

Recent Developments towards the Synthesis of Varitriol: an Antitumour Agent from Marine Derived Fungus *Emericella varicolor*

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Abstract:

Marine natural product is recognized as a fruitful source of drug development due to their rare structural entities and diverse biological activities, and consequently, publicized number of metabolites as new medicines. Although extensive progress has been made in identifying novel bioactive molecules from marine source, great endeavor are still needed to explore these molecules for medicinal applications. Marine fungi are one of the important source of natural products, exhibiting a wide range of biological activities. (+)-Varitriol, isolated from the marine fungus *Emericella varicolor*, has shown 100-fold increased potency over the mean toxicity towards variety of cancer cell lines. Hence (+)-varitriol, an antitumour marine natural product has been a fascinating target for total synthesis over the last decade. The intense search for developing new approaches coupled with its biological activity has resulted in a wealth of methods towards the synthesis of this molecule. But, unfortunately only limited analogues have been synthesized and evaluated for their biological activities. Thus, there are still demands to modify aromatic part as well as sugar moiety of varitriol, which could provide the opportunity for further SAR studies to discover potential lead anticancer agents. This review describes the different strategies developed for the synthesis of varitriol and its analogues in various laboratories around the world covering literature from 2002 till date. The construction of challenging fashionable furanoside ring as well as substituted styrene derivatives are crucial steps in most of the reported synthetic endeavors.

Keywords: Antitumour agent, Asymmetric synthesis, Carbohydrate, Natural product, Marine fungi, Varitriol

INTRODUCTION:

Ocean is considered to be an important source of potential drugs, wherein aquatic organisms produces structurally unique chemicals for their different ecological purposes i.e. either to protect themselves from predators/ pathogens or to communicate in marine ecosystem. Hence, natural products give good chances for the discovery of effective medication for different diseases either, by direct therapeutic effect, after semi-synthetic modification or by synthesizing new compounds based on the natural product lead. A large number of anticancer agents derived from marine natural products and their synthetic analogues are in market as well as in clinical trials [1]. Interestingly, micro-organisms associated with marine environment are proved to be valuable source for drug discovery [2]. Marine microorganisms, particularly fungi and bacteria, have provided new incentives for marine natural products research over the last 15 years, and also continue to be the subject of vigorous chemical investigation [3-5].

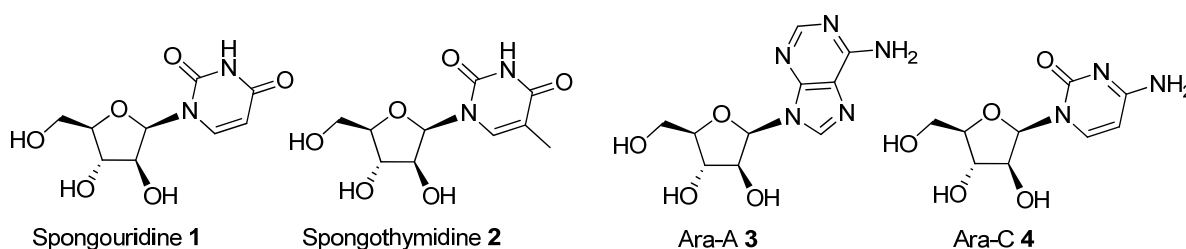


Figure 1. Drugs in market with the furanoside skeleton of marine metabolite

The first therapeutic agents from the marine environment were made in the 1950's by Bergmann and Feeney through their discovery of the nucleosides spongouridine **1** and spongothymidine **2** from the sponge *Tethya crypta* (Figure 1) [6]. Subsequent development of synthetic analogues has provided the clinically relevant agents arabinosyl adenine (Ara-A, **3**), and arabinosyl cytosine (Ara-C, **4**), an anti-cancer agents for the treatment of acute myelocytic leukemia and non-Hodgkin's lymphoma [7]. Arabinosyl cytosine (Ara-C, **4**) is currently sold by the Pharmacia and Upjohn Company under the brand name Cytosar-UR. Thus, nucleoside chemistry is continued to be an attractive research area for medicinal as well as synthetic chemists for developing new drugs [8-9]. It has been witnessed for several years that, the relation between marine natural product and nucleoside had given rise to exciting skeleton showing potentials as drug candidates.

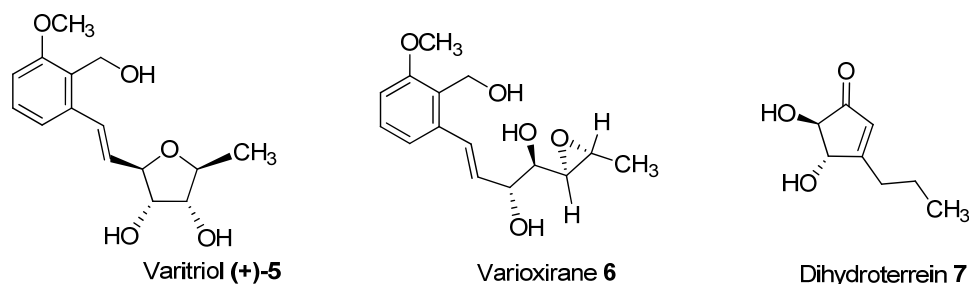


Figure 2. Chemical structures of selected metabolite from *Emericella varicolor*

In the recent decades, the scarcity of compounds from natural sources as well as their impressive bioactivity has fuel the chemists to develop more practical and scalable total synthesis of these natural products. The furanoside skeletons present in nucleosides are also encountered in many other bioactive compounds which has widely distributed in nature. Varitriol (+)-**5** is such a marine natural product isolated by Barrero and co-workers from a marine strain (M75-2) of the fungus *Emericella varicolor* along with other metabolites varioxirane **6** and dihydroterrein **7** in the year 2002. The fungus was isolated from a sponge collected in Venezuelan waters of the Caribbean Sea and showed potent cytotoxicity towards variety of cancer cell lines [10]. The structure assignment of (+)-**5** has been done using 1D and 2D NMR experiments. The number and localization of the OH groups was confirmed by preparing its triacetate. While, the relative configuration of the four stereogenic centers of the tetrahydrofuran ring unit was determined by carrying out NOE experiments for varitriol and its triacetate & acetonide protected products.

BIOLOGICAL ACTIVITIES

Varitriol shows more than 100-fold increased potency (over the mean toxicity) toward RXF 393 (renal cancer), T-47D (breast cancer) and SNB-75 (CNS cancer) cell lines and lower potency against prostate cancer, leukemia, ovarian cancer, and colon cancer cell lines [11]. This is a remarkable activity for such a small molecule, although the mode of action remains to be elucidated. The unique biological activity of varitriol (+)-**5** with still undefined mode of action has produced diverse interest in this natural products, which deserve more comprehensive studies pertaining to anticancer drug development of this molecule. A detail account on biological studies (Structural activity relationships) is included in the last section of this review.

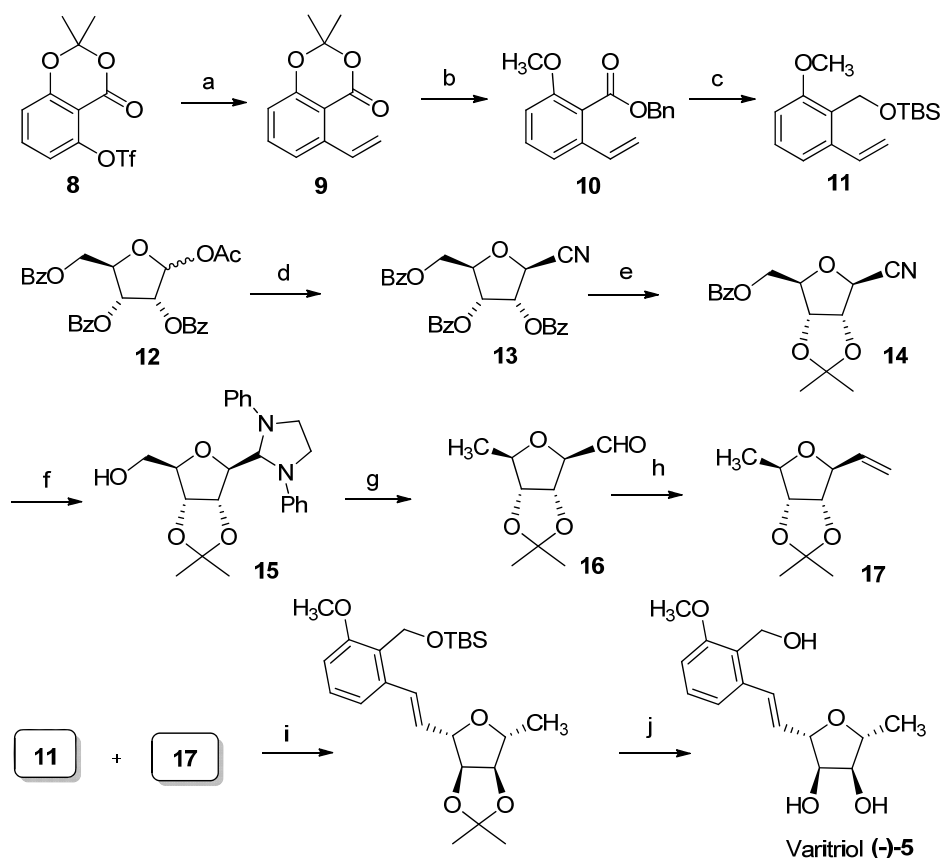
SYNTHETIC CHALLENGES:

Since 2006, about 15 total syntheses of varitriol have been reported in the literature, indicative of the intense interest of synthetic chemists. Biologically active varitriol, isolated from marine fungi comprises of four stereogenic centers. The publicity of varitriol as a synthetic target was arouse, not only for its medicinal value, but also for challenge posed by its structure featuring highly functionalized tetrasubstituted furanoside skeleton. **Most of the synthetic approaches** utilize the commercially available sugar or tartaric acid for the construction of furanoside moiety. Probably, it is the easiest way to access fully functionalized skeleton is the construction of central furan ring using chiral starting materials. A

final step involves the marriage between furanoside part and aromatic moiety to furnish varitriol. Focusing our research interest in isolations and synthesis of marine natural products [12-15], we have combined the scattered body of all the references relating to the total synthesis of varitriol covering literature from 2002 (since its isolation) until 2013.

Early Synthetic efforts:

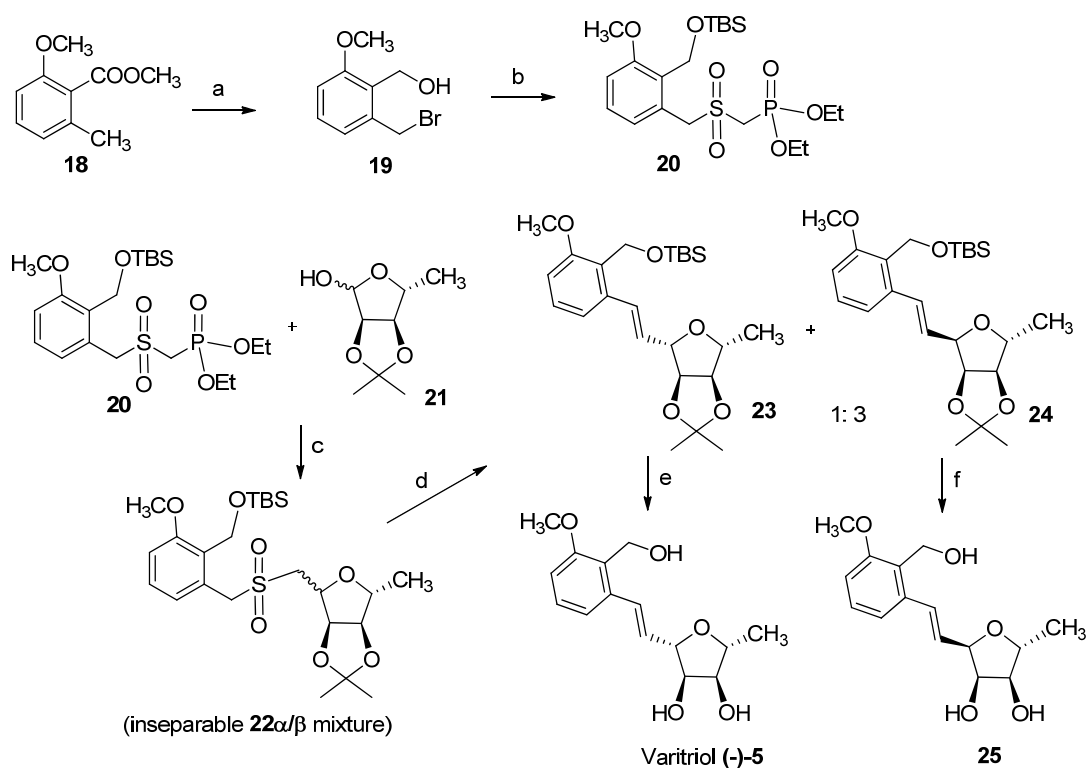
Before surveying the most recent studies towards varitriol, it is worthwhile to consider some of the earlier reports. In 2006, Jennings and Clemens reported an efficient approach towards the synthesis of varitriol (-)-**5** (an antipode of natural product) which is leading as first total synthesis for the determination of absolute configuration of varitriol (Scheme 1) [16]. The synthesis commenced with the preparation of styrene derivative wherein the Suzuki-Mayura coupling of aryl triflate **8** with potassium vinyl trifluoroborate gave substituted styrene **9** in 93% yield. Treatment of sodium anion of benzyl alcohol with 2,2-dimethyl-1,3-benzodioxan-4-one derivative **9** gave corresponding phenol which on etherfication with methyl iodide afforded methyl benzyl ester **10**. The reduction of ester **10** with DIBAL followed by protection with TBSCl provided substituted styrene derivative **11** which has been utilized in the final stage (olefin metathesis step) of varitriol synthesis. The second part of synthesis involves construction of functionalized furanoside subunit. Towards this, the benzoyl protected acetate **12** obtained from D-ribose was subjected to cyanation *via* anchimer assisted nucleophilic addition of TMSCN (in situ generated oxocarbenium cation) for the introduction of cyanide group on the furanose ring with required stereochemistry. This protocol was previously developed by Utimoto *et al.* [17] to give corresponding cyano derivative. Selective debenzoylation of secondary benzoate ester **13** using NH₃/MeOH followed by reprotection of 2,3-diol by 2,2-dimethoxypropane gave acetonide protected furanoside **14**. Reduction of nitrile group to aldehyde followed by treatment with *N,N'*-diphenyl ethylenediamine afforded corresponding aminal and then on removal of benzoate ester *via* LiAlH₄ reduction afforded compound **15**. The tosylation of free hydroxyl group of **15**, subsequent reduction with LiAlH₄ and removal of aminal group under acidic condition furnished aldehyde **16**. The olefination of aldehyde **16** with methylene phosphorane delivered required alkene **17**. Remarkably, the target was completed *via* coupling of two intermediates i.e. styrene derivative **11** and furanoside subunit **17** in the presence of Grubbs IInd generation catalyst and subsequent TBS and acetonide deprotection under acidic condition delivered varitriol (-)-**5**.



Scheme 1. Reagents and conditions: (a) Potassium vinyltrifluoroborate (1:1), Et₃N, Pd(dppf)Cl₂ (5 mol%), 80 °C, 4.5 h, 93%; (b) 1) benzyl alcohol (10 eqv.), NaH, DMF, 0 °C to rt, 3 h, 97%, 2) K₂CO₃, MeI, THF, 0 °C to rt, 2 h, 88%; (c) 1) DIBAL, toluene, -78 °C to rt, 85%, 2) TBSCl, imidazole, DMF, rt, 4 h, 97%; (d) TMSCN, BF₃·Et₂O, CH₂Cl₂, rt, 2 h, 85%; (e) 1) NH₃, MeOH, 0 °C, 4.5 h, 82%; 2) 2,2-Dimethoxypropane, HClO₄, acetone, rt, 2 h, 95%; (f) 1) Raney Nickel, sodium hypophosphite, *N,N'*-diphenyl ethylenediamine, AcOH-pyridine-H₂O (1:2:1), rt, 1 h, 82%; 2) LiAlH₄, THF, -78 °C, 3 h, 92%; (g) 1) TsCl, pyridine, 0 °C to rt, 24 h, 85%, 2) LiAlH₄, THF, -78 °C, 3 h, 92%, 3) PTSA, acetone, CH₂Cl₂, 5 min at 0 °C then at rt, 1 h, 48%; (h) ^tBuOK, methyltriphenylphosphonium bromide, Et₂O, 12 h, 56%; (i) Grubbs catalyst, CH₂Cl₂, reflux, 18 h, 59%; (j) 1M HCl, THF, rt, 2h, 72%

Another, total synthesis of varitriol (-)-5 has been described by Taylor and co-workers using Horner-Wadsworth-Emmon olefination/ conjugate addition/ Ramberg-Bäcklund reaction as key steps (Scheme 2) [18]. The first part involves the preparation of the functionalized benzylsulfonyl reagent **20** to construct the double bond of varitriol. The known benzoate **18** [19] was first subjected to bromination and then the ester group was reduced to give substituted benzyl bromide **19**. Treatment of benzyl bromide **19** with phosphonylmethane thiol [20], followed by *m*-CPBA oxidation afforded requisite

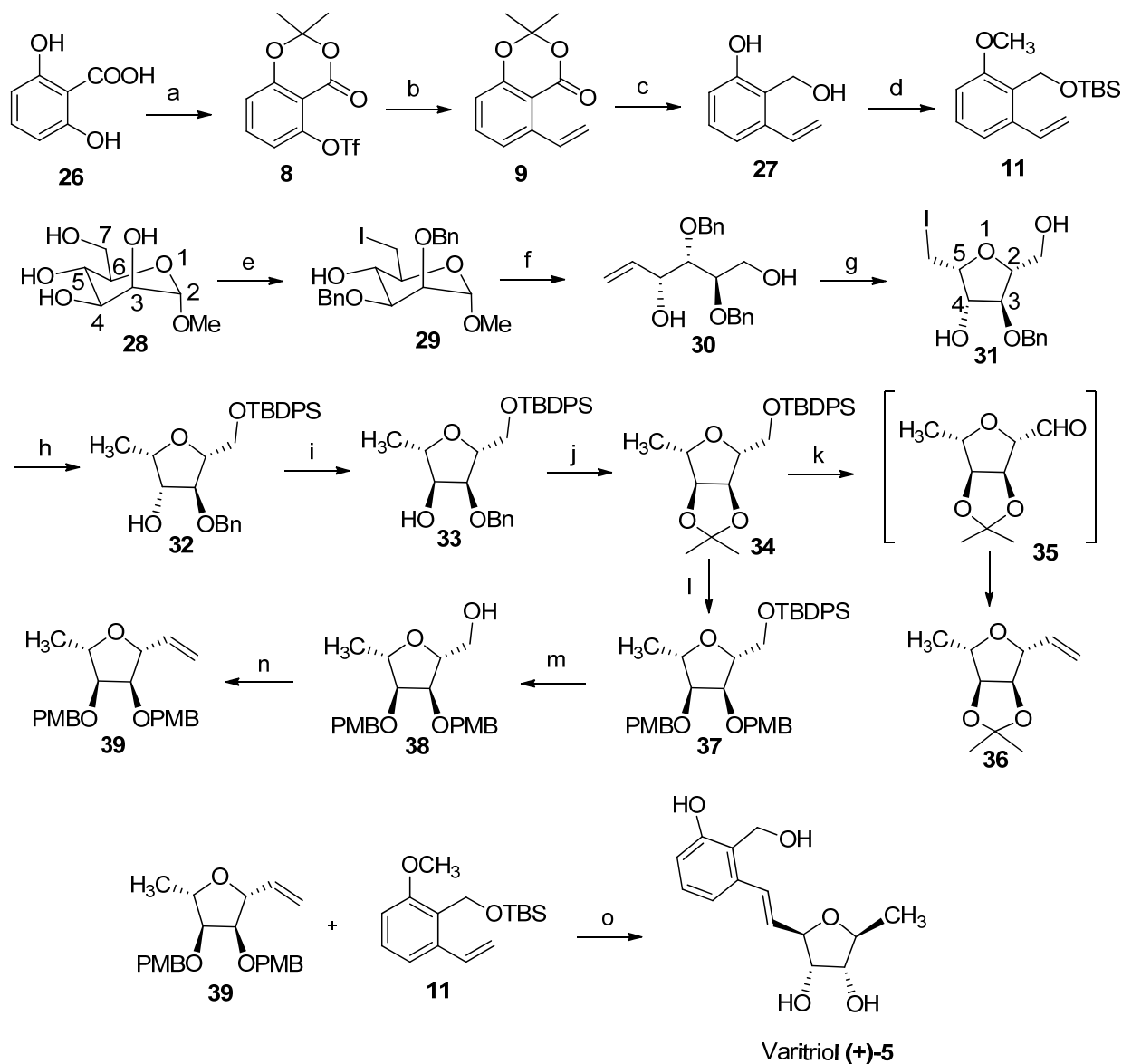
phosphonate. Further, the benzyl hydroxyl group of phosphonate was treated with TBSOTf to furnish phosphonate **20**. Next attempt involved HWE reaction/ Ramberg-Backlund sequence using unprotected phosphonate and lactol **21** (known lactol prepared from D-ribose) [21-22] with the intention of getting varitriol (-)-**5** in one-pot, but instead gave complex mixture of products. Corresponding to this fact, an attempt of sequential procedure using silylated phosphonate and lactol under basic condition (NaH, 0 °C) yielded inseparable mixture of sulfone (**22** α : **22** β = 2:3), wherein two reaction *i.e.* HWE/ conjugate addition occurred in one-pot. Lastly, Ramberg-Backlund reaction of this mixture of sulfone provided two epimers (**23**: **24** = 1:3) which was separated by silica gel column chromatography. Subsequently, the deprotection of acetonide group under acidic condition provided varitriol (-)-**5** in 72% yield. (-)-3'-*Epi*-varitriol **25** was also synthesized during this approach.



Scheme 2. Reagents and conditions: (a) 1) NBS, benzoyl peroxide, CCl₄, reflux, 1.5 h, 86%, 2) DIBAL, toluene, 0 °C, 3 h, 70%; (b) 1) SHCH₂P(O)(OEt)₂, K₂CO₃, EtOH, 78%, 2) *m*-CPBA, CH₂Cl₂, 79%, 3) TBSOTf, 2,6-lutidine, 98%; (c) NaH, THF, 0 °C to rt, 88%; (d) KOH-Al₂O₃, CH₂Cl₂-*t*BuOH, CBr₂F₂, 78%; (e) 1M aq. HCl, THF, 18 h, 72%; (f) 1M aq. HCl, THF, 7 days, 72%.

Recent synthesis of natural varitriol (+)-5:

Over the past five years, several research groups have made exciting discoveries that ultimately allowed access to the varitriol skeleton. In earlier studies, both groups have shown the total synthesis of unnatural varitriol (-)-5 by utilizing D-(-)-ribose to build the furanoside portion. The first total synthesis of natural varitriol (+)-5 has been reported by Shaw's group using commercially available 2,6-dihydroxybenzoic acid **26** and methyl- α -D-mannopyranoside **28** (Scheme 3) [23].



Scheme 3. Reagents and conditions: (a) 1) acetone, SOCl_2 , DMAP, DME, 96%, 2) triflic anhydride, pyridine, 85%; (b) tributylvinyl tin, $\text{Pd}(\text{PPh}_3)_4$, LiCl, THF, sealed tube, 80 °C, 30 h, 94%; (c) LiAlH_4 ,

THF, 0 °C to rt, 2 h, 72%; (d) 1) CH₃I, K₂CO₃, acetone, reflux, 5 h, 88%, 2) TBSCl, imidazole, CH₂Cl₂, rt, 1 h, 93%; (e) 1) PhCH(OMe)₂, CSA, DMF, rt, 24 h, 48%, 2) BnBr, KOH, toluene, reflux, 1 h, 69%, 3) I₂, MeOH, 80 °C, 1 h, 4) I₂, PPh₃, imidazole, toluene, 1 h, 85% (2 steps); (f) 1) Zn-dust, NH₄Cl, cyanocobalamin, MeOH, rt, 30 min, 2) NaBH₄, MeOH, 0 °C, 3 h, 60% (2 steps); (g) I₂, CH₂Cl₂, 0 °C, 2 h, 78%; (h) 1) LiAlH₄, THF, -78 to 0 °C, 3 h, 2) TBDPSCl, pyridine, 12 h, 85% (2 steps); (i) 1) Dess-Martin periodinane, CH₂Cl₂, 2 h, 0 °C to rt, 2) L-selectride, THF, -78 °C, 3 h, 90% (2 steps); (j) 1) H₂, Pd(OH)₂, MeOH, rt, 12 h, 2) 2,2-dimethoxypropane, acetone, CSA, rt, 6 h, 86% (2 steps); (k) 1) TBAF, THF, 0 °C to rt, 2 h, 78% 2) IBX, CH₃CN, 80 °C, 1 h, 3) PPh₃CH₃Br, KHMDS, THF, -78 °C to rt, 1 h (poor yield); (l) 1) 80% AcOH, 80 °C, 2 h, 94%, 2) PMBCl, NaH, TBAI, DMF, 0 °C to rt, 2 h, 54%; (m) 1) TBAF, THF, 0 °C to rt, 1 h, 95%; (n) 1) IBX, CH₃CN, 80 °C, 1 h, 2) PPh₃CH₃Br, KHMDS, THF, -78 °C to rt, 1 h, 77% (2 steps); (o) 1) Grubbs IInd generation catalyst, CH₂Cl₂, reflux, 12 h, 51%, 2) 1M HCl, THF, rt, 3 days, 46%.

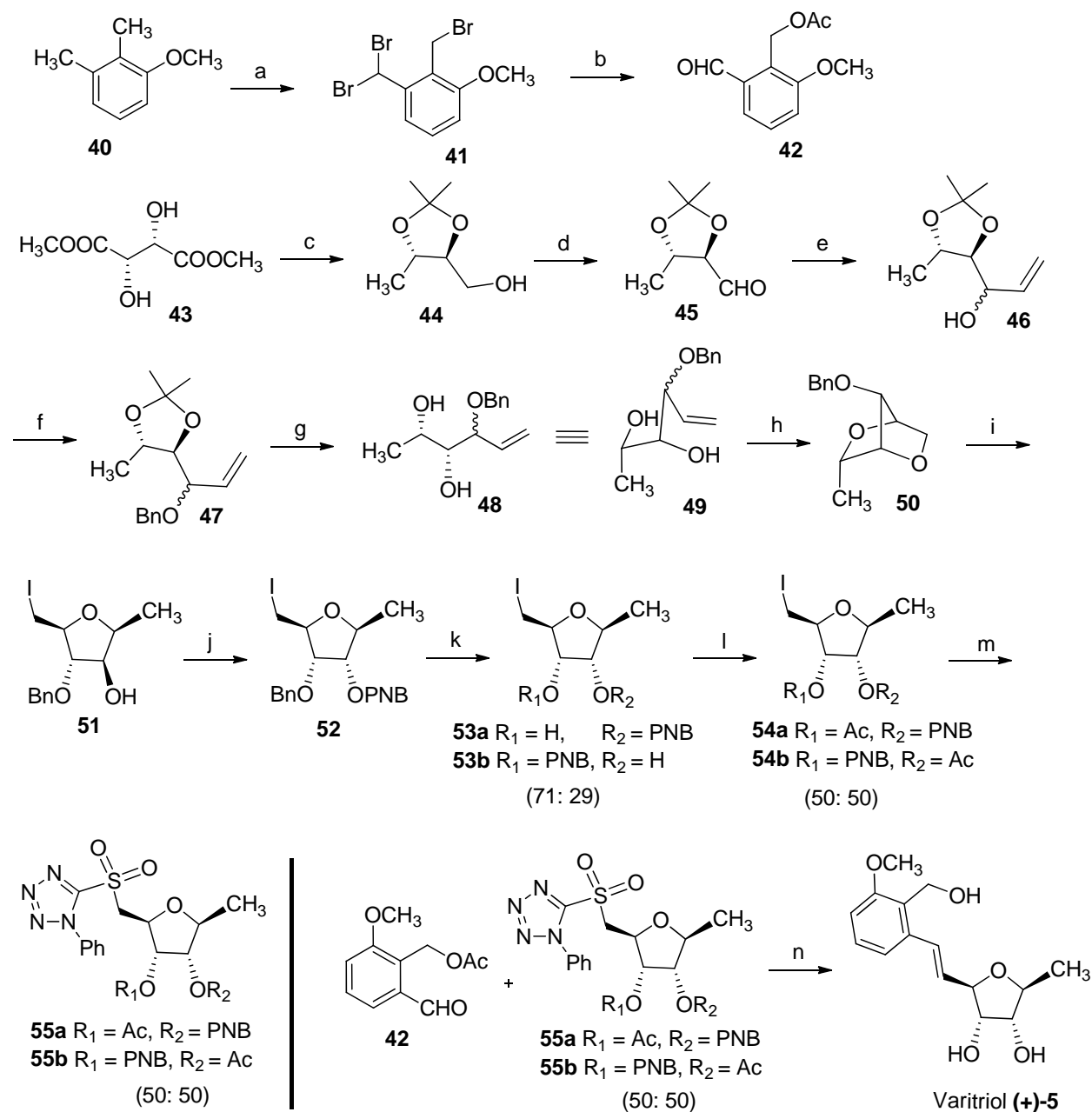
Authors have utilized the previously reported protocol for the construction of aromatic stilbene portion using phenolic acid. Towards this, 2,6-dihydroxybenzoic acid **26** was converted to isopropylidene derivative and subsequently treated with triflic anhydride to furnish triflate **8** [24]. The vinyl group was introduced by employing Stille coupling. The reaction of tributylvinyl tin (TBVT) with triflate in the presence of tetrakis (triphenylphosphine) palladium (0) and lithium chloride at 80 °C in sealed tube gave stilbene derivative **9**. This on LiAlH₄ reduction followed by methylation of phenol hydroxyl and protection of benzylic hydroxyl group by silyl provided the requisite aromatic alkene **11**.

An iodocyclization approach for the synthesis of highly functionalized tetrasubstituted tetrahydrofurans was previously reported by Shaw and co-workers [25]. Authors demonstrated the utility of their previous approach to prepare functionalized tetrahydrofuran derivative and hence for varitriol synthesis. The commercially available α -D-mannopyranoside **28** was subjected to 5,7-dihydroxy protection employing benzaldehyde dimethyl acetal to give corresponding acetal. Furthermore, the benzyl protection of remaining two hydroxyl groups gave dibenzyl protected acetal. After the selective deprotection of benzacetal, iodine was introduced at 7 position using molecular iodine to give iododerivative **29**. The opening of pyranoside ring using zinc dust followed by sodium borohydride reduction afforded allyl alcohol **30**. On further cyclization of allyl alcohol using molecular iodine

involving the participation of secondary benzyl protected oxygen and then debenylation gave 4, 5-*cis* substituted THF with high diastereoselectivity (>99: 1). The presence of benzyloxy group is crucial for the observed stereoselectivity, wherein the attack of iodine from *si*-face of allylic alcohol is completely blocked by the benzyloxy group. Conversion of methylene iodide to methyl group *via* LiAlH₄ reduction, followed by selective silyl protection of primary alcohol provided α -C-furanoside **32**. The required stereochemistry in varitriol is different at only C-4 position of α -C-furanoside and hence the C4-OH group is subjected to inversion *via* Dess-Martin periodinane oxidation followed by reduction. Amongst the different hydride reagent employed for reduction step, L-selectride resulted in good selectivity (>99:1) with 90% yield. The debenylation using H₂ in the presence of Pd(OH)₂ and acetonide protection gave furanoside **34**. The stereochemistry of compound was confirmed by NOESY experiment. The initial attempt for the preparation of furanoside side chain led to poor yield. Desilylation using TBAF, and on IBX oxidation of resultant alcohol gave corresponding aldehyde **35**. Although Wittig olefination of aldehyde **35** provided the desired furanoside **36**, but gave poor yield. The reason being attributed to the high volatile nature of aldehyde **35** as well as vinylic furanoside **36**. Hence, in the next attempt, acetonide protecting group was replaced by *p*-methoxybenzyl (PMB) moiety. Accordingly, acetonide deprotection under acidic condition followed by PMB protection afforded **37**. The silyl deprotection provided primary alcohol and subsequently IBX oxidation followed by Wittig olefination afforded desired olefin **39**. At the final stage, two building blocks were linked together under metathesis condition using Grubbs IInd generation catalyst to give protected varitriol (+)-**5**. Authors anticipated that the deprotection of PMB ether under standard procedure using (DDQ, 10% TFA/DCM) would give targeted product, but instead they obtained complex mixture of products. Furthermore, deprotection of PMB with 1M HCl in THF at room temperature for 3 days gave (+)-varitriol **5** in 46% yield. Thus, Shaw and co-workers nicely combined different methods such as diastereoselective iodocyclization, stereoselective L-selectride reduction of ketone, Stille coupling and cross metathesis to disclose the first total synthesis of antitumour natural product varitriol (+)-**5**.

In 2009, Gracza and co-workers has developed the synthesis of varitriol (+)-**5** by employing Kocienski-Julia olefination of furan derivative containing sulfonyl group with substituted benzaldehyde (Scheme 4) [26]. They also confirmed the absolute configuration of natural (+)-varitriol by single-crystal X-ray for the first time. The requisite fragment 2-formyl-6-methoxy benzyl acetate **42** was prepared by employing

known 3-steps procedure [27] using 2,3-dimethylanisole **40** as a starting material. The synthesis commenced from dimethyl L-tartrate **43** involving acetonide protection, ester reduction, selective monotosylation and hydride displacement to give acetonide protected alcohol **44**. Swern oxidation of alcohol followed by Grignard reaction using vinylmagnesium bromide provided the mixture of L-xylo/ L-lyxo **46** in 69:31 diastereomeric ratios. Benzylation of hydroxyl group followed by acetonide deprotection afforded diol **48** which is an important intermediate for crucial bicyclization step. Utilizing the previously reported work [28-29], the mixture of L-lyxo/ L-xylo was subjected to Pd^{II}-Cu^{II}-catalyzed bicyclization to give bicyclic ether with high substrate and threo selectivity. Among the mixture of product, only L-xylo diastereomer was selectively transformed to bicyclic derivative **50**. Next, the bicyclic derivative **50** was subjected to ring opening reaction using TBAI/ TMSCl/ HCl at room temperature to give iodide **51**. The hydroxyl group of furanoside was inverted under Mitsunobu condition using DIAD/ PPh₃/ *p*-nitrobenzoic acid to obtain protected tetrahydrofuran derivative **52**. Initially, author had prepared corresponding sulfones of protected THF derivative for the olefination, but the problematic debenylation at the final stage of synthesis led to the revision of this strategy. Removal of benzyl group of iodide **52** using BCl₃ in CH₂Cl₂ at -50 °C wherein, partial migration of *p*-nitrobenzoyl moiety occurred to give mixture of isomers **53a:53b** in 71:29 ratio, which on acetylation afforded the mixture of acetate **54a-54b** (1:1 ratio).

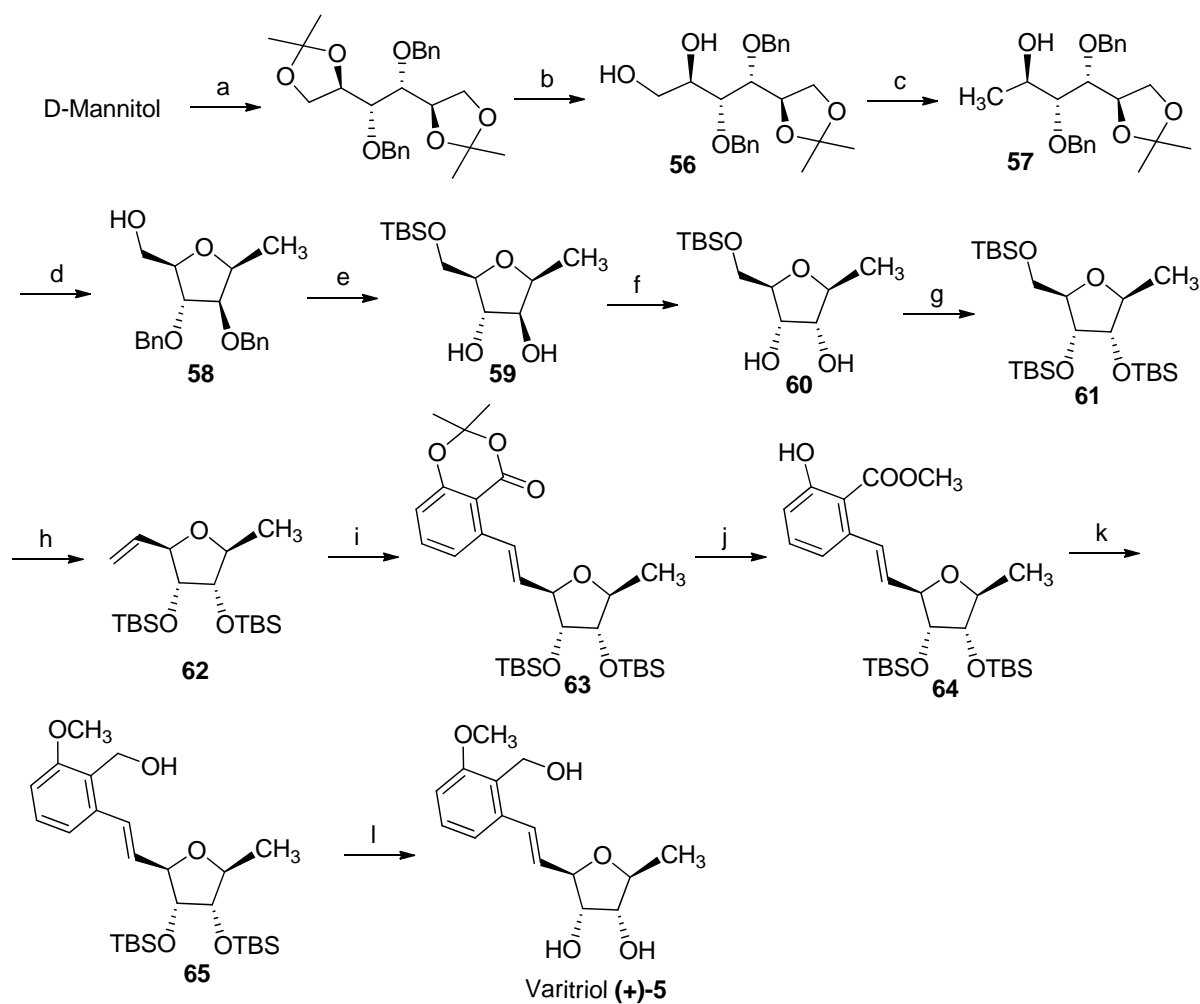


Scheme 4. Reagents and conditions: (a) NBS, **dibenzoyl peroxide**, CCl_4 , reflux, 20 h, quant. yield; (b) NaOAc, AcOH, reflux, aq. HCl, 25 °C, 2 h, 88%; (c) 1) 2,2-dimethoxypropane, PTSA, benzene, 6 h, 98%, 2) $NaBH_4$, MeOH, 80%, 3) TsCl, Bu_4NHSO_4 , 15% NaOH, CH_2Cl_2 , 86%, 4) $LiAlH_4$, Et_2O , 76%; (d) $(COCl)_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C to rt, 2 h; (e) vinylmagnesium bromide, THF, 0 °C to rt, 12 h, 63% (2 steps); (f) BnBr, NaH, DMF, 0 °C to rt, 12 h, 76%; (g) 60% AcOH, rt, 10 h, 83%; (h) $PdCl_2$ (0.1 equiv.), $CuCl_2$, AcONa, AcOH, rt, 12 h; (i) TMSCl, TBAI, HCl, CH_2Cl_2 , rt, 2 days, 61% (2 steps); (j) DIAD (5 equiv.), PPh_3 , *p*-nitrobenzoic acid, reflux, 2 h, 57%; (k) BCl_3 , CH_2Cl_2 , -50 °C, 50 min, 81%; (l)

Ac₂O, DMAP, pyridine, rt, 3 h, 90%; (m) 1) KSPT, DMF, rt, 8 h, 84%, 2) Mo(VI)/H₂O₂, EtOH, THF, 0 °C to rt, 10 h, 87%; (n) KHMDS, DME, 55 °C to rt, 10 h, 2) NaOMe, MeOH, rt, 4 h, (63%, 2 steps).

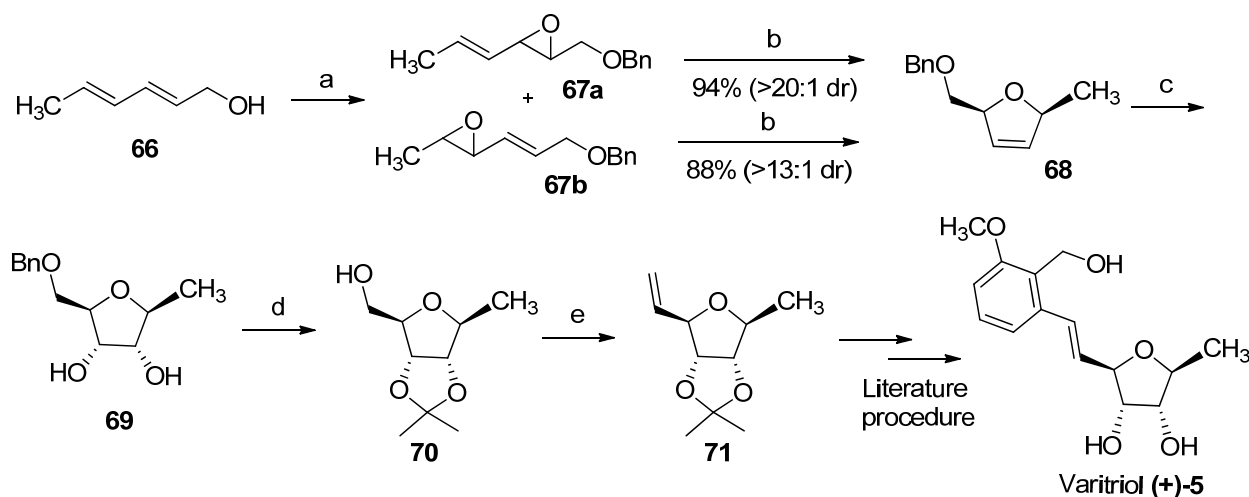
Nucleophilic displacement of iodine using potassium thiolate gave phenyltetrazole sulfide moiety which on oxidation provided sulfone fragment **55** for Kocienski-Julia olefination. Next, the coupling of aromatic aldehyde **42** with mixture of sulfones **55** was attempted under different reaction conditions for good *E*-selectivity of olefin. The Barbier protocol [30] utilizing KHMDS (1.4 equiv) in dimethoxyethane exclusively gave *E*-isomer. Finally, the removal of acetyl and benzoyl protecting groups using NaOMe in MeOH furnished natural varitriol which was purified by flash chromatography and then crystallized from EtOAc/hexane (1:1) as colorless needles. The absolute stereochemistry of natural varitriol (+)-**5** was confirmed by single crystal X-ray analysis.

Ghosh and Pradhan employed the Heck reaction to assemble the olefinic sugar moiety and the aromatic triflate moiety for the synthesis of varitriol (+)-**5** (Scheme 5) [31]. The synthesis of carbohydrate fragment commenced with D-mannitol which on acetonide protection followed by benzylation of secondary hydroxyl group and then selective monoacetonide deprotection afforded diol **56**. The chemoselective tosylation of primary alcohol which on treatment with LiAlH₄ in THF at 0 °C gave secondary alcohol **57**. The alcohol was subjected to mesylation and then treated with CSA to give tetrahydrofuran derivative **58**. The hydroxyl group of THF derivative **58** was subjected to TBS protection and then debenylation under hydrogenation delivered *trans* diol **59**. But the final compound demands *cis* diol. Hence, double bond was introduced at C-3, C-4 carbon using I₂ in PPh₃ and then OsO₄ mediated dihydroxylation furnished diol **60** with 10:1 dr ratio. Both the secondary hydroxyl groups were protected with TBS to furnish tri-TBS protected furan derivative **61**. The selective deprotection of the primary TBS with HF: pyridine gave alcohol, which on oxidation using Dess-Martin periodinane and finally Wittig reaction with methylenephosphorane furnished required olefin THF fragment **62**.



Scheme 5. Reagents and conditions: (a) 1) 2,2-dimethoxypropane, DMF, PTSA (*cat.*), 80%, 2) NaH, BnBr, TBAI, THF, 0 °C to rt, 95%; (b) MeOH, conc. HCl, 0 °C to rt, 60%; (c) 1) TsCl, Et₃N, CH₂Cl₂, DMAP (*cat.*), 0 °C to rt, 2 h, 2) LiAlH₄, THF, 0 °C to rt, 10 min (95%, 2 steps); (d) 1) MsCl, Et₃N, CH₂Cl₂, DMAP (*cat.*), 0 °C to rt, 15 min, 2) CSA, MeOH: CH₂Cl₂ (1:1), 0 °C to rt, 2 h (95%, 2 steps); (e) 1) TBSCl, Et₃N, CH₂Cl₂, DMAP (*cat.*), 0 °C to rt, 1 h, 94%, 2) H₂, Pd/C, EtOAc, 10 h, 96%; (f) 1) PPh₃, I₂, imidazole, toluene, reflux, 30 min, 2) OsO₄, NMO, methane sulfonamide, acetone:H₂O (1:1), 40 °C, 3-4 h, dr (10:1) (55%, 2 steps); (g) TBSOTf, CH₂Cl₂, 2,6-lutidine, 0 °C to rt, 10 min, 87%; (h) 1) HF:pyridine, THF, 10 h, 70%; 2) DMP, CH₂Cl₂, NaHCO₃, 0 °C to rt, 10 min, 3) Ph₃PCH₃Br, Et₂O, *t*-BuOK, 0 °C, (80%, 2 steps); (i) Ar-OTf, PdCl₂(PPh₃)₂, DMF, LiCl, Et₃N, 120 °C, 10 h, 80%; (j) LiOH, THF:MeOH:H₂O (3:1:1), 0 °C to rt, 30 min, 97%; (k) 1) MeI, acetone, K₂CO₃, reflux, 2.5 h, 2) DIBAL, CH₂Cl₂, -78 °C to rt, 10 min (97%, 2 steps); (l) 6N HCl, THF, 0 °C to rt, 5 h, 88%.

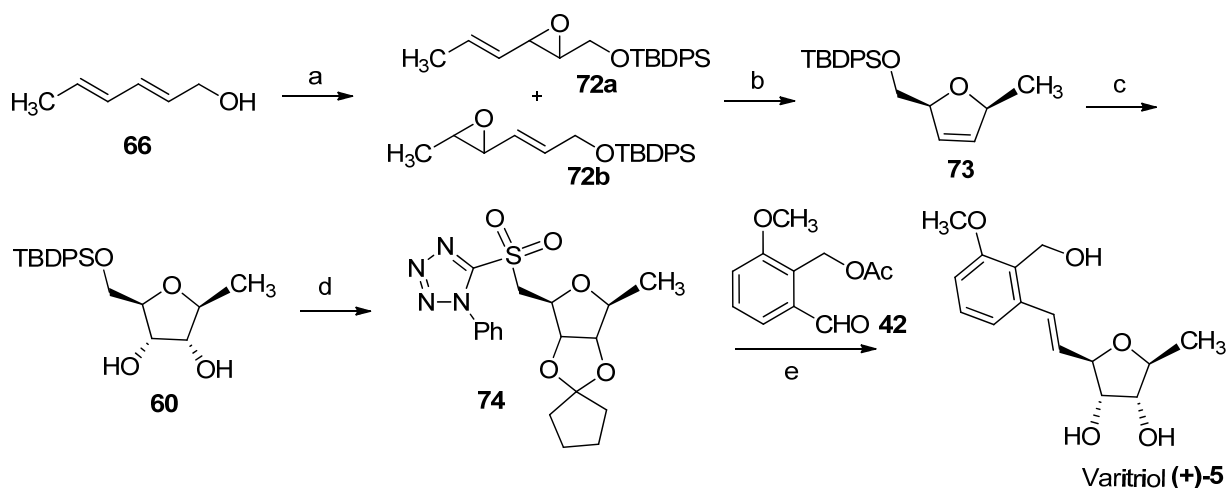
In the end, two fragments (olefinic compound **62** and aromatic triflate **8**) were coupled using the earlier reported procedure (Heck coupling) [32] employing Pd(PPh₃)₂Cl₂, LiCl and Et₃N in DMF at 120 °C to give alkene. The acetonide protection on aromatic ring was removed using LiOH/MeOH to give aromatic ring with hydroxyl and methyl ester moiety. Finally, *O*-methylation followed by reduction of ester functionality and then TBS deprotection gave varitriol (+)-**5**. Furthermore, the synthesis of (-)-varitriol and 4'-*epi*-(-)-varitriol were also reported using similar reaction as used earlier for the synthesis of varitriol (+)-**5**. Recently, the same research group has reported the structure activity relationship studies of varitriol analogues prepared using the above strategy which is discussed in details at the last section of this article.



Scheme 6. Reagents and conditions: (a) 1) BnBr, NaH, DMF, 0 °C, 2 h, 85%, 2) *m*-CPBA, CH₂Cl₂, 0 °C, 1 h, 98%; (b) Cu(hfacac)₂, toluene, reflux, 12 h, 88-94%; (c) OsO₄, acetone:H₂O (1:1), NMO, rt, 24 h, 88%; (d) 1) 2,2-dimethoxypropane, *cat.* pyridinium *p*-toluenesulfonate, CH₂Cl₂, rt, 3 h, 67%, 2) H₂, Pd/C, MeOH, 18 h, 93%; (e) 1) (COCl)₂, DMSO, Et₃N, -78 to 0 °C, 2) Ph₃PCH₃Br, *t*BuOK, Et₂O, 0 °C, 1 h, (18%, 2 steps).

Njardarson and co-workers has described the strength of the method developed in their laboratory involving copper-catalysed vinyl oxirane ring expansion reaction for the synthesis of common *cis*-2,5-tetrahydrofuran core and subsequently **the construction of** the varitriol skeleton (Scheme 6 & 7) [33]. The synthesis commenced with benzyl protection of diene alcohol **66** which on epoxidation furnished two epoxy compounds **67a-b**. The vinyl oxiranes was subjected to the copper-catalyzed rearrangement using Cu(hfacac)₂ to give *cis*-2,5-dihydrofuran **68** in excellent yield and with high stereoselectivity. *Cis* dihydroxylation using OsO₄/NMO followed by acetonide protection of diol and benzyl deprotection *via*

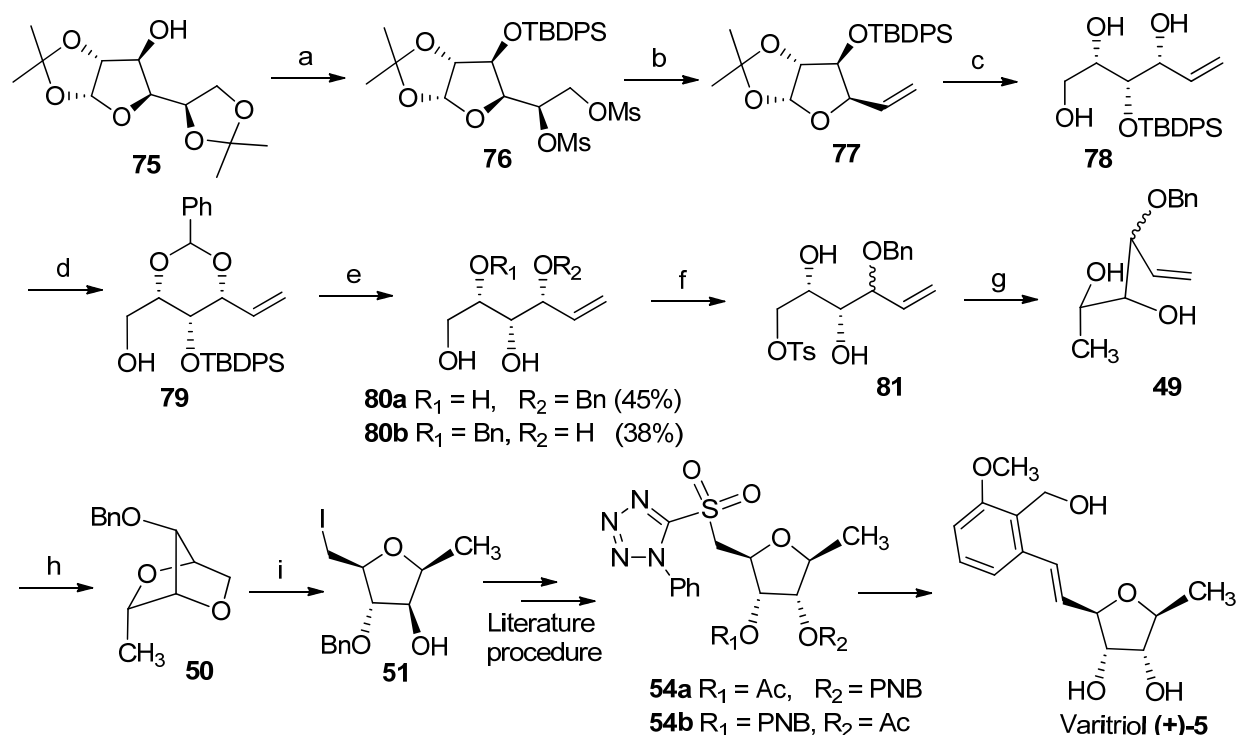
hydrogenolysis gave acetonide protected furanose alcohol **70**. Oxidation of alcohol to aldehyde and Wittig olefination gave furan alkene **71** which has been previously transformed to varitriol **5** by Jennings and co-workers. This formal synthesis comprises of 8 steps, which is 8 steps shorter than the approach reported by Jennings's group (Scheme 1) using D-ribose. Surprisingly, this new method has not been executed for chiral synthesis and has also led to decrease in overall yield (Wittig reaction: only 18% yield). Authors have also demonstrated their stereoselective vinyl oxirane ring expansion protocol for another synthesis of natural (+)-varitriol. This approach involves the preparation of key intermediate using methyl-D-mannopyranoside which was previously reported by Shaw and co-workers for the synthesis of varitriol. Corresponding to the very poor yield in the oxidation-Wittig reaction steps led to the revision of strategy by changing the protecting group. This problem of low yield was attributed to the formation of volatile aldehyde product **35** (small ring with acetonide protecting group is more volatile), which was also previously observed by Shaw's group [23]. Alternatively, to overcome the problem, the synthesis was started with silyl protection of dienol **66** followed by epoxidation to give readily separable oxiranes **72a-b**. Both the oxiranes were treated with $\text{Cu}(\text{hfacac})_2$ to produce the *cis* dihydrofuran in good yield and with good diastereoselectivity (20:1, dr). The excellent stereoselectivity of the newly developed copper catalysed vinyl oxirane ring expansion reaction is the highlight of this work. Furthermore, *cis* dihydroxylation using OsO_4 afforded diol **60** in 4 steps from dienol **66**. This is comparatively shorter method than the Shaw's 12-steps synthesis of the same diol from D-mannopyranoside [23].



Scheme 7. Reagents and conditions: (a) 1) TBDPSCl, imidazole, CH_2Cl_2 , rt, 10 h, 99%, 2) *m*-CPBA, CH_2Cl_2 , 0 °C, 1 h, 99%; (b) $\text{Cu}(\text{hfacac})_2$, toluene, reflux, 12 h (80-84%); (c) OsO_4 , acetone:H₂O (1:1),

NMO, rt, 12 h, 99%; (d) 1) dimethoxycyclopentane, *cat.* PPTS, CH₂Cl₂, rt, 12 h, 2) TBAF, THF, 0 °C to rt, 2 h (74%, 2 steps), 3) 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), PPh₃, DIAD, CH₂Cl₂, then (NH₄)₆Mo₇O₂₄, 30% H₂O₂, 81%; (e) 1) KHMDS, DMF:HMPA (4:1), -78 °C to rt, 12 h, 2) NaOMe, MeOH, rt, 1 h, then Amberlyte-15 (70%, 2 steps).

Both these new routes demonstrated for the formal synthesis of varitriol are shorter than the previous work. For the complete synthesis of varitriol, the synthesized diol **60** was subjected to acetal protection, the silyl deprotection and then Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by in situ oxidation with ammonium molybdate tetrahydrate to give corresponding sulfone **74**. The Julia olefination of sulfone **74** with aromatic aldehyde **42** produced exclusively *E*-olefin in high yield. Finally, the deprotection of acetate, methoxy and acetal group gave varitriol **5**.

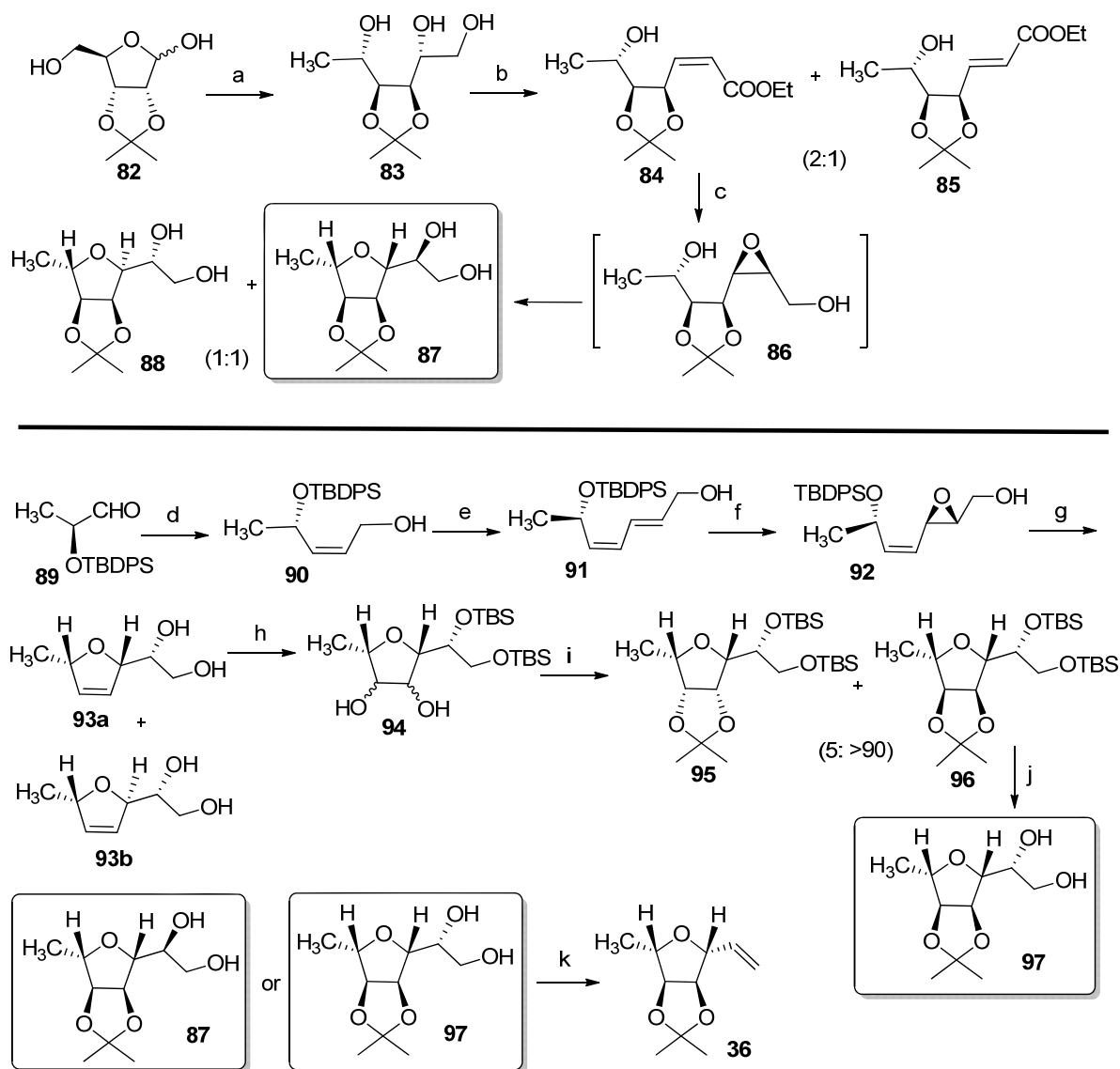


Scheme 8. Reagents and conditions: (a) 1) TBDPSCl, imidazole, DMF, 50 °C, 80 h, 2) 75% aq. AcOH, rt, 8 h (93%, 2 steps), 3) MsCl, pyridine, rt, 8h, 95%; (b) NaI, DMF, 120 °C, 3 h, 90%; (c) 1) 50% aq. AcOH, 90 °C, 3 days, 88%; 2) NaBH₄, MeOH/H₂O (3:1), rt, 5 days, 75%; (d) PhCH(OCH₃)₂, PTSA, rt, 18 h, 68%; (e) 1) NaBH₃CN, CH₃CN, TiCl₄, -35 °C to rt, 18 h, 2) TBAF, THF, rt, 18 h, 85%; (f) TsCl, pyridine, rt, 10 h; (g) LiAlH₄, Et₂O, 0 °C to rt, 10 h, (64%, 2 steps); (h) PdCl₂, CuCl₂, AcONa, AcOH, rt, 12 h, 83%; (i) TMSCl, TBAI, HCl, CH₂Cl₂, rt, 3 days, 76%.

A formal and improved synthesis of natural varitriol (+)-**5** from D-glucose and dimethyl-L-tartrate employing Pd(II)/Cu(II)-catalysed bicyclisation of *O*-benzyl protected triols as a key step was reported by Gracza and co-workers (Scheme 8) [34]. The synthesis started with silylation of bisacetone-D-glucose **75** followed by selective hydrolysis of the terminal acetonide, *O*-mesylation of both unprotected hydroxyl group to give dimesylate **76**. The reductive elimination of sodium iodide furnished alkene **77**. The hydrolysis of second acetonide with 50% aq. acetic acid gave D-xylo-5-hexenose which on sodium borohydride reduction provided alkene **78**. Selective acetalization of triol at 1,3-position with benzaldehyde dimethyl acetal in the presence of *p*-toluene sulfonic acid afforded acetal **79**. Further, the reduction of benzylidene ring with NaBH₃CN/ TiCl₄ system gave α -OBn-protected tetrol (45%) along with its regioisomer (38%). α -OBn-protected tetrol on desilylation using TBAF in THF afforded triol **80** in good yield. Upon selective tosylation of primary hydroxyl group, followed by LiAlH₄ reduction of tosylate gave L-xylo **49** in 64% yield over 2 steps. In the past, authors have demonstrated the tandem diastereoselective bicyclization and regioselective ring opening of bicyclic skeleton for the synthesis of heterocyclic compounds of defined stereochemistry [29, 35-36]. This intramolecular Pd(II)/ Cu(II)-catalysed *bis*-alkoxylation sequence has been utilized for the construction of the furanoside skeleton of varitriol. Furthermore, diol **49** was treated with PdCl₂ (0.1 equiv.), CuCl₂ (3 equiv.), and NaOAc (3 equiv.) in AcOH as buffer at room temperature to give bicyclic dihydro-alditol **50** in good yield with excellent threo-diastereoselectivity. Next crucial step involves the opening of less substituted ring of bicyclic skeleton. This was accomplished by reaction of dihydro alditol with TBAI/ TMSCl/ HCl in CH₂Cl₂ at room temperature for 3 days to furnish iodofuran derivative **51** which was earlier used as a intermediate for the synthesis of varitriol (+)-**5**. This completed the formal synthesis of (+)-varitriol from commercially available bisacetone-D-glucose.

Ram Rao and co-workers has accomplished the synthesis of (+)-varitriol *via* two approaches using the commercially available D-(-)-ribose and ethyl (*S*)-lactate (Scheme 9 and 10) [37]. The synthesis of furanoside part of varitriol is began with Grignard reaction of MeMgI with 2,3-*O*-isopropylidene-D-ribofuranose **82**. The oxidative cleavage of diol with NaIO₄ gave lactol, which on Wittig olefination using carboethoxymethylenetriphenyl phosphorane afforded α,β -unsaturated ester **84** with predominant *Z*-selectivity (*Z/E*, 2:1). This was easily separated by silica gel column chromatography. The *Z*-ester **84** on reduction with DIBAL provided allyl alcohol **86** followed by epoxidation with *m*-CPBA gave

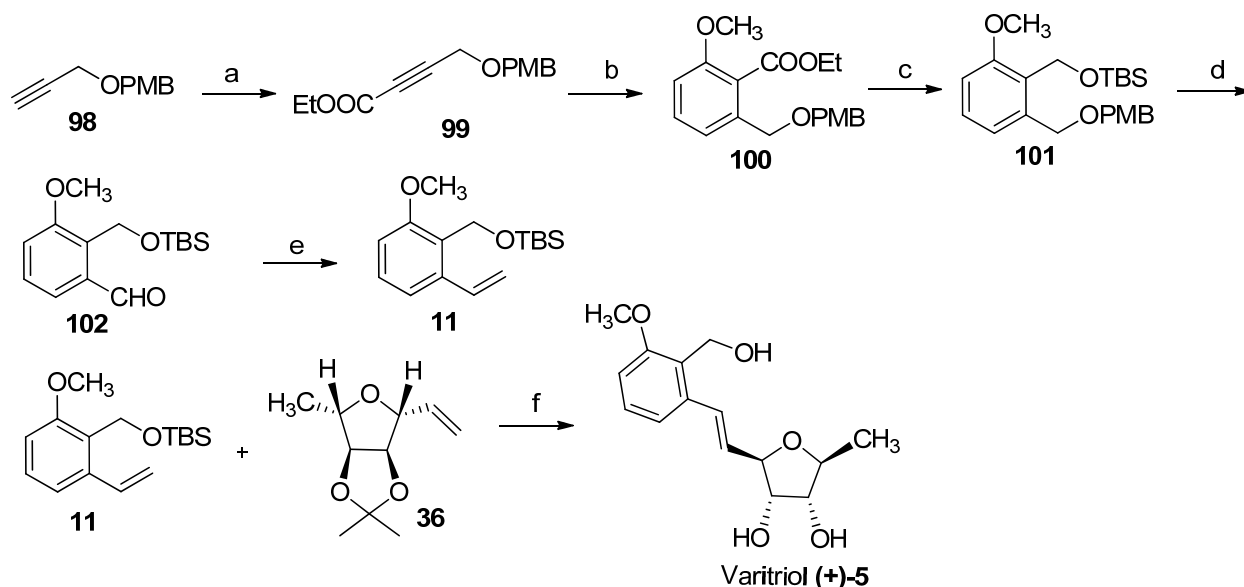
epoxide which was converted to cyclic diols **87** and **88** during chromatographic purification. The diol **87** with required stereochemistry of varitriol was used as a key intermediate for cross metathesis reaction at final stage of the reaction.



Scheme 9. Reagents and conditions: (a) CH_3MgI , Et_2O , 0°C to rt, 3 h, 71%; (b) 1) NaIO_4 , $\text{THF}/\text{H}_2\text{O}$ (9:1), 0°C to rt, 3 h, 77%, 2) $\text{Ph}_3\text{P}=\text{CHCOOEt}$, *cat.* PhCOOH , toluene, 90°C , 4 h, 65%; (c) 1) DIBAL, CH_2Cl_2 , 0°C , 3 h, 75%, 2) *m*-CPBA, CH_2Cl_2 , 0°C to rt, 24 h, 27.5% each isomer; (d) 1) $(\text{CF}_3\text{CH}_2\text{O})_2(\text{P}=\text{O})\text{CH}_2\text{COOCH}_3$, NaH , THF , -78°C , 3 h, 77%, 2) DIBAL, CH_2Cl_2 , 0°C , 2 h, 85%; (e) 1) $(\text{COCl})_2$, DMSO , Et_3N , CH_2Cl_2 , -78°C , 1 h, 80%, 2) $\text{Ph}_3\text{P}=\text{CHCOOEt}$, benzene, rt, 6 h, 78%, 3) DIBAL, CH_2Cl_2 , 0°C , 4 h, 82%; (f) (-)-DET, $\text{Ti}(\text{OiPr})_4$, cumene hydroperoxide, CH_2Cl_2 , -20°C , 3 h, 75%; (g) 1) TBAF, THF , 0°C to rt, 24 h, 2) *cat.* CSA, CH_2Cl_2 , rt, 6 h, 68%; (h) 1) TBSOTf, 2,6-

lutidine, CH₂Cl₂, 0 °C to rt, 12 h, 72%, 2) OsO₄, NMO, acetone:H₂O (4:1), 0 °C, 15 h, 70%; (i) 2,2-dimethoxypropane, *cat.* CSA, acetone, 6 h, 85%; (j) TBAF, THF, rt, 12 h, 68%; (k) PPh₃, imidazole, toluene, 50 °C, 30 min, 75%.

Since the key intermediate for cross metathesis reaction formed from D-ribose gave product only in 27.5% yield, an alternative approach has been developed for the synthesis of furanoside moiety starting from ethyl (*S*)-lactate. The protected lactaldehyde **89** was subjected to olefination reaction using Still-Gennari procedure [38-39] to afford corresponding α,β -unsaturated ester with *Z*-selectivity which upon DIBAL reduction gave allylic alcohol **90**. The Swern oxidation of alcohol to aldehyde followed by Wittig reaction with stabilized phosphorane (*trans* selectivity) and then DIBAL reduction furnished alcohol **91**. The Sharpless epoxidation of allyl alcohol and silyl deprotection using TBAF generated dihydrofuran as major product **93a** along with its isomer **93b** in minor amount (75:25). The small amount of uncyclic product was also converted to corresponding dihydrofurans by treating with CSA. The diol **93a** was protected with TBS and subjected to dihydroxylation with OsO₄ in the presence of NMO giving mixture of diol **94** with maximum diastereoselectivity (95:5). The reason for higher diastereoselectivity was attributed to the bulkiness of TBS substituent leading to approach of OsO₄ from the more sterically accessible top face. This observation was also proved by changing the acetonide as protecting group instead of TBS with 70:30 diastereoselectivity of diol.

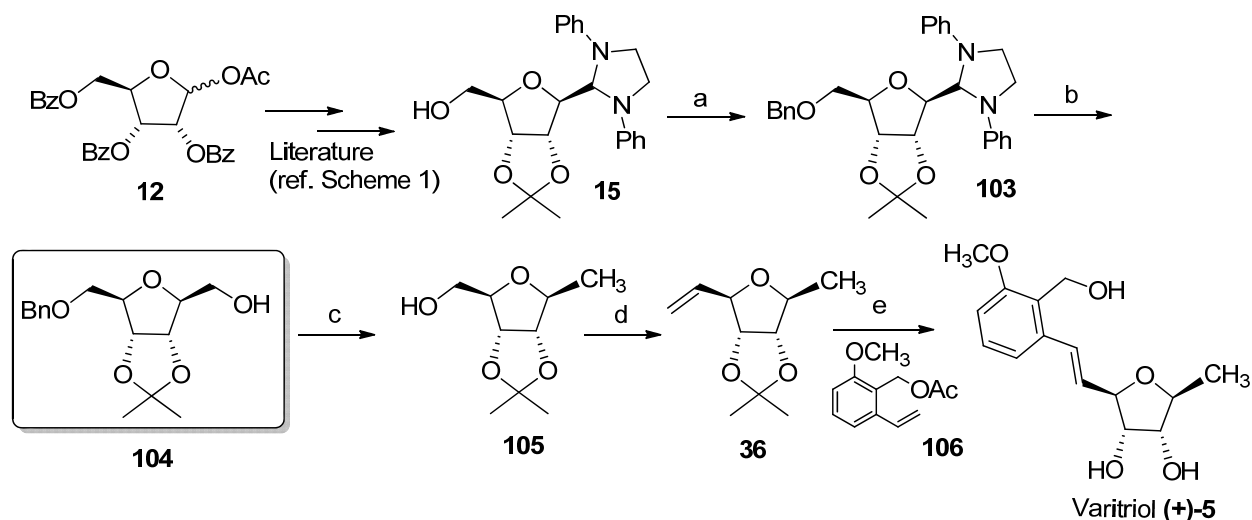


Scheme 10. Reagents and conditions: (a) *n*-BuLi, ClCOOEt, THF, -78 °C to rt, 45 min, 92%; (b) 1-methoxycyclohexa-1,4-diene, dichloromaleic anhydride, neat, 180 °C, 7 h, 75%; (c) 1) DIBAL, CH₂Cl₂, 0 °C, 4 h, 85%, 2) TBDMSCl, imidazole, DMAP, CH₂Cl₂, 0 °C to rt, 4 h, 90%; (d) 1) DDQ, CH₂Cl₂/

buffer pH = 7 (18:2), 0 °C to rt, 2 h, 72%, 2) Dess Martin periodinane, CH₂Cl₂, 0 °C to rt, 1 h, 87%; (e) *n*-BuLi, PPh₃CH₃Br, THF, 0 °C to rt, 2 h, 70%; (f) 1) Grubbs IInd generation catalyst, CH₂Cl₂, reflux, 18 h, 55%, 2) 1M HCl, THF, rt, 3 h, 70%.

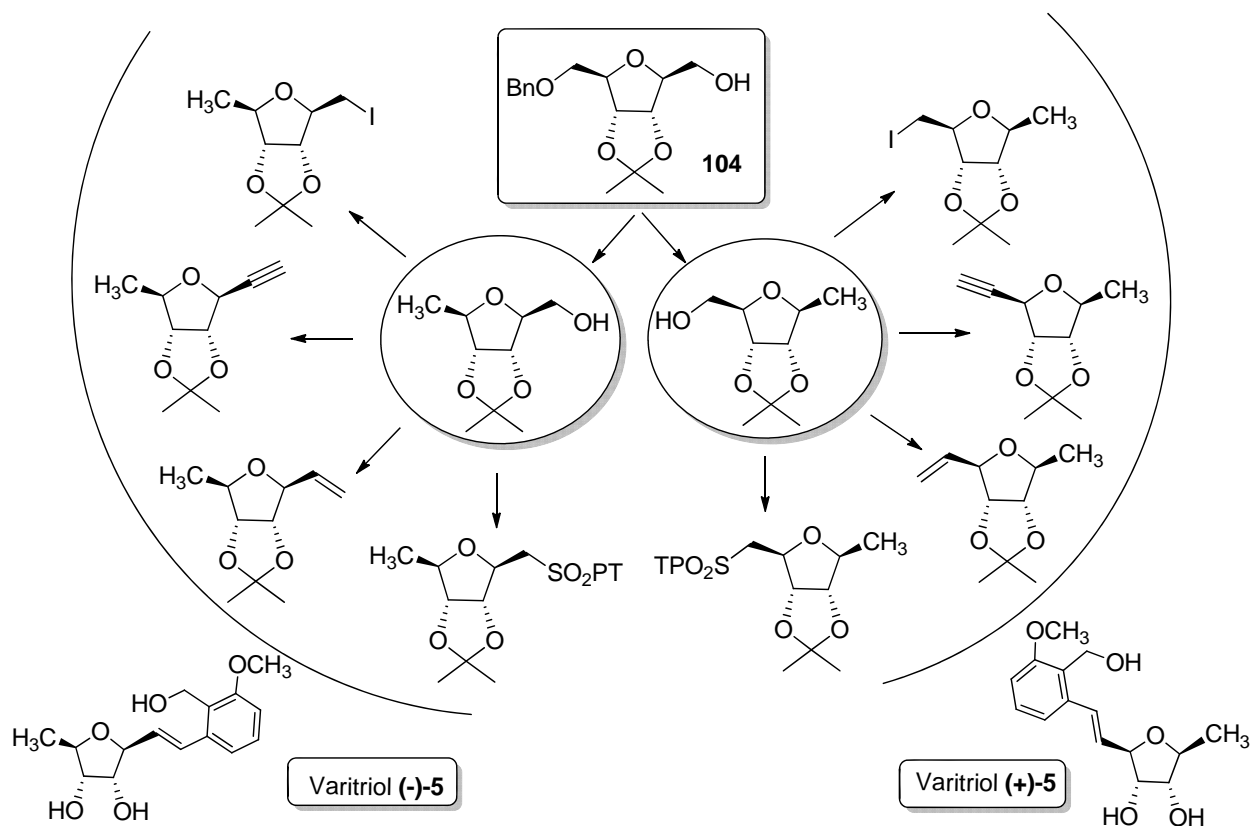
In the end, the furanoside skeleton **36** containing double bond required for metathesis reaction was prepared by treatment of diol (**87**, **97**) with PPh₃, imidazole and iodine in toluene at 50 °C. The second part involves the synthesis of aromatic moiety containing double bond for coupling reaction. Towards this, the PMB protected propargyl ether **98** was converted to substituted acetylene **99** by deprotonating acetylenic proton with *n*-BuLi followed by quenching with ethylchloro formate. The required 1-methoxy cyclohexa-1,4-diene was prepared from anisole by Birch reduction [40-41], which was treated with dienophile in the presence of *cat.* amount of dichloromaleic anhydride in a sealed tube at 150 °C for 7 h to give substituted anisole **100**. The protected anisole **101** was prepared by reduction of ester group to alcohol using DIBAL followed by TBS protection. The PMB deprotection using DDQ gave alcohol, which on Dess Martin periodinane (DMP) oxidation and Wittig olefination with Ph₃PCH₃Br afforded aromatic fragment **11**. Lastly, the two fragments *i.e* furanoside moiety **36** and aromatic part **11** was treated with the Grubbs second generation catalyst in CH₂Cl₂ to provide protected varitriol. The deprotection of TBS and acetonide group with 1N HCl/THF gave varitriol (+)-**5**. The construction of furanoside side chain using highly diastereocontrolled routes *via* epoxidation, cyclization and dihydroxylation as well as Diels Alder approach to prepare aromatic moiety is the highlight of this work.

Nagarapu and coworkers demonstrated the simple and efficient route for varitriol (+)-**5** using D-ribose as starting material wherein symmetrical diol with mono alcohol protection as an advance intermediate (Scheme 11) [42]. This intermediate is considered as a key furanoside building block for the synthesis of (+) and (-)-varitriol and their analogues. The synthesis commenced with the benzyl derivative of D-ribose followed by utility of Jennings's synthetic approach to give alcohol **15**. Alcohol **15** was protected as its benzyl ether by treatment with benzyl bromide to give furanoside **103**. Hydrolysis with PTSA followed by NaBH₄ gave symmetrical diol **104** with monobenzyl protection.



Scheme 11. Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C to rt, 4 h, 91%; (b) 1) PTSA, acetone, rt, 15 min, 2) NaBH₄, MeOH, rt, 2 h (75%, 2 steps); (c) 1) TsCl, pyridine, rt, 12 h then LiAlH₄, THF, 75 °C, 91%, 2) liq. NH₃, Na, -78 °C, 30 min, 72%; (d) 1) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h, 2) PPh₃CH₃Br, *t*-BuOK, THF, 0 °C to rt, 4 h, (18%, 2 steps); (e) 1) Grubbs IInd generation catalyst, CH₂Cl₂, reflux, 18 h, 45%, 2) 1M HCl, THF, rt, 3 h, 81%, 3) K₂CO₃, MeOH, rt, 1 h, 81%,

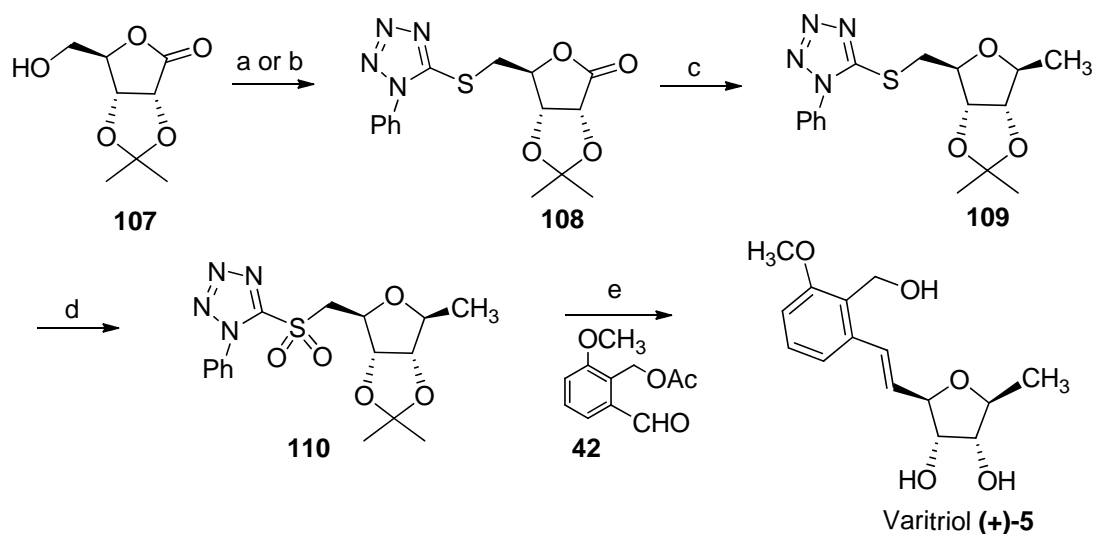
Tosylation and LiAlH₄ reduction in tandem fashion with further debenzoylation using Na/liq. NH₃ afforded alcohol **105**. Swern oxidation of alcohol to aldehyde followed by Wittig olefination with Ph₃P=CH₂ (insitu generated) allowed introduction of additional one carbon fragment leading to the synthesis of alkene **36** for the furanoside part of varitriol (+)-**5**. The substituted styrene **106** prepared using reported procedure [27] when subjected to cross metathesis with the furanoside moiety using Grubbs IInd generation catalyst followed by subsequent deprotection of acetonide and acetate group resulted in varitriol (+)-**5** in 30% overall yield. In brief, this method involves the preparation of monoalcohol protected symmetrical diol as an advance intermediate. The interesting part of this intermediate is the presence of alcohol group on either side that can be converted into number of other functional group by using simple synthetic manipulation making it very useful building block for the preparation of varitriol and its analogues (Scheme 12). In the previous report by Jenning towards the synthesis of varitriol (-)-**5** from D-ribose, the methyl group on the furanoside unit was obtained by deoxygenating at C-5 carbon of D-ribose. Whereas, Nagarapu's approach towards varitriol (+)-**5** from D-ribose involving the preparation of symmetrical diol *via* methylation at C-1 carbon of D-Ribose. In fact, D-ribose has become a useful template for the synthesis of both enantiomers of varitriol.



Scheme 12. Symmetrical diol as advance intermediate: possible synthetic approaches to varitriol (+)-**5** & (-)-**5** and their analogues

Gracza and coworkers reported a short and efficient synthesis of varitriol (+)-**5** starting from commercially available γ -D-ribonolactone **107** via diastereoselective introduction of methyl group at C-1 and the sulfonyl moiety at C-5 carbon of starting block (Scheme 13) [43]. The nucleophilic displacement of primary hydroxyl group of γ -D-ribonolactone **107** with 1-phenyl-1*H*-tetrazole 5-thiol (PTSH) using the Mitsunobu condition [44-45] gave sulfide **108** which was used in the next step prior to purification. The alternative two step approach for sulfide was also developed via mesylation of primary hydroxyl of ribonolactone followed by displacement using potassium thiolate. The introduction of *exo* methyl group was crucial step of this synthetic protocol. A three step sequence for stereoselective incorporation of the *exo* methyl group at C-1 was achieved via reduction of lactone to lactol using DIBAL at $-50\text{ }^{\circ}\text{C}$, followed by acylation using acetic anhydride and 4-DMAP at $0\text{ }^{\circ}\text{C}$. The final reaction with trimethylaluminium and subsequent purification on silica gel column afforded exclusively desired

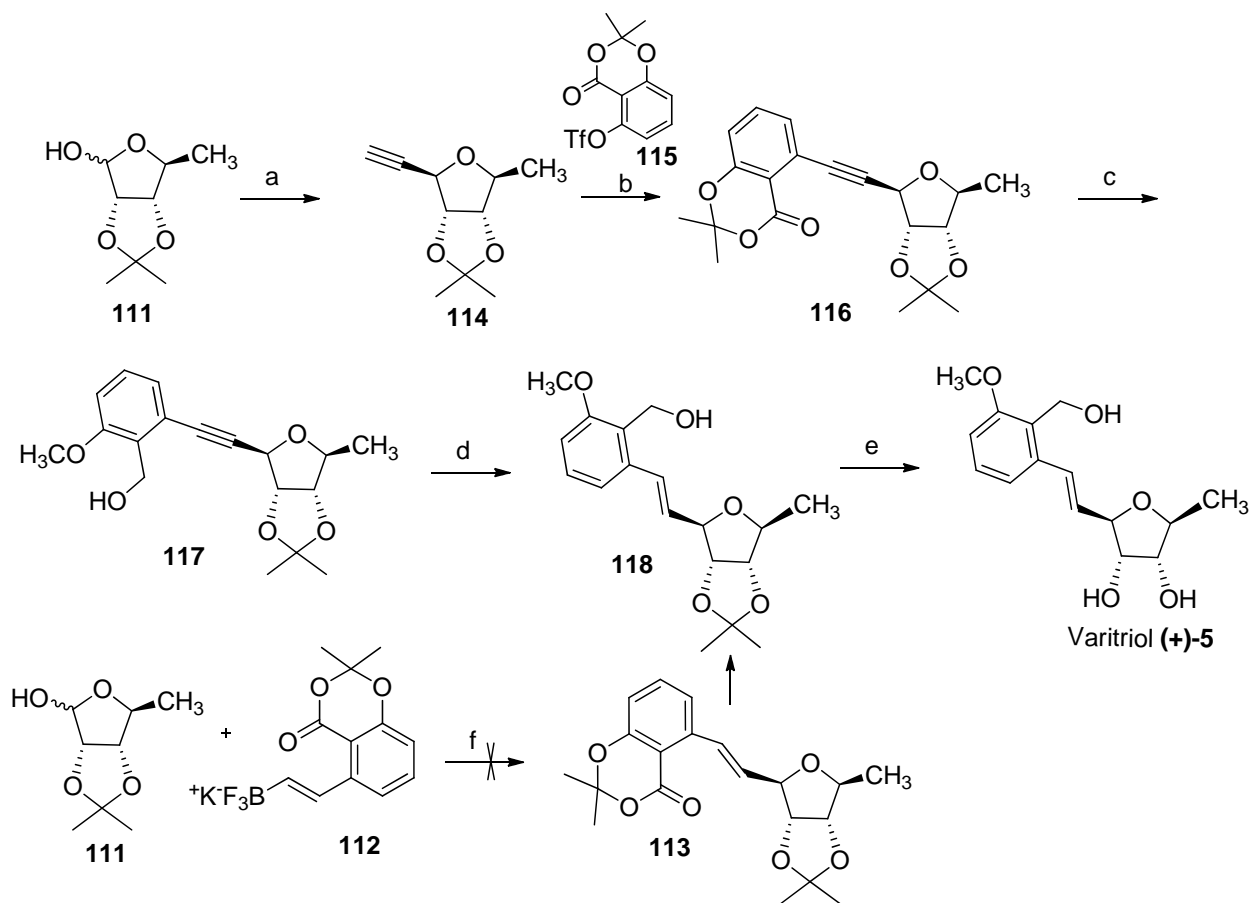
exo-methylated sulfone **109** which was confirmed by ^1H NMR. The excellence of this method lies in the high stereoselectivity in C-C bond formation.



Scheme 13. Reagents and conditions: (a) PTSH, PPh_3 , DIAD, THF, $0\text{ }^\circ\text{C}$, 1 h; (b) 1) MsCl, pyridine, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to rt, 2 d, 79%, 2) KSPT, DMF, rt, 8 h, 65%; (c) 1) DIBAL, THF, $-50\text{ }^\circ\text{C}$, 8 h, 2) Ac_2O , DMAP, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 12 h, 3) Me_3Al , CH_2Cl_2 , $-30\text{ }^\circ\text{C}$ to $-18\text{ }^\circ\text{C}$, 6 d (70%, 3 steps); (d) Mo(VI)/ H_2O_2 , THF, EtOH, rt, 24 h, 91%; (e) 1) KHMDS, DME, $-55\text{ }^\circ\text{C}$ to rt, 10 h, 2) NaOMe, MeOH, rt, 4 h, 3) HCl, THF, rt, 4 h, (64%, 3 steps).

Oxidation of sulfide using H_2O_2 -ammonium molybdate gave sulfone **110**. The crucial Kocienski-Julia olefination of aromatic aldehyde **42** with sulfone **110** (furanoside fragment) employing hexamethyldisilazamide in 1,2-dimethoxyethane yielded olefin ($E/Z = 6:1$). At the end, deprotection using sodium methoxide and then HCl in THF furnished varitriol (+)-**5**. Thus, the synthesis of varitriol (+)-**5** was achieved from γ -D-ribonolactone and dimethyl anisole in 8 steps and 41% overall yield.

Recently, Liu and coworkers have developed a mild, stereoselective and concise approach to access alkynyl and alkenyl C-glycosides *via* cross-coupling of potassium organofluoroborates with glycosyl fluoride and demonstrated its applicability in total synthesis of varitriol (+)-**5** in only 7 steps (Scheme 14) [46].

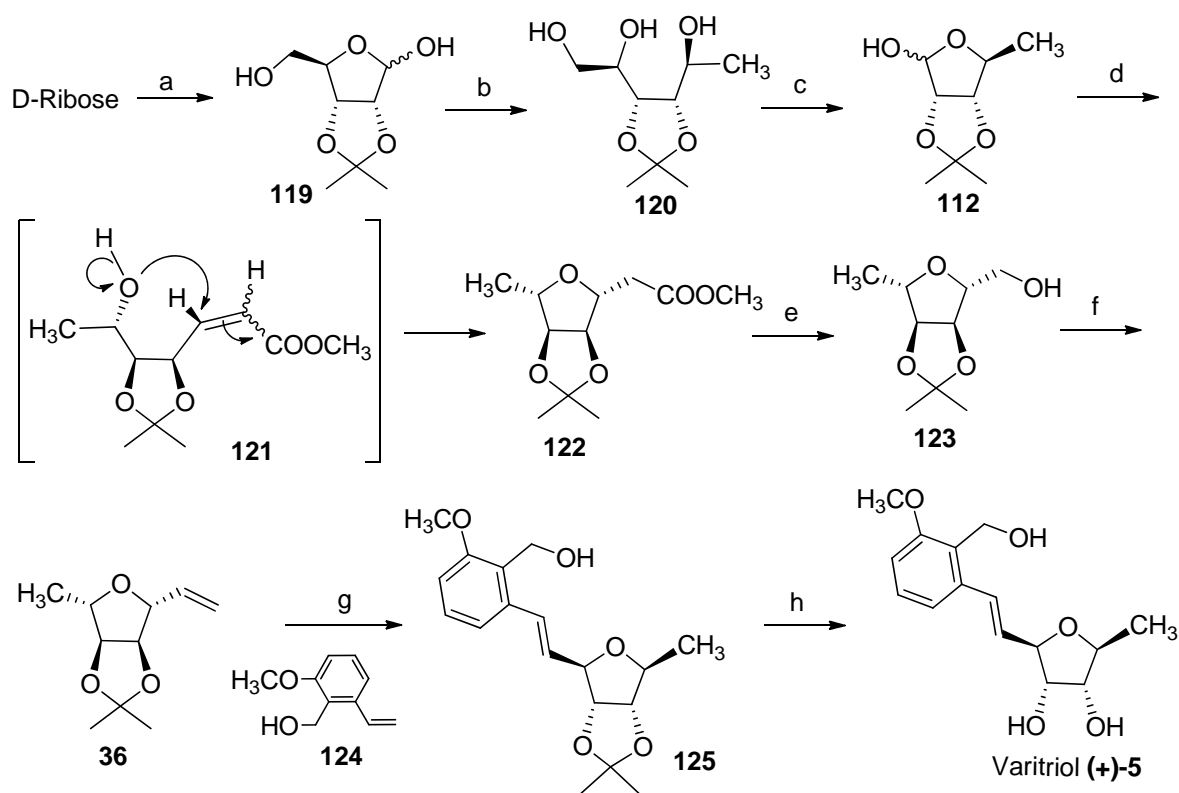


Scheme 14. Reagents and conditions: (a) 1) DAST, 2) $\text{BF}_3 \cdot \text{OEt}_2$, $\text{CH}=\text{C}-\text{BF}_3 \cdot \text{K}^+$ (65%, 2 steps); (b) Aromatic triflate, $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, CuI , 91%; (c) 1) LiAlH_4 , THF, 2) CH_3I , K_2CO_3 , (83%, 2 steps); (d) Red-Al (89%); (e) 1) 1M HCl, 2) silica column (93%, 2 steps); (f) $\text{BF}_3 \cdot \text{OEt}_2$.

The synthesis started with tetrahydro furan derivative which had been previously reported by Yadav and coworkers [47] was subjected to fluorination using DAST. The method developed [48] for C-glycosides using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and organotrifluoro borate has been extended initially for coupling of glycosyl fluoride and alkenyl trifluoroborate **112** containing aromatic ring without any success of getting desired product **113**. Furthermore, this problem of coupling reaction was overcome by replacing alkenyl trifluoroborate with ethynyl trifluoroborate. The coupling of glycosyl fluoride with ethynyl trifluoroborate gave ethynyl substituted furan moiety **114**, which was subsequently subjected to Sonogashira cross coupling reaction with aromatic triflate **115** leading to the formation of internal alkyne **116**. The reduction of ester group followed by selective protection of generated phenol group with iodomethane gave alkyne **117**. Next, the double bond was generated by chemoselective reduction

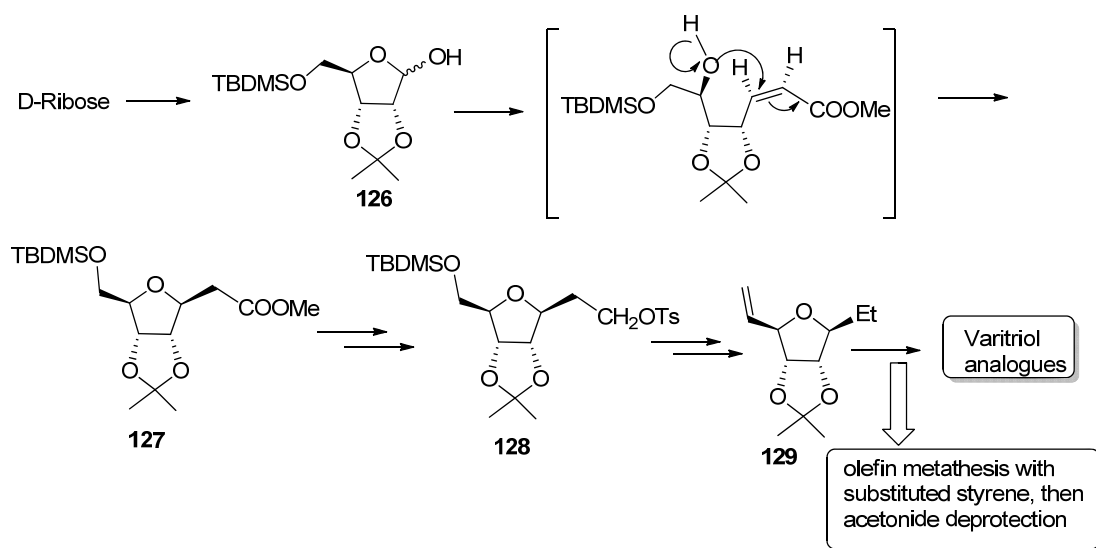
of triple bond using Red-Al to give alkene **118** ($E/Z = 2.8:1$) in 89% yield. During acetonide deprotection using 1N HCl followed by flash chromatography on silica gel, all the Z -isomer was exclusively transformed to the E -isomer to furnish varitriol (+)-**5** in 8 steps and 41% yield.

Recently, tandem strategies employing Wittig olefination in combination with many other reactions has been widely utilized in organic syntheses, particularly natural product syntheses which have been well reviewed by Parvatkar *et al.* [49]. Shaw and coworkers has disclosed an efficient route for their second generation synthesis of varitriol (+)-**5** from D-ribose wherein THF moiety was constructed *via* one-pot Wittig olefination and highly diastereoselective intramolecular oxa-Michael addition approach (Scheme 15-16) [50].



Scheme 15. Reagents and conditions: a) 2,2-dimethoxypropane, acetone, PTSA, 0 °C, 2 h, 90%; b) CH_3MgBr , -50 °C to rt, 12 h; (c) NaIO_4 , THF- H_2O , 4 h, rt (64%, 2 steps); (d) $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$, CH_3CN , 110 °C, 2 h then K_2CO_3 , rt, 4 h, 91%; (e) LiAlH_4 , dry THF, 0 °C to rt, 2 h, 91%; (f) 1) TsCl , Et_3N , dry CH_2Cl_2 , 0 °C to rt, 4 h, 96%, 2) $t\text{BuOK}$, dry THF, -20 °C to rt, 12 h, 85%, (g) 1) Grubbs IInd generation catalyst (6 mol%), dry CH_2Cl_2 , 50 °C, 32 h, 62%, 2) 1N HCl, THF, rt, 6 h, 90%.

This synthetic approach involves construction of two subunits which has been coupled together at final stage to give varitriol. Synthesis of tetrasubstituted THF subunit was started from D-ribose which on acetonide protection gave 2,3-*O*-isopropylidene-D-ribose **119** [51]. The Grignard reaction of 2,3-*O*-isopropylidene-D-ribose with an excess of methyl magnesium bromide at -50 °C to room temperature afforded triol **120** which on oxidative cleavage with NaIO₄ furnished known lactol **112** [47]. Lactol **112** was treated with triphenylphosphoranylidene acetate at reflux temperature in acetonitrile with intension of the intramolecular oxa-Michael addition to construct functional THF derivative **122**. However, the cyclization was not complete even after refluxing for 12 h. And hence, after Wittig reaction (2 h, 110 °C), K₂CO₃ was added in same vessel and stirred at room temperature for 4 h to give cyclized product with high diastereoselectivity (>99%). The NOE experiment of this product confirmed the presence of the requisite stereochemistry that is required for the varitriol (+)-**5**. Furthermore, the furan ester **122** on LiAlH₄ reduction furnished alcohol **123** which on tosylation followed by subsequent treatment with *t*-BuOK afforded the vinyl furanoside **36** in good yield. Previously it has been observed that, this furanoside requires special care in handling during work up and purification (below 30 °C), as vinylic furanoside is slightly volatile. The second part of synthesis involves the construction of substituted styrene from commercially available phenolic acid (Scheme 3). Isopropylidene protection between phenolic hydroxyl and COOH, followed by *O*-protection using triflic anhydride gave corresponding triflate. The Stille cross coupling of triflate with tributylvinyl tin (TBVT) in the presence of Pd(PPh₃) and lithium chloride, followed by LiAlH₄ reduction gave diol. This on selective methylation of phenolic hydroxyl afforded styrene derivative **124**. The cross metathesis coupling of styrene derivative **124** with vinylic furanoside **36** in the presence of Grubbs second generation catalyst in refluxing CH₂Cl₂ furnished exclusively *E*-isomer **125**. Finally, acetonide deprotection using aq. HCl gave varitriol (+)-**5**. Furthermore, author has utilized the above strategy for the preparation of higher analogues of natural varitriol (+)-**5** for their biological screening. Two modifications in varitriol skeleton employed includes: 1) replacement of methyl group in natural varitriol by ethyl group keeping aromatic part same, and 2) modification in the aromatic part.



Scheme 16. Approach for varitriol analogues

The synthesis was initiated using D-ribose as starting material (Scheme 16). The one-pot Wittig olefination-oxa-Michael addition is the crucial step to prepare symmetrical furanoside with different protecting group (OTBS, OTs). The vinylic furanoside containing ethyl group was prepared using straightforward synthetic manipulation, wherein, ethyl group was introduced by LiAlH_4 reduction of tosylate. While, the vinyl group was introduced *via* TBS deprotection, alcohol oxidation and Wittig olefination sequence. Finally, efforts have been made to synthesize different varitriol analogues **130a-j** by coupling of vinylic furanoside **129** with different substituted styrene in the presence of Grubbs second generation catalyst.

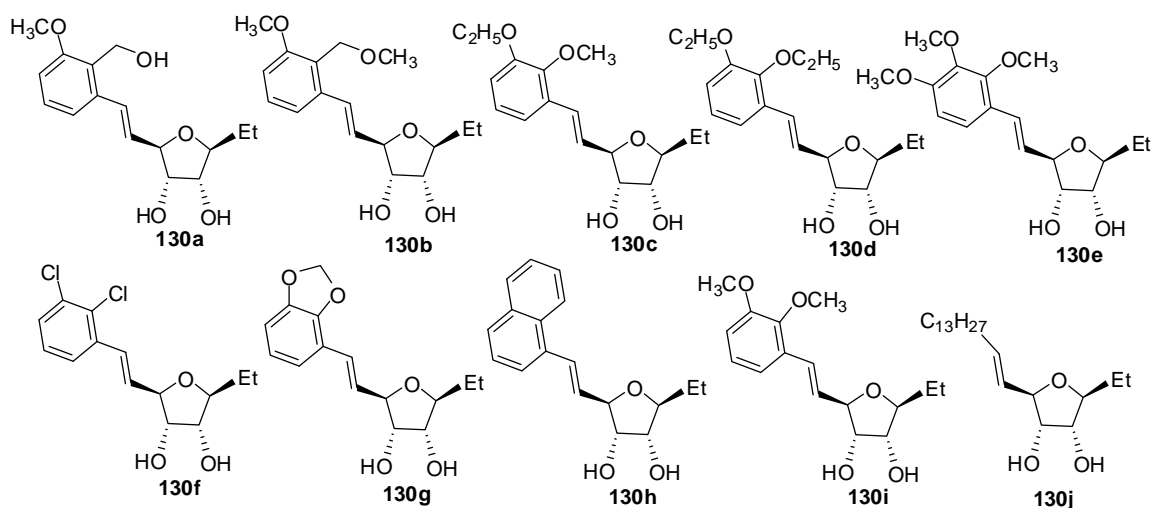
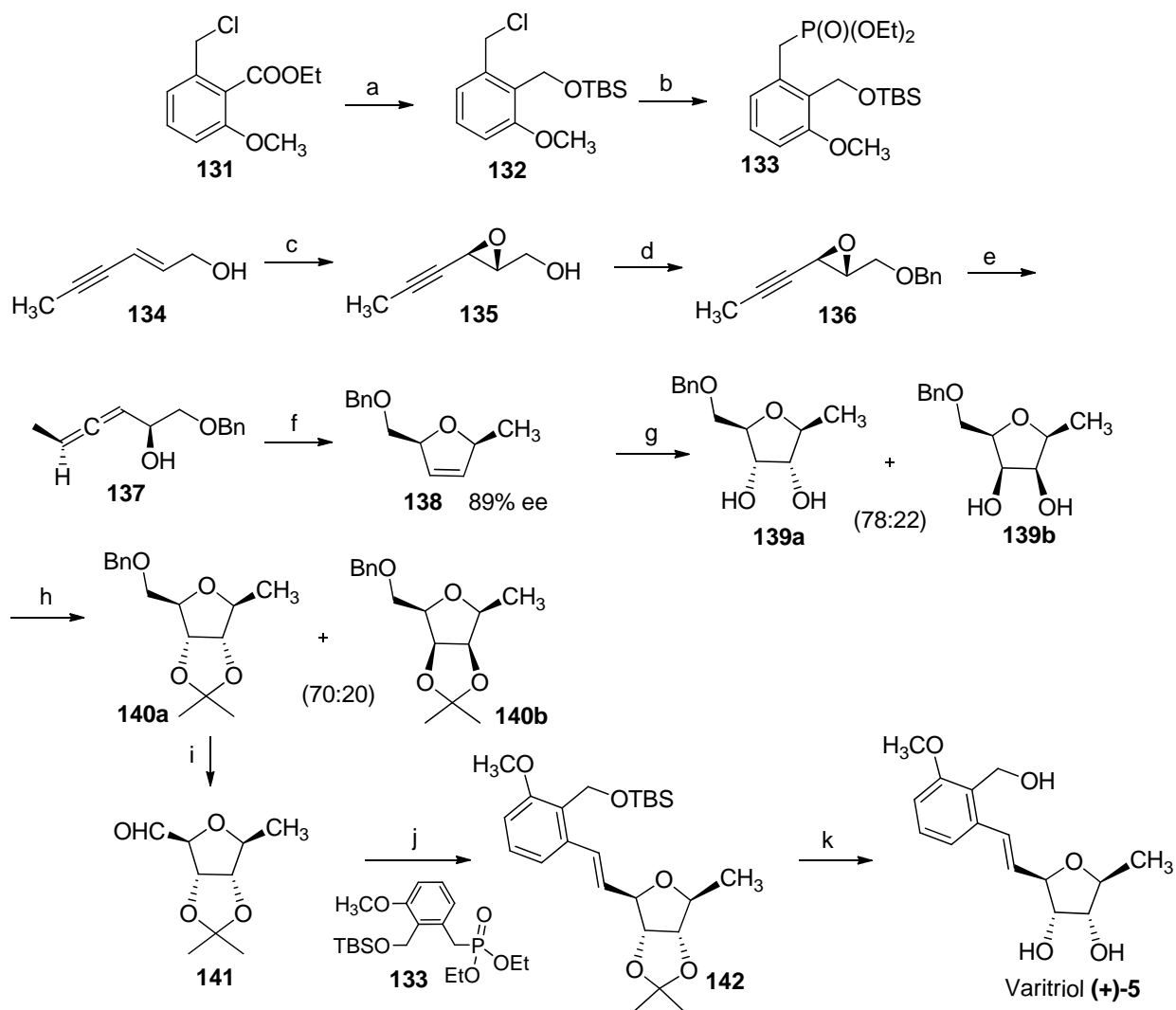


Figure 3. Varitriol analogues *via* olefin cross metathesis and acetonide deprotection.

The synthetic varitriol analogues **130a-j** were screened against different cell lines [KB (Oral squamous cell carcinoma), C-33A (Cervical cancer), MCF-7 (Breast cancer), A-549 (Lung carcinoma), NIH/3T3 (Mouse embryo fibroblast) cell lines] but unfortunately, they did not show any significant cytotoxicity ($IC_{50} > 20$ mM) against any of these cell lines.



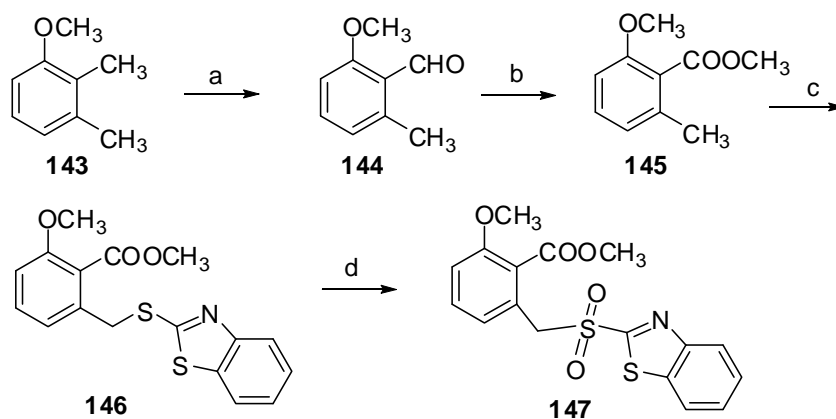
Scheme 17. Reagents and conditions: (a) 1) DIBAL, toluene, 97%, 2) TBSCl, imidazole, DMF, 96%; (b) P(OEt)₃, reflux, 96%; (c) *t*-BuOOH, Ti(Oi-Pr), D-(-)-DET, CH₂Cl₂, -23 °C, 3 days; (d) NaH, BnBr, *n*-Bu₄Ni (47%, 2 steps); (e) CuCl, *t*-BuONa, SIMes.HCl, PMHS, toluene, 0 °C to rt, 15 h, workup: HF-pyridine, 78%; (f) AuCl₃, THF, 0 °C, 2 h, 82%; (g) K₂OsO₂(OH)₄, (DHQD)₂PYR, K₃Fe(CN)₆, CH₃SO₂NH₂, NaHCO₃, Na₂CO₃, *t*-BuOH/H₂O (1:1), 0 °C, 46 h, 98%; (h) Me₂C(OCH₃)₂, PPTS, 91%;

(i) 1) Pd/C, H₂ (1 bar), THF, rt, 2 h, 2) DMP, CH₂Cl₂, rt, 19 h; (j) 1) *n*-BuLi, THF, 0 °C, 15 min, 2) benzyl phosphonate at 0 °C, rt, 1 h, 50 °C, 15 h, (40%, 3 steps); (k) 1M HCl, THF, rt, 26 h, 78%.

Norbert and coworkers designed the synthesis of (+)-varitriol *via* reagent-controlled introduction of all stereogenic centers using combined coinage metal catalyst approach [52]. Horner-Wadsworth-Emmons (HWE) olefination of the aromatic phosphonate with chiral furanoside aldehyde is the key step for varitriol synthesis (Scheme 17). The aromatic phosphonate required for HWE olefination in the later part of synthesis has been prepared using the Kamikawa's procedure [53]. Accordingly, ethyl-6-chloromethyl-2-methoxy benzoate **131** was subjected to reduction and the resultant alcohol was protected with TBSCl leading to the formation of substituted benzyl chloride **132**. The Arbuzov reaction of benzyl chloride with triethyl phosphite gave aromatic phosphonate **133**. The synthesis of furanoside moiety commenced with enyne **134** which on catalytic Katsuki-Sharpless epoxidation with D-(-)-DET at -23 °C for 3 days provided epoxide **135** in 91% ee. The crude product obtained after workup with ferrous sulfate and tartaric acid was subjected to benzylation to give propargyl oxirane **136**. The NHC-stabilized copper hydride chemistry was utilized to convert propargyl oxirane into α -hydroxy allene **137**. In the past, this research group has developed stereoselective synthesis and transformation of functionalized allenes to corresponding five or six membered heterocycles (wherein gold catalyzed cycloisomerization of allenes containing hydroxyl, amino or thiol group in α or β -position) [54-56]. The application of these coinage metals catalysts were nicely demonstrated for the synthesis of chiral furan moiety with stereocenters identical to varitriol. Towards this, α -hydroxy allene **137** was treated with 1 mol% gold (II) chloride in THF at 0 °C to give 2,5-dihydrofuran **138** with 89% ee. Next, the requisite two chiral centers of varitriol was introduced by reagent control protocol involving Sharpless dihydroxylation of 2,5-dihydrofuran. Alkene **138** was subjected to Sharpless asymmetric dihydroxylation using ligand (DHQD)PYR to give mixture of diol **139a-b** in 78:22 ratio. This mixture **139a-b** was further subjected to acetonide protection using 2,2-methoxypropane and PPTS to give the mixture of bicyclic acetal **140a-b** (70: 21 ratio) which was separated by column chromatography. The stereochemistry of the two diastereomers **140a-b** was confirmed by NOESY experiment. The bicyclic acetal with requisite stereochemistry of varitriol was converted to tetrasubstituted furan aldehyde **141** *via* debenylation and Dess- Martin periodinane oxidation. Subsequently, aldehyde **141** was treated with the aromatic phosphonate in the presence of *n*-BuLi and then heated at 50 °C for 15 h to give exclusively

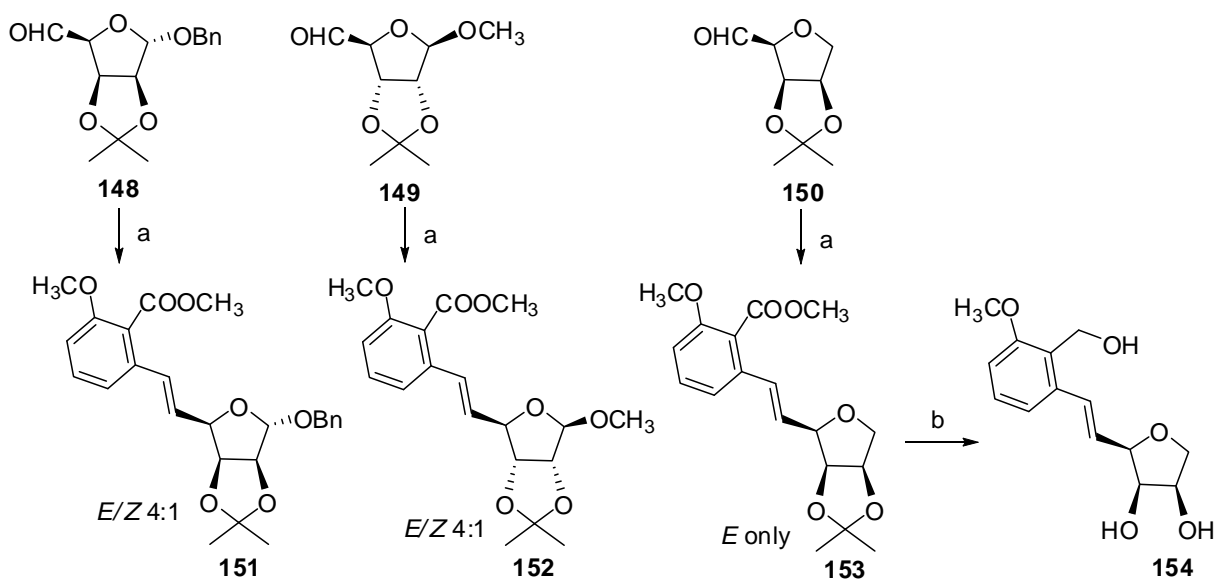
E-alkene **142** in 40% yield. Finally, deprotection of acetonide and TBS under acidic condition gave varitriol (+)-**5**. Moreover, the utility of this method has been demonstrated for the synthesis of the seven analogues of varitriol. Similarly, the different aromatic phosphonates prepared using Arbuzov reaction of substituted benzyl halide followed by HWE-olefination with different tetrasubstituted furanoside aldehyde gave different analogues of varitriol.

The synthesis of closely related analogues of varitriol *via* Julia olefination of aromatic sulfone with furanoside aldehyde has been accomplished by Senthilmurugan and Aidhen (Scheme 18-19) [57]. This approach towards varitriol represents an efficient and new **method** for preparation of aromatic sulfone (aromatic moiety of varitriol). The aromatic moiety present in varitriol skeleton was prepared using regioselective oxidation of C-2 methyl group of 2,3-dimethyl anisole **143** using $K_2S_2O_8$ [58]. The subsequent oxidation of aldehyde to acid using $CuBr/tBuOOH$ followed by esterification gave compound **145**. The benzylic bromination using NBS and reaction with 2-mercaptobenzothiazole/ K_2CO_3 afforded sulfide **146**. The oxidation of sulfide with 30% H_2O_2 in the presence of sodium tungstate gave sulfone **147** which has been employed in the final stage for Julia olefination reaction.



Scheme 18. Reagents and conditions: (a) $K_2S_2O_8$, $CuSO_4 \cdot 5H_2O$, CH_3CN/H_2O , reflux, 0.5 to 1 h, 75%; (b) 1) $CuBr$, 70% $tBuOOH$, CH_3CN , rt, 80%, 2) Me_2SO_4 , DBU, acetone, reflux, 90%; (c) 1) NBS, CCl_4 , AIBN, reflux. 2) 2-mercaptobenzothiazole, K_2CO_3 , acetone, reflux, 10 h (60%, 2 steps); (d) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2 , MeOH, 0 °C to rt, 6 h, 70%.

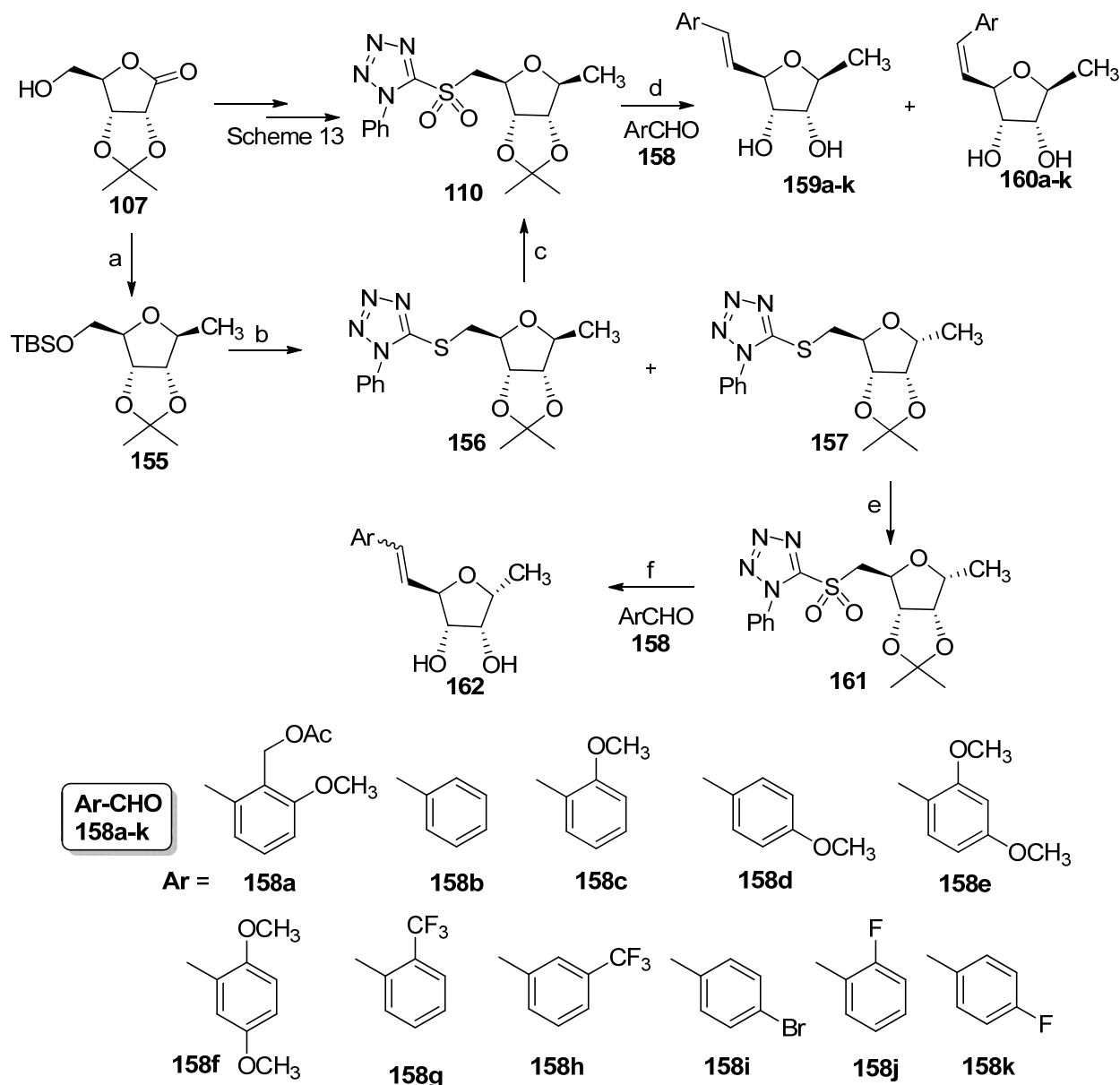
With the intension of synthesizing (+)-varitriol analogues by maintaining the aromatic part identical as required in natural product, sulfone **147** was treated with different aldehydes containing furanoside ring in the presence of NaH to give corresponding olefin **151-153**. The reduction of ester group of **153** followed by acetamide deprotection afforded varitriol analogue **154**.



Scheme 19. Reagents and conditions: (a) **147**, NaH, DMF, 0 °C to rt, 30 min, 1 h (67-77%); (b) 1) LiAlH₄, THF, 0 °C, 30 min, 2) 1M HCl, 4 h, rt (62%, 2 steps)

The most recent work by Gracza and co-workers demonstrated their second generation approach (analogous to earlier report) employing Julia–Kocienski olefination for the synthesis of new analogues of (+)-varitriol (Scheme 20) [59]. The key intermediate sulfone **110** was prepared from D-ribonolactone employing previously reported strategy (discussed in Scheme 13). Also, author has realized the importance of changing strategy for the rapid access to key intermediate **110** and **161** (in large scale) to prepare libraries of varitriol analogues for SAR studies. The methyl was introduced to carbonyl lactone in first step followed by installation of phenyltetrazole sulfide moiety. The primary hydroxyl of ribonolactone was protected with *tert*-butylmethylsilyl chloride and then partial reduction of lactone using DIBAL, which on acetylation and subsequent treatment with trimethyl aluminium gave mixture of methylated-THF. These pure diastereomers, after preparative MPLC separation was subjected to

Mitsunobu reaction with phenyltetrazolyl thiol to give corresponding sulfide **156** and **157**, which on oxidation with H₂O₂/ ammonium molybdate afforded required sulfone **110**.



Scheme 20. Reagents and conditions: (a) 1) TBDMSCl, Et₃N, DMAP, DMF, rt, 8 h, 95%; 2) DIBAL, THF, -50 °C, 4 h; 3) Ac₂O, DMAP, CH₂Cl₂, 0 °C to rt, 12 h, 4) Me₃Al, CH₂Cl₂, -30 to -18 °C, 6 d, preparative MPLC, (94% , 3 steps); (b) 1) TBAF, THF, rt, 12 h, (89%), 2) PTSH, PPh₃, DIAD, THF, 0 °C, 1 h, **156** (70%) and **157** (15%); (c) Mo(VI)/H₂O₂, THF, EtOH, rt, 24 h, 91%; (d) 1) KHDMS, DME, -30 °C to rt, 10 h, 2) HCl, THF, rt, 3-12 h; 41-88%; e) Mo(VI)/H₂O₂, THF, EtOH, rt, 24 h, 91%; (f) 1) KHMDS, DME, -30 °C to rt, 10 h, 2) NaOMe, MeOH, rt, 4 h, then HCl, THF, rt, 5 h, 78% overall yield (*E/Z*- mixture in the ratio 5:4).

Further, sulfone **110** was subjected to Julia olefination reaction with excess amount of substituted aldehyde (5 equiv.) to give mixture of *E/Z* olefins which was separated by preparative MPLC. Finally, acetonide deprotection gave series of compounds **159a-k** which were screened for their *in vitro* cytotoxicity towards certain human tumors and cancer cell line panel (Table 1). Furthermore, 2-*epi*-varitriol **162** was prepared from sulfone **161** and tested for its bioactivity. The varitriol molecule (+)-**5** had been modified by substitution in aromatic ring **159** and the geometry of the linker **160**, as well as configuration of furanoside part **162**. The compounds were evaluated for their *in vitro* cytotoxicity against human drug sensitive (CCRF-CEM, K562) versus multidrug resistant leukaemia cell lines (K562-Tax, CEM-DNR-BULK), colon cancer cells with normal (+/+) or inactive (-/-) p53 oncosuppressor (HCT116p53+/, HCT116p53-/-), lung adenocarcinoma (A549), normal foetal lung (MRC-5) and foreskin (BJ) fibroblasts (Table 1).

Table 1. Biological activity of varitriol analogues

Comp.	IC ₅₀ μM ^a								
	CCRF-CEM	A549	K562	K562-Tax	CEM-DNR-BULK	HCT116 p53 +/+	HCT116 p53 -/-	MRC 5	BJ
162	45.3	67	107	85	115	76	104	>166	150
159a	161	>166	>166	>166	153	>166	>166	166	-
160a	121	163	158	>166	132	111	>166	>166	>166
159b	145	>166	>166	>166	151	>166	>166	154	>166
160b	160	>166	>166	>166	149	>166	>166	152	>166
159c	142	>166	>166	>166	154	>166	>166	152	>166
159d	144	>166	>166	147	164	>166	>166	>166	>166
160d	157	>166	>166	153	>166	>166	>166	156	>166
160e	132	>166	149	159	133	140	155	>166	>166
159f	130	>166	155	>166	123	151	160	>166	>166
159g	147	>166	>166	>166	149	>166	>166	152	>166
159h	145	>166	>166	149	>166	154	>166	>166	>166
160h	147	>166	>166	151	135	>166	157	148	>166
159i	146	>166	>166	136	>166	162	150	154	>166

160i	147	>166	>166	148	>166	>166	>166	>166	>166
159j	138	>166	153	>166	141	153	>166	>166	>166
159k	136	>166	>166	>166	143	>166	>166	>166	>166
160k	131	143	142	155	121	158	136	>166	156

^aIC₅₀ values in a 3-day MTT assay. Presented values are averages of at least three independent experiments, where standard deviations were typically within 25% of the average

The configurationally modified varitriol **162** as a mixture of *E/Z*-isomers (in the ratio 5:4) showed the most significant activities against all tested cell lines, whereas varitriol **159a** (*E*-isomer) and its *Z*-analogue **160a** showed much lower activities or were inactive. Interestingly, the difference in the geometry of the linker **159a**, **159h**, **159k** (*E*-isomers) vs **160a**, **160h**, **160k**, caused in general, slightly higher cytotoxic activities of *Z*-isomers (**160a**, **160h**, **160k**). Compounds **159e** (2,4-dimethoxy), **159f** (2,5-dimethoxy), **159i** (4-bromo) showed broad spectrum of activities. Majority of the tested compounds demonstrated the highest activities against human T-lymphoblastic leukaemia cell line CCRF-CEM and its multidrug resistant subline CEM-DNR-BULK overexpressing the multidrug resistant protein 1 (MRP-1), thus showing compounds activity in multidrug resistant cancers. Unexpectedly, the *in vitro* anticancer activity of synthetic varitriol and its analogues were dramatically lower than that reported for natural varitriol by Barrero *et al.* [10], obtained from the tests against RXF 393, TD-47, SNB, DU-145, HL-60, CCRF-CEM, OVCAR-5, SNB-19 and COLO 205 cell lines.

Overall, the synthetic approaches described in this review could be summarized in nutshell as follows (Figure 4 and 5). All synthetic endeavors to varitriol are interrelated and most of them utilize the advantage of chiral centers of carbohydrate to construct functionalized furanoside skeleton as one building block. Second building block is substituted aromatic moiety which has been coupled with furanoside moiety in the final stage of synthesis to give varitriol architect. The key furanoside building blocks are depicted in figure 4.

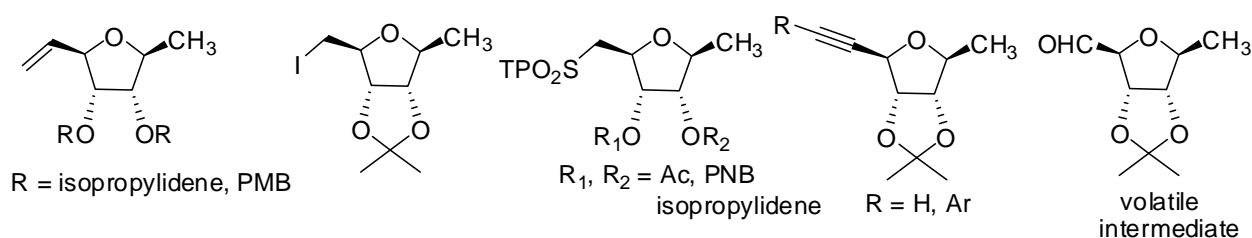


Figure 4. Furanoside building blocks used in the synthesis of varitriol.

Functionalised furanoside part was coupled together with aromatic moiety using either cross olefin metathesis/ HWE olefination/ Julia olefination. The key building blocks consisting of aromatic moiety is depicted in figure 5.

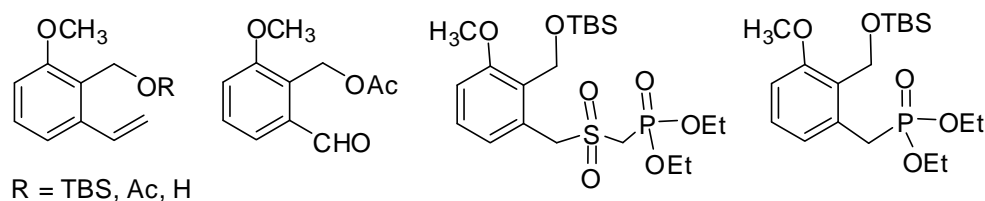


Figure 5. Aromatic building blocks used in the synthesis of varitriol.

OUTLOOK AND FUTURE PRESPECTIVES

Marine-derived biologically active natural products continue to be a source of potentially therapeutic compounds as well as motivation to develop new synthetic strategies for their constructions. The considerable number of synthetic approaches to varitriol has been recently reported in the [literature which has](#) been reviewed in this article. The challenge pose by its structure featuring novel skeleton, the aromatic moiety and the furanoside moiety with four consecutive stereogenic centers, make it an attractive target for synthetic chemists. However, there appear to be few synthetic routes amenable to large scale preparation. It is clear that the synthesis of varitriol and its derivatives will still attract the attention of synthetic chemists as well as biologists for the years to come due to its unique structural features and potent bioactivities. Although substantial progress has been made in identifying novel drugs from marine source, there is great scope to explore these molecules for medicinal applications. Many synthetic routes towards varitriol are disclosed but, unfortunately only limited varitriol analogues have been exploited in SAR studies. In fact, there is great demand to develop new and general methods for the synthesis of varitriol analogues in combination with its biological data in order to find structural activity relations, which could provide the opportunity to discover the potential lead anticancer agents. Moreover, from an ecological standpoint the synthesis of metabolites are highly desirable since it reduces our dependence on the scarce natural product resources. Hence, the problem associated with the supply issues from natural sources leading the breakpoint in the development of many promising metabolites of marine origin could be overcome by synthetic chemistry.

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ABBREVIATIONS

AcOH	= Acetic acid
AIBN	= Azobisisobutyronitrile
Bn	= Benzyl
Boc	= <i>tert</i> -Butoxycarbonyl
Boc-ON	= 2-(<i>tert</i> -Butoxycarbonyloxyimino)-2-phenylacetonitrile
<i>n</i> -BuLi	= <i>n</i> -Butyllithium
Bz	= Benzoyl
CAS	= Camphorsulfonic Acid
DAST	= Diethylaminosulfur trifluoride
DCC	= <i>N,N'</i> -Dicyclohexylcarbodiimide
DDQ	= 2,3-Dichloro-5,6-Dicyanobenzoquinone
DEAD	= Diethyl Azodicarboxylate
DEPC	= Diethyl Phosphorocyanidate
DHQD	= Dihydroquinidine
DIAD	= Diisopropyl Azodicarboxylate
DIBAL	= Diisobutylaluminium Hydride
DIPEA	= Diisopropylethylamine
DMAP	= 4-(<i>N,N'</i> -Dimethylamino)pyridine
DMF	= Dimethylformamide
DMSO	= Dimethyl Sulfoxide
DMP	= Dess Martin Periodinane
DPPA	= Diphenylphosphoryl Azide
EDC	= 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
Fmoc	= 9-Fluorenylmethoxycarbonyl
HMPA	= Hexamethylphosphoramide

HMDS	= Hexamethyldisilazane
HOBt	= <i>N</i> -Hydroxybenzotriazole
HPLC	= High-performance Liquid Chromatography
HWE	= Horner-Wadsworth-Emmons
LAH	= Lithium Aluminum Hydride
LDA	= Lithium Diisopropylamide
<i>m</i> -CPBA	= <i>meta</i> -Chloroperbenzoic Acid
MOM	= Methoxymethyl
MPLC	= Medium Pressure Liquid Chromatography
MPM	= <i>p</i> -Methoxyphenylmethyl
Ms	= Methylsulfonyl (Mesyl)
NBS	= <i>N</i> -Bromosuccinimide
NCS	= <i>N</i> -Chlorosuccinimide
NMO	= <i>N</i> -Methylmorpholine- <i>N</i> -oxide
NOESY	= Nuclear Overhauser Effect Spectroscopy
PCC	= Pyridinium Chlorochromate
PMHS	= Polymethylhydrosiloxane
PNBA	= <i>para</i> -Nitrobenzoic Acid
PTSA	= <i>p</i> -Toluene Sulfonic Acid
PTSH	= 1-Phenyl-1 <i>H</i> -tetrazole-5-thiol
PPTS	= Pyridinium Tosylate
Py	= Pyridine
TBAF	= Tetrabutylammonium Fluoride
TBAI	= Tetrabutylammonium iodide
TBDPS	= <i>tert</i> -Butyldiphenylsilyl
TBS	= <i>tert</i> -Butyldimethylsilyl
TBVT	= Tributylvinyl tin
TFA	= Trifluoroacetic Acid
THF	= Tetrahydrofuran
TIPS	= Triisopropylsilyl
TsCl	= <i>para</i> -Toluenesulfonyl (tosyl) Chloride
TMSCl	= Trimethylsilyl Chloride

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