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Abstract: *Tripterygium wilfordii* Hook.f. has a long history of use in traditional Chinese medicine. The diterpene triepoxide triptolide **1**, as the main bioactive constituent of *Tripterygium* extracts, has been used to treat a variety of autoimmune, inflammation-related conditions and neurodegenerative diseases, and it also displays antiinflammatory activity, antiproliferative and apoptotic effects, antifertility and insecticidal activity. Several synthetic studies and structure-activity relationships (SAR) have been carried out on triptolide as well as others structurally related molecules. This review focused on the biological and pharmacological activities, total syntheses and their structure-activity relationships of triptolide and congeners.

Keywords: *Tripterygium*, Triptolide, Diterpene, Antiinflammatory, Anticancer.

1. INTRODUCTION

Tripterygium wilfordii Hook.f (Celastraceae, TWHF) is a woody vine native to Eastern and Southern China, Korea, Japan [1]. In China this plant, known as Lei Kung Teng or Lei Gong Teng, is used in traditional Chinese medicine (TCM) for treating swelling, fever, chills, sores, joint pain, and inflammation [2]. Preparations of *Tripterygium* began to be used in allopathic medicine in China in the 1960s to treat rheumatoid arthritis (RA) and inflammation [3]. Since then they have also been used for cancer, chronic nephritis, hepatitis, systemic lupus erythematosus, ankylosing spondylitis, and a variety of skin conditions [4].

Biochemical analysis has shown that *Tripterygium* contains a vast array of natural products with strong biological activities, many purified components, such as (–)-triptolide (**1**), (–)-triptonide (**2**), tripdiolide (**3**), triptrilide (**4**), tripchlorolide (**5**) and tritolidenol (**6**) (Fig. **1**), have been separated from TWHF [5]. Triptolide, a diterpenoid triepoxide sometimes referred to as PG490, was first isolated from the medicinal plant TWHF and structurally characterized in 1972 [6], has been used for centuries in traditional Chinese medicine to treat inflammatory and autoimmune diseases including rheumatoid arthritis (RA), immune complex nephritis, systemic lupus erythematosus (SLE) and organ and tissue transplantations [7]. Due to the low contents of triptolide in TWHF, several synthetic studies have been carried out on triptolide itself as well as others structurally related molecules since 1970s [8]. Serve side effects, such as strong toxicity and less solubility, were found in further clinical studies [7]. In order to find derivatives with more active and less toxic, the structure-activity relationships (SAR) of triptolide and congeners have been carried out [9]. This review will describe the biological activities and syntheses developments of triptolide and congeners.

2. BIOLOGICAL ACTIVITIES

Clinical and experimental studies have demonstrated that triptolide has anti-inflammatory and immunosuppressive activities, and effectively prolongs allograft survival in organ transplantation including bone marrow, cardiac, renal and skin transplantation. Recently, the anti-tumor effect of triptolide has attracted extensive attention. Triptolide can not only inhibit tumor growth directly *in vitro* and *in vivo*, but can also enhance the anti-tumor effects of cytotoxic agents and chemotherapeutic agents [10].

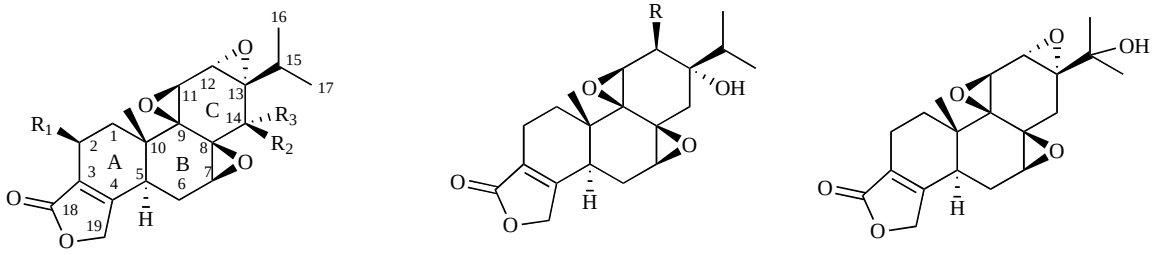

Fig. (1). Structures of triptolide (**l**) and analogues.

Triptolide, as the main bioactive constituent of *Tripterygium* extracts, shows strong activity in several standard *in vivo* assays for antiinflammatory activity [11], including the adjuvant-induced and carrageenan induced paw edema assays, allograft models, the carrageenan-induced air pouch model, the cotton-induced granuloma assay, and rheumatoid arthritis [12, 13]. The main mode of action of triptolide is the inhibition of expression of proinflammatory genes such as those for interleukin-2 (IL-2), inducible nitric oxide synthase (iNOS) [14], tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2) and interferon-gamma (IFN-γ) [15]. These small proteinaceous signaling molecules are also produced in the early stages of other inflammatory and immune reactions, and have many effects. However, triptolide does not affect DNA binding of nuclear factor kappa B (NF-κB); rather it inhibits the transcription of

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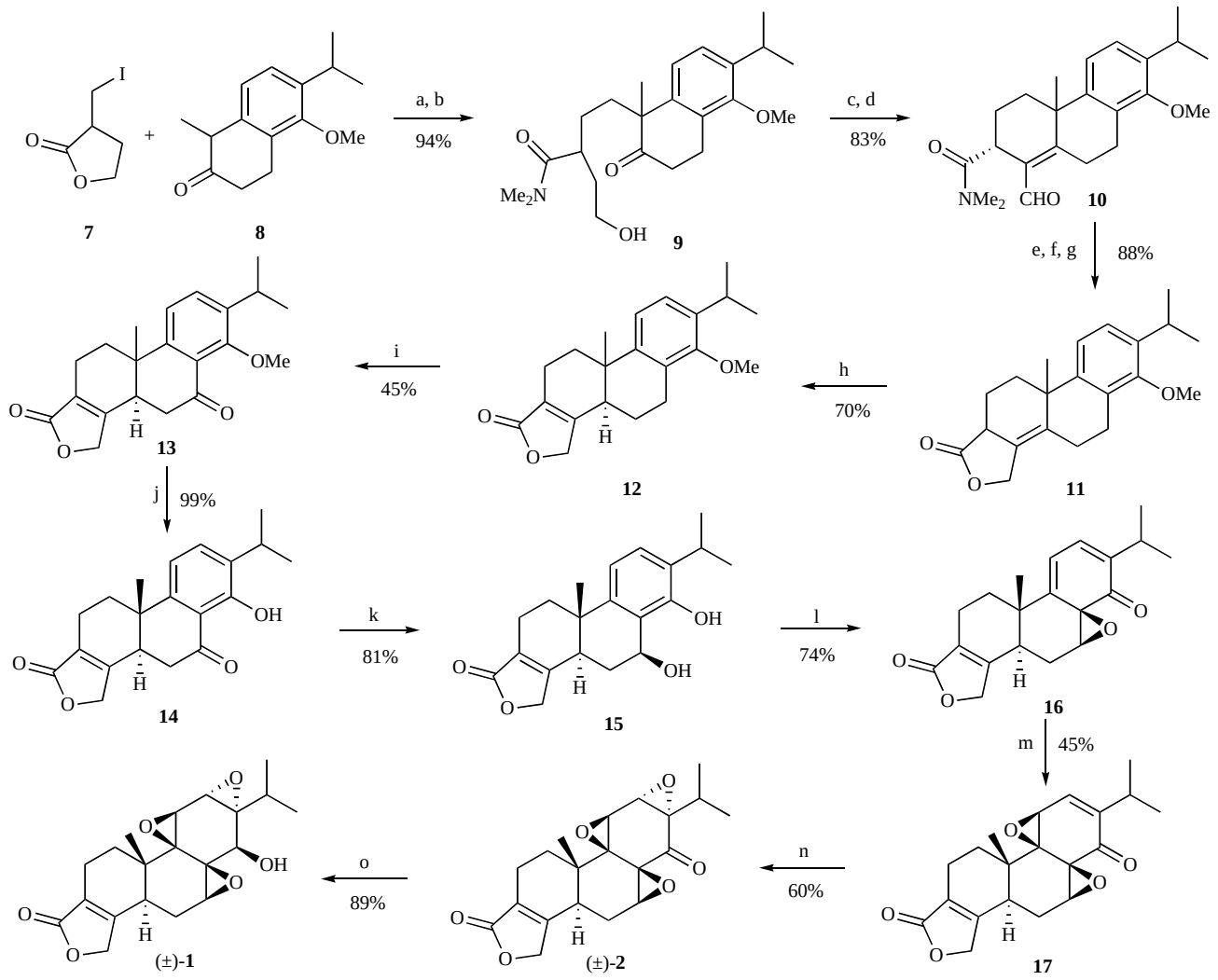


Scheme 1. Conditions: (a) NaH/DMF, rt; (b) Me_2NH, rt; (c) CrO_3.py, CH_2Cl_2, rt; (d) neutral Al_2O_3, rt; (e) p-TosOH, PhH, reflus; (f) $NaBH_4$, EtOH, rt; (g) aqueous HC1; (h) MeONa, MeOH, rt; (i) CrO_3, HOAc-H,O (9:1), rt; (j) BBr_3, CH_2Cl_2, rt; (k) $NaBH_4$, EtOH, rt; (1) $NaIO_4$, rt; (m) m-CPBA, CH_2Cl_2; (n) 30% H_2O_2, 1 M NaOH, MeOH; (o) $NaBH_4$, EtOH.

proinflammatory genes by blocking the transactivation of NF-κB, which occurs after its binding to promoter regions of these genes [16].

Early in 1972, Kupchan first reported the antileukemic effects of triptolide [6]. From then on, the antitumor effect of triptolide has been investigated in various tumor models *in vitro* and *in vivo*. It has been reported that triptolide could directly induce apoptosis of human promyelocytic leukemia, T cell lymphoma, human hepatocellular carcinoma, cervical adenocarcinoma, pancreatic carcinoma, multiple myeloma (MM) [17], cholangiocarcinoma [18] and oral cancer cell [19].

A recent further research showed that triptolide inhibited the proliferation of multiple myeloma cell line U266 in a time- and dose-dependent manner, potently induces G2/M cell cycle arrest and caspase-dependent apoptosis [20, 21]. Another research revealed that triptolide down regulates NF-κB pathway and its targeting genes associates with endothelial cell mobilization in human umbilical vein endothelial cells (HUVECs) and impaired VEGF expression in thyroid carcinoma TA-K cells. *In vivo*, triptolide inhibited TA-K cell induced tumor growth, vascular formation and VEGF expression. Triptolide may inhibit tumor angiogenesis by the dual action on vascular endothelial cells and tumor cells [22].

In addition, triptolide shows others biological activities, such as treatment to neurodegenerative diseases [23], antifertility [24] and insecticidal activity by antifeedant activity and contact toxicity [25].

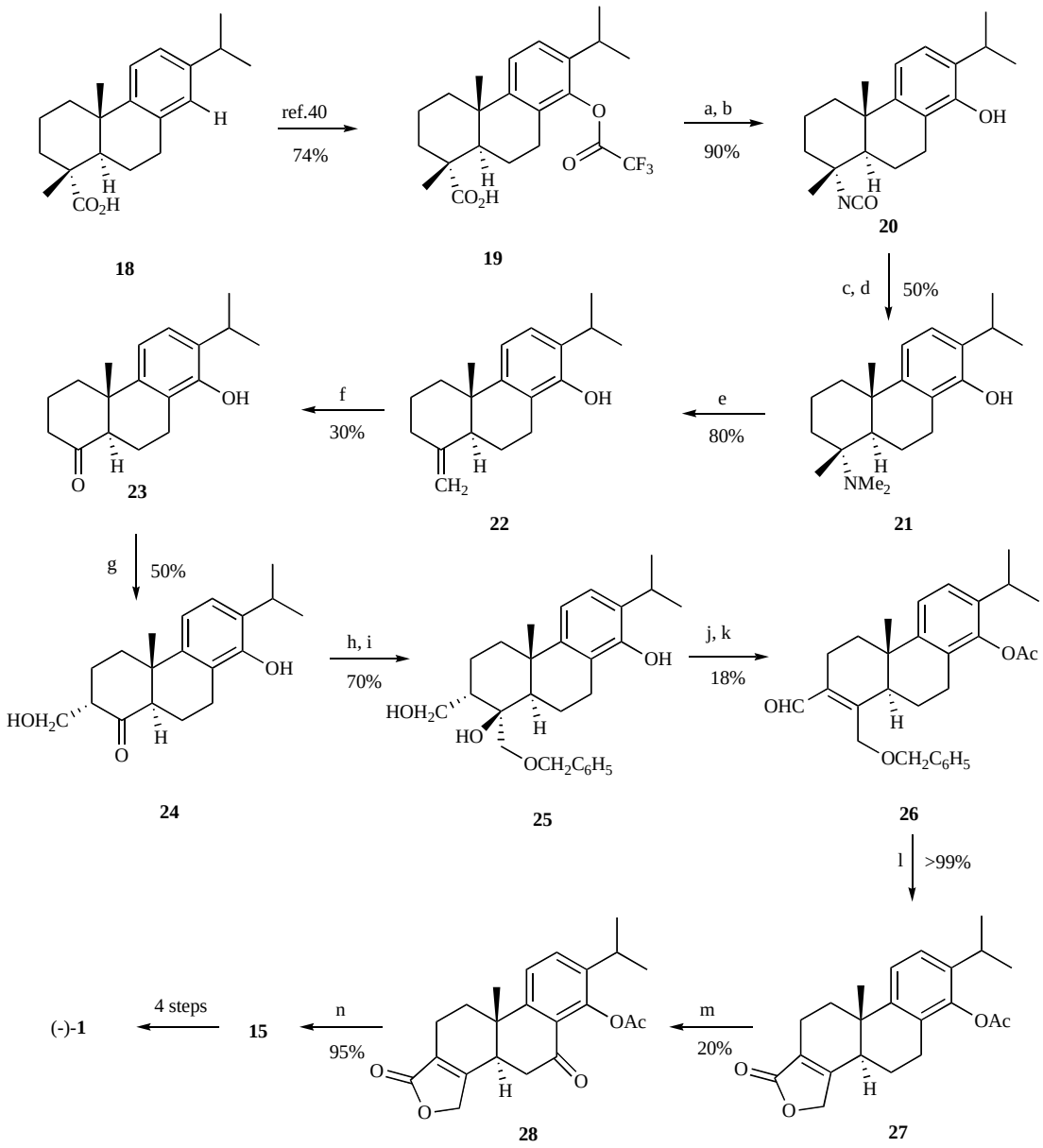
Diterpene triepoxide analogues **2**–**6** have, like triptolide **1**, also exhibited considerable anti-inflammatory, antoimmune, anticancer, antineurodegenerative, antifertility, insecticidal activities and so on [5, 26-27].

3. SYNTHESIS OF TRIPTOLIDE AND ANALOGS

The structure of triptolide **1** is characterized by the presence of nine stereogenic centers and three epoxides. After the pioneering synthesis of racemic triptolide **1** by Berchtold in 1977 [28], several racemic or asymmetric synthetic studies have been carried out on triptolid and analogues. In this section we will focus on total synthesis or formal synthesis of both triptolide **1** and its analogs.

3.1. Berchtold's Method

The first total syntheses of racemic **1** and **2** were described in 1980 by Berchtold as outlined in Scheme **1** [29, 30], the key step reactions are to construct A-ring by aldol condensation as well as the lactone ring by acid-catalyzed lactonization. Alkylation of the

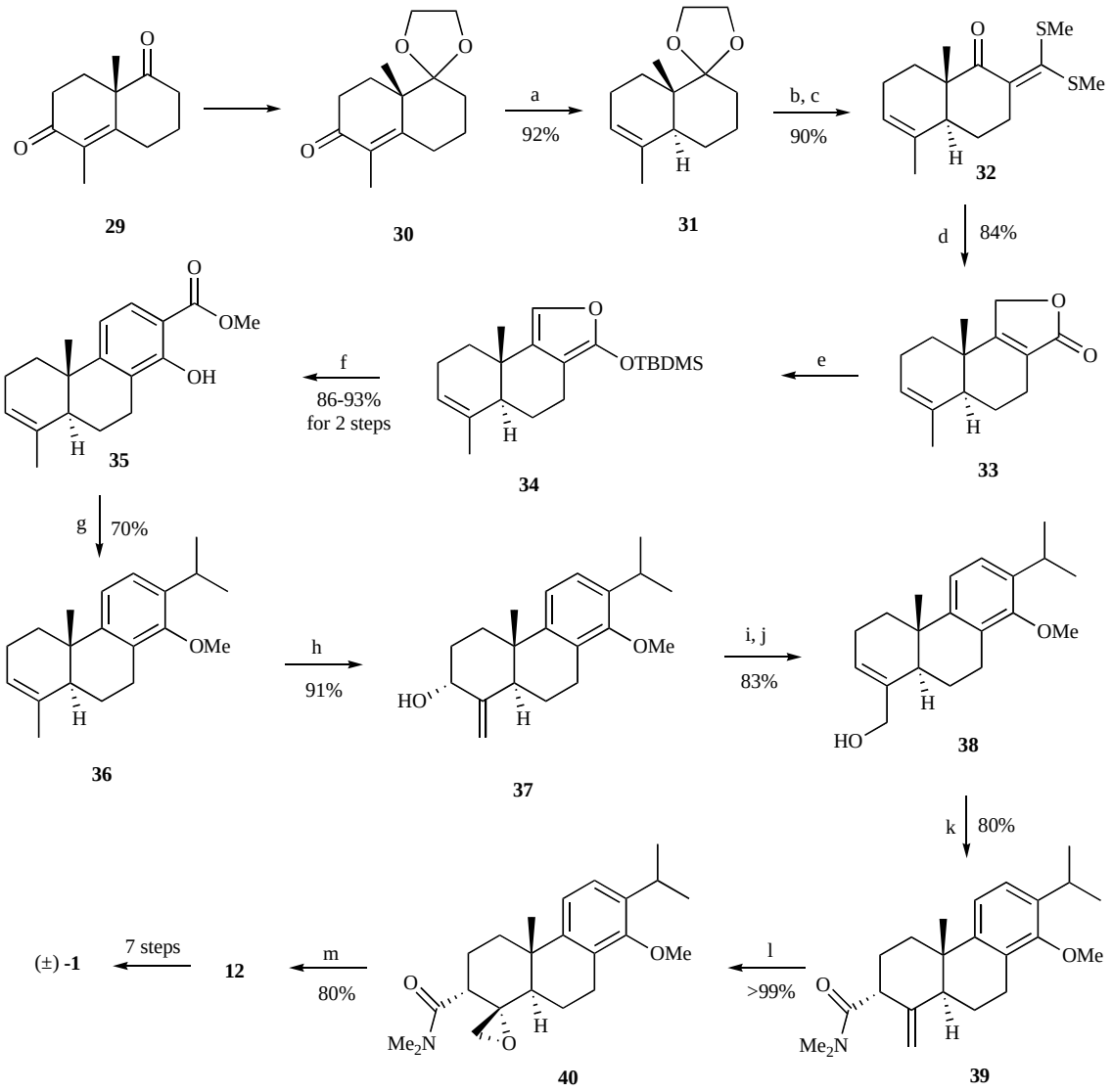


Scheme 2. Conditions: (a) $SOCl_2$, benzene-DMF, 50°C; (b) NaN_3, H_2O-acetone; toluene, 100°C; (c) $LiAlH_4$, THF, reflux; (d) HCO_2H-HCHO (aq); (e) m-CPBA, –20°C; then $CHCl_3$, reflux; (f) AcOH-dioxane-H_2O, OsO_4-$NaIO_4$, 20°C; (g) LDA, –78°C; HCHO (gas); (h) $MeOC(Me)=CH_2$, AcOH, 20°C; (i) $PhCH_2OCH_2Li$, –78°C; HCl-THF (pH 1), 20°C; (j) $MeOC(Me)=CH_2$-AcOH, Ac_2O-pyridine; HCl-MeOH (pH 1), CrO_3-pyridine, 20°C; (k) o-$C_6H_4(NH_2)PhCO_2H$, HCO_2OH, HCl-EtOH (pH 1), 20°C; (l) $NaClO_2$-$HOSO_2NH_2$, dioxane-H_2O; H_2-Pd/C, 20°C; (m) CrO_3, AcOH-H_2O, 40°C; (n) KOH, MeOH-H_2O; $NaBH_4$, EtOH, 20°C.

enolate of **7** with ketone **8**, which was a convenient starting material, obtained diastereomeric lactones followed by reaction with dimethylamine afforded a 1:1 mixture of diastereomers **9**. Oxidation of **9** with Collins reagent provided aldenhydes and aldol condensation **10** achieved using a tenfold weight excess of neutral alumina in ethyl acetate. Reduction of **10** with sodium borohydride and subsequent treatment with 2N HCl gave **11** as a single isomer; following methoxidation-catalyzed isomerization of **11** afforded key intermediate **12**. Benzylic oxidation of **12** gave **13** and followed by ether cleavage gave phenol, and subsequent borohydride reduction of the ketone afforded butenolide **15**. Compound **15** was converted into **2** by a periodate oxidation with $NaIO_4$, m-CPBA and basic H_2O_2, respectively. Finally, borohydride reduction of (±)-**2** afforded (±)-triptolide **(1)**. The total synthesis of (±)-**1** and (±)-**2** were completed from tetralone **8** in 16 and 15 steps in overall yield 2.5% and 1.65%, respectively.

3.2. Tamelen's Method A

The second synthetic approach by van Tamelen utilized the readily available resin acid (–)-dehydroabietic acid **18** as the practical starting material, the key step involved an elegant biomimetic cationic bicyclisation of a substituted benzene (Scheme **2**) [31]. In the construction of the lactone moiety, the trifluoroacetate **19** was prepared from (–)-dehydroabietic acid using Tahara's method [32]. Curtius degradation of **19** provided isocyanate **20**, which was converted to tertiary amine **21** by reduction with $LiAlH_4$ followed by treated with mixture of HCO_2H and aqueous HCHO. Oxidation to the *N*-oxide of **21**, effected Cope elimination, giving olefin **22**. Oxidative cleavage of **22** afforded ketone **23** with OsO_4-$NaIO_4$. Then, compound **23** was transformed to β-hydroxy ketone **24** by generation of the enolate and further reaction with gaseous HCHO. After the methylol unit of **24** was protected as the 2-methoxypropyl ether, giving triol monobenzyl ether **25** by successive treatment with lith-



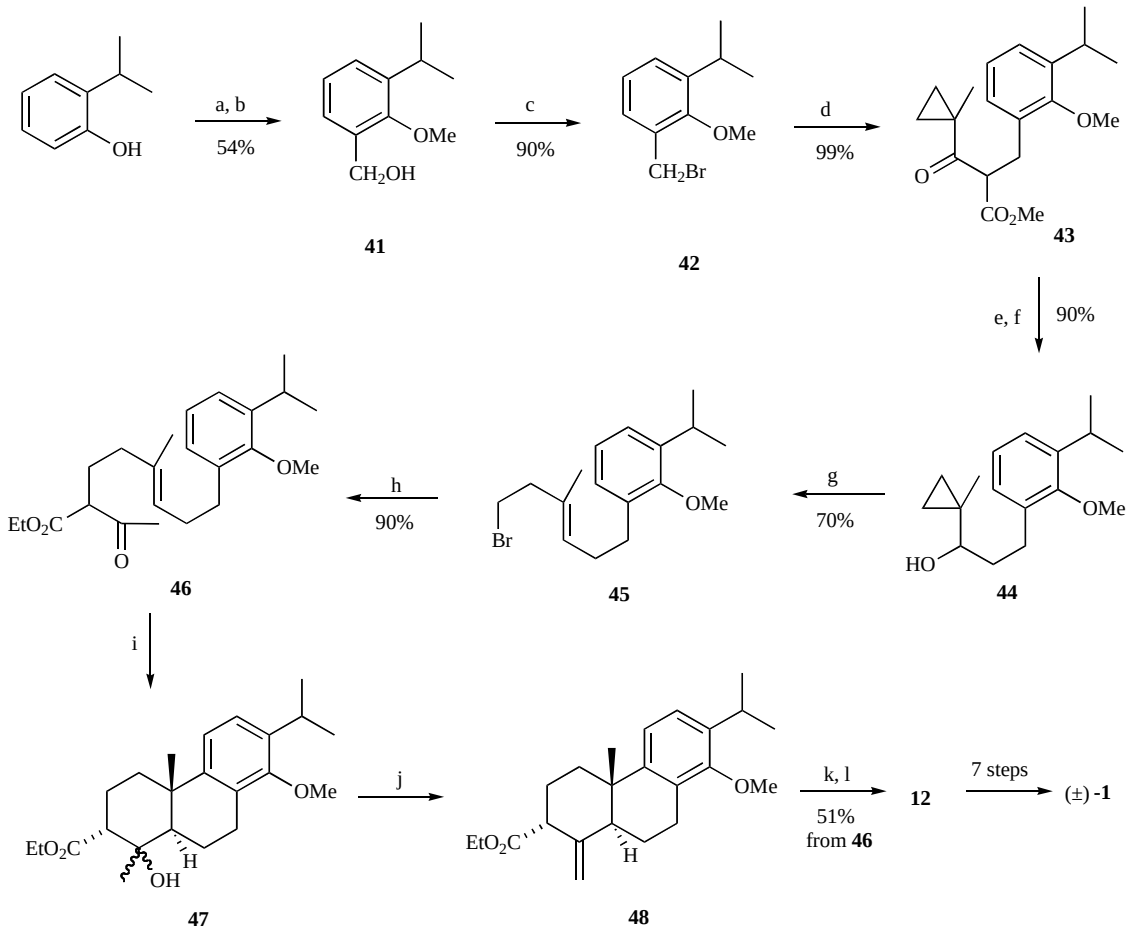
Scheme 3. Conditions: (a) Li/NH_3, t-BuOH, –78°C; diethyl chlorophosphate, 0°C; $Li/EtNH_2$, t-BuOH, 0°C; (b) H_2SO_4, THF, rt; (c) CS_2, lithium 4-methyl-2,6-di-t-butyl phenoxide, THF; MeI, rt; (d) dimethylsulfonium methylide, DMSO/THF, –10°C; 6M HCl-MeOH, rt; (e) $(i\text{-}Pr)_2NLi$-HMPA, THF, –78°C; TBDMSCl, THF, –78°C; (f) methyl acrylate, bezene, 70°C; HCl-MeOH, rt; (g) MeI, NaH, THF, rt; MeLi; MsCl/TEA; Li/NH_3, –78°C; (h) m-CPBA, DCM; LDA, THF; (i) $SOCl_2$-Py, 0°C; (j)AcOK, DMSO, 70°C; NaMe, MeOH, rt; (k) DMF, dimethylacetal xylene, reflux; (l) m-CPBA, DCM, rt; (m) LiHMDS, HCl, rt.

ium methyl benzyloxide and pH=1 hydrochloric acid. Through oxidation and dehydration formed the α,β-unsaturated aldehyde **26.** Oxidation of **26** to the carboxylic acid level followed by hydrogenolysis of the benzyloxy group was concluded by spontaneous lactonization affording butenolide **27**. After construction of the lactone **27**, it was oxidized to the ketone **28** and transformed into benzyl alcohol **15** by saponification and reduction. Though the prototypic oxidation course described by Adler *et a1*. [33], the first forming (–)-triptolide was synthesized though 16 steps in overall yield 0.19%.

3.3. Tamelen's Method B

In order to find efficient route to establish the key intermediate **12** in Scheme **1**, van Tamelen reported the third route to syntheses of triptolide **1** and triptonide **2** in 1982 as showed in Scheme **3** [34]. This sequence features two new methods of butenolide construction, one of which finds subsequent utilization in the assemblage of the benzenoid nucleus as an integral part of the synthesis rather than its origination in aromatic starting materials. In addition, the pathway requires fewer steps and proceeds in an overall yield 40-50 times than previously method [31].

Bicyclic diketone monoethylene ketal **30**, obtained by selectively ketalization of the Wieland-Miescher ketone **29**, was converted into octalin ketal **31** in a "one-pot" sequence involving Li/NH_3 reduction, phosphoesterification and enol phosphate reduction. Following reaction of **31** with CS_2 and MeI priority afford the ketene dithioacetal **32**. Subjection of **32** to the action of sulfur ylide followed by acid hydrolysis produced the unsaturated lactone **33**. In preparation for construction of the benzenoid ring in **12**, butenolide **33** was transformed into the corresponding α-(*tert*-butyldimethylsiloxy) furan **34** via enolization followed by subsequent reaction with *tert*-butyldimethylsilyl chloride. Compound **34** was subjected to a Diels-Alder reaction with methyl acrylate which was followed by spontaneous aromatization of the intermediate adduct to give salicyclic ester **35.** Conversion of **35** to *o*-isopropylphenyl methyl ether **36** was accomplished by successive treatment with methyl iodide, methyllithium, methanesulfonyl chloride and finally Li/NH_3 reduction. In order to set the stage for for-



Scheme 4. Conditions: (a) NaH, MeI, rt; (b) n-BuLi/TMEDA, rt; (HCHO)n, 140°C; (c) PBr_3, Et_2O, 0°C; (d) NaH, cyclopropyl ketoester, THF, 0°C; (e) $Ba(OH)_2$, H_2O/Et_2O, 90°C; (f) $LiAlH_4$, dry Et_2O, 0°C; (g) LiBr, PBr_3, collidine in Et_2O, 0°C; (h) ethyl acetoacetate, LiH, DMF, 75°C; (i) $SnCl_4/CH_2Cl_2$, 0°C; (j) $MeSO_2Cl$, Et_3N, 0°C; (k) *m*-CPBA, rt; (l) n-BuLi, i-$PrNH_2$, –78°C.

mation of a new carbon-arbon bond at C-3 by means of a [2,3]-sigmatropic rearrangement of a carbene, olefin **36** was converted to allylic alcohol **37** by epoxidation and elimination in the oxide moiety. Thionyl chloride induced rearrangement of alcohol **37** and substitution of halogen gave alcohol **38**. On being heated with dimethylformamide dimethylacetal, alcohol **38** generated the allylic amide **39**. Oxidation of **39** to epoxy amide **40** followed by lithium hexamethyldisilazide induced β elimination gave the intermediate α,β-unsaturated amide, which on direct acid hydrolysis yielded butenolide **12**. The latter procedures of synthesis of (±)-triptolide was managed as previously mentioned method [31].

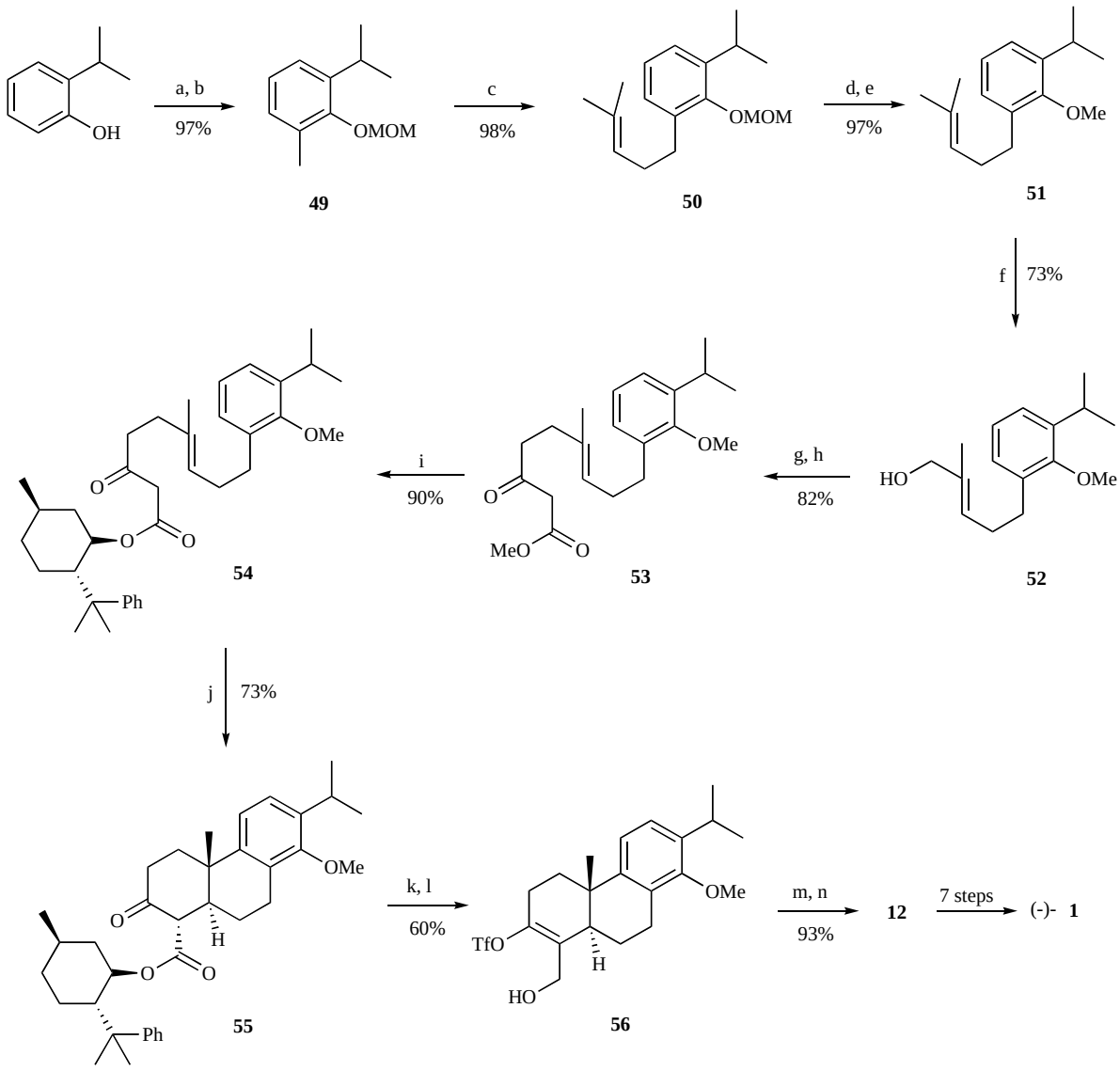
3.4. Tamelen's Method C

Van Tamelen developed the fourth approach to synthesize racemic **1** (Scheme **4**) [35]. 2-Isopropylphenol, as available starting material, was alkylated, o-metalated and reacted with formaldehyde gave rise to isopropyl benzylic alcohol **41**. Followed by bromide and nucleophilic substitution with the cyclopropyl β-ketoester easily generated **43.** Saponification, decarboxylation of **43** and reduction lead to the cyclopropyl carbinol **44**. Homoallylic bromide **45** obtained from **44** by the method of Julia. Alkylation of ethyl acetoacetate with bromide **45** gave rise to the substituted β-ketoester **46** desired for cyclization. Tricycle **47**, cyclization of β-ketoester **46**, was translated to unsaturated easter **48**. In order to generate the butenolide moiety, elimination, oxidization of olefinic ester **48** generates the γ-hydroxy α,β-unsaturated ester, which cyclizes *in situ* to the tetracycle **12**. The synthesis of **12** requires 12 steps from available materials, necessitates the purification of only 4 intermediates, and proceeds in a yield of ~15%, compared to 20-30 steps and ~0.3-1 5% yields in prior approaches [31, 34].

3.5. Yang's Method

More than 10 years later Yang published the first enantioselective total synthesis of (–)-triptolide and analogs, involved an oxidative radical bicyclisation, carrying a chiral auxiliary (Scheme **5**). The key step involves lanthanide triflate-catalyzed oxidative radical cyclization of (+)-8-phenylmenthyl ester **54** mediated by $Mn(OAc)_3$, providing intermediate **55** with good chemical yield and excellent diastereoselectivity [36-39].

Yang's route also started from commercially available 2-isopropyl phenol, in which the phenol hydroxyl group was protected with chloromethyl methyl ether (MOM). The resulting MOM ether was *ortho* lithiated and methylated with iodomethane, providing the intermediate **49**. Compound **49** was lithiated and quenched with 3,3-dimethylally bromide to gave olefin **50** which could be transformed into **51** by protecting group changed from MOM ether to methyl ether, followed by allylic oxidation of compound **51** with SeO_2/TBHP provided allylic alcohol **52**. Compound **52** was converted into allylic bromide and the dianion displacement furnished intermediate **53**. Ester exchanged of **53** with (+)-8-phenylmenthol in the presence of a catalytic amount of DMAP provided acyclic precursor **54**. The cyclization of **54** in the presence of $Mn(OAc)_3$ and $Yb(OTf)_3 \cdot H_2O$ in CF_3CH_2OH afforded the major diastereomer **55**. The construction of α,β–unsaturated γ–lactone **12** from tricyclic **55** by Crisp's method [40]. With the key intermediate (+)-**12** in



Scheme 5. Conditions: (a) MOMCl, NaH, THF, 65°C; (b) *n*-BuLi, THF; CH_3I, –78°C; (c) *s*-BuLi, THF; 3,3-dimethylally bromide, –78°C; (d) TMSCl, $LiBF_4$, CH_3CN, –25°C; (e) Me_2SO_4, K_2CO_3, acetone, reflux; (f) SeO_2, *t*-BuO_2H, CH_2Cl_2, 0°C; $NaBH_4$, MeOH; (g) MsCl, Et_3N, CH_2Cl_2; LiBr, THF, –40°C; (h) $CH_3COCH_2CO_2CH_3$, NaH, *n*-BuLi, THF, 0°C; (i) (–)-8-phenylmenthol, DMAP, toluene, reflux; (j) $Mn(OAc)3{\cdot}2H_2O$, $Yb(OTf)_3$, CF_3CH_2OH, –5°C; (k) KHMDS, THF, –78°C to –20°C; $PhNTf_2$, –78°C to rt; (l) DIBAL-H, CH_2Cl_2, –78°C to –30°C; (m) Bu_3N, $Pd(PPh_3)_4$, LiCl, CO (1 atm), CH_3CN, 65°C; (n) BBr_3, CH_2Cl_2, –78°C to rt.

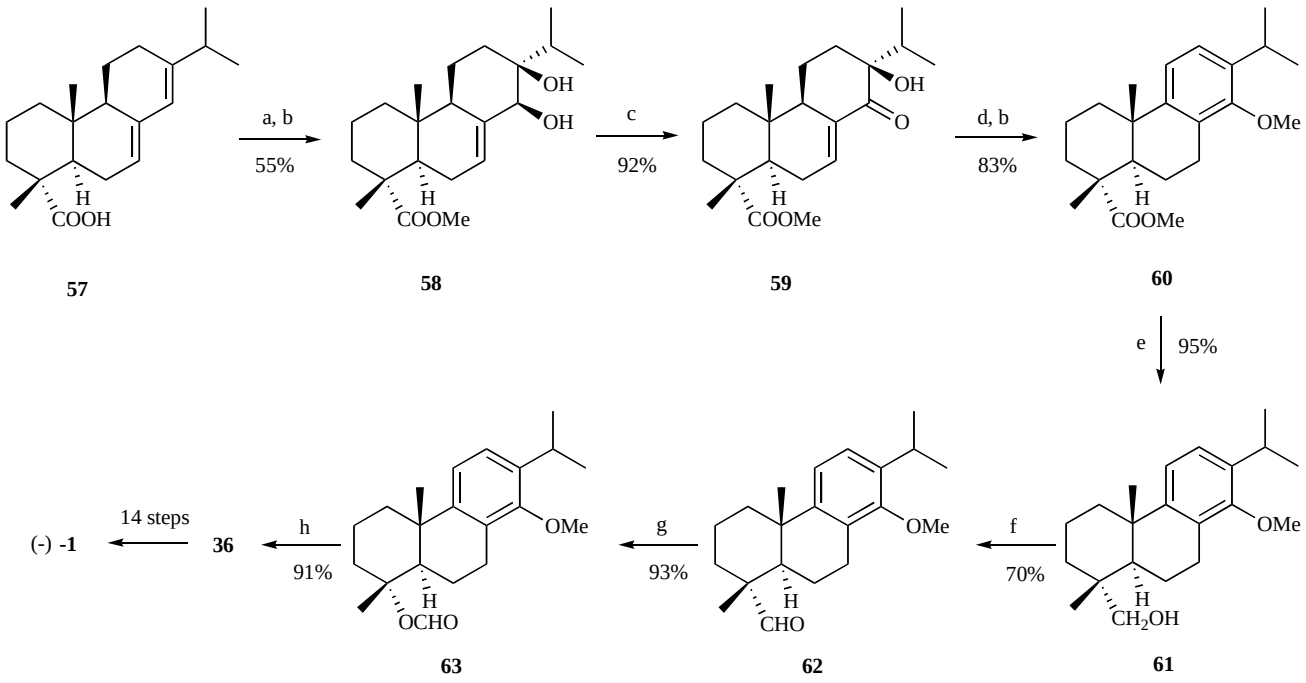
hand, (–)-triptolide and (–)-triptonide were completed though 20 steps in overall yield 2.8%.

3.6. Alvarez-Manzaneda's Method

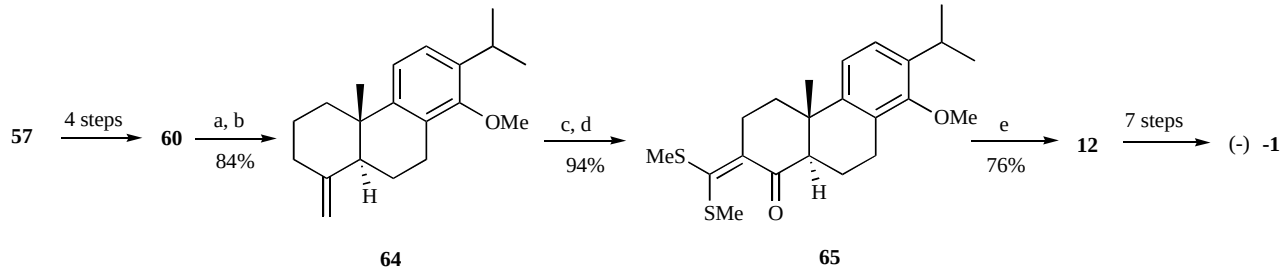
Alvarez-Manzaneda reported the formal synthesis of (–)-triptolide from (+)-abietic acid **57** as shown in Scheme **6** [41]. The procedure introduces an oxygenated function into the C-14 of abietane diterpenes with complete regioselectively. Firstly, (+)-abietic acid was changed into dihydroxy ester **58** by regioselective dihydroxylation and esterification. And oxidation of secondary hydroxyl group with PhSeSePh and t-BuOOH was attained, following A-ring aromatization, methylation, reduction and oxidation provided aldehyde **62**. Then trisubstituted alkene **36** was efficiently obtained by Baeyer-Villiger oxidation of aldehyde **62** and elimination under I_2 and PPh_3. Finally, the synthesis of (–)-triptolide was finished according to ref. [34]. The approach efficiently modified C-ring of triptolide from (+)-abietic acid, however, A-ring modification is necessary to complete though many steps.

3.7. Li's Method

Alternatively, an efficient synthesis of triptophenolide methyl ether **12** from (+)-abietic acid **57** developed by Li's group as shown in Scheme **7**, and successfully applied the procedure to the synthesis of (–)-triptolide **1** in large scale [42]. Hydrolysis of methoxy ester **60**, which prepared as mentioned in Scheme **6**, and reactions of the acid with oxalyl chloride gave acid chloride, which was converted into the corresponding pyridyl sulfide, followed subsequent oxidation with *m*-CPBA or oxone and underwent elimination afford the corresponding C4-(18)-alkenes **64** in high yield. Removal of the methylene of **64** by ozonolysis, following lithium and addition of MeI, afford the ketene dithioacetal **65**. Treatment of **65** by Corey-Chaykovsky epoxidation reaction followed by acid hydrolysis afforded triptophenolide methyl easter **12**. Authors accomplished the remaining steps towards (–)-triptolide by following Yang's procedure [38]. The route is of characteristic of low cost, high yield and easy operation.



Scheme 6. Conditions: (a) OsO_4, Me_3NO, Py, t-BuOH, reflux; (b) MeI, K_2CO_3, acetone, reflux; (c) PhSeSePh, t-BuOOH, CCl_4, reflux; (d) TsOH, toluene, reflux; (e) $LiAlH_4$, THF, rt; (f) PCC, CH_2Cl_2, rt; (g) mCPBA, $NaHCO_3$, CH_2Cl_2, reflux; (h) I_2, PPh_3, CH_2Cl_2, rt.



Scheme 7. Conditions: (a) KOH, ethyleneglycol, 130°C; (b) $(COCl)_2$, DMF; sodium salt of *N*-hydroxypyridine- 2-thione, DMAP, toluene, reflux; m-CPBA, –78°C; (c) O_3, CH_3OH/CH_2Cl_2, rt; (d) CS_2, lithium 4-methyl-2,6-di-tert-butyl-phenoxide, THF, rt; MeI, rt; (e) $(CH_3)_3SI$, n-BuLi, –78°C; then HCl/CH_3OH, rt.

With intermediate C4-(18)-alkenes **64** in hand, Li'group has finished the total synthesis of tripdiolide **3** in 5.8% overall yield as depicted in Scheme **8** [43]. The crucial steps include the introduction of C2-β-hydroxyl and α,β-unsaturated lactone ring and triepoxide construction from the 2β-hydroxyl triptophenolide methyl ether **72**. Allylic oxidation of **64** provided C-3 alcohol **66**, which was oxidized readily under Swern conditions to the enone **67**. Compound **67** was translated into 1,2-diol **68** as a single stereoisomer by nucleophilic addition and oxidative cleavage of the corresponding Si-C bond. Compound **69** was afforded by protection of primary hydroxyl group of **68** and following treatment with $SOCl_2$. Deprotection and subsequent oxidation of **69** with Dess-Martin periodinane to afford diene aldehyde **70**, upon oxidation of diene with N-bromosuccinimide (NBS) gave 1,4-product **71**. Lactonization of the resulting bromo acid occurred spontaneously to give the desired 2β-hydroxyl triptophenolide methyl ether **72**. With the key intermediate **72** in hand, the structure of triepoxide was easily constructed by modified procedure as described in Scheme **1**.

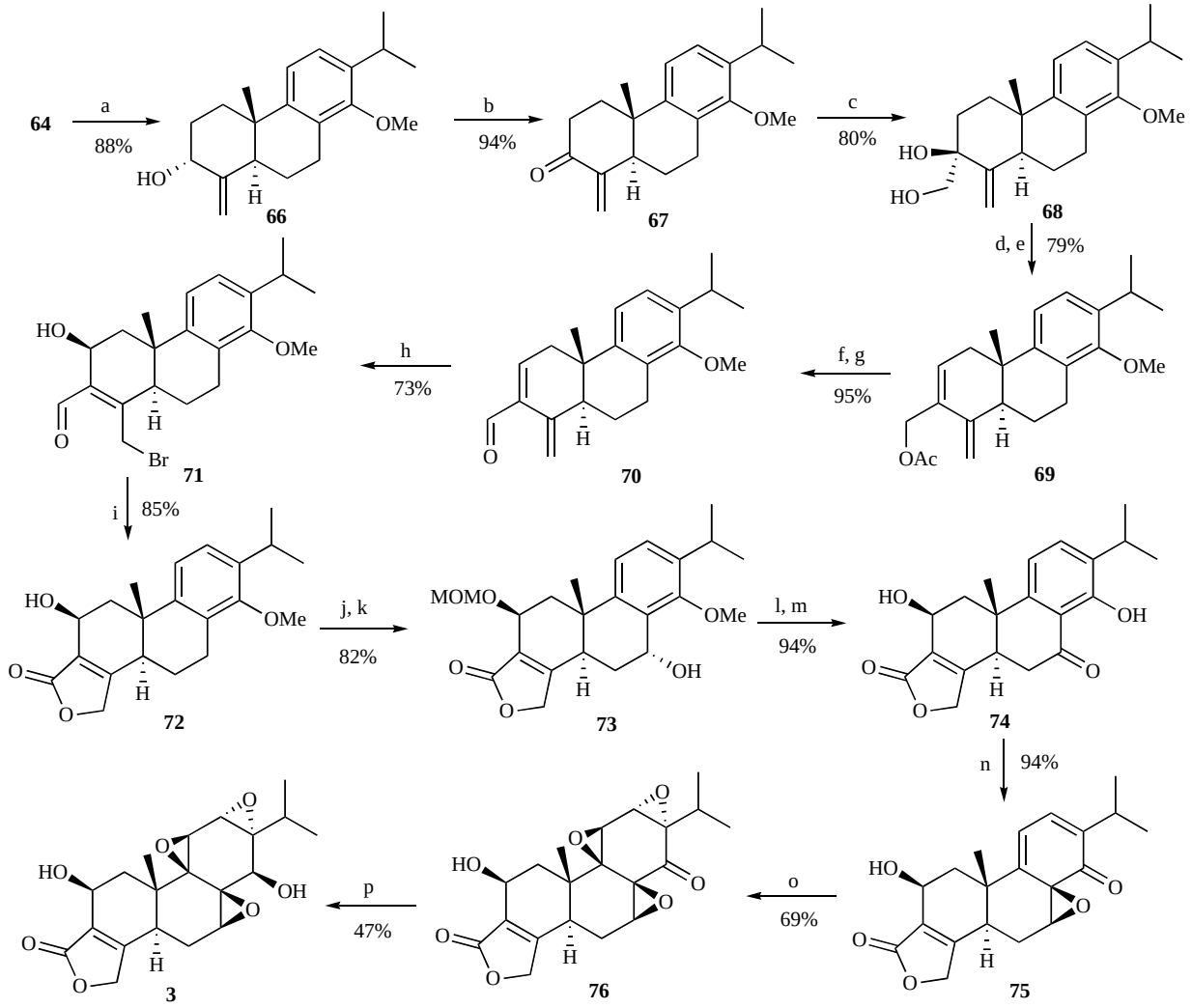
3.8. Sherburn's Method

Recently, Sherburn group reported a new formal total synthesis of (–)-triptolide, the method key features include two intermolecular Diels–Alder reactions and a new deoxygenative aromatisation process (Scheme **9**) [44]. The first Diels–Alder reaction, which underwent intermolecular cycloaddition lactonisation [45], was efficient enantioselective between iodide **76** with methyl acrylate under Mikami's catalyst [46]. The second Diels–Alder reaction involves the union of **78** and 2-isopropyl- 1,4-benzoquinone, in which the desired diastereomer **79** was obtained under high pressure conditions (19 kbar). Following a region and stereoselective reduction of the less hindered ketone delivered the C-14α-hydrooxy derivative, and further converted into the corresponding methyl ether **80**. C-11 deoxygenation and concomitant A-ring aromatization of **80** under triflic anhydride and sterically hindered base offered saturated lactone **81**, the later was easily converted into butenolide **82** through elimination of the selenoxide derivative [28]. The successful sequence to construct **82** involves only 6 steps, but 10 steps in ref. 29, and avoids the use of protecting groups.

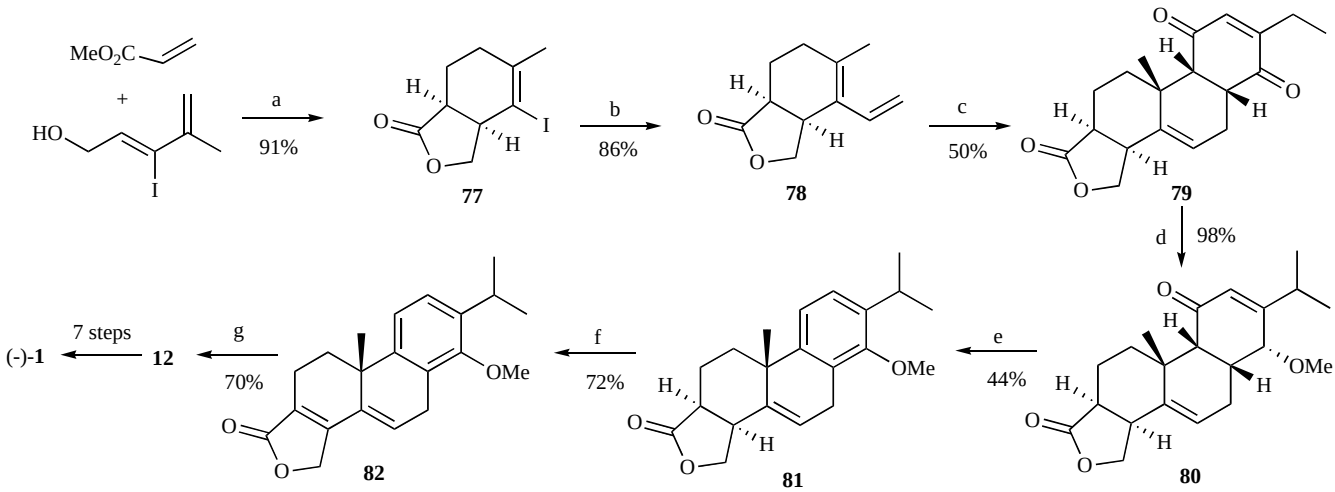
In summary, we described in this section all total and formal syntheses reported methods for compounds **1**-**3**. Following we will display structure-activity relationship of **1** and its congeners.

4. STRUCTURE ACTIVITY RELATIONSHIP

Early studies on the structure–activity relationship of **1** indicated that the characteristic hydrogen-bonded C9,C11-epoxy and C14β-hydroxy system may account for its autoimmune inhibition, antitumor effect [47], meanwhile, the configuration of the hydroxyl



Scheme 8. Conditions: (a) SeO_2, t-BuO_2H, CH_2Cl_2, rt; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78°C; (c) (isopropoxy-dimethylsilyl) methyl chloride, Mg, THF, –30°C; then KF, $KHCO_3$, 30% H_2O_2, rt; (d) Ac_2O, Py, rt; (e) $SOCl_2$, Py, rt; (f) K_2CO_3, MeOH/H_2O, rt; (g) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (h) NBS, acetone/H_2O, rt; (i) $NaClO_2$, 2-Methyl-2-butene, NaH_2PO_4, t-BuOH, THF, H_2O, rt; (j) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, rt; (k) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, rt; (l) PDC, CH_2Cl_2, rt; (m) BBr_3, CH_2Cl_2, –78°C to rt,; (n) $NaBH_4$, CH_3OH, 0°C; then $NaIO_4$, CH_3OH/H_2O, 0°C; (o) CF_3COCH_3, Oxone, $NaHCO_3$, CH_3CN/aqueous $Na_2(EDTA)$, rt; then H_2O_2, NaOH, MeOH, rt; (p) $Eu(fod)_3$, $NaBH_4$, CH_3OH, –78°C.



Scheme 9. Conditions: (a) $Cl_2TioPri$, R-binol, CH_2Cl_2, rt; (b) H_2C=$CHSnBu_3$, Pd (0); (c) 2-isopropyl-1,4- benzoquinone, CH_2Cl_2; (d) $NaBH_4$; Ag_2O, MeI; (e) 2,6-didiopropyl-4-methylpyridine, Tf_2O; (f) Et_3N, TIPSOTf; PhSeCl; H_2O_2; (g) Pd/C, H_2, AcOEt.

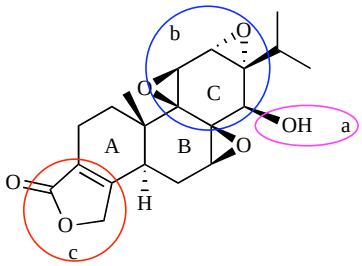
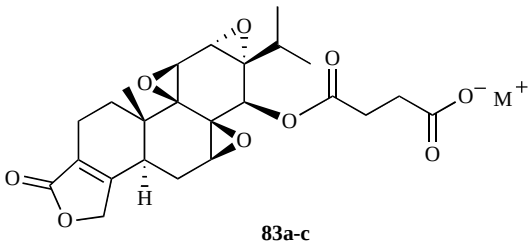


Fig. (2). Modification on triptolide.

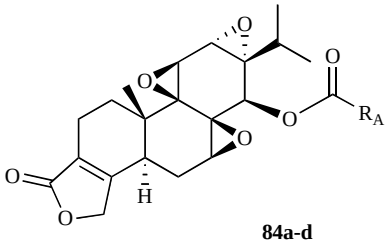


83a-c

83a M = Na

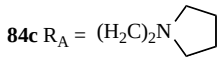
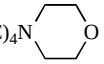
83b M = $(HOCH_2)_3CNH_3$

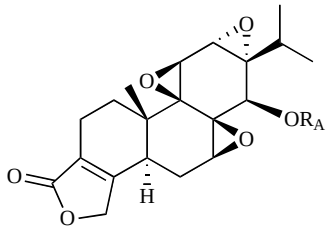
83c M = $NH_3(CH_2)_4CHNH_3COO$



84a-d

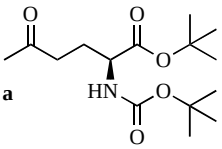
84a $R_A = CH_2NMe_2$ **84b** $R_A = (CH_2)_2NMe_2$

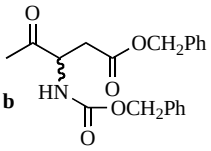
84c $R_A =$  **84d** $R_A = (H_2C)_4N$ 

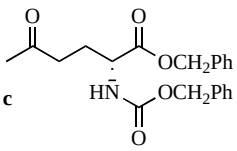


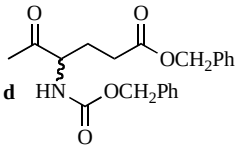
85a-f

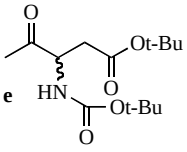
$R_A =$

a 

b 

c 

d 

e 

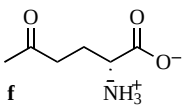
f 

Fig. (3). Structures of derivatives of triptolide **83**–**85.**

group at C-14 of **1** should be the β orientation [48, 49]. Recently, much work on structure modification of **1** has been carried out to improve biological activities and to overcome limitation of toxicity and less water solubility, most modification of triptolide focused on C-14 hydroxyl, C–ring and unsaturated lactone ring of parent compound **1** (Fig. **2**) [9].

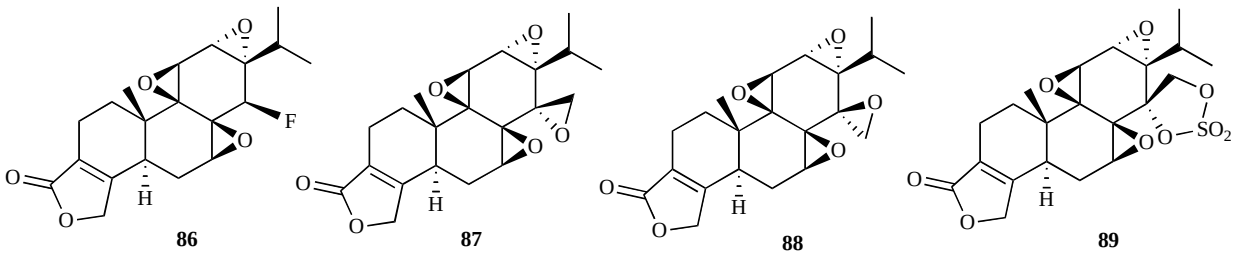
4.1. Modification on C-14-hydroxyl of Triptolide

C-14-Hydroxyl of triptolide is the easily modified and introduced many functions. However, for a long time the aim of C-14 modification was just to improve the lead compound's water solubility by carboxylation of β-OH at C-14 to introduce water solubility enhancing moieties.

Carboxylated esters of triptolide **83a-c** were prepared by succinylation of triptolide followed by salt formation [50]. Compounds **84a-d** and **85a-f** were easily prepared though condensation of triptolide with different acids in the presence of dicyclohexylcarbodiimide (DCC) and catayltic amount of 4-(dimethylamino)-pyridine (DMAP) (Fig. **3**) [51]. However, most of these derivatives possess less immunosuppressive and antitumor activity, and low cytotoxicity than triptolide itself. The results showed that they were prodrugs of triptolide and themselves are no activity and only part decomposed *in vivo*. PG490-88 (14-succinyl triptolide sodium salt, **83a**), a water-soluble prodrug of **1**, has been elucidated as a new immunosuppressant. It effectively prevents acute and chronic rejection in organ transplantation and shows potent antitumor activity [10]. PG490-88 has been approved entry into Phase I clinical trials for prostate cancer, suggesting that this drug might be a promising candidate for antitumor activity against prostate cells [52, 53].

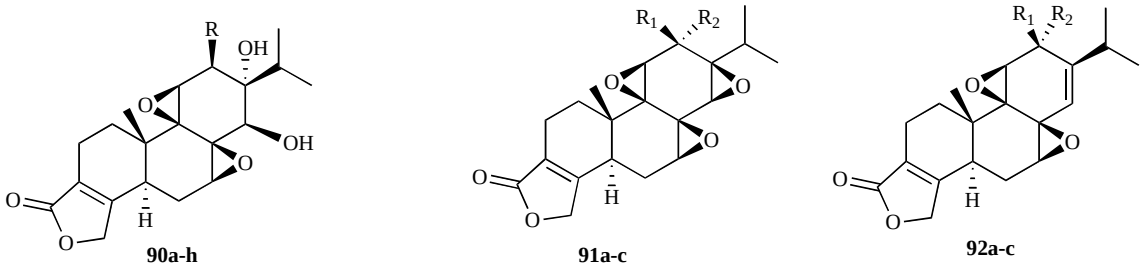
Another series derivatives with hydroxyl substituted at C-14 of triptolide by the different amine esters, including aliphatic chain amine esters, alicyclic amine esters and aralkyl amine esters, were synthesized. The biological results showed that some of them exhibited a potent inhibitory activity against chronic myelogenous leukemia (KBM5 and KBM5-T315I) cells, and the stereo-hindrance of C-14 group appeared to be responsible for the antitumor effects [54].

In addition, some medicinal chemists have found that substituting C14-hydroxyl with other groups while keeping β orientation of the substituent could retain the cytotoxicity of **1**. Recently, Takeya's group found that 14β-dehydroxy-14β-fluoro triptolide **86** showed more cytotoxic (the IC_{50} of **86** against A549 and HT-29 is 0.42 and 0.06 ng/mL, respectively) than the parent natural triptolide (Fig. **4**) [55]. Some 14,21-epoxy triptolides **87** and **88** and C14 five-member ring substituent analogue **89**, as anticancer agents, were also synthesized. The biological results showed that compound **87**



86 **87** **88** **89**

Fig. (4). Structures of derivatives of triptolide **86**–**89**.



90a-h **91a-c** **92a-c**

a R = Cl **b** R = Br **c** R = SPri

d R = OMe **e** R = OAc **f** R = SCN

g R = OSO_2Me **h** R = $OPO(OMe)_2$

91a R_1-R_2 = O

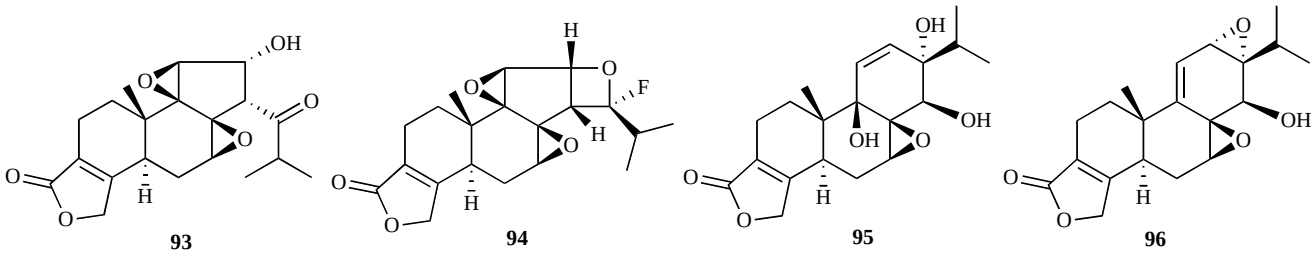
91b R_1 = H, R_2 = OH

91c R_1 = OH, R_2 = H

92a R_1 = H, R_2 = OH

92b R_1 = H, R_2 = F

92c R_1 = F, R_2 = H



93 **94** **95** **96**

Fig. (5). Structures of derivatives of triptolide **90**–**96**.

possessed broad spectrum *in vitro* anticancer activity and prominent selective *in vivo* anticancer activities, particularly against human ovarian SKOV-3 and prostate PC-3 cancers with obviously lower toxicity than **1**. However, C14 five-member ring substituent analogues reduced greatly against ovary (SK-OV-3), breast (MDA-MB-468), and prostate (PC-3) [56]. These results, clearly challenging the traditional viewpoint on the necessity of β-hydroxyl group at C-14 of triptolide, suggest that the anticancer activity of triptolide analogues may not be explained as simply as before [47]. Therefore, there is still big confusion on the role of β-hydroxyl group at C-14 of triptolide.

4.2. Modification on C-Ring of Triptolide

12,13-Epoxy of triptolides were easily attacked by nucleophilic reagent and gave 12,13-epoxy opened derivatives **90a-h**, the biological evaluation showed that compounds **90a**,**b** have comparable immune activity and less toxicity compared to triptolide. Other derivatives showed less potential immune or antitumor activity than triptolide [57]. The epoxide-transposition analogues **91a-c**, with 7,8-, 9,11-, and 13,14-β-epoxides showed very low marginal activity (Fig. **5**) [58].

The analogues **92a-c** with no 12,13-epoxide substructure and semi-synthetic derivatives **94** and **95** having five-membered C ring were shown to be only weakly cytotoxic activities on human lung A549 and human colon HT29 tumor cells [58]. Interestingly, compound **93**, in which 9,11-β-epoxide is instead by 9,11-olefin, shows much more active than triptolide with the IC_{50} value of 0.05 nM for ovarian carcinoma SKOV-3 cells, clearly challenging the traditional viewpoint on the necessity of 9,11-β-epoxide group of triptolide [59].

Jung *et al.* also synthesized a series of derivatives **97**-**103** (Fig. **6**) modified on two or three-epoxy triptolide at the same time [60, 61], among these derivatives, the biological studies of compound **99** showed obviously effects on inhibition of IL-2 expression and cytotoxicity with IC_{50} is 14 and 90 ug/L, respectively.

4.3. Modification on Lactone-Ring

Some aminofuran triptolide derivatives **104**, ester of furan triptolide derivatives **105** and lactone ring-opened derivatives **106** were synthesized by modified on lactone-ring of triptolide (Fig. **7**). However, these derivatives of triptolide analogs possess improved water solubility and generally lower toxicity than the parent compound **1** [62].

Recently, compounds **107** and **108**, in which five-membered unsaturated lactone ring were replaced with the five-membered unsaturated lactam ring, were found to be still effective against the two cell lines with the very low IC_{50} value (0.02 μM for SKOV-3 cells) and more soluble in water than triptonide (**2**) [63].

CONCLUSION AND PERSPECTIVE

In summary, the natural products, such as triptolide, triptonide and their analogs from TWHF, exhibit promising autoimmune, anti-inflammatory, immunosuppressive, antitumor and others biological

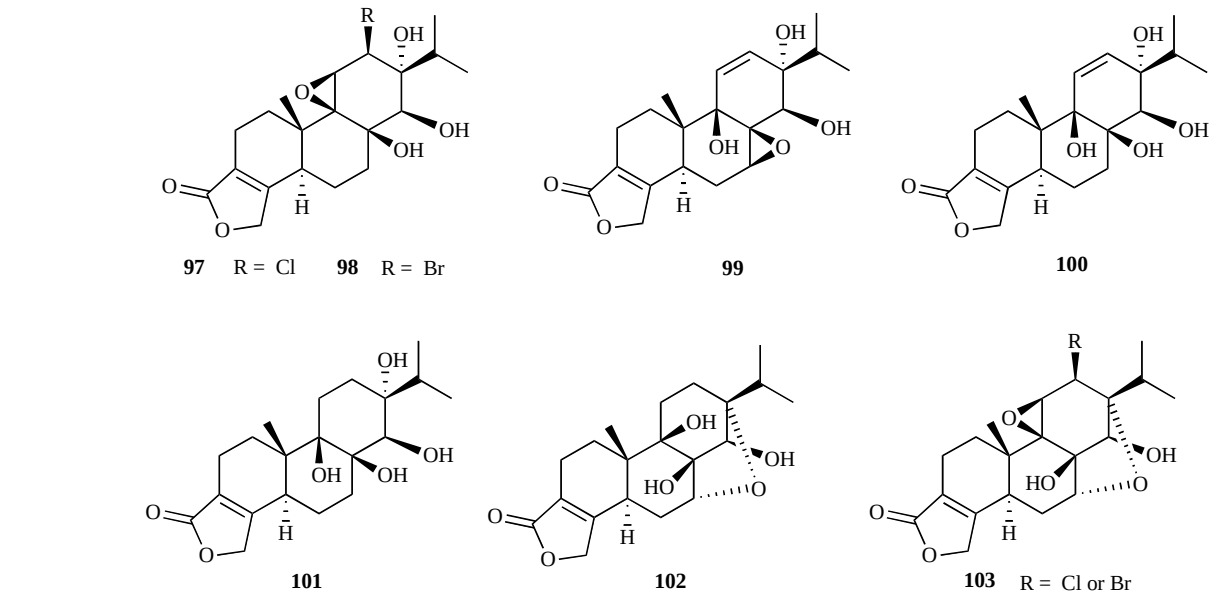


Fig. (6). Structures of derivatives of triptolide **97**–**103**.

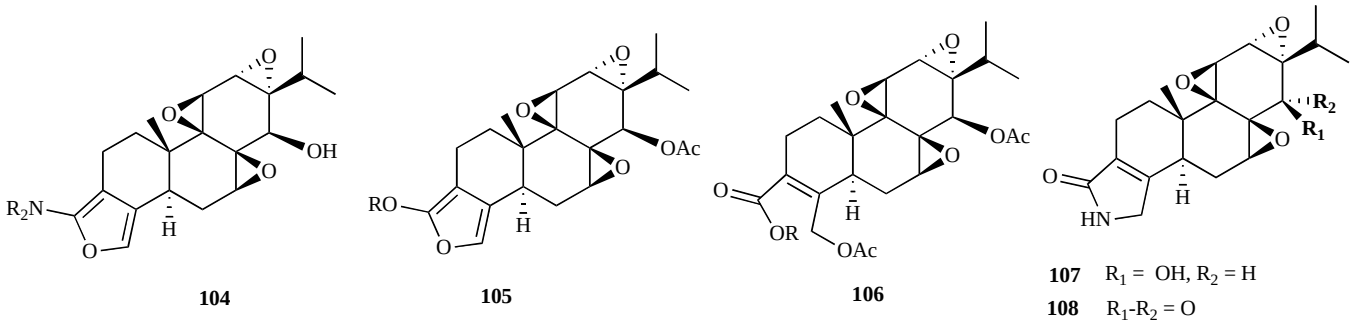


Fig. (7). Structures of derivatives of triptolide **104**–**108**.

activities. Because triptolide and triptonide remain scarcely accessible from the natural source, a great deal of effort was made on the total syntheses of triptolide and its related compounds. The present paper mainly reviewed the total or formal synthesis of triptolide and others, and the structure modifications of **1**. Although the safety of these agents in clinical use has not yet been established, these findings suggest that this important class of natural products could be investigated as a possible therapeutic agent for autoimmune, antiinflammatory and antitumor, and their pharmaceutical development could be significantly accelerated in the next few years.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

None declared.

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