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REGULAR ARTICLE

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Synthesis of four diastereomers of notoryne and their ^{13}C NMR chemical shifts analysis

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Abstract. In this manuscript we document the details of the synthesis of four diastereomers of notoryne. The synthesis of one of the diastereomer having a similar relative stereochemistry of substituents on the both THF rings like notoryne, however, being the relative stereochemistry between the bridging carbon of these two THF units is changed from anti to syn has been executed mainly to learn how the ring carbon chemical shifts vary with this change. Interestingly, the deviations are found mainly for the carbons of THF ring that bears the Br-group. In addition to this isomer, three more diastereomers having the relative stereochemistry of substituents on either of the THF rings varied have been also synthesized. All four diastereomers have been subjected for extensive NMR studies and their ^{13} C NMR chemical shifts have been compared with notoryne and laurendecumenyne B. In addition, chemical shifts for the four diastereomers along with these natural products were calculated with the help of DFT calculations and compared to the experimentally obtained chemical shift values.

1. Introduction

Acetogenins are a specialised class of polyketide natural products, isolated from the *Annonaceous* plants representing mainly this family.[1–5] Most of these acetogenins especially isolated from the *Annonaceous* species are white waxy derivatives of long-chain fatty acids (C32 or C34) and are characterized by the presence of a single, adjacent, or nonadjacent tetrahydrofuran (thf) or tetrahydropyran (thp) rings, one or two flanking hydroxyl groups and a γ-lactone terminus. In this regard, the acetogenins isolated from the red algae *Laurencia* need special mention, as they are quite different from plant acetogenins.[6–13] These acetogenins comprise of a C15 carbon core with an enyne or bromoallene terminal and are usually halogenated. Leaving the potent and biological activities that they display, the acetogenins, in general, and of this *Laurencia* family, in particular, have attracted a great deal of synthetic attention mainly due to the problems associated with their structural elucidation and because many of these family members have been assigned with the wrong structures.[14–20] The structure determination of the acetogenins with multiple tetrahydrofuran (thf) rings is challenging, as the thf rings are notorious for their high conformational flexibility.[21,22] Though single-crystal X-ray diffraction studies could solve this puzzle, in a majority of the cases, these acetogenins are either liquids or waxy solids. In this pursuit, the 2D NMR analysis or the ^{13}C NMR chemical shift comparison are the two important tools used for structure prediction.[23] However, as mentioned above, on several occasions these predicted structures have been shown to be wrong.

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For example, elatenynes A/B were isolated twice from different marine algae with the putative structure.[6–8] Later, a similar natural product chloroenyne was isolated by Sticher's group with the proposal of also a wrongly assigned structure.[11] The problems associated with their putative structures have been solved by a DFT calculation of ^{13}C NMR followed by laboratory synthesis by Burton and his co-workers.[18] Subsequently, the combination of DFT calculations and ^{13}C NMR spectral data analysis has been efficiently employed in assigning the relative stereochemistry acetogenins on several occasions.[24,25] For example, the putative structures of the laurefurenynes A and B were corrected by Britton and subsequently by Burton groups by total synthesis of diastereomers and ^{13}C NMR study.[14,15] Recently, we documented the total synthesis of notoryne, which is another member of these C15-acetogenins having a *bis*-thf ring.[19] Notoryne along with Laurefucin were isolated from the leaves of *Laurencia nipponica* in 1991 by the Suzuki group.[12,13] The structural assignment of notoryne does indeed pose its own challenge that has been manoeuvred elegantly by Suzuki's group by carrying a systematic chemical degradation/functional group modifications and characterization/comparison of the resulting intermediates with the known derivatives. The structure of notoryne comprises of a *bis*-thf unit and each thf ring is substituted with a bromo or chloro group, with the chloro-substituted thf ring having the characteristic enyne unit. Indeed, in parallel, we have also synthesized a couple of diastereomers of notoryne having a *threo*-stereochemistry between the ring oxygen-bearing C9 and C10 carbons. This has been planned to understand the variation of the ^{13}C NMR chemical shifts when the stereochemistry of the pendant thf-ring, especially of the stereochemistry of the carbon that is directly connected to the ring, is varied. In this article, we document the complete details about the synthesis of these four diastereomers **1**–**4** of notoryne and a comparison of the chemical shifts observed for these isomers with the calculated chemical shifts (Figure 1).

As shown in Scheme 1, our initial plan was to synthesize the diastereomer **1** in which the relative configuration of both thf rings was similar to that present in notoryne, except that all the three centers of Br-bearing thf ring (thf-Br) were inverted. The synthesis of this diastereomer is planned to provide unambiguous support for the stereochemistry of notoryne to be confirmed, as it was expected to have a similar ^{13}C chemical shift pattern to that of notoryne with minor deviations that might be resulting from the change of the relative configuration between C9 and C10 centers (as the other natural products bear a *cis*-1,4-linked THF-Br unit). However, due to the poor diastereoselectivity during the construction of the thf-Br, it provided an opportunity to synthesize the other three possible diastereomers **2**–**4**. Scheme 1 provides a brief retrosynthetic plan for diastereomer **1** that involves a relay cross-metathesis reaction of the key intermediate **1a** with **6** to introduce the terminal *Z*-enyne unit. The key intermediate **1a** was planned from the homoallylic alcohol **7** *via* bromo-cycloetherification followed by anomeric *C*-allylation. The synthesis of **7** was a straight forward proposition from the known epoxide **8** *via* opening with lithiated 1-butyne and subsequent *E*-selective reduction of the alkyne unit under Birch reduction conditions and methanolosis of the 1,2-acetonide group.

2. Experimental

2.1 *Synthesis of Alkynol 9*

To a stirred solution of *n*-Butyne (16.11 mL, 5.0 M, 80.56 mmol) in dry THF (60 mL) were added dropwise *n*-BuLi (43 mL, 1.5 M, 64.44 mmol) followed by $BF_3.OEt_2$ (7.95 mL, 64.44 mmol) at − 78 °C. After stirring for 30 min, a solution of epoxide **8** (3.0 g, 16.11 mmol) in dry THF (30 mL) was added dropwise to the above solution at the same temperature. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated ammonium chloride. The organic layer was partitioned with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mixture with silica gel column chromatography gave alkynol **9** (3.15 g, 81%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: −34.9 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.12 (t, *J* = 7.5 Hz, 3H), 1.33 (s, 3H), 1.56 (s, 3H), 1.61 (br. s., 1H), 2.13–2.20 (m, 3H), 2.26 (ddd, *J* = 6.1, 8.4, 14.5 Hz, 1H), 2.43 (dd, *J* = 2.3, 6.1 Hz, 1H), 2.88 (s, 1H), 3.88 (dd, *J* = 6.1, 12.6 Hz, 1H), 4.24 (td, *J* = 3.4, 8.4 Hz, 1H), 4.77 (dd, *J* = 3.4, 5.0 Hz, 1H), 5.82 (d, *J* = 3.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.4 (t), 14.1 (q), 23.9 (t), 26.0 (q), 27.0 (q), 33.7 (t), 71.2 (d), 74.9 (s), 80.8 (d), 83.2 (d), 84.1 (s), 106.1 (d), 112.5 (s) ppm; HRMS: calcd for $C_{13}H_{20}O_4$ $[M+Na]^+$ 263.1260, found 263.1254.

2.2 *Synthesis of Alkenol 10*

At − 78 °C, ammonia (200 mL) was condensed on a three necked 500 mL round bottom flask, lithium

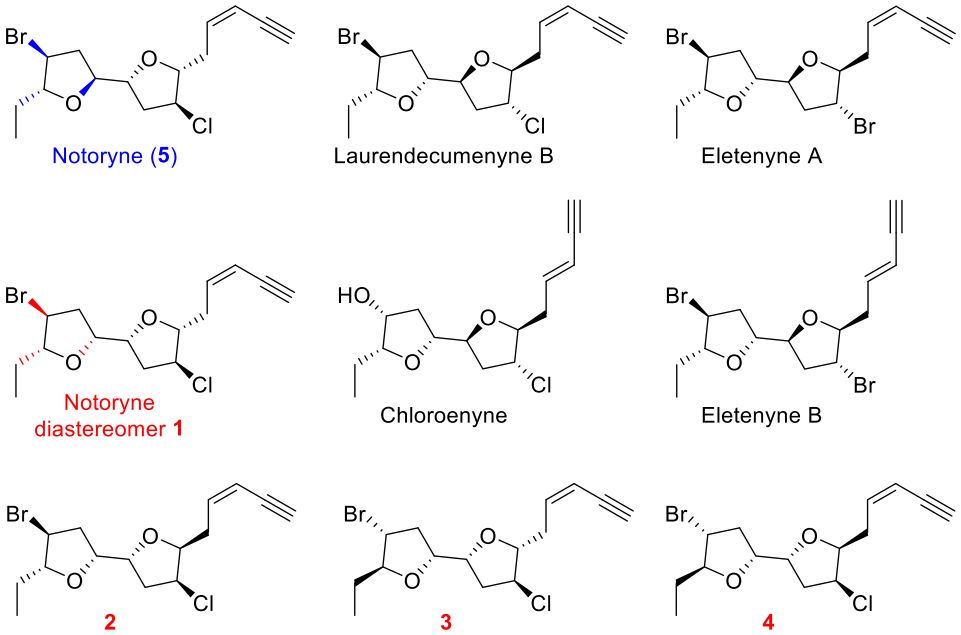
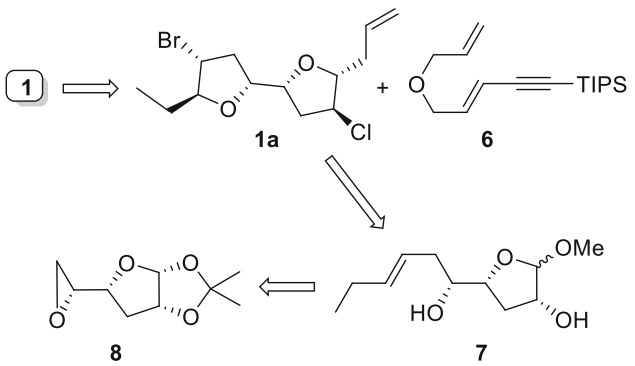


Figure 1. The structures of *bis*-THF unit natural products and the synthesized notoryne diastereomers **1–4**



Scheme 1. Retrosynthetic plan for diastereomer **1**

metal (433 mg, 62.4 mmol) was added in small pieces to it with vigorous stirring. After five minutes, alkynol **9** (3.1 g, 12.5 mmol) in dry THF was added slowly to the blue supernatant solution over a period of 15 min. The reaction was stirred for 3 h at − 50 °C, quenched with solid ammonium chloride (∼ 5 g) and ammonia was allowed to evaporate. The reaction mixture was diluted with water and partitioned with ethyl acetate, solvent was evaporated under reduced pressure and purification of the crude reaction mixture afford alkenol **10** (2.70 g, 89%) as a colourless liquid. R_f = 0.35 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 11.4 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 0.97 (t, *J* = 7.6 Hz, 3H), 1.32 (s, 3H), 1.55 (s, 3H), 1.97–2.08 (m, 3H), 2.08–2.27 (m, 3H), 2.73 (br. s., 1H), 3.75–3.85 (m, 1H), 4.00 (td, *J* = 8.1, 3.4 Hz, 1H), 4.72–4.80 (m, 1H), 5.43–5.52 (m, 1H), 5.52–5.61 (m, 1H), 5.80 (d, *J* = 3.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7 (q), 25.6 (t), 26.0 (q), 27.0 (q), 33.6 (t), 36.6 (t), 72.6 (d), 80.8 (d), 83.9 (d), 106.1 (d), 112.5 (s), 124.4 (d), 135.0 (d) ppm; HRMS: calcd for $C_{13}H_{22}O_4Na$ 265.1409 $[M + Na]^+$, found 265.1410.

2.3 *Synthesis of methyl glycosides 7α and 7β*

At 0 °C, 0.5 mL of concentrated sulfuric acid was added to a stirred solution of alkenol **10** (2.6 g, 10.73 mmol) in methanol (50 mL). The reaction was warmed to room temperature and kept for 6h at the same temperature. After completion of the starting material, the reaction mixture was diluted with saturated $NaHCO_3$ solution (20 mL) and the solvent was evaporated under reduced pressure. The crude reaction mixture was diluted with ethylacetate and water. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification of the crude reaction mixture with silica gel column chromatography gave compound **7α** (1.82 g, 78%) and compound **7β** (180 mg, 8%) as colorless liquids.

Characterisation Data of **7β**: R_f = 0.3 (50% EtOAc in petroleum ether);$\alpha]^{25}_D$: +69.9 (*c* 4.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); 1.00 (t, *J* = 7.3 Hz, 3H), 1.68 (br. s., 1H), 1.79 (dd, *J* = 14.0, 3.1 Hz, 1H), 2.06 (dt, *J* = 7.3, 14.1 Hz, 2H), 2.38 (t, *J* = 7.9 Hz, 2H), 3.35 (s, 3H), 3.55 (t, *J* = 6.1 Hz, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 4.17 (dt, *J* = 9.2, 2.0 Hz, 1H), 4.84 (s, 1H), 5.43

(dt, J = 14.6, 7.3 Hz, 1H), 5.67 (dt, J = 14.6, 6.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7 (q), 25.6 (t), 34.9 (t), 37.4 (t), 54.5 (d), 72.1 (d), 74.0 (d), 79.3 (d), 109.8 (d), 124.4 (d), 137.0 (d) ppm; HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1254.

Characterisation Data of **7α**:R_f = 0.25 (50% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 1.9 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (t, J = 7.3 Hz, 3H), 1.66–1.76 (m, 2H), 2.04 (quintet, 2H), 2.18 (dd, J = 7.3, 14.1 Hz, 2H), 2.27 (dt, J = 7.3, 12.2 Hz, 2H), 2.39 (d, J = 9.8 Hz, 1H), 2.52 (br. s., 1H), 3.45 (d, J = 4.9 Hz, 1H), 3.49 (s, 1H), 4.00 (dt, J = 6.2, 8.3 Hz, 1H), 4.25 (dt, J = 4.3, 8.0 Hz, 1H), 4.76 (d, J = 4.3 Hz, 1H), 5.45 (dt, J = 6.7, 15.3 Hz, 1H), 5.58 (dt, J = 6.1, 15.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 13.7 (q), 25.6 (t), 33.3 (t), 36.8 (t), 54.6 (d), 72.7 (d), 74.1 (d), 80.3 (d), 102.1 (d), 124.3 (d), 134.5 (d) ppm; HRMS: calcd for $C_{11}H_{20}O_4Na$ 239.1254 $[M + Na]^+$, found 239.1252.

2.4 *Synthesis of compound 11 and 12*

To a stirred solution of the methyl glycoside **7β** (1.7 g, 10.22 mmol) in dry dichloromethane (30 mL) at 0 °C, N-Bromo Succinimide (1.82 g, 10.22 mmol) was added and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (85:15 petroleum ether/EtOAc) gave compound **12** (910 mg, 39%) and **11** (720 mg, 31%) in 1:1.3 ratio as colourless liquids.

Characterisation Data of Compound **11**: R_f = 0.4 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: –38.7 (*c* 3.7, $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_3$): 1.01 (t, J = 7.3 Hz, 3H), 1.50–1.56 (m, 1H), 1.70–1.78 (m, 1H), 1.85 (dd, J = 1.7, 13.8 Hz, 1H), 2.27 (ddd, J = 5.3, 7.0, 13.1 Hz, 1H), 2.45 (ddd, J = 5.5, 10.0, 15.1 Hz, 1H), 2.67 (dt, J = 7.0, 13.8 Hz, 1H), 3.34 (s, 3H), 4.00 (dd, J = 5.8, 11.3 Hz, 1H), 4.04–4.14 (m, 2H), 4.20–4.23 (m, 2H), 4.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$); 10.3 (q), 26.4 (t), 34.4 (t), 38.2 (t), 49.0 (d), 54.6 (q), 73.7 (d), 77.8 (d), 79.3 (d), 89.1 (d), 110.0 (d) ppm; HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0358.

Characterisation Data of Compound **12**: R_f = 0.35 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: –102.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); 1.01 (t, J = 7.3 Hz, 3H), 1.45–1.52 (m, 1H), 1.80 (dd, J = 2.3, 14.0 Hz, 1H), 1.88 (ddd, J = 3.1, 7.5, 14.2 Hz, 1H), 2.48 (ddd, J = 5.5, 10.0, 15.3 Hz, 1H), 2.56 (t, J = 8.6 Hz, 2H), 3.35 (s, 3H), 3.81 (q, J = 9.0 Hz, 1H), 3.91 (td, J = 3.3, 9.0 Hz, 1H), 3.97–4.03 (m, 2H), 4.19 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 11.0 Hz, 1H), 4.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.1 (q), 25.0 (t), 34.6 (t), 38.2 (t), 46.7 (d), 54.6 (q), 73.6 (d),78.1 (d), 78.8 (d), 86.9 (d), 109.8 (d) ppm; HRMS: calcd for $C_{11}H_{19}BrO_4$ $[M+Na]^+$ 327.0359 found 327.0359.

2.5 *Preparation of compound 11-Ac*

To a solution of compound **11** (20 mg, 0.06 mmol) in dry dichloromethane (10 mL) at 0 °C was added Et_3N (0.06 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.02 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction mixture by column chromatography (90:10 petroleum ether/EtOAc) gave the **11-Ac** (22 mg, 96%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: −35.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.60–1.71 (m, 3H), 2.07 (s, 3H), 2.22–2.33 (m, 2H), 2.46 (ddd, J = 7.0, 8.3, 14.6 Hz, 1H), 3.37 (s, 3H), 4.02 (dt, J = 5.3, 6.6 Hz, 1H), 4.07–4.13 (m, 2H), 4.22 (q, J = 7.0 Hz, 1H), 4.97 (s, 1H), 5.03 (dd, J = 2.0, 6.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (q), 21.0 (q), 26.6 (t), 32.3 (t), 39.0 (t), 48.9 (d), 54.8 (q), 77.5 (d), 79.4 (d), 79.8 (d), 89.0 (d), 107.2 (d), 170.4 (s) ppm; HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0461 and 361.0439.

2.6 *Preparation of compound 12-Ac*

To a solution of **12** (30 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.03 mL, 0.3 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the **12-Ac** (31 mg, 90%) as colourless syrup: R_f = 0.6 (20% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 77.0 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.64 (m, 1H), 1.72–1.82 (m, 1H), 2.06 (s, 3H), 2.08 (dt, J = 8.3, 13.2 Hz, 1H), 2.47 (ddd, J = 6.8, 8.5, 14.6 Hz, 1H), 2.65 (dt, J = 7.1, 13.3 Hz, 1H), 3.38 (s, 3H), 3.90 (dt, J = 7.6, 8.5 Hz, 1H), 4.01 (td, J = 4.5,

7.3 Hz, 1H), 4.08 (dd, J = 7.3, 15.1 Hz, 1H), 4.23 (ddd, J = 5.5, 7.7, 13.3 Hz, 1H), 4.97 (s, 1H), 5.04 (dd, J = 1.8, 6.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.7 (q), 21.0 (q), 25.1 (t), 32.0 (t), 39.1 (t), 46.9 (d), 54.8 (q), 77.4 (d), 79.4 (d), 80.0 (d), 86.7 (d), 107.1 (d), 170.3 (s) ppm; HRMS (ESI): calcd for $C_{13}H_{21}BrO_5$ $[M+Na]^+$ 359.047, 361.047, found 359.0460 and 361.0440.

2.7 *Preparation of compound 4α and 4β*

To a solution of methyl glycoside **11** (850 mg, 2.88 mmol) and allyltrimethylsilane (2.28 mL, 14.40 mmol) in acetonitrile (10 mL) was added dropwise an equimolar amount of trimethylsilyl triflate (0.52 mL, 2.88 mmol) at − 40 ˚C. The solution was allowed to warm to 0 ˚C over a period of 8 h. As soon as it reached 0 ˚C, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was concentrated under reduced pressure and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtrated, concentrated in *vacuo* and purified by column chromatography to afford compound **4β** (440 mg, 50%) and **4α** (90 mg, 10%) as colourless liquids.

Characterisation of Compound **4β**: R_f = 0.3 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: –11.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.03 (t, J = 7.3 Hz, 3H), 1.53–1.64 (m, 1H), 1.70–1.81 (m, 1H), 2.01 (dd, J = 2.4, 14.0 Hz, 1H), 2.19–2.15 (m, 1H), 2.35–2.46 (m, 3H), 2.62 (quin, J = 6.7 Hz, 1H), 3.70 (td, J = 1.2, 6.7 Hz, 1H), 3.98 (s, 2H), 4.03–4.11 (m, 3H), 4.21 (t, J = 7.0, 1H), 5.06 (d, J = 10.4 Hz, 1H), 5.13 (dd, J = 1.1, 17.1 Hz, 1H), 5.87 (ddt, J = 6.7, 9.8, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.4 (q), 26.6 (t), 33.9 (t), 37.7 (t), 38.1 (t), 49.4 (d), 71.1 (d), 76.9 (d), 80.0 (d), 83.9 (d), 89.1 (d), 116.8 (t), 135.1 (d) ppm; HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

Characterisation Data of Compound **4α**: R_f = 0.35 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 16.8 (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, J = 7.6 Hz, 3H), 1.53–1.62 (m, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, J = 14.1, 2.3 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.41 (ddd, J = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.61 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, J = 11.1 Hz, 1H), 5.07–5.12 (m, 2H), 5.79 (ddt, J = 6.9, 13.7, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (s), 77.9 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm; HRMS: calcd for $C_{13}H_{21}BrO_3$ $[M+Na]^+$ 327.0566 found 327.0568.

2.8 *Preparation of compound 4β-Ac*

To the stirred solution of compound **4β** (35 mg, 115 μmol) in dry dichloromethane (3 mL) were added triethyl amine (96 μL, 688 μmol), acetic anhydride (33 μL, 344 μmol), and DMAP (1.4 mg, 12 μmol) at 0 ˚C. The reaction was stirred at room temperature for 3h and after completion it was diluted with water (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the reaction mixture by silica gel chromatography gave compound **4β-Ac** (37 mg, 93%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 23.6 (*c* 2.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.0 (t, J = 7.2 Hz, 3H), 1.57–1.67 (m, 2H), 1.75 (ddd, J = 14.1, 7.2, 2.3 Hz, 1H), 2.07 (s, 3H), 2.21–2.32 (m, 2H), 2.36–2.42 (m, 2H), 2.44–2.50 (m, 1H), 3.80 (td, J = 6.9, 4.4 Hz, 1H), 3.85 (dd, J = 13.7, 7.3 Hz, 1H), 4.01 (dt, J = 7.3, 5.0 Hz, 1H), 4.06 (dd, J = 5.7, 11.8 Hz, 1H), 4.21 (dd, J = 6.9, 13.3 Hz, 1H), 5.04 (d, J = 9.9 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.78 (ddt, J = 17.2, 9.9, 6.9 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 9.9 (q), 21.0 (q), 26.6 (t), 33.5 (t), 35.4 (t), 38.9 (t), 49.1 (d), 74.0 (d), 79.1 (d), 79.2 (d), 81.2 (d), 88.9 (d), 117.1 (t), 134.1 (d), 170.5 (s) ppm; HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0670.

2.9 *Preparation of compound 4α-Ac*

Following the procedure used in the preparation of **4β-Ac**, Compound **4α** (30 mg, 98 μmol) on acetylation, gave compound **4α-Ac** (30 mg, 86%) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $\alpha]^{25}_D$: − 29.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, J = 7.6 Hz, 3H), 1.56–1.59 (m, 1H), 1.63–1.71 (m, 1H), 1.82 (ddd, J = 13.7, 6.5, 5.0 Hz, 1H), 2.06 (s, 3H), 2.19–2.14 (m, 1H), 2.26–2.33 (m, 3H), 2.43 (dt, J = 13.7, 7.6 Hz, 1H), 4.0–4.12 (m, 4H), 4.22 (dt, J = 13.7, 6.5 1H), 4.96 (dt, J=7.2, 4.6 Hz, 1H), 5.09 (d, J =10.3 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1H), 5.81 (ddt, J =17.2, 10.3, 6.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 10.0 (q), 21.1 (q), 26.8 (t), 33.8 (t), 37.3 (t), 38.9 (t), 49.3 (d), 77.0 (d), 79.2 (d), 79.6 (d), 82.4 (d), 89.0 (d), 117.7 (t), 133.6 (d), 170.7

(s) ppm; HRMS: calcd for $C_{15}H_{23}BrO_4$ $[M+Na]^+$ 369.0673 found 369.0672.

2.9a *Preparation of compound 1a*: To a cooled (0 ˚ C) solution of alcohol **4β** (300 mg, 0.98 mmol) in dry dichloromethane (10 mL) were added 2,6-lutidine (2.28 mL, 19.6 mmol) followed by chloromethanesulfonyl chloride (1.34 mL, 14.74 mmol). The resulting mixture was stirred for 2 h at the same temperature, quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *In vacuo*. Purification of the crude reaction mixture by flash chromatography (petroleum ether/EtOAc, 80:20) gave the chloromethanesulfonated compound (390 mg, 95%) as a brown oil, which was immediately used for the next step.

To a stirred solution of the crude chloromethane sulfonated compound (390 mg, 0.93 mmol) in dry THF (10 mL) was added *n*-tetrabutylammonium chloride (1.30 mg, 4.67 mmol) at room temperature. The resulting mixture was stirred at 80 ˚C for 4 h, quenched with H_2O at room temperature, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc, 95:5) to afford the chlorinated compound **1a** (240 mg, 79%) as a colourless oil. R_f = 0.5 (10% EtOAc/petroleum ether). $\alpha]^{25}{}_D$: +18.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3): 1.0 (t, *J* = 7.3 Hz, 3H), 1.48–1.58, (m, 1H), 1.61–1.72 (m, 1H), 2.05–2.14 (m, 1H), 2.19–2.25 (m, 1H), 2.30–2.47 (m, 4H), 3.99–4.09 (m, 4H), 4.12–4.19 (m, 2H), 5.10 (s, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.83 (ddt, *J* = 6.7, 10.4, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 37.8 (t), 38.0 (t), 38.5 (t), 49.4 (d), 59.3 (d), 78.6 (d), 78.7 (d), 86.5 (d), 88.8 (d), 117.7 (t), 133.6 (d) ppm; HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0198 found 347.0193.

2.9b *Preparation of compound 1*: To a stirred solution of compound **1a** (100 mg, 0.33 mmol) in dry benzene (5 mL) were added TIPS-enyne **6** (273 mg, 982 μmol) in benzene (2 mL) followed by Hoveyda-Grubbs 2nd generation catalyst (28 mg, 32.76 μmol, 10 mol%) in benzene (2 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 60 ˚C for 1.5 h. The addition of TIPS-enyne **6** (273 mg, 982 μmol) in benzene (2 mL) and catalyst (28 mg, 32.76 μmol) in benzene (2 mL) was repeated three times for every 1.5 h. Dimethyl sulfoxide (0.5 mL) was added to the solution, and it was stirred open to the air for 15 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:EtOAc 92:8) gave *cis*-enyne compound (94 mg, 59%) as a colourless oil. R_f = 0.6 (10% EtOAc/petroleum ether).

To a stirred solution of the TIPS-enyne compound (90 mg, 185 μmol) in dry THF (10 mL), was added *n*-tetra butyl ammonium fluoride (73 mg, 278 μmol) and stirred at − 10 ˚C for 0.5 h. The reaction mixture was quenched by adding few drops of triethylamine. Solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford **1** (59 mg, 97%) as colourless oil. R_f = 0.6 (20% EtOAc/petroleum ether);$\alpha]^{25}{}_D$: +13.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, 7.6 Hz, 3H), 1.50–1.56 (m, 1H), 1.64–1.72 (m, 1H), 2.13 (ddd, *J* = 4.6, 6.5, 13.4, 1H), 2.23 (ddd, *J* = 4.6, 6.5, 13.4 Hz, 1H), 2.38–2.47 (m, 2H), 2.58 (dt, *J* = 7.3, 14.5 Hz, 1H), 2.69 (dt, *J* = 7.3, 14.5 Hz, 1H), 3.13 (d, *J* = 1.9 Hz, 1H), 4.01–4.03 (m, 2H), 4.05–4.12 (m, 2H), 4.14–4.20 (m, 2H), 5.61 (dd, *J* = 1.9, 10.7 Hz, 1H), 6.07 (dt, *J* = 7.3, 10.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.3 (q), 26.8 (t), 34.6 (t), 37.8 (t), 38.5 (t), 49.4 (d), 59.4 (d), 76.7 (d), 77.3 (d), 78.6 (d), 78.9 (d), 80.0 (d), 82.3 (s), 86.1 (d), 88.8 (d), 110.9 (d), 140.2 (d) ppm; HRMS: calcd for $C_{15}H_{20}BrO_2Cl[M+Na]^+$ 371.0207 found 371.0197.

2.9c *Preparation of compound 2a*: Following the procedure used in the preparation of **1a**, chlorination of compound **4α** (60 mg, 196 μmol) gave **2a** (51 mg, 80%) as colourless oil. R_f = 0.5 (10% EtOAc in petroleum ether).$\alpha]^{25}{}_D$: + 6.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 (t, *J* = 7.63 Hz, 3H), 1.48–1.56 (m, 1H), 1.62–1.71 (m, 1H), 2.22–2.29 (m, 2H), 2.40–2.47 (m, 1H), 2.47–2.55 (m, 3H), 4.02–4.06 (m, 2H), 4.09 (dt, *J* = 5.0, 6.9 Hz, 1H), 4.16 (td, *J* = 3.1, 6.9 Hz, 1H), 4.29 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, 3.1, 5.0 Hz, 1H), 5.09 (dd, *J* = 0.8, 10.3 Hz, 1H), 5.18 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 35.7 (t), 38.7 (t), 38.8 (t), 49.7 (d), 62.8 (d), 78.0 (d), 79.2 (d), 82.4 (s), 88.7 (d), 117.7 (d), 133.7 (d) ppm; HRMS: calcd for $C_{13}H_{20}BrO_2Cl[M+Na]^+$ 347.0207 found 347.0198.

2.9d *Preparation of compound 2*: By accompanying the procedure used for the preparation

of compound **1**, Compound **2a** (35 mg, 108 μmol) on relay cross-metathesis followed by TIPS deprotection gave compound **2** (17 mg, 52%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether).α]$^{25}_D$: + 7.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 (t, *J* = 7.3 Hz, 3H), 1.48–1.54 (m, 1H), 1.62–1.70 (m, 1H), 2.23–2.30 (m, 3H), 2.48–2.55 (m, 3H), 2.65–2.70 (m, 1H), 2.76–2.84 (m, 1H), 3.12 (d, *J* = 1.9 Hz, 1H), 4.02–4.06 (m, 1H), 4.06–4.11 (m, 1H), 4.16 (td, *J* = 3.1, 7.3 Hz, 1H), 4.30 (ddd, *J* = 3.1, 6.5, 9.5 Hz, 1H), 4.46 (dd, *J* = 3.1, 5.0 Hz, 1H), 5.58 (dt, *J* = 1.1, 11.1 Hz, 1H), 5.06 (dt, *J* = 7.25, 11.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 26.8 (t), 32.4 (t), 38.6 (t), 38.8 (t), 49.6 (d), 62.7 (d), 79.1 (d), 79.9 (d), 81.8 (d), 82.3 (s), 88.7 (d), 110.7 (d), 140.4 (d) ppm; HRMS: calcd for $C_{15}H_{20}BrO_2Cl$[M+Na]$^+$ 371.0207 found 371.0199.

2.9e *Preparation of compound 4´α and 4´β*: Following the procedure used in the preparation of compounds **4α**and **4β** compound **12** (750 mg, 2.54 mmol) on ***C***-glycosidation gave compound **4´α** (70 mg, 9%) and **4´β** (380 mg, 49%) as colourless liquids.

Characterisation of Data of Compound **4´β**: R_f = 0.35 (20% EtOAc in petroleum ether); α]$^{25}_D$: –20.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.03 (t, *J* = 7.6 Hz, 3H), 1.42–1.52 (m, 1H), 1.64 (br. s., 1H), 1.88 (dqd, *J* = 3.1, 7.6, 14.9 Hz, 1H), 1.97 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.38–2.47 (m, 3H), 2.49–2.54 (m, 2H), 3.74 (td, *J* = 2.7, 6.9 Hz, 1H), 3.79 (td, *J* = 7.6, 9.9 Hz, 1H), 3.92 (td, *J* = 3.0, 8.8 Hz, 1H), 3.98 (td, *J* = 1.1, 8.8 Hz, 1H), 4.01–4.05 (m, 1H), 4.07 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.08 (dt, *J* = 1.1, 10.3 Hz, 1H), 5.16 (dq, *J* = 1.5, 17.2 Hz, 1H), 5.91 (ddt, *J* = 7.3, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.2 (q), 25.0 (t), 34.0 (t), 38.1 (t, 2C), 46.9 (d), 71.1 (d), 77.6 (d), 79.5 (d), 84.1 (d), 87.2 (d), 116.9 (t), 135.1 (d) ppm; HRMS: calcd for $C_{13}H_{21}O_3Br$ [M+Na]$^+$ 327.0566 found 327.0566.

Characterisation Data of Compound **4´α**: R_f = 0.3 (20% EtOAc in petroleum ether);α]$^{25}_D$: –76.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 (t, *J* = 7.3 Hz, 3H), 1.58 (dq, *J* = 7.3, 14.1 Hz, 1H), 1.69–1.78 (m, 1H), 1.93 (dd, *J* = 2.3, 14.1 Hz, 1H), 2.09–2.14 (m, 1H), 2.17–2.26 (m, 2H), 2.40 (ddd, *J* = 6.5, 9.9, 14.1 Hz, 1H), 2.61–2.66 (m, 1H), 3.98–4.05 (m, 2H), 4.06–4.10 (m, 2H), 4.15–4.20 (m, 2H), 4.32 (d, *J* = 11.1, 1Hz), 5.07–5.12 (m, 2H), 5.79 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.3 (q), 26.6 (t), 36.6 (t), 38.3 (t), 38.6 (t), 49.3 (d), 74.5 (d), 76.7 (d), 80.5 (d), 88.0 (d), 89.3 (d), 117.3 (t), 134.2 (d) ppm; HRMS: calcd for $C_{13}H_{21}O_3Br$ [M+Na]$^+$ 327.0566 found 327.0565.

2.9f *Preparation of compound 4´β-Ac*: Following the procedure used in the preparation **4β-Ac**, compound **4´β** (30 mg, 98 μmol) on acylation gave acylated compound **4´β-Ac** (29 mg, 85%) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).α]$^{25}_D$: –54.9 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.01 (t, *J* = 7.3 Hz, 3H), 1.56 (sept., *J* = 7.3 Hz, 1H), 1.65–1.80 (m, 3H), 2.07 (s, 3H), 2.08–2.12 (m, 1H), 2.36–2.52 (m, 3H), 2.58–2.67 (m, 1H), 3.83 (dt, *J* = 6.7, 9.8 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.96–4.02 (m, 2H), 4.07 (q, *J* = 7.3 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 5.09 (dd, *J* = 1.2, 17.7 Hz, 1H), 5.22–5.28 (m, 1H), 5.79 (ddt, *J* =17.1, 10.4, 7.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 9.8 (q), 21.0 (q), 25.3 (t), 33.5 (t), 35.3 (t), 38.9 (t), 47.2 (d), 74.0 (d), 79.2 (d), 79.6 (d), 81.3 (d), 86.9 (d), 117.2 (t), 134.1 (d), 170.4 (s) ppm; HRMS: calcd for $C_{15}H_{23}O_4Br$ [M+Na]$^+$ 369.0672 found 369.0673.

2.9g *Preparation of compound 4´α-Ac*: Following the procedure used in the preparation **4α-Ac**, compound **4´α** (14 mg, 46 μmol) on acylation gave acylated compound **4´α-Ac** (14 mg, 88%) as a colourless liquid. R_f = 0.5 (20% EtOAc in petroleum ether).α]$^{25}_D$: –51.9 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 1.00 (t, *J* = 7.6 Hz, 3H), 1.51–1.60 (m, 1H), 1.69–1.80 (m, 2H), 2.03 (s, 3H), 2.04–2.09 (m, 1H), 2.27–2.34 (m, 2H), 2.42 (dt, *J* = 7.6, 13.7 Hz, 1H), 2.57 (dt, *J* = 7.3, 13.0 Hz, 1H), 3.85 (dt, *J* = 7.6, 8.8 Hz, 1H), 3.93 (dt, *J* = 7.3, 13.0 Hz, 1H), 4.03 (dt, *J* = 6.9, 8.0 Hz, 1H), 4.08 (td, *J* = 3.8, 6.5 Hz, 1H), 4.13 (dt, *J* = 6.5, 7.6 Hz, 1H), 4.97 (dt, *J* = 3.8, 6.9 Hz, 1H), 5.07 (d, *J* = 10.7 Hz, 1H), 5.11 (dd, *J* = 1.1, 17.5 Hz, 1H), 5.81 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 9.8 (q), 21.1 (q), 25.1 (t), 33.6 (t), 37.3 (t), 38.9 (t), 47.1 (d), 77.1 (d), 79.4 (d), 79.8 (d), 82.5 (d), 86.5 (d), 117.7 (t), 133.5 (d), 170.6 (s) ppm; HRMS: calcd for $C_{15}H_{23}O_4Br$ [M+Na]$^+$ 369.0672 found 369.0673.

2.9h *Preparation of compound 3a´*: Following the procedure used in the preparation **1a**, compound **4´β** (270 mg, 884 μmol) on chlorination gave chlorinated compound **3a** (218 mg, 76%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether);α]$^{25}_D$: –33.4 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.02 (t, *J* = 7.3 Hz, 3H), 1.45–1.55 (m, 1H), 1.81 (dqd, *J* = 3.8, 7.6, 14.9 Hz, 1H), 2.09–2.15 (m, 1H), 2.24–2.34 (m, 2H), 2.35–2.39 (m, 2H), 2.57 (dt, *J* = 6.9, 13.0 Hz, 1H), 3.81 (ddd, *J* = 7.6, 9.5, 17.2 Hz, 1H), 3.91 (td, *J* = 3.8, 8.0 Hz, 1H), 3.96 (ddd, *J* = 3.8, 6.9, 8.4 Hz, 1H), 4.06–4.12 (m, 2H), 4.21 (ddd, *J* = 4.2, 6.9, 8.0 Hz,

1H), 5.10–5.17 (m, 2H), 5.85 (ddt, J = 6.9, 10.3, 17.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 10.0 (q), 25.1 (t), 37.8 (t), 38.0 (t), 38.6 (t), 47.1 (d), 59.4 (d), 78.2 (d), 79.4 (d), 86.6 (d), 86.7 (d), 117.9 (t), 133.5 (d) ppm; HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0195.

2.9i *Preparation of Compound 3*: Following the procedure used in the preparation of compound **1**, relay cross-metathesis and followed by TIPS deprotection of compound **3a** (50 mg, 154 µmol) gave compound **3** (27 mg, 50%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether);$\alpha]^{25}{}_D$: –33.4 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (t, J = 7.4 Hz, 3H), 1.46–1.55 (m, 1H), 1.76–1.86 (m, 1H), 2.10–2.17 (m, 1H), 2.24–2.40 (m, 2H), 2.54–2.65 (m, 2H), 2.66–2.74 (m, 1H), 3.14 (s, 1H), 3.81 (q, J = 8.5 Hz, 1H), 3.88–3.93 (m, 1H), 3.94–4.00 (m, 1H), 4.10–4.17 (m, 2H), 4.20–4.27 (m, 1H), 5.61 (d, J = 11.0 Hz, 1H), 6.09 (dt, J = 7.3, 11.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.1 (q), 25.1 (t), 34.6 (t), 37.8 (t), 38.6 (t), 47.1 (d), 59.6 (d), 78.2 (d), 79.6 (d), 80.0 (d), 82.3 (s), 86.3 (d), 86.7 (d), 111.0 (d), 140.1 (d) ppm; HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0194.

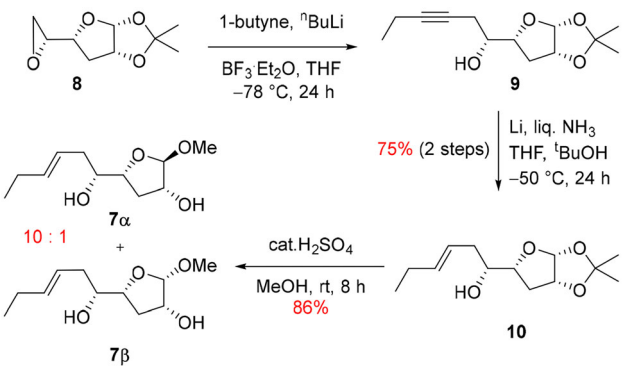
2.9j *Preparation of compound 4a*: Following the procedure used in the preparation of compound **1a**, chlorination of compound **4´α** (250 mg, 819 µmol) gave compound **4a** (194 mg, 73%) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]^{25}{}_D$: –39.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.01 (t, J = 7.4 Hz, 3H), 1.44–1.56 (m, 1H), 1.76–1.87 (m, 1H), 2.25–2.34 (m, 2H), 2.37–2.50 (m, 2 H), 2.53–2.63 (m, 2H), 3.81 (q, J = 8.2 Hz, 1H), 3.85–3.91 (m, 1H), 3.92–3.97 (m, 1H), 4.02 (td, J = 2.4, 6.8 Hz, 1H), 4.30–4.37 (m, 1H), 4.48 (bs, 1H), 5.11 (d, J = 9.8 Hz, 1H), 5.20 (d, J = 17.7 Hz, 1H), 5.81 (ddt, J = 7.3, 9.8, 17.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 10.0 (q), 25.0 (t), 35.6 (t), 38.7 (t, 2C), 47.1 (d), 62.6 (d), 78.8 (d), 78.9 (d), 82.2 (d), 86.5 (d), 117.8 (t), 133.6 (d) ppm; HRMS: calcd for $C_{13}H_{20}O_2BrCl$ $[M+Na]^+$ 347.0198 found 347.0193.

2.9k *Preparation of compound 4*: Following the procedure used in the preparation of compound **1**, relay cross-metathesis followed by TIPS deprotection of compound **4a** (25 mg, 77 µmol) gave compound **4** (11 mg, 41%) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether);$\alpha]^{25}{}_D$: –6.0 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.0 (t, J = 7.3 Hz, 3H), 1.50 (dt, J = 7.3, 14.50 Hz, 1H), 1.80 (ddd, J = 3.4, 7.6, 14.1 Hz, 1H), 2.27–2.33 (m, 2H), 2.42 (ddd, J = 5.0, 9.5, 14.1 Hz, 1H), 2.56–2.62 (m, 1H), 2.64–2.74 (m, 1H), 2.82 (dt, J = 6.5, 13.7 Hz, 1H), 3.14 (d, J = 1.9 Hz, 1H), 3.78–3.88 (m, 2H), 3.94 (ddd, J = 3.8, 7.3, 8.4 Hz, 1H), 4.07 (td, J = 2.7, 6.9 Hz, 1H), 4.34 (ddd, J = 3.8, 6.5, 9.9 Hz, 1H), 4.48 (t, J = 3.8 Hz, 1H), 5.58 (ddt, J = 1.5, 1.9, 10.7 Hz, 1H), 6.10 (dt, J = 6.9, 10.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$); 10.1 (s), 25.0 (t), 32.4 (t), 38.7 (t, 2C), 47.2 (d), 62.6 (d), 78.8 (d), 78.9 (d), 80.0 (s), 81.5 (d), 82.4 (d), 86.6 (d), 110.7 (d), 140.5 (d) ppm; HRMS: calcd for $C_{15}H_{20}O_2BrCl$ $[M+Na]^+$ 371.0198 found 371.0197.

3. Results and discussion

As planned, the synthesis of diastereomer **1** was started with the preparation of the epoxide **8** from glucose diacetonide in five steps as described earlier.[26] The epoxide **8** was subjected to opening with lithiated 1-butyne in the presence of $BF_3.Et_2O$ to afford alkyne **9**, which upon selective controlled alkyne reduction under Birch conditions, gave alkene **10** in an overall yield of 75%. The homoallylic alcohol **10** was treated with *cat.* H_2SO_4 in methanol to afford the methyl glycosides **7α** and **7β** in a 10:1 ratio (Scheme 2).

Next, the major anomer **7α** was subjected for the key bromoetherification to construct the thf-Br unit. Interestingly, unlike in the case of its C5-epimer that we employed during the notoryne synthesis, the bromoetherification of homoallylic alcohol **7α** resulted in a 1:1.3 mixture of diastereomers. For characterization purpose, the resulting diastereomers **11** and **12** were converted to their acetate derivatives. A strong through space correlation between **C**(5)**H**-**C**(8)**H** distinguishes the *trans* linked THF compound **12-Ac** from the *cis* linked THF compound **11-Ac** (See Spectra, Supplementary Information). This poor diastereoselectivity could be explained by considering the equal possibility



Scheme 2. Synthesis of methyl glycosides **7**

of two possible conformational isomers A and B during the initial addition of the bromonium ion to the alkene unit. The conformers A and B are favoured due to facile rotation around the **C9–C10** bond of the compound **7α**, leading to the formation of two minimum energy bromonium ion transition states.[27] Conformer A is favoured on steric ground (the THF unit at the equatorial position) whereas the other conformer B, is favoured due to the hydrogen bonding between the hydroxy group and the ring oxygen atom, which enhances the nucleophilicity of the participating –OH group (Figure 2).[28,29]

Next, the diastereomer **11** was subjected independently for the modified diastereoselective allylation protocol employing allylTMS and TMSOTf in acetonitrile at − 40 °C to afford the diastereomers **4β** and **4α** in a 5:1 ratio with good yields.[30–34] The resulting diastereomers were further converted to their acetate derivatives for stereochemistry characterization by 2D NMR correlation. A strong H–H NOE correlation between the ring protons **C**(4)**H**–**C**(7)**H**–**C**(8)**H** distinguishes clearly the *threo* diastereomer from the *erythro* diastereomer. After successfully synthesizing the allylic diastereomers, we applied the relay cross-metathesis protocol for the elongation of the alkyne unit to complete the synthesis. The synthesis of the diastereomers **1** and **2** were thus completed in good to moderate yields by applying the relay cross-metathesis followed by TIPS deprotection. (Scheme 3).

After successfully synthesizing the diastereomers **1** and **2**, we focused our attention on the synthesis of the other two Notoryne diastereomers from the anomer **12**. As had been observed earlier, the synthesis proceeded smoothly, with the requisite stereoselectivity. Compound **12** upon treatment with the diastereoselective allylation condition provided compound **4´β** and **4´α** in the same ratio with good yields. Moving forward, the corresponding allylic diastereomeric compounds **4´α** and **4´β** were converted to their chloro derivatives and subsequently to the final Notoryne diastereomeric compounds **3** and **4**, upon the application of the S_N2 chlorination and relay cross-metathesis protocols respectively (Scheme 4).

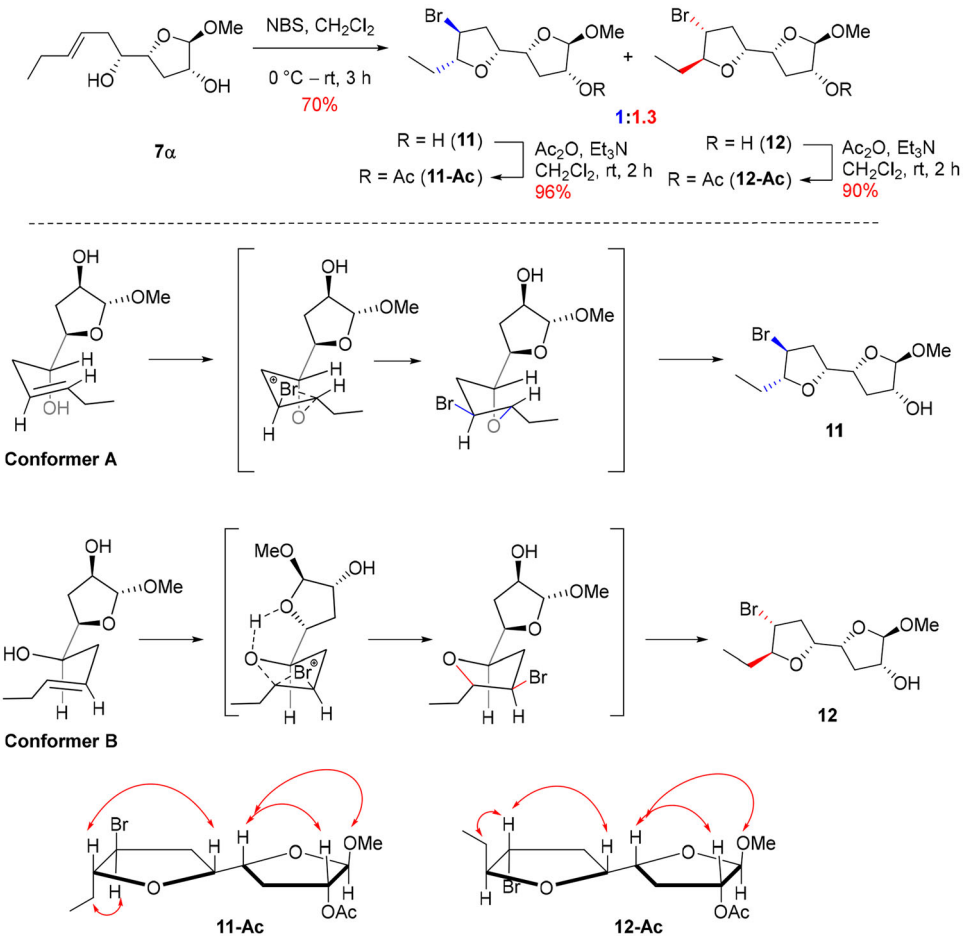
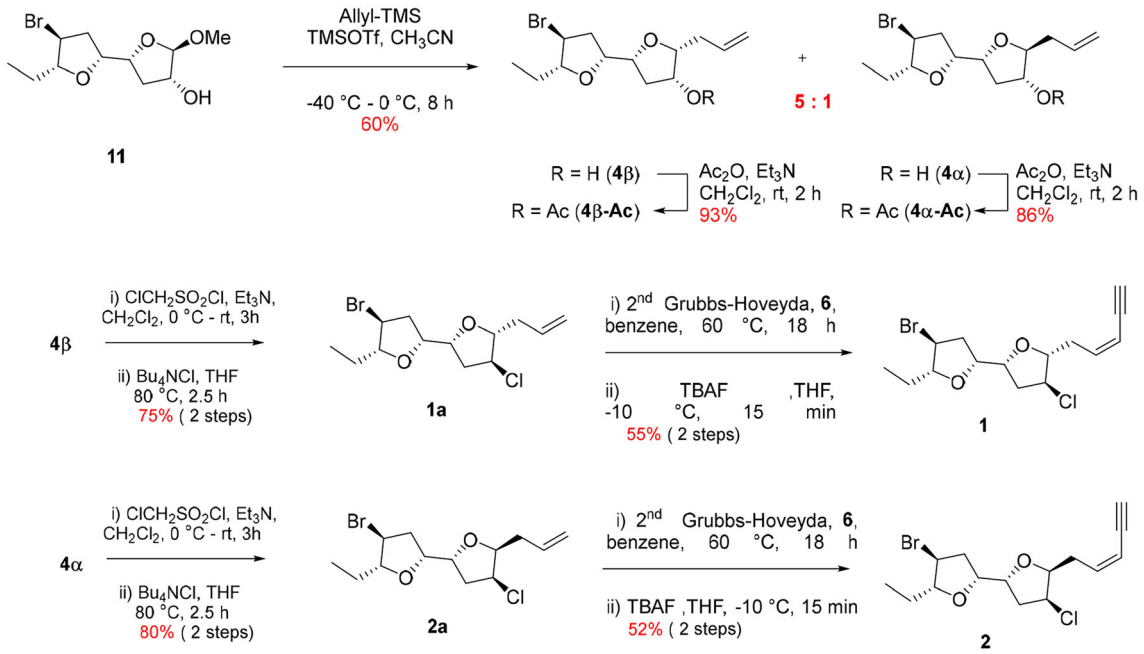
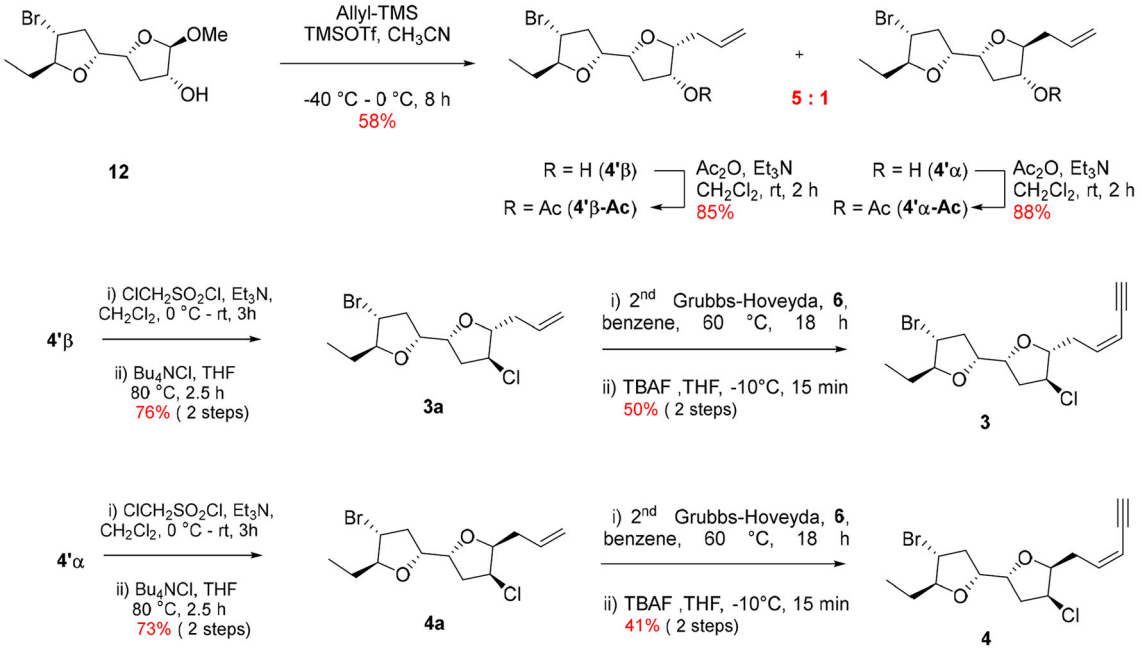


Figure 2. Proposed model for bromo-etherification and observed N*O*E correlations



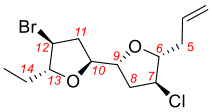
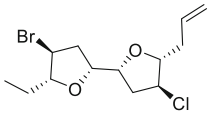
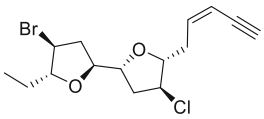
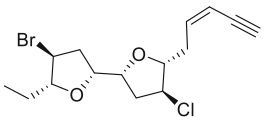
Scheme 3. Synthesis of Notoryne diastereomers (**1** and **2**)



Scheme 4. Synthesis of Notoryne diastereomers (**3** and **4**)

The four diastereomers were fully characterised by 2D NMR analysis and by comparing the ^{13}C NMR value of the subsequent steps (Supplementary Information). Table 1 provides the comparative chemical shifts of the notoryne and the diastereomer 1. As mentioned earlier, the deviations in the ^{13}C NMR chemical shifts of these two diastereomers are expected to reflect the overall influence of the change in the stereochemistry between the bridging carbons as the relative stereochemistry of the three substituents on each THF ring does not change. In parallel, ^{13}C NMR chemical shifts the corresponding chloroallyl

Table 1.. ^{13}C NMR Chemical Shift comparison of Notoryne with diastereomer 1

^{13}C	 Notoryne Precursor	 Diastereomer1 Precursor	 Notoryne	 Diastereomer1
5	37.8	37.9	34.5	34.6
6	86.3	86.4	86.1	86.1
7	58.9	59.0	59.3	59.4
8	38.0	38.6	38.2	37.8
9	79.9	79.3	80.1	**78.9**
10	78.9	79.4	78.9	78.6
11	39.3	39.4	39.4	38.5
12	47.2	48.8	47.3	49.3
13	87.1	88.6	87.2	88.8
14	25.4	26.7	25.4	26.8
15	10.0	10.0	10.0	10.3

derivatives have been also tabulated as a control. As is evident from Table 1, a strong deviation in chemical shifts of the carbons of the THF-Br unit particularly the C12, C13 and C14 (Table 1) is seen. However, the chemical shifts of the respective carbon atoms of the THF-Br unit of diastereomer 1, exactly match with the THF-Br unit of Laurendecumenyne B. (Table 2, Supplementary Information), which suggests that the second THF (THF-Br) unit in Notoryne is *trans*-1,4 linked.

With several substituted halo/hydroxy tetrahydrofuran diastereomers in hand, a comparison of ^{13}C NMR chemical shifts was carried out. Coming to the hydroxy *bis* THF isomers, the hydroxy group has an ***alpha***, ***beta*** and ***gamma*** effect on the respective carbon atoms. We observed that in the *cis* isomer, the hydroxy group shields the adjacent carbon atom by **4** ppm, the ring carbon by **4** ppm and the allylic carbon by **3** ppm than the corresponding *trans* isomer. A similar observation has been documented by Britton's group during the total synthesis of Laurefurenyne B. However, altering the stereocenter at **C10** makes a gamma effect on **C8**, which deshields the carbon by **4** ppm and a ***beta*** effect on **C11**, which shields the corresponding carbon by **1** ppm. The following observations summarize the ^{13}C NMR chemical shifts variation of different hydroxy-THF diastereomers.

i. A relative difference of **4** ppm, **3** ppm and **3** ppm were observed at the allylic carbon (**C5**), ring carbon (**C6**) and at the hydroxy carbon (**C7**-OH) respectively by altering the stereochemistry of the allylic group from *syn* to *anti*.

ii. A significant difference of **1** ppm is observed at **C8** by altering the stereocenter at **C10**.

In other words, all the carbon centres ranging from **C5** to **C8** gets shielded in cis (2-OH) diastereomers relative to trans (2-OH) diastereomers (Figure 3).

A similar deviation is also observed on the acetate derivatives of the subsequent isomers. Coming to the di-halo *bis*-THF diastereomers, in the chloro THF unit, interestingly, the trend for ^{13}C NMR chemical shift variation at chlorine carbon atom is seen to get reversed. The ring carbon(**C6**) in the *cis*-diastereomer shields to about 5 ppm while the adjacent carbon(**C7**) deshields by 3 ppm with respect to the *trans*-diastereomer. Also, a significant difference of **2** ppm was observed in the *gamma* carbon (allylic carbon) of the chlorine atom in *cis* and *trans*-diastereomers. The chlorine atom shields the *alpha* carbon and deshields the *beta* and *gamma* carbon in *trans* diastereomer unlike in the *cis* diastereomer. The difference in chemical shift is about 3, 5 and 2 ppm in the *alpha*, *beta* and *gamma* carbons respectively. Moving to the bromo THF unit, in the 1,4-*cis* linked THF ring, all the carbon atoms attached to *alpha*, *beta*, and *gamma* to bromine atom is getting shielded by 2 ppm than the 1,4-*trans* linked THF ring (Figure 3).

Furthermore, the six diastereomers were analysed by computational results. The chemical shifts for the six diastereomers were calculated and compared to the experimentally obtained chemical shift values. The DFT calculated chemical shifts data is shown in Table S2 (Supplementary Information). The trend for the calculated chemical shift of the carbon atoms

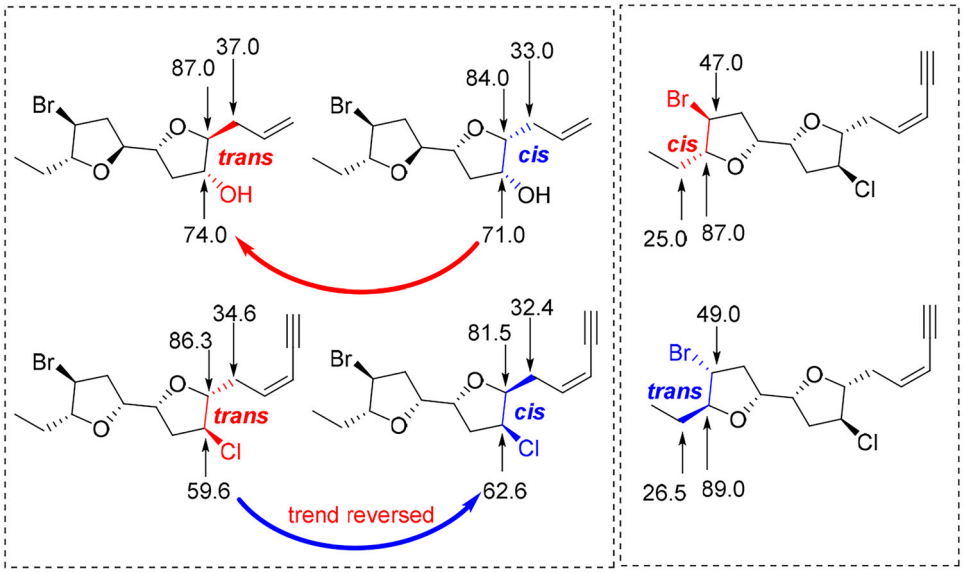


Figure 3. Characteristics ^{13}C NMR values of 2-hydroxy/halo-THF units

attached to the chlorine atom matches perfectly with the experimental values. However, for the remaining carbon atoms, the trend noticed with their chemical shifts does not follow the order as that of the experimental results. The errors in the calculated chemical shifts of the heavy atoms substituted carbons **C7** (chlorine) and **C12** (bromine) are due to the spin-orbit coupling effect in heavy atoms.[35] Errors of similar magnitude in chemical shift values have been reported previously.[21,36,37] In order to nullify the effect of spin-orbit coupling, Rzepa's approach[21] of systematically correcting the shifts can be applied. Alternatively, one can address this issue by excluding heavy carbon atoms from the analysis. This approach has the advantage of being simpler and also avoids the need to make assumptions about the transferability of the corrections.

4. Conclusions

The four diastereomers of notoryne have been synthesized in the context of understanding mainly how the ^{13}C NMR chemical shifts of various 2-halo THF moieties will change with respect to the change in the relative stereochemistry of the two carbon atoms that connect the two THF moieties. Along with the final molecules, the ^{13}C NMR chemical shifts of various intermediates synthesized have also compared in order to come up with some tentative observations on how the variation in the relative stereochemistry adjacent groups influences the ^{13}C NMR chemical shifts and identify how some characteristic shielding and deshielding of the ring carbons, especially of C1 and C2, vary with respect to their relative stereochemistry. This has also been done for the C4 in a 2, 5-disubstituted THF moiety.

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