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Journal Name

RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Diastereoselective synthesis of highly functionalized *cis*-1-Oxadecalines via *6-endo-tet*-cyclizations of 2-C-branched sugars

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Zinc mediated Barbier reaction of 4-chloro-2-eno-C-allyl pyranoside with aryl aldehydes provided benzylic alcoholic products which underwent $FeCl_3$ catalyzed highly stereoselective 6-endo-tet cyclization giving access to functionalized cis-1-oxadecalins at room temperature.

Introduction

Optimal drug-like parameters and characteristics are a prerequisite for medicinal chemistry and the understanding of a successful drug profile is vital in the development of future small molecule New Chemical Entities (NCEs).[1] One of the key components in medicinal chemistry is the ring system, the fundamental building block of most drugs in the market today. The importance of rings is not difficult to realize because they play a significant role in molecular properties such as the electronic distribution, three dimensionality, lipophilicity or polarity, metabolic stability, toxicity and scaffold rigidity.[2]

1-Oxadecalins are ubiquitous in several bioactive natural products which contain cis/trans fused 6,6 bicyclic framework.[3] These structurally intriguing compounds are selective antagonists of platelet activating factor[4] and show antifungal,[5a] antitumor,[5b] adenylyl cyclase inhibitory,[6] and glycosidase inhibitory activities.[7] There are methods[8] available in the literature which describe the construction of 1-oxadecalin ring system as depicted in Fig.1 Most of the methods[9-11] deal with the construction of cyclohexane ring on the pyran backbone through intermolecular Diels-Alder reaction of pyran based dienes or dienophiles except one which starts from anisole.[9] While the synthesis using pyranyl dienophiles suffer from lack of stereoselectivity,[10] synthesis from pyranyl dienes with electron deficient alkenes have issues such as poor reactivity or the requirement of drastic reaction conditions.[11] The use of Lewis acid promoters to enhance the reactivity of dienophiles with these pyranyl dienes remains largely unexplored, most likely due to the low reactivity of the dienes and their high propensity to decompose in the presence of Lewis acids.

Rich in functionality and stereochemistry, carbohydrates are excellent ‘‘chiral pool’’ constituents for the enantioselective synthesis of biologically active natural and non-natural products.[12] Advantages of using carbohydrates as starting materials include their known absolute stereochemistry, low cost in many cases, and multifarious synthetic utility. Even so, the synthesis of key intermediates by incorporation of suitable functional groups onto carbohydrates, which can then be further exploited, has always been a challenging task. Out of all the methods, there is only one report. where enantiomerically pure carbohydrate dienes have been utilized for the synthesis of 1-oxadecalin scaffolds.[11c] With our continuing interest in the synthesis of useful derivatives from carbohydrates,[13] we planned the use of 2-C branched sugar derivatives derived from D-glucal as starting material for the synthesis of cis fused highly functionalized enantiopure oxadecalin core.

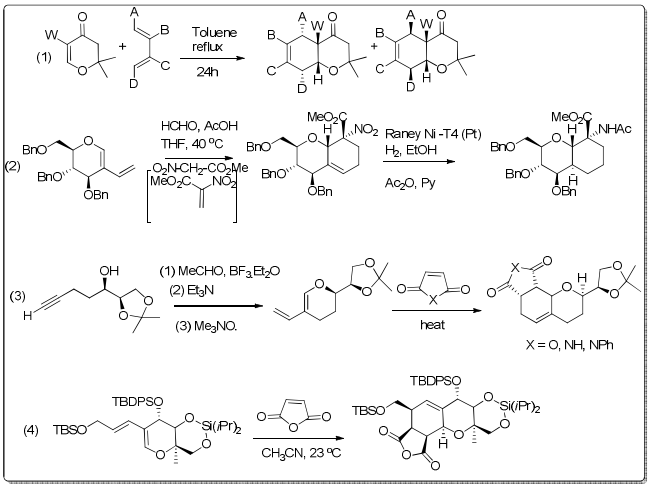

Fig. 1. Prior art to the synthesis of 1-oxadecalin scaffolds.

There are several notable contributions to the area of carbohydrate annulations involving ring-closing metathesis,[14] Robinson annulation,[15] intramolecular aldol condensation,[16] radical cyclization,[17] and Diels-Alder cycloaddition[18] for the construction 6,6 bicyclic rings. In order to assemble 1-

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oxadecalin framework in stereoselective fashion, we thought of a new cyclization method as depicted in fig. 2. The idea was to generate a benzylic carbocation (stabilized by aromatic ring) at C2-position of a suitably substituted pyranose sugar carrying a C-allyl moiety at C1 position. Subsequent electrophilic attack of benzylic carbocation[19] by the terminal alkene at C-1 of the pyranose in 6-*endo-trig* fashion followed by capture of a nucleophile would constitute an efficient synthesis of highly functionalized 1-oxadecalins (Fig. 2). This may be considered as Prins type cyclization without aldehyde component.

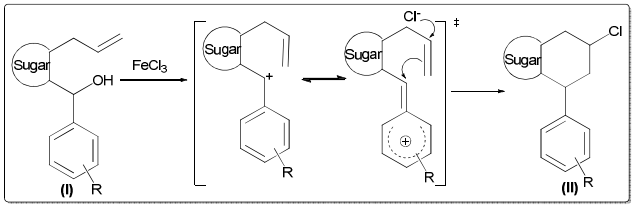
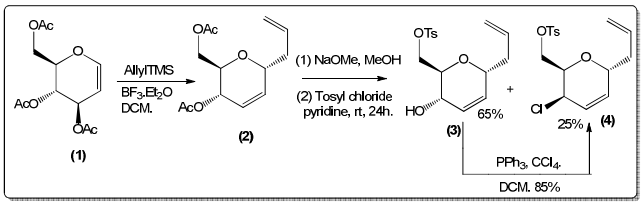


Fig. 2 Schematic route to 1-oxadecalin scaffolds.

In this communication we would like to report the successful use of suitably protected D-glucal as chiral pool for the synthesis of cis fused highly functionalized diastereopure oxadecalin core from iron catalysed ring annulation of 2-C-branched sugar derivatives.

In order to construct the building block for cyclization we selected 4-chloro-2-eno-C-allyl pyranoside (**4**), a side product we earlier encountered while working with the synthesis of pyran embedded macrolides.[20] To obtain the desired derivative **4** as the sole product, the tosyl hydroxy derivative (**3**) was chlorinated in satisfactory yield under Appel reaction condition.[21] Our next aim was to covert this chloro derivative **4** into a 2-C-branched sugar carrying a phenyl hydroxymethyl side chain. For this purpose we replaced the earlier reported indium[22] with cheaper Zn powder for the synthesis of the C-branched sugar derivatives under Barbier condition (Scheme 1).

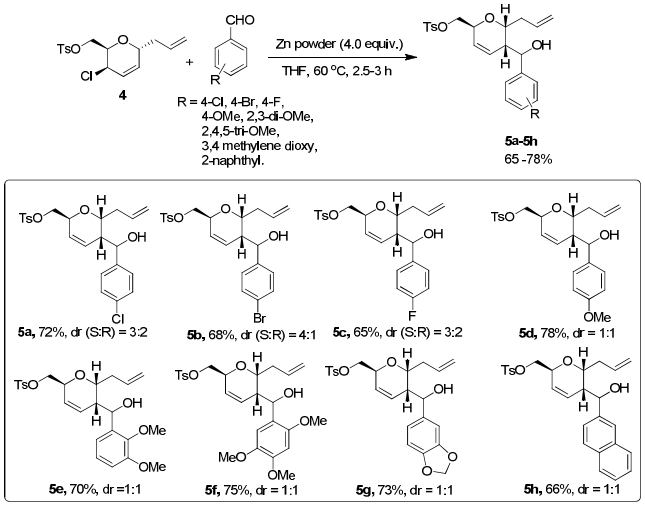


Scheme 1: Synthesis of various 2-*C* branched sugars under zinc mediated Barbier conditions.

The structure of the product was confirmed by spectroscopic analysis. The appearance of new peaks at δ7.46-7.44 (m, 2H) and 7.20-7.16 (m, 2H) for aromatic protons, and at δ4.62 (d, J = 3.2 Hz) for the benzylic proton is in agreement with the proposed structure. Further, the migration of double bond from 2,3 to 3,4 position was confirmed from the observed coupling constant of H-5 ($J_{3,5}$ = 2.8 Hz) indicative of SN_2' type substitution**.** The reaction proceeds smoothly with other electron donating group and halogen substituted aromatic aldehydes as listed in Table 1.

In this particular Barbier type allylation we obtained a mixture of two diastereomeric products only. This may be due to the fact that the electrophile prefers to approach from the side opposite to the departing group (Fig. 3). However, we failed to control the enantioselectivity at the benzylic position and in most of the cases almost equal amounts of diastereomers were obtained except in cases of halogen substituted compounds (table 1) where the *S* isomer was the major product. Nonetheless, this was not a hindrance as the subsequent cyclization step (possibly passing through the carbocation derived by elimination of hydroxy group)

Table 1: Synthesis of various C-branched sugar derivatives.



provided a single stereoisomer at benzylic position in all the cases as detailed below.

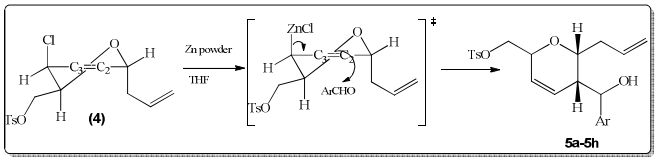


Fig. 3. Conformation of 2,3-D-glycals for the formation Barbier product.

After achieving the synthesis of 2-C branched sugar derivatives (5a-h), we turned our attention to the synthesis of the 1-oxadecalin framework. In order to prove our hypothesis put forward in fig. 2, compound **5g** was chosen as the model substrate for annulations under Prins reaction conditions without aldehyde component. The optimization studies under different acid catalysts similar to Prins reaction revealed $FeCl_3$ as the most suitable catalyst for the *6-endo-tet* cyclization reaction (see optimization table in SI). When compound **5g** was treated with 1.0 mmol of $FeCl_3$ in DCM, the desired oxadecalin derivative 6 was obtained modest yield (30%, entry 1, Table 2).[23] Gratifyingly, lowering the molar proportion of $FeCl_3$ increased the yield of cyclization product and 0.5 mol $FeCl_3$ was found to be the best (68%, entry 3, Table 2). The structure of **6** was confirmed by detailed spectroscopic analysis. Disappearance of peaks characteristic of allyl group such as peaks at δ = 4.98-5.09 (=CH_2, 2H), 5.73-5.65 (=CH, 1H) in ^{1}H NMR, and of δ = 117 (=CH_2) in ^{13}C NMR, combined with appearance of new peaks at δ = 4.65 – 4.57 (m, 1H, H-7) and 2.74 (td, ***J*** = 12.1, 3.1 Hz, 1H, H-5) in 1H NMR, and at

δ = 57.6 (C-Cl, C-7), 44.7 (C-Ph, troscopic analysis (Fig. 4). The cross peaks between H-9, H-5 and H-10 indicated all these protons as cis related (all βH), and no cross peaks between H-5, H-7 suggested them to be trans related (i.e. αH-7). This confirms *S* configurations at C-5 and C-7 of the products.

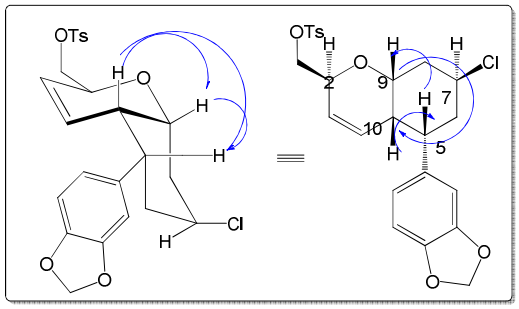
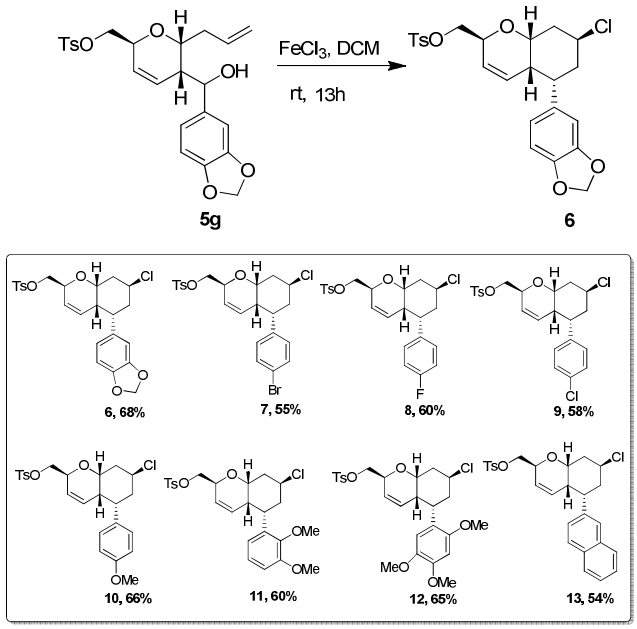


Fig. 4. NOSEY correlations of compound 6.

Annulation reactions of the all the synthesized 2-*C*-branched sugars proceeded smoothly to form the corresponding 1-oxadecalins (**6-13**, Scheme 3) with moderate yields. Reactions proceeded faster and the yields were also better when substrates carrying electron donating groups on the aromatic rings were employed (Scheme 3).



Scheme 3: Synthesis of various highly functionalized 1-Oxadecalins under $FeCl_3$ mediated Prins cyclizations.

Conclusion

In conclusion we have developed the iron catalyzed room temperature ring annulation reactions of *C*-branched sugars, themselves synthesized from Barbier reaction of 4-chloro-2-eno-allyl-pyranoside, leading to the formation of the biologically significant functionalized 1-oxadecalin products diastereoselectively and in moderate yields. This is the first example of halo-Prins type annulation where carbocation instead of oxocarbenium ion involved in cyclization step preclude carbonyl component such as aldehyde or ketone.

Experimental Section

All the reagents used were purchased from sigma Aldrich and Alfa Aesar. Solvents were distilled before use. ^1H and ^{13}C NMR spectra were recorded on 400 and 500 MHz spectrometers (Model No. D 205/ 52-2382, Avance 500) with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). Silica gel coated aluminium plates were used for TLC. The products were purified by column chromatography on silica gel (60-120/100-200 mesh) using petroleum ether–ethyl acetate as the eluent to obtain the pure products. Elemental analyses were performed on Elementar. LCMS was recorded on waters (Model No. Symapt MS) and optical rotation was measured with Perkin Elmer (Model No. 241). The molecular formula some of compounds were determined by HRMS (Agilent, Model No. 6540).

General procedure for the synthesis of *C*-branched sugar derivatives (I):

To a solution of 4-chloro-2-eno-C-allyl pyranoside (**4**) in THF were added zinc powder (4.0 equiv.) and aromatic aldehyde (1.5 equiv.). The resulting reaction mixture was refluxed at 60 ^oC until the reaction was complete as monitored by TLC. Saturated NH_4Cl solution was poured on to reaction mixture which was extracted with ethyl acetate (thrice). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The resulting crude mixture was subjected to column chromatography using petroleum ether/ethyl acetate as eluent to give the corresponding 2-*C*-branched sugars.

Spectral analysis of the compound 5a:

It was prepared by the general procedure **I** using 0.73 mmol (250 mg) of **4,** 4-chloro benzaldehyde (102 mg) to yield the desired product **5a** (72%, 235 mg) as oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.71 (m, 2H), 7.38 – 7.20 (m, 6H), 5.80 – 5.69 (m, 2H), 5.44 (d, *J* = 10.3 Hz, 1H), 5.13 – 4.98 (m, 2H), 4.65 (dd, *J* = 16.7, 7.3 Hz, 1H), 4.41 – 4.26 (m, 1H), 4.26 – 4.18 (m, 1H), 4.12 – 3.96 (m, 2H), 2.45 (s, 3H), 2.25 (dd, *J* = 17.1, 11.0 Hz, 1H), 2.21 – 2.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 141.3, 140.8, 134.5, 133.6, 133.5, 133.2, 132.8, 132.7, 130.9, 129.9 (2C), 128.6, 128.5 (2C), 128.02, 127.9, 127.0, 126.3, 123.47, 117.9, 71.3, 69.3, 66.8, 44.3, 36.1, 21.7. ESI-MS; 461 $(M+Na)^+$; Anal. Cal. For $C_{23}H_{25}ClO_5S$; C, 61.53; H, 5.61; Cl, 7.90; S, 7.14; Found C, 61.58; H, 5.57; Cl, 7.95; S, 7.18.

Spectral analysis of compound 5b:

It was prepared by the general procedure **I** using 0.73 mmol (250 mg) of **4,** 4-bromo benzaldehyde (133 mg) to yield the desired product **5b** (68%, 244 mg) as oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.46-744 (m, 2H), 7.38-7.34 (m, 2H), 7.20-7.16 (m, 2H), 5.85 – 5.60 (m, 2H), 5.43 (dd, *J* = 10.0, 5.3 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.62 (dd, *J* = 18.7, 7.5 Hz, 1H), 4.32 – 4.25 (m, 1H), 4.25 – 4.19 (m, 1H), 4.11 – 3.99 (m, 2H), 2.45 (s, 4H), 2.29 – 2.22 (m, 1H), 2.22 – 2.13 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 141.8, 134.5, 133.6, 132.2, 130.6, 129.9, 129.7, 128.3, 128.1, 127.9, 127.7, 127.0, 126.4, 121.5, 117.3, 74.7, 71.3, 71.0, 66.8, 44.3, 36.1, 21.7.

ESI-MS; 515 $(M+Na)^+$; Anal. Calc. For $C_{23}H_{25}BrO_5S$; C, 55.99; H, 5.11; Br, 16.19; S, 6.50; Found. C, 55.93; H, 5.16; Br, 16.23; S, 6.53.

Spectral analysis of compound 5d.

It was prepared by the general procedure **I** using 0.87 mmol (300 mg) of **4,** 4-methoxy benzaldehyde (119 mg), to yield the desired product **5d** (78%, 313 mg) as oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2H), 7.38 – 7.31 (m, 2H), 7.23-7.19 (m, 2H), 6.91 – 6.86 (m, 2H), 5.90 – 5.71 (m, 2H), 5.65 (dd, *J* = 20.0, 10.4 Hz, 1H), 5.15 – 5.03 (m, 2H), 4.59 (dd, *J* = 14.6, 7.9 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.11 – 3.98 (m, 2H), 3.81 (s, 3H), 2.45 (s, 3H), 2.32 – 2.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (S-isomer) 159.2, 144.8, , 134.7, 133.8, 130.5, 130.0, 129.0, 128.0, 127.9, 127.7, 123.9, 117.6, 113.8, 74.9, 71.1, 69.5, 68.6, 55.2, 44.6, 39.2, 21.6. (R-isomer) 159.1, 144.8, 134.9, 134.5, 133.0, 129.0, 127.9, 127.4, 125.8, 117.0, 113.7, 71.5, 69.3, 66.9, 55.2, 42.0, 36.24, 21.6. ESI-MS; 445 $(M+H)^+$; Anal. Calc. For $C_{24}H_{28}O_6S$; C, 64.84; H, 6.35; S, 7.21; Found. C, 64.87; H, 6.41; S, 7.25.

Spectral analysis of the compound 5e.

It was prepared by the general procedure **I** using 1.0 mmol (250 mg) of **4, 2,3**-dimethoxy benzaldehyde (121 mg) to yield the desired product **5e** (70%, 242mg) as oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.35-7.31 (m, 2H), 7.09 – 6.99 (m, 1H), 6.94 – 6.80 (m, 2H), 5.89 – 5.57 (m, 3H), 5.16 – 4.97 (m, 2H), 4.83 (dd, *J* = 16.4, 7.6 Hz, 1H), 4.37 – 4.20 (m, 2H), 4.08 – 3.95 (m, 2H), 3.85 (s, 3H), 3.82 (d, *J* = 8.1 Hz, 3H), 2.74 (s, 1H), 2.51 (s, 3H), 2.37 – 2.08 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 152.5, 146.2, 135.7, 134.7, 132.9, 129.8 (2C), 128.1, 127.4 (2C), 124.1 , 119.9, 117.6, 111.7, 71.6, 69.4, 68.5, 60.8, 55.7 (2C), 43.5, 39.2, 21.6. ESI-MS; 497 $(M+Na)^+$; Anal. Cal. For $C_{25}H_{30}O_7S$; C, 63.27; H, 6.37; S, 6.76; Found. C, 63.31; H, 6.40; S, 6.72.

Spectral analysis of compound 5g.

It was prepared by the general procedure **I** using 0.73 mmol (250 mg) of **4,** and 109 mg of 3,4-methylene dioxy benzaldehyde to yield the desired product **5g** (**dr = 1;1**, 73%, 244 mg) as oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.35-7.32 (m, 2H), 6.84 – 6.69 (m, 3H), 5.86 – 5.71 (m, 2H), 5.64 (m, 1H), 5.14 – 5.00 (m, 2H), 4.53 (dd, *J* = 17.1, 8.0 Hz, 1H), 4.29-4.24 (m, 2H), 4.09 – 3.97 (m, 2H), 2.51(m, 3H), 2.35 – 2.05 (m, 3H). ESI-MS; 481 $(M+Na)^+$; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.2, 144.9, 136.8, 134.7, 132.9, 129.8, 128.6, 128.0, 127.9, 127.3, 125.9, 120.0, 117.7, 108.0, 106.8, 101.0, 75.15, 71.07, 69.4, 66.8, 44.5, 39.17, 21.6. Anal. Calc. For $C_{24}H_{26}O_7S$; C, 62.87; H, 5.72; S, 6.99; Found. C, 62.91; H, 5.67; S, 6.95.

General procedure for the synthesis of highly functionalized 1-oxadecalines using $FeCl_3$ (II).

To a solution of C-branched sugar compound (**5a-5h**,1mmol) in dry DCM, add the $FeCl_3$ (0.5 equiv.) was added and stirred at rt for 12-15h, after completion of reaction as monitored by TLC, the reaction mixture was diluted with water and extracted with DCM (3x15mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The crude reaction mixture was subjected to silica gel chromatography using petroleum ether/ethyl acetate as elute to yield the desired products **6-13**.

Synthesis of ((2*S*,4a*S*,5*S*,7*S*,8a*R*)-5-(benzo[d][1,3]dioxol-5-yl)-7-chloro-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (6).

It was prepared by the general procedure **II** using 0.43 mmol (200 mg) of **5g** to yield the desired product **6** (68%, 141 mg) as a white powder. $[\alpha]^{20}_D$ = +4.2 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.37-7.35 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 1.4 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.94 (s, 2H), 5.60 (d, *J* = 10.3 Hz, 1H), 5.52 (dt, *J* = 10.3, 2.5 Hz, 1H), 4.65 – 4.57 (m, 1H), 4.47 – 4.37 (m, 1H), 4.11 (dd, *J* = 10.6, 7.4 Hz, 1H), 4.00 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.73 – 3.64 (m, 1H), 2.74 (td, *J* = 12.1, 3.1 Hz, 1H), 2.19 – 2.05 (m, 3H), 1.97 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 146.4, 144.8, 135.2, 132.6, 130.3, 130.2, 129.9, 128.0, 127.9, 124.2, 121.1, 108.4, 100.8, 71.1, 69.8, 68.3, 57.6, 44.7, 42.5, 40.4, 38.7, 21.5. ESI-MS; 477 $(M+H)^+$; Anal. Cal. For C, $C_{24}H_{25}ClO_6S$; C, 60.44; H, 5.28; Cl, 7.43; S, 6.72; Found; C, 60.48; H, 5.25; Cl, 7.46; S, 6.76.

Synthesis of ((2*S*,4a*S*,5*S*,7*S*,8a*R*)-5-(4-bromophenyl)-7-chloro-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (7).

It was prepared by the general procedure **II** using 0.38 mmol (190 mg) of **5b** to yield the desired product **7** (55%, 108 mg) as oily liquid. $[\alpha]^{20}_D$ = +7.6 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.82 (m, 2H), 7.45 – 7.43 (m, 2H), 7.37 – 7.35 (m, 2H), 7.06-7.03 (m, 2H), 5.56 – 5.50 (m, 2H), 4.70 – 4.57 (m, 1H), 4.44 – 4.35 (m, 1H), 4.15 – 4.08 (m, 1H), 4.00 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.76 – 3.68 (m, 1H), 2.80 (td, *J* = 12.1, 3.3 Hz, 1H), 2.47 (s, 3H), 2.20 – 2.08 (m, 3H), 1.97 – 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 140.6, 132.7, 131.9, 131.8, 131.6, 130.5, 129.9, 129.7, 129.4, 128.2, 128.0, 124.6, 120.7, 71.5, 69.8, 68.3, 57.8, 44.5, 42.4, 40.4, 38.7, 21.7. ESI-MS; 511 $(M+H)^+$; Anal. Cal. For C, $C_{23}H_{24}BrClO_4S$; C, 53.97; H, 4.73; Br, 15.61; Cl, 6.93; S, 6.26. Found; C, 53.93; H, 4.76; Br, 15.58; Cl, 6.95; S, 6.22.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-5-(4-fluorophenyl)-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (8).

It was prepared by the general procedure **II** using 0.32 mmol (140 mg) of **5c** to yield the desired product **8** (60%, 87.5 mg) as oily liquid. $[\alpha]^{20}_D$ = +2.3 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.37-7.35 (m, 2H), 7.14 – 7.11 (m, 2H), 7.03-6.99 (m, 2H), 5.58 – 5.48 (m, 2H), 4.62 (s, 1H), 4.40 (dd, *J* = 10.8, 7.3 Hz, 1H), 4.11 (dd, *J* = 10.1, 7.6 Hz, 1H), 4.01 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.75 – 3.68 (m, 1H), 2.81 (td, *J* = 12.1, 3.0 Hz, 1H), 2.46 (s, 3H), 2.20 – 2.08 (m, 3H), 1.98 – 1.81 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 144.9, 137.1, 132.8, 132.2, 130.0, 129.9, 129.8, 129.4, 129.3, 128.0, 124.5, 115.7, 115.5, 71.2, 69.8, 68.4, 57.8, 44.6, 42.5, 40.2, 38.8, 21.6. ESI-MS; 473 $(M+Na)^+$; Anal. Cal. For C, $C_{23}H_{24}ClFO_4S$; C, 61.26; H, 5.36; Cl, 7.86; F, 4.21; S, 7.11; Found. C, 61.23; H, 5.39; Cl, 7.82; F, 4.25; S, 7.14.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-5-(4-chlorophenyl)-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (9).

It was prepared by the general procedure **II** using 0.34 mmol (170 mg) of **5a** to yield the desired product **9** (58%, 94 mg) as oily liquid. $[\alpha]^{20}_{D}$ = +3.8 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.39-7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.13-7.08 (m, 2H), 5.59 – 5.48 (m, 2H), 4.69 – 4.56 (m, 1H), 4.48 – 4.37 (m, 1H), 4.14 – 4.08 (m, 1H), 4.00 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.75 – 3.68 (m, 1H), 2.81 (td, *J* = 12.1, 3.3 Hz, 1H), 2.46 (s, 3H), 2.19-2.08 (m 3H), 1.98 – 1.81 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 139.9, 132.7, 132.6, 130.1, 130.0, 129.9, 129.8, 129.3, 128.9, 128.5, 128.0, 124.6, 71.1, 69.8, 68.3, 57.8, 44.5, 42.3, 40.3, 38.7, 21.7. ESI-MS; 489 $(M+Na)^+$; Anal. Cal. For $C_{23}H_{24}Cl_2O_4S$; C, 59.10; H, 5.18; Cl, 15.17; S, 6.86; Found. C, 59.14; H, 5.13; Cl, 15.19; S, 6.82.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-4a,5,6,7,8,8a-hexahydro-5-(4-methoxyphenyl)-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (10).

It was prepared by the general procedure **II** using 0.42 mmol (200 mg) of **5d** to yield the desired product **9** (66%, 137 mg) as white powder. $[\alpha]^{20}_{D}$ = +4.2 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.37-7.35 (m, 2H), 7.08-7.06 (m, 2H), 6.86-6.84 (m, 2H), 5.57 (d, *J* = 10.3 Hz, 1H), 5.50 (dt, *J* = 10.3, 2.5 Hz, 1H), 4.70 – 4.55 (m, 1H), 4.46 – 4.37 (m, 1H), 4.11 (dd, *J* = 10.5, 7.4 Hz, 1H), 4.06 – 3.96 (m, 1H),3.79 (s, 3H), 3.74 – 3.66 (m, 1H), 2.76 (td, *J* = 12.1, 3.2 Hz, 1H), 2.13-2.09 (m, 3H), 1.98 – 1.89 (m, 1H), 1.89 – 1.80 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 144.9, 133.3, 132.7, 130.4,130.2 129.97, 127.95, 128.9, 128.00, 127.9, 124.1, 114.1, 114.0, 71.2, 69.8, 68.4, 58.0, 55.2, 44.7, 42.6, 39.9, 38.7, 21.4. ESI-MS; 485 $(M+Na)^+$; Anal. Cal. For C, $C_{24}H_{27}ClO_5S$; C, 62.26; H, 5.88; Cl, 7.66; S, 6.93; Found. C, 62.30; H, 5.85; Cl, 7.69; S, 6.96.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-5-(2,3-dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (11)

It was prepared by the general procedure **II** using 0.37 mmol (180 mg) of **5e** to yield the desired product **10** (60%, 122 mg) as oily liquid. $[\alpha]^{20}_{D}$ = + 5.6 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.38-7.36 (m, 2H), 7.05 (dd, *J* = 16.5, 8.2 Hz, 1H), 6.82 (t, *J* = 9.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.59 – 5.44 (m, 2H), 4.62 (s, 1H), 4.42 (s, 1H), 4.19 – 4.08 (m, 1H), 3.99 (dd, *J* = 10.6, 3.5 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.74-3.72 (m, 1H), 3.45 (t, *J* = 12.8 Hz, 1H), 2.46 (s, 3H), 2.13-2.06 (m, 3H), 1.89-1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 148.3, 144.9, 135.4, 132.8, 130.6, 129.99, 129.94, 129.88, 128.02, 128.00, 124.4, 118.7, 110.4, 71.4, 69.7, 68.4, 61.0, 58.1, 55.7, 44.4, 42.0, 38.8, 32.0, 21.7. ESI-MS; 493 $(M+H)^+$; Anal. Cal. For C, $C_{25}H_{29}ClO_6S$; C, 60.90; H, 5.93; Cl, 7.19; S, 6.50. Found. C, 60.93; H, 5.97; Cl, 7.15; S, 6.47.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-4a,5,6,7,8,8a-hexahydro-5-(2,4,5-trimethoxyphenyl)-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (12).

It was prepared by the general procedure **II** using 0.33 mmol (150 mg) of **5f** to yield the desired product **11** (65%, 113 mg) as white powder. $[\alpha]^{20}_{D}$ = + 2.9 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.40-7.36 (m, 2H), 6.64 (s, 1H), 6.54 – 6.50 (m, 1H), 5.57-5.45 (m, 2H), 4.39 (s, 1H), 4.13 (dd, *J* = 10.6, 7.3 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.93-3.89 (m, 1H) 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.24 – 3.11 (m, 1H), 2.85 (td, *J* = 12.2, 3.1 Hz, 1H), 2.47 (s, 3H), 2.28-2.16 (m, 2H), 2.13 – 2.02 (m, 1H), 1.80 – 1.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 148.3, 145.0, 143.6, 133.1, 130.5, 129.9, 129.7, 128.0, 124.0, 120.5, 110.8, 97.8, 71.6, 71.3, 69.9, 56.8, 56.5, 56.2, 55.1, 44.3, 43.2, 41.9, 34.9, 21.6. HRMS calc. 523.1557 $(M+H)^+$; HRMS found 523.1556 $(M+H)^+$.

Synthesis of ((2S,4aS,5S,7S,8aR)-7-chloro-5-(naphthalen-2-yl)-4a,5,6,7,8,8a-hexahydro-2H-chromen-2-yl)methyl 4-methylbenzenesulfonate (13).

It was prepared by the general procedure **II** using 0.21 mmol (100 mg) of **5h** to yield the desired product **12** (54%, 56 mg) as oily liquid. $[\alpha]^{20}_{D}$ = +3.0 (c, 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (m, *J* = 20.7, 10.2 Hz, 5H), 7.63 (s, 1H), 7.47-7.43 (m, 1H), 7.41 – 7.27 (m, 4H), 5.63 – 5.41 (m, 2H), 4.66 (s, 1H), 4.53 – 4.38 (m, 1H), 4.22 – 4.11 (m, 2H), 4.02 (dd, *J* = 10.6, 3.5 Hz, 2H), 3.87 – 3.71 (m, 1H), 3.07 – 2.97 (m, 1H), 2.49 (s, 3H), 2.35 (dd, *J* = 25.6, 14.5 Hz, 1H), 2.25 – 2.05 (m, 3H), 1.97 – 1.88 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 139.6, 133.4, 130.2, 130.1, 130.01, 129.7, 129.4, 128.7, 128.5, 128.0, 127.7, 127.0, 126.9, 126.4, 126.2, 126.01, 125.7, 124.4, 124.2, 71.3, 69.8, 68.5, 58.0, 44.5, 42.4, 41.2, 38.8, 21.7. ESI-MS; 483 $(M+H)^+$; Anal. Cal. For C, $C_{27}H_{27}ClO_4S$; C, 67.14; H, 5.63; Cl, 7.34; S, 6.64. Found; C, 67.17; H, 5.60; Cl, 7.30; S, 6.67.

ACKNOWLEDGMENT

Authors are thankful to Dr Ram A Vishwakarma, Director IIIM Jammu, DST (GAP 1145) for generous funding, MRL thankful to CSIR-UGC New Delhi for senior research fellowship

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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23. Indeed we obtained side products in very minor quantities which we failed to characterize.

Graphical abstract

Diastereoselective synthesis of highly functionalized cis-1-Oxadecalines via *6-endo-tet*-cyclizations of 2-C-branched sugars