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Stereoselective synthesis of C1–C5 and C4–C5 linked deoxy disaccharides via a ring closing metathesis protocol☆

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Abstract—The stereoselective synthesis of C–C linked deoxy disaccharides by a short and efficient route is described. An RCM strategy was adopted for the assembly of the required ring skeleton on the sugar unit, while OsO_4 was used to introduce the *vic*-diol unit.

1. Introduction

The discovery of naturally occurring *C*-nucleosides with important pharmacological properties[1] gave impetus to synthetic efforts for preparing active carbohydrate analogs. The glycoconjugates found on cell surface membranes play an important role in cell–cell recognition and interaction and as such, increasing efforts have been directed towards the design and synthesis of glyco-substances for the study of glycobiology and as candidates for therapeutic and pharmaceutical development.[2] However, like proteins and nucleic acids, carbohydrates are susceptible to biodegradation, thus limiting their therapeutic potential and use in biological studies. *C*-Glycosides[3] have therefore attracted considerable interest, particularly in view of their hydrolytic stability and potential enzyme inhibitory properties. Additionally, such furo-pyran systems are constituents of the structures of several bio-active natural products. In continuation of our interest in this area, herein, we report the synthesis of anomeric and C-5 linked deoxy disaccharides **1**–**5** via an RCM strategy.

Thus, RCM on chirons **6a/b** was efficiently accomplished to produce the disaccharides **1**, **2** and **3**. Accordingly, the known aldehydes, **6a**[4] and **6b**[5] (Scheme 1), prepared from D-mannose and L-sorbose, respectively, were treated with allyl bromide and activated zinc[6] in THF–aq NH_4Cl at 0 °C to give the alcohols **7a** (62%) and **7b** (71%), respectively. The formation of carbinols **7a** (9:1) and **7b** (exclusive) with *anti*-selectivity can be explained through a Felkin–Ahn nonchelation model.[7]

The homoallylic alcohols **7a** and **7b** were treated with acryloyl chloride and Et_3N in CH_2Cl_2 to afford esters **8a** (58%) and **8b** (64%), respectively. The bis-olefins **8a** and **8b** on reaction with Grubbs' 1st generation catalyst [bis(tricyclohexylphosphine)benzylidene–ruthenium(IV) dichloride] and $Ti(O^iPr)_4$[8] in CH_2Cl_2 afforded the respective enones **9a** (67%) and **9b** (60%). Reaction of the enones **9a** and **9b** with OsO_4 and NMO in acetone–water afforded the C(1)–C(5)-linked 4-deoxy disaccharides **1**, **2** and **3**, respectively. Olefin **9a** on *cis*-dihydroxylation gave **1** (72%) exclusively, while **9b** afforded a separable mixture of **2** and **3** in a 1:3 ratio. The new disaccharides **1**–**3** were unambiguously characterized by spectral analysis.

Earlier, we reported an efficient protocol for the stereoselective synthesis of C–C linked disaccharides[9] from furanyl sugar moieties.[10] In continuation of our RCM mediated studies, this protocol was extended to the synthesis of C(4)–C(5) linked deoxy disaccharides. Accordingly, the known[11] aldehyde **6c** (Scheme 2), prepared from D-glucose, on reaction with allyl bromide and activated zinc, under Barbier reaction conditions, gave alcohol **7c** (65%) as a separable diastereomeric mixture (4:1). The *anti*-stereoselective formation of **7c** can be

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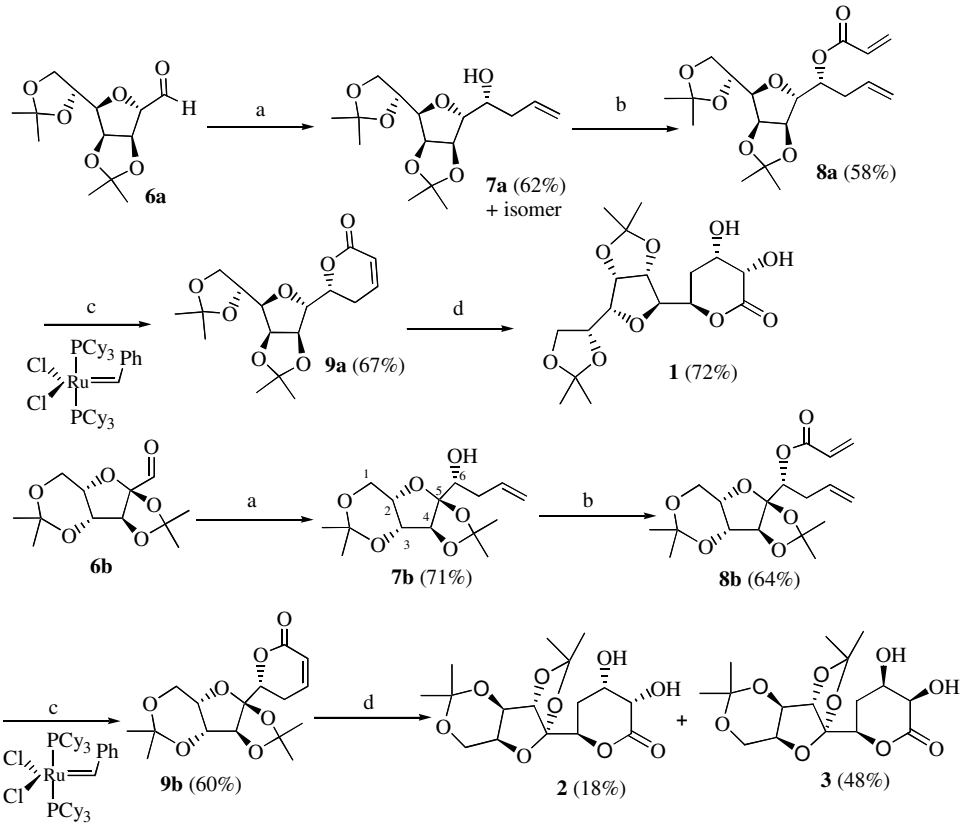
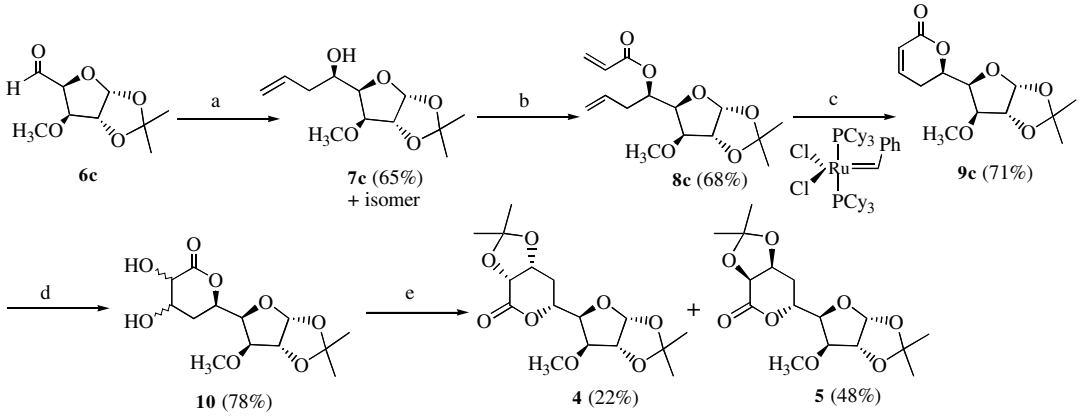


Scheme 1. Reagents and conditions: (a) allyl bromide, activated zinc, aq NH_4Cl, THF, 0 °C, 6 h; (b) acryloyl chloride, Et_3N, CH_2Cl_2, rt, 6 h; (c) [bis(tricyclohexylphoshine)benzylidene–ruthenium(IV) dichloride], $Ti(O^iPr)_4$, CH_2Cl_2, 40 °C, 18 h; (d) OsO_4, NMO, acetone–water, rt, 12 h.



Scheme 2. Reagents and conditions: (a) allyl bromide, activated zinc, aq NH_4Cl, THF, 0 °C, 6 h; (b) acryloyl chloride, Et_3N, CH_2Cl_2, rt, 6 h; (c) [bis(tricyclohexylphosphine)benzylidene–ruthenium(IV) dichloride], $Ti(O^iPr)_4$, CH_2Cl_2, 40 °C, 18 h; (d) OsO_4, NMO, acetone–water, rt, 12 h; (e) 2,2-dimethoxypropane, PTSA, DMSO, rt, 6 h.

attributed to a nonchelation controlled approach.[7] Treatment of carbinol **7c** with acryloyl chloride and Et_3N afforded ester **8c** (68%). The bis-olefin **8c** was subjected to reaction with Grubbs' 1st generation catalyst and $Ti(O^iPr)_4$ in CH_2Cl_2 to afford **9c** (71%), which on *cis*-dihydroxylation (OsO_4) gave diol **10** as an inseparable mixture. Reaction of **10** with 2,2-dimethoxypropane and PTSA afforded C(4)–C(5)-linked-4-deoxy-D-disaccharides **4** (22%) and **5** (48%), which were separable by column chromatography.

Extensive NMR studies were carried out for the structural characterization of disaccharides **1**–**5** making use of the vicinal couplings (^3J) as well as data from 2D NOESY experiments. For disaccharide **1**, the six-membered ring adopts a chair conformation. A strong NOE cross-peak (Fig. 1) between H8 and H10 in **1** as well as a large vicinal coupling $J_{7,8}$ = 12.3 Hz and small couplings $J_{8',9}$ = 3.9 Hz and $J_{9,10}$ = 3.2 Hz confirm the *trans*-diaxial relationship between H7 and H8 and the equatorial orientation of the furanoside ring. The pres-

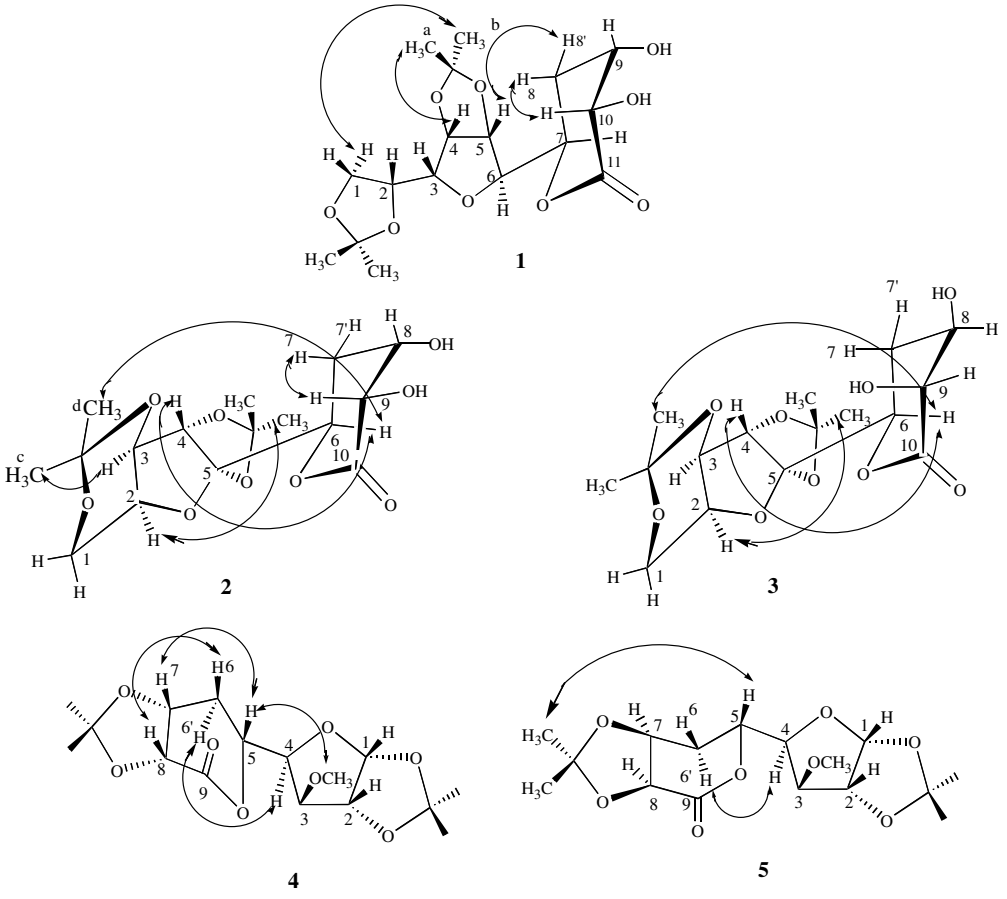


Figure 1. NOE measurements of saccharides **1**–**5** (selected NOEs are indicated).

ence of an inter-ring NOE between H5 and H8′ further supports the assigned structure. The energy minimization studies (Fig. 2) gave additional proof for the structure of **1**.

For disaccharide **2** (Fig. 1), the strong NOE cross-peak between H7–H9, and the large coupling value of $J_{6,7} = 11.0$ Hz and small values of $J_{7,8} = 1.6$ and $J_{6,7'} = 4.5$ Hz support the stereochemistry of the new sugar ring and chair conformation. Similarly, for disaccharide **3**, the absence of an NOE between H7 and H9 and the coupling constants $J_{7',8} = 1.7$ and $J_{8,9} = 3.0$ Hz confirm the new sugar ring stereochemistry. Furthermore, the presence of inter-ring NOEs between H4–H6 and H6–CH_3(d) confirm that the stereochemistry at C-6 is the same in both **2** and **3**. This data amply supports

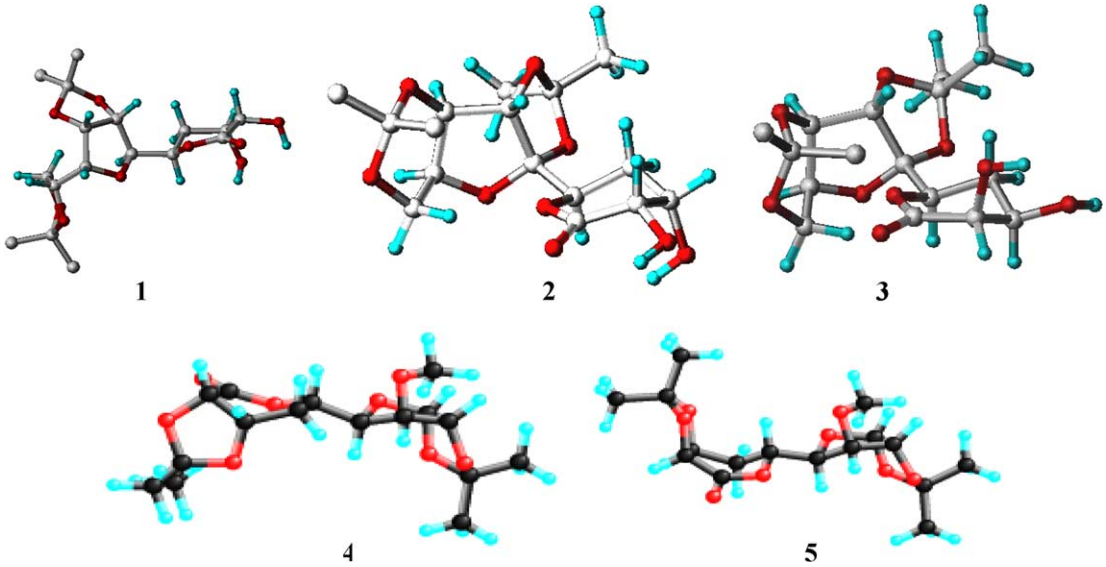


Figure 2. Energy minimized structures of compounds **1**–**5**.

the proposed stereochemistry at C-6 in homoallylic alcohol **7b**. Energy minimization studies (Fig. 2) further proved the proposed structures for disaccharides **2** and **3**.

The new sugar ring in **4** adopts a half chair conformation, the stereochemistry of which is supported by NOE cross-peaks between H4–H6′, H5–OMe, H5–H7 and H6–H8 as well as coupling constants $J_{7,8} = 1.9$, $J_{6,7} = 2.4$ and $J_{6',7} = 11.9$ Hz. Similarly, for **5**, an NOE cross-peak between H5 and CH_3(a), H4 and H6′, along with the couplings $J_{7,8} = 6.7$, $J_{6,7} = 2.2$ and $J_{6',7} = 3.3$ Hz, are consistent with the proposed structure. The value of $J_{4,5} = 8.6$ Hz and the NOE between H4 and H6′ for **4** and **5** suggests a dihedral angle of around 180° for H4–H5. This was further confirmed by the minimum energy structures obtained by molecular mechanics calculations performed using the sibyl programme.[12] The presence of NOE cross peaks between CH_3(c)–H1 and CH_3(c)–H2 indicates that the five-membered ring is in an envelope conformation in both **4** and **5**. Molecular mechanics studies on **1**–**5** agree with the experimental data.

Thus in conclusion, a simple and efficient protocol for the synthesis of C(1)–C(5) and C(4)–C(5)-linked 4-deoxy disaccharides has been successfully achieved via a RCM approach, wherein 4-deoxy L-*gulo*- and L-*manno*-sugar moieties were incorporated at the off template site in **6a** and **6b** to give **1**, **2** and **3**, while L-*manno*- and L-*gulo*-moieties, respectively, were installed in **4** and **5** starting from **6c**. This flexible method should be adaptable to the synthesis of several non-natural saccharides linked to furanoses/pyranoses.

2. Spectral data for selected disaccharides

2.1. Compound 1

$[\alpha]_D^{25}$ −29.28 (*c* 0.1, $CHCl_3$); IR (neat): 1150, 1200, 1225, 1315, 1460, 1615, 3159 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (dd, 1H, $J_{4,5} = 6.2$, $J_{5,6} = 1.0$ Hz, H-5), 4.81 (dd, 1H, $J_{4,5} = 6.2$, $J_{3,4} = 3.7$ Hz, H-4), 4.75 (ddd, 1H, $J_{7,8} = 12.3$, $J_{6,7} = 6.8$, $J_{7,8'} = 3.9$ Hz, H-7), 4.39 (ddd, 1H, $J_{9,10} = 3.2$, $J_{8',9} = 3.9$, $J_{8,9} = 1.6$ Hz, H-9) 4.37 (ddd, 1H, $J_{2,3} = 7.2$, $J_{1',2} = 5.0$, $J_{1,2} = 6.3$ Hz, H-2), 4.12 (d, 1H, $J_{9,10} = 3.2$ Hz, H-10), 4.08 (dd, 1H, $J_{1,1'} = 8.7$, $J_{1,2} = 5.0$ Hz, H-1), 4.02 (dd, 1H, $J_{1,1'} = 8.7$, $J_{1',2} = 6.3$ Hz, H-1′), 4.01 (dd, 1H, $J_{5,6} = 1.0$, $J_{6',7} = 6.8$ Hz, H-6), 3.95 (dd, 1H, $J_{2,3} = 7.2$, $J_{3,4} = 3.7$ Hz, H-3), 2.36 (dt, $J_{8,8'} = 14.9$, $J_{8',9} = 3.9$ Hz, H-8′), 1.89 (ddd, 1H, $J_{8,9} = 1.6$, $J_{7,8} = 12.3$ Hz, $J_{8,8'} = 14.9$ Hz, H-8), 1.50 (s, 3H, H-b), 1.44 (s, 3H, H-d), 1.37 (s, 3H, H-c), 1.35 (s, 3H, H-a). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.1, 113.0, 109.1, 85.8 (2 × C), 82.3, 81.9, 80.8, 76.5, 70.4, 66.6, 65.6, 30.9, 26.7, 26.1, 25.0, 24.5. FABMS (*m*/*z*, %): 376 (M^++2, 30), 333 (35), 297 (57), 243 (100), 91 (100).

2.2. Compound 2

$[\alpha]_D^{25}$ −6.36 (*c* 0.55, $CHCl_3$); IR (neat): 1145, 1280, 1325, 1385, 1460, 1615, 3050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (dd, 1H, $J_{6,7'} = 4.5$, $J_{6,7} = 11.0$ Hz, H-6), 4.65 (s, 1H, H-4), 4.39 (ddd, 1H, $J_{7,8} = 1.7$, $J_{8,9} = 3.0$, $J_{7',8} = 4.5$ Hz, H-8), 4.33 (d, 1H, $J_{2,3} = 2.4$ Hz, H-3), 4.12 (dd, 1H, $J_{1,2} = 2.2$, $J_{2,3} = 2.4$ Hz, H-2), 4.17 (d, 1H, $J_{8,9} = 3.0$ Hz, H-9), 4.05 (ABq, 1H, $J_{1,2} = 2.2$, $J_{1,1'} = 13.5$ Hz, H-1), 3.99 (ABq, 1H, $J_{1',2} = 0$, $J_{1,1'} = 13.5$ Hz, H-1′), 3.74 (br s, 1H, OH), 3.18 (br s, 1H, OH), 2.59 (dt, 1H, $J_{6,7'} = 4.5$, $J_{7,7'} = 14.8$ Hz, H-7′), 2.21 (ddd, 1H, $J_{7,8} = 1.7$, $J_{6,7} = 11.0$, $J_{7,7'} = 14.8$ Hz, H-7), 1.49 (s, 3H, H-a), 1.41 (s, 3H, H-c), 1.35 (s, 3H, H-d), 1.34 (s, 3H, H-b). FABMS (*m*/*z*, %): 361 (M^++1, 20), 281 (8), 184 (68), 93 (100), 73 (56), 57 (34). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.14, 113.61, 112.87, 97.39, 84.25, 77.38, 76.96, 76.54, 72.93, 72.82, 66.08, 60.15, 28.79, 27.59, 26.45, 18.56.

2.3. Compound 3

$[\alpha]_D^{25}$ −10 (*c* 0.5, $CHCl_3$); IR (neat): 1154, 1275, 1350, 1385, 1450, 1615, 3159 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (dd, 1H, $J_{6,7'} = 4.6$, $J_{6,7} = 11.6$ Hz, H-6), 4.67 (s, 1H, H-4), 4.07 (ddd, 1H, $J_{7,8} = 1.6$, $J_{8,9} = 2.2$, $J_{7',8} = 4.6$ Hz, H-8), 4.33 (d, 1H, $J_{2,3} = 2.1$ Hz, H-3), 4.12 (dd, 1H, $J_{1,2} = 2.1$, $J_{2,3} = 2.3$ Hz, H-2), 4.07 (d, 1H, $J_{8,9} = 2.2$ Hz, H-9), 4.05 (ABq, 1H, $J_{1,2} = 2.1$, $J_{1,1'} = 13.5$ Hz, H-1), 3.99 (ABq, 1H, $J_{1',2} = 0$, $J_{1,1'} = 13.5$ Hz, H-1′), 3.48 (br s, 1H, OH), 3.02 (br s, 1H, OH), 2.53 (dt, 1H, $J_{6,7'} = 4.6$, $J_{7,7'} = 14.8$ Hz, H-7′), 2.35 (ddd, 1H, $J_{7,8} = 1.6$, $J_{6,7} = 11.6$, $J_{7,7'} = 14.8$ Hz, H-7), 1.50 (s, 3H, H-a), 1.41 (s, 3H, H-c), 1.35 (s, 3H, H-b), 1.34 (s, 3H). FABMS (*m*/*z*, %): 361 (M^++1, 4), 341 (8), 324 (12), 281 (26), 207 (40), 147 (100), 133 (74), 119 (57).

2.4. Compound 4

$[\alpha]_D^{25}$ +9.62 (*c* 1.2, $CHCl_3$); IR (neat): 1180, 1425, 1585, 1756, 2885, 2925 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.93 (ddd, 1H, $J_{5,6} = 2.2$, $J_{4,5} = 8.6$, $J_{5,6'} = 11.2$ Hz, H-5), 4.69 (ddd, 1H, $J_{7,8} = 6.7$, $J_{6,7} = 2.2$, $J_{6',7} = 3.3$ Hz, H-7), 4.59 (d, 1H, $J_{7,8} = 6.7$ Hz, H-8), 4.58 (d, 1H, $J_{1,2} = 3.8$ Hz, H-2), 4.12 (d, 1H, $J_{4,5} = 8.6$ Hz, H-4), 3.90 (d, 1H, $J_{3,4} = 2.9$ Hz, H-3), 3.46 (s, 3H, OMe), 2.39 (dt, 1H, $J_{5,6} = 2.2$, $J_{6,6'} = 15.3$ Hz, H-6), 1.87 (ddd, 1H, $J_{6',7} = 3.3$, $J_{5,6'} = 11.2$, $J_{6,6'} = 15.3$ Hz, H-6′), 1.42 (s, 3H, H-b), 1.38 (s, 3H, H-d), 1.32 (s, 3H, H-c), 1.27 (s, 3H, H-a). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.64, 26.75, 27.96, 29.83, 58.46, 65.73, 69.33, 82.05, 82.51, 82.99, 99.16, 105.10, 111.35, 111.82, 126.03, 170.08; FABMS (*m*/*z*, %): 345 (M^++1, 8), 287 (12), 221 (14), 147 (24), 85 (38), 73 (100).

2.5. Compound 5

$[\alpha]_D^{25}$ −13.55 (*c* 0.7, $CHCl_3$); IR (neat): 1180, 1425, 1585, 1756, 2885, 2925 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.81 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.53 (d, 1H, $J_{1,2} = 3.8$ Hz, H-2), 4.43 (d, 1H, $J_{7,8} = 1.9$ Hz, H-8), 4.25 (ddd, 1H, $J_{7,8} = 1.9$, $J_{6,7} = 2.4$, $J_{6',7} = 11.9$ Hz, H-7), 4.19 (ddd, 1H, $J_{5,6} = 2.4$, $J_{4,5} = 8.6$, $J_{5,6'} = 11.7$ Hz, H-5), 4.39 (dd, 1H, $J_{4,5} = 8.6$, $J_{3,4} = 3.3$ Hz, H-4), 3.76 (d, 1H, $J_{3,4} = 3.3$ Hz, H-3), 3.42 (s, 3H, OMe), 1.86 (ddd, 1H, $J_{6',7} = 11.9$, $J_{5,6'} = 11.7$, $J_{6,6'} = 12.8$ Hz, H-

6′), 1.65 (dt, 1H, $J_{5,6}$ = 2.4, $J_{6,6'}$ = 12.8 Hz, H-6), 1.48 (s, 3H, H-b), 1.46 (s, 3H, H-d), 1.40 (s, 3H, H-c), 1.31 (s, 3H, H-a). FABMS (*m*/*z*, %): 345 (M^++1, 8), 287 (12), 221 (14), 147 (24), 85 (38), 73 (100).

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12. The energy minimization was carried out using sibyl 6.8 with default Tripose force field parameters. Minimization was done first with steepest descent followed by conjugate gradient methods for a maximum of 2000 iterations each or RMS deviation of 0.005 kcal/mol, which ever was earlier.