Total Synthesis of Heliannuol-D: An over view

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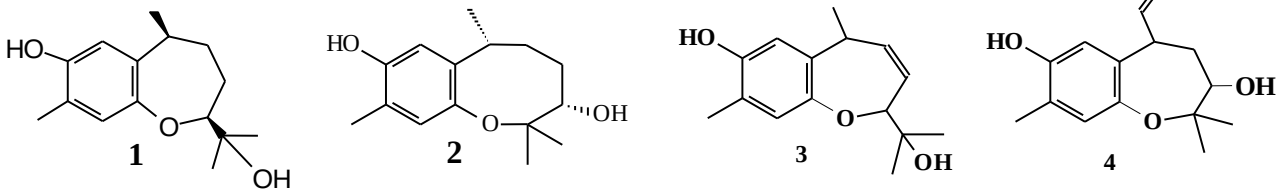
Abstract: *This review describes the total synthesis of the sesquiterpene heliannuol-D (1), an important allelopathic compound, employing different methodologies to generate the central benzoxepane ring system.*

Key words: Allelochemicals, Heliannouls, sesquiterpene, RCM, photolysis, Bergallini condensation.

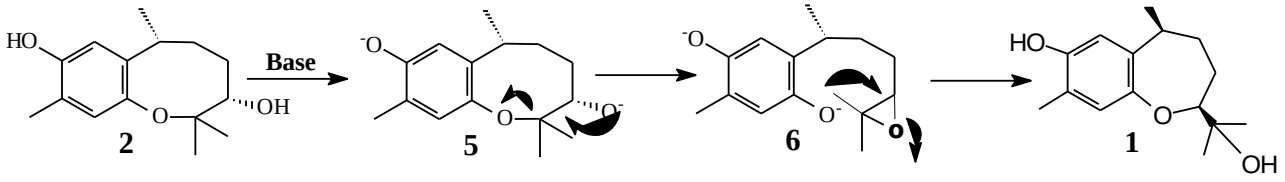
Introduction: Heliannnuol D (**1**), represents a new class of compounds among the heliannuol family of allelopathic ("inhibitory" chemical when released into the environment affects the development and growth of neighboring plants) sesquiterpenes isolated [**1**] from cultivar sunflower *Helianthus annus L. var. SH-222 and VYP*. The other primary constituents are heliannuols A (**2**), B (**3**), C (**4**) and these have been implicated in the powerful allelopathic activity displayed by sunflowers [**2**]. Subsequently, other oxidized variants of some of these primary compounds have also been isolated from these flowers [**3**].



Allelopathy, involving plant–plant and plant–microorganism interactions, has been proposed as an alternative weed management policy [**4**]. The growing concern on the natural ecological balance and the arguments against indiscriminate use of synthetic pesticides have provided an impetus for exploration of allelochemicals for effective weed control devoid of any hazardous side effects. In this context, the heliannuols, due to their novel structural features and associated bio-activity, have served as one of the most attractive targets for synthesis in the field of natural products industry [**5**].

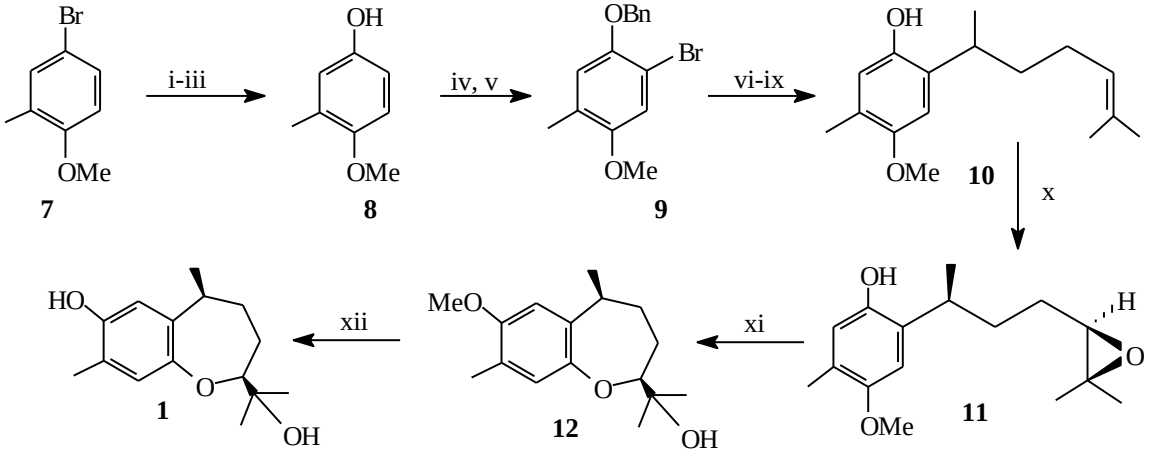
Isolation and structural elucidation Heliannuol D*:* Heliannuol **D** (**1**) was isolated from the polar bioactive fraction of the aqueous extract of the fresh leaves of cultivated sun flowers and along with heliannuol **B (3)** and **C (4).** These heliannuol systems constitute the major component of the extract, all enclosing a benzoxepane ring system. Heliannuol **D** was obtained as a crystalline solid and the structure was arrived through extensive spectral studies. An additional support for the

assigned structure was also obtained from the base catalyzed opening of heliannuol **A** (**2**) and recyclisation to (**1**), mimicking the proposed biogenetic pathway (**Scheme-1**). The assignment of structure to heliannuol **D** also enabled the structural assignment to heliannuol **B** since the latter on hydrogenation furnished heliannuol **D [6]**.



Scheme-1

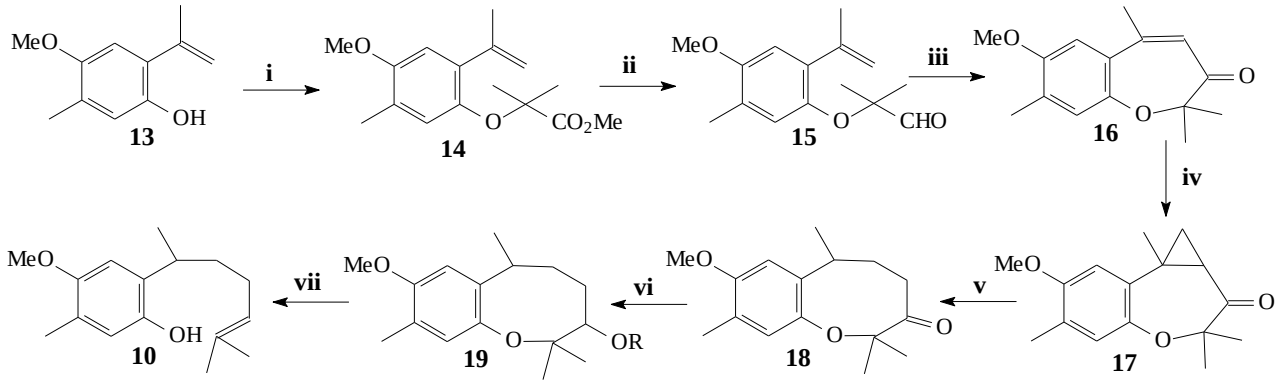
Syntheses: The first synthesis of heliannuol D (**1**) was disclosed by Vyvyan and Looper [**7]**. The key step in that synthesis relied on an intramolecular phenol epoxide cyclisation to generate the benzoxepane ring system. The aryl lithium generated from 4-bromo-2-methylanisole (**7**) on reaction with triisopropylborate followed by oxidation of the resultant aryl borate ester with *t*-butyl hydrogen peroxide (**TBHP**) furnished the 4-methhoxy-3-methyl phenol (**8**). Bromination and subsequent protection of the free phenolic hydroxyl groups as benzyl ether provided the differentially protected phenol derivative (**9**). The corresponding aryl zinc species of (**10**) generated from transmetallation of the lithium exchange product was subjected to palladium catalysed coupling with the enol triplet of 6-methyl-5-heptene-2-one. Reduction of the product with lithium-liquid ammonia led to the desired monomethyl ether (**11**) through simultaneous reduction of the conjugate alkene and the cleavage of the benzylic ether. Epoxidation of the alkene (**10**) resulted in a (1:1) mixture of diastereomeric epoxides which were easily separated. Base catalyzed cyclisation of the epoxide (**11**) produced heliannuol D methyl ether (**12)**. Finally demethylation furnished heliannuol **D** (**1**) (**scheme-2**).



(**Scheme 2**)

Reagents and conditions: (i) Li, Et_2O, reflux; (ii) $B(O^iPr)_3$, -78^{0}C to r.t; (iii) TBHP, aq. NH_4Cl; (iv) NaH, THF, BnBr, 0^0 C; (v) Br_2, $CHCl_3$, 0^{0}C; (vi) tetr-BuLi (2.2 equiv), -78^0 C; (vii) $ZnCl_2$, THF; (viii) CH_2=C(OTf)CH_2CH=C$(CH_3)_2$, $Pd(PPh_3)_4$ (5mol%), THF, reflux; (ix) Li (6 equiv.), liquid NH_3. (x) mCPBA,Na_2HPO_4, CH_2Cl_2, 0^{0}C; (xi) KOH, DMSO, 70-100^0 C, (xii) NaSEt (15 equiv.), DMF, reflux.

Another formal synthesis of heliannuol-D was reported by Tuhina *el. al.* [**8**] adopting a regioselective cleavage of benzo-fused bicycle [5.1.0] octanone system under catalytic hydrogenation followed by the radical induced ring opening. The epoxidation of the alkene results in formation of epoxide (**11**) which under base treatment affords heliannuol-D. The synthesis began with styrenol (**13**) obtained from appropriate coumarin. The styrenol (**13**) on a Bargellini reaction involving condensation with acetone in presence of chloroform and sodium hydroxide followed by diazomethane treatment furnished the *gem*-dimethyl incorporated ester (**14**) which was reduced to the corresponding alcohol. Swern oxidation to the corresponding aldehyde (**15)** followed by the treatment with PCC resulted in an intramolecular aldo-ene reaction and re-oxidation to furnish the benzoxepinenone (**16**). Palladium catalyzed addition of diazomethane to (**16**) produced the cyclopropyl ketone (**17**). Catalytic hydrogenation of (**17**) proved to be completely regioselective delivering the benzoxocanone (**18**) which on a hydride reduction afforded heliannuol **A** methyl ether (**19a**). Then the alcohol (**19a**) was converted to the thionocarbonate (**19b**). When this thionocarbonate derivative (**19b**) was subjected to the reaction with tributyltin hydride in refluxing toluene, ring opening furnished the alkene (**10**) which was converted to heliannuol-**D** in the previous synthesis (**Scheme-3**).

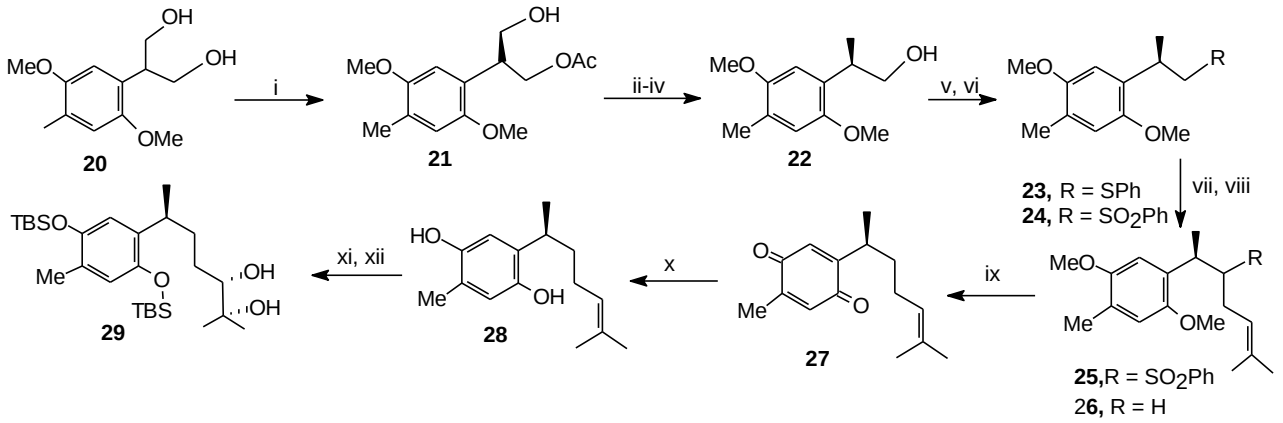


(**Scheme 3**)

Reagents and conditions: (i)a. $CHCl_3$, MeCOMe, NaOH, Reflux; b. H_3O^+; CH_2N_2. (iia). $LiAlH_4$, (b).Swern oxidation; (iii). PCC, DCM, 12h. (iv). CH_2N_2, $Pd(OAc)_4$, (v). Pd-C, H_2, EtOH. (vi).a $NaBH_4$, MeOH. (b). NaH, THF, CS_2, MeI. (viii). n-Bu_3SnH, AIBN, Toluene, reflux.

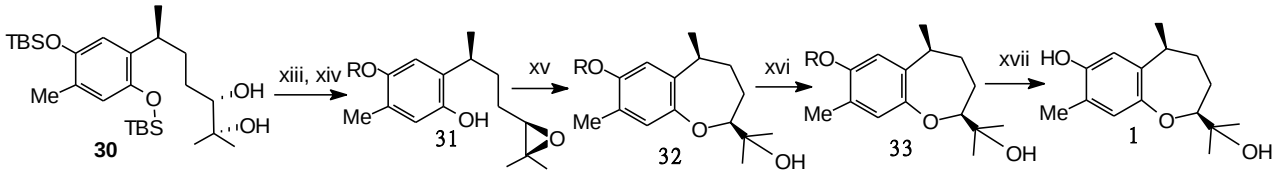
The first enantioselective synthesis of heliannuol **D** (**1**) was reported by Shishido *et. al* [**9**]. They have also employed base mediated intramolecular cyclisation of a phenol epoxide to generate the benzoxepane ring system of (**1**). The prochiral diol (**20**) was subjected to an enzyme catalyzed trans-esterification to furnish the mono acetate (**21**) in high enantiomeric excess (>99%). The hydroxy function generated from de-acetylation (**22**) was converted to the sulfone (**24**). Alkylation of this sulfone (**24**) with prenyl bromide followed by reductive removal of the sulfonyl appendage delivered curcuphenol dimethyl ether (**26**). Ceric ion induced oxidation to the curcuquinone (**27**) followed by re-aromatization furnished the (*S*) curcuhydroquinone (**21**) which was correlated with the natural (*R*) isomer. In the next course of reaction, this hydroquinone (**28**), as the bis-*t*-butyl dimethyl silyl ether was subjected to an asymmetric dihydroxylation to furnish the diol (**29**). Mesylation followed by base treatment resulted in the formation of the desired epoxide accompanied by cleavage of one of the ether protecting groups to provide a (4:1) mixture of phenolic epoxides (**31**). It was presumed the major isomer was arising from the hydrolysis of the

sterically less hindered silyl ether. The phenolic hydroxy moiety was reprotected as the MOM and subjected to desilylation. The resulting phenolic epoxide(s) on base treatment followed by an acid hydrolysis furnished (**1**) as the major product, which was found to be an enantiomer of the natural product .



(**Scheme-4**)

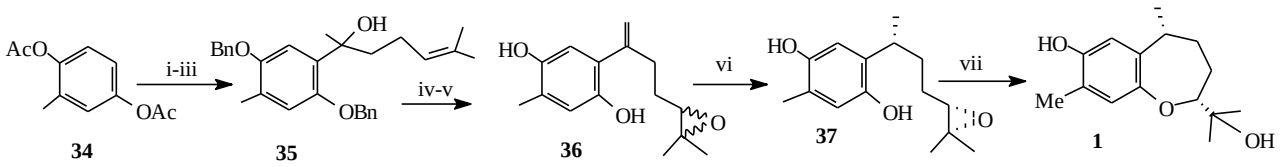
and conditions : (i) *Candid Antacrtical Lipase* (CAL), Et_2O, rt (>99%0 ee); (ii) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt; (iii) $NaBH_4$, DMSO, 60^0C; (iv) $LiAlH_4$, THF, rt; (v) PhSSPh, $^nBu_3P$, Py, rt; (vi) m-CPBA, $KHCO_3$, CH_2Cl_2, rt; (vii) ^{n}BuLi, HMPA, THF, $Me_2C{=}CHCH_2Br$, -78^0C; (viii) 5% Na-Hg, $NaHPO_4$, MeOH, sonication, rt; (ix) CAN, MeCN, MeOH, H_2O, rt; (x) $Na_2S_2O_4$, THF, H_2O, rt; (xi) ^{t}Bu(Me)$_2$SiCl, imidazole, DMAP, CH_2Cl_2, rt; (xii) AD-mix-α, $MeSO_2NH_2$, ^{t}BuOH, H_2O, 0^0C,



(**Scheme 5**)

Reagents and conditions: (xiii) MsCl, Py, CH_2Cl_2, rt; (xiv) K_2CO_3, MeOH, rt; (xv) CsF, DMF, rt; (xvii) NaOH (aq), rt; (xvi) MOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2,rt; (xvii) 6 M HCl,THF, rt.

Macias *et. al*. [**10**] have reported their contribution to synthesis of this compound [**1**], once again invoking an intramolecular phenol epoxide cyclisation to generate the oxepane ring system. They have started with the di-benzylated acetophenone (**34**), which was subjected to a Grignard reaction with 5-bromo-2-methyl-2-heptene to afford the alcohol (**35**). Dehydration followed by selective epoxidation produced the epoxide (**36**), which was hydrogenated to afford a mixture of diastereomeric epoxides (**37**). This epoxide(s) on base catalysed cyclisation furnished (**1**) and its epimer respectively.

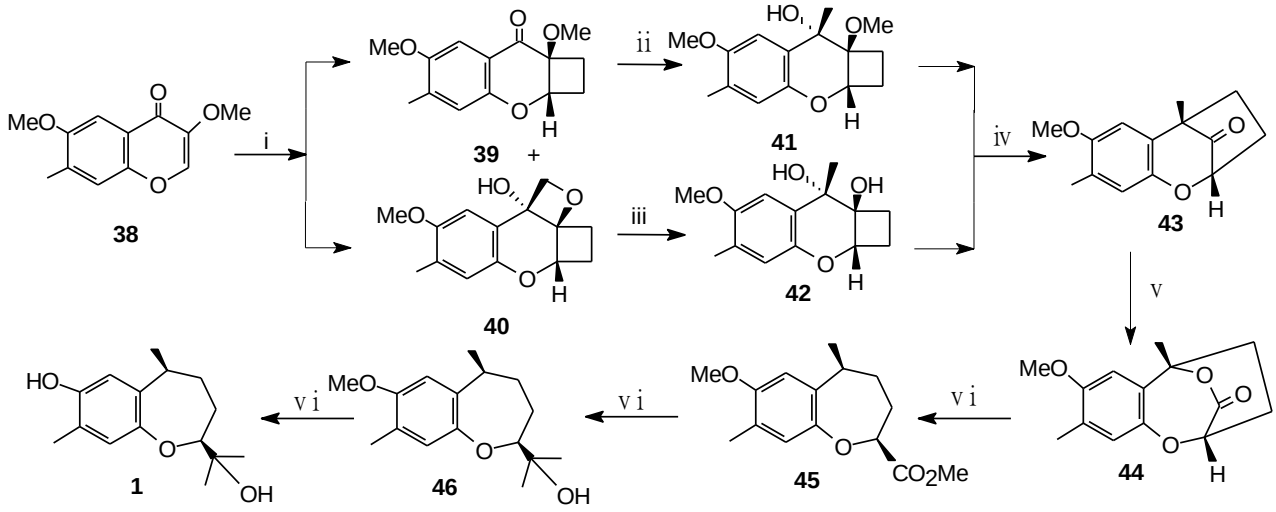


(**Scheme 6**)

Reagents and conditions : (i) $BF_3.Et_2O$, 3h, 120^0C; (ii) benzyl bromide, K_2CO_3, dimethoxyethane, 12h, 120^0C, (iii) 5-Br-2-methyl-2-pentene, Mg, I_2, THF,1h, 65^0C; (iv) $KHSO_4$, N,N-dimethylformamide, 2h; (v)

m-CPBA, $KHCO_3$, H_2O, rt, 2h; (vi) H_2, Pd-C, N,N-dimethylformamide, 2h, rt.NH_4Cl 20h; (vii) Bu_3SnH, AIBN, toluene, reflux, 4h.

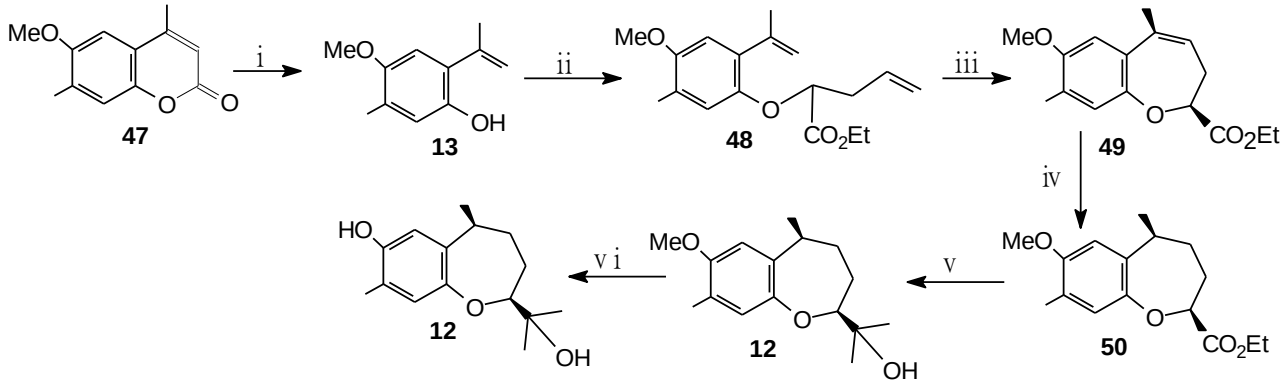
Sabui *et. al.* [**11**] reported a synthesis of heliannuol-D starting from employing chromone (**84**). A benzene solution of the chromone (**38**) was subjected to irradiation while a continuous flow of ethylene was bubbled through the solution. Column chromatography of the resulting product afforded two compounds, identified as the cyclo-adduct (**39**) and the oxetanol (**40**), with the former predominating. Reduction of the oxetanol (**40**) and keto-ether (**39**) with lithium aluminium hydride yielded the diol (**42**) and ether-ol (**41**) respectively, in excellent yield. Both the alcohols are suitably poised for an acid catalysed rearrangement to afford tricyclic ketone (**43**). The bridged ketone (**43**) on oxidation with *meta*-chloro perbenzoic acid (*m*-**CPBA**) furnished the lactone (**44**), also as a single regioisomer. A methanolic solution of this lactone (**44**) on hydrogenolysis preceeded the bicyclic ester (**45**) which on reaction with MeMgI followed by demethylation finally affords heliannoul-D. (**Scheme 7**).



(**Scheme 7**)

Reagents and conditions : (i) hν, CH_2=CH_2, Benzene, 6 h, 62%; (ii) MeMgI, $(C_2H_5)_2O$, reflux, 5 h, 87%; (iii) LAH, THF, reflux, 8 h, 90%; (iv) $BF_3.Et_2O$, Bz, rt, 2 h, 85%.

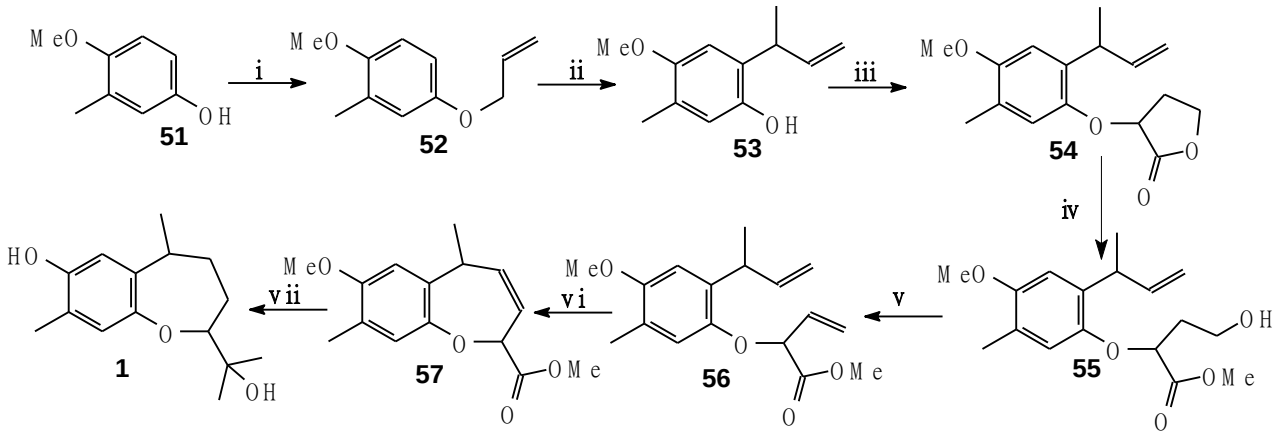
Sabui *et. al.* [**12**] reported another short and high yield method for the synthesis of heliannoul-D (1) starting from appropriately substituted methoxy coumarin (**47**). Under controlled hydrolysis of coumarin affords the corresponding styrenol (**13**) which on alkylation produces diene (**48**). The treatment of 2nd generation Grubbs catalyst with the diene (**48**) led to the ring closing metathesis reaction to afford the cyclic ene-ester (**49**). On catalytic hydrogenation the ene-ester (**49**) affords ester (**50**). The ester (**50**) was subjected to interaction with excess methyl magnesium iodide and afforded a tertiary alcohol (**12**), which on demethylation finally affords the heliannoul-D. (**Scheme 8**).



Scheme 8

Reagents and conditions: (i) KOH, Ethylene glycol, 120^{o}C, (ii) $H_2C{=}CHCH_2CHBrCO_2Et$, K_2CO_3, acetone, reflux. (iii) Grubbs Catalyst **B**, (5 mol%), CH_2Cl_2, rt, 5h, (iv) Pd-C (10%), H_2, EtOH, 5h. (v) MeMgI, Et_2O, reflux, 3h. vi. NaSEt. DMF, Heat.

Roy *el.al* [**13**] reported another short synthesis of heliannouls-D (**1**) during their synthesis of heliannuol-B (**3**). The methoxy phenol (**51**) was alkylated with crotyl bromide and the resultant ether (**52**) subjected to a thermal Claisen rearrangement to furnish styrenol (**53**). This styrenol (**53**) was subjected to an alkylation with 2-bromobutyrolactone in the presence of potassium carbonate in DMF, which afforded lactone ether(s) (**54**). Controlled alkaline hydrolysis of lactone(s) (**54**) followed by treatment of the resultant hydroxy ester with diazomethane furnished hydroxyester(s) (**55)**, which was converted to ester mesylate(s) through reaction with methanesulfonyl chloride in the presence of pyridine. Displacement of the mesylate with o-nitrophenyl selenocyanate followed by in situ oxidative elimination8 delivered ester diene(s) (**56**). Then treatment of this diene(s) (**56**) with Grubbs' 2nd generation catalyst in methylene chloride resulted in clean cyclization furnishing benzoxepane carboxylate(s) (**57**). The catalytic hydrogenation of (**57**) afforded the cyclic ester (**50**) which ultimately converted to the target heliannouls-D (**1**) (**Scheme 9).**

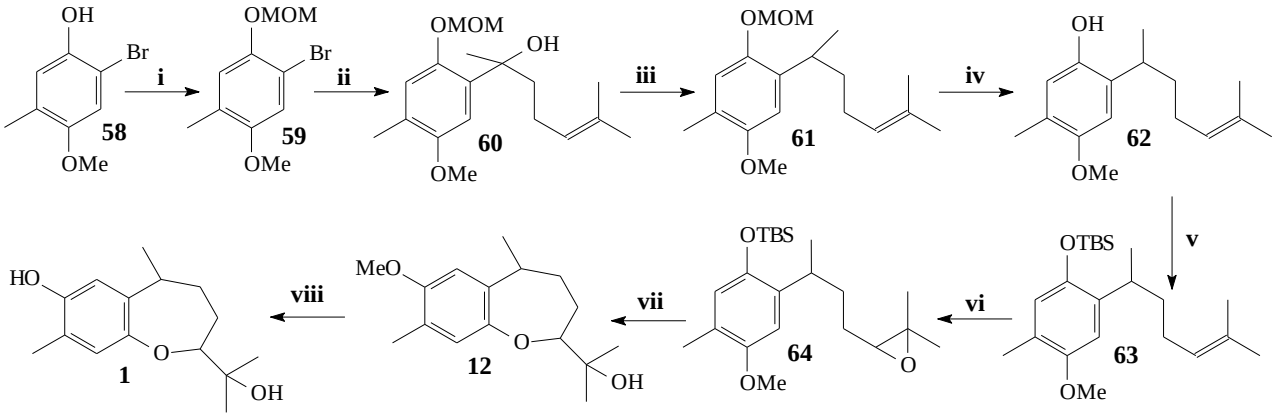


(Scheme 9*)*

Reagents and conditions: (i) K_2CO_3, acetone, $CH_3CH{=}CHCH_2Br$, reflux, 3 h; (ii) $PhNEt_2$, 180^{o}C, 12 h; (iii) K_2CO_3, 2-bromo-butyrolactone, DMF, 90 ^{o}C, 8 h; (iv)a. NaOH, MeOH, rt, 4 h, H_3O^{+}; b. CH_2N_2, Et_2O, 0 ^{o}C, 2 h; (v)a. MsCl, Py, CH_2Cl_2, rt, 14 h; b. o-NO_2–PhSeCN, $NaBH_4$, DMF, rt, 8 h; c. H_2O_2, THF, rt, 3 h. (vi) Grubbs' 2nd generation catalyst, rt, 8 h, (vii)a. Pd–C, H_2, rt, 8 h, b. MeLi, Et_2O, 0 ^{o}C , c. NaSEt, DMF, Heat.

Another synthesis of heliannoul-D (**1**) is reported by Zhang *et. al.* at the same time [**14**]. As the methodologies were similar, so to avoid the repetition details scheme of the synthesis is not mentioned.

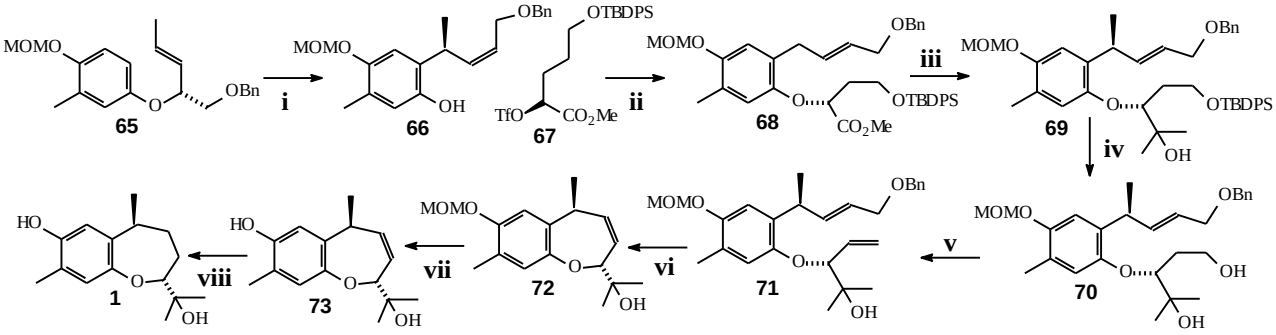
Zhang *et. al.* **[15]** recently disclosed a cost effective synthesis of (±)-heliannoul-D (**1**). The synthesis commenced with properly methoxy bromocresol (**58**) which on MOM-protection produced (**59**) which was lithiated smoothly and then coupled to 6-methyl-3-hepten-2-one to the ene-ol (**60**). Selective reduction of the tertiary alcohol in the presence of triethylsilane and boron trifluoride etherate (to) affords the bisabolene sequiterpene skeleton (**61**) which was then converted to the epoxide (**64**) after replacement of MOM-protecting group by TBs-gr. The S_N2 type ring opening of epoxides (**64**) produced the desired heliannuol D methyl ether (**12)** which on de-methylation finally produced heliannuol D (1) (**Scheme 10).**



(Scheme 10)

Reagents and conditions: (i) $EtN(^{i}Pr)_2$, MOMCl, CH_2Cl_2; (ii) *n*-BuLi, 6-methyl-3-hepten-2-one, (iii) Et_3SiH, BF_3 .Et_2O, CH_2Cl_2;(iv) 3M HCl, MeOH; (v) TBSCl, imidazole, DMF, (vi) *mCPBA*, CH_2Cl_2, (vii) MeOH, K_2CO_3, (viii) NaSEt, 130^{o}C.

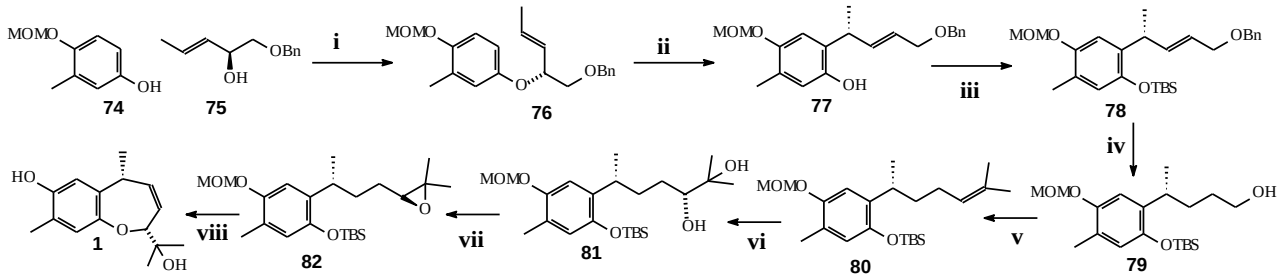
Very recently Shishido *et. al* [**16**] disclosed an efficient enantioselective synthesis of heliannuol-B (**3**) and D [**14**]. In this synthesis, properly functionalized dienyl alcohol (**71**) is used for ring closing metathesis to generate the dihydrobenzo[b]oxepine framework (**72**) of heliannuol-B (**3**) which after deprotection followed by catalytic hydrogenation finally affords heliannuol-D (**1**). The synthesis was started by the substrate controlled charility transfer through acid catalysed Claisen rearrangement of phenyl ether (**65**). The coupling of resultant phenol derivative (**66**) with (**67**) produces the diene (**71**) (**Scheme 11).**



(Scheme 11)

Reagents and conditions: (i) Me_3Al, hexane, r.t, (ii) Tf_2O, 2,6-lutitine, CH_2Cl_2, -20^oC; (iii) K_2CO_3, MeCN, r.t; (iv) MeMgBr, THF, 0^oC, 0.5 h, (v) TBAF, THF, r.t, (vi) o-$NO_2C_6H_4SeCN$, nBu_3P, THF, room temperature, 0.5 h; (vii) H_2O_2 (aqueous), THF, 60^oC, 15 min, (vii) Grubbs' second-generation cat. (5 mol %), CH_2Cl_2 or toluene reflux; (viii) HF, pyridine, THF, pyridine, room temperature, 1.5 h.

A highly enantiocontrolled synthesis of (+)-heliannoul-D (**1**) is also disclosed by Shishido *el.al.* [**17**] employing a chirality transfer Lewis acid mediated Claisen rearrangement and asymmetric dihydroxylation reaction as a key step. The synthesis was started with appropriate MOM-protected phenol (**74**) and (S, E)-1-(benzyloxy)pent-3-en-2-ol (**75**) which are condensed by Mitsunobu reaction follow by Me_3Al mediated chiral Claisen rearrangement. The obtained product (**77**) was converted to epoxide (**82**) through a series of reactions. The epoxides (**82**) then deprotection and spontaneous 7-exo-cyclisation produced MOM-protected-heliannoul-D (**83**) which on acid hydrolysis finally affords (+)-heliannoul-D (**1**) (**Scheme 11)**.



Scheme 11

Reagents and conditions: (i) ADDP, $^nBu_3P$, Benzene, 60^oC. (ii) Me_3Al (3 eqvt.), hexane, r.t, (iii) TBSCl, imadizole, 4-DAMP, CH_2Cl_2, r.t, (iv) H_2, Pd-C, THF, rt. (v) a. $(COCl)_2$, DMSO,Et_3N, CH_2Cl_2, -78^oC. b. Kocienski-Julia olefination with the sulfone [**18**] (vi) AD-mix-β, $MeSONH_2$, ^tBuOH, H_2O, rt. (vii) NaH *N*-tosylimidazole, THF, rt, (viii) K_2CO_3, MeOH, 50 ˚C, (viii) 6 M HCl *aq.* THF, rt, 3 h,

From the above studies it is very clear that total synthesis of sesquiterpene heliannuol-D (1) have achieved a revolution through these years specially stereospecific synthesis as well as cost effectiveness.

Conclusion: In conclusion, this review article describes different approaches towards the racemic as well as stereoselective total synthesis of sesquiterpene heliannuol-D (1) which exhibits allelochemicals activity and can serve as potential agrochemicals as herbicides.

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