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One-pot synthesis of carbohydrate *exo*-cyclic enones and hemiketals with 6,8-dioxabicyclo-[3.2.1]octane moieties. Serendipitous formation of a spironolactone when 2-pyridinecarboxaldehyde is used as the reactant. Part II☆

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ABSTRACT

A library of exo-cyclic carbohydrate enones **2**–**13** were prepared *via* a base-catalyzed, highly stereoselective aldol condensation of dihydrolevoglucosenone **1** (cyrene) with various aromatic aldehydes. In the case of 4-chlorobenzaldehyde as a reactant, under conditions of the aldol condensation, exo-cyclic enone **9** and a secondary product **9A** was isolated. When 2-pyridinecarboxaldehyde was used as a reactant, an unexpected spironolactone **19** was exclusively observed. ^{1}H NMR, ^{13}C NMR, MS analyses and single-crystal x-ray diffraction of the representative enone **9**, the secondary product **9A**, hemiketal **18**, and spironolactone **19** unequivocally confirms the structural assignments. Mechanistic insights leading to the synthesized products are also proposed and discussed.

1. Introduction

Over the last several years conjugated enones [1], including *exo*-cyclic enones, have attracted increased interest from the scientific community in view of their chemical properties such as their push-pull reactivity [2–4]. Furthermore, they are excellent substrates for various and important classes of branched-chain sugars [5], aminosugars [6], thiosugars [7] and *C*-disaccharides [8] with important various biological activities [9]. Recently, we reported a concise and efficient synthesis of novel *exo*-cyclic carbohydrate enones [10] *via* a base-catalyzed aldol condensation of dihydrolevoglucosenone with five-membered aromatic aldehydes. Logically, there is no reason to expect the reaction to be limited to five-membered aromatic aldehydes. Thus, it was of interest for us to further explore the scope of the reaction. Many functionalizations of synthesized enones offer entry into new carbohydrate building blocks containing fully protected core structures towards the synthesis of various heterocyclic systems starting from simple carbohydrate synthons. Moreover, the naturally abundant bridgehead cyclic acetal of the 6,8-dioxabicyclo-[3.2.1]-octane scaffold is related to a number of natural products or is a subunit in a complex molecular system [11].

For example, insect pheromones multistriatin [12], brevicomin [13], frontalin [14], (+) attenol B [15], serinol marine natural product, (+) didemniserinolipid B [16] and marine toxin pinnatoxins [17], all contain the 6,8-dioxa-bicyclo-[3.2.1]-octane (DOBCO) motif as a structural fused bicyclic acetal scaffold subunit depicted in Fig. 1.

This particular DOBCO framework has prompted a wide interest amongst the synthetic organic chemists and biochemists toward the synthesis of new analogues of these biologically active compounds. Furthermore, the 1,6-anhydro bicyclic acetal scaffold DOBCO was also proposed as a potential functional carbohydrate pharmacophore (FCP) and previously developed in a few analogous motifs by our team [18].

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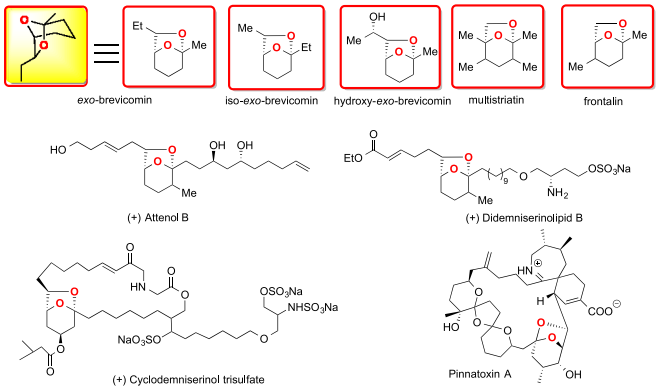


Fig. 1. 6,8-Dioxabicyclo-[3.2.1]octane motif of various natural products.

2. Results and discussion

The present paper shows our work employing the reaction of various aromatic aldehydes that are reacted with dihydrolevoglucosenone in the presence of piperidine as a relatively mild base. Specifically, we detail condensations of dihydrolevoglucosenone with compounds containing an aldehyde moiety connected directly to various substituted benzenes, naphthalenes, imidazoles and indoles. In our previous paper [10], we presented the condensation results when various bases were used. Surprisingly, piperidine turned out to be the best base from a plethora that was investigated. Piperidine appears to offer the ideal basicity for our current process. Stronger bases such as tetramethylguanidine (TMG) were found to be harsh and we often observed complicated reaction mixtures and unsatisfactory yields.

On the other hand, typical tertiary amines such as triethylamine or diisopropylethylamine are probably not sufficiently basic and led to low yields or even no reaction at all, even after prolonged heating conditions of the reaction mixture. Since piperidine is a secondary amine, it can form imines/enamines with ketones. However, we did not identify any enamine-derived products when reacting dihydrolevoglucosenone with five-membered aromatic aldehydes.

The general mechanism of the process, involving dihydrolevoglucosenone aldol condensations reactions, seems to be that of a Knoevenagel-type [19] condensation reaction, where an active methylene center in the ketone forms a C–C linkage with an aldehyde. The resulting products offer interesting features. Some potential reactive sites of dihydrolevoglucosenone (DHLG) (A) and product enone (B) are depicted in Fig. 2.

- They can be functionalized by taking advantage of:
- the *exo*-cyclic double bond (which can be hydrogenated, brominated, hydroxylated, etc)
- conjugated unsaturated ketones (possible object of Michael addition with various reactants including carbohydrate thiols to form *S*-dithiodisaccharides),
- carbonyl groups (which can be reduced to CH_2 or alcohol, transformed to a double bond {creating a 1,3-diene})
- 1,6-ahydro moieties (after hydrolysis modified, 4-deoxy-saccharides are formed).

The piperidine-catalyzed reactions with benzaldehydes proceeded smoothly and formed the expected *C*-3 functionalized *exo*-cyclic crystalline enones in a one-pot reaction with good to excellent yields. (See Table 1 in supplemental data). It should be emphasized that the reaction protocol is exceptionally simple. However, most reactions were only run at one set of conditions and not optimized. It is very likely that the yields would be higher if optimal reaction time, amount of the catalyst, reaction temperature and optimal solvent were screened. Table 1 (see supplemental data) shows the compiled results. Entries **2**–**13** represent the expected enone products [10]. It is worth mentioning that the heterocyclic system, based on γ-benzopyrone produces *endo*-cyclic enones upon reaction with aromatic aldehydes substituted with electron withdrawing group (EWG) [20]. Entries **14**–**18** represent products arising from the reaction between dihydrolevoglucosenone and aromatic aldehydes with a hydroxyl group in the position *ortho* to the aldehyde. As expected, the resulting condensation carbonyl group forms a hemiketal with the aromatic OH group. Note that the product formation requires the aromatic ring to be *Z* with respect to the carbonyl group.

Interestingly, the condensation of *p*-chlorobenzaldehyde with dihydrolevoglucosenone gave an unexpected result. The main product **9** was accompanied by a second product **9A** as depicted in Scheme 2. The product ratio was determined to be 5:2 with yields of 65% and 26% respectfully. The structure of the minor condensation product, **9A**, was determined using x-ray crystallography and is shown in Fig. 3 [22]. Single crystal x-ray crystallography (Fig. 3) of the expected product **9** and an additional cyclic product **9A**, resulting from enamine participation, unambiguously confirmed the structure of the minor product. Specifically, it nicely illustrates the presence of an *exo*-cyclic double bond at C-5 position. We did not expect the formation of the product **9A**, since we did not observe its analogues in other reactions. We do not have a satisfactory answer to the question as to why it was formed, we only observed the compound when *p*-chlorobenzaldehyde was employed as the starting material.

The minor product, **9A**, appears to arise from a double condensation with the incorporation of one unit base catalyst and two cyrene units (**1**). The reaction may proceed *via* a domino-type process. The plausible reaction mechanism of our proposed condensation of dihydrolevoglucosenone with 4-chlorobenzaldehyde catalyzed by piperidine is depicted in Scheme 2.

It is possible that the first piperidine molecule forms a dihydrolevoglucosenone enamine, which subsequently can react with aldehyde-derived *exo*-cyclic enone in a stereoselective manner to form a domino product, **9A**, with *E*-stereochemistry (according to

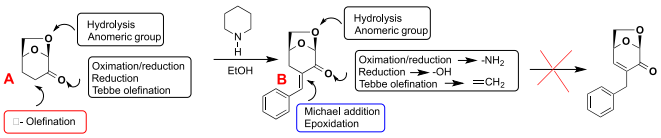


Fig. 2. Reactive sites of dihydrolevoglucosenone (Cyrene) and exo-cyclic enones.

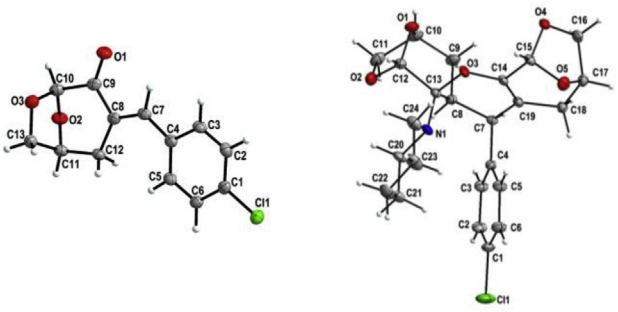


Fig. 3. ORTEP diagrams of enone **9** and minor product **9A**.

Cahn-Ingold-Prelog (CIP) priority rules) [23]. The product was unambiguously confirmed by ^{1}H NMR and x-ray analysis. It is worth noting that **9A** is a modified 6-membered *N*-glycoside. It is therefore not related to nucleosides and any formation of such structures is of high interest to the biological community.

While this work was in progress, Greatrex and co-workers [21] published an interesting paper describing condensations along similar lines to those we performed. They also condensed dihydrolevoglucosenone with aromatic aldehydes. However, they used TMG as a base and solvents other than ethanol. While most of Greatrex et al. [21] results are similar to ours, there is one fundamental and significant difference, they observed the formation of small quantities of additional products; *endo*-cyclic enones.

Since we did consider the possibility of the formation of *endo*-cyclic enones, we examined our reaction mixtures very carefully using TLC. Under our reaction conditions (piperidine/ethyl alcohol), we were not able to detect any of the *endo* products either by TLC or by ^{1}H NMR. This is most likely due to the fact that we employed a milder base and a very polar solvent. Furthermore, our reaction times are significantly longer.

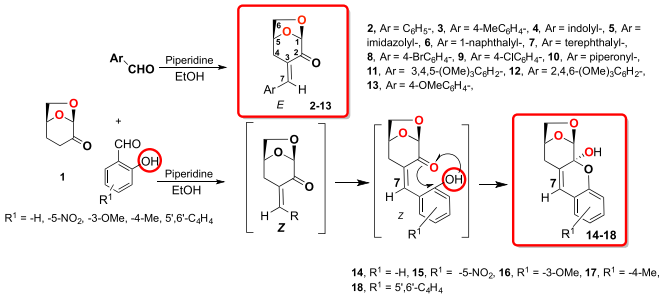
The NMR analysis offers some structural diagnostic details of all synthesized *exo*-cyclic enones (**2**–**13**). In particular, the H-5, and C-7 and C-2 signals confirm the *E*-*exo*-cyclic geometry of molecules. The data are shown in Table 2 (in supplementary data). We grouped the products in Tables 1 and 2 into a few categories. The first group represents *exo*-cyclic enone products derived from aromatic and heteroaromatic aldehydes with electron donating group (EDG) or electron withdrawing group (EWG). The second group consists of products derived from aldehydes having an –OH group in the position *ortho* to the aldehyde functionality. This particular category of starting aldehyde templates yields cyclization products (hemiketals) *via* intermolecular cyclization of 2′-OH group with C-2 keto function of dihydrolevoglucosenone. We isolated five hemiketals (**14**–**18**) in 58–64% yield. The cyclization reaction presumably proceeds *via* prior the *E*/*Z* isomerization, as only the *Z*-isomer is capable of forming hemiketals with the chromene core structure. (See Scheme 1).

The chromene structure of the representative hemiketal **17** was determined by single x-ray diffraction analysis and is shown in Fig. 4 [22].

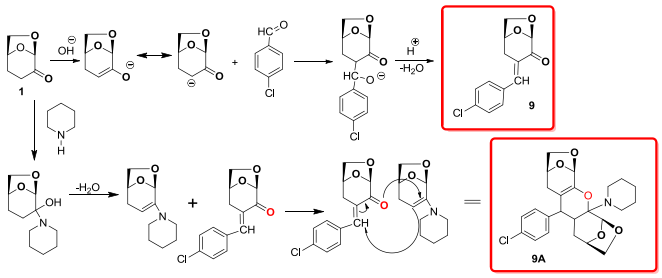
A similar formation of chromene structural core unit was reported by Samet and co-workers [28].

Attempts to isolate *Z*-isomers were unsuccessful, suggesting that they are kinetic products quickly undergoing cyclization with the formation of thermodynamically more stable hemiketals. Detailed studies of this interesting phenomenon are currently under investigation and will be published in due course.

All the NMR spectra are consistent with assigned structures. As expected the position of H-7 signals (in the ^{1}H-spectrum) and C-7 signals (in the carbon spectrum) is significantly lower for



Scheme 1. Reaction mechanism of dihydrolevoglucosenone with aromatic aldehydes leading to the formation of exo-cyclic enones **2**–**13** and hemiketals **14**–**18**.



Scheme 2. Plausible reaction mechanism of dihydrolevoglucosenone with 4-chlorobenzaldehyde.

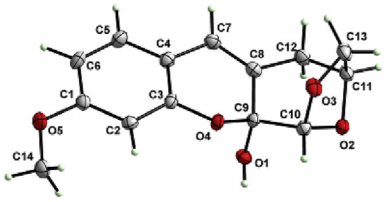
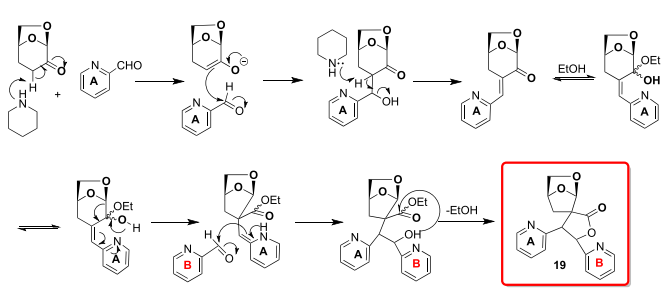


Fig. 4. ORTEP diagram of hemiketal **17**.

hemiketals **14**–**18** than for enones **2**–**13**. For example, the (H-7) proton signals are located between δ 6.46 and 7.27 ppm for hemiketals and between δ 7.43 and 8.07 for enones. It reflects the *Z* or *E* configuration of the relevant proton. Not surprisingly, the difference between the location of signals representing C-2 in the carbon spectrum is even more profound (ketone and hemiketal). In general, the presence of electron donating and withdrawing substituents in the aromatic ring have a small effect on the location of the ^{1}H signal. However, for some enone products there is an intriguing difference between the position of C-7 signals; compounds with hydroxy or alkoxy groups in ortho position (compounds **12**, **13**) have their C-7 signal located around 133 ppm while compounds with these group in the meta position have the signal around 139 ppm. The spectra were taken in a few deuterated solvents, and it can be said that the differences are rather insignificant. All the MS spectra are also consistent with the proposed structures. In almost all spectra the mass of a molecular peak (signal) differs by 1 from the molecular mass. Interestingly, in two spectra (compounds **14** and **15**), the molecular peak is additionally missing an oxygen atom (molecular mass minus 17). Ions of similar compounds (**17**–**19**) with electron donating groups (EDG) in the ring are more stable (under the MS conditions) with the oxygen atom still present.

Surprisingly, when reacting DHLG with 2-pirydinecarboxaldehyde we observed spironolactone **19** as the only isolated product (48% yield). We can offer two possible mechanisms for the formation of **19**, which, we consider plausible at this point. A more plausible mechanism, is depicted in Scheme 3.



Scheme 3. Plausible reaction mechanism of dihydrolevoglucosenone with 2-piridinecarboxaldehyde.

The first step involves the formation of *exo*-cyclic enone, which can undergo further condensation with a second molecule of aldehyde, followed by the split of C-1-C-2 bond and the formation of a five-membered lactone ring.

Another possible mechanistic explanation is the formation of an equilibrium between enone and hemiacetal, which can be intramolecularly hydrogen-bonded to the pyridine moiety. This sets up a partial positive charge on the pyridine ring and reverses the polarization of the alkene so the migration is electronically possible. This is quite similar to the vinylogous pinacol-type rearrangement [24]. The final step is lactonization, which is generally considered facile for the formation of gamma-lactones and assisted by a Thorpe-Ingold effect [25].

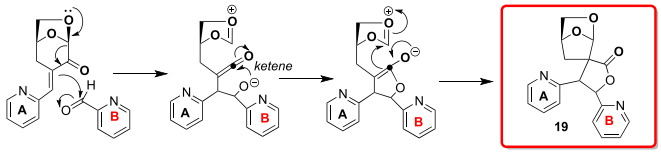
The second possible reaction mechanism (Scheme 4) for the synthesis of **19** requires the formation of a reactive ketene [26] intermediate, which undergoes a 1,6-anhydro-ring split, followed by spirocyclization forming the γ-lactone.

Both proposed reaction mechanisms end up with the spironolactone formation [27] and a simultaneous 1,6-anhydro-ring split.

This particular combination of two independent steps fits nicely with the definition of a domino reaction. Interestingly, this sequence of the 1,6-anhydro-ring split and lactonization has never been observed in this family of carbohydrate derivatives. Importantly, similar rearrangement products were not observed when other aromatic aldehydes were utilized as reactants. This serendipitous observation prompted us to investigate the reactivity of other structurally related pyridine carboxaldehydes. These and other results will be reported soon. Single x-ray crystal diffraction analysis of the spironolactone is shown in Fig. 5.

3. Conclusion

In conclusion, we have shown that the reaction between dihydrolevoglucosenone and aromatic aldehydes in the presence of piperidine produces stereoselective *exo*-cyclic enones in good (72–86%) yields. The isolation of products from the reaction mixture is exceptionally facile. In one case, an additional by-product arising from enamine participation was isolated. Surprisingly, the reaction of dihydrolevoglucosenone with 2-piridynecarboxaldehyde gave a single (spironolactone) product containing two pyridine units and a five-membered lactone ring. The reaction process conforms to the definition of a domino process. When the starting aldehydes have a hydroxyl group in the *ortho* position, the intermolecular cyclization event produces unique carbohydrate hemiketals derived from an aromatic OH group *via Z*-enones.



Scheme 4. Plausible reaction mechanism of condensation of dihydrolevoglucosenone with 2-pirydinecarboxaldehyde *via* ketene intermediate.

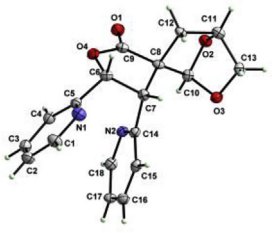


Fig. 5. ORTEP diagram of spironolactone **19**.

4. Experimental section

4.1. General information

All reagents and solvents were used as purchased without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 Ultrashield Plus spectrometer to assign chemical shift and to determine C–H coupling constants. 2D (COSY and HSQC) experiments were performed to enhance assignments. Chemical shifts (δ-scale) are reported in ppm with TMS (0 ppm) as an internal standard for ^{1}H NMR and the residual solvent signals ($CDCl_3$: 7.26 ppm, acetone-d_6: 2.05 ppm, DMSO-d_6: 2.50 ppm) for ^{1}H NMR and ($CDCl_3$: 77.16 ppm, acetone-d_6: 206.26 ppm, 29.84 ppm, DMSO-d_6: 39.52 ppm) for ^{13}C NMR. Thin layer chromatography was performed on silica gel coated TLC plates and visualized under UV light (at 254 nm) or by exposing to iodine (I_2) vapor. The mass spectrometry was performed with an Advion CMS single quadrupole instrument. The solid products were run without any sample preparation using a direct insertion probe; the ASAP® (Atmospheric Solids Analysis Probe) which employs an Atmospheric Pressure Chemical Ionization (APCI) source. All data was collected in positive ion mode. The instrument was run in scan mode from 67 to 500 Da (*m*/*z* units). The instrument was calibrated the same day the samples were analyzed demonstrating a mass accuracy of±0.05 Da (*m*/*z* units) and resolution of 0.5–0.7 *m*/*z* units (FWHM). The melting points (mp) were obtained on a Techne Stuart digital melting point apparatus and were uncorrected. Optical rotation was measured using a JASCO P-2000 Digital Polarimeter. Chemical names were generated by ChemDraw Professional V.15.1.0.144 software.

4.2. General procedure for the synthesis of exocyclic enones **2-13**

To a solution of dihydrolevoglucosenone, (1) 1.28 g (0.010 mol) in 30 mL of ethyl alcohol a 0.010 mol of corresponding aldehyde was added and magnetically stirred for 5 min. After that time, 1.0 mL of piperidine was added drop-wise and the solution was refluxed for 16–48 h. Upon overnight cooling at 5° C the crystalline residue was filtered off, the crystals were air-dried and recrystallized from ethyl alcohol.

4.2.1. (1S, 5R)-3-((E)-benzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**2**)

The reaction was carried under reflux for 72 h. Yellow needles m.p. 107–110 °C; 2.28 g 68% yield); Lit [21]. 107–110 °C; $R_f = 0.29$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -224.6 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (d, $J = 17.2$ Hz, 1H), 3.34 (ddd, $J = 18.2$, 4.0, 2.8 Hz 1H), 3.81 (d, $J = 5.3$ Hz, 2H), 4.96 (m, 1H), 5.35 (s, 1H), 7.45 (m, 3H), 7.60 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.2, 68.5, 72.5, 100.3, 129.2, 129.3, 130.15, 131.0, 134.8, 139.1, 190.3. MS APCI *m*/*z*: calcd. for $C_{13}H_{12}O_3$, 216.0786, found [M – 1] 215, 0708.

4.2.2. (1S,5R)-3-((E)-4-methylbenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**3**)

The reaction was carried under reflux for 16 h. Yellow needles m.p. 99–101 °C; 2.28 g 81% yield); $R_f = 0.89$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = 187.8 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.88 (d, $J = 16.8$, 1H), 3.34 (ddd, $J = 16.8$, 4.4, 3.0 1H), 3.79 (dd, $J = 6.8$, 1.2 Hz, 1H), 3.92 (ddd, $J = 7.2$, 7.0, 1.6 Hz, 1H), 4.87 (t,

J = 1.4 Hz, 1H), 5.34 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 34.6, 68.4, 72.5, 101.0, 127.0, 129.4, 130.6, 131.9, 140. 140.0, 140.1, 189.8. MS APCI m/z: calcd. for $C_{14}H_{14}O_3$, 230.0943, found [M − 1] 229,0865.

4.2.3. (1S,5R,E)-3-((1H-indol-3-yl)-methylene)-6,8-dioxabicyclo [3.2.1]octan-4-one (**4**)

The reaction was carried under reflux for 30 h. Orange needles m.p. 274–275 °C, 2.52 g, 48% yield); R_f = 0.21 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -213.2 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.75 (d, J = 17.2 Hz, 1H), 3.20 (dd, J = 13.6, 1.8 Hz, 1H), 3.80 (d, J = 7.2 Hz 1H), 3.85 (t, J = 5.6 Hz, 1H), 5.02 (t, J = 5.2 Hz, 1H), 5.30 (s, 1H), 7.182 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 8.06 (s, 1H), 12.10 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.7, 68.9, 72.3, 100.5, 111.7, 112.6, 118.5, 121.2, 121.9, 123.2, 128.0, 129.6, 131.2, 136.23, 189.5. MS APCI m/z: calcd. for $C_{15}H_{14}NO_3$, 255.0895, found [M+1] 256.1.

4.2.4. (1S,5R,E)-3-((1H-imidazole-4-yl)methylene)-6,8-dioxabicyclo [3.2.1]octan-4-one (**5**)

The reaction was carried under reflux for 16 h. Yellow crystals m.p. 199–201 °C. 2.28 g 84% yield); R_f = 0.78 (EtOAc/Hex 2/1), $[\alpha]_{24}^{D}$ = −116.1 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05 (d, J = 17.2 Hz, 1H), 3.17 (dd, 16, 1.8 Hz, 1H), 3.78 (dd, J = 8.0, 2.0, 1H), 3.83 (t, J = 8.0 Hz, 1H). 4.98 (t, J = 5.2 Hz, 1H), 5.28 (s, 1H), 7.572 (s, 1H), 7.625 (s, 1H), 7.879 (s, 1H), 12.59 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.1, 68.8, 72.4, 100.3, 123.8, 125 (br), 131 (br), 138.0, 190.0. MS APCI m/z: calcd. for $C_{10}H_{10}N_2O_3$, 206.0691, found [M+1] 207.0770.

4.2.5. (1S,5R)-3-E)-3-(naphthalen-1-ylmethylene)-6,8-dioxabicyclo [3.2.1]octan-4-one (**6**)

The reaction was carried under reflux for 16 h. Yellow crystals m.p. 124–126 °C. 2.28 g 84% yield); R_f = 0.78 (EtOAc/Hex 2/1), $[\alpha]_{24}^{D}$ = -225.1 (c 1.13, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.68 (d, J = 16.0 Hz, 1H), 3.34 (ddd, J = 18.8, 3.0, 1.6 Hz 1H), 3.76 (dd, J = 8.0, 1.0 Hz, 1H), 3.88 (ddd, J = 8.0, 2.8, 1.6 Hz, 1H), 4.76 (m, 1H), 5.40 (s, 1H), 7.39 (d, 7.2 Hz, 1H), 7.47 (t, 7.2 Hz, 1H), 7.52 (m, 2H), 7.86 (m, 2H), 7.94 (m, 1H), 8.28 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 34.5, 68.2, 72.8, 101.1, 124.3, 124.9, 126.4, 126.4, 126.8, 128.7, 129.7, 130.9, 131.6, 131.7, 133.5, 137.8, 189.7. MS APCI m/z: calcd. for $C_{17}H_{14}O_3$, 266.0943, found [M − 1] 265.08650.

4.2.6. (1S,5R)-3-((E)-4-((E)-((1R,5S)-4-oxo-6,8-dioxabicyclo[3.2.1] octan-3-ylidene)methyl)-benzylidene)-6,8-dioxabicyclo[3.2.1]octan -4-one (**7**)

The reaction was carried under reflux for 72 h. Yellow crystals m.p. 202–204 °C; (2.4 g, 62% yield); R_f = 0.58 (EtOAc/Hex 1/1), $[\alpha]_{30}^{D}$ = -267.5 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.97 (d, 2H), 3.35 (br s, 2H), 3.82 (s, 4H), 5.08 (s, 2H), 5.36 (s, 2H), 7.61 (s, 2H), 7.69 (s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 33.8, 68.1, 72.1, 99.9, 129.6, 130.0, 130.9, 131.0, 135.4, 137.7, 189.8. ^{1}H NMR (400 MHz, acetone-d_6): δ 2.96 (d, J = 17.2 Hz, 2H), 3.35 (m, 2H), 3.81 (d, J = 3.2 Hz, 4H), 4.97 (m, 2H), 5.364 (s, 2H), 7.61 (br s, 2H), 7.68 (s, 4H). ^{13}C NMR (100 MHz, acetone-d_6): δ 31.1, 34.3, 68.5, 72.5, 100.3, 130.5, 131.3, 135.8, 138.1, 190.2. MS APCI m/z: calcd. for $C_{20}H_{18}O_6$, 354.1103, found [M − 1] 353.1025.

4.2.7. (1S,5R)-3-((E)-4-bromobenzylidene)-6,8-dioxabicyclo[3.2.1] octan-4-one (**8**)

The reaction was carried under reflux for 26 h. Yellow needles m.p. 118–120 °C, (2.52 g, 84% yield); R_f = 0.89 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -146.3 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (d, J = 18.4 Hz, 1H), 3.30 (ddd, J = 16.8, 4.4, 3.0 1H), 3.80 (dd, J = 6.8, 1.2 Hz, 1H), 3.93 (ddd, J = 7.2, 7.0, 1.6 Hz, 1H), 4.88 (t, 5.2 Hz, 1H), 5.349 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.54 (m, 2H), 7.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.5, 68.4, 72.4, 100.9, 123.9, 128.8, 131.8, 131.9, 133.5, 138.5, 189.4. MS APCI m/z: calcd. for $C_{13}H_{11}BrO_3$, 293.9892, found [M+2] 295.1.

4.2.8. (1S,5R)-3-((E)-4-chlorobenzylidene)-6,8-dioxabicyclo[3.2.1] octan-4-one (**9**)

The reaction was carried under reflux for 48 h. Yellow crystals m.p. 84–86 °C; (1.2 g, 48% yield); R_f = 0.77(EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -199.5 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (d, J = 16.8 Hz, 1H), 3.32 (d, J = 16.8 Hz, 1H), 3.80 (d, J = 7.2 Hz, 1H), 3.94 (t, J = 7.2 Hz, 1H), 4.88 (t, J = 1.2 Hz, 1H), 5.35 (s, 1H), 7.38 (s, 4H), 7.647 (br s, 1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 34.6, 68.5, 72.5, 101.0, 128.8, 129.1, 131.7, 133.2, 135.7, 138.6, 189.5. MS APCI m/z: calcd. for $C_{13}H_{11}ClO_3$, 250.0397, found [M+1] 251.1.

4.2.9. 1-((1S,4R,8S,11R)-6-(4-chlorophenyl)-1,4,5,5a,7,8,9,12a-octahydro-3H-1,4:8,11-diepoxypyrano[2,3-c:6,5-c']bis(oxepine)-11a(11H)-yl)piperidine (**9A**)

White crystals m.p. 150–153 °C; 0.42 g, 23% yield); R_f = 0.71 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -84.5 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.763 (br s, 2H), 0.945 (m, 2H), 1.120 (m, 2H), 1.61 (m, 2H), 1.61 (m, 2H), 1.85 (m, 1H), 2.13 (m, 2H), 2.69 (overlapping m, 5H), 3.53 (br t, J = 5.8 Hz, 1H), 3.63 (dd, J = 8.0, 1.8 Hz, 1H), 3.85 (t, J = 6.6 Hz, 1H), 3.96 (d, J = 6.8 Hz, 1H), 4.49 (m, 1H), 4.71 (t, J = 4.0 Hz, 1H), 5.29 (s, 1H), 5.373 (s, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.5, 24.8, 30.5, 31.2, 33.1, 34.1, 43.2, 46.2, 66.5, 67.6, 71.4, 71.8, 87.1, 95.9, 96.8, 97.9, 127.4, 129.8, 130.85, 140.8, 144.1. MS APCI m/z: calcd. for $C_{24}H_{28}ClNO_5$, 445.1656, found [M+1] 446.1.

4.2.10. (1S, 5R, E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**10**)

The reaction was carried under reflux for 16 h. Tan crystal m.p. 112–116 °C. (1.89 g, 73% yield); Lit [21]. 129–131 °C; R_f = 0.89 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 219.4 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (d, J = 16.8 Hz, 1H), 3.32 (dt, J = 16.8, 3.2 Hz, 1H), 3.80 (d, J = 7.2 Hz, 1H), 3.93 (t, J = 7.2 Hz, 1H), 4.88 (t, J = 4.4 Hz, 1H), 5.33 (s, 1H), 6.02 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.95 (d, 1.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.6, 68.4, 72.4, 101.0, 101.6, 108.7, 109.7, 125.9, 126.6, 128.9, 139.9, 148.0, 148.9, 189.6. MS APCI m/z: calcd. for $C_{14}H_{12}O_5$, 260.0685, found [M − 1] 259.1.

4.2.11. (1S,5R)-3-((E)-3,4,5-trimethoxybenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**11**)

The reaction was carried under reflux for 24 h. Yellow crystals m.p. 70–72 °C, (2.52 g, 84% yield); Rf = 0.87 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 187.2 (c 1.0, (CH3)2CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.00 (d, J = 17.2 Hz, 1H), 3.40 (m, 1H), 3.71 (s, 3H), 3.80 (br s, 2H), 3.81 (s, 6H), 4.96 (m, 1H), 5.33 (s, 1H), 6.92 (s, 2H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.3, 55.9, 60.0, 68.0, 72.0, 99.8, 108.3, 127.7, 129.8, 138.8, 152.7, 189.7. MS APCI m/z: calcd. for $C_{16}H_{18}O_6$, 306.1103, found [M − 1] 305.2.

4.2.12. (1S,5R)-3-((E)-2,4,6-trimethoxybenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one (**12**)

The reaction was carried under reflux for 16 h. Yellow crystals m.p. 89–92 °C. (2.08 g, 68% yield); R_f = 0.89 (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -237.5 (c 1.0, $(CH_3)_2CO$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (d, J = 17.2 Hz, 1H), 2.93 (ddd, J = 16.8, 4.4, 3.0 1H), 3.65 (dd J = 8.0,

1.2 Hz, 1H), 3.76 (m, 1H), 3.80 (s, 6H), 3.83 (s, 3H), 4.85 (t, $J = 4.8$ Hz, 1H), 5.28 (s, 1H), 6.28 (s, 2H), 7.43 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.7, 55.0, 55.2, 67.4, 72.2, 90.3, 99.7, 104.1, 129.0, 132.2, 158.5, 162.2, 189.3. MS APCI *m/z*: calcd. for $C_{16}H_{18}O_6$, 306.1103, found [M − 1] 305.2.

4.2.13. (1S,5R)-3-((E)-4-methoxybenzylidene)-6,8-dioxabicyclo [3.2.1]octan-4-one (**13**)

The reaction was carried under reflux for 15 h. Colorless crystals m.p. 82–84 °C; (1.59 g, 65% yield); $R_f = 0.61$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 236.1 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (d, $J = 17.2$ Hz, 1H), 3.30 (ddd, $J = 16.8$, 4.4, 3.0 1H), 3.80 (d, $J = 1.6$ Hz, 2H), 3.81 (s, 3H), 4.96 (td, $J = 4$, 2 Hz, 1H), 5.31 (s, 1H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.57 (s, 1H), 7.58 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.1, 55.8, 68.6, 72.4, 100.4, 114.7, 126.4, 127.5, 133.2, 139.1, 160.9, 190.2. MS APCI *m/z*: calcd. for $C_{14}H_{14}O_4$, 246.0892, found [M − 1] 245.1.

4.2.14. (1R,4S,11aS)-4,5-dihydro-3H-1,4-epoxyoxepino[3,4b] chromen-11a(1H)-ol (**14**)

The reaction was carried under reflux for 26 h. White crystals m.p. 183–186 °C, lit [21]. 190–192 °C; (1.57 g, 68%); $R_f = 0.13$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 40.2 (c 1.0), $(CH_3)_2CO$); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.436 (dt, $J = 14.8$, 0.8 Hz, 1H), 3.00 (m, 2H), 3.72 (ddd, $J = 6$, 5.6, 1.6 Hz, 1H), 3.78 (dd, $J = 7.2$, 0.8 Hz, 1H), 4.72 (m, 1H), 5.26 (s, 1H), 5.91 (s, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.90 (m, 2H), 7.14 (m, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 34.7, 67.3, 73.6, 93.3, 102.0, 116.2, 121.0, 121.1, 122.7, 126.0, 128.3, 129.7, 151.5. MS APCI *m/z*: calcd. for $C_{13}H_{12}O_4$, 232.0736, found [M − 16] 215.1.

4.2.15. (1R,4S,11aS)-8-nitro-4,5-dihydro-3H-1,4-epoxyoxepino[3,4-b]chromen-11a(1H)-ol (**15**)

The reaction was carried under reflux for 16 h. Orange crystals m.p. 191–193 °C, (1.32 g, 48% yield); $R_f = 0.11$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -25.8 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.55 (d, $J = 15.2$ Hz, 1H), 3.05 (d, $J = 16$ Hz, 1H), 3.74 (t, $J = 6$ Hz, 1H), 3.81 (d, $J = 7.2$ Hz, 1H), 4.77 (t, $J = 4$ Hz, 1H), 5.31 (s, 1H), 6.71 (s, 1H), 7.07 (d, $J = 10$ Hz, 1H), 8.06 (s, 1H), 8.07 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 35.8, 68.4, 74.7, 95.6, 102.6, 117.8, 122.2, 122.4, 122.5, 124.9, 133.4, 142.9, 157.7. MS APCI *m/z*: calcd. for $C_{13}H_{11}NO_6$, 277.0586, found [M − 16] 260.1.

4.2.16. (1R,4S,11aS)-10-methoxy-4,5-dihydro-3H-1,4-epoxyoxepino [3,4-b]chromen-11a(1H)-ol (**16**)

The reaction was carried under reflux for 16 h. Yellow crystals m.p. 214–216 °C (1.99 g, 76% yield); $R_f = 0.47$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = -45.4 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (d, $J = 15.2$ Hz, 1H), 3.05 (d, $J = 15.2$ Hz, 1H), 3.83 (d, $J = 2.8$ Hz, 1H), 3.88 (s, 3H), 4.73 (m, 1H), 5.53 (s, 1H), 6.48 (d, 2.4 Hz, 1H), 6.71 (dd, $J = 7.6$, 0.8 Hz, 1H), 6.81 (dd, $J = 8$, 0.8 Hz, 1H), 6.89 (t, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 34.9, 55.9, 67.9, 73.8, 93.2, 101.75, 111.9, 118.5120.8, 121.6, 123.9, 127.9, 139.7, 148.3. MS APCI *m/z*: calcd. for $C_{13}H_{12}O_4$, 232.0736, found [M − 16] 215.1.

4.2.17. (1R,4S,11aS)-9-methoxy-4,5-dihydro-3H-1,4-epoxyoxepino [3,4-b]chromen-11a(1H)-ol (**17**)

The reaction was carried under reflux for 36 h. Yellow crystals m.p. 181–183 °C (1.7 g, 65% yield); $R_f = 0.74$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 46.5 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (d, $J = 14.8$ Hz, 1H), 2.82 (br d, $J = 7.6$ Hz, 1H), 3.64 (m, $J = 5–6$ Hz, 2H), 3.718 (s, 3H), 4.68 (t, 4.0 Hz, 1H), 5.17 (s, 1H), 6.41 (d, $J = 2$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 6.50 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.87 (s, 1H), 7.04 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.8, 55.7, 67.6, 73.6, 93.8, 101.8, 102.1, 107.6, 114.4, 122.3, 126.9, 127.1, 152.8, 160.1. MS APCI *m/z*: calcd. for $C_{14}H_{14}O_5$, 262.0841, found [M − 1] 261.1.

4.2.18. (7aS,8R,11S)-11,12-dihydro-10H-8,11-epoxybenzo[f]oxepino [3,4-b]chromen-7a(8H)-ol (**18**)

The reaction was carried under reflux for 24 h. Gray-beige crystals m.p. 208–212 °C, (1.94 g, 69% yield); $R_f = 0.42$ (EtOAc/Hex 2/1), $[\alpha]_{30}^{D}$ = - 49.2(c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 1H), 2.93 (d, $J = 15.2$ Hz, 1H), 3.65 (m, $J = 2.4–8$ Hz, 2H), 4.76 (br s, 1H), 5.29 (s, 1H), 7.03 (s, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 7.30 (s, 1H), 7.36 (t, $J = 7.2$ Hz, 1H), 7.50 (t, $J = 7.2$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 1H), 8.13 (d, Hz, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.2, 67.7, 73.6, 93.6, 101.7, 113.6, 118.5, 118.7, 122.0, 135.7, 124.1, 127.1, 128.8, 128.9, 129.1, 129.3, 129.5, 149.3. MS APCI *m/z*: calcd. for $C_{17}H_{14}O_4$, 282.0892, found [M − 1] 281.1.

4.3. General procedure for the synthesis of spironolactone **19**

4.3.1. (1R,4S)-4′,5′-di(pyridin-2-yl)-dihydro-2′H-6,7 dioxaspiro [bicyclo[2.2.1]heptane-2,3′-furan]-2′-one (**19**)

To a solution of dihydro-levoglucosenone (2), 1.28 g (0.010 mol) in 30 mL of ethyl alcohol, a 1.07 g (0.010 mol) of 2-pyridinecarboxaldehyde was added and magnetically stirred for 5 min. After that time, 1.0 mL of piperidine was added drop-wise and the solution was refluxed for 48 h. Upon overnight cooling at 5 °C the crystalline residue was filtered off, the crystals were air-dried and recrystallized from ethyl alcohol. White crystals m.p. 242–244 °C, (0.72 g, 48% yield); $R_f = 0.09$ (EtOAc/Hex 3/1), $[\alpha]_{30}^{D}$ = -80.7 (c 1.0, $(CH_3)_2CO$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (m, 1H), 2.42 (d, $J = 12$ Hz, 1H), 3.33 (m, 1H), 3.81 (d, $J = 6.4$ Hz, 1H), 4.18 (d, $J = 5.2$ Hz, 1H), 4.18 (dd, $J = 4.0$, Hz, 1H), 5.02 (t, 1H), 5.54 (s, 1H), 5.89 (d, $J = 5.6$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 7.01 (dd, 5.6, 6.0 Hz, 1H), 7.08 (dd, $J = 6.0$, 5.6 Hz), 7.32 (t, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 8.35 (d, $J = 4.4$ Hz, 1H), 8.43 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3, 58.8, 68.4, 67.9, 76.1, 81.7, 100.7, 120.1, 122.2, 122.9, 124.7, 136.2, 136.6, 148.1, 148.5, 149.0, 156.3, 157.9, 176.4. MS APCI *m/z*: calcd. for $C_{18}H_{16}N_2O_4$, 324.1110, found [M+1] 325.2.

5. Crystallographic data

Crystal data were collected at 120 K (**9**, **9A**), 150 K (**17**) and 140 K (**19**) with a Bruker platform diffractometer equipped with an IμS Cu-source (CuKα = 1.54178 Å) and an Apex II CCD detector Data were integrated using SAINT 8.38A [29]; corrections for absorption and decay were applied using multi-scan method SADABS [30]. A partial structure solution was obtained by intrinsic phasing, remaining atoms including H-atoms were located with difference Fourier techniques. All nonhydrogen atoms were refined with anisotropic atomic displacement parameters, hydrogen atoms were refined with isotropic atomic displacement factors. All calculations were performed using SHELXTL [30]. Final Flack parameter refined to 0.001(6) (**9**), 0.002(2) (**9A**), 0.03(5) (**17**), 0.08(6) (**19**) indicating the correct choice of the enantiomer. Final refinements converged to R1 ($I > 2\sigma(I)$) = 0.026 (**9**), 0.044 (**9A**), 0.024 (**17**), and 0.026 (**19**).

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Note added in proof

After this manuscript was completed we found the publication by Hunt and coworkers [31], which became available on line on 25 of May 2018. We read it with surprise. It does not quote closely related work by us [10] and the Greatrex group [21]. The described results are sometimes different from ours. It is not surprising since their conditions are different. However, there are errors and omissions. For example, no melting points are reported. Also, the entry **3** (hemiketal formed by condensation of salicylaldehyde) contains two unexpected carbon atoms (13C NMR −191.77 and 150.40). Are these carbon atoms representing carbonyl and hemiketal carbon atoms? Our NMR spectrum is significantly different.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2018.10.049.

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