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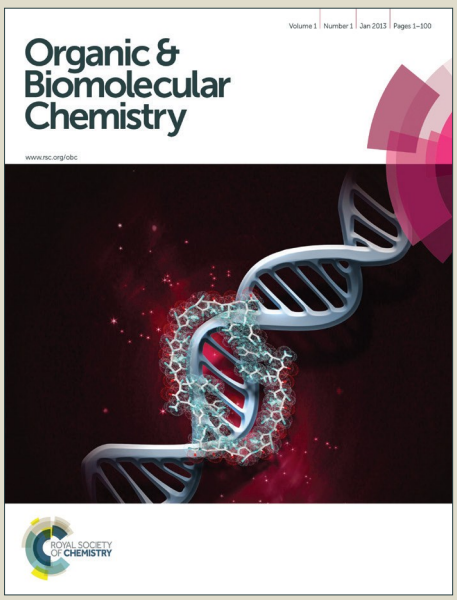

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paper

Substrate and stereocontrolled iodocycloetherification of highly functionalized enantiomerically pure allylic alcohols: Application to synthesis of cytotoxic 2-*epi* jaspine B and its biological evaluation.

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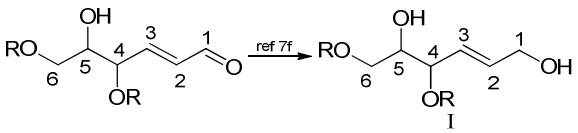
Stereoselectivities of electrophilic additions of molecular iodine to enantiomerically pure highly functionalized allylic alcohols with internal nucleophiles have been investigated. The intramolecular nucleophilic attack to I_2-π complex by *oxygen* nucleophile to obtain tri- and tetrasubstituted THFs are highly regio-, stereoselective and substrate controlled. The application of this study has been shown by utilizing one of the THFs **4a** as a key intermediate to complete the total synthesis of marine anti-cancer natural product 2-*epi* jaspine B.

1. Introduction.

Creation of new stereocenters by using asymmetric induction is a challenging task of chemical research. One of the remarkable strategies in this endeavor is electrophile induced halocycloetherification of olefins using various halonium ions generated from I_2, NIS, NBS, ICl, IBr, and Br_2 etc.[1a-e] Among them, the use of molecular iodine in various organic synthesis and transformation reactions is widely accepted owing to its various functional group tolerability, relatively inexpensive, commercial availability and nontoxic mild Lewis acidic catalyst nature.[2] The first iodocyclization was studied by Bougault in 1904 to disclose the synthesis of β-iodo-butyrolactones from β, γ-unsaturated carboxylic acid using I_2/KI/Na_2CO_3.[3a-d] The biologically important active heterocycles like furans, benzofurans, thiophenes, benzothiophenes, benzopyrans, indoles, quinolines, chromones, pyrroles, furopyridines and furanones have been prepared by iodocycloetherification reactions.[4]

Highly substituted tetrahydrofurans (THFs) represents a group of preeminent heterocyclic scaffolds present in a number of various biologically active natural products as a substructure and chiral building blocks in organic synthesis.[5a-e] In recent years, attempts have been devoted towards the development of methods for the construction of THFs, for example, by nucleophilic substitution, cycloaddition, palladium catalyzed cyclization of alkenic alcohols, alkene hydroetherification, alkene haloetherification etc.[6a-f] Amongst these strategies, iodocycloetherification is one of the frequently used reactions to obtain THF scaffolds. Since last one decade our group has been actively involved for the syntheses of various types of chiral building blocks,[7a-h] biologically relevant molecules[8a-j] and natural products of both plant[9a-b] and marine origin[10a-f, 11] starting from glycal derived enantiomerically pure α, β-unsaturated δ-hydroxy aldehydes commonly known as Perlin aldehydes.[12] Further, our recent reports have shown the applications of iodocyclization approach to the synthesis of biologically active significant molecules[10g] and natural products.[10a,10e]

Thus, with our enduring interest in the syntheses of biologically active natural products or natural product like molecules as mentioned above, we are encouraged to undertake the title study by exploring the green qualities of molecular iodine in iodocycloetherification strategy onto Perlin aldehyde derived allylic alcohols of the type (I). Herein, we wish to report the scope and limitation of diastereoselective iodocycloetherification of allylic alcohols (Figure 1) and its application in the total synthesis of cytotoxic marine natural product 2-*epi* jaspine B by using one of the building blocks derived from this study.



I

Figure 1. Perlin aldehyde derived allylic alcohols (I).

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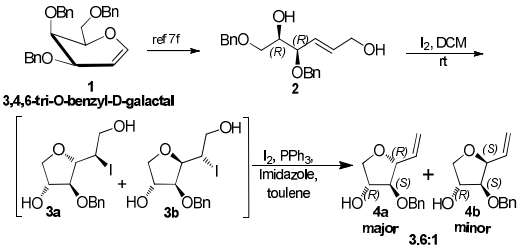
2. Result and discussion.

Our study began with the iodocycloetherification of highly substituted enantiomerically pure allylic alcohol **2** derived from ready available 3,4,6-tri-*O*-benzyl-D-galactal **1**. The allylic alcohol **2** in DCM was treated with 1.5 equiv. of molecular iodine at room temperature leading to the formation of an inseparable mixture of two compounds which were presumed to be **3a** and **3b**. In order to separate them by making their vicinal diiodo derivatives, the mixture was further treated with iodine in the presence of triphenylphospine and imidazole at 40 ˚C. Their chromatographic purification followed by spectroscopic analysis led to identify them as olefins **4a** and **4b** in the ratio of 3.6:1 (by HPLC) with 36% and 15% yield respectively (Scheme 1).



Scheme 1. Iodocycloetherification of allylic alcohol **2**

The formation of THF skeleton was confirmed by performing 1D and 2D NMR studies on **4a** and **4b**. To establish the absolute stereochemistry of the newly formed stereocentre at C2 in both the molecules, we decided to study the NOESY experiments of **4b** instead of **4a** for the reason that the C2 and C4 protons in **4a** were overlapped at 4.28 ppm in its 1D NMR spectra whereas these two protons were separated by 0.19 ppm in **4b**. In its NOESY spectra the C3 and C4 protons showed the correlations with H_a and H_b at C5 respectively and the C2 proton showed the correlation with C3 proton translated from C3 in D-galactal **1** or C4 in allylicalcohol **2**. This study thus revealed that the C2 and C3 protons are *cis* to each other (Figure 2).

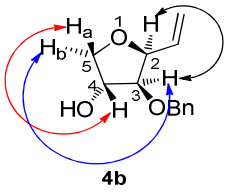
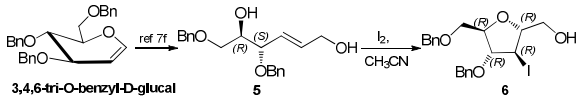


Figure 2. NOESY correlations of compound **4b**

In order to generalize the above study, we were further interested to carry out this reactions on other similar benzyl and methyl protected allylic alcohols. To begin with, the allylic alcohol **5** derived from 3,4,6-tri-*O*-benzyl-D-glucal was subjected to iodocycloetherification reaction with molecular iodine. Here, we observed that the cyclization took place by the participation of C5 free hydroxyl group instead of C6 benzyloxy group (-OBn) to furnish the tetra substituted five membered THF **6** (Scheme 2). This may be ascribed to the closure spatial disposition of free hydroxyl to the double bond compared to the C6-OBn.



Scheme 2. Iodocycloetherification of allylic alcohol **5**

The newly formed stereocenters at C2 and C3 in compound **6** were established by its NOESY experiment. The protons at C2 and C3 showed their correlations with protons at C4 and C5 of THF skeleton respectively (Figure 3). These correlations clearly indicated the anti-disposition of C2 and C3 protons.

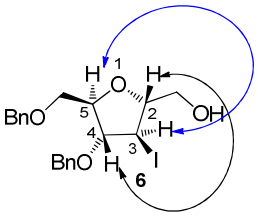
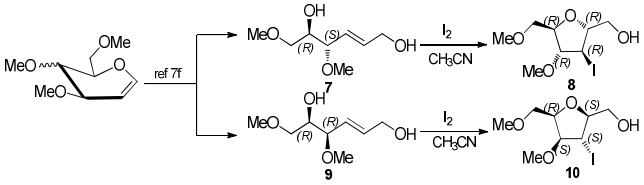


Figure 3. NOESY correlations of compound **6**

Inspired by these results, scope of our study was investigated with methyl protected allylic alcohols **7** and **9** derived from their respective methyl protected glycals. In both the cases it was observed that only C5-OH took part as internal nucleophiles in the cyclization process leading to the formation of the corresponding cyclized C3 iodo THFs **8** and **10** respectively (Scheme 3).



Scheme 3. Iodocycloetherification of methyl protected allylic alcohols **7** and **9**

The structures of C3 iodo THFs **8** and **10** were also confirmed by their 1D and 2D spectral studies. The newly created stereo-centers C2 and C3 in both the THFs were established by their NOESY experiments as were done for **4b** and **6.** The correlations between protons attached to the chiral centers in both the molecules are shown in figure 4.

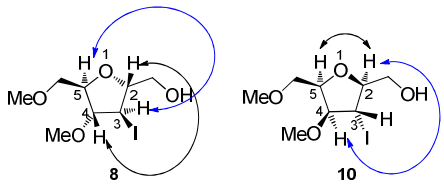


Figure 4. NOESY correlations of compounds **8** and **10**

The optimal reaction conditions of iodocycloetherification (Table 1) indicated acetonitrile to be the solvent of choice both

in terms of yields and reaction time with all the substrates except **2** which furnished an inseparable mixture of **3a, 3b** with a little higher yield in DCM compared to the yield in acetonitrile.

Table 1. Optimization of iodocycloetherification reaction.

Entry	Substrate	Solvent	Product	Yield[a] (%)	Time (h)
1	**2**	DCM	**3a**+**3b**	**73**	0.5
2	**2**	CH_3CN	**3a**+**3b**	66	0.4
3	**2**	THF	**3a**+**3b**	68	0.5
4	**5**	DCM	**6**	43	5
5	**5**	CH_3CN	**6**	**68**	1
6	**5**	THF	**6**	**67**	1
7	**7**	DCM	**8**	51	3
8	**7**	CH_3CN	**8**	**73**	1
9	**7**	THF	**8**	61	5
10	**9**	DCM	**10**	55	3
11	**9**	CH_3CN	**10**	**87**	1
12	**9**	THF	**10**	69	5

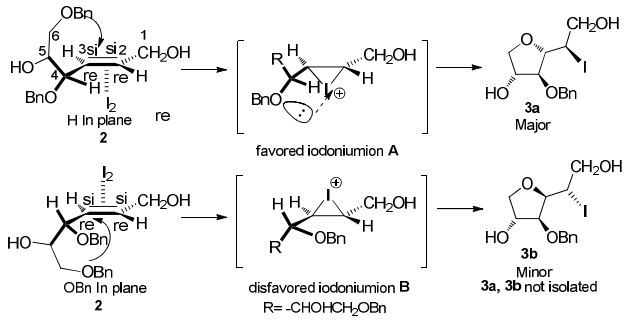
[a]The yield of the product isolated after column purification.

Far ahead the different electrophiles like NIS, $I_2/NaHCO_3$ on iodocyclization were also studied and found to be $I_2/NaHCO_3$ giving the better yields (Table 2). From Table 1 and Table 2 it was concluded that $I_2/NaHCO_3$ in acetonitrile found to be the suitable reaction conditions for the title study.

Table 2. Iodocyclization using different electrophles

Entry	Substrate	Reagent	Product	Yield[a] (%)	Time (h)
1	**2**	I_2	**3a**+**3b**	66	0.5
2	**2**	$I_2/NaHCO_3$	**3a**+**3b**	78	5min
3	**2**	NIS	**3a**+**3b**	72	1h
4	**5**	I_2	**6**	68	5
5	**5**	$I_2/NaHCO_3$	**6**	**82**	1
6	**5**	NIS	**6**	**84**	1
7	**7**	I_2	**8**	73	3
8	**7**	$I_2/NaHCO_3$	**8**	**86**	1
9	**7**	NIS	**8**	88	1
10	**9**	I_2	**10**	87	3
11	**9**	$I_2/NaHCO_3$	**10**	**92**	1
12	**9**	NIS	**10**	87	5

The different mode of cyclization in this study can be explained by considering the well documented Chamberlins molecular models[13a] for the iodonium ions **A**, **B**, **C**, **D** of their respective substrates (Schemes 4 and 5). In the case of allylic alcohol **2**, the -OBn at C6 position which is spatially in close proximity to olefinic C3 triggered the diastereofacial cyclization by involving a favored C4 H in-plane conformer to develop stabilizing interactions between the developing positive charge and benzyloxy oxygen lone pairs as shown in favored pi-complex **A** and thereby the most stable iodonium ion was formed preferentially and trapped by the internal nucleophile to furnish the THF intermediate **3a**. The lesser reaction time also indicates that the conformational strain in the molecule during the course of the reaction did not allow the C5-OH to participate in the cyclization. The formation of minor product **3b** could be explained by considering the disfavored -OBn in-plane conformer **B**. Its instability can be easily rationalized in terms of an unfavourable steric interaction between the eclipsed allylic -R (-$CHOHCH_2OBn$) and the terminal methylenic center that would allow stabilization of the incipient positive charge by the oxygen lone pairs on C4-OBn (Scheme 4).[13]



Scheme 4. Mechanism for iodocycloetherification of allylic alcohol **2**

Finally **3b** was obtained only after C3-C4 bond rotation to dispose C6-OBn in cyclization process (Figure 5).

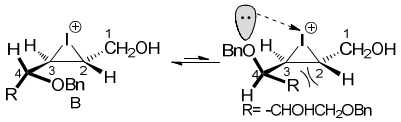
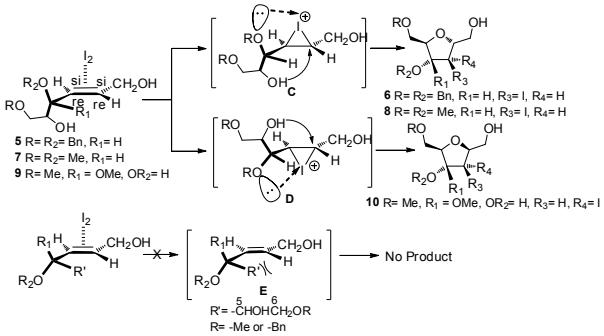


Figure 5. Disfavored iodoniumion **B**.

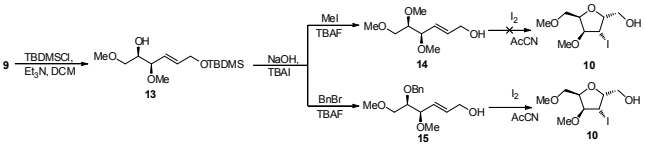
In the case of substrate **5**, the C5-OH is gauche to the double bond and C6-OBn is far away from the olefin to participate in cyclization, as a consequence C5-OH, being closer to C3 of the iodonium ion **C,** took part in the cyclization to furnish the *endo* trig cyclized product **6** (Scheme 5). The cyclization mode was similar in the case of methyl protected allylic alcohols **7** and **9** where the internal nucleophile C5-OH triggered *endo* cyclization due to much poor degree of lability of -OMe compared to both -OBn and -OH to furnish the THFs **8** and **10** respectively (Scheme 5). However, we believe from our present study as well as recent report on debenzylative cycloetherification of an unsaturated acyclic compound with terminal bond to give *endo* trig cyclized THF[13b], the benzyl protected allylic alcohols derived from D- or L-arabinal will behave in a similar way where only primary benzyl will trigger *endo* cyclization to obtain THF.

Further, the exclusive formation of **6**, **8** and **10** each from their respective substrates were presumably due to the involvement of the iodonium ion intermediates **C, D**. The other stereoisomer similar to **4b** was not observed in each case otherwise it would involve the intermediate **E** which will be energetically more costly due to the unfavourable steric repulsion between the eclipsed allylic bulky alkyl group R' and the C2 methylenic center[13a] (Scheme 5).



Scheme 5. Mechanism for iodocycloetherification of allylic alcohols **5**, **7** and **9**.

However substrate **2** which differs from **9** only in its protecting group, and should experience the same energy cost, underwent cyclization to a different outcome to furnish the isomeric THFs **4** via the intermediate **3** which could be attributed to the poor degree of lability of -OMe compared to -OBn. In order to put forward our argument, the free secondary hydroxyl group (C5-OH) in **9** was protected to -OMe and -OBn to obtain its derivatives **14** and **15** respectively. While the allylic alcohol **15** on iodocycloetherification furnished THF **10,** the substrate **14** didn't lead to any result. Thus, these anomalous results very clearly indicated that the debenzylative iodocycloetherification was possible because of high degree of lability of -OBn compared to -OMe (Scheme 6).



Scheme 6.

Further the different mode of cyclization in compounds **2** and **9** was explicated by computational studies as well.

2.1 Computational studies of iodocyclization

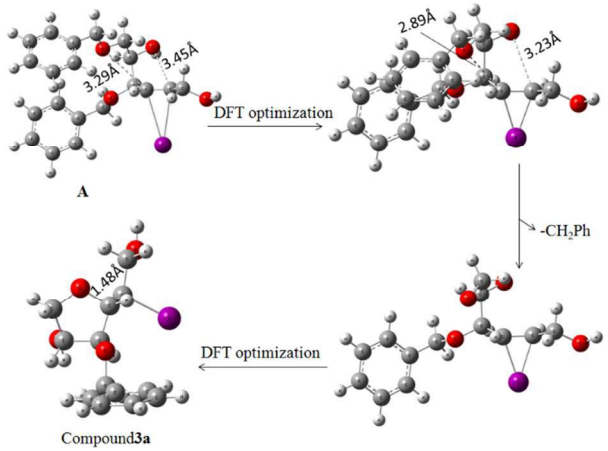


Figure 6. Computational prediction of reaction mechanism of iodocyclization of compound **2** using Gaussian09.

After DFT optimization of compound **2** and compound **9**, we observed striking difference in their optimized conformation. In case of compound **2** (Figure 6), two -OBn groups appeared to form stacking interaction, due to which oxygen atom of C6-OBn group was placed near the C3 atom at a distance of 3.29Å. Moreover, oxygen atom of C5-OH group was placed at 3.49 Å distance from C2 atom. Further optimization of corresponding iodinium ion, led to the decrease in bond distance between C6-OBn and C3atom, suggesting the optimum distance for C6-OBn for the nucleophillic attack on C3 atom (2.89 Å). After removal of benzyl group, we observed that the iodinium ion is optimized to the compound **3a.**

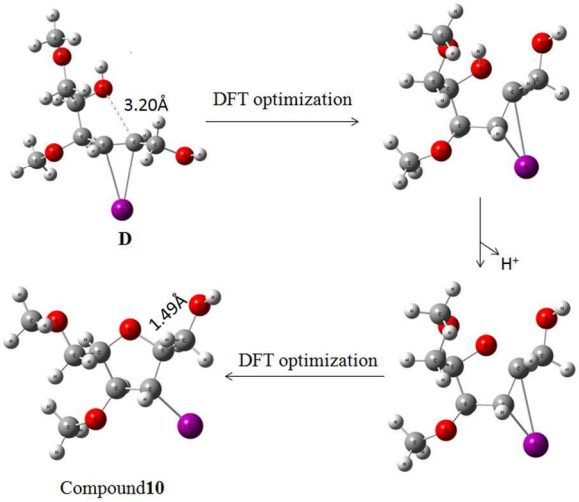


Figure 7. Computational prediction of reaction mechanism of iodocyclization of compound **9** using Gaussian09.

However, in case of compound **9** (Figure 7), we observed that the C5-OH group lies near C2 atom at a distance of 3.20Å and optimization of corresponding iodinium ion led to the significant decrease in the distance to 1.49Å, optimum for the nucleophillic attack. Optimization after removal of proton led to the *endo*-cyclized THF **10**. Thus from above computational studies, we can clearly explain the different mode of cyclization of compound **2** and **9.**

In order to illustrate the application of our above study and also as a part of our ongoing program towards chiron approach to total synthesis of biologically active natural products, we moved forward to total synthesis of marine natural product 2-*epi* jaspine B and its cytotoxic activity starting from **1**. Higa and coworkers isolated a novel marine anhydrophytospingosine derivative pachastrissamine from okinawan marine sponge *Pachastrissa sp.* in 2002.[5c] In the subsequent year Debitus *et al* isolated the same natural product from the vanuatuan marine sponge *Jaspis sp.*, and named it as jaspine B.[14] They also reported the isolation and characterization of jaspine A and the structurally related jaspine B analogues including 2-*epi* jaspine B from the same species (Figure 8).[14] Jaspine B and 2-*epi* jaspine B exhibited remarkable biological activities against various cancer cell lines.[15] The impressive biological activities of jaspine B, 2-*epi* jaspine B and their analogues encouraged

synthetic chemists to develop various synthetic routes for these natural products during the last few years. Although, several reports are available in the literature for the synthesis of jaspine B, only few synthetic approaches have been disclosed for the synthesis of 2-*epi* jaspine B since its isolation[16].

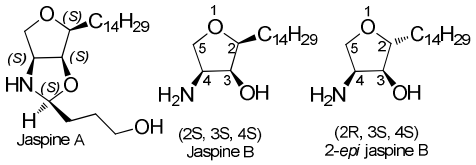
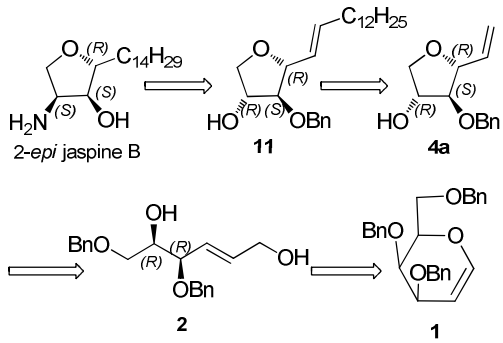


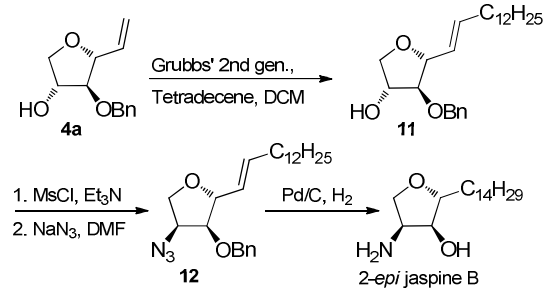
Figure 8. Structure of natural jaspines

Herein, we now propose a practical approach to its synthesis starting from the allylic alcohol **2**. As per our retro synthetic analysis delineated in scheme 6, the stereostructure of the major isomer **4a** obtained via the iodocycloetherification of **2** as discussed above had the stereo-structural resemble with 2-*epi* jaspine B and therefore, it could be utilized as a key intermediate to complete the total synthesis of title natural product. The olefin cross metathesis (OCM) of **4a** with 1-tetradecene followed by azidation of the resulting olefin **11** could furnish the THF azide **12** and finally its hydrogenation could give the desired natural product.



Scheme 6. Retro synthetic pathway of 2-*epi* jaspine B

The fourteen carbon side chain of the natural product was installed by OCM of **4a** with 4 equiv. of 1-tetradecene in dry DCM using 10% Grubbs' 2nd generation catalyst at 45˚C to obtain the olefin **11** in 60% yield.[10e] The azido functionality at C4 was achieved by successive mesylation[7d] and azidaton[17] of the crude mesylate to obtain the azide **12** in 70% yield over two steps.



Scheme 7. Synthesis of 2-*epi* jaspine B

The global hydrogenation of the azide **12** with Pd/C and H_2 in ethanol furnished the target 2-*epi* jaspine B in 96% yield (Scheme 7).[10f] All the spectral data of synthesized natural product 2-*epi* jaspine B were found in good agreement with that of previous reports in the literature.[18]

The *in vitro* anticancer activity for 2-*epi* jaspine B was evaluated by a standard colorimetric SRB (sulforhodamine B) assay against A549 (Lung), DU-145 (prostate), MCF-7 (breast), A-172 (brain), PLC/PRF/5 (liver), 786-O (Renal), DLD-1 (colon) and VERO (Normal Epithelial) cancer cell lines and compared with marketed anticancer drug Doxorubicine as a standard reference. First, we have evaluated cytotoxic effect of 2-*epi* jaspine B and doxorubicin both at 10 µM doses in a broad range different cancer cell lines (Figure 9).

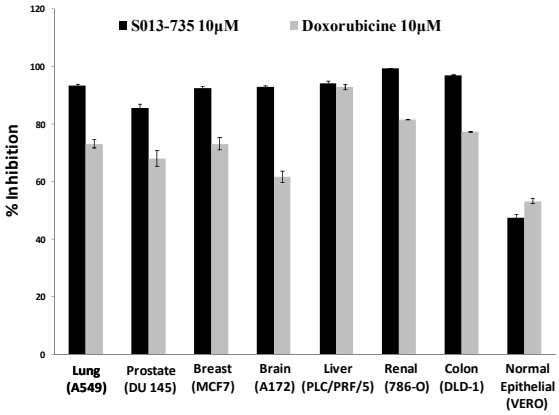


Figure 9. Effect of 2-*epi* jaspine B on inhibition of cancer cell proliferation. Doxorubicine is used as a standard drug.

Interestingly, we observed that 2-*epi* jaspine B was found to be more effective at the same dose compared to doxorubicin against every cancer cell lines tested but its inhibitory effect was less in the case of normal epithelial cells in contrast to doxorubicin suggesting less toxic profile of 2-*epi* jaspine B. Next, we performed dose response studies of 2-*epi* jaspine B to calculate IC_{50} value against the same cell lines. The IC_{50} values are given

Table 2. Determination of IC_{50} of 2-*epi* jaspine B against different cancer cell lines

	IC_{50} [a](µM)						
A549	DU 145	MCF7	A172	PLCPRF 5	786O	DLD 1	VERO
4.8	2	4.04	4.59	1.36	1.08	0.5	>10

[a]IC_{50} (µM) is 50% inhibitory concentration and values are the means of three experiments each done in duplicate.

in table 2. While it showed the best cytotoxicity against colon (DLD-1) cancer cells with IC_{50} 0.5 µM, the IC_{50} value against normal epithelial cells is more than 10µM again indicating its non-toxic nature.

The anti-cancer activity of 2-*epi*-jaspine B was reported earlier[15] against A549 (Lung cancer) cell lines and LD_{50} was reported 1.25 µM which was assessed by MTT assay. In our

case, we determined the IC_{50} values in 'multiple cancer cell lines' including A549 which was found to be 4.8 μM in case of A549 assessed by SRB assay, which is quite comparable. We think that the IC_{50} and LD_{50} value difference was found to be minimal (4.8 μM versus 1.25 μM) and can easily be varied as assay procedures are different.

3. Conclusion

In summary, we demonstrate substrate and stereocontrolled iodocycloetherifications of highly functionalized monosaccharide derived pure allylic alcohols to obtain stereochemically pure tri-and tetrasubstituted THF building blocks. While the allylic alcohol **2** derived from 3,4,6-tri-*O*-benzyl-D-galactal underwent *exo* trig iodocyclization to furnish the THFs **3a** and **3b**, the allylic alcohols **5**, **7** derived from 3,4,6-tri-*O*-benzyl-D-glucal, 3,4,6-tri-*O*-methyl-D-glucal respectively under the identical condition led to the formation of THFs **6**, **8** under *endo* trig fashion. The allylic alcohols **2** and **9** differing in their protecting groups only showed different outcomes in their cyclization process to afford the respective THFs. The mechanistic explanations on the current study have been elucidated on the basis of Chamberlain's models. Computational studies are also done in order to authenticate the same. In continuation, our study has been successfully exploited in stereoselective total synthesis of marine natural product 2-*epi* jaspine B. Its anti-cancer activity was evaluated against different cell lines and showed the most promising results against DLD-1 cancer cell line with IC_{50} 0.5 μM and compared with the reported values. The bioassay study also revealed that unlike the standard reference drug doxorubicin, the synthetic 2-*epi* jaspine B described herein selectively kills cancer cells but not Vero cells. To the best of our knowledge, it will be the first report in the literature on cytotoxic activity of the synthetic 2-*epi* jaspine B against these multiple cancer cell lines.

4. Experimental

4.1 Biological studies

4.1.1. Determination of *in vitro* anti-cancer efficacy using human cancer cell lines

The cancer cell lines A549 (Lung carcinoma), DU-145 (Prostate carcinoma), MCF-7 (Breast adenocarcinoma), A-172 (Brain glioblastoma), PLC/PRF/5 (Liver hepatoma), 786-O (Renal cell adenocarcinoma), DLD-1 (Colorectal adenocarcinoma), and non–cancer cell line VERO (African Green Monkey Kidney Cell Line) were obtained from American Type Culture Collection (ATCC), USA. These cells were grown in recommended media supplemented with 10% FBS, 10,000 units/ml of Pencillin, 10,000 μg/ml of Streptomycin and 25 μg/ml of Amphotericin B in a 5% CO_2 humidified atmosphere at 37 ˚C. No cultures beyond 25 passages are used in this study. A colorimetric sulforhodamine B assay was used for the measurement of cell cytotoxicity.

4.1.2 Cell Viability Assay: A standard colorimetric SRB (sulforhodamine B) assay was used for the measurement of cell cytotoxicity as described before.[19a-b] In brief, 10,000-30,000 cells (depending on the doubling time of each cell type) were seeded to each well of 96-well plate in 5% serum containing growth medium and incubated overnight to allow for cell attachment. Cells were then treated with the test sample (100μl) to give a final concentration of 10μM and duplicate wells were included. Untreated cells receiving the same volume of vehicle containing medium served as control. After 48 h of exposure, cells were fixed with ice-cold 50% TCA, stained with 0.4% (w/v) SRB in 1% acetic acid, washed and air dried. Bound dye was dissolved in 10mM Tris base and absorbance was measured at 510 nm on a plate reader (Epoch Microplate Reader, Biotek, USA). The cytotoxic effects of compounds were calculated as percentage inhibition in cell growth as per the formula.

$$\% \text{ of cells killed} = 100 - \left[\frac{(\text{mean OD}_{\text{test}}) \times 100}{(\text{mean OD}_{\text{control}})} \right]$$

4.1.3 Selection criteria

During initial screening, the samples showing equal to or more than 80% growth inhibition of cancer cells at 10μM concentration are considered as 'Hits' and further screened at 2-fold serial dilutions (10 to 0.625 μM) against different cancer cell lines to calculate their half maximal inhibitory concentration (IC_{50}) value. IC_{50} values are derived using Graph Prism software.

4.2. General (chemistry)

Organic solvents were dried by standard methods. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F- 254), visualization was done with $CeSO_4$ and subsequent charring over hot plate. Silica gel (60- 120 mesh) and silica gel (230- 400 mesh) were used in Column chromatography. All the products were characterized by ^1H, ^{13}C, heteronuclear single quantum coherence (HSQC), IR and ESI-HRMS. NMR spectra were recorded on Bruker Avance 300 MHz spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), 400 MHz spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) Experiments were recorded in $CDCl_3$ and CD_3OD at 25 ºC. 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. For ^{13}C NMR reference $CDCl_3$ appeared at 77.40 ppm and CD_3OD appeared at 48.70 ppm. For IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Optical rotations were determined on an Autopol III polarimeter and Digipol 781M6U, NOVA polarimeter using a 1 dm cell at 17 ºC- 32 ºC in chloroform and methanol and ethanol as the solvents; concentrations mentioned are in g/100 mL. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. ESI- HRMS were recorded on a JEOL-AccuTOF, JMS-T100LC spectrometer.

4.2.1. Synthesis of (3R,4S,5R)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-ol(4a) and (3R,4S,5S)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-ol(4b) (compounds 4a and 4b)

To a stirred solution of **2** (2g, 6.13 mmol) in DCM (5ml), I_2 (2.32g, 9.54mmol) was added. The mixture was stirred for 30 min. at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with DCM and washed sequentially with aqueous $Na_2S_2O_3$ and brine. The aqueous layer was washed with DCM (10mLx3); the combined organic layers were dried over Na_2SO_4, evaporated to dryness to give yellow oil (**3a**, **3b**).

To the stirred solution of crude obtained above (**3a**, **3b)** in dry toluene were added consecutively iodine (1.673g, 6 mmol), triphenyl phospine (1.723g, 6.5mmol) and imidazole (950mg, 13.18mmol). The mixture was stirred at 45 °C for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. It was then diluted with EtOAc and sequentially washed with aqueous $Na_2S_2O_3$, and brine. The aqueous layer was washed with EtOAc (10mLx3); the combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure. Purification on flash column chromatography furnished pure compounds **4a** (350 mg, 1.59 mmol) and **4b** (140 mg, 0.63 mmol) in 36% and 15% respectively.

4.2.1.1 Compound 4a. Eluent for column chromatography: EtOAc/Hexane (4/21, v/v); $[\alpha]_D^{27}$+19.723 (c 0.44, EtOH); R_f= 0.40 (3/7, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (bs, 1H), 3.87-3.90 (m, 1H), 3.98-4.03 (m, 1H), 4.28 (m, 2H), 4.61 (s, 2H), 5.18 (d, 1H. *J*= 10.38Hz), 5.37 (d, 1H, *J*= 17.16), 5.90-6.01 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.1, 74.1, 76.5, 84.7, 89.7, 116.5, 127.7, 127.9, 128.5, 136.8, 137.7; IR (neat, cm^{-1}) 482, 698, 772, 1097, 1219, 1454, 1643, 2144, 2917, 3436; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_3^+$ 243.0992, measured 243.0992;

4.2.1.2 Compound 4b. Eluent for column chromatography: EtOAc/Hexane (9/41, v/v); $[\alpha]_D^{27}$+35.185 (c 0.54, EtOH); R_f= 0.33 (3/7, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66-3.69 (m, 1H), 3.83-3.84 (m, 1H), 4.14-4.19 (m, 1H), 4.34 (bs, 1H), 4.48-4.52 (m, 1H), 4.58 (s, 2H), 5.27 (d, 1H, *J*= 10.32 Hz), 5.37 (d, 1H, *J*= 17.25 Hz), 5.96-6.08 (m, 1H), 7.31 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.2, 73.4, 75.4, 81.7, 85.7, 118.3, 127.5, 127.8, 128.4, 133.6, 137.9; IR (neat, cm^{-1}) 482, 668, 697, 771, 1092, 1163, 1219, 1344, 1455, 1497, 1639, 2087, 2852, 2923, 2958, 3436; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_3^+$ 243.0992, measured 243.0989.

4.2.2 General procedure for iodocycloetherification of allylic alcohols 5, 7 and 9

To the stirred solution of the allylic alcohol (**5** or **7** or **9**) in acetonitrile, 1.5 eq. of I_2 was added. The mixture was stirred for 5h at room temperature. After completion of the reaction (monitored by TLC), the mixture was diluted with EtOAc and washed sequentially with aqueous $Na_2S_2O_3$ and brine. The aqueous layer was washed with EtOAc (5mLx3); the combined organic layers were dried over Na_2SO_4, evaporated to dryness. Column purification of the above crude material furnished the desired tetra substituted THFs (**6** or **8** or **10** respectively).

4.2.2.1 ((2R,3R,4R,5R)-4-(benzyloxy)-5((benzyloxy)methyl)-3-iodotetrahydrofuran-2-yl)methanol (compound 6)

Eluent for column chromatography: EtOAc/Hexane (4/21, v/v); $[\alpha]_D^{27}$ -8.051 (c 0.11, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40-3.43 (m, 1H), 3.54-3.60 (m, 2H), 3.71-3.72 (m, 1H), 3.66-3.68 (m, 1H), 4.10-4.13 (m, 1H), 4.36-4.47 (m, 5H), 4.58-4.61 (m, 1H), 7.17-7.28 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.7, 29.7, 62.8, 69.3, 72.4, 73.6, 78.7, 81.4, 87.8, 127.9, 127.8, 128.0, 128.1, 128.4, 125.6, 135.3; IR (neat, cm^{-1}): 669, 758, 929, 1085, 1216, 1404, 1634, 2400, 2926, 3020, 3401; ESI-HRMS: *m/z* $[M+NH_4]^+$ calcd for $C_{20}H_{27}INO_4^+$ 472.0985, measured 472.0979.

4.2.2.2 ((2R,3R,4R,5R)-3-iodo-4-methoxy-5(methoxymethyl) tetrahydrofuran-2-yl)methanol (compound 8)

Eluent for column chromatography: EtOAc/Hexane (4/21, v/v); $[\alpha]_D^{27}$ -18.055 (c 0.08, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H), 3.54 (s, 3H), 3.59-3.61 (m, 2H), 3.68-3.69 (dd, J_1= 2.40, J_2= 12.48 Hz, 1H), 3.71-3.72 (m, 1H), 3.76-3.77 (bs, 1H), 3.90-3.94 (dd, J_1= 2.32, J_2= 12.44 Hz, 1H), 4.18-4.21 (m, 1H), 4.26-4.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.2, 59.3, 60.1, 60.9, 71.5, 80.0, 82.9, 84.8; IR (neat, cm^{-1}): 669, 758, 1092, 1215, 1404, 1644, 1735, 2851, 2918, 3019, 3409; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_8H_{16}IO_4^+$ 303.0093, measured 303.0087.

4.2.2.3 ((2R,3R,4S,5R)-3-iodo-4-methoxy-5(methoxymethyl) tetrahydrofuran-2-yl)methanol (compound 10)

Eluent for column chromatography: EtOAc/Hexane (4/21, v/v); $[\alpha]_D^{27}$ -13.160 (c 0.07, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93 (bs, 1H), 3.45 (s, 3H), 3.57-3.58 (m, 5H), 3.72-3.75 (m, 1H), 3.87-3.90 (m, 1H), 4.01-4.05 (m, 1H), 4.13-4.18 (m, 2H), 4.26-4.30 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6, 58.8, 59.4, 60.3, 73.3, 82.2, 86.7, 90.5; IR (neat, cm^{-1}): 627, 669, 757, 929, 1036, 1088, 1216, 1404, 1525, 1639, 1733, 2400, 2853, 2927, 3019, 3412, 3685; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_8H_{16}IO_4^+$ 303.0093, measured 303.0089.

4.2.3. Synthesis of (3R, 4S, 5R)-4-(benzyloxy)-5-((E)-tetradec-1-en-1-yl) tetrahydrofuran-3-ol (compound 11)

To a 50 ml two necked oven dried round bottomed flask fitted with reflux condenser and septum was added Grubbs' second generation catalyst (17 mg, 0.02 mmol) under argon atmosphere. The THF **4a** (90 mg, 0.409mmol) in dry DCM and 1- tetradecene were added simultaneously through a syringe to the above flask. The reaction mixture was then degassed. The septum was replaced with a glass stopper while the stirring was continued. The solution was refluxed for 6 h. The temperature of the reaction mixture was cooled slowly to room temperature. The organic solvent was evaporated under reduced pressure to give a brown residue, which was directly purified by column chromatography (230-400 mesh) to furnish pure compound **11** as a colorless oil (85mg, 0.21mmol, 58%).

Eluent for column chromatography: EtOAc/Hexane (3/22, v/v); $[\alpha]_D^{27}$+21.412 (c 0.6, MeOH); R_f= 0.46 (1/4, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.88 (m, 3H), 1.26 (s, 21H), 2.03-2.05 (m, 2H), 3.71 (m, 1H), 3.84-3.87 (m, 1H), 3.94-3.98 (m, 1H), 4.19-4.23 (m, 1H), 4.28 (brs, 1H), 4.6 (s, 2H), 5.51-5.59 (m, 1H), 5.75-5.84 (m, 1H), 7.33 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 28.9, 29.2, 29.4, 29.5, 29.7, 31.9, 32.2, 53.4, 72.0, 73.8, 76.4, 84.7, 89.9, 127.7, 127.9, 128.3, 128.5, 134.6, 137.8; IR (neat, cm^{-1}): 769, 972, 1102, 1218, 1369, 1460, 1641, 2854, 2923, 3438; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{40}NaO_3^+$ 411.2870, measured 411.2867.

4.2.4. Synthesis of (2R, 3S, 4S)-4-azido-3-(benzyloxy)-2-((E)-tetradec-1-en-1-yl)tetrahydrofuran (compound 12)

To a stirred solution of the alcohol **11** (388 mg, 0.219 mmol) in dry DCM (4ml), were added Et_3N (0.046 ml, 0.328 mmol) and MsCl (0.021 ml, 0.2628 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. After completion of the reaction, aq. $NaHCO_3$ solution was added and the reaction mixture was heated to room temperature and afterwards diluted with DCM. The aqueous layer was extracted with DCM (5mLx3). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to obtain the crude mesylated derivative (103 mg, 0.22 mmol). It was dissolved in dry DMF, and then NaN_3 (57.3 mg, 0.88 mmol) was added. The resulting mixture was stirred at 100 °C until the reaction was completed (about 5h.). After completion of the reaction (monitored by TLC), the mixture was diluted with EtOAc. Excess water was added and the aqueous layer was washed with EtOAc (5mLx3). Evaporation of the solvent under reduced pressure followed by silica gel column chromatography of the residue gave the pure azide **12** as colorless oil (62 mg, 0.15 mmol, 68% over two steps). Eluent for column chromatography: EtOAc/Hexane (1/19, v/v); $[\alpha]_D^{27}$+22.542 (c 0.56, MeOH); R_f= 0.75 (5/95, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.9 (m, 3H), 1.26 (brs, 20H), 2.01-2.08 (m, 2H), 3.79-3.97 (m, 2H), 3.92-3.97 (dd, 1H, *J*= 5.25Hz, 9.69Hz), 4.06-4.11 (dd, 1H, *J*= 5.58, 9.36Hz), 4.25-4.3 (t, 1H, *J*= 7.23Hz), 4.61-4.74 (dd, 2H, *J*= 12, 25.32Hz), 5.33-5.40 (dd, 1H, *J*= 7.32, 15.18Hz), 5.76-5.86 (m, 1H), 7.30-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 28.9, 29.7, 31.9, 32.3, 60.7, 69.9, 72.7, 81.7, 83.4, 127.3, 127.8, 128.0, 128.5, 135.9, 137.3; IR (neat, cm^{-1}) 482, 772, 1219, 1467, 1638, 2106, 2852, 2923, 3436; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{39}N_3NaO_2^+$ 436.2934, measured 436.2933.

4.2.5. Synthesis of 2-*epi* jaspine B:

To the solution of azide **12** (150 mg, 0.36 mmol) in methanol (1 mL) taken in a round bottomed flask was added catalytic amount of Pd/C. A vacuum was created in this flask containing the above reaction mixture with the help of pump. The reaction mixture was stirred under hydrogen in balloon. After completion of the reaction (10 h.) catalyst was removed by filtration. The filtrate washed with EtOAc (5mLx2) and the combined filtrate was concentrated to obtain the crude product which on column chromatographic purification gave the pure 2-*epi* jaspine B as a white solid (104 mg, 0.34 mmol, 96%). Eluent for column chromatography: MeOH/EtOAc (1/9, v/v); $[\alpha]_D^{27}$+18.855 (c 0.28, MeOH); mp 96-98 °C; R_f= 0.22 (1/4, MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 0.91-0.93 (m, 3H), 1.32-1.39 (m, 24H), 1.47-1.54 (m, 2H), 3.33-3.35 (m, 1H), 3.44-3.54 (m, 1H), 3.70-3.77 (m, 1H), 3.98-4.06 (m, 1H), 4.08-4.21 (m, 1H); ^{13}C (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.9, 29.6, 29.6, 29.6, 29.7, 31.9, 33.7, 52.7, 73.1, 74.8, 85.3; IR (KBr, cm^{-1}) 626, 669, 758, 929, 1048, 1216, 1405, 1467, 1521, 1639, 2400, 2855, 2928, 3020, 3685; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{18}H_{38}NO_2^+$ 300.2897, measured 300.2894.

4.2.6.1. (E)-6-((tert-butyldimethylsilyl)oxy)-1,3-dimethoxyhex-4-en-2-ol (compound 13)

To a stirred solution of compound **9** (200 mg, 1.13 mmol) in dry DCM at 0 °C were added Et_3N (0.31 mL, 2.27 mmol) and TBSCl (203 mg, 1.356 mmol). The mixture was allowed to stir for 2 h and allowed it to room temperature. On completion, the reaction was quenched with aqueous $NaHCO_3$ solution. The reaction mixture was extracted with DCM (3×5 mL). The extracted organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil which on column purification yielded **13** (290 mg, 94%).

Eluent for column chromatography: EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{27}$ –12.9639 (c 3.7, MeOH); R_f= 0.54 (1/1, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.92 (s, 9H), 2.78 (s, 1H), 3.35 (s, 3H), 3.39 (s, 3H), 3.50-3.51 (m, 2H), 3.65-3.68 (m, 2H), 4.22-2.23 (m, 2H), 5.53-5.59 (m, 1H), 5.82-5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ - 5.2, 25.9, 56.5, 59.2, 62.9, 72.9, 73.0, 82.4, 125.8, 135.3.; IR (neat, cm^{-1}): 669, 764, 839, 977, 1102, 1216, 1254, 1392, 1462, 1641, 2933, 3015, 3423; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{30}NaO_4Si^+$ 313.1811, measured 313.1812.

4.2.6.2. (E)-5-(benzyloxy)-4,6-dimethoxyhex-2-en-1-ol (compound 14)

To a stirred solution of compound **13** (150 mg, 0.5 mmol) in dry THF (2 mL), sodium hydroxide (40 mg, 1.0 mmol), Iodomethane (0.13 mL, 2.08 mmol) and TBAI (catalytic amount) were added at 0 °C and stirred at room temperature for 6 to 8 h. After completion of the reaction, THF was evaporated, extracted with $CHCl_3$, dried over Na_2SO_4, concentrated and evaporated under reduced pressure to obtain the crude oil and it was dissolved in dry THF and slowly added TBAF (0.285mL, 0.98 mmol). After completion of the reaction solvent was evoparated and the residue was purified over column chromatogratphy to yield the pure compound **14** (91 mg, 0.47 mmol, 87%).

Eluent for column chromatography: EtOAc/Hexane (2/3, v/v); $[\alpha]_D^{27}$+8.0441 (c 4.1, $CHCl_3$); R_f= 0.44 (1/1, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33(s, 3H), 3.35-3.38(m, 4H), 3.41-3.45(m, 1H), 3.49(s, 3H), 3.58-3.55(m, 1H), 3.77-3.80 (m, 1H), 4.21(m, 2H), 5.63-5.70(m, 1H), 5.88-5.95(m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.9, 58.9, 59.1, 62.8, 71.8, 81.4, 82.3, 127.8, 133.5; IR (neat, cm^{-1}): 668, 757, 1092, 1215, 1384, 1643, 2935, 3018, 3411; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_9H_{18}NaO_4^+$ 213.1103, measured 213.1099.

4.2.6.3. (E)-4,5,6-trimethoxyhex-2-en-1-ol (compound 15)

To a stirred solution of compound **13** (150 mg, 0.5 mmol) in dry THF (2 mL), sodium hydroxide (40 mg, 1.0 mmol), benzyl bromide (0.13 mL, 1.1 mmol) and TBAI (catalytic amount) were added at 0 °C and stirred at room temperature for 6 to 8 h. After completion of the reaction, THF was evaporated, extracted with $CHCl_3$, dried over Na_2SO_4, concentrated and evaporated under reduced pressure to obtain the crude product and the crude oil was dissolved in dry THF and slowly added TBAF (0.23mL, 0.82 mmol). After completion of the reaction solvent was evoparated and the residue was purified over column chromatogratphy to yield the pure compound **15** (140 mg, 0.52 mmol, 95%).

Eluent for column chromatography: EtOAc/Hexane (1/1, v/v); $[\alpha]_D^{27}$ –10.6769 (c 3.2, $CHCl_3$); R_f= 0.3 (1/1, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04(s, 3H), 3.35(s, 3H), 3.45-3.49(m, 1H), 3.56-3.60(m, 2H), 3.76-3.79(m, 1H), 4.11-4.12(m, 2H), 4.64-4.74(m, 2H), 5.60-5.65(m, 1H), 5.82-5.89(m, 1H), 7.27-7.38(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.0, 59.1, 62.7, 72.5, 73.2, 80.0, 81.7, 127.6, 127.9, 128.2, 133.3, 138.6; IR (neat, cm^{-1}): 669, 757, 1089, 1216, 1402, 1453, 1630, 2929, 3018, 3411; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{22}NaO_4^+$ 289.1416, measured 289.1412.

4.3. Computational studies:

Compound **2** and compound **9**, their proposed iodinium ion and products were sketched using Argus lab and Gauss view5 program[20]. 3D structures were optimized using DFT method b3lyp[21a-c] with a Lanl2dz basis set[22] in the Gaussion09[23]. Acetonitrile solvent model was used to mimic the actual reaction condition. Images were generated with the help of Gauss view5.

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Note: 1. To selectively kill cancer cells but not normal cells, if it is "true toxin" it would kill both types of cells and would have huge side effects. In this regard, our synthesized 2-epi-jaspine B is better than doxorubicine (used as standard reference) as it did not kill normal cells versus cancer cells in similar efficiency (2-epi-jaspine B IC_{50} value DLD1 0.5 μM versus IC_{50} value Vero normal cells >10 μM).

2. National Cancer Institute (NCI), USA also starts their anticancer screening from 10 μM dose and anything less than that is considered to be significant.