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Synthesis of 4a-carba-β-L-lyxofuranose, 4a-carba-β-L-arabinofuranose and 2,2,5-trimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one using Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis

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ABSTRACT

A common method for the synthesis of 4a-carba-β-L-lyxofuranose and 4a-carba-β-L-arabinofuranose from D-mannose and 2,2,5-trimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one from D-ribose is described using catalytic Nozaki-Hiyama-Kishi (NHK) conditions and ring closing metathesis (RCM). In this transformation, ω-deoxy-ω-iodo manno/ribo furanoside undergoes reductive elimination in the presence of Mn/$CrCl_3$ to give the corresponding olefin-aldehyde which was trapped by nucleophile under the same conditions to afford the desired diolefinic species. The ring closing metathesis reaction on these diolefinic species with Grubbs second generation catalyst produced the required carbocycles.

1. Introduction

Carbasugars[1] are analogues of sugars, where the ring oxygen is replaced with a methylene.[2] They belong to a broad class of compounds called cyclitols. The absence of an anomeric functionality makes them resistant to enzymatic degradation; therefore these compounds can be viewed as excellent inhibitors of glycoprocessing enzymes.[3,4]

Cyclitols are broadly classified into cyclohexitols and cyclopentitols and these are important structural units for many biologically active compounds. Cyclopentitols exist as polyhydroxy structures and also notably as aminocarbafuranoses and carbanucleosides.[5] Some important cyclitols are caryose,[6,6a] calditol,[6b] neplanocin[6e] and aristeromycin[6f] (Fig. 1).

The conversion of available carbohydrates into densely functionalized carbocyclic derivatives is an attractive strategy that has been adopted by many synthetic chemists.[7] Over the last few years, our group has been involved in the synthesis of glycosidase inhibitors, iminosugars[7s] and carbasugars.[11,12] In connection with this, we have developed some strategies for the synthesis of carbasugars. We utilized a Nozaki-Hiyama-Kishi (NHK)[8] reaction and ring closing metathesis (RCM)[9] for the synthesis of some cyclohexitols such as gabosine C, (+)-gabosine N, gabosine O, some carbapyranoses, (+)-pericosine B and (+)-pericosine C [7j,10a,b]. We also developed a Tebbe mediated cascade reaction for the synthesis of carbafuranoses.[11] Recently we developed a domino reaction involving a Bernet-Vasella reductive elimination and NHK reaction in the presence of Zn/$CrCl_3$ for the short synthesis of the cyclopentitols 4a-carba-β-D-arabinofuranose and 4a-carba-β-D-lyxofuranose from D-ribose[12]. Herein we report the application of this NHK-RCM strategy with improved reaction conditions for the synthesis of 4a-carba-β-L-lyxofuranose **1**,[13] 4a-carba-β-L-arabinofuranose **2**[14] and compound **7**.[15] Compound **7** is a key intermediate in the synthesis of estrone and some other natural products.

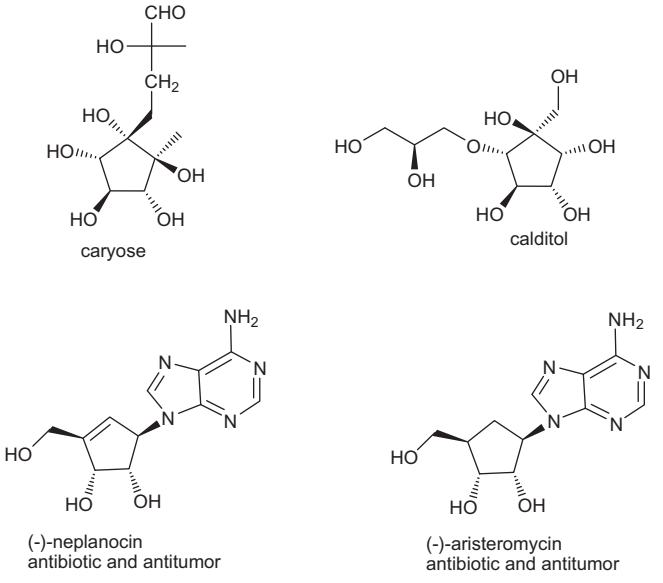

Figure 1. Structures of some important cyclopentitols.

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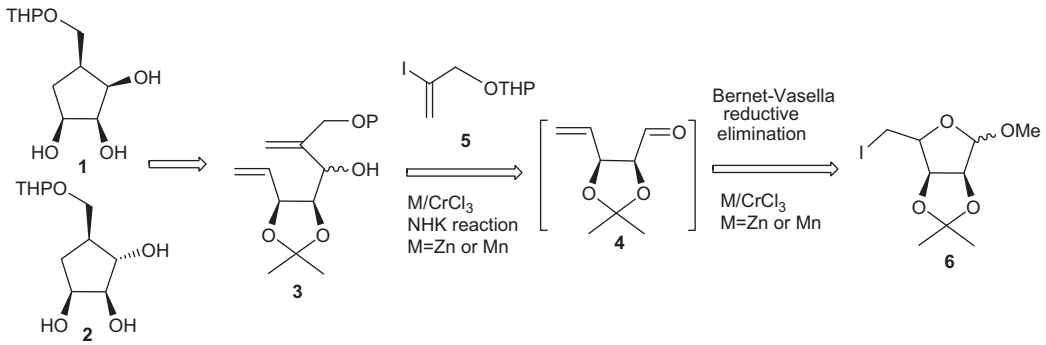


Scheme 1.

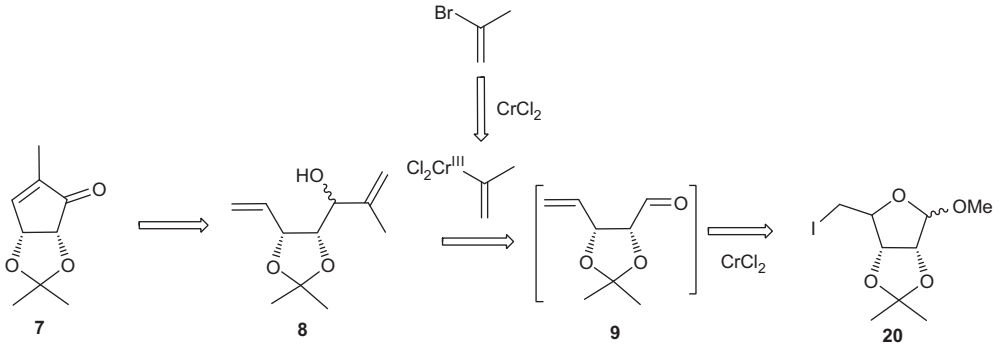
In our earlier work, ω-iodoglycosides were treated under Zn/$CrCl_3$ conditions to undergo a Bernet-Vasella reductive elimination[16] to give a chiral olefin aldehyde, which upon further treatment with a vinyl halide in the same pot for the NHK reaction gave the diene precursor required for the RCM. In this reaction, Zn is used for the conversion of $CrCl_3$ to $CrCl_2$ which facilitates reductive elimination and NHK reaction. The Bernet-Vasella reaction has been exploited very well in organic synthesis.[17,18] Some alternative conditions have also been developed for this reaction.[19] The application of this reaction for the synthesis of pentenoycin[20] and carbapentofuranoses[12] has also been reported.

Herein we adopted Furstner's modified NHK conditions[21] for the generation of $CrCl_2$ from $CrCl_3$ using Mn as the reductant. The development of this method is based on the fact that the use of excess toxic $CrCl_2$ is replaced by the easy to handle, nontoxic, air-stable $CrCl_3$ and inexpensive Mn metal as a reductant which remains inert throughout the reaction.[21] As reported earlier,[12] the ratio of Zn/$CrCl_3$ was 1:1 whereas herein we used Mn/$CrCl_3$ in a 20:1 ratio. This condition decreased the ratio of starting material to $CrCl_3$ from 6:1 (Zn as a reductant) to 1.5:1 and also gave the required product in better yields.

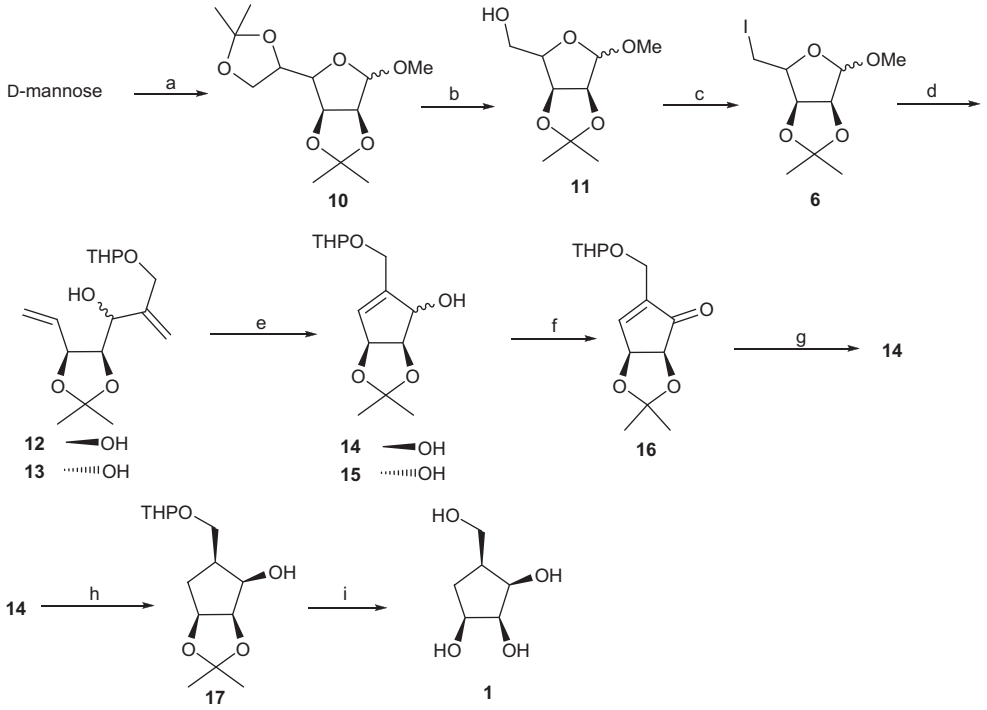
2. Results and discussion

The retrosynthetic analysis of compounds **1** and **2** is depicted in Scheme 1. The required diene precursor **3** can be obtained from aldehyde **4** and vinyl iodide derivative **5**.[22] The aldehyde **4** can in turn be generated from compound **6**, which can be easily obtained from D-mannose (Scheme 1). Similarly compound **7** can be prepared from D-ribose via **8** and **9** (Scheme 2).

First D-mannose was converted into methyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside **10** in 95% yield.[23] The 5,6-*O*-acetonide functionality in **10** was cleaved in the presence of H_5IO_6 in THF and the resulting diol was simultaneously cleaved in the same reaction mixture to give an aldehyde.[24] The crude aldehyde was reduced using $NaBH_4$ in methanol to afford compound **11**. The primary hydroxyl group in **11** was iodinated with TPP, I_2 and imidazole to give product **6** in 91% yield as reported in the literature.[25] The iodo compound **6** was treated with Mn/$CrCl_3$ (20:1 equiv) for 8 h in THF/DMF (5:1). The formation of anhydrous $CrCl_2$ was confirmed by a colour change from violet to pale blue. After the generation of the aldehyde (monitored by TLC), a catalytic amount of anhydrous $NiCl_2$ was added to the reaction mixture to carry out the NHK reaction. The addition of 2.5 equiv of vinyl iodide **5** followed by 1.5 equiv of TMSCl at 50 °C for 7 h afforded an inseparable mixture of diastereomers **12** and **13** in a 1:1 ratio in 55% yield (over two steps). When the reaction was carried out in Zn/$CrCl_3$ (20:1), it gave the products in low yields (20%). Reaction of the mixture of **12** and **13** with Grubbs second generation catalyst afforded the cyclic compounds **14** and **15** in 81% yield which could be separated by column chromatography. The mixture of **14** and **15** was converted into **16** in 98% using PDC in DCM. Luche reduction[26] of compound **16** afforded **14** in 93%. The bicyclic [3 3 0] system in **16** probably allowed the hydride to approach exclusively from the less hindered concave face to yield **14**. The reduction of the double bond in **14** using Pd/C under H_2 afforded the saturated compound **17** as the only product.[27] Global deprotection of the THP and acetonide functionality in **17** gave the required carbasugar **1** in 95% yield, whose spectroscopic and physical data were in agreement with the reported values[28] (Scheme 3).

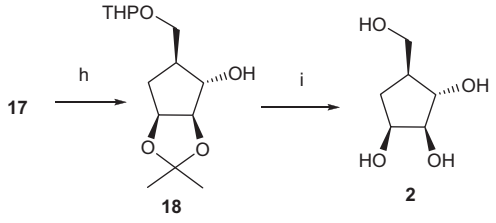


Scheme 2.



Scheme 3. Synthesis of 4a-carba-β-L-lyxofuranose. Reagents and conditions: (a) MeOH, acetone, H_2SO_4 (cat.), 0 °C to rt, 6 h, 95%; (b) (i) H_5IO_6, THF, 0 °C to rt, 3 h (ii) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 65% for two steps (c) TPP, I_2, imidazole, toluene, 0 °C to rt, 4 h, 91%; (d) Mn/$CrCl_3$ (20:1), THF:DMF (1:1), 8 h then $NiCl_2$ (cat), **4**, TMSCl, 50 °C, 7 h, TBAF, rt, 2 h, 55%; (e) Grubbs 2nd gen. cat. DCM, reflux, 6 h, 81%; (f) PDC, DCM, 4 Å, MS, rt, 5 h, 98%; (g) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, DCM, 6 h, −78 °C 93%; (h) Pd-C/H_2, MeOH, 2 h, 98%; (i) 2 M HCl in MeOH, 0 °C, 15 min, 95%.

Mitsunobu inversion[29] of **17** gave compound **18** in 93% yield. Complete deprotection of **18** gave the required carbasugar **2** in 95% yield whose spectroscopic data were also in good agreement with the reported values[28] (Scheme 4).

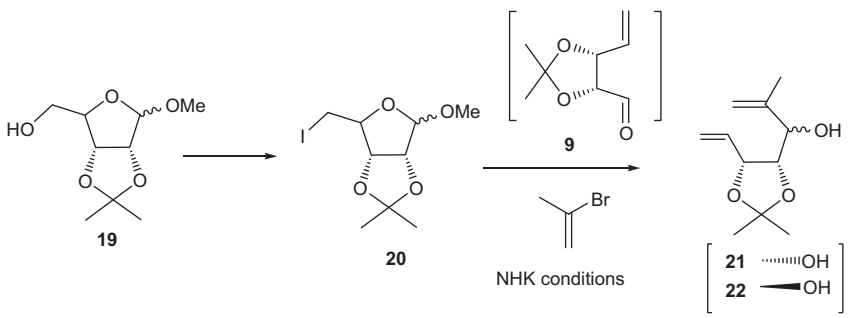


Scheme 4. Synthesis 4a-carba-β-L-arabinofuranose. Reagents and conditions : (h) (i) TPP, PNB, DIAD, THF, 0 °C, 12 h; (ii) LiOH·H_2O, 5 h, 93%; (i) 2 M HCl in MeOH, 0 °C, 15 min, 95%.

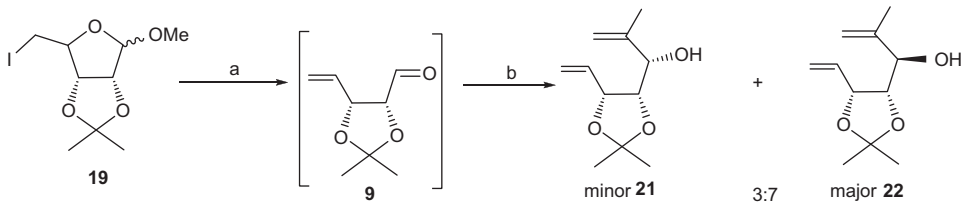
We extended this strategy to the synthesis of 2,2,5-trimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one **7** starting from D-ribose. It is noteworthy to mention here that the methyl cyclopentenones **7** and *ent*-**7** are key intermediates for the synthesis of estrone,[15a] physostigmine, (−)-physovenine and (−)-aphanorphine.[15b,c] Most of the reported procedures for making **7** and *ent*-**7** initially involve the preparation of cyclopentenones without a substituent on the olefin and then introduction of the methyl group to give the desired skeleton.[15b] However, these methods are lengthy, whereas our approach generates compound **7** in good overall yield with high enantiomeric purity.

The reaction of 2-bromo propene and **20** under the above modified NHK conditions gave alcohols **21** and **22** in a 7:3 diastereomeric ratio (Scheme 5).

When aldehyde **9** was treated with a Grignard reaction using 2-bromopropene and Mg in THF at −78 °C, products **21** and **22** were obtained in a 3:7 ratio.[10a,c] (Scheme 6).



Scheme 5. Reagents and conditions: (a) I_2, TPP, Imidazole, DCM, 0 °C to rt, 3 h; (ii) Mn/$CrCl_3$ (20:1), THF/DMF (1:1), 8 h then $NiCl_2$ (cat), 2-bromopropene, TMSCl, rt, 4 h, TBAF, 2 h, 60% [**21:22** = 7:3].



Scheme 6. Reagents and conditions: (a) Mn/$CrCl_3$ (20:1), THF:DMF (1:1), 8 h, 65%, (b) 2-bromopropene, Mg, THF, −78 °C to rt, 2 h, 75%.

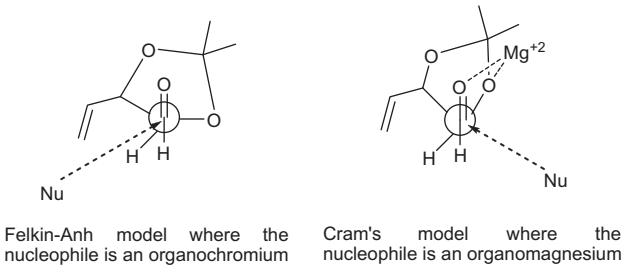
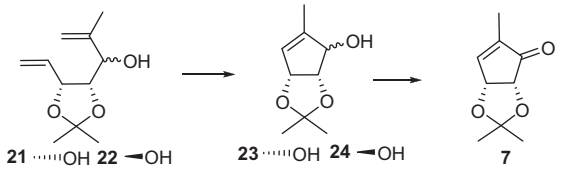


Figure 2.

The reversal of selectivity in this case can be explained as follows. Generally during an NHK reaction the nucleophile undergoes addition via a non-chelated Felkin-Anh model,[30] whereas in the case of the Grignard addition, chelation[31a,b] of the magnesium ion gave *syn* isomer **22** as the major product (Fig. 2).

The RCM reaction of the mixture of compounds **21** and **22** using Grubbs second generation catalyst afforded compounds **23** and **24**, which could be easily separated by column chromatography. The mixture of **23** and **24** was oxidized using PDC to give methyl cyclopentenone **7** as the sole product; the physical and spectroscopic data were in good agreement with the reported values[15a] (Scheme 7).



Scheme 7. Reagents and conditions: (a) Grubbs 2nd gen. cat. DCM, reflux, 5 h, 85%; (b) PDC, DCM, 4 Å MS, rt, 3 h, 95%.

3. Conclusion

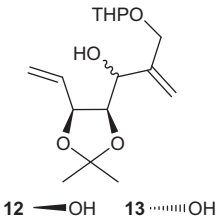
In conclusion, we have developed a general strategy for the synthesis of 4a-carba-β-L-lyxofuranose **1**, 4a-carba-β-L-arabinofuranose **2** and 2,2,5-trimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one **7** by using domino reductive elimination and nucleophilic addition using modified NHK conditions and ring-closing metathesis as the key steps. This strategy is helpful in making different analogues of carbanucleosides. Compounds **14** and **15** can also be used in the synthesis of neplanocin, carbasugars and their derivatives.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded either in $CDCl_3$ or CD_3OD solvent on 200, 300 or 400 MHz spectrometer at ambient temperature. Chemical shifts (δ) are given in ppm and coupling constant J is in Hertz. Chemical shifts are reported in ppm on scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FTIR spectra were recorded as KBr thin films or neat. Optical rotations were measured on Jasco digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. All reagents and solvents were of reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether were used for column chromatography and distilled prior to use. Tetrahydrofuran (THF) when used as a solvent for reactions was freshly distilled from sodium benzophenoneketyl. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. All reactions were performed under a nitrogen atmosphere in flame-dried or oven-dried glassware with magnetic stirring. The ^{13}C NMR spectra of all THP-protected compounds showed a doubling of peaks because of the diastereomers due to the presence of a stereogenic centre in the THP functionality.

4.2. (*S*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)prop-2-en-1-ol) 12 and (*R*)-1-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)prop-2-en-1-ol 13



To a flame dried two-necked round bottom flask, $CrCl_3$ (0.345 g, 2.16 mmol) and powdered activated Mn (1.62 g, 43.2 mmol) were taken in THF/DMF (21 mL/6 mL) and stirred for 2 h at rt under an inert atmosphere until the colour changed from violet to green. Compound **11** (0.45 g, 1.44 mmol) in THF (9 mL) was slowly added to it and stirred for 8 h. When TLC showed the absence of starting material, $NiCl_2$ (90 mg, 0.69 mmol) was added to the reaction mixture and stirred for 30 min. Then vinyl iodo compound **5** (9.7 g, 3.6 mmol) in DMF (6 mL) was added to it followed by the addition of TMSCl (0.234 g, 2.16 mmol). The reaction mixture was allowed to stir for an additional 7 h at 50 °C, and diluted with diethyl ether (70 mL). Next, n-Bu_4NF (9 mL, 1 M in THF) was added and stirred at rt for 2 h. The reaction mixture was filtered through a sintered funnel, concentrated and purified by column chromatography using ethyl acetate/hexane (2:8) to afford a mixture of **12** and

13 (240 mg, 55 %) in a 1:1 ratio (by ^{1}H NMR) as a yellow oil. $[\alpha]_D^{25} = +4.2$ (*c* 0.5, $CHCl_3$) lit.[13] for its enantiomer $[\alpha]_D^{25} = -10.6$ (*c* 1.18, $CHCl_3$]; IR (KBr): ν_{max} 3446, 2926, 2854, 1377, 1255, 1215, 1163, 1119, 1029, 909, 871, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : 6.0 (m, 1H), 5.43–5.19 (m, 4H), 4.70–4.56 (m, 2H), 4.45–3.98 (m, 4H), 3.85 (m, 1H), 3.5 (m, 1H), 2.74–2.42 (two br s, 1H), 1.88 –1.46 (m, 6H), 1.44 (s, 3H, –C*H*$_3$), 1.39 (s, 3H, –C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 144.7, 144.4, 134.2, 119.3, 117.7, 117.0, 115.4, 108.7, 98.5, 98.0, 97.8, 79.2, 79.17, 78.8, 72.5, 71.1, 70.9, 69.1, 68.2, 67.9, 62.6, 62.4, 62.2, 30.5, 27.8, 27.2, 27.16, 25.4, 25.37, 25.3, 24.91, 24.9, 19.5, 19.3. The extra peaks in the ^{13}C NMR is because of the mixture of diastereomers due to the stereogenic centre present in the THP functionality and epimers of allylic hydroxy functionality. HRMS (LC–MS) *m*/*z* calcd for $C_{16}H_{26}O_5Na$ 321.1780, found 321.1714.

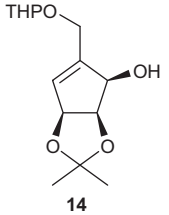
4.3. Procedure for ring closing metathesis reaction

To the diastereomeric mixture of compounds **12** and **13** (750 mg, 2.5 mmol) in anhydrous DCM (750 mL) under a nitrogen atmosphere, was added Grubbs second generation catalyst (210 mg, 0.25 mmol) and the reaction mixture was refluxed for 6 h. After completion of the reaction, the reaction mixture was evaporated at reduced pressure to give a crude residue, which was purified by column (ethyl acetate/hexane = 3:7) to give compounds **14** (170 mg, 41%) and **15** (157 mg, 40%) as yellow oils.

4.4. Procedure for the Luche reduction

To a solution of enone **16** (130 mg, 0.48 mmol) taken in DCM, cerium trichloride heptahydrate (0.90 mL, 0.36 mmol) in methanol was added, followed by the addition of sodium borohydride (13.6 mg, 0.36 mmol) at −78 °C under a nitrogen atmosphere. The reaction was completed in 6 h after which a saturated solution of potassium bicarbonate (2 mL) was added along with diethyl ether (2 mL). The resulting mixture was extracted with diethyl ether (2 × 5 mL). The combined ether layers were washed with a saturated solution of sodium bicarbonate (3 mL), followed by brine (5 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified on a column (ethyl acetate/hexane = 3:7) to give compound **14** (122 mg, 0.45 mmol) in 93% yield.

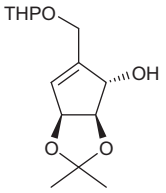
4.5. (3a*R*,4*R*,6a*S*)-2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 14



14

$[\alpha]_D^{20} = -5$ (*c* 1.0, $CHCl_3$) {lit.[13] for *ent*-**14** $[\alpha]_D^{20} = +3$ (*c* 0.57, $CHCl_3$)}; IR (KBr): ν_{max} 3448, 2927, 2854, 1456, 1378, 1209, 1153, 1118, 1073, 1029, 974, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 5.75 (s, 1H), 4.97 (d, 1H, *J* = 5 Hz), 4.78–4.59 (m, 2H), 4.51–4.28 (m, 2H), 4.1–4.05 (2d, 1H, *J* = 13.7 Hz), 3.85 (m, 1H), 3.5 (m, 1H), 2.59 (2d, 1H, *J* = 9.4 Hz, D_2O exchanged), 1.93–1.44 (m, 6H), 1.41 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 144.6, 144.1, 130.9, 130.2, 111.3, 111.2, 99.1, 98.7, 86.0, 85.9, 83.4, 83.3, 80.8, 81.615, (63.3, 65.1, 62.8, 62.4, 30.5, 30.3, 27.3, 27.2, 25.6, 25.5, 25.2, 25.1, 19.6, 19.3. The doubling of peaks is due to the presence of diastereomers because of the THP group; HRMS (ESIMS) *m*/*z* calcd for $C_{14}H_{22}O_5Na$ 293.1364, found 293.1376.

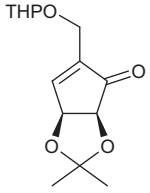
4.6. (3a*R*,4*S*,6a*S*)-2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 15



15

$[\alpha]_D^{20} = +34$ (*c* 0.5, $CHCl_3$) {lit.[13] for *ent*-**15** $[\alpha]_D^{20} = -35.8$ (*c* 1.78, $CHCl_3$)}; IR (KBr): ν_{max} 3443, 2928, 2857, 1457, 1376, 1206, 1157, 1122, 1036, 904, 864 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : 5.82 (2s, 1H), 5.2 (br s, 1H), 4.71–4.58 (m, 2H), 4.51 (d, 1H, *J* = 5.9 Hz), 4.4 (d, 1H, *J* = 12.6 Hz), 4.15 (d, 1H, *J* = 12.6 Hz), 3.85 (m, 1H), 3.51 (m, 1H), 2.95–2.5 (br d, 1H), 1.96–1.37 (m, 6H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.5, 144.1, 131.0, 130.3, 111.3, 111.2, 98.8, 99.2, 86.1, 85.9, 81.7, 80.9, 83.5, 65.4, 65.2, 62.8, 62.4, 30.6, 30.4, 27.34, 27.3, 25.6, 25.5, 25.2, 25.1, 19.7, 19.4. The doubling of peaks is due to the presence of diastereomers because of the THP group. HRMS: *m*/*z* calcd for $C_{14}H_{22}O_5Na$ 293.1364, found 293.1376.

4.7. (3a*S*,6a*S*)-2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-3aH-cyclopenta[*d*][1,3]dioxol-4(6aH)-one 16

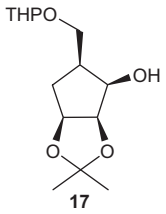


16

To a solution of **14** and **15** (0.327 g, 0.643 mmol) in DCM (20 mL) were added molecular sieve powder (4 Å) and PDC (pyridinium dichlorochromate) (0.605 g, 1.6 mmol) at 0 °C. The reaction mixture was then stirred at rt for 5 h. The crude reaction mixture was filtered through Celite, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude brownish syrup. The syrupy liquid was purified on a column (ethyl acetate/hexane = 2:8) to give a single product **16** (0.318 g, 98%) as a liquid. $[\alpha]_D^{25} = +5$ (*c* 1.0, $CHCl_3$) {lit.[13] for *ent*-**16** $[\alpha]_D^{20} = -5$ (*c* 0.85, $CHCl_3$)}; IR (KBr): ν_{max} 2931, 2856, 1725, 1458, 1377, 1248, 1204, 1130, 1099, 1036, 980, 915, 864, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.49 (s, 1H), 5.21 (d, 1H, *J* = 5.5 Hz), 4.64 (s, 1H), 4.51 (d, 1H, *J* = 5.5 Hz), 4.4 (dd, 1H, *J* = 15.4, 1.8 Hz), 4.15 (dd, 1H, *J* = 15.4, 1.8 Hz), 3.85 (m, 1H), 3.51 (m, 1H), 1.90–1.45 (m, 6H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 201.4, 153.3, 153.2, 114.5, 114.4, 115.4, 98.8, 77.7, 76.6, 62.31, 62.25, 60.87, 60.81, 30.4, 27.5, 26.12, 26.07, 25.3, 19.31,19.3. The doubling of peaks is due to the presence of diastereomers because

of the THP group. HRMS: *m*/*z* calcd for $C_{14}H_{20}O_5Na$, 291.1208 found 291.1210.

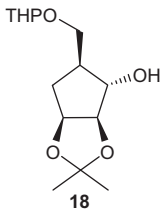
4.8. (3a*R*,4*R*,5*S*,6a*S*)-2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-tetrahydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 17



17

To compound **14** (0.1 g, 0.37 mmol) in dry methanol (5 mL), Pd/C (10 wt %, 10 mg) was added and the mixture was stirred for 2 h under a hydrogen atmosphere. After completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was concentrated to give compound **17** (0.099 g, 98%) as a thick syrup. $[\alpha]_D^{20} = +10.2$ (*c* 0.175, $CHCl_3$) {lit.[13] for *ent*-**17** $[\alpha]_D^{20} = -10.6$ (*c* 0.175, $CHCl_3$)}; IR (KBr): ν_{max} 3448, 2924, 2854, 1459, 1378, 1262, 1209, 1121, 1074, 1029, 866, 762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 4.66–4.54 (m, 2H), 4.45 (dd, 1H, *J* = 6.8, 5.3 Hz), 4.11–3.36 (m, 5H), 2.20 (m, 1H), 1.9 (m, 1H), 1.87–1.51 (m, 7H), 1.52 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 113.8, 113.1, 99.1, 80.9, 80.9, 79.3, 71.2, 70.6, 66.9, 66.5, 62.3, 44, 43.5, 31.8, 30.6, 26.1, 25.4, 24.2, 19.6. The doubling of peaks is due to the presence of diastereomers because of the THP group. HRMS: *m*/*z* calcd for $C_{14}H_{24}O_5Na$ 295.1521, found 295.1514.

4.9. (3a*R*,4*S*,5*S*,6a*S*)-2,2-Dimethyl-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-tetrahydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 18

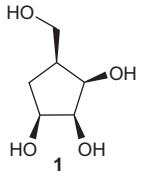


18

4.10. Procedure for the Mitsunobu reaction

To a stirred solution of **17** (0.1 g, 0.64 mmol) were added triphenylphosphine (0.418 g, 1.6 mmol) and 4-nitrobenzoic acid (0.268 g, 1.6 mmol) in THF (10 mL) followed by the slow addition of a solution of di-isopropyl azodicarboxylate (DIAD) (0.33 mL, 1.6 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature, while being stirred and covered with aluminium foil. The reaction mixture was diluted with THF (10 mL), washed with a saturated solution of sodium bicarbonate (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and to it, THF/H_2O (10 mL, 1:1), and LiOH.H_2O (2.5 equiv, 0.068 g, 1.6 mmol) were added at 0 °C and stirred for 5 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the crude product was purified on a column (ethyl acetate/hexane = 1:4) to afford pure product **18** in quantitative yield. $[\alpha]_D^{20} = +60.0$ (*c* 0.2, $CHCl_3$) {lit.[13] for *ent*-**18** $[\alpha]_D^{20} = -62$ (*c* 0.25, $CHCl_3$)}; IR (KBr): ν_{max} 3448, 2933, 2840, 1673, 1600, 1508, 1543, 1489, 1453, 1358, 1256, 1174, 1028, 836, 770, 702, 586 cm^{-1}; ^1H NMR: (200 MHz, $CDCl_3$): 4.65 (m, 1H), 4.58 (m, 1H), 4.37 (m, 1H), 4.0 (m, 1H), 3.88–3.75 (m, 2H), 3.53–3.38 (m, 2H), 2.24–2.07 (m, 2H), 1.89–1.49 (m, 7H), 1.47 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 111.9, 99.1, 98.8, 87.0, 80.5, 80.2, 78.7, 78. 6, 69.4, 62.3, 62.2, 46.5, 46.4, 32.63, 30.5, 30.4, 26.8, 25.3, 24.4, 19.5, 19.4. The doubling of peaks is due to diastereomers because of the THP group. HRMS : *m*/*z* calcd for $C_{14}H_{24}O_5Na$ 295.1521, found 295.1514.

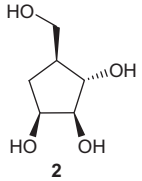
4.11. (1*S*,2*S*,3*R*,4*S*)-4-(hydroxymethyl)cyclopentane-1,2,3-triol[4a-Carba-β-L-lyxofuranose] 1



1

To compound **17** (50 mg, 0.18 mmol) in methanol (2 mL) was added HCl (2 N, 0.04 mL) in methanol at ice cooled temperature and stirred for 15 min. After completion of the reaction, the reaction mixture was concentrated and dried to give compound **1** (26 mg, 95%). $[\alpha]_D^{20} = +10$ (*c* 0.4, MeOH), {lit.[24] *ent*-**1** $[\alpha]_D^{20} = +10.1$ (*c* 0.3, MeOH)}. IR (KBr): ν_{max} 3445, 2925, 2858, 1640, 1454, 1218, 1031, 762, 441 cm^{-1}; ^1H NMR (300 MHz, D_2O): 4.1-4.18 (m, 2H), 3.88 (dd, 1H, *J* = 4.9, 4.7 Hz), 3.77 (dd, 1H, *J* = 10.7, 10.5 Hz), 3.62 (dd, 1H, *J* = 10.7, 10.5 Hz), 2.28–2.05 (m, 2H), 1.43 (ddd, 1H, *J* = 13.4, 8.3 Hz, 4.5 Hz); ^{13}C NMR (75 MHz, D_2O): 74.5, 73.3, 71.4, 62.1, 40.8, 33.9**;** HRMS: m/z calcd for $C_6H_{12}O_4Na$ 171.0633, found 171.0625.

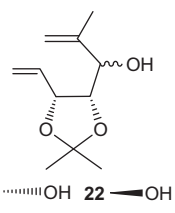
4.12. (1*S*,2*S*,3*S*,4*S*)-4-(Hydroxymethyl)cyclopentane-1,2,3-triol-[4a-Carba-β-L-arabinfuranose] 2



2

To compound **18** (50 mg, 0.18 mmol) in methanol (2 mL) was added HCl (2 M in methanol, 0.04 mL) at ice cooled temperature and stirred for 15 min. After completion of the reaction, the MeOH was evaporated under reduced pressure to give compound **2** (0.026 g, 95%). The physical and spectroscopic data of compound **2** were in exact agreement with the reported literature values. $[\alpha]_D^{20} = -6$ (*c* 0.55, MeOH), {lit.[24] $[\alpha]_D^{20} = -7.9$ (*c* 1.2, MeOH)}. IR (KBr): ν_{max} 3447, 2924, 2854, 2366, 1627, 1461, 1216, 761, 670 cm^{-1}; ^1H NMR (300 MHz, D_2O): 4.08 (m, 1H), 3.81–3.74 (m, 2H), 3.70 (dd, 1H, *J* = 10.8, 5.5 Hz), 3.55 (dd, 1H, *J* = 10.8, 7.6 Hz), 2.24 (ddd, 1H, *J* = 14.4, 9.4, 6.0 Hz), 1.98-1.9 (m, 1H), 1.34 (ddd, 1H, *J* = 14.4, 7.2, 3.9 Hz); ^{13}C NMR (75 MHz, D_2O): 78.9, 77.8, 70.6, 64.7, 43.4, 32.2; HRMS: *m*/*z* calcd for $C_6H_{12}O_4Na$ 171.0633, found 171.0627.

4.13. (*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol 21 and (*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol 22



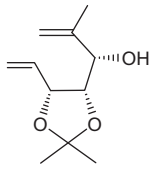
4.14. Procedure for the *in situ* NHK reaction

To a flame dried two-necked round bottom flask, $CrCl_3$ (0.115 g, 0.72 mmol) and powdered activated Mn (0.54 g, 14.5 mmol) were taken in THF/DMF (7 mL:2 mL) and stirred for 2 h at rt under an inert atmosphere until the colour changed from violet to green. Compound **19** (0.15 g, 0.48 mmol) in THF (3 mL) was added slowly to it and stirred further for 8 h. When TLC showed the absence of starting material, $NiCl_2$ (30 mg, 0.23 mmol) was added to the reaction mixture and stirred for 30 min. Next, 2-bromo propene (1.45 g, 1.2 mmol) in DMF (2 mL) was added to it followed by the addition of TMSCl (0.078 g, 0.72 mmol). The reaction mixture was allowed to stir for an additional 4 h at rt, and then diluted with diethyl ether (50 mL). Next, *n*-Bu_4NF (3 mL, 1 M in THF) was added and stirred at rt for 2 h. The reaction mixture was filtered through a sintered funnel, concentrated and purified by column chromatography using ethyl acetate/hexane (8:92) to afford **21** (42%) and **22** (18%) as yellow oils in a ratio of 7:3 (90 mg, 60%).

4.15. Procedure for the Grignard reaction

To a solution of isopropenyl magnesium bromide prepared from Mg (0.384 g, 16 mmol) and 2-bromopropene (1.55 mL, 12.8 mmol) in THF (10 mL) was added a solution of aldehyde **9** (0.5 g, 3.2 mmol) in THF over 10 min at −78 °C under nitrogen. After stirring for 4 h at room temperature, the mixture was poured into saturated NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The collected organic layers were combined, washed with water, brine, and then dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane (8:92) to afford the corresponding alcohol **21** (22.5%) and **22** (52.5%) as yellow oils in a ratio of 3:7 (475 mg, 75% for two steps).

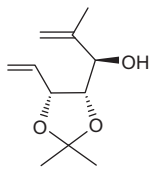
4.16. (*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol 21



21

$[\alpha]_D^{20} = -46$ (*c* 3.2, $CHCl_3$); IR (KBr) : ν_{max} 3451, 2925, 2855, 1462, 1391, 1257, 1215, 1080, 839, 764 cm^{-1}; ^1H NMR (300 M Hz, $CHCl_3$): 6.09 (m, 1H), 5.33 (d, 1H, *J* = 17 Hz), 5.27 (d, 1H, *J* = 10 Hz), 4.94 (s, 1H), 4.91 (s, 1H), 4.59 (t, 1H, *J* = 7.2 Hz), 4.20 (dd, 1H, *J* = 7.2 Hz), 3.94 (t, 1H, *J* = 4.91 Hz), 2.28 (d, –OH, 1H, *J* = 6 Hz), 1.78 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.2, 133.9, 119.3, 113.2, 108.6, 79.2, 78.6, 72.9, 27.2, 24.8, 19.0; ESIMS: $[M+Na]^+$ = 221.

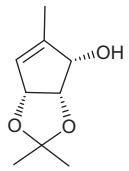
4.17. (*R*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol 22



22

$[\alpha]_D^{20} = -14$ (*c* 1.6, $CHCl_3$). IR (KBr): ν_{max} 3456, 2923, 2854, 1461, 1396, 1217, 760 cm^{-1}; ^1H NMR (300 M Hz, $CHCl_3$): 6.10 (m, 1H), 5.42 (d, 1H, *J* = 17.3 Hz), 5.27 (d, 1H, *J* = 10.6 Hz), 5.00 (s, 1H), 4.92(s, 1H), 4.65 (t, 1H, *J* = 6.04 Hz), 4.12-3.99 (m, 2H), 1.8 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.9, 134.1, 118.1, 114.1, 108.9, 78.8, 78.5, 73.7, 27.8, 25.4, 17.9; ESIMS: $[M+Na]^+$ = 221.

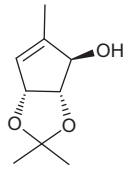
4.18. (3a*S*,4*S*,6a*R*)-2,2,5-Trimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 23



23

To compound **21** (0.5 g, 2.5 mmol) in anhydrous DCM (500 mL) under nitrogen atmosphere, was added Grubbs second generation catalyst (0.212 mg, 0.25 mmol) and the reaction mixture was allowed to reflux for 6 h. After completion of the reaction, the reaction mixture was evaporated at reduced pressure to give a crude residue, which was purified by column chromatography (ethyl acetate/hexane = 1:9) to give compound **23** (0.36 g, 85%) as a yellow oil. $[\alpha]_D^{20} = -13.3$ (*c* 0.18, $CHCl_3$); IR (KBr): ν_{max} 3433, 2985, 2927, 1448, 1377, 1245, 1210, 1161, 1048, 861, 763 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): 5.46 (s, 1H), 4.91 (d, 1H, *J* = 5.66 Hz), 4.68 (dd, 1H, *J* = 6.04, 5.66 Hz), 4.21 (dd, 1H, *J* = 6.04, 9.84 Hz), 2.46 (d, 1H, *J* = 9.84 Hz, D_2O excahnged), 1.79 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.0, 125.5, 111.9, 82.5, 75.7, 77.2, 26.4, 27.6, 13.6; ESIMS: $[M+Na]^+$ = 193.

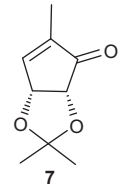
4.19. (3a*S*,4*R*,6a*R*)-2,2,5-Trimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-ol 24



24

To compound **22** (0.4 g, 2 mmol) in anhydrous DCM (400 mL) under a nitrogen atmosphere was added Grubbs second generation catalyst (0.17 g, 0.2 mmol) and the reaction mixture was allowed to reflux for 6 h. After completion of the reaction, the reaction mixture was evaporated at reduced pressure to give a crude residue, which was purified by column chromatography (ethyl acetate/hexane = 1:9) to give compound **23** (0.29 g, 85 %) as a yellow oil. $[\alpha]_D^{20} = -56$ (*c* 1.5, $CHCl_3$). IR (KBr): ν_{max} 3448, 2926, 1395, 1216, 1034, 761 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$): 5.63 (s, 1H), 5.17 (d, 1H, *J* = 4.999 Hz), 4.53 (s, 1H), 4.53 (s, 1H), 1.81 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.7, 128.7, 111.4, 86.7, 83.4, 83.3, 27.3, 25.6, 14.2; ESIMS**:** $[M+Na]^+$ = 193.

4.20. (3a*R*,6a*R*)-2,2,5-Trimethyl-3aH-cyclopenta[*d*][1,3]dioxol-4(6aH)-one 7



7

To a solution **23** (0.34 g, 2 mmol) in DCM (20 mL) were added molecular sieve powder (4 Å) and PDC (pyridinium dichlorochromate) (1.6 g, 4.4 mmol) at 0 °C. The reaction mixture was stirrred at rt for 5 h. After completion of the reaction, the crude reaction mixture was filtered through Celite, washed with water, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to give a crude brownish syrup. The syrupy liquid was purified on a column (ethyl acetate/hexane = 1:9) to give a single product **25** (0.302 g, 90 %) as a white solid. mp: 48 °C; $[\alpha]_D^{20} = -17$ (*c* 1.33, $CHCl_3$) {lit.[30] $[\alpha]_D^{20} = -17.7$ (*c* 0.9, $CHCl_3$)}; IR (KBr) : ν_{max} 3449, 2923, 2852, 1654, 1460, 1379, 1022 cm^{-1}; ^1H NMR: (300 M Hz, $CHCl_3$): 7.23 (m, 1H), 5.18 (m, 1H), 4.50 (d, 1H, *J* = 5.665 Hz), 1.83 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 203.2, 153.1, 143.2, 115.2, 76.9, 76.83, 27.4, 26.03, 10.4; ESIMS: *m*/*z* calcd for $C_9H_{12}O_3Na$ 191.06814, found 191.06787.

Acknowledgements

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