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Diastereoselective annulation of 4-hydroxypyran-2*H*-ones with enantiopure 2,3-dideoxy-α,β-unsaturated sugar aldehydes derived from respective glycals☆

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Abstract—One-pot condensations of 4-hydroxypyran-2*H*-ones **1** and **2**, respectively, with various enantiopure 2,3-dideoxy-α,β-unsaturated carbohydrate enals in the presence of L-proline in EtOAc at room temperature generated pyrano-pyrones. It was observed that, while benzyl-protected carbohydrate enals on condensation with **1** or **2** under the above conditions produced an inseparable diastereomeric mixture in a ratio of 1:1, the acyl-protected carbohydrate enals on treatment with **1** or **2** under identical conditions yielded products with moderate to very high diastereoselectivity. A remarkable asymmetric induction was noticed from the C-4 stereogenic center of the acyl-protected carbohydrate enals. An almost complete diastereoselectivity was observed in those reactions that involved condensation of **1** with acetyl-protected enals **5** and **7**. The reaction of **2** with **5** also proceeded diastereoselectively to furnish the corresponding annulated product. The reaction presumably took place by *C*-1,2-addition of the pyrone onto the iminium salt of the α,β-unsaturated carbohydrate enal generated in situ, followed by β-elimination and cyclization of the 1-oxatriene involving a 6π-electron electrocyclic process to yield a 2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one derivative.

Keywords: 4-Hydroxycoumarin; 4-Hydroxy-6-methylpyran-2*H*-ones; Carbohydrate enals; L-Proline; Diastereoselective

1. Introduction

A great deal of interest among synthetic and medicinal chemists to recognize the importance of the naturally occurring polyketide derivatives originating from 4-hydroxycoumarin (4-hydroxy-2*H*-benzopyran-2-one) (**1**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) has been seen during the last decades.[1] These molecules are well known for their unique structural features and pharmacological properties.[2] There has been an ongoing effort in the synthesis of 3-alkyl/aryl-substituted 4-hydroxycoumarins and 4-hydroxy-6-methyl-2*H*-pyran-2-ones[3–6] owing to their synthetic and pharmacological importance. Similarly, several derivatives of pyran or fused pyran ring systems have been shown to possess different types of biological activities[7a] such as antidiabetic[7b] and anti-Alzheimer[7c,d] activities. Various other medicinal activities exhibited by pyran derivatives, including antimicrobial,[8] antifungal,[9] antitumor,[10a–c] hypotensive,[11] platelet antiaggregating,[12] local anesthetic,[13] and antidepressant[14] activities, are also noteworthy. Thus, it is evident from the literature reports that extensive research efforts have been directed toward the development of 4-hydroxycoumarin and pyrone derivatives.

Cycloaddition and annulation reactions are most versatile methods in organic synthesis due to their ability to provide multiple bond formations with regio- and stereochemical control leading to the formation of polycyclic carbocycles and heterocycles through a concerted, stepwise or sequential process.[15] An annulation reaction of the anticoagulant rodenticide, warfarin, 3-(α-acetonylbenzyl)-4-hydroxycoumarin (**A**, Fig. 1) with alcohols

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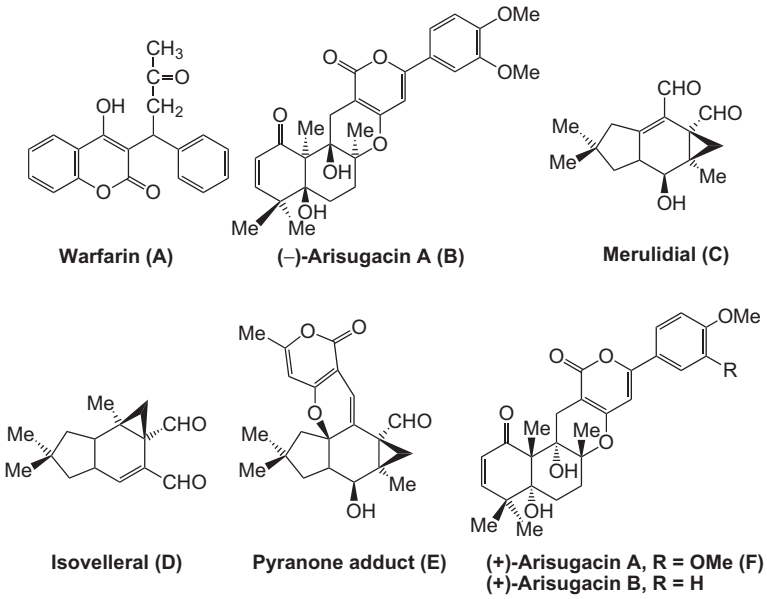


Figure 1. Some pyran and fused pyran systems of importance.

containing 4% hydrogen chloride under refluxing conditions to form cyclic alkyl ketals was pioneered by Link and co-workers[16] about 60 years ago. For the last few decades, much interest has been shown toward several systematic studies on condensation reactions of **1**[17–20] and **2**,[21,22] respectively, with acyclic α,β-unsaturated enones and enals to generate various angular pyran-fused pyrone derivatives owing to different types of biological activities associated with them.[7] After Link's first report on the annulation reaction of 4-hydroxycoumarin and an α,β-unsaturated ketone,[16a] Moreno-Mañas and co-workers reported a detailed study on the reactions of **2** and crotyl aldehyde in the presence of a secondary amine leading to the formation of 2*H*-pyrano-pyrones.[21] The first total synthesis of (−)-arisugacin A (**B**, Fig. 1) that was isolated from a *Penicillium* sp. Fo-4259 by Ömura et al.[23] and identified as an inhibitor of acetylcholinesterase (AChE) with highest potency and selectivity among all known inhibitors of AChE, thereby possessing significance in treatment of dementia diseases,[24] was archived by Cole and Hsung.[25] A formal [3+3] cycloaddition reaction of an α,β-unsaturated iminium salt with 4-hydroxy-2*H*-pyrone that proceeded through a highly diastereoselective 6π-electron electrocyclic ring closure[22,26,27] of a 1-oxatriene was the key feature of its synthesis. Hua et al. reported[22] that, while the L-proline-catalyzed condensation of **2** with cyclohexene carboxaldehyde in EtOAc at 70 °C produced the racemic tricyclic pyrone, the condensation of **2** with (*S*)-(−)-perillaldehyde, 4-β-isopropenyl-1-cyclohexene carboxaldehyde, led to the formation of the tricyclic pyrone as a single diastereomer. They have also shown that several of the tricyclic pyrones synthesized by them strongly inhibited acetylcholineesterase (AChE) activity, DNA synthesis, and tumor cell growth in vitro. Cravotto et al.[19] recently reported the exclusive formation of tricyclic pyrones by 1,2-addition of 4-hydroxycoumarin to α,β-unsaturated iminium salts derived from various enals. Mechanistically, it has been proposed that the annulation reaction of **2** with α,β-unsaturated aldehydes in the presence of a secondary amine involves a *C*-1,2-addition to an iminium salt generated in situ, followed by β-elimination that gives a 1-oxatriene (i.e., a Knoevenagel condensation). The 6π-electron electrocyclic ring closure of them forms two σ-bonds and a new stereocenter adjacent to the oxygen atom, thereby constituting a sequential anionic-pericyclic process that is formally the equivalent of a [3+3] cycloaddition.[22,26,27] The other synthetic approaches to 2*H*-pyran-fused pyrone derivatives include the recent report by Cravotto et al.[20] on the synthesis of pyranocoumarins from the annulation of 4-hydroxycoumarin with different enals under heterogeneous, high-intensity sonochemical conditions and the stereoselective reactions of naturally occurring terpenoids, merulidial (**C**) and isovelleral (**D**) with **2**, respectively, in refluxing EtOAc. This process forms pentacyclic pyrone adducts involving a 6π-electron electrocyclic ring closure of a hypothetical 1-oxatriene intermediate reported by Sterner and co-workers.[27] Recently Sunazuka et al. reported the total synthesis of (+)-arisugacin A and (+)-arisugacin B (**F**) by applying this methodology.[28] Thus, the above precedents in the literature on annulations of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-2*H*-one with various enals under different experimental conditions and also our growing interest on the synthetic applications of α,β-unsaturated carbohydrate enals of the type **3** derived from different glycals[29] for construction of chain extended higher

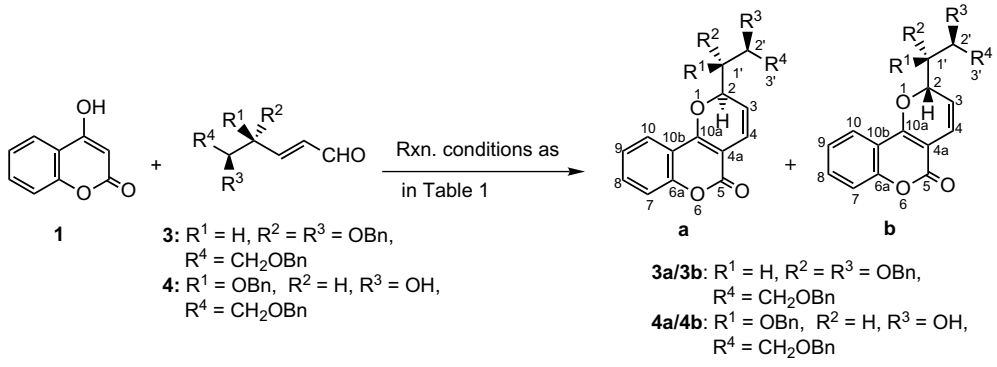
acyclic sugar derivatives of biological importance[30] prompted us to study the coupling reaction of enantiopure carbohydrate enals **3**–**10**, respectively, with 4-hydroxycoumarin and 4-hydroxy-6-methylpyran-2*H*-ones. To our knowledge, such a highly diastereoselective condensation reaction of either **1** or **2** with any type of carbohydrate enal has not been reported.

2. Results and discussion

2.1. Chemical syntheses

Several coupling reactions of **1** with **3** under different conditions were carried out. The first attempt of this reaction was made by treating 1.2 equiv of **1** with 1 equiv of **3** in the presence of $TiCl_4$ (1.2 equiv) in acetonitrile at 0 °C (Scheme 1). The tricyclic pyrones **3a/3b** were isolated as an inseparable 1:1 diastereomeric mixture in 46% yield after chromatographic purification of the crude product mixture. It can be presumed that the reaction was initiated by 1,2-addition of **1** onto titanium-coordinated enal **3**, followed by dehydration and intramolecular 6π-electron electrocyclic cyclization[22,26] to furnish **3a/3b**. The structure of the tricyclic pyrone **3a/3b** was established by analytical and spectral data. The ^1H NMR spectrum of **3a/3b** displayed two doublets at δ 6.63 and 6.59 (each $J_{4,3}$ 9.0 Hz) and two broad doublets at δ 5.57 and 5.47 (each $J_{3,4}$ 9.0 Hz) for the protons at C-4 and C-3, respectively, of the two diastereomers. Similarly, the diastereomeric mixture **3a/3b** also showed two doublets at δ 5.53 ($J_{2,3}$ 4.0 Hz) and 5.44 ($J_{2,3}$ 3.3 Hz) assigned to protons at C-2. Its ^{13}C and DEPT NMR spectra displayed signals to confirm that the product was a mixture of two diastereomers **3a/3b**. Their FAB mass spectra showed the molecular ion peak at *m/z* 561 $[M+1]^+$ and a base peak at *m/z* 199 due to the cleavage of side chain $[M-C_{24}H_{25}O_3]^+$.

Our attempts to improve the yield and selectivity of the annulation by changing the reagent from the Lewis acid, titanium tetrachloride, to L-proline and ethylenediamine diacetate (EDDA)[18] as mentioned in Table 1, and performing the reaction at room temperature as well as at the refluxing temperature of the solvent did not give much success. The heterocyclization also occurred in boiling EtOAc, but the yield of the product was low (30%, Table 1, entry 3). Further, when the same reaction was carried out in methanol at room temperature, the yield was reduced to 18% compared to 51% in EtOAc (Table 1, entries 2 and 4). Other bases like cinchonidine, piperidine, and *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) did not work here. These results thus indicated



Scheme 1.

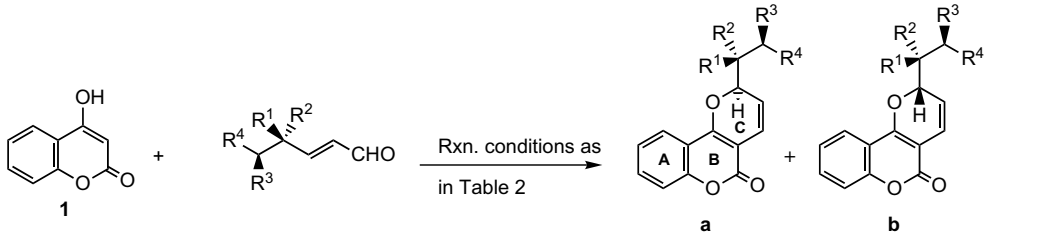
Table 1. Reaction of 4-hydroxycoumarin (**1**) with alkyl-protected carbohydrate enals

Entry	Enals	Catalyst (0.5 equiv)	Solvent	Temperature	Time (h)	Product	Yield (%)	Dr[a]
1	**3**	$TiCl_4$[b]	CH_3CN	0 °C	6	**3a/3b**	46	1:1
2	**3**	L-Proline	EtOAc	Rt	1	**3a/3b**	51	1:1
3	**3**	L-Proline	EtOAc	70 °C	1	**3a/3b**	30	1:1
4	**3**	L-Proline	CH_3OH	Rt	4	**3a/3b**	18	1:1
5	**3**	Cinchonidine	EtOAc	Rt	4	**3a/3b**	NR	—
6	**3**	Piperidine	EtOAc	Rt	3	**3a/3b**	NR	—
7	**3**	Piperidine	EtOAc	70 °C	6	**3a/3b**	NR	—
8	**3**	EDDA	EtOAc	Rt	5	**3a/3b**	43	1:1
9	**4**	L-Proline	EtOAc	Rt	3	**4a/4b**	47	1:1
10	**4**	L-Proline	EtOAc	70 °C	1	**4a/4b**	20	1:1

[a] Diastereomeric ratio (dr) determined by ^1H NMR and ^{13}C NMR spectroscopy of the crude product. NR = no reaction.
[b] 1.2 equiv of $TiCl_4$ was used in this example.

that the coupling reagent, either $TiCl_4$ or L-proline, did not influence the yield and diastereoselectivity of the reaction. Among the various reaction conditions employed in the present study as mentioned in Table 1, the preparation of **3a/3b** from **1** and **3** using 0.5 equiv of L-proline in EtOAc[22] at room temperature was most convenient. Similarly, the L-proline-catalyzed condensation of **1** with enal **4** (Scheme 1) derived from the benzylated galactal in EtOAc at room temperature furnished **4a/4b** as an inseparable diastereomeric mixture in 47% yield (Table 1, entry 9). Heating the reaction mixture in EtOAc at 70 °C reduced the yield significantly (Table 1, entry 10). Thus heating conditions probably favor polymerization or degradation of these enals. In all the experiments, the tricyclic pyrone was the only product that could be isolated as an inseparable diastereomeric mixture. The identification of mixture **4a/4b** was also completed with the help of NMR and FAB mass spectra. Its mass fragmentation was similar to the pattern observed in **3a/3b**.

In order to improve the yield of the product and selectivity of the process, the protocol of the reaction disclosed herein was modified. Therefore, the L-proline-catalyzed, one-pot experiment was also applied to acyl-protected enals **5**–**10** (Scheme 2) derived from their respective acyl-protected glycals. The yields ranged from 43% to 49% and very high to moderate diastereoselectivity was observed in each case. Almost complete stereoselectivity was observed in the annulation of **1** with **5** and **7** producing **5a** and **7a**, respectively, as single diastereomers. But the condensation of **1** with enals **6**, **8**, and **9** showed moderate to good selectivity to produce their corresponding products **6a/6b**, **8a/8b**, and **9a/9b** in diastereomeric ratios (dr) of 70:30, 75:25, and 80:20, respectively. These compounds were isolated as an inseparable diastereomeric mixture after column chromatographic purification of crude product mixture. At this point we noticed a few things that deserve detailed discussion. Both **5** and **6** are fully acyl protected, and the selectivity was found lower in the reaction of **1** with **6** producing **6a/6b** (70:30) in comparison to its reaction with **5** to furnish **5a** as a single diastereomer. Similarly, when enals **7** and **8**, with an unprotected hydroxyl at C-5 derived from 3,4,6-tri-*O*-acetyl-D-glucal and 3,4,6-tri-*O*-acetyl-D-galactal, respectively, were treated with **1** (Scheme 2) in presence of L-proline in EtOAc at room temperature, their respective products **7a/7b** and **8a/8b** were produced in almost the same yield, but in different dr's, >99:1 and 75:25, respectively. Further, the 5-*O*-acetyl-4,6-di-*O*-*p*-nitrobenzoyl-protected enal (i.e., the fully acyl-protected derivative) **9** under the same reaction conditions furnished **9a/9b** in 47% yield in a dr of 80:20 (Table 2). Condensation of enal **10** derived from 3,4-di-*O*-acetyl-D-arabinal with pyrone **1** provided an inseparable mixture



5: R^1 = H, R^2 = R^3 = OAc, R^4 = CH_2OAc
6: R^1 = R^3 = O Ac, R^2 = H, R^4 = CH_2OAc
7: R^1 = H, R^2 = OAc, R^3 = OH, R^4 = CH_2OAc
8: R^1 = OAc, R^2 = H, R^3 = OH, R^4 = CH_2OAc
9: R^1 = H, R^2 = O*p*NB, R^3 = OAc, R^4 = CH_2O*p*NB
10: R^1 = H, R^2 = OAc, R^3 = OAc, R^4 = H

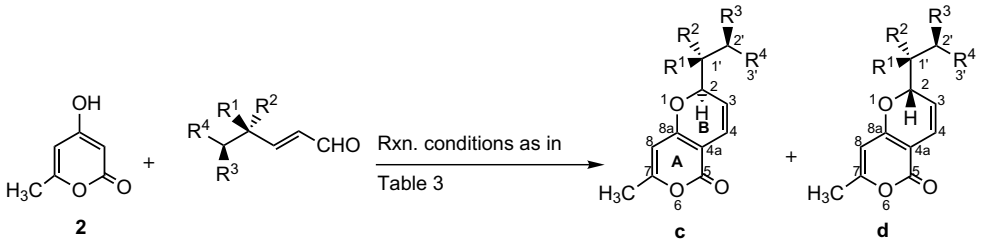
5a/5b: R^1 = H, R^2 = R^3 = OAc, R^4 = CH_2OAc
6a/6b: R^1 = R^3 = OAc, R^2 = H, R^4 = CH_2OAc
7a/7b: R^1 = H, R^2 = OAc, R^3 = OH, R^4 = CH_2OAc
8a/8b: R^1 = OAc, R^2 = H, R^3 = OH, R^4 = CH_2OAc
9a/9b: R^1 = H ,R^2 = O*p*NB, R^3 = OAc, R^4= CH_2O*p*NB
10a/10b: R^1 = H, R^2 = OAc, R^3 = OAc, R^4 = H

Scheme 2.

Table 2. Reaction of 4-hydroxycoumarin (**1**) with acyl-protected carbohydrate enals in EtOAc

Entry	Enals	Catalyst (0.5 equiv)	Temperature	Time (h)	Product	Yield (%)	Dr[a]
1	**5**	L-Proline	Rt	9	**5a/5b**	49	>99:1
2	**5**	EDDA	Rt	10	**5a/5b**	47	>99:1
3	**5**	$TiCl_4$	0 °C	5	**5a/5b**	43	>99:1
4	**6**	L-Proline	Rt	24	**6a/6b**	46	70:30[b]
5	**7**	L-Proline	Rt	8	**7a/7b**	43	>99:1
6	**8**	L-Proline	Rt	7	**8a/8b**	46	75:25[b]
7	**9**	L-Proline	Rt	13	**9a/9b**	47	80:20
8	**10**	L-Proline	Rt	17	**10a/10b**	45	66:44

[a] Diastereomeric ratio determined by ^1H NMR and ^{13}C NMR spectroscopy of the crude product.
[b] Diastereomeric ratio may be reversed.



3: R^1 = H, R^2 = R^3 = OBn, R^4 = CH_2OBn
4: R^1 = OBn, R^2 = H, R^3 = OH, R^4 = CH_2OBn
5: R^1 = H, R^2 = R^3 = OAc, R^4 = CH_2OAc
6: R^1 = R^3 = OAc, R^2 = H, R^4 = CH_2OAc
7: R^1 = H, R^2 = OAc, R^3 =OH, R^4 = CH_2OAc
8: R^1 = OAc, R^2 = H, R^3 = OH, R^4 = CH_2OAc
9: R^1 = H, R^2 = O*p*NB, R^3 = OAc, R^4 = CH_2O*p*NB
10: R^1 = H, R^2 = OAc, R^3 = OAc, R^4 = H

3c/3d: R^1 = H, R^2 = R^3 = OBn, R^4 = CH_2OBn
4c/4d: R^1 = OBn, R^2 = H, R^3 = OH, R^4 = CH_2OBn
5c/5d: R^1 = H, R^2 = R^3 = OAc, R^4 = CH_2OAc
6c/6d: R^1 = R^3 = OAc, R^2 = H, R^4 = CH_2OAc
7c/7d: R^1 = H, R^2 = OAc, R^3 = OH, R^4 = CH_2OAc
8c/8d: R^1 = OAc, R^2 = H, R^3 = OH, R^4 = CH_2OAc,
9c/9d: R^1 = H, R^2 = O*p*NB, R^3 = OAc, R^4 = CH_2O*p*NB
10c/10d: R^1 = H, R^2 = OAc, R^3 = OAc, R^4 = H

Scheme 3.

of **10a** and **10b** in a ratio of 66:34. These results thus clearly indicate that the necessary requirement for a high degree of stereoselectivity in the annulation of **1** with **5**–**9** is acyl protection of their hydroxyl functionalities. Furthermore, these must be derived from hexoses, as it was evident from the case of **10**, which was obtained from the pentose sugar, D-arabinose, and showed a lower order of selectivity in its condensation with **1** under identical conditions to yield a mixture of **10a** and **10b**. At this time it is not possible to explain why the condensation of **10** with **1** proceeded much less selectively compared to the same reaction of **5** (completely acyl protected) and **7** (acyl protected with 5-OH unprotected) with **1**, which showed almost complete diastereoselectivity. However, the lack of selectivity in this reaction with **9** to produce mixture of **9a** and **9b** may be attributed to the bulky nature of *p*-nitrobenzoyl-protected hydroxyl groups, respectively, at C-4 and C-6 in **9**. Thus we found from these observations of the present study that annulation reactions of **1** with 3,4,6-tri-*O*-acetyl-D-glucal-derived enals **5** (completely acyl protected) and **7** (acyl protected with 5-OH unprotected) were highly stereoselective (Table 2, entries 1 and 5), whereas these reactions with 3,4,6-tri-*O*-acetyl-D-galactal-derived enals **6** (fully acyl protected) and **8** (5-OH unprotected), respectively, met with only moderate selectivity. Therefore, it can be argued that the hydroxyl group at C-5, whether it is either protected or unprotected, does not influence the selectivity in the process of ring closure via a 6π-electron electrocyclic process. All compounds were characterized by means of their ^{1}H NMR and ^{13}C NMR spectra and mass fragmentations.

The condensation reactions of carbohydrate enals **3**–**10** with pyrone **2** in presence of 0.5 equiv of L-proline[22] following the above reaction conditions were also performed (Scheme 3). The trend of the reaction of **2** with each enal in terms of yield and selectivity was found similar as it was observed in the case of L-proline-catalyzed condensation of enals **3**–**10** with **1** in EtOAc. The details of the outcome of the reaction are provided in Table 3. Here also the L-proline-catalyzed condensation of **2** with enal **3** in EtOAc either at room temperature or refluxing temperature of the solvent did not show any selectivity, and the product **3c/3d** was isolated as an inseparable but pure 1:1 diastereomeric mixture. Similarly, no selectivity was observed in the reaction of **2** with **4** catalyzed by either L-proline[22] or EDDA[‡] in EtOAc at room temperature to furnish **4c/4d** as an inseparable diastereomeric mixture. However, almost complete diastereoselectivity (>99:1) was observed in the condensation of **2** with fully acetyl-protected enal **5** in the presence of L-proline or EDDA in EtOAc at room temperature to yield **5c** as the almost pure single isomer. Further good-to-moderate stereoselective annulation reactions of **2** with enals **6**, **7**, and **10** proceeded to generate the corresponding pyrano-pyrones **6c/6d** and **10c/10d** in diastereomeric ratios of 75:25 and 60:40, respectively (Table 3). Unfortunately, the reactions of **2** with enals **7** and **8** under the same conditions were not clean. These reactions were also studied at −40 °C, but the reactions did not proceed, even after continuous stirring for several hours, whereas at 0 °C the reaction was very slow with L-proline, only.

2.2. Proposed mechanism

The structures of **5a** and **5c** were established unambiguously by single-crystal X-ray analysis. The X-ray structures showing the molecular conformation of **5a** and **5c**, respectively, with the atomic numbering scheme are shown in Figure 2. The structure of **5a** (Fig. 2) shows the pyrano-benzopyrone fused rings (A/B/C) to be

[‡] Change of catalyst from L-proline to ethylenediamine diacetate (EDDA) did not influence either yield or selectivity in the annulation reaction.

Table 3. Reaction of 4-hydroxy-6-methylpyran-2*H*-one (**2**) with alkyl/acyl-protected carbohydrate enals in EtOAc

Entry	Enals	Catalyst (0.5 equiv)	Temperature	Time (h)	Product	Yield (%)	Dr[a]
1	**3**	L-Proline	Rt	2	**3c/3d**	57	1:1
2	**3**	L-Proline	70 °C	1.5	**3c/3d**	14	1:1
3	**4**	L-Proline	Rt	3	**4c/4d**	40	1:1
4	**4**	EDDA	Rt	7	**4c/4d**	34	1:1
5	**5**	L-Proline	Rt	12	**5c/5d**	45	>99:1
6	**5**	EDDA	Rt	10	**5c/5d**	48	>99:1
7	**5**	$TiCl_4$	0 °C	8	**5c/5d**	27	>99:1
8	**6**	L-Proline	Rt	18	**6c/6d**	46	75:25[b]
9	**7**	L-Proline	Rt	24	**7c/7d**	NI	—
10	**8**	L-Proline	Rt	24	**8c/8d**	NI	—
11	**9**	L-Proline	Rt	20	**9c/9d**	57	64:36
12	**10**	L-Proline	Rt	25	**10c/10d**	44	60:40

[a] Diastereomeric ratio determined by ^{1}H NMR and ^{13}C NMR spectroscopy on the crude product. NI = not isolated.
[b] Diastereomeric ratio may be reversed.

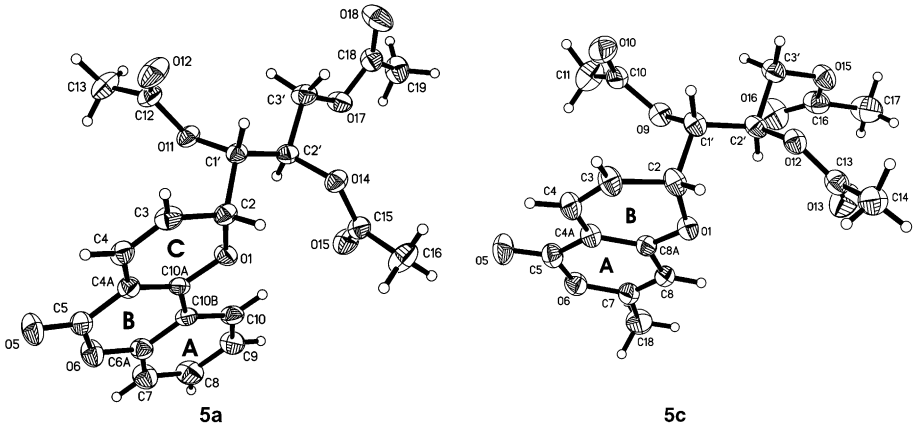
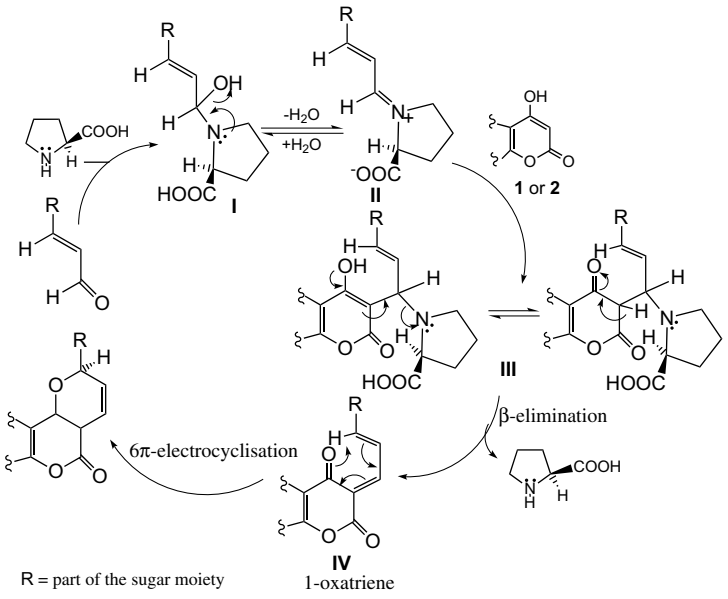


Figure 2. ORTEP diagrams (displacement ellipsoids at 30% probability) showing the molecular structures of **5a** and **5c**.

planar to which a side chain C1′–C2′–C3′ system is attached at C-2 with β-orientation. While the pyrano-pyrone fused rings (A/B) in structure **5c** (Fig. 2) are non-planar, a methyl side chain is attached at C-7, and C1′–C2′–C3′ the side-chain system is attached at C-2 with β-orientation. Ring B of **5c** adopts a puckered conformation with the C-2 atom deviated by 0.331(5) Å from the least-squares mean plane through atoms C-3, C-4, C-4A, C-8A, and O-1. Although the present study did not establish the absolute configuration of the molecule, the stereochemistry of the newly generated stereocenter C-2 in both **5a** and **5c** has been assigned as the *R*-configuration through known stereochemistry of the other stereocenters, C-1′ and C-2′ having *S*- and *R*-configuration, respectively, in both compounds. These stereocenters remained unaltered during the course of reaction.

Based on the X-ray structures of **5a** and **5c**, it can be presumed that an identical mechanistic pathway is operative in the L-proline-catalyzed one-pot condensation of both 4-hydroxycoumarin and 4-hydroxy-6-methylpyran-2*H*-one with carbohydrate enals (Fig. 2). This reaction presumably involves the generation of the iminium salt in situ, thus making the whole process a one-pot reaction leading to the formation of the 2*H*-pyranyl product exclusively via the *C*-1,2-addition pathway. The reaction proceeds as follows: first, the carbinolamine **I** is formed, which then releases a molecule of water to equilibrate with the iminium salt **II**.[19,31] The next step involves the *C*-1,2-addition of **1** or **2** to **II** to form **III**, followed by formation of the conjugated intermediate (1-oxatriene)[22,27] **IV**, along with the regeneration of L-proline. The 1-oxatriene **IV** then undergoes cyclization through a 6π-electron electrocyclic process forming the pyrano-pyrone (Scheme 4). The diastereoselectivities observed here are moderate (Table 2, entries 4, 6, and 7 and Table 3, entries 8 and 9) to high (Table 2 entries 1 and 5 and Table 3, entry 5) with acyl-protected enals, which is quite surprising. At this time we are unable to explain exact reason(s) behind the observed products. However, it may be hypothesized here that the diastereofacial cyclization of **IV** obtained from condensation of pyrone **1** or **2** with acetylated enals can be attributed to the formation of a close cyclic transition state, TS-I, (Fig. 3) that will not be possible with alkyl-protected enal **3** or **4**, and therefore, **3a** and **3b**, as



Scheme 4. Proposed mechanism of L-proline-catalyzed condensation of 4-hydroxypyran-2*H*-ones with carbohydrate enals.

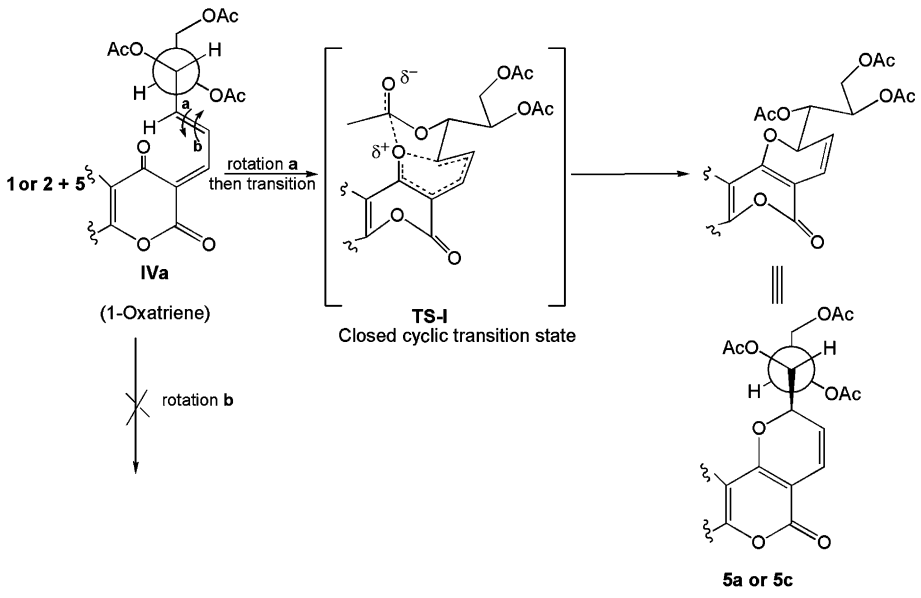


Figure 3. Proposed mechanism for cyclization involving the putative cyclic transition state, TS-I.

well as **4a** and **4b** were obtained as a 1:1 mixture of diastereomers in the same amount in these reactions. These results lead one to argue that the annulation reactions of **1** or **2** with alkyl-protected enals **3** or **4**, which lead to the formation of the corresponding diastereomeric products in a ratio of 1:1, represent the best evidence for the reversibility of this ring closure.

Similarly the formation of **6a/6b**, **8a/8b**, **9a/9b**, and **10a/10b**, respectively, in various diastereomeric ratios suggests that the stereoselective annulation reaction is facilitated through a reversible electrocyclic ring closure of 1-oxatriene,[32] and thus the observed selectivity is usually a result of thermodynamic distribution. However, the exclusive formation of **5a** or **7a** as a single diastereomer via 6π-electron electrocyclic ring closure of its 1-oxatriene intermediate **IV** is irreversible, and thus the whole process is kinetically controlled. Here the observed high diastereoselectivity can be presumed to be a result of the rotational preference in the 1-oxatriene **IV**.[32] The rotation of the vinyl strand in **IVa** along a direction '*a*' leading to single diastereomer **5a** via a closed cyclic transition state,[33] TS-I (Fig. 3) can be presumed on the basis of its X-ray crystal structural analysis (Fig. 2), which showed that the side chain was β in

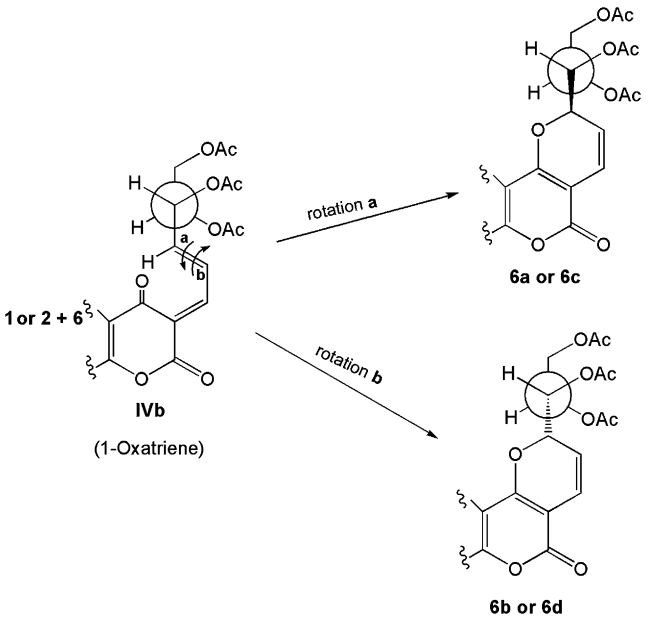


Figure 4. Proposed mechanism for cyclization with rotation to give diastereomers.

both **5a** and **7a**. The formation of **6a** and **6b** as a mixture of diastereomers could be attributed to the rotation of the vinyl strand in its 1-oxatriene intermediate **IVb** in directions '*a*' and '*b*', which would lead to a mixture of diastereomers **6a** and **6b** in a ratio 70:30 or 30:70, respectively (Fig. 4). The same arguments hold for the other diastereomeric mixtures, **8a/8b** and **9a/9b**. The above mechanistic explanation on a stereoselective condensation of **1** with various enals (**3**–**10**) could also be applied to reactions of **2** with enals **3**–**10**. In both the cases rotational preference played the key role in stereoselective ring closure.[§] The stereochemistry of newly formed stereocenter (C-2) in both **5a** and **5c** was unambiguously resolved through their X-ray structural analysis.

3. Conclusions

In summary, L-proline-catalyzed diastereoselective one-pot condensations of 4-hydroxypyran-2*H*-ones **1** and **2**, respectively, with enantiopure carbohydrate enals **3**–**10** in EtOAc at room temperature have been described. The 1,2-addition reaction, followed by dehydration and then in situ ring closure via a 6π-electron electrocyclic process,[22,26] are the main features of this reaction. A stereoselective ring-closure reaction was observed when carbohydrate enals were acyl protected, indicating that acyl protection of enals played the key role in the diastereoselectivity, and thus the two remaining centers of asymmetry were carried through to the product. High diastereoselectivity was observed in the condensation reaction of 4-hydroxycoumarin (**1**) with enals **5** and **7** to furnish **5a** and **7a**, respectively. Similarly the reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) with **5** to produce **5c** proceeded with high stereoselectively. Both the above enals were derived from 3,4,6-tri-*O*-acetyl-D-glucal.[29] The stereochemistry of the newly generated stereocenter was established unambiguously on the basis of X-ray structural analysis of **5a** and **7a**, showing that the side chains were attached at C-2 with a β-orientation. The acyl-protected enals **6** and **8** derived from 3,4,6-tri-*O*-acetyl-D-galactal[29] underwent condensation reactions with **1** leading to the formation of diastereomeric mixtures **6a/6b** and **8a/8b**, respectively, with moderate selectivity. The marked difference in selectivity in the reactions of **1** with enals derived from glucal and galactal, respectively, might be due to the opposite configuration of C-4 in glycals (or in respective enals), for example, the '*S*' configuration in **5** and **7** and the '*R*' configuration in **6** and **8**, respectively, thus resulting in conformationally different transition states. But the moderate selectivity in the annulation of **1** with enal **9** prepared from the 3,4,6-tri-*O*-*p*-nitrobenzoyl (*p*NB)-protected glucal, to produce an inseparable diastereomeric mixture of **9a** and **9b** compared to what was observed in the condensation of **1** with **5** and **7**, respectively, was presumably due to the bulky nature of the *p*NB substituent at the 4-O and 6-O positions of **9**.

The protected or free OH at C-5 in **5** or **7** and **6** or **8** did not influence the selectivity in their reactions with **1** (Table 2). Similarly, the reaction of 4-hydroxy-6-methylpyran-2*H*-one (**2**) with enal **5** under identical conditions furnished compound **5c** with a very high diastereoselectivity (>99:1, Table 3, entries 5 or 6). It is worth mentioning that the rotation preferences played the key role in the stereoselective 6π-electron electrocyclic ring closure of the intermediate 1-oxatriene **IVa** and **IVb**, respectively. Although the yields of all the new compounds are satisfactory, the synthetic protocol for the construction of 2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one derivatives described herein from easily available low cost enantiopure 2,3-dideoxy-α,β-unsaturated sugar aldehydes of type **5** and **7** will find wide application in the stereoselective synthesis of many biologically active tricyclic compounds with nitrogen or sulfur as the heteroatom[34] at the 1-position.

4. Experimental

4.1. General procedures

All reactions were monitored by TLC using precoated silica gel plates, with visualization by warming a $CeSO_4$

[§]Our explanation on rotational preferences leading to diastereoselective induction during 6π-electron electrocyclic ring closure was based on the recent report on highly stereoselective 6π-electron electrocyclic ring closure of 1-azatrienes by Hsung and co-workers.[32]

(1% in 2 N H_2SO_4) sprayed plate to 100 °C. NMR spectra were recorded on either a Bruker Avance DPX 200 FT or a Bruker Robotics and Bruker DRX 300 spectrometers at 200, 300 MHz (^{1}H) and 50, 75 MHz (^{13}C). In the ^{13}C NMR determinations, $CDCl_3$, which appeared at 77.4 ppm, was used as the reference unless otherwise stated. Fast-atom bombardment mass spectra (FABMSs) were recorded on a JEOL SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 100 mA) as the gas. Organic solvents used were dried by standard methods. Carbohydrate enals[29] used were prepared in the laboratory, and 4-hydroxycoumarin (**1**) and 4-hydroxy-6-methylpyran-2-one (**2**) were purchased from Aldrich Chemical Co. IR spectra were recorded on a Perkin–Elmer model 881 or on a Shimadzu FTIR-8210 PC spectrophotometer. Optical rotations were determined on an Autopol III polarimeter using a 1-dm cell at 28 °C in chloroform. Concentrations are in g/100 mL. Elemental analyses were carried out on a Carlo–Erba model 1108 or a Vario EL III elemental analyzer. The designation 'Rt' indicates 'room temperature' of 30 °C. All solvents used for column chromatography were freshly distilled. The minor diastereomers are arbitrarily named as D in the assignment of ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixtures. These mixtures are indicated by (*) in Section 4.

4.2. Single-crystal X-ray structural analyses

Crystals of **5a** and **5c** were obtained by slow evaporation from a 1:3 acetone–hexane solution at room temperature. Diffraction-quality crystals were selected after examination under a polarizing microscope, and these were then mounted on a Bruker P4 diffractometer for unit cell measurement and intensity data collection. The data were collected and reduced using XSCANS.[35a] Structures were solved by direct methods and refined anisotropically for the non-H atoms by a full-matrix-least-squares methods using SHELXTL.[35b] All H-atoms were placed in calculated positions and allowed to ride on their parent atoms during refinements. Table 4 shows the X-ray crystallographic experimental data.

Data for the X-ray studies have been filed with the Cambridge Crystallographic Data Centre (see Section 5).

Table 4. X-ray crystallographic experimental data

Compound no.	**5a**	**5c**
Crystal data		
Chemical formula	$C_{21}H_{20}O_9$	$C_{18}H_{20}O_9$
Chemical formula weight (M_r)	416.4	380.3
Cell setting, space group	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$
a (Å)	5.416(1)	8.533(1)
b (Å)	18.071(2)	10.490(2)
c (Å)	10.242(1)	21.045(3)
β (°)	95.77(1)	—
V (Å^3)	997.3(2)	1884.6(5)
Z	2	4
D_x (Mg/m^3)	1.386	1.341
μ (mm^{-1})	0.11	0.109
Radiation type; λ (Å)	Mo-Kα; 0.71073	Mo-Kα; 0.71073
No. of reflection for cell parameters	47	47
Θ range (°)	2.5–12.5	1.9–15.7
Temperature (K)	293(2)	293(2)
Crystal form, color	Block, light yellow	Block, transparent
Crystal size (mm)	$0.35 \times 0.17 \times 0.1$	$0.42 \times 0.25 \times 0.22$
Data collection		
Diffractometer	Bruker P4	Bruker P4
Data collection method	$\theta/2\theta$-scan	ω-scan
No. of measured, independent, and observed reflections	2601, 1951, and 1342	2550, 2365, and 1695
Criterion for observed reflection	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.02	0.037
θ_{max} (°)	25	25
Range of h, k, l	$-1 \rightarrow 6$, $-1 \rightarrow 21$, $-12 \rightarrow 12$	$-1 \rightarrow 10$, $-1 \rightarrow 12$, $-1 \rightarrow 25$
Absorption correction	None	None
Extinction correction	None	None
Refinement		
Refinement on	F^2	F^2
R, wR, S	0.042, 0.085, 0.989	0.047, 0.107, 1.032
No. of reflections and parameters used in refinement	1951 and 274	2365 and 248
H-atom treatment	Constrained	Constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^3)	0.16, −0.18	0.18, −0.19

4.3. Typical reaction procedure for the synthesis of compounds 3a/3b–10a/10b and 3c/3d–10c/10d

To a stirred solution of carbohydrate enals **3**–**10** (1 equiv each), in dry solvent (10 mL, see Tables 1–3) was added catalyst ($TiCl_4$, L-proline or EDDA), and after stirring at temperature as specified in the tables for 2 min, 4-hydroxy-2*H*-pyrone **1** or **2** (1.2 equiv) was added. The reaction mixture was stirred for the specified time depending on the 4-hydroxy-2*H*-pyrones, carbohydrate enals and catalyst used. A satd aq $NaHCO_3$ was added to quench the reaction, and the mixture was filtered through a Celite pad. The organic layer from the filtrate was separated, and the aq layer was again extracted with EtOAc (3×10 mL). The organic layers were then combined, washed with brine, and dried over Na_2SO_4. The crude product obtained after evaporation of the solvent was chromatographed to yield pure compounds.

4.4. Physiochemical and spectral data of compounds 3a/3b–10a/10b and 3c/3d–10c/10d

4.4.1. (1′*S*,2′*R*)-2-(1′,2′,3′-Tri-*O*-benzyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (3a/3b). Amorphous solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 1:9 EtOAc–hexane. R_f 0.52 (1:4 EtOAc–hexane). IR (KBr, cm^{-1}): ν 3027 (=C–H str), 2906 (–C–H str), 1734 (C=O str), 1607, 1488, 1451 (C=C str); ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.08 (m, 19H, Ar*H*), 6.63 (d, $J_{4,3}$ 9.0 Hz, 1H, H-4), 6.59 (d, $J_{4,3}$ 9.0 Hz, 1H, H_D-4), 5.57 (br d, $J_{3,4}$ 9.0 Hz, 1H, H-3), 5.53 (d, $J_{2,3}$ 4.0 Hz, 1H, H-2), 5.47 (br d, $J_{3,4}$ 9.0 Hz, 1H, H_D-3), 5.44 (d, $J_{2,3}$ 3.3 Hz, 1H, H_D-2), 4.81–4.58 (m, 6H, $3 \times CH_2Ph$), 4.58 (m, 1H, H_D-1′), 4.56 (m, 1H, H-1′), 3.90–3.82 (m, 2H, H-2′ and H-3′a), 3.63 (dd, $J_{3'b,3'a}$ 10.2 Hz and $J_{3'b,2'}$ 3.0 Hz, 1H, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 160.4, 159.7, 153.6, 153.5 (C-6a, C-10b, C-10a, and C-5), 138.4, 138.0 (Ar*qC*), 132.4 (C-8), 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1 (Ar*C*), 124.4 (C-9), 123.2 (C_D-9), 123.0 (C-10), 122.9 (C_D-10), 120.3 (C-7), 120.2 (C_D-7), 119.3 (C-4), 118.4 (C_D-4), 117.8 (C-3), 117.1 (C_D-3), 101.2 (C-4a), 101.1 (C_D-4a), 81.2 (C_D-1′), 80.5 (C-1′), 78.7 (C-2′), 77.3 (C_D-2′), 76.8 (C-2), 76.0 (C_D-2), 75.6, 72.5, 73.9 ($3 \times CH_2Ph$), 68.7 (C-3′), 68.1 (C_D-3′); FABMS: *m*/*z* (%) 561 (50) $[M+1]^+$, 331 (20), 199 (100) $[M-C_{24}H_{25}O_3]^+$. Anal. Calcd for $C_{36}H_{32}O_6 \cdot H_2O$: C, 74.72; H, 5.92. Found: C, 74.57; H, 6.18.

4.4.2. (1′*R*,2′*R*)-2-(1′,3′-Di-*O*-benzyl-2′-hydroxy-D-*threitol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (4a/4b). Sticky solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 1:4 EtOAc–hexane. R_f 0.48 (3:7 EtOAc–hexane). IR (KBr, cm^{-1}): ν 3448 (O–H str), 3066 (=C–H str), 2918 (–C–H str), 1709 (C=O str), 1568, 1492, 1454 (C=C str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (t, $J_{10,9 \text{ or } 10,8}$ 6.7 Hz, 1H, H-10), 7.52 (br t, J 7.7 Hz, 1H, H-9), 7.30–7.25 (br m, 12H, Ar*H*), 6.70 (d, $J_{4,3}$ 10.8 Hz, 1H, H-4), 6.65 (d, $J_{4,3}$ 10.0 Hz, 1H, H_D-4), 5.80 (dd, $J_{3,4}$ 10.2 Hz and $J_{3,2}$ 3.5 Hz, 1H, H-3), 5.67 (dd, $J_{3,4}$ 10.1 Hz and $J_{3,2}$ 4.0 Hz, 1H, H_D-3), 5.45 (m, 1H, H-2), 5.38 (d, $J_{2,3}$ 4.2 Hz, 1H, H_D-2), 4.75–4.50 (m, 4H, $2 \times CH_2Ph$), 4.13–4.04 (m, 1H, H-1′), 3.93 (dd, $J_{2',3'a}$ 6.0 Hz and $J_{2',3'b}$ 2.2 Hz, 1H, H-2′), 3.82 (dd, $J_{2',3'a}$ 6.0 Hz and $J_{2',3'b}$ 3.0 Hz, 1H, H_D-2′), 3.59 (dd, $J_{3'a,3'b}$ 10.0 Hz and $J_{3'a,2'}$ 5.1 Hz, 1H, H-3′a), 3.49 (m, 1H, H-3′b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.0, 153.6, 153.5 (C-6a, C-10b, C-10a, and C-5), 138.4, 138.0 (Ar*qC*) 132.7 (C-8), 128.8, 128.4, 128.3 (Ar*C*), 124.5 (C-9), 122.9 (C-10), 120.2 (C-7), 119.7 (C-4), 119.5 (C_D-4), 117.3 (C_D-3), 117.2 (C-3), 101.3 (C-4a), 101.2 (C_D-4a), 80.3 (C-1′), 80.2 (C_D-1′), 78.9 (C-2′), 76.8 (C_D-2′), 75.6, 71.3 ($2 \times CH_2Ph_D$), 73.9, 71.2 ($2 \times CH_2Ph$), 69.5 (C-3′), 69.4 (C_D-3′); FABMS: *m*/*z* (%) 471 (50) $[M+1]^+$, 307 (10), 199 (100) $[M-C_{17}H_{19}O_3]^+$. Anal. Calcd for $C_{29}H_{26}O_6 \cdot 2H_2O$: C, 68.76; H, 5.96. Found: C, 69.07; H, 5.67.

4.4.3. (1′*S*,2′*R*)-2-(1′,2′,3′-Tri-*O*-acetyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (5a). Solid. Mp 118–20 °C. Purification was by column chromatography using 11:39 EtOAc–hexane. R_f 0.40 (3:7 EtOAc–hexane). $[\alpha]_D$ +144 (*c* 0.225, $CHCl_3$); IR (KBr, cm^{-1}): ν 3076 (=C–H str), 1740 (C=O str), 1653 (O–C=O str), 1222 (C–O str); ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (dd, $J_{10,9}$ 7.8 Hz and $J_{10,8}$ 1.2 Hz, 1H, H-10), 7.56 (dt, $J_{9,10 \text{ or } 9,8}$ 7.9 Hz and $J_{9,7}$ 1.5 Hz, 1H, H-9), 7.36–7.28 (m, 2H, H-7 and H-8), 6.71 (dd, $J_{4,3}$ 10.0 Hz and $J_{4,2}$ 1.0 Hz, 1H, H-4), 5.58 (ddd, $J_{2',1'}$ 9.0 Hz, $J_{2',3'a}$ 2.4 Hz, and $J_{2',3'b}$ 4.5 Hz, 1H, H-2′), 5.50 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 3.6 Hz, 1H, H-3), 5.46 (m, 1H, H-2), 5.40 (dd, $J_{1',2'}$ 9.0 Hz and $J_{1',2}$ 1.8 Hz, 1H, H-1′), 4.35 (dd, $J_{3'a,3'b}$ 12.6 Hz and $J_{3'a,,2'}$ 2.4 Hz, 2H, H-3′a), 4.18 (dd, $J_{3'b,3'a}$ 12.6 Hz and $J_{3'b,2'}$ 4.5 Hz, 1H, H-3′b), 2.17 (s, 3H, OCOC*H*$_3$), 2.08 (s, 3H, OCOC*H*$_3$) 2.01 (s, 3H, OCOC*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 170.1, 170.0 ($3 \times COCH_3$), 161.4 (C-5), 153.0 (C-6a and C-10b), 133.0 (C-8), 125.0 (C-9), 123.2 (C-10), 121.1 (C-7), 117.2 (C-3 and C-4), 115.0 (C-10a), 100.5 (C-4a), 76.0 (C-2), 71.7 (C-2′), 67.8 (C-1′), 62.1 (C-3′), 21.3, 21.0 ($3 \times CO CH_3$); FABMS: *m*/*z* (%) 417 (100) $[M+1]^+$, 375 (10) $[M-CH_2=C=O]^+$, 255 (40) $[M-C_6H_9O_5]^+$, 199 (90) $[M-C_9H_{13}O_6]^+$. Anal. Calcd for $C_{21}H_{20}O_9 \cdot 0.5H_2O$: C, 59.29; H, 4.97. Found: C, 59.79; H 5.03.

4.4.4. (1′*R*,2′*R*)-2-(1′,2′,3′-Tri-*O*-acetyl-D-*threitol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (6a/6b). Solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 13:37 EtOAc–hexane.

R_f 0.30 (3:7 EtOAc–hexane). IR (KBr, cm^{-1}): ν 3021 (=C–H str), 1730 (C=O), 1645 (–C=O), 1212 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (dd, $J_{10,9}$ 7.9 Hz and $J_{10,8}$ 1.6 Hz, 1H, H_D-10), 7.67 (dd, $J_{10,9}$ 8.5 Hz and $J_{10,8}$ 1.8 Hz, 1H, H-10), 7.56 (dt, $J_{9,10\text{ or }9,8}$ 7.8 Hz and $J_{9,7}$ 1.5 Hz, 1H, H-9), 7.36–7.30 (m, 2H, H-7 and H-8), 6.76 (dd, $J_{4,3}$ 9.0 Hz and $J_{4,2}$ 1.2 Hz, 1H, H-4), 6.71 (dd, $J_{4,3}$ 9.7 Hz and $J_{4,2}$ 1.5 Hz, 1H, H_D-4), 5.51 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 3.7 Hz 1H, H-3), 5.57 (dd, $J_{2,3}$ 3.7 Hz and $J_{2,4}$ 1.5 Hz, 1H, H-2), 5.35 (dd, $J_{1',2'}$ 3.8 Hz and $J_{1',2}$ 1.1 Hz, 1H, H-1′), 5.42 (m, 1H, H-2′), 4.40 (dd, $J_{3'a,3'b}$ 11.8 Hz and $J_{3'a,2'}$ 4.3 Hz, 1H, H-3′a), 4.25 (dd, $J_{3'b,3'a}$ 11.8 Hz and $J_{3'b,2'}$ 5.3 Hz, 1H, H_D-3′a), 4.13 (br t, J 7.0 Hz, 1H, H_D-3′b), 4.02 (dd, $J_{3'b,3'a}$ 11.6 Hz and $J_{3'b,2'}$ 6.7 Hz, 1H, H-3′b), 2.13 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.2, 170.0 ($3\times COCH_3$), 159.4 (C-5), 153.7 (C-6a and C-10b), 133.0 (C-8), 124.6 (C-9), 124.3 (C_D-9), 123.3 (C_D-10), 122.7 (C-10), 121.5 (C-7), 120.9 (C_D-7), 117.4 (C-4), 116.5 (C-3), 115.0 (C-10a), 101.3 (C-4a), 76.0 (C-2), 74.5 (C_D-2), 71.7 (C-2′), 68.7 (C-1′), 68.3 (C_D-1′), 62.2 (C-3′), 21.1, 21.0, 20.9 ($3\times COCH_3$); FABMS: m/z (%) 417 (15) $[M+1]^+$, 255 (25), 199 (35) $[M-C_9H_{15}O_{16}]^+$. Anal. Calcd for $C_{21}H_{20}O_9\cdot 0.5H_2O$: C, 59.29; H, 4.97. Found: C, 59.71; H, 4.82.

4.4.5. (1′*S*,2′*R*)-2-(1′,3′-Di-*O*-acetyl-2′-hydroxy-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (7a). Sticky solid. Purification was by column chromatography using 7:13 EtOAc–hexane. R_f 0.43 (1:1 EtOAc–hexane). $[\alpha]_D$ +96.4 (c 0.225, $CHCl_3$); IR (KBr, cm^{-1}): ν 3449 (O–H str), 3077 (=C–H str), 1739 (C=O str), 1495, 1456, 1422 (C=C str), 1230 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.78 (dd, $J_{10,9}$ 8.0 Hz and $J_{10,8}$ 1.0 Hz, 1H, H-10), 7.56 (dt, $J_{9,10\text{ or }9,8}$ 8.0 Hz and $J_{9,7}$ 1.5 Hz, 1H, H-9), 7.34–7.15 (m, 2H, H-7 and H-8), 6.69 (dd, $J_{4,3}$ 10.2 Hz and $J_{4,2}$ 1.5 Hz, 1H, H-4), 5.69 (m, 1H, H-2), 5.52 (dd, $J_{3,4}$ 10.2 Hz and $J_{3,2}$ 3.7 Hz, 1H, H-3), 5.10 (dd, $J_{1',2'}$ 9.0 Hz and $J_{1',2}$ 2.0 Hz, 1H, H-1′), 4.33–4.12 (m, 3H, H-2′, H-3′a, and H-3′b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 170.3 ($2\times COCH_3$), 161.0 (C-5), 153.6 (C-10b), 152.7 (C-6a), 133.3 (C-8), 124.6 (C-9), 122.8 (C-10), 120.8 (C-7), 117.3 (C-4), 117.0 (C-3), 115.1 (C-10a), 100.7 (C-4a), 76.1 (C-2), 74.0 (C-2′), 67.2 (C-1′), 66.0 (C-3′), 21.1 and 21.0 ($2\times COCH_3$); FABMS: m/z (%) 375 (100) $[M+1]^+$, 255 (30), 241 (25), 199 (60) $[M-C_7H_{11}O_5]^+$, 149 (65). Anal. Calcd for $C_{19}H_{18}O_8\cdot 1.5H_2O$: C, 56.85; H, 5.27. Found: C, 56.87; H, 4.88.

4.4.6. (1′*R*,2′*R*)-2-(1′,3′-Di-*O*-acetyl-2′-hydroxy-D-*threitol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (8a/8b). Solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 2:3 EtOAc–hexane. R_f 0.36 (1:1 EtOAc–hexane). IR (KBr, cm^{-1}): ν 3448 (O–H str), 1739 (C=O str), 1690 (O–C=O str), 1567, 1454, 1419 (C=C str), 1228 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (dt, $J_{9,10\text{ or }9,8}$ 8.5 Hz and $J_{9,7}$ 1.8 Hz, 1H, H_D-9), 7.63 (br d, J 8.0 Hz, 1H, H-10), 7.55 (dt, $J_{9,10\text{ or }9,8}$ 8.0 Hz and $J_{9,7}$ 1.5 Hz, 1H, H-9), 7.32–7.25 (m, 2H, H-7 and H-8), 7.22–7.15 (m, 2H, H_D-7 and H_D-8), 6.76 (d, $J_{4,3}$ 10.6 Hz, 1H, H-4), 6.70 (d, $J_{4,3}$ 9.7 Hz, 1H, H_D-4), 5.66 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 4.2 Hz, 1H, H-3), 5.50 (m, 1H, H-2), 5.27 (dd, $J_{1',2}$ 6.7 Hz and $J_{1',2'}$ 3.0 Hz, 1H, H-1′), 4.15–4.07 (m, 3H, H-2′, 3′a, and 3′b), 2.12 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$) 2.07 (s, 3H, $COCH_{3D}$), 2.05 (s, 3H, $COCH_{3D}$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 170.3 ($2\times COCH_3$), 161.0 (C-5), 153.6 (C-6a and C-10b), 133.0 (C-8), 124.7 (C_D-9), 124.6 (C-9), 123.0 (C_D-10), 122.8 (C-10), 121.3 (C-7), 117.4 (C-4), 117.0 (C-3), 115.1 (C-10a), 101.6 (C-4a), 101.0 (C_D-4a), 76.5 (C-2), 75.7 (C_D-2), 73.5 (C-2′), 68.1 (C-1′), 65.5 (C-3′), 21.1, 21.0 ($3\times COCH_3$); FABMS: m/z (%) 375 (45) $[M+1]^+$, 199 (55) $[M-C_7H_{11}O_5]^+$, 147 (100). Anal. Calcd for $C_{19}H_{18}O_8\cdot 1.5H_2O$: C, 56.85; H, 5.27. Found: C, 57.09; H, 4.62.

4.4.7. (1′*S*,2′*R*)-2-(2′-*O*-Acetyl-1′,3′-di-*O*-*p*-nitrobenzoyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (9a/9b). Amorphous solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 11:39 EtOAc–hexane. R_f 0.42 (3:7 EtOAc–hexane). IR (KBr, cm^{-1}): ν 3022 (=C–H str), 2927 (–C–H str), 1731 (C=O str), 1608, 1529, 1495 (C=C str); ^1H NMR (200 MHz, $CDCl_3$): δ 8.34–7.35 (m, 14H, Ar*H*), 6.85 (dd, $J_{4,3}$ 9.2 Hz and $J_{4,2}$ 1.5 Hz, 1H, H_D-4), 6.63 (dd, $J_{4,3}$ 9.2 Hz and $J_{4,2}$ 1.0 Hz, 1H, H-4), 5.89 (ddd, $J_{2',1'}$ 9.0 Hz, $J_{2',3'a}$ 2.2 Hz and $J_{2',3'b}$ 4.5 Hz, 1H, H-2′), 5.79 (dd, $J_{3,4}$ 9.1 Hz and $J_{3,2}$ 2.9 Hz, 1H, H-3), 5.77 (m, 1H, H-2), 5.56 (dd, $J_{1',2'}$ 6.0 Hz and $J_{1',2}$ 3.6 Hz, 1H, H-1′), 4.85 (dd, $J_{3'a,3'b}$ 12.5 Hz and $J_{3'a,2'}$ 2.1 Hz, 1H, H-3′a), 4.51 (dd, $J_{3'b,3'a}$ 12.4 Hz and $J_{3'b,2'}$ 5.3 Hz, 1H, H_D-3′b), 4.38 (dd, $J_{3'b,3'a}$ 12.5 Hz and $J_{3'b,2'}$ 4.5 Hz, 1H, H-3′b), 2.22 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_{3D}$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0 ($OCOCH_3$), 164.6 (C-5), 164.0 (C_D-5), 153.6 (C-6a and C-10b), 151.4 (Ar*qC*), 135.0 (Ar*qC*), 134.0 (Ar*qC*), 133.4 (C-8), 131.3 (Ar*C*), 125.1 (C-9), 124.1 (Ar*C*), 123.1 (C-10), 121.8 (C-7), 117.4 (C-4), 116.8 (C-3), 114.7 (C-10a), 101.3 (C-4a), 75.7 (C-2), 73.3 (C-2′), 67.5 (C-1′), 63.5 (C-3′), 21.3 ($OCOCH_3$); FABMS: m/z (%) 631 (20) $[M+1]^+$, 307 (10), 199 (100) $[M-C_{19}H_{15}N_2O_{10}]^+$. Anal. Calcd for $C_{31}H_{22}N_2O_{13}$: C, 59.05; H, 3.51; N, 4.44. Found: C, 58.84; H, 4.13; N, 4.56.

4.4.8. (1′*S*)-2-(1′,2′-Di-*O*-acetyl-D-*glyceritol*-1′-yl)-2*H*,*H*-pyrano[3,2-*c*]benzopyran-5-one (10a/10b). Sticky solid. Isolated as a diastereomeric mixture*. Purification

was by column chromatography using 1:4 EtOAc–hexane. R_f 0.55 (3:7 EtOAc–hexane). IR (neat, cm^{-1}): ν 2928 (C–H str), 1629 (C=O), 1594, 1363; ^1H NMR (200 MHz, $CDCl_3$): δ 7.75 (dd, $J_{10,9}$ 8.0 Hz and $J_{10,8}$ 1.9 Hz, 1H, H_D-10), 7.71 (br d, $J_{10,9}$ 7.8 Hz, 1H, H-5), 7.56 (dt, $J_{9,10\,or\,9,8}$ 8.5 Hz and $J_{9,7}$ 1.5 Hz, 1H, H-9), 7.33–7.27 (m, 2H, H-7 and H-8), 6.74 (d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 5.63 (dd, $J_{3,4}$ 10.1 Hz and $J_{3,2}$ 3.1 Hz 1H, H_D-3), 5.54 (dd, $J_{3,4}$ 10.1 Hz and $J_{3,2}$ 3.4 Hz, 1H, H-3), 5.42–5.32 (m, 2H, H-2 and H-1′), 4.51 (dd, $J_{2'a,2'b}$ 12.0 Hz and $J_{2'a,1'}$ 4.5 Hz, H-2′a), 4.30 (dd, $J_{2'b,2'a}$ 11.3 Hz and $J_{2'b,1'}$ 5.2 Hz, 1H, H-2′b), 2.09 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_{3D}$), 2.04 (s, 3H, $COCH_{3D}$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.3 ($2\times COCH_3$), 153.6 (C-6a and C-10b), 159.5 (C-5), 133.0 (C-8), 124.6 (C-9), 123.0 (C_D-10), 122.8 (C-10), 121.2 (C-7), 121.0 (C_D-7), 117.3 (C-4), 116.8 (C-3), 115.0 (C-10a), 101.3 (C-4a), 76.4 (C-2), 76.2 (C_D-2), 72.7 (C_D-1′), 72.0 (C-1′), 61.6 (C-2′), 21.1 and 21.0 ($2\times CH_3CO$); FABMS: *m/z* (%) 345 (45) $[M+1]^+$, 225 (100), 199 (50) $[M-C_6H_9O_4]^+$, 163 (90), 121 (95). Anal. Calcd for $C_{18}H_{16}O_7{\cdot}0.5H_2O$: C, 61.18; H, 4.85. Found: C, 60.57; H, 5.58.

4.4.9. (1′*S*,2′*R*)-7-Methyl-2-(1′,2′,3′-tri-*O*-benzyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (3c/3d). Oil. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 3:17 EtOAc–hexane. R_f 0.43 (3:7 EtOAc–hexane). IR (neat, cm^{-1}): ν 3028, 3024 (=C–H str), 2920 (–C–H str), 1711 (C=O str), 1643, 1565 (C=C str), 1216 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.43–7.13 (m, 15H, Ar*H*), 6.50 (d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 6.45 (d, $J_{4,3}$ 10.0 Hz, 1H, H_D-4), 5.64 (s, 1H, H-8), 5.60 (s, 1H, H_D-8), 5.40 (m, 1H, H-2), 5.34 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 3.7 Hz, 1H, H-3), 4.77–4.55 (m, 6H, $3\times CH_2Ph$), 4.47 (m, 1H, H-1′), 3.80 (m, 1H, H-2′), 3.69–3.59 (m, 2H, H-3′a and H-3′b), 2.19 (s, 3H, CH_3); FABMS: *m/z* (%) 525 (80) $[M+1]^+$, 295 (30), 181 (40), 163 (100) $[M-C_{24}H_{25}O_3]^+$.

4.4.10. (1′*R*,2′*R*)-7-Methyl-2-(1′,3′-di-*O*-benzyl-2′-hydroxy-D-*threitol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (4c/4d). Sticky solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 1:3 EtOAc–hexane. R_f 0.39 (7:13 EtOAc–hexane). IR (neat, cm^{-1}): ν 3428 (O–H str), 3030 (=C–H str), 2923 (–C–H str), 1710 (C=O str), 1645, 1564 (C=C str), 1216 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.30–7.20 (br m, 10H, Ar*H*), 6.55 (d, $J_{4,3}$ 10.0 Hz, 1H, H_D-4), 6.52 (d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 5.78 (s, 1H, H_D-8), 5.75 (s, 1H, H-8), 5.62 (dd, $J_{3,4}$ 10.2 Hz and $J_{3,2}$ 3.1 Hz, 1H, H_D-3), 5.52 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 4.0 Hz, 1H, H-3), 5.28 (m, 1H, H_D-2), 5.20 (m, 1H, H-2), 4.70–4.20 (m, 4H, $2\times CH_2Ph$), 3.98 (m, 1H, H-1′), 3.74 (dd, $J_{2',3'a}$ 6.0 Hz and $J_{2',3'b\,or\,2',1'}$ 3.0 Hz, 1H, H-2′), 3.56 (dd, $J_{3'a,3'b}$ 9.3 Hz and $J_{3'a,2'}$ 6.0 Hz, 1H, H-3′a), 3.44 (dd, $J_{3'b,3'a}$ 9.5 Hz and $J_{3'b,2'}$ 4.6 Hz, 1H, H-3′b), 2.19 (s, 3H, CH_3);^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9 (C-7), 163.5 (C-8a), 163.3 (C_D-8a), 162.4 (C-5), 138.0 (Ar*qC*), 137.7 (ArqC_D), 128.8, 128.4, 128.3 (Ar*C*), 119.8 (C-4), 119.3 (C_D-4), 118.0 (C_D-3), 117.3 (C-3), 100.2 (C-8), 99.3 (C-4a), 80.3, 80.1 ($2\times CH_2Ph$), 75.6 (C-2), 75.5 (C_D-2), 73.8 (C-1′), 71.2 (C-2′), 69.5 (C-3′), 69.3 (C_D-3′), 20.6 (CH_3); FABMS: *m/z* (%) 435 (40) $[M+1]^+$, 163 (60) $[M-C_{17}H_{19}O_3]^+$, 149 (100) $[M-C_{17}H_{19}O_3+CH_3+H]^+$. Anal. Calcd for $C_{26}H_{26}O_6{\cdot}H_2O$: C, 69.01; H, 6.23. Found: C, 69.30; H, 6.43.

4.4.11. (1′*S*,2′*R*)-7-Methyl-2-(1′,2′,3′-tri-*O*-acetyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (5c). Solid. Mp 105 °C. Purification was by column chromatography using 1:3 EtOAc–hexane. R_f 0.61 (1:1 EtOAc–hexane). $[\alpha]_D$ +67.5 (*c* 0.080, $CHCl_3$). IR (KBr, cm^{-1}): ν 2959 (C–H str), 1730, 1718 (C=O str), 1575 (C=C str), 1371 (C–H def. of CH_3), 1215 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 6.56 (d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 5.82 (s, 1H, H-8), 5.45 (dd, $J_{3,4}$ 10.2 Hz and $J_{3,2}$ 3.2 Hz, 1H, H-3), 5.40 (m, 1H, H-2′), 5.30 (br t, $J_{2,1'=3}$ 2.2 Hz, 1H, H-2), 5.24 (m, 1H, H-1′), 4.38 (dd, $J_{3'a,3'b}$ 12.3 Hz and $J_{3'a,2'}$ 2.2 Hz, 1H, H-3′a), 4.17 (dd, $J_{3'b,3'a}$ 12.0 Hz and $J_{3'b,2'}$ 6.6 Hz, 1H, H-3′b), 2.23 (s, 3H, CH_3), 2.11 (s, 3H, $OCOCH_3$), 2.06 (s, 3H, $OCOCH_3$) 2.02 (s, 3H, $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9, 170.1 ($3\times OCOCH_3$), 165.0 (C-7), 163.8 (C-5 and C-8a), 120.8 (C-4), 115.7 (C-3), 100.0 (C-8), 98.3 (C-4a), 75.8 (C-2), 72.0 (C-2′), 68.6 (C-1′), 62.1 (C-3′), 21.2 (CH_3), 21.1, 21.0, 20.6 ($3\times COCH_3$); FABMS: *m/z* (%) 381 (80) $[M+1]^+$, 219 (40), 163 (100) $[M-C_9H_{13}O_6]^+$. Anal. Calcd for $C_{18}H_{20}O_9$: C, 56.84; H, 5.30. Found: C, 56.36; H, 5.25.

4.4.12. (1′*R*,2′*R*)-7-Methyl-2-(1′,2′,3′-tri-*O*-acetyl-D-*threitol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (6c/6d). Oil. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 1:3 EtOAc–hexane. R_f 0.60 (1:1 EtOAc–hexane). IR (neat, cm^{-1}): ν 2961 (C–H str), 1746, 1720 (C=O str), 1371 (C–H def. of CH_3), 1218 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 6.60 (d, $J_{4,3}$ 9.8 Hz, 1H, H-4), 6.56 (d, $J_{4,3}$ 8.3 Hz, 1H, H_D-4), 5.82 (s, 1H, H_D-8), 5.76 (s, 1H, H-8), 5.39 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 3.0 Hz, 1H, H-3), 5.34 (m, 1H, H-2′), 5.30 (m, 1H, H-2), 5.14 (m, 1H, H-1′), 4.33 (dd $J_{3'a,3'b}$ 11.9 Hz and $J_{3'a,2'}$ 4.6 Hz, 1H, H-3′a), 4.12 (dd, $J_{3'b,3'a}$ 11.6 Hz and $J_{3'b,2'}$ 3.1 Hz, 1H, H-3′b), 2.23 (s, 3H, CH_3), 2.15 (s, 3H, CH_{3D}), 2.11 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.06 (s, 3H, $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.2, ($3\times OCOCH_3$), 164.6 (C-7), 163.8 (C-5 and C-8a), 121.0 (C-4), 120.5 (C_D-4), 115.3 (C_D-3), 115.0 (C-3), 100.0 (C-8), 99.9 (C_D-8), 98.3 (C-4a), 76.0 (C-2), 71.8 (C-2′), 71.0 (C_D-2′), 70.3 (C_D-1′), 68.9 (C-1′), 62.1 (C-3′), 21.0 (CH_3),

21.0, 20.6 ($3\times OCOCH_3$); FABMS: *m/z* (%) 381 (100) $[M+1]^+$, 219 (50), 163 (90), $[M-C_9H_{13}O_6]^+$. Anal. Calcd for $C_{18}H_{20}O_9$: C, 56.84; H, 5.30. Found: C, 56.22; H, 4.92.

4.4.13. (1′*S*,2′*R*)-7-Methyl-2-(2′-*O*-acetyl-1′,3′-di-*O*-*p*-nitrobenzoyl-D-*erythritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*]pyran-5-one (9c/9d). Solid. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 1:3 EtOAc–hexane. R_f 0.45 (2:3 EtOAc–hexane). IR (KBr, cm^{-1}): *v* 3113 (=C–H str), 1728 (C=O str), 1575 (C=C str), 1220 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 8.34–8.01 (m, 8H, Ar*H*), 6.67 (d, $J_{4,3}$ 10.8 Hz, 1H, H_D-4), 6.47 (d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 5.92 (s, 1H, H-8), 5.77 (s, 1H, H_D-8), 5.74–5.68 (m, 2H, H-3 and H-2′), 5.58 (dd, $J_{3,4}$ 10.0 Hz and $J_{3,2}$ 3.3 Hz, 1H, H_D-3), 5.42–5.30 (m, 2H, H-1′ and H-2), 4.77 (dd $J_{3'a,3'b}$ 12.5 Hz and $J_{3'a,2'}$ 2.2 Hz, 1H, H-3′a), 4.37 (dd, $J_{3'b,3'a}$ 12.0 Hz and $J_{3'b,2'}$ 3.4 Hz, 1H, H-3′b), 2.29 (s, 3H, C*H*$_3$), 2.16 (s, 3H, OCOC*H*$_3$), 2.12 (s, 3H, OCOC*H*$_{3D}$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0 ($3\times COCH_3$), 164.8 (C-7), 164.3 (C_D-7), 164.0 (C-8a and C-5), 135.0, 134.2 (Ar*qC*), 131.2 (Ar*C*), 124.2, 124.1 (Ar*C*), 121.4 (C-4), 115.3 (C-3), 114.5 (C_D-3), 99.7 (C-8), 98.4 (C-4a), 75.6 (C-2), 74.2 (C_D-1′), 73.6 (C-1′), 68.3 (C-2′), 63.5 (C-3′), 21.2 (*C*H$_3$), 20.7 (CO*C*H$_3$); FABMS: *m/z* (%) 595 (30) $[M+1]^+$, 219 (30) $[M-C_{16}H_{11}N_2O_9]^+$, 163 (100) $[M-C_{19}H_{15}N_2O_{10}]^+$, 149 (100). Anal. Calcd for $C_{28}H_{22}N_2O_{13}\cdot 0.5H_2O$: C, 55.72; H, 3.84; N, 4.64. Found: C, 55.32; H, 4.30; N, 4.19.

4.4.14. (1′*S*)-7-Methyl-2-(1′,2′-di-*O*-acetyl-D-*glyceritol*-1′-yl)-2*H*,5*H*-pyrano[3,2-*c*] pyran-5-one (10c/10d). Oil. Isolated as a diastereomeric mixture*. Purification was by column chromatography using 3:7 EtOAc–hexane. R_f 0.34 (7:13 EtOAc–hexane). IR (neat, cm^{-1}): *v* 2959 (C–H str), 1745 (C=O str), 1567 (C=C str), 1372 (C–H def. of CH_3), 1222 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 6.58 (br d, $J_{4,3}$ 10.0 Hz, 1H, H-4), 5.83 (s, 1H, H_D-8), 5.80 (s, 1H, H-8), 5.45 (dd, $J_{3,4}$ 10.3 Hz and $J_{3,2}$ 3.0 Hz, 1H, H_D-3), 5.37 (dd, $J_{3,4}$ 10.1 Hz and $J_{3,2}$ 3.6 Hz, 1H, H-3), 5.31 (m, 1H, H-2), 5.21 (m, 1H, H-1′), 4.37 (dd, $J_{2'a,2'b}$ 11.9 Hz and $J_{2'a,1'}$ 4.2 Hz, 1H, H-2′a), 4.21 (dd, $J_{2'b,2'a}$ 11.8 Hz and $J_{2'b,1'}$ 6.3 Hz, 1H, H-2′b), 2.23 (s, 3H, C*H*$_3$), 2.15 (s, 3H, C*H*$_{3D}$), 2.08 (s, 3H, OCOC*H*$_3$), 2.07 (s, 3H, OCOC*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.4 ($2\times OCOCH_3$), 164.8 (C-7), 163.8 (C_D-8a), 163.7 (C-8a), 162.2 (C-5), 162.1 (C_D-5), 120.8 (C-4), 120.5 (C_D-4), 115.3 (C-3), 100.0 (C-8), 99.8 (C_D-8), 98.6 (C-4a), 76.2 (C-2), 72.8 (C_D-1′), 72.0 (C-1′), 62.0 (C-2′), 61.6 (C_D-2′), 21.0 (*C*H$_3$), 21.0, 20.6 ($2\times CO CH_3$); FABMS: *m/z* (%) 309 (30) $[M+1]^+$, 163 (30) $[M-C_6H_9O_4]^+$, 105 (100). Anal. Calcd for $C_{15}H_{16}O_7\cdot H_2O$: C, 55.21; H, 5.56. Found: C, 54.92; H, 5.04.

5. Supplemental data

Complete crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 262608 (for compound **5a**) and CCDC no. 262609 (for compound **5c**). Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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