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# A short alternative preparation of the bengazoles polyol side-chain segment

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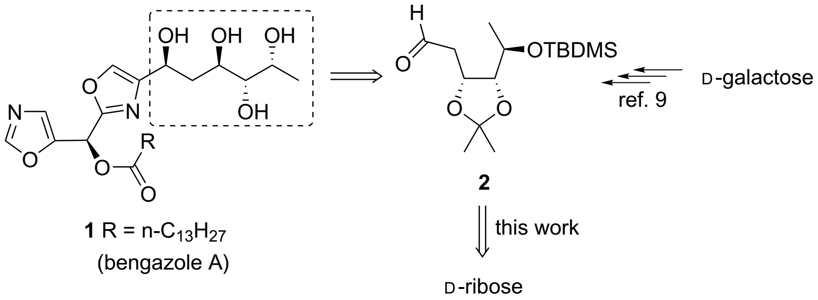
**Abstract**—A new short and efficient synthesis of the bengazoles side chain is reported using a sequential Grignard addition–hydroboration approach on a readily available D-ribose derivative.

*Keywords:* Bengazoles; Antihelminthic; D-Ribose; Grignard addition; Hydroboration

Whereas oxazole containing natural products were rare until the late 1980s, a number of naturally occurring oxazoles were isolated from marine organisms during the last 15 years.[1] Among them, Bengazole A (**1**, Scheme 1) and related homologues, are marine natural products isolated from sponges of the genus *Jaspis*.[2–5] Initially, bengazoles were found to have antihelminthic activity against *Nippostrongylus braziliensis*.[2] Later, Molinski and co-workers[6] discovered that they also exhibit a potent in vitro antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*.[6] This action is comparable to that of amphotericin B but more likely does not follow the same mode.[7] Bengazoles are in general fatty acid esters of a biogenically rare bis(oxazolyl)methanol heterocyclic core, which is further substituted with a polyol side chain, reminiscent of a sugar analogue. Their structure was elucidated by Molinski and co-workers[8] combining NMR, chiroptical methods and synthesis of model compounds. The first total synthesis of bengazole A was accomplished by Molinski's group,[9–11] as well. Their synthetic scheme follows a stepwise construction of the bis-oxazolyl core on the D-galactose derived



**Scheme 1.**

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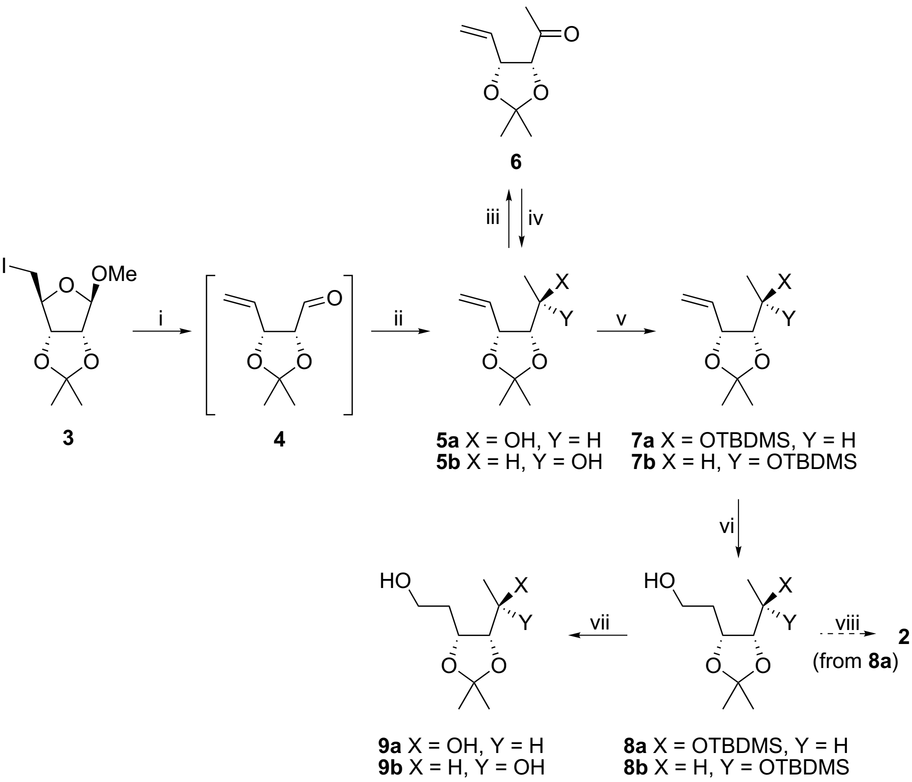
polyol chain segment **2**. According to a second approach by Shioiri and co-workers[12,13] deacylbengazole was prepared by $SnCl_4$ assisted coupling of a preformed bis-oxazolyl aldehyde subunit with a δ-alkoxystannane partner. The obtained intermediate was then further functionalized by Sharpless asymmetric dihydroxylation. Additionally, preliminary studies on the synthesis of bengazoles were lately communicated by Ley.[14] In continuation of our previous work,[15] regarding the synthesis of molecules with intriguing characteristics and properties from carbohydrates, we wish to report here an alternative preparation of aldehyde **2** using a readily available D-ribose derivative as the starting material.

It has been reported in the literature[15] that D-ribose is easily converted to iodide **3** following a simple two-step procedure and with an overall yield higher than 60%. Since pentenal **4** is also accessible in a straightforward manner from **3** we envisioned a synthetic scheme, which could lead from **4** to **2** using a Grignard addition-*anti*-Markovnikov oxidation sequence approach.

Indeed, treatment of iodide **3** with Zn in refluxing methanol for 2 h, afforded aldehyde **4**, which, being volatile, was roughly purified by removal of the solids and careful evaporation of the solvent at temperature not exceeding 35 °C (Scheme 2). Without any further purification a reasonable excess of MeMgI was added to **4**, to produce in excellent yield (91% overall from **3**) secondary alcohols **5a** and **5b** as an inseparable mixture of two diastereoisomers, lacking any appreciable selectivity (~3:2). The absolute configuration of the newly formed stereocentre in **5** was undoubtfully assigned after the conversion of **5** to diols **9** (vide infra).

Obviously, intermediate alcohol **5a** could be used to prepare the targeted aldehyde **2** but an improved pathway to it, regarding diastereoselectivity, had to be investigated. As it was not possible to separate the undesirable isomer **5b** from **5a**, in order to invert its C-2 stereocentre, we initially explored the possibility of altering the diastereoselection of the Grignard addition step. After several attempts, we realized that we could not achieve any significant change in the ratio of **5a** and **5b** and an indirect approach was adopted. According to this the mixture of alcohols **5** was oxidized to ketone **6** and the latter, without isolation was diastereoselectively reduced back to **5**. The best results we achieved hitherto were obtained when DIBAL-H (Table 1) was employed at a low temperature, favouring alcohol **5a**, with the desired C-2 configuration (dr ~8:1). Then, silylation of secondary alcohols **5** gave a mixture of alkenes **7**, which were chromatographically inseparable as well. Hydroboration of **7** followed by oxidation yielded alcohols **8**. At this stage it was practically feasible to separate **8a** and **8b** using



Scheme 2. Reagents and conditions: (i) Zn, MeOH, reflux, 2 h; (ii) MeMgI, $Et_2O$, 0–20 °C, 4 h, 91% from **3**; (iii) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −60–20 °C; (iv) DIBAL-H, THF, −130 °C, 90 min, 85% overall for two steps; (v) TBDMSCl, imidazole, $CH_2Cl_2$, 20 °C, 20 h, 81%; (vi) $BH_3{\cdot}SMe_2$, THF, 0–20 °C, 1 h, then NaOH, $H_2O_2$, 0–20 °C, 1 h, 65% of **8a** and 8% of **8b**; (vii) TBAF, THF, 0–20 °C, 30 min, 96% for **9a** and 97% for **9b**; (viii) Ref. 9.

Table 1. Diastereoselective reduction of ketone **6**

| Entry | Reductant | Temperature (°C) | Solvent | Yield (%) | Ratio of **5a**/**5b**[a] |
|---|---|---|---|---|---|
| 1 | K-Selectride | −78 | THF | 89 | 65:35 |
| 2 | L-Selectride | −78 | THF | 91 | 55:45 |
| 3 | L-Selectride | −130 | THF | 91 | 62:38 |
| 4 | $LiBH_4$ | −78 | THF | 88 | 45:55 |
| 5 | DIBAL-H | −130 | THF | 93 | 89:11 |
| 6 | (*R*)-MCBSO/$BH_3$[b] | −78 | $CH_2Cl_2$ | 85 | 48:52 |
| 7 | (*S*)-MCBSO/$BH_3$[b] | −78 | $CH_2Cl_2$ | 87 | 72:28 |

[a] Calculated from the $^1$H NMR spectra of their mixture.

[b] MCBSO = Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (2-methyl-CBS-oxazaborolidine).

standard column chromatography and subsequently the two C-5 epimers were individually deprotected to afford diols **9**. The correct stereochemistry was assigned to the major isomer (**9a**) since this was found to have identical physical and spectra data with the one reported in the literature.[10] Finally, as it is known from the literature,[9] Swern oxidation of **8a** gives the targeted aldehyde **2**. It is noteworthy that attempted oxidation of the double bond in **6** could directly lead to the desired aldehyde **2** (together with its epimer) using the Wacker oxidation procedure.[16,17] However, this plan was practically proved unsuccessful.

In conclusion, an alternative formal synthesis of the bengazoles polyol side-chain segment is reported in this paper. This uses a readily available in multigram quantities D-ribose derivative as the starting material and produces the precursor of targeted aldehyde **2** in six steps and an overall yield higher than 40% applying simply executable and efficient procedures.

## 1. Experimental

### 1.1. General methods

All commercially available reagents were used without further purification. Solvents were dried by standard methods. Reactions progress was checked by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ glass plates (0.25 mm). The spots were visualized by heat staining with anisaldehyde in ethanol/sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.063–0.200 mm). Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. The $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or on an IONSPEC FTMS spectrometer (matrix-assisted laser-desorption ionization, MALDI) with 2,5-dihydroxybenzoic acid (DHB) as the matrix.

### 1.2. (2*R*,3*S*,4*R*)-3,4-*O*-Isopropylidene-hex-5-ene-2,3,4-triol (5a) and (2*S*,3*S*,4*R*)-3,4-*O*-Isopropylidene-hex-5-ene-2,3,4-triol (5b)

Activated Zn (13.1 g, 200 mmol) was added to a solution of iodide **3** (6.28 g, 20.0 mmol) in MeOH (200 mL). The mixture was heated to reflux for 2 h, and at that time TLC analysis revealed that no starting material had remained. Then, it was cooled to room temperature and filtered through a short silica gel pad. The filtrate was carefully concentrated under reduced pressure, keeping the temperature below 35 °C, and the residue, containing crude aldehyde **4**, was used directly to the next step without any further purification. Thus, it was dissolved in dry ether (100 mL) and the resultant solution was added dropwise (about 1 h) to a 1.0 M ethereal solution of MeMgI (100 mL, 100 mmol) at 0 °C under an Ar atmosphere. After the addition the mixture was left to reach room temperature while stirring was continued for another 4 h. The reaction was quenched carefully with a satd aq solution of $NH_4Cl$ (100 mL). The organic phase was separated whereas the aqueous one was extracted with $CH_2Cl_2$ ($3 \times 200$ mL). The combined organic phases were dried ($Na_2SO_4$), concentrated and the residue was purified by column chromatography (eluent: hexanes–EtOAc, 7/1) to afford 3.13 g (91% overall from **3**) of diastereoisomeric alcohols **5a** and **5b** as an inseparable mixture (oil, ratio of ca. 3:2). Compound **5a**: $^1$H NMR ($CDCl_3$): $\delta$ 6.02 (ddd, $J = 17.1$, 11.0, 7.3 Hz, 1H, H-5), 5.42 (d, $J = 17.1$ Hz, 1H, H-6a), 5.29 (d, $J = 11.0$ Hz, 1H, H-6b), 4.66 (br t, $J = 6.6$ Hz, 1H, H-4), 3.93 (br t, $J = 7.0$, 1H, H-3), 3.83–3.77 (m, 1H, H-2), 2.47 (br s, 1H, OH), 1.47 (s, 3H, Me), 1.37 (s, 3H, Me), 1.26 (d, $J = 6.1$ Hz, 3H, H-1); $^{13}$C NMR ($CDCl_3$): $\delta$ 134.2, 118.0, 108.4, 81.7, 78.7, 66.0, 27.5, 25.1, 20.1. Compound **5b**: $^1$H NMR ($CDCl_3$): $\delta$ 6.01 (ddd, $J = 17.1$, 10.4, 7.9 Hz, 1H, H-5), 5.40 (d, $J = 17.1$ Hz, 1H, H-6a), 5.28 (d, $J = 10.4$ Hz, 1H, H-6b), 4.65 (br t, $J = 7.3$ Hz, 1H, H-4), 3.92 (dd, $J = 7.3$, 6.1 Hz, 1H, H-3), 3.80–3.74 (m, 1H, H-2), 2.76 (br s, 1H, OH), 1.47 (s, 3H, Me), 1.37 (s, 3H, Me), 1.25 (d, $J = 6.1$ Hz, 3H, H-1); $^{13}$C NMR ($CDCl_3$): $\delta$ 134.2, 117.7, 108.2, 81.6, 78.4, 65.8, 27.4, 25.0, 20.1. IR (neat, for the mixture) 3460, 2987, 2936, 1645, 1456, 1428, 1381, 1372, 1244, 1218, 1164, 1086, 1059, 1034, 1007, 931, 873, 799 $cm^{-1}$; HRMS (for the mixture) *m*/*e* calcd for $C_9H_{16}O_3Na$ $[(M+Na)^+]$: 195.0997, found: 195.0996.

### 1.3. Procedure for the improvement of diastereoselectivity ratio of alcohols 5

**1.3.1. (3*R*,4*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxy-hex-5-en-2-one (6).** A solution of DMSO (3.48 mL, 46.4 mmol) in $CH_2Cl_2$ (15 mL) was added to a stirred solution of $(COCl)_2$ (2.16 mL, 23.3 mmol) in $CH_2Cl_2$ (30 mL) at −60 °C under Ar atmosphere. The mixture was stirred at this temperature for 10 min, at which time a solution of diastereomeric alcohols **5** (1 g, 5.80 mmol) in $CH_2Cl_2$ (40 mL) was added dropwise. The resulting mixture was stirred for 30 min keeping the temperature at −40 °C. Then, it was cooled again at −78 °C and $Et_3N$ (13.3 mL, 92.8 mmol) was added slowly. Stirring was continued for 30 min, the cooling bath was removed and the mixture was left for an additional period of 45 min at room temperature. The resulting slurry was diluted with $CH_2Cl_2$ (120 mL) and washed with brine (2 × 100 mL) and water (1 × 100 mL). The organic phase was dried ($Na_2SO_4$) and concentrated to give crude ketone **6**, which was used in the next reaction without further purification.

**1.3.2. Reduction of ketone 6 to alcohols 5 with DIBAL-H.** A solution of crude ketone **6** (5.80 mmol based on previous step) in dry THF (60 mL) was cooled to −130 °C (EtOAc–liq $N_2$) and a 1 M DIBAL-H solution in toluene (7 mL, 7 mmol) was added during 1 h period. After addition, the mixture was stirred at this temperature for an additional hour, at which point MeOH (5 mL) was added and it was left to reach room temperature. EtOAc was used to dilute the solution, satd aq tartaric sodium–potassium salt (50 mL) was added and the mixture was stirred vigorously for 90 min. The organic layer was then separated and the aqueous one was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (1 × 150 mL), dried with $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified as previously described to afford 852 mg (85% overall for two steps) of diastereomeric alcohols **5a** and **5b** as an inseparable mixture (ratio of ca. 8:1) as estimated by NMR analysis of the mixture.

### 1.4. (2*R*,3*R*,4*R*)-2-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-isopropylidene-hex-5-ene-2,3,4-triol (7a) and (2*S*,3*R*,4*R*)-2-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-hex-5-ene-2,3,4-triol (7b)

The mixture of alcohols **5** (1.72 g, 10.0 mmol) was dissolved in dry $CH_2Cl_2$ (75 mL) and the solution was cooled to 0 °C. At this temperature imidazole (1.70 g, 25.0 mmol) and TBDMSCl (2.26 g, 15.0 mmol) were sequentially added under an Ar atmosphere. The temperature was left to slowly rise to 20 °C and the mixture was stirred for another 24 h. Then a satd aq solution of $NH_4Cl$ (20 mL) was added and the mixture was stirred vigorously for 10 min. After the addition of water (50 mL), it was strongly shaked. The aqueous phase was removed and the organic one was washed with brine (2 × 70 mL). The combined aqueous phases were re-extracted with $CH_2Cl_2$ (100 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (eluent: hexanes–EtOAc, 30/1) providing 2.32 g (81%) of diastereoisomeric silyl-alcohols **7a** and **7b** as an inseparable mixture (oil, ratio of ca. 8:1). Compound **7a**: $^1H$ NMR ($CDCl_3$): $\delta$ 5.85 (ddd, $J = 17.0$, 10.4, 8.6 Hz, 1H, H-5), 5.23 (d, $J = 17.0$ Hz, 1H, H-6a), 5.20 (d, $J = 10.4$ Hz, 1H, H-6b), 4.37 (dd, $J = 8.6$, 6.1 Hz, 1H, H-4), 3.93 (t, $J = 8.5$ Hz, 1H, H-3), 3.81–3.76 (m, 1H, H-2), 1.47 (s, 3H, Me), 1.33 (s, 3H, Me), 1.08 (d, $J = 6.1$ Hz, 3H, H-1), 0.88 (s, 9H, *t*-Bu), 0.06 (s, 6H, $SiMe_2$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 134.6, 117.6, 108.1, 82.8, 79.1, 67.5, 27.8, 25.9, 25.5, 19.7, 18.3, −4.5. Compound **7b**: $^1H$ NMR ($CDCl_3$): $\delta$ 5.94 (ddd, $J = 17.1$, 10.4, 7.3 Hz, 1H, H-5), 5.32 (d, $J = 17.1$ Hz, 1H, H-6a), 5.21 (d, $J = 7.3$ Hz, 1H, H-6b), 4.57 (br t, $J = 6.4$ Hz, 1H, H-4), 3.85–3.74 (m, 2H, H-3 and H-2), 1.45 (s, 3H, Me), 1.35 (s, 3H, Me), 1.22 (d, $J = 6.1$ Hz, 3H, H-1), 0.85 (s, 9H, *t*-Bu), 0.05 (s, 3H, SiMe), 0.02 (s, 3H, SiMe); $^{13}C$ NMR ($CDCl_3$): $\delta$ 134.6, 118.6, 108.4, 82.3, 78.9, 67.4, 28.0, 25.8, 25.4, 21.2, 18.0, −3.4, −4.7. IR (neat, for the mixture) 2987, 2932, 2896, 2858, 1473, 1371, 1253, 1219, 1164, 1112, 1074, 1040, 995, 978, 927, 874, 834, 809, 776 $cm^{-1}$; HRMS (for the mixture) *m*/*e* calcd for $C_{15}H_{30}O_3SiNa$ $[(M+Na)^+]$: 309.1862, found: 309.1860.

### 1.5. (3*R*,4*R*,5*R*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-isopropylidene-hexane-1,3,4,5-tetraol (8a) and (3*R*,4*R*,5*S*)-5-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-hexane-1,3,4,5-tetraol (8b)

The mixture of alkenes **7** (1.8 g, 6.3 mmol) was dissolved in dry THF (80 mL) and this was added dropwise in a 2.0 M solution of $H_3B{\cdot}SMe_2$ in THF (6.30 mL, 12.6 mmol) at 0 °C. When the addition was completed, the cooling bath was removed and stirring was continued for 1 h. At this point the reaction was re-cooled and a 3 N aq solution of NaOH (6 mL) along with 30% $H_2O_2$ (1.5 mL) were added. The mixture was warmed to room temperature and left with stirring for another 1 h. Then, $Et_2O$ (200 mL) was added and the mixture was washed with brine (2 × 200 mL) and water (150 mL). The organic layer was collected, dried

($Na_2SO_4$) and concentrated under reduced pressure. The obtained residue was purified by column chromatography (eluent: hexanes–EtOAc, 8/1) to afford in the order of elution alcohols **8b** (0.15 g, 8%) and **8a** (1.25 g, 65%). Compound **8a**: colourless syrup; $[\alpha]_D$ +35.7 (*c* 3.0, $CHCl_3$); IR (neat) 3435, 2959, 2931, 2857, 2886, 1473, 1378, 1251, 1104, 1066, 833, 777 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 4.23 (ddd, $J = 11.0$, 4.9, 2.4 Hz, 1H, H-3), 3.95–3.82 (m, 4H, H-1 and H-4 and H-5), 2.50 (br s, 1H, OH), 1.91–1.78 (m, 1H, H-2a), 1.65–1.56 (m, 1H, H-2b), 1.48 (s, 3H, Me), 1.34 (s, 3H, Me), 1.15 (d, $J = 6.1$ Hz, 3H, H-6), 0.89 (s, 9H, *t*-Bu), 0.09 (s, 3H, SiMe), 0.08 (s, 3H, SiMe); $^{13}C$ NMR ($CDCl_3$): $\delta$ 108.1, 81.7, 77.7, 67.1, 61.4, 31.9, 28.1, 25.75, 25.74, 21.5, 17.9, −3.2, −4.6; HRMS *m*/*e* calcd for $C_{15}H_{32}O_4SiNa$ $[(M+Na)^+]$: 327.1968, found: 327.1971. Compound **8b**: colourless syrup; $[\alpha]_D$ +39.6 (*c* 3.0, $CHCl_3$); IR (neat) 3437, 2957, 2932, 2859, 1473, 1370, 1253, 1116, 1087, 1058, 834, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 4.32 (dt, $J = 8.6$, 5.5 Hz, 1H, H-3), 3.97–3.81 (m, 4H, H-1 and H-4 and H-5), 2.77 (br s, 1H, OH), 1.85–1.78 (m, 2H, H-2), 1.45 (s, 3H, Me), 1.34 (s, 3H, Me), 1.27 (d, $J = 6.1$ Hz, 3H, H-6), 0.86 (s, 9H, *t*-Bu), 0.10 (s, 3H, SiMe), 0.08 (s, 3H, SiMe); $^{13}C$ NMR ($CDCl_3$): $\delta$ 108.3, 82.1, 76.6, 67.2, 61.3, 31.7, 28.0, 25.8, 25.7, 20.2, 18.3, −4.5, −4.7; HRMS *m*/*e* calcd for $C_{15}H_{32}O_4SiNa$ $[(M+Na)^+]$: 327.1968, found: 327.1970.

### 1.6. (3*R*,4*S*,5*R*)-3,4-*O*-Isopropylidene-hexane-1,3,4,5-tetraol (9a)

Silyl-alcohol **8a** (0.5 g, 1.6 mmol) was dissolved in THF (20 mL) and TBAF (1.0 M in THF, 2.1 mL, 2.1 mmol) was slowly added at 0 °C. After stirring for 30 min at this temperature, the reaction was quenched by the addition of a satd aq solution of $NH_4Cl$ (20 mL). Then, $CH_2Cl_2$ (50 mL) was added, the organic layer was collected and the aqueous one was extracted with $CH_2Cl_2$ ($4 \times 70$ mL). The combined organic phases were dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography (eluent: hexanes–EtOAc, 1/1) to afford 0.29 g of diol **9a** (96%). Compound **9a**: oil; $[\alpha]_D$ +17.0 (*c* 0.6, $CHCl_3$) {lit.[10] $[\alpha]_D$ +16.9 (*c* 0.55, $CHCl_3$)}; IR, $^1H$ NMR and $^{13}C$ NMR were identical with those reported in the literature;[10] HRMS *m*/*e* calcd for $C_9H_{18}O_4Na$ $[(M+Na)^+]$: 213.1103, found: 213.1106.

### 1.7. (3*R*,4*S*,5*S*)-3,4-*O*-isopropylidene-hexane-1,3,4,5-tetraol (9b)

Silyl-alcohol **8b** (0.6 g, 2.0 mmol) was deprotected as described in the preceding procedure to give 0.37 g of diol **9b** (97%). Compound **9b**: oil; $[\alpha]_D$ +22.5 (*c* 2.0, $CHCl_3$); IR (neat) 3401, 2985, 2934, 1381, 1371, 1241, 1220, 1158, 1056, 1010, 931, 875 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 4.35 (dt, $J = 8.5$, 5.5 Hz, 1H, H-3), 3.90–3.78 (m, 4H, H-1 and H-4 and H-5), 2.68 (br s, 2H, OH), 2.07–1.98 (m, 1H, H-2a), 1.92–1.83 (m, 1H, H-2b), 1.43 (s, 3H, Me), 1.35 (s, 3H, Me), 1.31 (d, $J = 6.1$ Hz, 3H, H-6); $^{13}C$ NMR ($CDCl_3$): $\delta$ 107.9, 81.5, 77.3, 65.8, 61.1, 31.7, 28.1, 25.6, 21.2; HRMS *m*/*e* calcd for $C_9H_{18}O_4Na$ $[(M+Na)^+]$: 213.1103, found: 213.1105.

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