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Terpenoids derived Natural products from Euphorbiaceae and Thymelaeaceae families

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CONTENTS:

1. Introduction:

Natural products have played an important role throughout the world in the treatment and prevention of human diseases. Natural products serve as a vast source of compounds with a broad range of chemical and functional diversity, as well as providing a rich source of new drugs and therapeutic agents.[1-3]

Diterpenes occurring in plants of the genus Euphorbia are the focus of natural product drug discovery because of the wide range of their therapeutically relevant biological activities. Their great structural diversity, resulting from various macrocyclic and polycyclic skeletons including different aliphatic and aromatic acids.[4]

Diterpenes are considered to be important taxonomic markers because of their limited occurrence. These types of diterpenes are specific to the Thymelaeaceae and Euphorbiaceae families. Over 650 diterpenoids, incorporating more than 20 skeletal types, have been isolated from Euphorbia plant.[5]

Terpenoids isolated from Euphobia and Thymelaeace families.

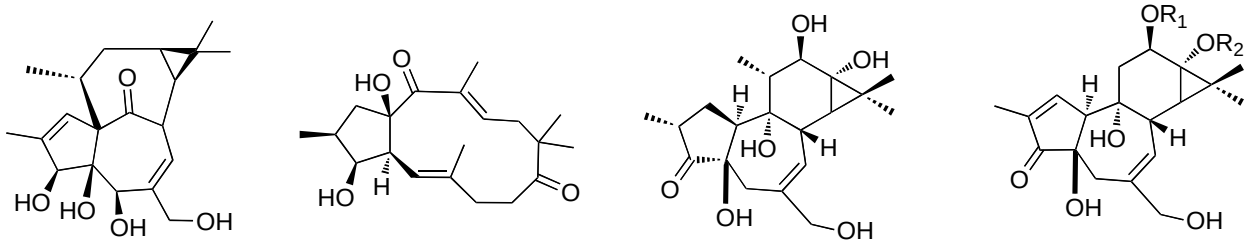
Diterpenes isolated from species belonging to the Euphorbiaceae and Thymelaeaceae families the tigliane diterpenoids are based on a 5/7/6/3- tetracyclic ring system consisting of a five-membered ring A, a seven-membered ring B, a six-membered ring C, and a cyclopropane system D. The skeleton contains 20 carbons, consisting of five methyl, five methylene, and nine methane groups, as well as one quaternary carbon. Almost all of the reported tigliane diterpenoids exist in the form of aglycons, and only three tigliane glycosides have been isolated, to date, from plant species belonging to the Euphorbiaceae and Thymelaeaceae families.[6]

2.1. Phorbol Esters

Plant species belonging to the Euphorbiaceae and Thymelaeaceae families are known to produce "cryptic" phorbol esters. Phorbol, the parent diterpene of phorbol esters, contains five hydroxyl groups that possess different levels of reactivity towards a acylation. Most phorbol esters exist as the diesters, although a few phorbol esters also exist in the form of triesters.[7]

2.2. Esters of 12-Deoxyphorbol:

A new parent alcohol, 12-deoxyphorbol, was obtained from a variety of different plants including Excoecaria bicolor, Euphorbia triangularis and Euphorbia resinifera. 12-Deoxyphorbol can be readily esterified at the C-13 and C-20 positions, and 12-deoxyphorbol esters exist predominantly in one of two groups. The first group consists of diesters with an acetate moiety at C-20 and a long-chain fatty acid at C-13, whereas the second group consists of 13-monoesters with a free hydroxy group at C-20. Although these compounds are more widely distributed than phorbol esters, they are less stable.[8-10]



Scheme 1. Terpenoids isolated from Euphobia and Thymelaeace families.

2.3. Esters of 4,12-Dideoxyphorbol and 4,12-Dideoxy(4α) phorbol

4,12-Dideoxyphorbols are oxygenated at C-13 and C-20, and have either 4β-H or 4α-H. 4,12-Dideoxy(4α)phorbol and three of its esters have been isolated previously only from Excoecaria bicolor and Euphorbia guyoniana (Euphorbiaceae). To date, there have been no reports in the literature focused on investigating the pharmacological potential of 4,12-dideoxyphorbol esters.[11]

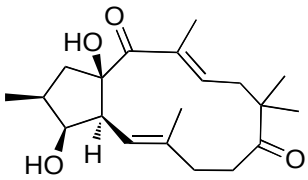
2.4. Esters of 12,20-Dideoxyphorbol

To date, only two 12,20-dideoxyphorbols have been isolated from plants belonging to the Euphorbiaceae family.[12]

2.5. Esters of 20-Deoxyphorbol

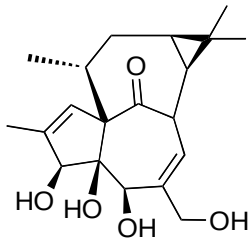
Although very few 20-deoxyphorbols have been discovered to date, two 20-deoxyphorbols bearing a 5α-hydroxy moiety have been isolated from Synadenium grantii.[13]

2.6. Jatrophanes.



Jatrophane diterpenes occur exclusively in the Euphorbiaceae family, in general in the form of Polyesters. Natural jatrophane diterpenes are mainly polyacylated derivatives, the number of ester moieties ranging between three and eight. The most heterogeneously esterified molecules are euphopeplin. El-Bassuony isolated two new jatrophane-type diterpenes, guyonianins C and D, from the aerial parts of E. guyoniana.[13] Later, Hegazy et al. also investigated the chemical constituents of this species and isolated two new jatrophane diterpenes and one known jatrophane diterpene from the aerial parts of the plant. E. guyoniana is used traditionally in Algeria for curing the venomous bites of scorpions and for removing warts.[14]

2.7. Ingenanes.



Ingenane diterpenoids have a 5/7/7/3-tetracyclic ring system including a ketone bridge between C-8 and C-10. A double bond can be found in ring A between C-1 and C-2 and another between C-6 and C-7 in ring B. Moreover, a β-hydroxy group is linked to C-4, and rings A and B are transfused. In 2008, Lu et al. isolated new ingenane diterpenoids from the ethanol extract of E. esula.[15]

3. Biological activities:

Compounds isolated from different Euphorbia and Thymelaeaceae species exert many different activities, including anti-inflammatory, MDR reversing, anticancer activities.

3.1. Anticancer Activity

Generally, diterpenes exhibit tumor-promoting activity, research published in the last 20 years has also shown that some derivatives show significant anticancer activity. For example, the 12-deoxyphorbol derivatives showed antileukemic activity with ED50 values in the range of 0.4−3.4 μg/mL in a P-388 lymphocytic leukemia system in vitro. Jatrophane diterpenes possess tumor cell growth inhibitory activities on MCF7 (breast epithelial adenocarcinoma) cells.[16]

3.2 Anti-inflammatory Activity

Pepluanone, a diterpene component of Euphorbia peplus, possesses a high anti-inflammatory effect in vivo. They investigated the anti-inflammatory activity of six compounds with pepluane and paraliane skeletons. The results showed that all compounds have NO2− production inhibitory activity in LPS-stimulated J774 macrophages by iNOS.[17]

3.3 Anti-viral Activity

Diesters of phorbol showed a potent anti-HIV activity in MT4 cells with EC_{90} values in the range of 0.00050− 1.52 μM, and relatively low levels of cytotoxicity, with IC_{50} values in the range of 3.5−17.2 μM.[18]

3.4 Multi Drug Resistance Reversing Activity

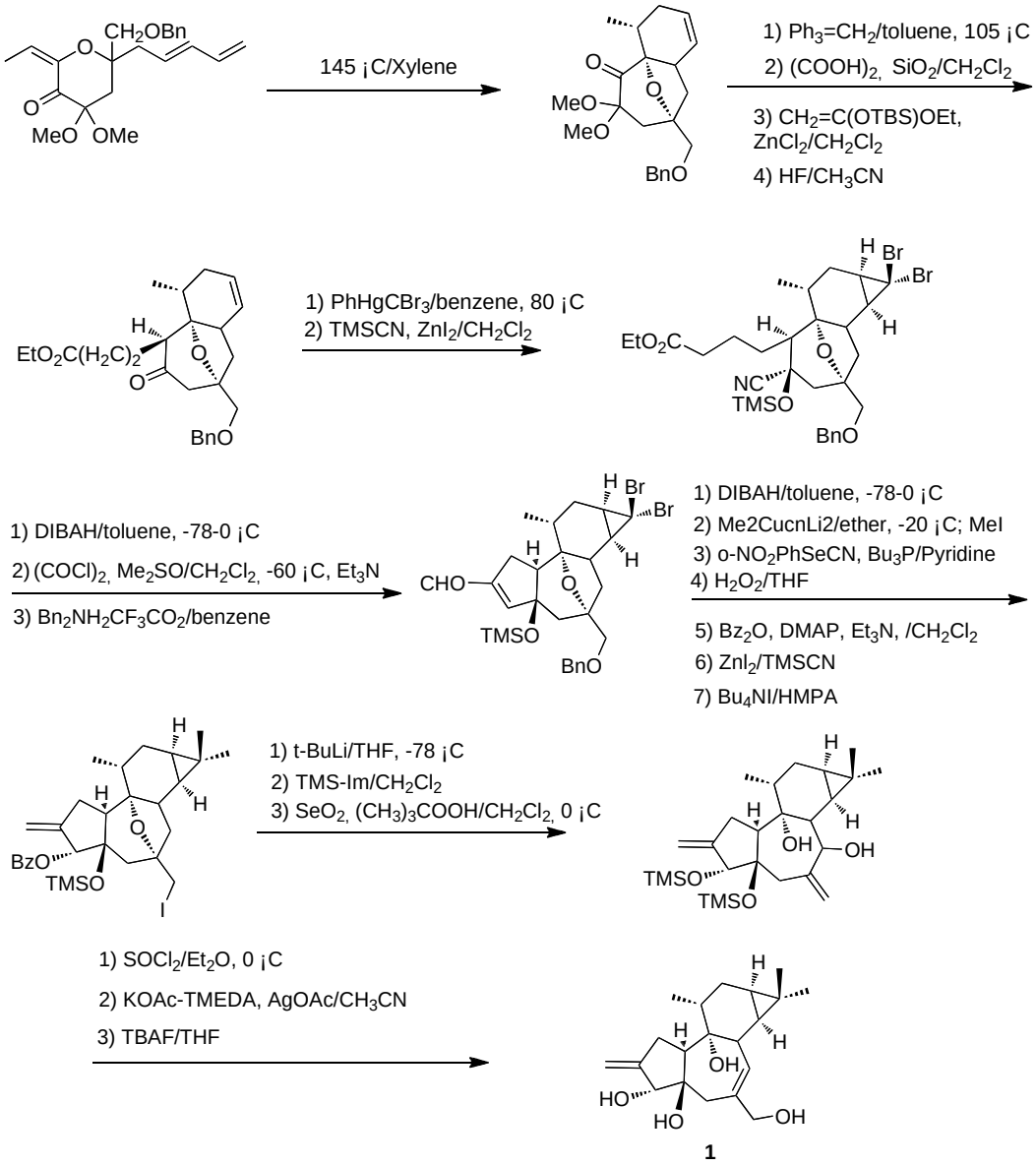
The most common tumors are resistant to available drugs because of inhibition of P-glycoprotein which represents a promising approach for overcoming the multiple drug resistance. Diterpenens investigated for MDR reversing activity, Compounds withvarious skeletal types e.g., jatrophanes, lathyranes, and “euphoractine-type” showed a significant MDR-reversal effects.[19]

4. Synthesis of Diterpens:

Diterpenes from Euphorbia and Thymelaeaceae familes which exhibit a variety of interesting biological activities. The complex structure and striking biological properties of diterpenoids have prompted chemists to devise a series of synthetic strategies and methodologies for the constructing of their complexes structural frameworks.

Intramolecular Diels−Alder Approach to synthesis Tigliane skeleton:

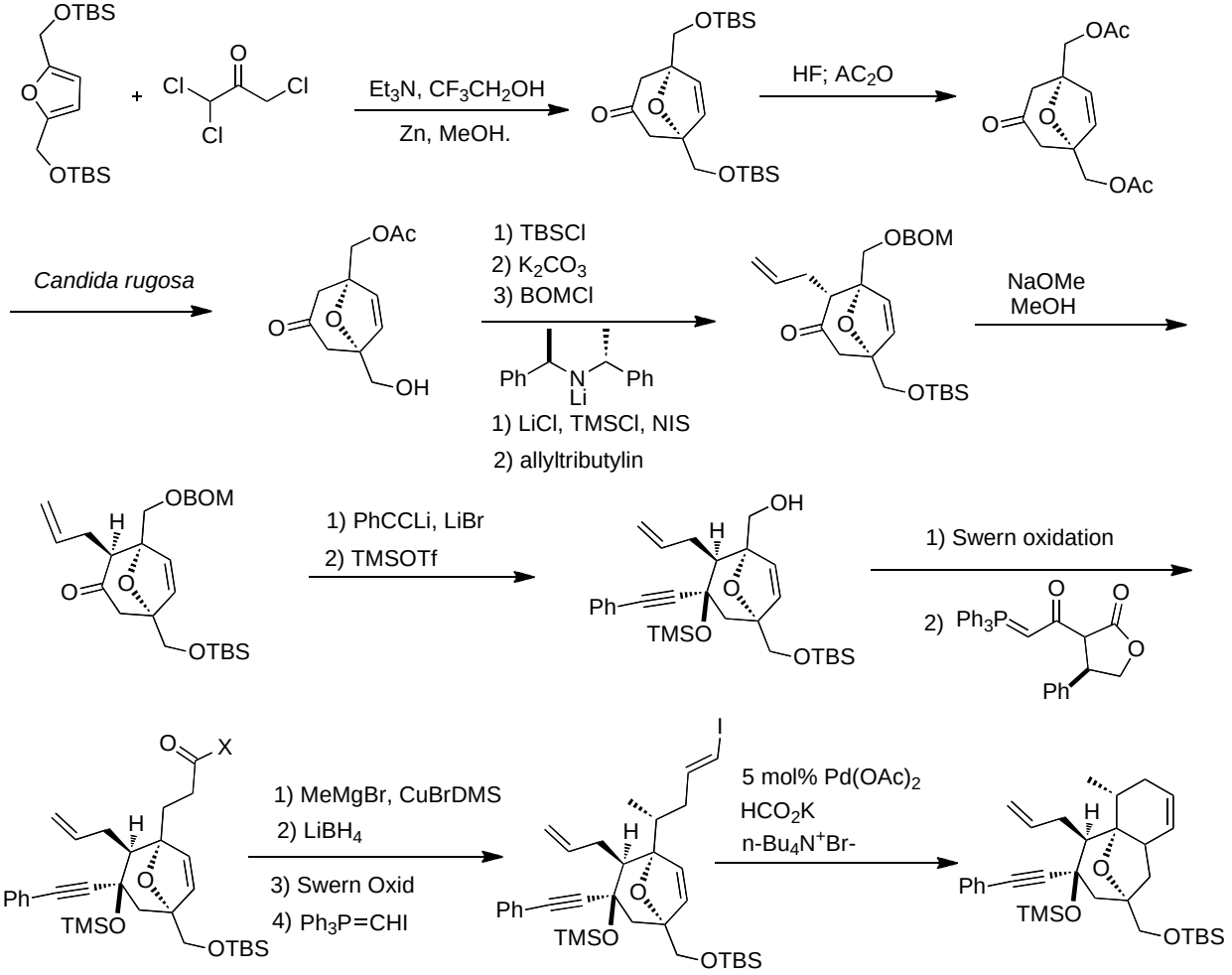
Wender et al.[20] published the first total synthesis of the tigliane skeleton in 1987, using an intramolecular Diels−Alder cycloaddition and an intramolecular aldol condensation as key steps in their synthesis (Scheme 1). The resulting phorboid was the first compound to be prepared synthetically possessing the complete tigliane skeleton and stereochemistry. However, it was devoid of oxygenation at C-12 and C-13 and did not possess the A-ring functionalities required for conformational rigidity or the attachment of lipophilic groups.

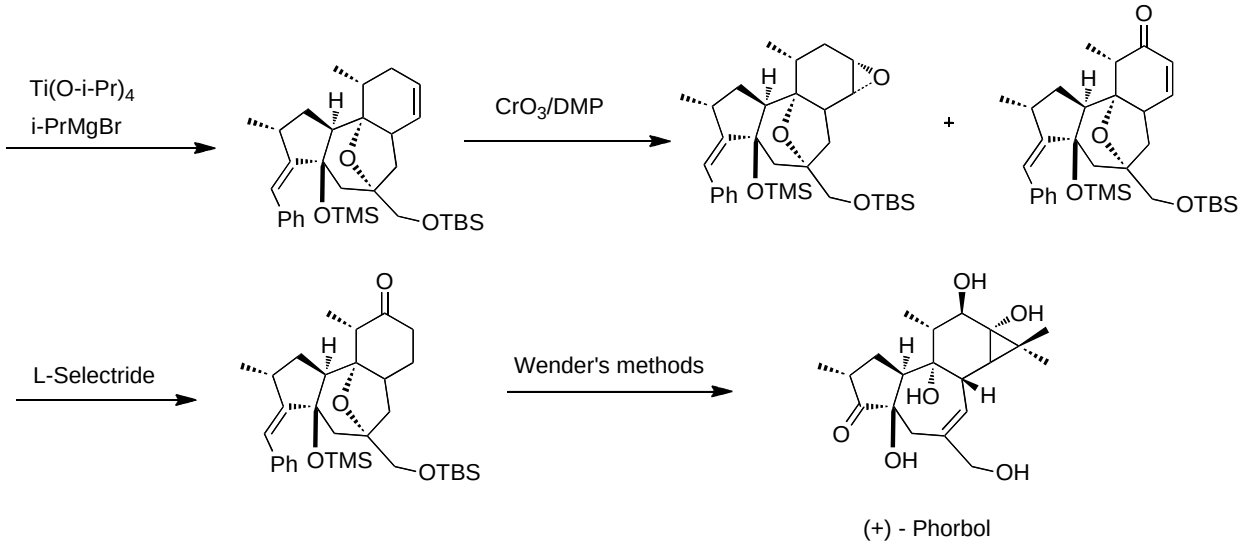


Scheme 2. Synthesis of Tigliane skeleton and its stereochemistry

Total synthesis of synthesis (+)-Phorbol: Oxyallyl [4+3] Cycloaddition Approach

In 2001, Cha et al [21] reported the formal synthesis of (+)-phorbol using Wender's advanced intermediate. As shown in Scheme 2, their synthetic plan was built upon a [4+3] oxyallyl cycloaddition and subsequent intramolecular Heck reaction for the stereocontrolled construction of the BC-ring system of phorbol, followed by an adaptation of Wender's efficient method for the construction of the A ring. This synthesis of the phorbol intermediate required more steps and was less efficient than the method developed by Wender, although this work effectively demonstrated the applicability of this strategy to the construction of tiglianes and daphnanes.

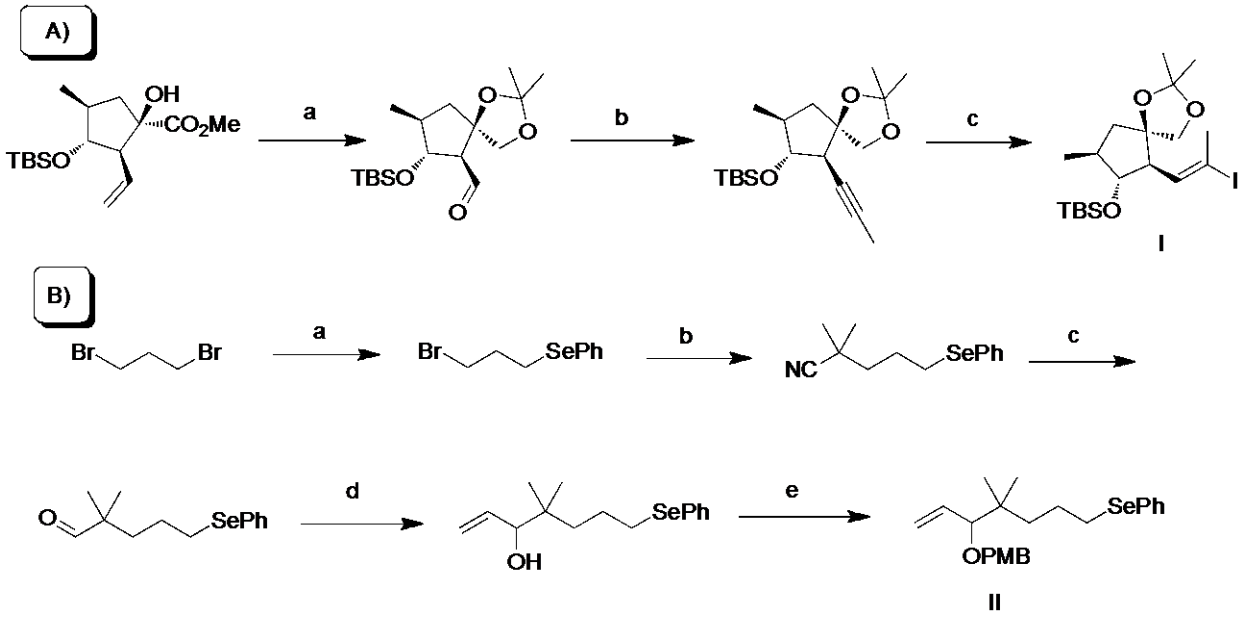


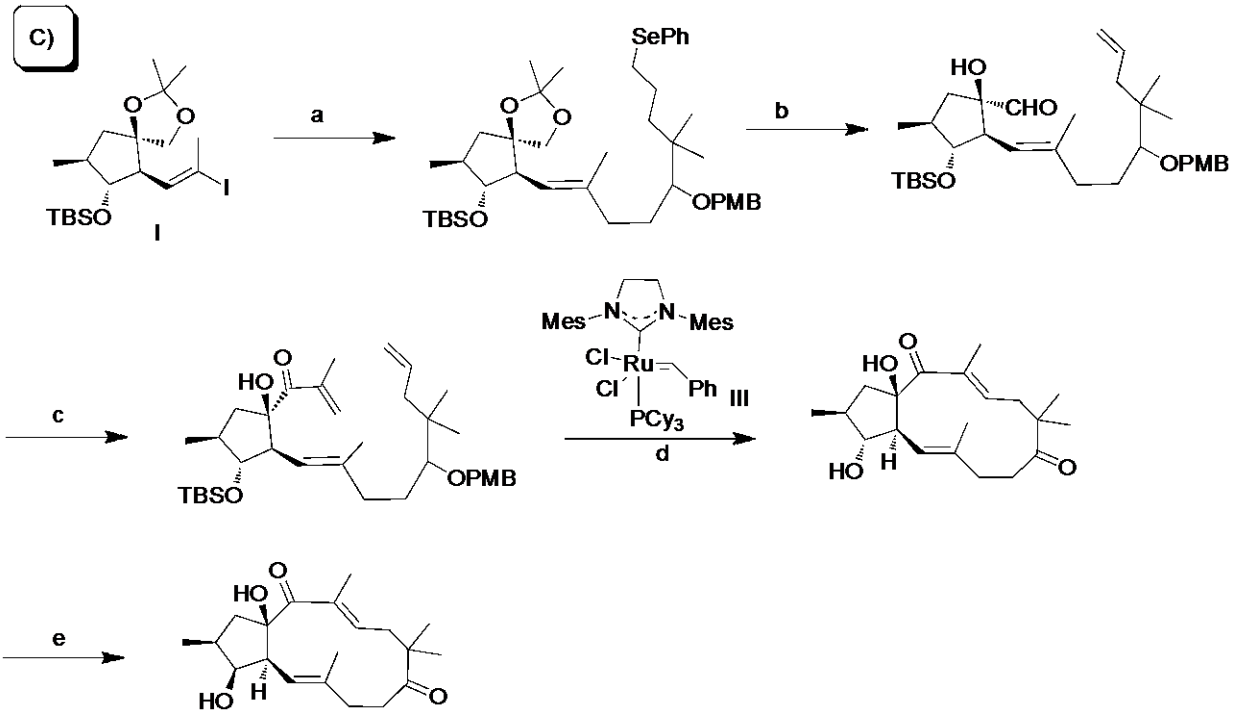


Scheme: 3. Formal synthesis of (+) - Phorbol

Synthesis of a Jatrophane diterpene:

In 1989, the total synthesis of (±)-jolkinolides A, B, and E from 10-(methoxycarbonyl)-β-ionone was performed by Katsumura et al.[22] The synthetic route contained approximately 20 reaction steps.





Scheme. 4: (A) Synthetic route toward the production of a jatrophane diterpene structural fragment. Reagents and conditions: (a) (i) $LiAlH_4$, THF, rt (90%); (ii) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt (85%);(iii) O_3, CH_2Cl_2, MeOH, −78 °C, PPh_3 (90%); (b) (i) CBr_4, PPh_3,CH_2Cl_2, −78 °C; (ii) MeLi, THF, −78 °C; MeI, −78 °C to rt (78%); (c) $Cp_2Zr(H)Cl$, THF, 40 °C, 1.5 h, then 12, CH_2Cl_2, (80%).

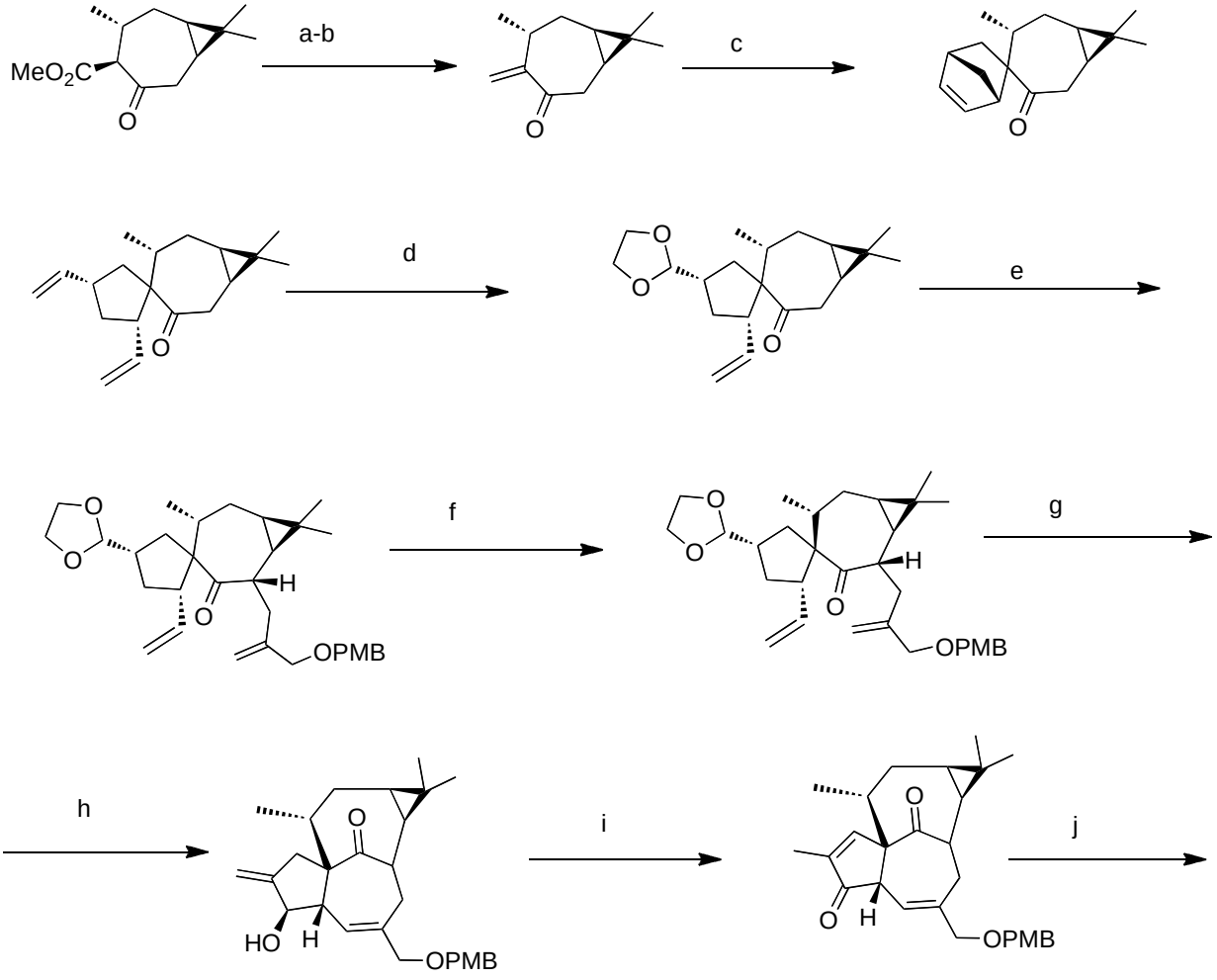
(B) Synthetic route toward the production of a jatrophane diterpene structural fragment.

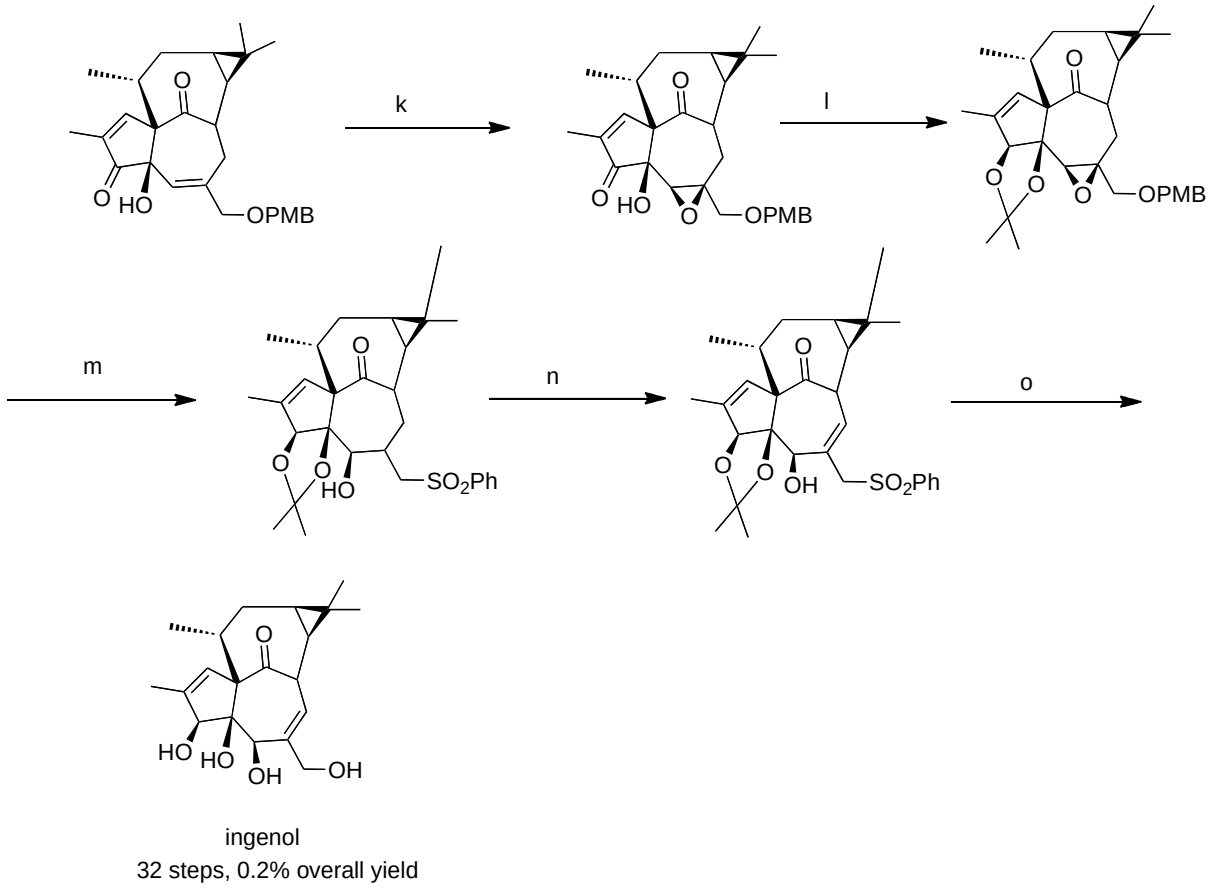
Reagents and conditions: (a) $(PhSe)_2$, $NaBH_4$, MeOH, 0 °C, 30 min, to rt (91%); (b) $LiNiPr_2$, iPrCN, Et_2O, 0 °C to rt (93%); (c) iBu_2AlH, toluene, −78 °C, 1 h (81%); (d) BrMgCH=CH2, THF, −78 °C, 45 min (76%); (e) NAH, (PMB)Cl, n-Bu_4NI, THF, DMSO (90%).

(C) Total synthesis of a jatrophane diterpene. Reagents and conditions: (a) 9-BBN, THF, 40 °C, 24 h, + II (100 mol%), $(dppf)PdCl_2$ (7 mol %), Ph_3As (20 mol %), Cs_2CO_3 (270 mol %),THF, DMF, H_2O (14/2/1), 80 °C, 8 h (86%); (b) (i) H_2O_2, NaHCO3, H_2O, THF, rt (68%); (ii) $La(NO_3)_3{\cdot}6H_2O$, MeCN, 50 °C, (54%); (iii) IBX, CH_2Cl_2, DMSO (1/1), rt (81%); (c) (i) H_2C=C(Me)Br, tBuLi, THF, −78 °C, 15 min (91%); (ii) DDQ, CH_2Cl_2, aq pH 7 buffer, rt, 2.5 h; (iii) IBX, CH_2Cl_2, DMSO (1/1), rt, 6 h (75%); (d) (i) III (10 mol %), toluene (c = 1.3 × 10−3 mol/L), 110 °C, 2 h; (ii) HF·Py, THF, 0 °C, 3 h; (e) (i) PPh_3, DIAC, p-BrC_6H_4COOH, THF, 0 °C (87%); (ii) MeOH, K_2CO_3, rt, 5 h (91%).

Total synthesis of Ingenol:

Ingenol has also been of great interest not only because of its unusual structure containing an "inside−outside" bridged BC ring, but also because of a broad spectrum of pharmacological activities. The synthesis of the highly strained ingenane framework required special approaches and strategically distinct methods.[23] The first total synthesis of ingenol was performed by Winkler with the use of an intramolecular de Mayo reaction. Other successful synthetic approaches (Winkler, Wood, and Tanino/Kuwajima) and promising partial syntheses have since been reported and reviewed.





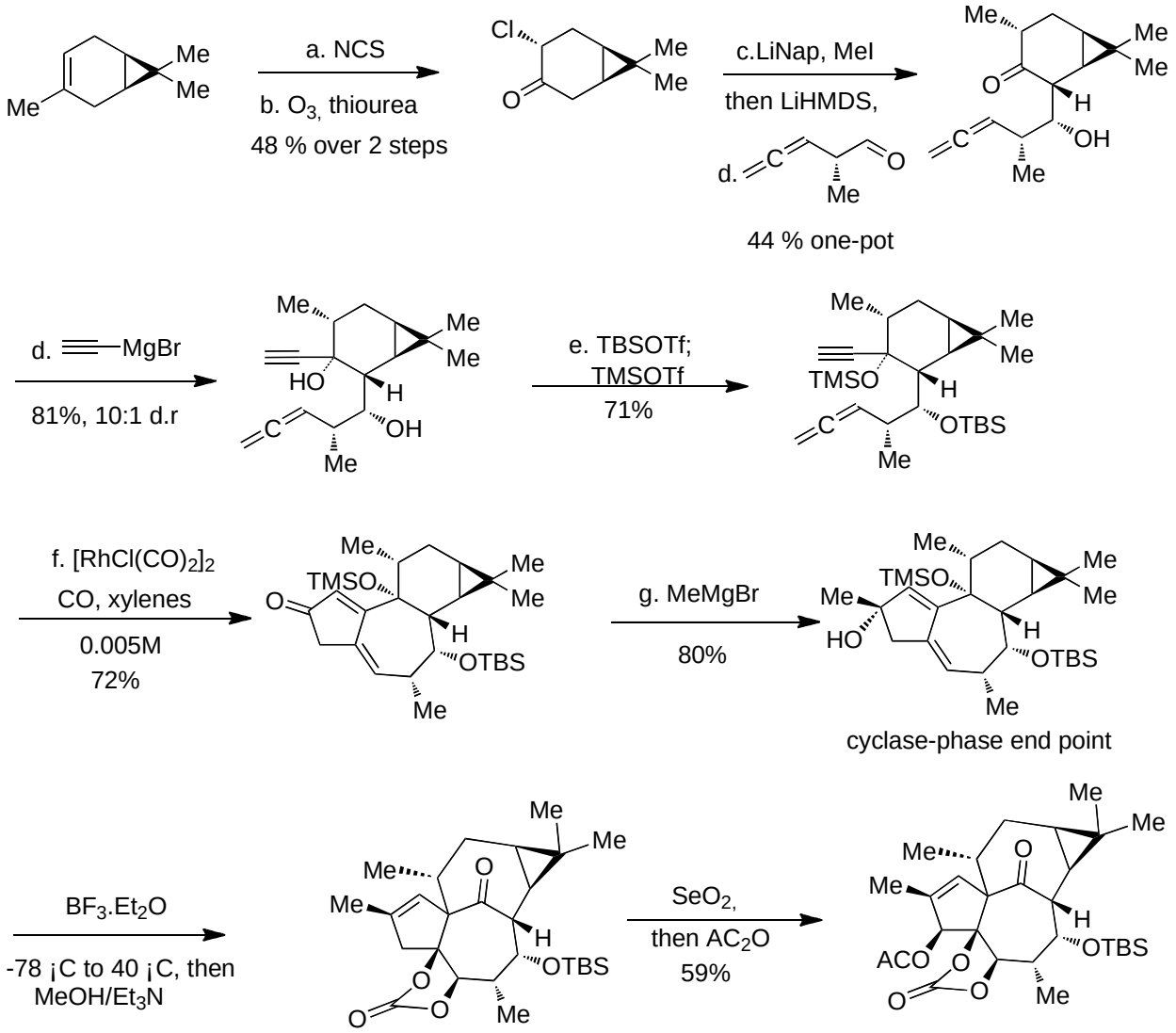
Scheme: 5. Wood's total synthesis of ingenol.

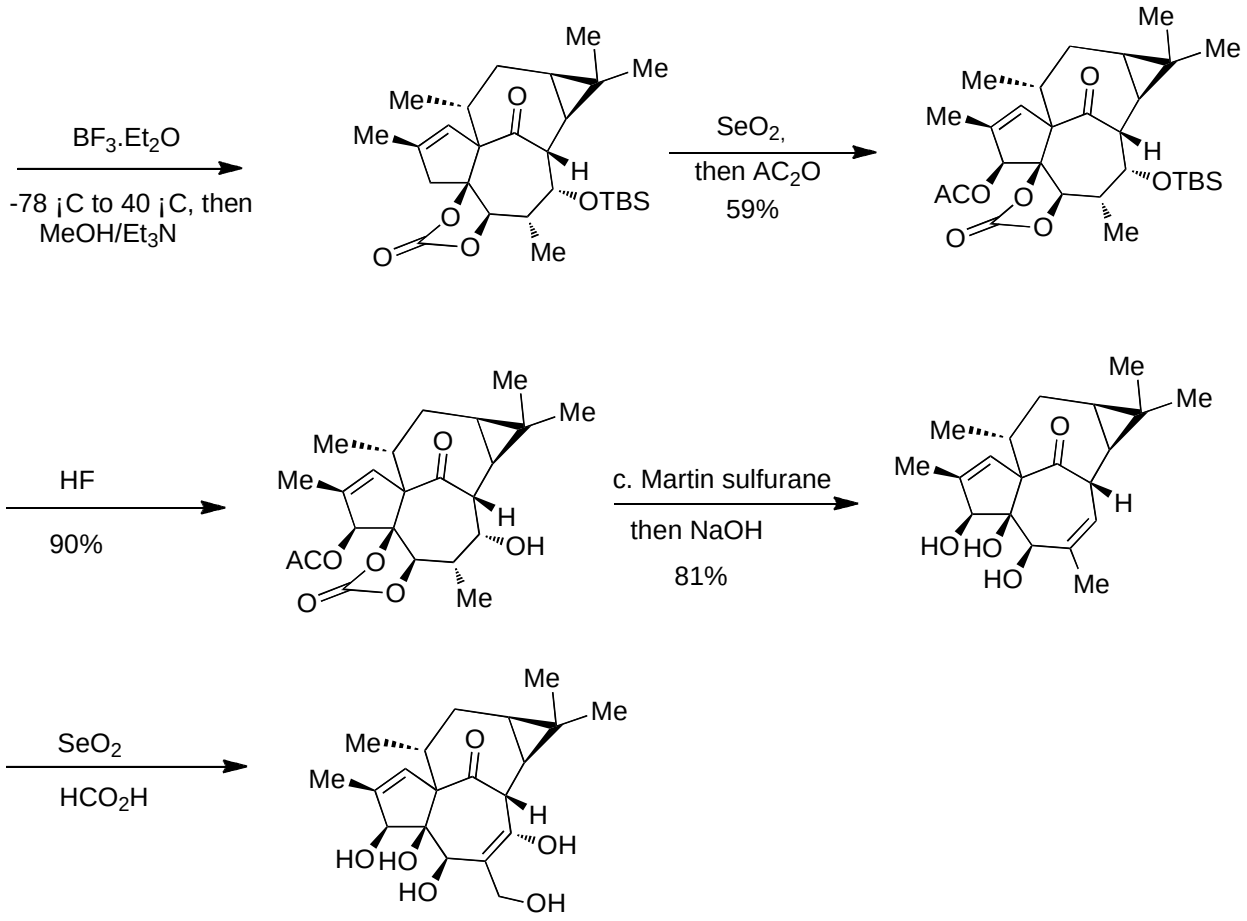
Reagents and conditions: (a) (i) $(HOCH_2)_2$, p-TsOH, C_6H_6, Δ, 96%, dr = 43:23:18:16; (ii) $LiAlH_4$, Et_2O; (iii) HCl, acetone, H_2O, 95% (two steps); (b) (i) Ac_2O, pyridine, DMAP, 96%; (ii) DBU, C_6H_6, Δ, 80%; (c) cyclopentadiene, $BF_3{\cdot}OEt_2$, $PhCH_3$, −78 °C, 59%; (d) Grubbs-I, ethylene, CH_2Cl_2, 98%; (e) (i) OsO_4, NMO, THF−H_2O (4:1); (ii) $NaIO_4$, MeOH−THF (4:1); (iii) $(HOCH_2)_2$, p-TsOH, C_6H_6, Δ, 73% (three steps); (f) $ClCH_2C(\cdot\ CH_2)CH_2O$(PMB), KH, THF, Δ, 98%; (g) RCM, P, hCH_3, Δ, 76%; (h) (i) HCl, THF−H_2O, Δ; (ii) $NaBH_4$, EtOH−THF, 0 °C, 77% (two steps); (iii) I2, PPh_3 imidazole, THF, 0 °C; (iv) KOtBu, THF−DMSO, 94% (two steps);
(i) (i) SeO_2, ^{t}BuOOH, CH_2Cl_2−H_2O−HOAc, 0 °C, rt, 68% based on recovered starting material (brsm); (ii) Dess−Martin periodinane (DMP), CH_2Cl_2, −40 → +10 °C, 74%; (iii) $RhCl_3$, EtOH, 115 °C, 74%; (j) KO^{t}Bu, O_2, P(OMe)3, THF, ^{t}BuOH (4:1), −40 °C, 94%; (k) $VO(acac)_2$, ^{t}BuOOH, C_6H_6, 10 °C to rt, 73%; (l) (i) (TMS)OTf, Et_3N, CH_2Cl_2, −10 to −5 °C, 72%; (ii) $NaBH_4$, MeOH; (iii) 2,2-DMP, PPTS, CH_2Cl_2, Δ,86% (two steps); (m) (i) DDQ, CH_2Cl_2, 90%;

(ii) MsCl, Et_3N, CH_2Cl_2, −78 °C, 96%; (iii) PhSH, Li_2CO_3, DMF, 55 °C, 76%; (iv) $(NH_4)_6Mo_7O_{24}$,H_2O_2, EtOH, 97%; (n) DBU, C_6H_6, Δ, 47%; (o) (i) Na−Hg, Na_2HPO_4, MeOH, −20 → −10 °C, 76%; (ii) HCl, THF−H_2O, 92%; (iii) SeO_2/SiO_2,THF, 80 °C, 85% brsm.

Total synthesis of Ingenol by Phil Baran et al :[24]

Finally the shorthest synthesis of ingenol by Professor Phil S. Baran is following described.





5. CONCLUSIONS

Diterpenes from Euphorbiaceae and Thymelaeaceae families are considered to be important taxonomic markers because of their limited occurrence and structural diversity. In the past few years, more than 200 novel diterpenes have been isolated from different Euphorbia and Thymelaeaceae species.[25] Recent pharmacological experiments encompassed the assessment of anti-proliferative, ant-cancer, MDR inhibitory, anti-inflammatory, and antimicrobial activities. Researchers are working towards the elucidation and biological activity of different diterpenoids, and it is envisaged that some of these diterpenoid derivatives will be developed into useful materials with a variety of different applications in the future.[25]

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