

Diastereoselective one-pot Wittig olefination–Michael addition and olefin cross metathesis strategy for total synthesis of cytotoxic natural product (+)-varitriol and its higher analogues†Partha Ghosal,^a Deepty Sharma,^b Brijesh Kumar,^b Sanjeev Meena,^c Sudhir Sinha^c and Arun K. Shaw^{*a}

Received 28th June 2011, Accepted 29th July 2011

DOI: 10.1039/c1ob06039b

A stereoselective route for the total synthesis of anticancer marine natural product (+)-varitriol (**1**) is detailed herein. The impressive biological activity and interesting structural features of natural (+)-varitriol fuelled us to undertake the synthesis of some higher analogues (**1a–j**) of this molecule. The key features of the synthetic strategy include one-pot Wittig olefination followed by a highly diastereoselective oxa-Michael addition to assemble stereochemically pure tetrasubstituted THF moiety of the natural varitriol and olefin cross metathesis to couple the aromatic part with tetrasubstituted THF moiety. The total synthesis of title natural product is efficient with 21.8% overall yield for 9 linear steps from D-ribose and thus facilitates the more scaled-up practical route for the synthesis of **1** and its analogues as well. The synthetic (+)-varitriol (**1**) and its analogues were screened for their cytotoxicity. The present synthetic approach paves the way for preparation of numerous analogues of the title natural product for drug development.

Recent decades have seen cancer as the number one killer among all the deadly diseases both in the developed and developing countries.¹ Therefore, development of novel and more selective therapeutics for the treatment of cancer by chemical synthesis as well as chemical modification of known structural classes have become an important research area as it can lead to the discovery of several promising classes of small molecules with improved anticancer activity and also provide useful information about the biochemistry of the cancer cell and their structure–activity relationship.²

Natural products have since long been recognized as an invaluable source of lead structures in the anticancer drug discovery field.² A very large percentage, about 75% of anticancer agents in clinical trials for cancer treatment are either natural products or pharmacophores derived from natural products.³ In the recent decades, natural products, especially marine natural products having anticancer activity received more attention from chemists and motivated them to develop more practical and scalable total syntheses of these natural products as well as their novel analogues for improved activity.² (+)-Varitriol⁴ (**1**, Fig. 1) is such a marine natural product isolated by Barrero *et al.* from a marine strain (named M75-2) of the fungus *Emericella variegata*, collected in

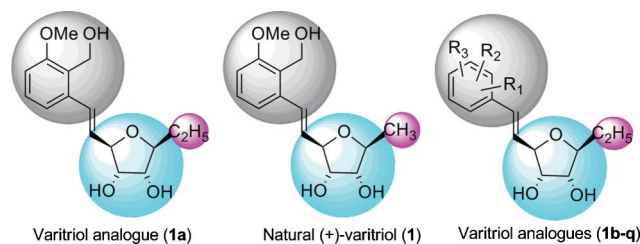


Fig. 1 Structure of natural (+)-varitriol (**1**) and its analogues (**1a–q**).

Venezuelan waters of the Caribbean Sea in 2002 and showed potent cytotoxicity toward a variety of cancer cell lines.⁵

The potent anticancer activity of natural (+)-varitriol (**1**), a more than 100-fold increased potency (over the mean toxicity) toward the RXF 393 (renal cancer, $GI_{50} = 1.63 \times 10^{-7}$ M), SNB-75 (CNS cancer, $GI_{50} = 2.44 \times 10^{-7}$ M) and T-47D (breast cancer, $GI_{50} = 2.10 \times 10^{-7}$ M) cell lines has attracted an immense synthetic interest from synthetic community. As a result several elegant approaches toward the total synthesis of (+) and (–)-varitriol as well as its analogues have been reported to date.

In 2006 Clemens *et al.*⁶ disclosed the total synthesis of unnatural (–)-varitriol from D-(–)-ribose by utilizing olefin cross metathesis as the key step. Subsequently in that year the Taylor group⁷ reported the total synthesis of unnatural (–)-varitriol and (–)-3'-*epi*-varitriol via a Ramberg–Bäcklund route from D-(–)-ribose. The first total synthesis of natural (+)-varitriol was achieved by our group involving a highly diastereoselective iodocyclization reaction for the construction of tetrasubstituted THF part of

^aDivision of Medicinal and Process Chemistry, Central Drug Research Institute (CDRI), CSIR, Lucknow, 226 001, India

^bSophisticated Analytical Instrument Faculty, Central Drug Research Institute (CDRI), CSIR, Lucknow, 226 001, India

^cDrug Target Discovery and Development, Central Drug Research Institute (CDRI), CSIR, Lucknow, 226 001, India

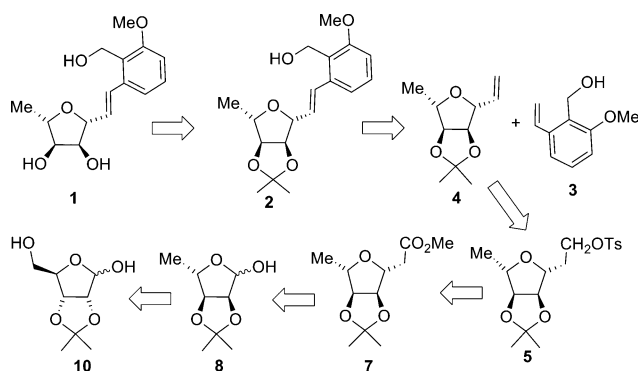
† Electronic supplementary information (ESI) available: ¹H (1D and 2D), ¹³C NMR spectra and GC chromatograms. See DOI: 10.1039/c1ob06039b

the natural product which was later coupled with the required aromatic moiety by olefin cross-metathesis.⁸ Gracza *et al.* reported the synthesis of (+)-**1** by applying Kociński-Julia olefination of sulfonyl furan derivative with corresponding aromatic aldehyde.⁹ Ghosh and coworkers disclosed the synthesis of both (+) and (–)-**1** and their epimers by using Heck coupling between the olefinic sugar moiety and the aromatic triflate.¹⁰

Brichacek *et al.* furnished a report on synthesis of (+)-varitriol by copper catalyzed vinyl oxirane ring expansion reaction and Julia olefination.¹¹ Latter Srinivas *et al.* reported two synthetic strategies toward (+)-**1** by using olefin cross metathesis strategy starting from D(–)-ribose and ethyl (S)- lactate respectively.¹² Recently Zeng *et al.* described an efficient total synthesis of (+)-**1** in which the THF part was constructed by BF₃·Et₂O promoted coupling of ethynyltrifluoroborate with glycosyl fluoride, derived from D(–)-ribose and later it was linked with the corresponding aromatic triflate by utilizing Sonogashira cross-coupling.¹³ Very recently Gracza *et al.* reported a total synthesis of natural varitriol from D-ribonolactone by utilizing Julia-Kociński olefination.¹⁴ Furthermore, synthetic analogues of (+)-**1** were also reported by various approaches.¹⁵

In spite of promising biological activity of (+)-varitriol, its mode of action is still unknown. To the best of our knowledge, the synthesis and screening of unprotected analogues of natural varitriol have not yet been reported. Therefore, the impressive biological activity, interesting structural features, natural scarcity, lack of literature report on cytotoxicity of unprotected (+)-varitriol analogues and also as a result of our interest toward the utilization of carbohydrate-based chiral building blocks (CBBs)¹⁶ for the synthesis of natural product or biologically important molecules^{8,17} motivated us to synthesize natural (+)-varitriol and its higher analogues for anticancer drug development through high efficiency chemical synthesis. Herein, we wish to disclose a short and efficient route for second generation synthesis of (+)-varitriol from D-ribose in which the construction of the THF part was achieved by an efficient one-pot Wittig olefination and highly diastereoselective intramolecular oxa-Michael addition followed by coupling with the aromatic part by olefin cross metathesis reaction. Synthesis of some analogues of this natural product was also completed by the similar strategy.

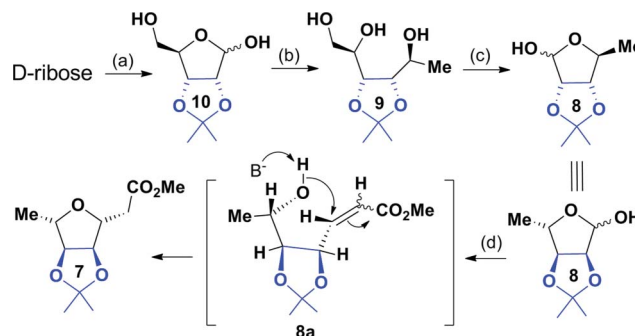
The retrosynthetic strategy for (+)-varitriol (**1**) is depicted in Scheme 1. We envisaged that **1** could be elaborated from protected varitriol **2** by acetonide deprotection which could in turn be prepared by coupling the aromatic part **3** with the vinylic



Scheme 1 Retrosynthetic analysis of (+)-varitriol (**1**).

furanoside **4** involving the olefin cross metathesis strategy. The latter, which have all the four stereocentres identical to that of natural (+)-varitriol could be obtained from tosylate **5** by reductive elimination of the tosyl group. Tosylate **5** could be derived from the methyl ester **7** by LiAlH₄ reduction followed by tosylation of the resulting alcohol **6**. The ester **7** whose synthesis could be possible from lactol **8** by its Wittig olefination followed by oxa-Michael addition and lactol **8** which in turn could be prepared easily from 2,3-*O*-isopropylidene-D-ribose **10** by methyl Grignard addition followed by NaIO₄ mediated oxidative cleavage.

Thus, as per the retrosynthesis shown above, the stereochemically pure tetrasubstituted THF subunit **4** was synthesized from 2,3-*O*-isopropylidene-D-ribose¹⁸ **10** which could be easily prepared from commercially available inexpensive D-ribose. The treatment of 2,3-*O*-isopropylidene-D-ribose with an excess methyl magnesium bromide in diethyl ether at –50 °C to rt afforded the triol **9** which on oxidative cleavage with NaIO₄ without further purification furnished the known lactol **8**^{12,19} in 64% yield over two steps (Scheme 2). A solution of lactol **8** in CH₃CN was then subjected to undergo Wittig olefination on reflux with methyl (triphenyl-phosphoranylidene)acetate at 110 °C for 2 h. Presuming that open chain intermediates (**8a**) could have been formed, refluxing of the same reaction mixture was continued overnight to facilitate the intramolecular oxa-Michael addition to obtain THF derivative **7**.²⁰ However, the cyclization was not completed even after overnight refluxing.



Scheme 2 One-pot Wittig and oxa-Michael addition reaction. *Reagent and conditions:* (a) 2,2-dimethoxypropane, acetone, PTSA, 0 °C, 2h, 90%; (b) MeMgBr, –50 °C to rt, 12 h; (c) NaIO₄, THF–H₂O, 4 h, rt, 64% over two steps; (d) Ph₃P=CHCO₂Me, acetonitrile, 110 °C, 2 h then K₂CO₃, rt, 4 h, 91%.

We, then, decided to use a weak base like NaHCO₃ or K₂CO₃ to complete the cyclization of the Wittig intermediate. Among these two weak bases used, K₂CO₃ was found to be the best in terms of yield of **7**. Thus, after completion of Wittig olefination (2h, TLC control) K₂CO₃ was added to the stirred solution of the reaction mixture in CH₃CN. The stirring was continued for 4 h to obtain the cyclized Wittig product **7** in 91% yield with high diastereoselectivity (>99%, determined by GC) (Scheme 2). The stereochemistry of the newly created chiral centre was established on the basis of its NOE spectrum (Fig. 2) that led to confirm the presence of same stereochemistry as required for the synthesis of natural (+)-varitriol. Thus, we have developed an efficient one-pot Wittig olefination/oxa-Michael addition procedure to obtain the stereochemically pure tetrasubstituted THF core **7** and the reaction was very efficient even in multigram scale. The

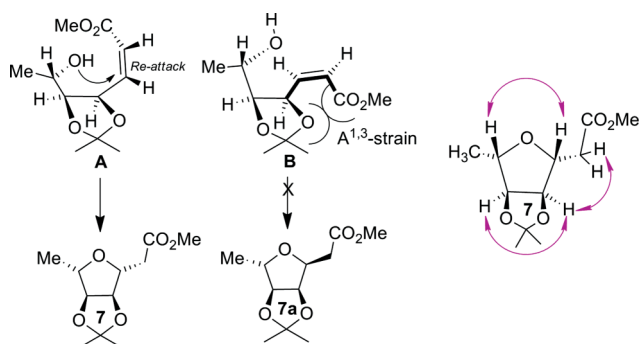
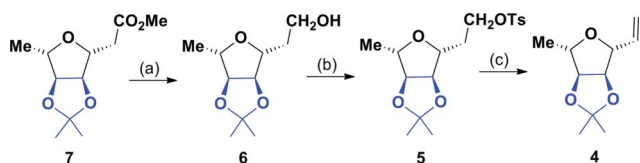


Fig. 2 Conformational analysis and NOE correlations for compound 7.

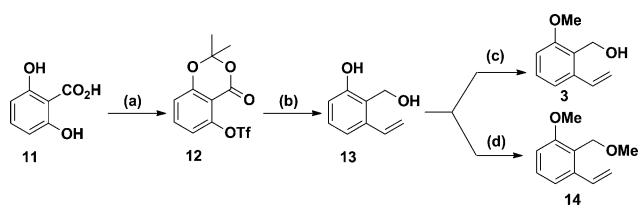
high diastereoselective cyclization of the intermediate **8a** may be attributed to the isopropylidene protection in **8**. Our argument can be rationalized on the basis of the fact that the favorable conformation (**A**) of **8a** with *Z*-geometry^{20b} was involved in this process leading to the formation of 2,5 *cis* fused adduct **7** through *Re*-face attack. The severe *A*^{1,3} strain in the conformer (**B**) makes it unfavorable and therefore cannot take part in the cyclization to give *trans* fused adduct **7a** (Fig. 2).^{20c}

To complete the synthesis of compound **4**, LiAlH₄ reduction of the ester **7** furnished alcohol **6** in 91% yield (Scheme 3). Tosylation of the alcohol **6** with tosyl chloride in the presence of triethylamine afforded tosylate **5** in 96% yield and its subsequent treatment with ^tBuOK afforded the vinylic furanoside **4** in good yield.^{17g} It is worth mentioning that the vinylic furanoside **4** was slightly volatile and therefore the work-up and purification process were done below 30 °C.



Scheme 3 Synthesis of vinylic furanoside **4**. Reagent and conditions: (a) LiAlH₄, Dry THF, 0 °C to rt, 2 h, 91%; (b) TsCl, Et₃N, dry DCM, 0 °C to rt, 4 h, 96%; (c) ^tBuOK, Dry THF, -20 °C to rt, 12 h, 85%.

With the furanoside part **4** in hand, our next attempt was focused toward the construction of substituted styrene **3**.⁸ Its synthesis was initiated from commercially available phenolic acid **11**. The Stille cross-coupling reaction²¹ of the intermediate triflate **12**^{22,23} with tributylvinyl tin (TBVT) in the presence of tetrakis (triphenylphosphine)palladium(0) and lithium chloride followed by LiAlH₄ reduction²⁴ furnished the diol **13** (Scheme 4). While the selective methylation of the phenolic alcohol **13** by treating it



Scheme 4 Synthesis of styrene **3** and **14**. Reagent and conditions: (a) & (b) Ref. 22, 23; (c) Ref. 8, MeI, K₂CO₃, dry acetone, rt, 88%; (d) MeI, NaH, dry DMF, 0 °C to rt, 85%.

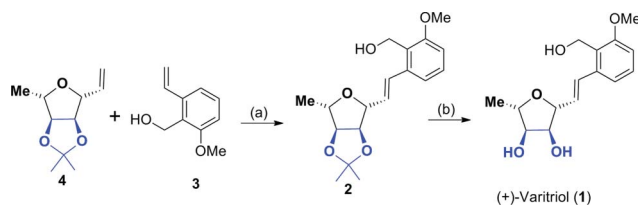
with methyl iodide and potassium carbonate in acetone afforded **3**, the methylation of the diol **13** with MeI in the presence of sodium hydride in DMF furnished the corresponding dimethoxy derivative **14** which was used later (Scheme 4).

Having two types of building blocks, **3** and **4** in our hand, coupling of the styrene **3** with the vinylic furanoside **4** was carried out by olefin cross metathesis reaction and the beneficial result was obtained when **4** was treated with 2-fold excess of **3** in the presence of Grubbs' second generation catalyst (6 mol %) in dry DCM under refluxing condition to furnish exclusively *E* isomer of the cross coupled product **2** in 62.4% yield.

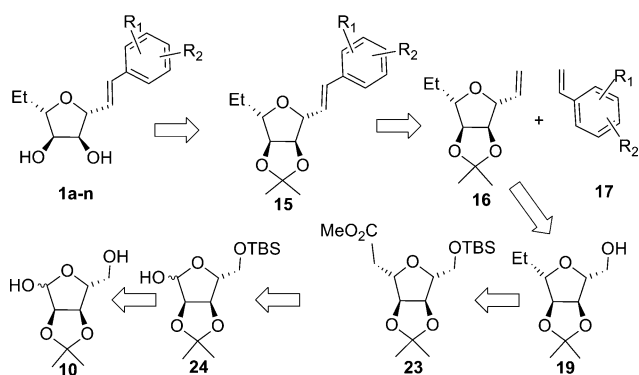
Finally, the natural (+)-varitriol (**1**) was obtained in 90% yield by exposing the cross coupled product **2** to aqueous HCl. The spectral and analytical data were in close agreement with the reported values.⁴

The unique biological activity of (+)-varitriol with still undefined mode of action has produced diverse interests in this natural product, which deserve more comprehensive studies pertaining to anticancer drug development on this molecule. Lack of literature report about the cytotoxicity of unprotected (+)-varitriol analogues and also as a result of our interest toward the synthesis of natural products or natural product like molecules^{8,17} inspired us to synthesize some higher analogues of natural (+)-varitriol (**1**). Therefore, after completion of the total synthesis of (+)-varitriol (**1**), we focused our attention toward the synthesis of some higher analogues and their biological screening. First, we thought to replace the methyl group in natural varitriol by an ethyl group keeping the aromatic part same and in our subsequent strategy we thought to change aromatic part to monitor the effect of these changes on cytotoxicity of the new varitriol analogues. Thus, we followed the same synthetic strategy as discussed above to complete the synthesis of (+)-varitriol (**1**) that involved one-pot Wittig olefination followed by oxa-Michael addition sequence to obtain ethyl containing vinylic furanoside part and afterwards its coupling with the styrenes by olefin cross metathesis reaction.

The general retrosynthetic strategy for varitriol analogues is shown in Scheme 6. We envisaged that **1a–n** could be elaborated from protected varitriol analogues **15** by their acetonide deprotection which could in turn be prepared by coupling between aromatic and carbohydrate portions **17** and **16** respectively, involving the olefin cross metathesis strategy. The carbohydrate fragment **16**, having all the four stereocentres similar to that of natural (+)-varitriol could be obtained from alcohol **19** by oxidation followed by Wittig methylation. Synthesis of alcohol **19** could be possible from the ester **23** that could be obtained from 2,3-*O*-isopropylidene-5-*O*-*tetr*-butyldimethyl silyl-D-ribose **24** which in turn could be easily prepared from commercially available inexpensive D-ribose.

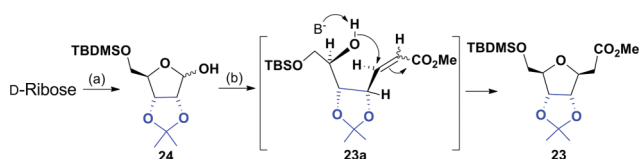


Scheme 5 Synthesis of (+)-varitriol (**1**). Reagent and conditions: (a) Grubbs' second generation catalyst (6 mol%), dry DCM, 50 °C, 32 h, 62.4%; (b) 1 N HCl, THF, rt, 6 h, 90%.



Scheme 6 General retrosynthetic analysis of (+)-varitriol analogues.

The primary hydroxyl group of 2,3-*O*-isopropylidene-D-ribose was protected as silyl ether by using TBDMSCl and imidazole to give the known hemiacetal **24**¹⁸ in 90% yield. A solution of hemiacetal **24** in CH₃CN was subjected to undergo Wittig olefination with methyl (triphenyl-phosphoranylidene)acetate at 110 °C and in this case also cyclization of the open chain intermediate **23a** was not completed even after overnight refluxing (Scheme 7).



Scheme 7 One-pot Wittig and oxa-Michael addition reaction of **24**. *Reagent and conditions:* (a) 1) 2,2-dimethoxypropane, acetone, PTSA, 0 °C, 2 h, 90%; 2) TBDMSCl, imidazole, dry DCM, 0 °C, 2 h, 90%; (b) Ph₃P=CHCO₂Me, CH₃CN, 110 °C, 2 h then dry K₂CO₃, rt, 4 h, 87%.

We then decided to go through our standardized procedure as discussed above. Thus, after completion of Wittig olefination (2 h, TLC control), the reaction mixture was cooled to room temperature and then K₂CO₃ was added to the stirred solution of the reaction mixture in CH₃CN. The stirring was continued for 6 h to obtain the cyclized Wittig product **23** in a very good yield and with high diastereoselectivity (>99%, determined by GC) (Scheme 7). The stereochemistry of the newly created chiral centre was established on the basis of its NOE spectrum (Fig. 3).

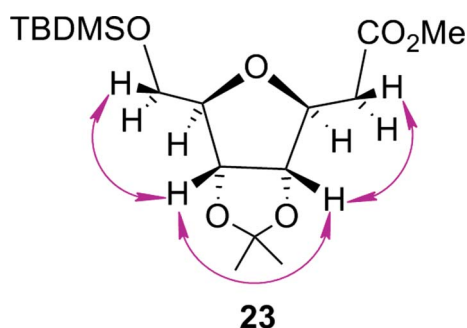
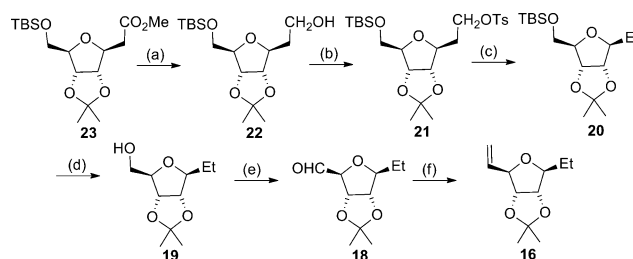


Fig. 3 NOE correlations for compound **23**.

To complete the synthesis of compound **16**, the ester **23** was reduced with LiAlH₄ to furnish alcohol **22** in 87% yield. Its tosylation furnished the tosylate **21** in 87% yield (Scheme 3) whose

subsequent treatment with LiAlH₄ afforded the furanoside **20** in 72% yield (Scheme 8).^{17b} Its TBS deprotection with TBAF in THF furnished the alcohol **19** in 90% yield. Its oxidation with IBX in acetonitrile under refluxing condition yielded the aldehyde **18** which was directly used for the next step without further purification. Wittig olefination of the aldehyde **18** furnished the desired vinylic furanoside **16**, which was structurally very closely related to the THF portion of (+)-varitriol (**1**).



Scheme 8 Synthesis of vinylic furanoside, **16** for varitriol analogues. *Reagent and conditions:* (a) LiAlH₄, dry THF, 0 °C to rt, 2 h; (b) TSCl, Et₃N, dry DCM, 0 °C to rt, 4 h; (c) LiAlH₄, Dry THF, -20 °C to rt, 2 h; (d) TBAF, THF, 0 °C to rt, 2 h; (e) IBX, Acetonitrile, 100 °C, 1 h; (f) Ph₃P=CH₂, dry THF, -20 °C to 0 °C, 2 h.

It should be noted here that the vinylic furanoside **16** was slightly volatile and therefore the work-up and purification process were done below 30 °C. With the furanoside part in hand, our next attempt was focused toward the coupling of two types of building blocks, vinylic furanoside **16** and styrenes (**3**, **14**, **17a-i**) (Fig. 4).

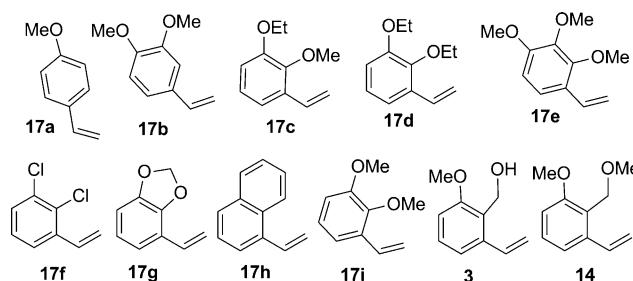


Fig. 4 Structures of various styrenes used for cross metathesis reaction.

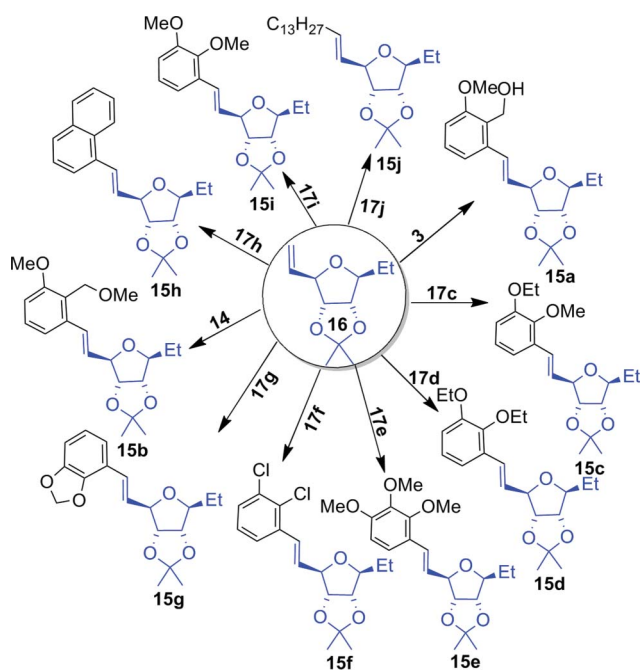
Now, the coupling of vinylic furanoside **16** with styrenes (**3**, **14**, **17a-i**), should furnish the desired protected varitriol analogues. Thus, when the cross metathesis of **16** with the above styrenes was carried out in the presence of Grubbs' second generation catalyst (5 mol %) in dry DCM under refluxing condition, the acetonide protected varitriol analogues **15a-i** were obtained. In this study the styrenes **17a** and **17b** did not undergo cross metathesis reaction (Scheme 9). Since the metathesis reaction proceeds under thermodynamic control,²⁵ the yield and stereoselectivity of a cross metathesis reaction can be improved by increasing the equivalent of one alkene and the reaction time. Thus, from our previous experiences,^{17a,b,c,f} the best results were obtained when the ratios **3**:**16** = 2:1, **14**:**16** = 2:1 and **17c-i**:**16** = 4:1 were maintained to obtain exclusively *E* isomer in all the cases (Table 1).

Some interesting cytotoxic natural products with long hydrocarbon chain in nature²⁶ inspired us to synthesize one varitriol analogue by replacing aromatic portion with a long hydrocarbon chain. Therefore, the cross-coupling reaction of the vinylic

Table 1 Optimization of cross metathesis reaction of **16** with styrenes (**3**, **14**, **17c–j**) in DCM under refluxing condition in presence of Grubbs' second generation catalyst (5 mol%)

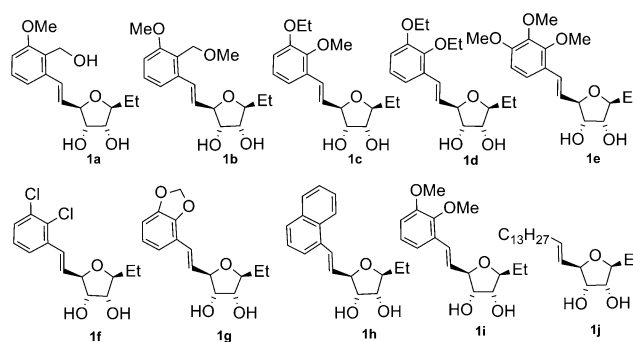
Entry	Equiv. of 16	Styrene	Equiv. of styrene	Time/h	Product	Yield (%)
1	1.5	3	1	12	15a	70
2	1.5	14	1	12	15b	NC ^b
3	1	17c	4	18	15c	74
4	1	17d	4	18	15d	64.4
5	1	17e	4	18	15e	NC ^b
6	1	17f	4	24	15f	90
7	1	17g	4	24	15g	NC ^b
8	1	17h	4	24	15h^a	81
9	1	17i	4	24	15i	NC ^b
10	1	17j	6	6	15j	81

^a Compound **15h** was not so stable and it was used immediately for the next step after its purification; ^b NC = In case of **15b**, **15e**, **15g** and **15i** the desired cross metathesis products were formed along with the aromatic dimers which were not separated by silica gel column chromatography and so the yields are not calculated for this step.

**Scheme 9** Synthesis of protected varitriol analogues **15a–j** via olefin cross metathesis reaction.

furanoside **16** with 1-pentadecene (**17j**) in presence of Grubbs' second generation catalyst (5 mol%) furnished **15j** (**17j**: **16** = 6 : 1) (Scheme 9).

The deprotection of acetonide derivatives **15a–j** should now furnish the target molecules **1a–j**, structurally closely related to natural (+)-varitriol (**1**) (Fig. 5). Thus, the unprotected analogues **1a–j** (Fig. 5) were obtained by exposing their respective precursors **15a–j** to aqueous HCl (Scheme 10). As shown in the Table 1, the cross metathesis products **15b**, **15e**, **15g** and **15i** were obtained as inseparable mixture with some unidentified side products on silica gel column chromatography. However, the desired products were separated and purified after the treatment of each of the mixtures with aqueous HCl. The conditions and yields for acetonide deprotection are given in Table 2.

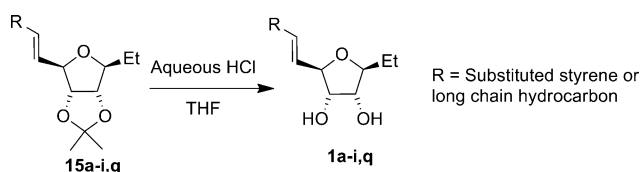
**Fig. 5** Varitriol analogues (**1a–i** and **1q**) after acetonide deprotection.

The natural (+)-varitriol was tested in the National Cancer Institute (NCI) 60-cell-line *in vitro* panel and showed activity

Table 2 Reaction conditions and yield for acetonide deprotection reaction of compounds **16a–i** and **16q**

Entry	CM product	Time/h	Temp./° C	HCl strength	Product	Yield (%)
1	15a	8	30	2 N	1a	82
2	15b	8	30	2 N	1b	43 ^a
3	15c	12	30	2 N	1c	89
4	15d	12	30	2 N	1d	71
5	15e	12	30	2 N	1e	40 ^a
6	15f	12	30	2 N	1f	73
7	15g	12	30	2 N	1g	44 ^a
8	15h	4	0–10	1 N	1h	69
9	15i	8	30	2 N	1i	44 ^a
10	15j	12	60	6 N	1j	64

^a Yield over two steps, *i.e.* cross metathesis and acetonide deprotection.



Scheme 10 Acetonide deprotection of varitriol analogues **15a–i** and **15q**.

against RXF 393 (renal cancer), T-47D (breast cancer), SNB-75 (CNS cancer), DU-145 (prostate cancer), HL-60 (TB) (leukemia), CCRFCM (leukemia), OVCAR-5 (ovarian cancer), SNB-19 (CNS cancer), and COLO 205 (colon cancer) cell lines and was inactive against the remaining cell lines at a concentration of 10^{-4} M.⁴ The synthetic natural varitriol (**1**) and its newly synthesized higher analogues (**1a–j**) described herein were screened for their cytotoxicity against KB (Oral squamous cell carcinoma), C-33A (Cervical cancer), MCF-7 (Breast cancer), A-549 (Lung carcinoma), NIH/3T3 (Mouse embryo fibroblast) cell lines according to the reported screening protocol (see ESI†) but they did not show any significant cytotoxicity ($IC_{50} > 20 \mu\text{M}$) against any of these cell lines.

Conclusion

Our laboratory had previously succeeded in first total synthesis of natural (+)-varitriol (**1**)⁸ and now we have achieved a greatly improved short and efficient second generation route for the total synthesis of natural (+)-varitriol from D-ribose. Here we have accomplished the construction of the tetrasubstituted furanoside part **4** of the title natural product by one-pot Wittig olefination followed by diastereoselective oxa-Michael addition of lactol **8** with 21.8% overall yield for 9 linear steps from D-ribose. Our synthetic protocol that involved one-pot Wittig/oxa-Michael addition reactions to obtain stereochemically pure densely functionalized tetrahydrofurans (**7** and **23**) with four/five point diversity (Fig. 6) did not require dry condition and was very efficient, even on multigram scale, with high diastereoselectivity (>99%). The coupling between THF subunit **4** with aromatic counterpart **3** has been successfully achieved by utilizing olefin cross metathesis strategy and in every case the *E* isomer was formed exclusively.

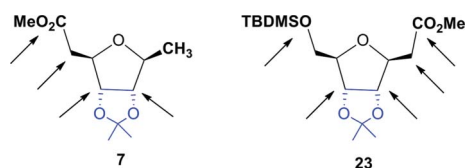


Fig. 6 Sites of diversification in the synthesized THF core.

By applying this convergent strategy we also synthesized some higher analogues (**1a–j**) of cytotoxic marine natural product (+)-varitriol and screened them for their cytotoxicity against KB (oral squamous cell carcinoma), C-33A (cervical cancer), MCF-7 (breast cancer), A-549 (lung carcinoma) and NIH/3T3 (mouse embryo fibroblast) cell lines. The synthetic varitriol (**1**) and its analogues reported in this publication were found to be inactive against the above mentioned cell lines. The flexibility of this synthetic strategy gives us the opportunity to rapid library generation of numerous varitriol analogues, keeping the furanoside part structurally same as present in natural (+)-varitriol, for our ongoing

project on biological activity and drug discovery under CDRI drug development programme which will be presented in due course.

Experimental

General

Organic solvents were dried by standard methods. NMR spectra of the synthesized compounds were recorded on Bruker Avance DPX 200FT, Bruker Robotics, and Bruker DRX 300 Spectrometers at 200, 300 MHz (¹H) and 50, 75 MHz (¹³C) respectively. Experiments were recorded in CDCl₃ and CD₃OD at 25 °C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. Reference CDCl₃ for ¹³C NMR appeared at 77.4 ppm. Using DART and ESI mode mass spectra were recorded on a JEOL ACCUTOF DARTMS and 6520 Accurate Mass Q-TOF LC/MS high resolution spectrometer and IR spectra on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28 °C in chloroform as the solvents; concentrations mentioned are in g/100 mL. The Auto System XL GC spectrum was recorded on Parkin Elmer Instrument on OB-1 column (10 feet) within temperature range 50 °C to 200 °C with a temperature rising rate 4 °C/min and hold time 3 min. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and visualization was accomplished with CeSO₄ (1% in 2 N H₂SO₄) followed by charring over hot plate. Silica gel (100–200 and 230–400 mesh) was used for column chromatography. All the products were characterized by ¹H, ¹³C, IR, ESI-MS spectroscopy. Low-temperature reactions were performed by using immersion cooler with ethanol as the cooling agent. Grubbs' second generation catalyst was purchased from Sigma–Aldrich Co.

General procedure for preparation of compound **10**

D-Ribose (10 g, 66.2 mmol) and 2,2-dimethoxypropane (12.2 mL, 99.3 mmol) were taken in dry acetone (50 mL) and the mixture was cooled to 0 °C. A catalytic amount of *p*-toluenesulfonic acid (1.5 g) was added to the mixture and it was stirred for 2 h at 0 °C. After completion of the reaction, the reaction mixture was quenched with Et₃N and the mixture was evaporated under reduced pressure to give an oily residue. Water (80 ml) was added to it and extracted with EtOAc (3 × 60 mL). The combined organic layer was washed once with water, dried over Na₂SO₄ and evaporated under reduced pressure to obtain a residue. Column chromatographic purification of the residue yielded compound 2,3-*O*-isopropylidene-D-ribose, **10**¹⁷ as an oil (11.31 g, 59.60 mmol, 90%).

General procedure for preparation of lactol **8**

To a stirred solution of MeMgI (82.1 mL, 246.3 mmol), 2,3-*O*-isopropylidene-D-ribofuranose **10** (5.2 g, 27.37 mmol) in ether (15 mL) was added at –50 °C and the stirring was continued for 6 h at this temperature. The reaction mixture was then slowly warmed to rt and stirred for another 12 h. Afterward it was quenched with saturated aqueous NH₄Cl (25 mL) and extracted with EtOAc (5 × 50 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude triol **9** was used for the next step without further purification.

To the above obtained crude triol **9** dissolved in THF/H₂O (10 : 1, 50 mL) was added NaIO₄ (7.72 g, 36 mmol) at 0 °C and stirred for 5 h without further cooling. The reaction mixture was quenched with saturated Na₂S₂O₃ (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure to give a residue which after column chromatographic purification afforded lactol **8**^{12,19} (3.05 g, 17.52 mmol, 64% over two steps) as pale yellow liquid.

Compound 7

To a solution of lactol **8** (304 mg, 1 mmol) in acetonitrile (5 mL), Ph₃P=CHCO₂Me (500 mg, 1.5 mmol) was added and the reaction mixture was allowed to stir under reflux (110 °C) for 2 h. After completion of the Wittig olefination (TLC control), the reaction mixture was cooled to room temp., K₂CO₃ (276 mg, 2 mmol) was added to it and left for stirring at this temperature. After 4 h, water (10 mL) was added to the reaction mixture and was extracted with EtOAc (3 × 15 mL). The combined organic layer was evaporated under reduced pressure to get an oily residue which after column chromatographic purification afforded compound **7** (327 mg, 0.91 mmol, 91% from **8**) as a colorless oil.

Eluent for column chromatography: EtOAc/hexane (1 : 11, v/v); [α]_D²⁵ +2.5 (*c* 1.76, CHCl₃); *R*_f 0.75 (1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 2982, 2932, 2364, 1740, 1375, 1244; ¹H NMR (300 MHz, CDCl₃) δ 1.19(d, *J* = 6.4, 3H), 1.24 (s, 3H), 1.44 (s, 3H), 2.47–2.63 (m, 2H), 3.60 (s, 3H), 3.81–3.90 (m, 1H), 4.07–4.13 (m, 1H), 4.17–4.21 (m, 1H), 4.41 (dd, *J* = 4.7, 6.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.1 (CH₃), 25.7 (CH₃), 27.5 (CH₃), 38.4(CH₂), 51.8 (CH), 80.3 (CH), 80.5 (CH), 84.8(CH), 86.3 (CH), 115.0 (qC), 170.9 (C=O); DART-HRMS: *m/z* [M+H]⁺ Calcd for C₁₁H₁₉O₅, 231.1232, found 231.1230.

Compound 6

The ester **7** (500 mg, 2.17 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C. To this cooled solution was added LiAlH₄ (124 mg, 3.26 mmol) in 3 portions over a period of about 5 min. The resulting reaction mixture was allowed to stir at 0 °C for 1 h and then left stirring for another 1 h without cooling. After completion of the reaction, excess LiAlH₄ was quenched by addition of EtOAc. The reaction mixture was then passed through a short silica gel bed and washed with EtOAc (3 × 10 mL). The combined organic layer was evaporated under reduced pressure and purified by column chromatography to afford compound **6** (400 mg, 1.97 mmol, 91%).

Eluent for column chromatography: EtOAc/hexane (1 : 6, v/v); [α]_D²⁵ +7.0 (*c* 0.896, CHCl₃); *R*_f 0.33 (1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 3423, 2980, 2931, 2361, 1378, 1214; ¹H NMR (300 MHz, CDCl₃) δ 1.26(d, *J* = 6.4, 3H), 1.28 (s, 3H), 1.48 (s, 3H), 1.75–1.91 (m, 2H), 2.61 (br m, 1H), 3.71–3.75 (m, 2H), 3.86–3.91 (m, 2H), 4.21 (dd, *J* = 5.0, 7.0, 1H), 4.33–4.37 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.3 (CH₃), 25.8 (CH₃), 27.6 (CH₃), 36.1 (CH₂), 60.7 (CH₂), 80.6 (CH), 83.5 (CH), 85.4 (CH), 86.3 (CH), 115.4 (qC); DART-HRMS: *m/z* [M+H]⁺ Calcd for C₁₀H₁₉O₄, 203.1283, found 203.1281.

Compound 5

To a stirred solution of alcohol **6** (650 mg, 3.21 mmol) in dry DCM (10 mL) at 0 °C Et₃N (1.3 mL, 9.3 mmol) was added. TsCl

(1.23 g, 6.4 mmol) was added to the reaction mixture portion wise and stirring was continued for one hour at the same temperature and afterwards for 3 h without cooling. After completion of the reaction, a saturated aqueous solution of NH₄Cl (15 mL) was added and the resulting solution was extracted with CH₂Cl₂ (4 × 20 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Column chromatographic purification of the residue furnished **5** as an oil (1.1 g, 3.09 mmol, 96%).

Eluent for column chromatography: EtOAc/hexane (1 : 9, v/v); [α]_D²⁵ +6.4 (*c* 1.00, CHCl₃); *R*_f 0.44 (1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 2982, 2931, 2369, 2339, 1599, 1458, 1363; ¹H NMR (300 MHz, CDCl₃) δ 1.19(d, *J* = 6.4, 3H), 1.27 (s, 3H), 1.47 (s, 3H), 1.80–1.87 (m, 1H), 1.98–2.05 (m, 1H), 2.42 (s, 3H), 3.71–3.80 (m, 2H), 4.08–4.19 (m, 3H), 4.26–4.30 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 19.1 (CH₃), 21.9 (CH₃), 25.8 (CH₃), 27.6 (CH₃), 33.2 (CH₂), 67.5 (CH₂), 80.40 (CH), 80.43 (CH), 85.3 (CH), 86.4 (CH), 115.4 (qC), 128.3 (2 × Ar-CH), 130.1 (2 × Ar-CH), 133.4 (Ar-qC), 145.0 (Ar-qC); DART-HRMS: *m/z* [M+H]⁺ Calcd for C₁₇H₂₅O₆S 357.1372, found 357.1378.

Compound 4

The tosylate **5** (500 mg, 1.4 mmol) was dissolved in dry THF (30 mL) and cooled to –30 °C. To the cooled solution was added ^tBuOK (400 mg, 3.6 mmol) portion wise over a period of about 2 h. The resulting reaction mixture was allowed to stir at this temperature for another 4 h and then left stirring overnight without cooling. After completion of the reaction, the reaction mixture was quenched by addition of aqueous NH₄Cl solution (20 mL) and was extracted with DCM (3 × 20 mL). The combined organic phase was evaporated under reduced pressure and purified by column chromatography to afford compound **4** (219 mg, 1.19 mmol, 85%). Here all the workup, purification and evaporation of column fractions were done below 30 °C.

Eluent for column chromatography: EtOAc/hexane (1 : 13, v/v); [α]_D²⁵ +5.1 (*c* 0.345, CHCl₃); *R*_f 0.45(1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 2981, 2931, 2365, 1376, 1218; ¹H NMR (300 MHz, CDCl₃) δ 1.29–1.31(m, 6H), 1.52 (s, 3H), 3.93–4.01(m, 1H), 4.22–4.29 (m, 2H), 4.42 (dd, *J* = 5.1, 6.8 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.82–5.94 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.3 (CH₃), 25.8 (CH₃), 27.7 (CH₃), 80.5 (CH), 85.3 (CH), 85.7 (CH), 86.5 (CH), 115.2 (qC), 117.5 (CH₂), 136.4 (CH); DART-HRMS: *m/z* [M+H]⁺ Calcd for C₁₀H₁₇O₃, 185.1178, found 185.1160.

Compound 2

Under argon atmosphere Grubbs' second generation catalyst (28 mg, 0.0335 mmol) was added to a 50 mL oven dried two necked round bottomed flask fitted with a reflux condenser and septum. Dry CH₂Cl₂ (2 mL) was added to the flask through a syringe and the solution was kept for stirring. Vinylic furanoside **4** (100 mg, 0.54 mmol) and the alkene **3** (180 mg, 1.1 mmol) in DCM (2 mL each) were added in succession through a syringe to the reaction mixture. The septum was replaced with a glass stopper while the stirring was continued. The solution was refluxed for 32h. After completion of the reaction, the organic solvent was evaporated

under reduced pressure to give a black residue which was purified by column chromatography to give compound **2** as an oil (108 mg, 0.337 mmol, 62.4% from alkene **4**).

Eluent for column chromatography: EtOAc/hexane (1 : 3, v/v); $[\alpha]_{\text{D}}^{25} +17.1$ (*c* 0.375, CHCl₃); *R*_f 0.42 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3457, 2931, 2371, 1580, 1219; ¹H NMR (300 MHz, CDCl₃) δ 1.36–1.38 (m, 6H), 1.59 (s, 3H), 2.30 (brm, 1H, OH), 3.87 (s, 3H), 4.02–4.10 (m, 1H), 4.35 (dd, *J* = 4.7, 6.9 Hz, 1H), 4.44–4.48 (m, 1H), 4.54–4.58 (m, 1H), 4.80 (s, 2H), 6.17 (dd, *J* = 6.6, 15.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.05–7.11 (m, 2H), 7.22–7.28 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.4 (CH₃), 25.9 (CH₃), 27.7 (CH₃), 56.0 (CH), 57.1 (CH₂), 80.7 (CH), 85.2 (CH), 85.9 (CH), 86.6 (CH), 110.1 (CH), 115.4 (qC), 119.7 (CH), 126.8 (Ar-qC), 129.2 (Ar-CH), 129.8 (Ar-CH), 131.1 (Ar-CH), 137.7 (Ar-qC), 158.4 (Ar-qC); DART-HRMS: *m/z* [M]⁺ Calcd for C₁₈H₂₄O₅ 320.1624, found 320.1609.

Compound 1

A solution of compound **2** (80 mg, 0.25 mmol) in THF (5 mL) was stirred with 1 N HCl (5 mL) for 4 h at room temperature. After completion of the reaction, EtOAc (10 ml) was added to it and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was then washed with water, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue which was purified by column chromatography to obtain (+)-varitriol (**1**) as a semisolid (63 mg, 0.225 mmol, 90%).

Eluent for column chromatography: EtOAc/hexane (3 : 1, v/v); $[\alpha]_{\text{D}}^{25} +13.9$ (*c* 0.52, CH₃OH) {Ref. 4 $[\alpha]_{\text{D}}^{25} +18.5$ (*c* 2.30, CH₃OH)}; *R*_f 0.52 (EtOAc); IR (KBr, cm⁻¹): 3366, 2926, 2366, 1583, 1356, 1219; ¹H NMR (300 MHz, CDCl₃ + CD₃OD) δ 1.31 (d, *J* = 6.3 Hz, 3H), 2.34 (brm, 3H, 3OH), 3.67 (t, *J* = 5.54, 1H), 3.84–3.91 (m, 5H), 4.29 (t, *J* = 6.44, 1H), 4.76 (dd, *J* = 11.8, 32.0 Hz, 2H), 6.09 (dd, *J* = 7.0, 15.7 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.99–7.10 (m, 2H), 7.20–7.28 (m, 1H); ¹³C NMR (75 MHz, CDCl₃ + CD₃OD) δ 19.4 (CH₃), 56.0 (CH), 56.2 (CH₂), 75.5 (CH), 76.3 (CH), 80.2 (CH), 84.4 (CH), 110.2 (CH), 119.5 (CH), 126.3 (Ar-qC), 129.4 (CH), 129.8 (CH), 131.5 (CH), 138.0 (Ar-qC), 158.3 (Ar-qC); DART-HRMS: *m/z* [M]⁺ Calcd for C₁₅H₂₀O₅ 280.1311, found 280.1297.

General procedure for preparation of compound 24

To a precooled (0 °C) solution of 2,3-*O*-isopropylidene -D-ribose **10** (10.31 g, 54.28 mmol) in dry DCM (40 mL) was added imidazole (5.54 g, 81.4 mmol). TBDMSCl (9.00 g, 59.71 mmol) was then added to the reaction mixture and stirring was continued for 2 h. After completion of the reaction, a saturated aqueous solution of NH₄Cl (15 mL) was added and the resulting solution was extracted with dichloromethane (4 × 20 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography to furnish **24**¹⁸ (14.87 g, 48.85 mmol, 90%) as a colorless oil.

Compound 23

To a solution of the hemiacetal **24** (305 mg, 1 mmol) in acetonitrile (5 mL), Ph₃P=CHCO₂Me (500 mg, 1.5 mmol) was added and the reaction mixture was allowed to stir under reflux (110 °C) for 2 h. After completion of the Wittig olefination, the reaction

mixture was cooled to room temp., K₂CO₃ (276 mg, 2 mmol) was added to it and left for stirring at this temperature. After 4 h, water (10 ml) was added to the reaction mixture which was then extracted with EtOAc (3 × 15 mL). The combined organic layer was evaporated under reduced pressure to get an oily residue which after column chromatographic purification afforded compound **23** (312 mg, 0.87 mmol, 87% from **24**) as a colorless oil.

Eluent for column chromatography: EtOAc/hexane (1 : 15, v/v); $[\alpha]_{\text{D}}^{25} -17.9$ (*c* 1.135, CHCl₃); *R*_f 0.64 (1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 2936, 2365, 1740, 1465, 1378, 1218; ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 6H), 0.89 (brs, 9H), 1.33 (s, 3H), 1.52 (s, 3H), 2.61–2.64 (m, 2H), 3.68–3.69 (m, 5H), 4.06 (dd, *J* = 3.25, 6.51 Hz, 1H), 4.28–4.34 (m, 1H), 4.41 (dd, *J* = 4.50, 6.24 Hz, 1H), 4.65 (dd, *J* = 3.05, 6.37 Hz, 1H); ¹³C (75 MHz, CDCl₃) δ -5.1 (CH₃), -5.0 (CH₃), 18.7 (qC), 25.9 (CH₃), 26.3 (3 × CH₃), 27.8 (CH₃), 39.0 (CH₂), 52.1 (CH₃), 64.2 (CH₂), 81.6 (CH), 82.4 (CH), 85.0 (CH), 85.3 (CH), 114.2 (qC), 171.5 (C=O); IR (neat, cm⁻¹): 3021, 2936, 2365, 1740, 1650, 1218; ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₇H₃₃O₆Si 361.2046, found 361.2028.

Compound 22

The ester **23** (500 mg, 1.39 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C. To the cooled solution was added LiAlH₄ (80 mg, 2.1 mmol) in 3 portions over a period of about 5 min. The resulting reaction mixture was allowed to stir at 0 °C for 1 h and then left stirring for another 1 h without cooling. After completion of the reaction, excess LiAlH₄ was quenched by addition of EtOAc. The reaction mixture was then passed through a short silica gel bed and washed with EtOAc (3 × 10 mL). The combined organic layer was evaporated under reduced pressure and purified by column chromatography to afford compound **22** (400 mg, 1.20 mmol, 87%).

Eluent for column chromatography: EtOAc/hexane (1 : 4, v/v); $[\alpha]_{\text{D}}^{25} -15.9$ (*c* 0.71, CHCl₃); *R*_f 0.33 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3452, 2935, 2862, 2360, 1518, 1464, 1217; ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 6H), 0.88 (brs, 9H), 1.32 (s, 3H), 1.51 (s, 3H), 1.75–1.94 (m, 2H), 2.50 (brm, 1H, OH), 3.71 (d, *J* = 3.67, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.98–4.04 (m, 2H), 4.32–4.36 (m, 1H), 4.61 (dd, *J* = 3.5, 6.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -5.1 (CH₃), -5.0 (CH₃), 18.7 (qC), 25.9 (CH₃), 26.2 (3 × CH₃), 27.8 (CH₃), 35.8 (CH₂), 60.9 (CH₂), 63.7 (CH₂), 81.9 (CH), 84.4 (CH), 84.8 (CH), 85.1 (CH), 114.5 (qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₆H₃₃O₅Si 333.2097, found 333.2106.

Compound 21

To a stirred solution of alcohol **22** (500 mg, 1.5 mmol) in dry DCM (20 mL) at 0 °C Et₃N (0.6 mL, 4.3 mmol) was added. TsCl (575 mg, 3 mmol) was then added to the reaction mixture portion wise and stirring was continued first for one hour at the same temperature and then for 3 h without cooling. After completion of the reaction, a saturated aqueous solution of NH₄Cl (15 mL) was added and the resulting solution was extracted with CH₂Cl₂ (4 × 20 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Column chromatographic purification of the residue furnished **21** as an oil (635 mg, 1.3 mmol, 87%).

Eluent for column chromatography: EtOAc/hexane (1 : 5, v/v); $[\alpha]_{\text{D}}^{25} -27.8$ (*c* 0.83, CHCl₃); *R*_f 0.42 (1 : 3, EtOAc/hexane); IR

(neat, cm^{-1}): 2933, 2362, 1643, 1365, 1217; ^1H NMR (300 MHz, CDCl_3) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (brs, 9H), 1.31 (s, 3H), 1.49 (s, 3H), 1.86–1.91 (m, 1H), 1.98–2.03 (m, 1H), 2.44 (s, 3H), 3.65 (d, $J = 2.7$, 2H), 3.83–3.89 (m, 1H), 3.93 (dd, $J = 3.3$, 6.7 Hz, 1H), 4.11–4.17 (m, 2H), 4.24–4.27 (m, 1H), 4.60 (dd, $J = 3.4$, 6.5 Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ -5.1 (CH_3), -5.0 (CH_3), 18.6 (qC), 21.9 (CH_3), 25.8 (CH_3), 26.2 ($3 \times \text{CH}_3$), 27.8 (CH_3), 33.4 (CH_2), 63.8 (CH_2), 67.8 (CH_2), 81.0 (CH), 82.1 (CH), 84.9 (CH), 85.2 (CH), 114.3 (qC), 128.3 ($2 \times \text{Ar-CH}$), 130.1 ($2 \times \text{Ar-CH}$), 133.4 (Ar-qC), 145.0 (Ar-qC); ESI-HRMS: m/z [$\text{M}+\text{H}$] $^+$ Calcd for $\text{C}_{23}\text{H}_{30}\text{O}_7\text{Si}$ 487.2186, found 487.2168.

Compound 20

The tosylate **21** (500 mg, 1.03 mmol) was dissolved in dry THF (10 mL) and cooled to -20 °C. To this cooled solution was added LiAlH_4 (78 mg, 2.06 mmol) in 3 portions over a time period of about 15 min. The resulting reaction mixture was stirred at -20 °C for about 1 h then the reaction mixture was allowed to stir for another one hour without further cooling. After completion of the reaction, excess LiAlH_4 was quenched with EtOAc at 0 °C. The reaction mixture was then passed through a short silica gel bed and washed with EtOAc (3×15 mL). The combined organic layer was evaporated under reduced pressure to obtain an oily residue which on column chromatographic purification yielded compound **20** (235 mg, 0.74 mmol, 72%).

Eluent for column chromatography: EtOAc /hexane (1 : 9, v/v); $[\alpha]_{\text{D}}^{28}$ -5.8 (c 1.18, CHCl_3); R_f 0.54 (1 : 4, EtOAc /hexane); IR (neat, cm^{-1}): 2935, 2864, 2366, 1465, 1378, 1218; ^1H NMR (300 MHz, CDCl_3) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (brs, 9H), 0.93 (t, $J = 7.4$, 3H), 1.30 (s, 3H), 1.49 (s, 3H), 1.51–1.61 (m, 2H), 3.67 (d, $J = 2.7$, 2H), 3.72–3.78 (m, 1H), 3.93 (dd, $J = 3.8$, 7.6 Hz, 1H), 4.23 (dd, $J = 4.9$, 6.7 Hz, 1H), 4.57 (dd, $J = 3.7$, 6.7 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ -5.1 (CH_3), -5.0 (CH_3), 10.1 (CH_3), 18.7 (qC), 25.9 (CH_3), 26.2 ($3 \times \text{CH}_3$), 27.1 (CH_2), 27.8 (CH_3), 64.0 (CH_2), 82.2 (CH), 84.6 (CH), 85.2 (CH), 86.1 (CH), 114.1 (qC); ESI-HRMS: m/z [$\text{M}+\text{Na}$] $^+$ Calcd for $\text{C}_{16}\text{H}_{32}\text{O}_4\text{SiNa}$ 339.1968, found 339.1957.

Compound 19

To a stirred solution of silyl ether **20** (500 mg, 1.58 mmol) in THF (10 mL) was added TBAF (1.8 mL, 1 M solution in THF) at 0 °C and left for stirring at room temperature. After 2 h, saturated aqueous solution of NH_4Cl (15 mL) was added to the reaction mixture and it was extracted with EtOAc (3×15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which on column purification afforded compound **19** (287 mg, 1.42 mmol, 90%) as a colorless oil.

Eluent for column chromatography: EtOAc /hexane (1 : 5, v/v); $[\alpha]_{\text{D}}^{28}$ +7.2 (c 1.12, CHCl_3); R_f 0.4 (1 : 4, EtOAc /hexane); IR (neat, cm^{-1}): 3460, 2973, 2935, 2879, 2366, 1460, 1379, 1216; ^1H NMR (300 MHz, CDCl_3) δ 0.93 (t, $J = 7.4$ Hz, 3H), 1.27 (s, 3H), 1.47 (s, 3H), 1.54–1.59 (m, 2H), 2.64 (brs, 1h, OH), 3.58–3.61 (m, 1H), 3.70–3.74 (m, 2H), 3.87–3.89 (m, 1H), 4.21–4.24 (m, 1H), 4.49–4.53 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.0 (CH_3), 25.7 (CH_3), 26.7 (CH_2), 27.6 (CH_3), 62.9 (CH_2), 81.7 (CH), 84.4 (CH),

84.9 (CH), 86.0 (CH), 114.8 (qC); ESI-HRMS: m/z [$\text{M}+\text{Na}$] $^+$ Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_4\text{Na}$ 225.1103, found 225.1108.

Compound 16

A solution of CH_3CN (10 mL) containing alcohol **19** (500 mg, 2.47 mmol) and IBX (2.77 g, 9.9 mmol) in a 100 mL round bottom flask was refluxed for 1 h with cold water circulation. The reaction mixture was then cooled to 0 °C and diluted with ether. After 1 h, the reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to obtain an oil **18** (485 mg) which was immediately used for the next step without further purification.

Methyl triphenylphosphonium bromide (3.03 g, 8.3 mmol) and $t\text{-BuOK}$ (683 mg, 6.1 mmol) were taken in a flame dried two necked round bottomed flask and cooled to -20 °C. Dry THF (25 mL) was added to the reaction mixture under nitrogen atmosphere and it was stirred for 1 h without further cooling. The reaction mixture was then again cooled to -20 °C and the aldehyde **18** in THF (3 mL) was added to the mixture drop wise. The reaction mixture was allowed to warm to 0 °C and the stirring was continued for another 2 h. After completion of the reaction, saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with EtOAc (3×20 mL). The combined organic layer was washed twice with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. Column chromatographic purification of the residue yielded compound **16** as an oil (310 mg, 1.56 mmol, 63% for two steps). Here the work-up, purification and evaporation of column fractions were done below 30 °C.

Eluent for column chromatography: EtOAc /hexane (1 : 49, v/v); $[\alpha]_{\text{D}}^{28}$ +10.0 (c 0.23, CHCl_3); R_f 0.9 (1 : 40, EtOAc /hexane); IR (neat, cm^{-1}): 2983, 2933, 2877, 2364, 1460, 1378, 1216; ^1H NMR (300 MHz, CDCl_3) δ 0.99 (t, $J = 7.4$ Hz, 3H), 1.33 (s, 3H), 1.54 (s, 3H), 1.60–1.66 (m, 2H), 3.78–3.82 (m, 1H), 4.25 (dd, $J = 5.00$, 6.1, 1H), 4.31–4.42 (m, 2H), 5.18–5.22 (m, 1H), 5.37 (dt, $J = 1.3$, 17.3 Hz, 1H), 5.83–5.94 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 25.8 (CH_3), 26.9 (CH_2), 27.7 (CH_3), 85.1 (CH), 85.2 (CH), 85.5 (CH), 85.8 (CH), 115.1 (qC), 117.6 (CH_2), 136.4 (CH); ESI-HRMS: m/z [$\text{M}+\text{H}$] $^+$ Calcd for $\text{C}_{11}\text{H}_{19}\text{O}_3$ 199.1334, found 199.1327.

Compound 14

To a precooled solution of **13** (100 mg, 0.67 mmol) in DMF (5 mL) was added anhydrous NaH (48 mg, 2 mmol), methyl iodide (0.16 mL, 2.68 mmol) and the resulting mixture was allowed to stir for 2 h at 0 °C and then at rt. After 2 h the reaction mixture was quenched by adding MeOH and the resulting solution was concentrated under reduced pressure to a residue that was dissolved in ethyl acetate (15 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to an oil which was purified by column chromatography to give **14** (105 mg, 0.58 mmol, 88%) as a colorless oil.

Eluent for column chromatography: EtOAc /hexane (1 : 10, v/v); R_f 0.5 (2 : 7, EtOAc /hexane); IR (neat, cm^{-1}): 3011, 2929, 2368, 1646, 1577, 1467, 1262; ^1H NMR (300 MHz, CDCl_3) δ 3.38 (s, 3H), 3.81 (s, 3H), 4.58 (s, 2H), 5.33 (dd, $J = 1.2$, 11.0 Hz, 1H), 5.68 (dd, $J = 1.2$, 17.4 Hz, 1H), 6.80 (d, $J = 7.9$, 2H), 7.03–7.27 (m,

3H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.2 (CH_3), 58.4 (CH_3), 65.0 (CH), 110.3 (CH), 116.9 (CH_2), 118.6 (CH), 123.7 (Ar-qC), 129.5 (CH), 134.8 (CH), 140.2 (Ar-qC), 158.5 (Ar-qC); DART-HRMS: m/z $[\text{M}]^+$ Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ 178.0994, found 178.0982.

Compound 15a

Under argon atmosphere Grubbs' second generation catalyst (28 mg, 0.0335 mmol) was added to a 50 mL oven dried two necked round bottomed flask fitted with a reflux condenser and septum. Dry CH_2Cl_2 (2 mL) was then added to the flask through a syringe and the solution was kept for stirring. Vinylic furanoside **16** (100 mg, 0.5 mmol) and the alkene **3** (164 mg, 1 mmol) in DCM (2 mL each) were added in succession through a syringe to the reaction mixture. The septum was replaced with a glass stopper and the stirring was continued. The solution was refluxed for 12h. After completion of the reaction, the organic solvent was evaporated under reduced pressure to give a black residue which was purified by column chromatography to give compound **15a** as a semi-solid (117 mg, 0.35 mmol, 70%).

Eluent for column chromatography: EtOAc/hexane (1 : 10, v/v); $[\alpha]_{\text{D}}^{25} +36.9$ (c 0.13, CHCl_3); R_f 0.52 (1 : 9, EtOAc/hexane); IR (neat, cm^{-1}): 3452, 3009, 2930, 2367, 1579, 1466, 1218; ^1H NMR (300 MHz, CDCl_3) δ 1.03 (t, $J = 7.4$ Hz, 3H), 1.36 (s, 3H), 1.58 (s, 3H), 1.62–1.74 (m, 3H), 3.84–3.91 (m, 4H), 4.37–4.53 (m, 3H), 4.79 (s, 3H), 6.14 (dd, $J = 6.4$, 15.8 Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 7.03–7.09 (m, 2H), 7.20–7.26 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 25.9 (CH_3), 27.0 (CH_2), 27.8 (CH_3), 56.0 (CH), 57.2 (CH_2), 85.1 (CH), 85.2 (CH), 85.8 (CH), 85.9 (CH), 110.1 (CH), 115.3 (qC), 119.7 (CH), 126.8 (Ar-qC), 129.2 (CH), 129.7 (CH), 131.2 (CH), 137.7 (Ar-qC), 158.5 (Ar-qC); ESI-HRMS: m/z $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_5\text{Na}$ 357.1678, found 357.1670.

Compounds **15b–j** were synthesized by following the same procedure as adopted for compound **15a**. The respective equivalents of alkenes and time are given in Table 1.

Compound 15c

Eluent for column chromatography: EtOAc/hexane (1 : 10, v/v); $[\alpha]_{\text{D}}^{25} +46.4$ (c 0.79, CHCl_3); R_f 0.50 (1 : 8, EtOAc/hexane); IR (neat, cm^{-1}): 3022, 2934, 2365, 1469, 1218; ^1H NMR (300 MHz, CDCl_3) δ 1.02 (t, $J = 7.4$ Hz, 3H), 1.35 (s, 3H), 1.43 (t, $J = 6.9$ Hz, 3H), 1.57 (s, 3H), 1.61–1.71 (m, 2H), 3.81 (s, 3H), 3.84–3.89 (m, 1H), 4.05 (dd, $J = 6.9$, 13.9 Hz, 2H), 4.37–4.41 (m, 1H), 4.45–4.53 (m, 2H), 6.23 (dd, $J = 6.6$, 16.1 Hz, 1H), 6.79 (d, $J = 7.2$ Hz, 1H), 6.93–7.07 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 10.2 (CH_3), 15.2 (CH_3), 25.8 (CH_3), 27.0 (CH_2), 27.7 (CH_3), 61.1 (CH), 64.5 (CH_2), 85.2 (CH), 85.4 (CH), 85.8 (CH), 85.9 (CH), 113.2 (CH), 115.0 (qC), 118.6 (CH), 124.1 (CH), 127.3 (CH), 128.7 (CH), 130.9 (Ar-qC), 147.5 (Ar-qC), 152.6 (Ar-qC); ESI-HRMS: m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{29}\text{O}_5$ 349.2015, found 349.1999.

Compound 15d

Eluent for column chromatography: EtOAc/hexane (1 : 10, v/v); $[\alpha]_{\text{D}}^{25} +39.4$ (c 0.49, CHCl_3); R_f 0.54 (1 : 8, EtOAc/hexane); IR (neat, cm^{-1}): 2973, 2927, 2358, 2334, 1577, 1463, 1265, 1213; ^1H NMR (300 MHz, CDCl_3) δ 1.03 (t, $J = 7.4$ Hz, 3H), 1.35–1.45 (m, 9H), 1.58 (s, 3H), 1.64–1.71 (m, 2H), 3.87–3.88 (m, 1H), 3.99–4.08

(m, 4H), 4.37–4.41 (m, 1H), 4.47–4.51 (m, 2H), 6.23 (dd, $J = 6.4$, 16.1 Hz, 1H), 6.78 (dd, $J = 1.1$, 8.0 Hz, 1H), 6.92–6.98 (m, 1H), 7.02–7.08 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 15.3 (CH_3), 16.0 (CH_3), 25.9 (CH_3), 27.1 (CH_2), 27.8 (CH_3), 64.6 (CH_2), 69.4 (CH_2), 85.3 (CH), 85.4 (CH), 85.9 (CH), 85.94 (CH), 113.3 (CH), 115.0 (qC), 118.6 (CH), 124.0 (CH), 127.6 (CH), 128.5 (CH), 131.3 (Ar-qC), 146.7 (Ar-qC), 152.7 (Ar-qC); ESI-HRMS: m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{31}\text{O}_5$ 363.2171, found 363.2156.

Compound 15f

Eluent for column chromatography: EtOAc/hexane (1 : 12, v/v); $[\alpha]_{\text{D}}^{25} +51.2$ (c 1.06, CHCl_3); R_f 0.74 (1 : 9, EtOAc/hexane); IR (neat, cm^{-1}): 2975, 2934, 2367, 1459, 1377, 1217; ^1H NMR (300 MHz, CDCl_3) δ 1.05 (t, $J = 7.4$ Hz, 3H), 1.37 (s, 3H), 1.60 (s, 3H), 1.64–1.76 (m, 2H), 3.91 (dd, $J = 6.5$, 10.9 Hz, 1H), 4.40–4.43 (m, 1H), 4.48–4.54 (m, 2H), 6.24 (dd, $J = 5.8$, 15.8 Hz, 1H), 7.08–7.17 (m, 2H), 7.39 (dd, $J = 7.8$, 21.4 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 25.8 (CH_3), 27.0 (CH_2), 27.7 (CH_3), 30.0 (Grease), 84.7 (CH), 85.2 (CH), 85.6 (CH), 86.0 (CH), 115.2 (qC), 125.5 (CH), 127.4 (CH), 128.6 (CH), 129.7 (CH), 131.8 (CH), 133.7 (Ar-qC), 137.4 (2 \times Ar-qC); ESI-HRMS: m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{O}_3$ 343.0868, found 343.0861.

Compound 15h

Eluent for column chromatography: EtOAc/hexane (1 : 15, v/v); $[\alpha]_{\text{D}}^{25} +42.8$ (c 0.97, CHCl_3); R_f 0.62 (1 : 12, EtOAc/hexane); IR (neat, cm^{-1}): 2932, 2362, 1377, 1218; ^1H NMR (300 MHz, CDCl_3) δ 1.06 (t, $J = 7.4$ Hz, 3H), 1.38 (s, 3H), 1.61 (s, 3H), 1.66–1.78 (m, 2H), 3.92 (dd, $J = 6.7$, 11.1 Hz, 1H), 4.41–4.45 (m, 1H), 4.56–4.58 (m, 2H), 6.24–6.31 (m, 1H), 7.40–7.53 (m, 4H), 7.60 (dd, $J = 6.9$, 1H), 7.76–7.85 (m, 2H), 8.10–8.13 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 25.9 (CH_3), 27.0 (CH_2), 27.8 (CH_3), 85.2 (CH), 85.3 (CH), 85.85 (CH), 85.9 (CH), 115.2 (qC), 124.2 (CH), 124.3 (CH), 125.9 (CH), 126.1 (CH), 126.4 (CH), 128.5 (CH), 128.8 (CH), 129.8 (CH), 130.9 (CH), 131.5 (Ar-qC), 133.9 (Ar-qC), 134.6 (Ar-qC); ESI-HRMS: m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_3$ 325.1804, found 325.1784.

Compound 15j

Eluent for column chromatography: EtOAc/hexane (1 : 11, v/v); $[\alpha]_{\text{D}}^{25} +17.1$ (c 0.34, CHCl_3); R_f 0.44 (1 : 9, EtOAc/hexane); IR (neat, cm^{-1}): 2926, 2856, 2368, 1462, 1216; ^1H NMR (300 MHz, CDCl_3) δ 0.85–0.90 (m, 3H), 0.99 (t, $J = 7.4$ Hz, 3H), 1.25 (m, 2H), 1.33 (s, 3H), 1.54 (s, 3H), 1.60–1.67 (m, 2H), 2.04 (dd, $J = 6.5$, 13.3 Hz, 2H), 3.73–3.79 (m, 1H), 4.19 (dd, $J = 5.2$, 7.0 Hz, 1H), 4.30–4.39 (m, 2H), 5.47 (dd, $J = 7.5$, 15.6 Hz, 1H), 5.77–5.85 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH_3), 14.5 (CH_3), 23.1 (CH_2), 25.9 (CH_3), 26.9 (CH_2), 27.8 (CH_3), 29.3 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 29.96 (CH_2), 30.0 (CH_2), 30.0–30.1 (3 \times CH_2), 32.3 (CH_2), 32.7 (CH_2), 85.3 (2 \times CH), 85.6 (CH), 85.8 (CH), 115.2 (qC), 127.9 (CH), 135.7 (CH); ESI-HRMS: m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{45}\text{O}_3$ 381.0974, found 381.0992.

Compound 1a

A solution of compound **15a** (100 mg, 0.3 mmol) in THF (5 mL) was stirred with 2 M HCl (10 mL) for 8 h at room temperature.

After completion of the reaction, EtOAc (10 ml) was added to it and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was then washed with water, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue which was purified by column chromatography to obtain varitriol analogue (**1a**) as a colorless oil (70 mg, 0.238 mmol, 79%).

Eluent for column chromatography: EtOAc/hexane (1 : 2, v/v); [α]_D²⁸ -7.2 (c 0.77, CHCl₃); *R*_f 0.34 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3347, 2923, 2364, 1571, 1461, 1253; ¹H NMR (300 MHz, CDCl₃) δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.43–1.50 (m, 2H), 3.59–3.63 (m, 4H), 3.72 (s, 3H), 4.16 (t, *J* = 6.5 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 5.96 (dd, *J* = 7.0, 15.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 15.7 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 10.2 (CH₃), 27.1 (CH₂), 55.9 (CH₂), 56.0 (CH), 74.7 (CH), 75.8 (CH), 83.5 (CH), 85.7 (CH), 110.2 (CH), 119.3 (CH), 126.2 (Ar-qC), 129.3 (CH), 129.8 (CH), 131.4 (CH), 138.0 (Ar-qC), 158.2 (Ar-qC); ESI-HRMS: *m/z* [M+Na]⁺ Calcd for C₁₆H₂₂O₅Na 317.1365, found 317.1345.

The other analogues **1b–j** were synthesized by following the same procedure as described above for **1a**. The respective strength of the HCl solution and time are given in Table 2.

Compound 1b

Eluent for column chromatography: EtOAc/hexane (1 : 3, v/v); [α]_D²⁸ +2.4 (c 0.65, CHCl₃); *R*_f 0.44 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3391, 2927, 2365, 1578, 1464, 1259; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.60–1.64 (m, 2H), 3.21 (m, 1H, OH), 3.37 (s, 3H), 3.57 (m, 1H, OH), 3.74 (brm, 3H), 3.82 (s, 3H), 4.29 (t, *J* = 5.7 Hz, 1H), 4.59 (dd, *J* = 10.6, 17.4 Hz, 2H), 6.10 (dd, *J* = 6.9, 15.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 15.8 Hz, 1H), 7.11–7.14 (m, 1H), 7.21–7.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 10.3 (CH₃), 27.1 (CH₂), 56.2 (CH), 58.3 (CH), 65.0 (CH₂), 74.8 (CH), 76.0 (CH), 83.9 (CH), 85.6 (CH), 110.3 (CH), 119.0 (CH), 123.5 (Ar-qC), 129.7 (CH), 129.9 (CH), 130.9 (CH), 139.0 (Ar-qC), 158.6 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₇H₂₅O₅ 309.1702, found 309.1687.

Compound 1c

Eluent for column chromatography: EtOAc/hexane (2 : 5, v/v); [α]_D²⁸ +18.8 (c 0.47, CHCl₃); *R*_f 0.33 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3435, 2928, 2358, 1602, 1466, 1263; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.46 (t, *J* = 6.9 Hz, 3H), 1.59–1.67 (m, 2H), 3.19–3.34 (brm, 2H, 2 OH), 3.72–3.87 (m, 6H), 4.05 (dd, *J* = 6.9, 13.9 Hz, 2H), 4.28–4.32 (m, 1H), 6.18 (dd, *J* = 7.2, 16.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.93–7.07 (m, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 10.2 (CH₃), 15.3 (CH₃), 27.1 (CH₂), 30.0 (Grease), 61.2 (CH), 64.6 (CH₂), 74.9 (CH), 76.0 (CH), 84.3 (CH), 85.6 (CH), 113.2 (CH), 118.7 (CH), 124.3 (CH), 127.3 (CH), 129.2 (CH), 130.9 (Ar-qC), 147.3 (Ar-qC), 152.6 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₇H₂₅O₅ 309.1702, found 309.1722.

Compound 1d

Eluent for column chromatography: EtOAc/hexane (2 : 5, v/v); [α]_D²⁸ +15.1 (c 0.87, CHCl₃); *R*_f 0.40 (1 : 2, EtOAc/hexane); IR (neat, cm⁻¹): 3426, 2925, 2858, 2362, 1580, 1463, 1217; ¹H NMR

(300 MHz, CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.34–1.45 (m, 6H), 1.61–1.67 (m, 2H), 3.20 (m, 2H, 2OH), 3.74–3.84 (m, 3H), 3.98–4.07 (m, 4H), 4.30 (t, *J* = 5.9 Hz, 1H), 6.17 (dd, *J* = 7.0, 16.0 Hz, 1H), 6.78(d, *J* = 7.4 Hz, 1H), 6.92–7.07 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 10.3 (CH₃), 15.3 (CH₃), 16.0 (CH₃), 27.1 (CH₂), 64.6 (CH₂), 69.5 (CH₂), 74.9 (CH), 76.1 (CH), 84.2 (CH), 85.5 (CH), 113.2 (CH), 118.5 (CH), 124.1 (CH), 127.5 (CH), 128.9 (CH), 131.2 (Ar-qC), 146.3 (Ar-qC), 152.7 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₈H₂₇O₅ 323.1858, found 323.1857.

Compound 1e

Eluent for column chromatography: EtOAc/hexane (1 : 2, v/v); [α]_D²⁸ +15.7 (c 0.75, CHCl₃); *R*_f 0.40 (1 : 2, EtOAc/hexane); IR (neat, cm⁻¹): 3395, 2930, 2368, 1462, 1220; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.61–1.66 (m, 2H), 3.04 (m, 2H, 2 OH), 3.71–3.76 (m, 1H), 3.84 (brm, 11H), 4.25–4.29 (m, 1H), 6.09 (dd, *J* = 7.2, 15.9 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.85–6.90 (m, 1H), 7.13–7.17 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 10.3 (CH₃), 27.1 (CH₂), 56.4 (CH), 61.2 (CH), 61.5 (CH), 74.9 (CH), 76.1 (CH), 84.4(CH), 85.5 (CH), 108.1(CH), 121.6 (CH), 123.9 (Ar-qC), 127.1 (CH), 127.4 (CH), 142.6 (Ar-qC), 151.9 (Ar-qC), 153.7 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₇H₂₅O₆ 325.1651, found 325.1642.

Compound 1f

Eluent for column chromatography: EtOAc/hexane (1 : 3, v/v); [α]_D²⁸ +29.0 (c 0.24, CHCl₃); *R*_f 0.42 (1 : 3, EtOAc/hexane); IR (neat, cm⁻¹): 3448, 3022, 2927, 2361, 1568, 1419, 1218; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (t, *J* = 7.4 Hz, 3H), 1.65–1.73 (m, 2H), 3.03 (brm, 2H, 2 OH), 3.77–3.82 (m, 1H), 3.86–3.93 (m, 2H), 4.35 (t, *J* = 5.7 Hz, 1H), 6.20 (dd, *J* = 6.5, 15.8 Hz, 1H), 7.07–7.16 (m, 2H), 7.33–7.44 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 10.3 (CH₃), 27.1 (CH₂), 74.9 (CH), 76.1 (CH), 83.5 (CH), 85.8 (CH), 125.5 (CH), 127.5 (CH), 128.9 (CH), 129.8 (CH), 131.7 (Ar-qC), 131.9 (CH), 133.8 (Ar-qC), 137.3 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₄H₁₇Cl₂O₃ 303.0555, found 303.0535.

Compound 1g

Eluent for column chromatography: EtOAc/hexane (1 : 2, v/v); [α]_D²⁸ +20.1 (c 0.39, CHCl₃); *R*_f 0.46 (1 : 2, EtOAc/hexane); IR (neat, cm⁻¹): 3387, 2926, 2362, 1579, 1453, 1220; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.59–1.69 (m, 2H), 3.13–3.25 (m, 2H, 2 OH), 3.71–3.77 (m, 1H), 3.81–3.89 (m, 2H), 4.24–4.28 (m, 1H), 5.96 (m, 2H), 6.39 (dd, *J* = 6.8, 16.0 Hz, 1H), 6.60–6.81 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 10.3 (CH₃), 27.0 (CH₂), 53.8 (solvent peak, DCM), 74.9 (CH), 76.0 (CH), 84.1 (CH), 85.6 (CH), 101.2 (CH₂), 108.0 (CH), 119.5 (Ar-qC), 121.4 (CH), 121.9 (CH), 127.2 (CH), 130.7 (CH), 145.2 (Ar-qC), 147.9 (Ar-qC); ESI-HRMS: *m/z* [M+H]⁺ Calcd for C₁₅H₁₉O₅ 279.1232, found 279.1221.

Compound 1h

Eluent for column chromatography: EtOAc/hexane (1 : 3, v/v); [α]_D²⁸ +20.6 (c 0.80, CHCl₃); *R*_f 0.50 (1 : 4, EtOAc/hexane); IR (neat, cm⁻¹): 3407, 2362, 1646, 1458, 1218; ¹H NMR (300 MHz, CDCl₃) δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.67–1.72 (m, 2H), 3.29 (brm,

2H, 2 OH), 3.82–3.99 (m, 3H), 4.46 (t, $J = 6.3$ Hz, 1H), 6.25 (dd, $J = 6.8, 15.6$ Hz, 1H), 7.40–7.53 (m, 4H), 7.60–7.63 (m, 1H), 7.78–7.87 (m, 2H), 8.11–8.14 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.3 (CH₃), 27.1 (CH₂), 75.0 (CH), 76.2 (CH), 84.1 (CH), 85.6 (CH), 124.0 (CH), 124.3 (CH), 125.9 (CH), 126.1 (CH), 126.5 (CH), 128.5 (CH), 128.9 (CH), 130.0 (CH), 130.9 (CH), 131.5 (Ar-qC), 134.0 (Ar-qC), 134.4 (Ar-qC); ESI-HRMS: m/z [M+H]⁺ Calcd for C₁₈H₂₁O₃, 285.1491, found 285.1492.

Compound 1i

Eluent for column chromatography: EtOAc/hexane (1 : 2, v/v); $[\alpha]_{\text{D}}^{28} +13.7$ (c 0.79, CHCl_3); R_f 0.34 (1 : 3, EtOAc/hexane); IR (neat, cm^{-1}): 3415, 3020, 2929, 2365, 1470, 1217; ^1H NMR (300 MHz, CDCl_3) δ 1.00 (t, $J = 7.4$ Hz, 3H), 1.59–1.70 (m, 2H), 3.06–3.21 (brm, 2H, 2OH), 3.74–3.88 (m, 9H), 4.28–4.32 (m, 1H), 6.19 (dd, $J = 7.0, 16.1$ Hz, 1H), 6.79–6.82 (m, 1H), 6.97–7.10 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.2 (CH₃), 27.1 (CH₂), 56.1 (CH), 61.3 (CH), 74.9 (CH), 76.0 (CH), 84.3 (CH), 85.6 (CH), 112.0 (CH), 118.7 (CH), 124.4 (CH), 127.2 (CH), 129.3 (CH), 130.9 (Ar-qC), 147.0 (Ar-qC), 153.0 (Ar-qC); ESI-HRMS: m/z [M+H]⁺ Calcd for C₁₆H₂₃O₅, 295.1545, found 295.1543.

Compound 1j

Eluent for column chromatography: EtOAc/hexane (1 : 3, v/v); $[\alpha]_{\text{D}}^{28} +8.7$ (c 0.39, CHCl_3); R_f 0.46 (1 : 3, EtOAc/hexane); IR (neat, cm^{-1}): 3399, 2924, 2363, 1644, 1219; ^1H NMR (300 MHz, CDCl_3) δ 0.85–0.90 (m, 3H), 1.00 (t, $J = 7.4$ Hz, 3H), 1.25–1.38 (m, 22H), 1.58–1.67 (m, 2H), 2.01–2.08 (m, 2H), 2.74 (brm, 2H, 2OH), 3.67 (dd, $J = 6.1, 10.7$ Hz, 1H), 3.74–3.80 (m, 2H), 4.02–4.07 (m, 1H), 5.44 (dd, $J = 7.4, 15.3$ Hz, 1H), 5.77–5.85 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.3 (CH₃), 14.5 (CH₃), 23.1 (CH₂), 27.1 (CH₂), 29.4 (CH₂), 29.6 (CH₂), 29.7 (CH₂), 29.9 (CH₂), 30.0 (CH₂), 30.1 (4 × CH₂), 32.3 (CH₂), 32.8 (CH₂), 74.9 (CH), 75.9 (CH), 84.2 (CH), 85.5 (CH), 128.0 (CH), 136.0 (CH); ESI-HRMS: m/z [M+H]⁺ Calcd for C₂₁H₄₁O₃, 341.3056, found 341.3057.

Acknowledgements

We are thankful to Sophisticated Analytical Instrument Facility, CDRI for providing spectral data, DST (project SR/SI/OC-17/2010) for financial support and Mr. A.K. Pandey for technical assistance. P. G. thanks CSIR, New Delhi, for financial support. CDRI communication no. 8103.

References

- (a) Q. P. Peterson, D. C. Hsu, D. R. Goode, C. J. Novotny, R. K. Totten and P. J. Hergenrother, *J. Med. Chem.*, 2009, **52**, 5721–5731; (b) A. Jemal, R. Siegel, E. Ward, Y. Hao, J. Xu and M. J. C. A. Thun, *Cancer J. Clin.*, 2009, **59**, 225–249.
- S. Danishefsky, *Nat. Prod. Rep.*, 2010, **27**, 1114–1116.

- Y. Dong, Q. Shi, H.-C. Pai, C.-Y. Peng, S.-L. Pan, C.-M. Teng, K. Nakagawa-Goto, D. Yu, Y.-N. Liu, P.-C. Wu, K.-F. Bastow, S. L. Morris-Natschke, A. Brossi, J.-Y. Lang, J. L. Hsu, M.-C. Hung, E.-Y.-H. P. Lee and K.-H. Lee, *J. Med. Chem.*, 2010, **53**, 2299–2308.
- J. Malmstrom, C. Christophersen, A. F. Barrero, J. E. Oltra, J. Justicia and A. Rosales, *J. Nat. Prod.*, 2002, **65**, 364–367.
- A. M. S. Mayer and K. R. Gustafson, *Eur. J. Cancer*, 2004, **40**, 2676–2704.
- R. T. Clemens and M. P. Jennings, *Chem. Commun.*, 2006, 2720–2721.
- G. D. McAllister, J. E. Robinson and R. J. K. Taylor, *Tetrahedron*, 2007, **63**, 12123–12130.
- V. Kumar and A. K. Shaw, *J. Org. Chem.*, 2008, **73**, 7526–7531.
- M. Palik, O. Karlubikova, A. Lasikova, J. Kozisek and T. Gracza, *Eur. J. Org. Chem.*, 2009, 709–715.
- S. Ghosh and T. K. Pradhan, *J. Org. Chem.*, 2010, **75**, 2107–2110.
- M. Brichacek, L. A. Batory, N. A. McGrath and J. T. Njardarson, *Tetrahedron*, 2010, **66**, 4832–4840.
- B. Srinivas, R. Sridhar and K. R. Rao, *Tetrahedron*, 2010, **66**, 8527–8535.
- J. Zeng, S. Vedachalam, S. Xiang and X.-W. Liu, *Org. Lett.*, 2010, **12**, 3971–3974.
- O. Karlubiková, M. Palik, A. Lásiková and T. Gracza, *Synthesis*, 2010, **20**, 3449–3452.
- (a) L. Nagarapu, V. Paparaju and A. Satyender, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2351–2354; (b) A. Senthilmurugan and I. S. Aidhen, *Eur. J. Org. Chem.*, 2010, 555–564.
- D. R. B. Ducatti, A. Massi, M. D. Nosedá, M. E. R. Duarte and A. Dondoni, *Org. Biomol. Chem.*, 2009, **7**, 576–588.
- (a) P. Ghosal, V. Kumar and A. K. Shaw, *Tetrahedron*, 2010, **66**, 7504; (b) P. Ghosal and A. K. Shaw, *Tetrahedron Lett.*, 2010, **51**, 4140–4142; (c) P. Ghosal, V. Kumar and A. K. Shaw, *Carbohydr. Res.*, 2010, **345**, 41–44; (d) L. V. R. Reddy, G. N. Swamy and A. K. Shaw, *Tetrahedron: Asymmetry*, 2008, **19**, 1372–1375; (e) L. V. R. Reddy, P. V. Reddy and A. K. Shaw, *Tetrahedron: Asymmetry*, 2007, **18**, 542–546; (f) P. Pal and A. K. Shaw, *Tetrahedron*, 2011, **67**, 4036–4047; (g) V. Kumar, P. Das, P. Ghosal and A. K. Shaw, *Tetrahedron*, 2011, **67**, 4539–4546.
- (a) Y. H. Jin, P. Liu, J. Wang, R. Baker, J. Huggins and C. K. Chu, *J. Org. Chem.*, 2003, **68**, 9012–9018; (b) Y. A. Kim, A. Sharon, C. K. Chu, R. H. Rais, O. N. Al. Safarjalani, F. N. M. Naguib and M. H. el. Kouni, *J. Med. Chem.*, 2008, **51**, 3934–3945.
- (a) M. Kinoshita, M. Arai, K. Tomooka and M. Nakata, *Tetrahedron Lett.*, 1986, **27**, 1811–1814; (b) P. Srihari, B. P. Kumar, K. Subbarayudu and J. S. Yadav, *Tetrahedron Lett.*, 2007, **48**, 6977–6981.
- (a) H. Ohru, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen and S. K. Byram, *J. Am. Chem. Soc.*, 1975, **97**, 4602–4613(i); (b) J. K. Gallos, A. E. Koumbis and N. E. Apostolakis, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2457–2460 (ii); C.-W. Chang, Y.-N. Chen, A. K. Adak, K.-H. Lin, D.-L. M. Tzou and C.-C. Lin, *Tetrahedron*, 2007, **63**, 4310–4318; (c) J. K. Gallos, A. E. Koumbis, V. P. Xiraphaki, C. C. Dellios and E. Coutouli-Argyropoulou, *Tetrahedron*, 1999, **55**, 15167–15180(i); (d) R. H. Bates, J. B. Shotwell and W. R. Roush, *Org. Lett.*, 2008, **10**, 4343–4346 (ii); R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841–1860.
- Q. Han and D. F. Wiemer, *J. Am. Chem. Soc.*, 1992, **114**, 7692–7697.
- (a) A. Hadfield, H. Schweitzer, M. P. Trova and K. Green, *Synth. Commun.*, 1994, **24**, 1025–1028.
- A. Furstner and I. Konetzki, *Tetrahedron*, 1996, **52**, 15071–15078.
- N. Bajwa and M. P. Jennings, *J. Org. Chem.*, 2006, **71**, 3646–3649.
- J. Llavera, Y. Diaz, M. I. Matheu and S. Castillón, *Org. Lett.*, 2009, **11**, 205–208.
- Examples of some naturally occurring cytotoxic natural products with long alifatic chain: (+)-Jaspine B or Pachastrissamine, (–)-Muricatacin, (+)-Spisulosine etc.