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Synthesis and Hydrolysis of New Aspirin- and Triflusal-Derived Ortho Esters and Anhydrides

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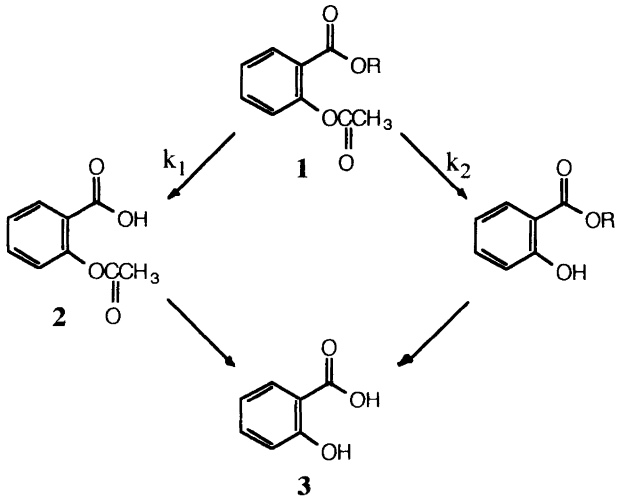
Ten new 2-substituted 2-methyl-2-oxy-4*H*-1,3-benzodioxin-4-ones, **4a-i** and **6**, have been synthesized and their rate constants of pseudo-first-order non-enzymatic hydrolysis determined. One of the compounds, 2-(2-acetoxybenzoyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one, **6**, is a new anhydride of aspirin. The analogous triflusal derivative, **10**, has also been synthesized.

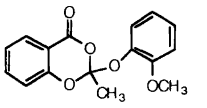
Aspirin (**2**), with its antiinflammatory, analgesic, antirheumatic and antithrombotic properties, is still one of the most widely used drugs. Unfortunately, in a significant number of patients, aspirin causes gastrointestinal side effects after oral administration. Attempts have been made to reduce these side effects by masking the carboxylic group as an ester group as in the potential prodrugs **1**. A characteristic feature of these diesters is that the acetoxy group of **1** is usually hydrolyzed more rapidly than the other ester group, i.e., $k_1 < k_2$ in Scheme 1. This means that most diesters **1** are salicylic acid (**3**) prodrugs rather than aspirin prodrugs. Only a few examples of **1** acting as true aspirin prodrugs in human plasma (all with ultra-short biological half-lives) are known.[1–4]



Scheme 1. Hydrolysis of the diesters **1**.

With the intent to design a true aspirin prodrug with a hydrolytic half-life which allows the bulk of the orally administered drug to reach the blood stream before breakdown this and other laboratories have, during the last decade or so, synthesized a number of 2-substituted 2-methyl-2-oxy-4*H*-1,3-benzodioxin-4-ones **4** where the latent carboxylic acid group is part of a cyclic ortho ester function.[5–10] The theoretically possible hydrolytic pathways of these ortho esters are shown in Scheme 2.

These potential prodrugs upon hydrolysis form **2** and **3** in ratios between 100 : 0 (i.e., true aspirin prodrugs) and 0 : 100 (i.e., salicylic acid prodrugs). Most compounds **4** belong to the latter type rather than the first or possess inconveniently short hydrolytic half-lives. So far the most



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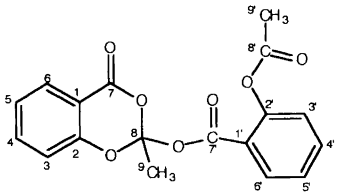

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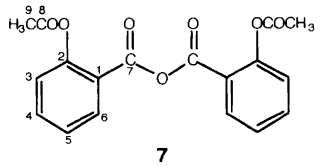

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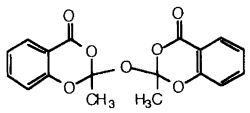

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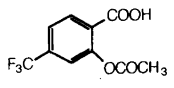

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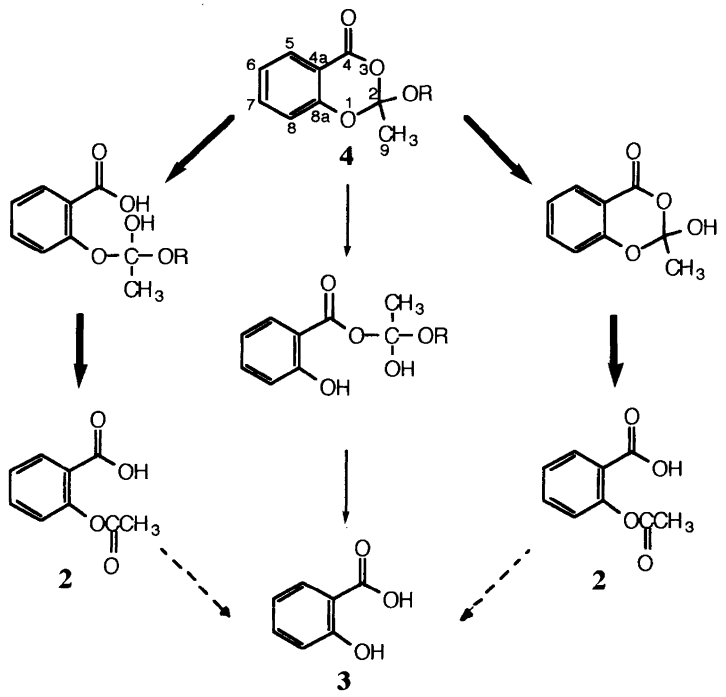


Scheme 2. Hydrolysis of the ortho esters **4**.

promising aspirin prodrug is 2-[2-methoxyphenoxy]-2-methyl-4*H*-1,3-benzodioxin-4-one (MR 693) **5**,[11,12] with a hydrolytic half-life in human plasma of 80 min and a hydrolytic **2** : **3** product ratio of 70 : 30.[10]

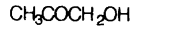
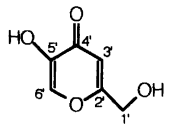
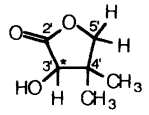
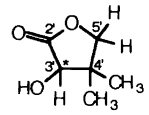
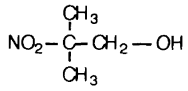
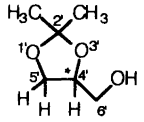
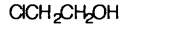
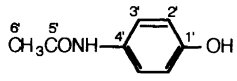
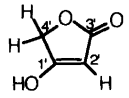
In an extension of earlier work from this laboratory[5–10] we now report the synthesis, characterization and hydrolysis of ortho esters **4**, **6** and **10** derived from aspirin **2** and triflusal (4-trifluoromethyl-2-acetoxybenzoic acid) **9**, respectively. The aim was to develop compounds with higher hydrophilicity than the previously examined compounds in order to see the consequences it would have for the rate of hydrolysis as well as for the outcome of the hydrolysis, i.e. leading to aspirin **2** or to salicylic acid **3**.

In this paper we also describe the synthesis and spectroscopic characterization of 2-(2-acetoxybenzoyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one **6** and its triflusal analog **10**. It is highly surprising that dehydration of **2** under our conditions (see the Experimental section) leads to substantial amounts of the unsymmetrical anhydride **6** rather than the known symmetrical anhydride **7**[13] or the still unknown **8** (no trace of **8** could be detected spectroscopically in our crude dehydration product). Dehydration of the aspirin-derived antithrombotic triflusal **9**[14] gives the analogous triflusal anhydrides **10** and **11**.

Results and discussion

Table 1 shows the alcohol components of the nine ortho esters **4a-i**. In the case of **4b** the reaction could also have led to the isomeric ortho ester with esterification of the enolic hydroxy group. However, only one product is observed, and we assign it the structure, with the aliphatic alcohol function incorporated in the ortho ester. The main argument for this is the coupling constant of the AB system which is probably larger the closer the diastereotopic group is to the chiral center. In our spectra we find a coupling constant which, in size, looks like other well described compounds like **4a**, **4c**, **4e** and **4i** with two or three bonds between the chiral and the diastereotopic center. Another reason is that substitution of the enol group should lead to an upfield movement in the chemical shift of the ^{13}C signal for C-5′ as described for **4i**. This is not the case. Furthermore simple steric considerations support the assigned structure. Because of the generation of a chiral center in the formation of the ortho esters racemic mixtures are obtained in most of the syntheses. For each of **4c** and **4d**, prepared from the same optically active alcohol, the two diastereomers (formed in the ratio 1 : 2) were isolated and characterized. The system **4f** corresponds to four stereoisomers because of the two centers of chirality. Unfortunately we were unable to separate the diastereomers. Compound **4h** is not new,[15,16] but from a pharmaceutical point of view the hydrolytic investigation of this compound is very interesting because of its known pharmacological activity. The products of the hydrolysis of **4h** have not been examined before. Compound **4i** is interesting as it is the first enolic type of **4** that has ever been synthesized. What influence will the side chain double bond have on the hydrolysis of **4i**? Acylation of the enol could theoretically happen either at C-2′ or at the enolic oxygen atom. *C*-Acylation would result in an upfield displacement of the ^{13}C signal from C-2′ because of the rehybridization from sp^2 to sp^3 of that carbon atom. But what really happens is a downfield shift of about 8 ppm which may be due to the electronic movements

Table 1. Presentation of the alcohol components ROH of the nine ortho esters **4a–i**.

Ortho ester	Starting ROH compound[a]	ROH structure
4a	1-Hydroxypropan-2-one	
4b	5-Hydroxy-2-hydroxymethyl-4*H*-pyran-4-one	
4c	(−)-3-Hydroxy-4,4-dimethyl-4,5-dihydrofuran-2(3*H*)-one	
4d	(−)-3-Hydroxy-4,4-dimethyl-4,5-dihydrofuran-2(3*H*)-one	
4e	2-Methyl-2-nitropropan-1-ol	
4f	(±)-2,2-Dimethyl-1,3-dioxolan-4-ylmethanol	
4g	2-Chloroethanol	
4h	*N*-(4-Hydroxyphenyl)acetamide	
4i	4-Hydroxyfuran-2-(5*H*)-one	

[a]The numbering of the alcohol corresponds to the NMR data from the Experimental section.

Table 2. NMR data of **4a–i**.

	δ(^{1}H)					δ(^{13}C)								
	H-5	H-6	H-7	H-8	CH_3-9	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9
4a	8.03	7.23	7.64	7.07	1.90	113.1	160.1	117.2	129.8	123.7	136.9	117.1	154.7	22.7
4b	8.03	7.25	7.65	7.07	1.93	112.9	159.9	117.2	129.9	123.9	137.0	117.0	154.7	22.7
4c	8.04	7.23	7.64	7.10	2.01	113.4	159.7	117.3	129.7	123.7	136.7	117.3	154.4	24.0
4d	8.01	7.23	7.66	7.11	2.05	113.4	159.7	117.4	129.3	123.6	136.9	117.4	154.9	24.1
4e	7.99	7.21	7.63	7.06	1.86	113.1	160.1	116.8	129.6	123.3	136.8	117.0	154.6	22.3
4f	7.98	7.18	7.60	7.03	1.86	113.2 113.3	160.4	117.1	129.6	123.3	136.6	117.0	154.8	22.4
4g	7.95	7.18	7.60	7.04	1.86	113.1	159.9	116.8	129.3	123.2	136.5	116.8	154.5	22.2
4h	8.02	7.21	7.65	7.11	1.87	113.5	160.1	117.4	129.6	123.6	136.9	116.9	154.5	22.9
4i	8.05	7.33	7.71	7.12	2.16	112.9	157.5	118.0	129.9	124.9	137.5	116.9	152.9	22.0

through the double bond system. Furthermore, the ^{13}C signal of C-1′ after acylation of the tetronic acid moves upfield by about 10 ppm, which can be explained by *O*-acylation and the electron-donating properties of the cyclic part of the ortho ester. The ^{1}H and ^{13}C NMR data of **4a-i** are shown in Table 2 and in the Experimental section. In Table 2 are collected the characteristic data from the aspirin part of the molecules. They seem to be quite similar throughout the table with some deviations in **4i**, especially at C-4, C-4a, and C-8a. Moreover the proton absorption from the CH_3-9 group is extraordinary in its low-field shift. This may be due to through-space effects of the enolic alcohol component.

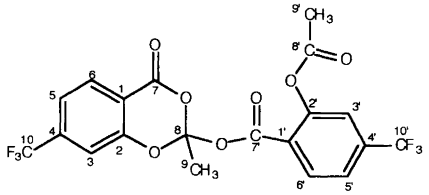
The exact configurations of **4c** and **6** have been determined by X-ray analysis.[17] Knowing that the alcohol component in **4c** had the *R*-configuration we found that the asymmetric carbon center generated by the ring closure has the *S*-configuration.

The ^{1}H NMR spectra of **4c** and **4d** are different with respect to H-5′. In **4c** the prochiral methylene group gives an AB system, while for **4d** the chemical shifts for the two diastereotopic protons are identical. The two methyl groups display magnetic non-equivalence in the ^{1}H spectrum of **4d**, while in **4c** they have the same absorption. However, in the ^{13}C spectra the signals of the methyl groups of both diastereomers have different chemical shifts.

In Table 3 are shown the ^{1}H and ^{13}C chemical shifts of the four anhydrides **7**, **11**, **6**, and **10**. The most characteristic signal is that of C-8 in **6** at δ 113.2 ppm (analogous to C-2 in **4a-i**). This carbon atom changes its hybridization in the course of the reaction from sp^2 in **2** to sp^3 in **6** and **4a-i**. Another feature is the increase by about 3 ppm to δ 23.7 ppm of the C-9 signal in the ortho esters when the methyl group becomes attached to a benzodioxin moiety. These features are in accordance with the NMR data of similar compounds.[5–9] The analogous C-8 signal in **10** lies at δ 115.8 (vs. δ 113.2 ppm in **6**), due to the influence of the CF_3 group. In the ^{1}H NMR spectrum H-9 of **6** absorbs at δ 2.36 ppm. In **4** where ROH corresponds to an aliphatic alcohol or a phenol this CH_3 group absorbs in the narrow range 1.60–2.00 ppm. Thus in **6** we see a substantial change because of the carbonyl C-7′ which makes the corresponding ROH a carboxylic acid.

Table 3. ^{1}H and ^{13}C chemical shifts for **7**, **11**, **6**, and **10**.

Atom	δ(^{1}H)				δ(^{13}C)			
No.	**7**	**11**	**6**	**10**	**7**	**11**	**6**	**10**
1					121.7	124.9	116.9	117.3
1′							122.2	125.6
2					152.0	152.1	153.8	153.7
2′							151.1	151.0
3	7.23	7.53	7.13	7.42	124.6	122.0	117.1	114.7
3′			7.07	7.36			124.1	121.4
4	7.72		7.64		135.8	137.3	137.1	138.5
4′			7.56				134.8	136.4
5	7.42	7.69	7.24	7.50	126.5	123.3	124.2	121.0
5′			7.24	7.52			126.2	122.9
6	8.12	8.20	8.04	8.17	132.4	132.9	129.6	130.6
6′			7.74	7.89			131.9	132.4
7					159.5	158.3	160.7	159.8
7′							158.6	157.1
8					169.8	169.2	113.2	115.8
8′							169.8	169.2
9	2.34	2.37	2.36	2.38	20.7	20.6	23.8	23.7
9′			2.39	2.40			20.8	20.6
10						122.7		122.7
10′								122.7



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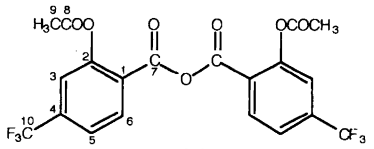

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In Table 4 are shown the H–H and the C–F coupling constants of **7**, **11**, **6**, and **10**.

The IR spectra (Experimental section) of these four compounds each contain two carbonyl absorbances although for **6** and **10** one could expect three C=O peaks. This could be due to wavenumber differences below the resolution of the instrument.

The hydrolysis of **4a-i**, **6**, **10** and **11** in a preheated phosphate buffer at pH 7.4 and 37 °C was followed by HPLC. The decrease in the concentration of the ortho ester as a function of time turned out to follow first-order kinetics [eqn. (1)].

$$C = C_0 \exp(-kt) \qquad (1)$$

Table 4. H–H and C–F coupling constants for **7**, **11**, **6** and **10**.

Proton	J_{H-H}/Hz				Carbon	J_{C-F}/Hz			
Nos.	**7**	**11**	**6**	**10**	No.	**7**	**11**	**6**	**10**
3,4	8.1		8.3		3		3.6		4.0
3′,4′			8.1		3′				3.9
3,5	1.1	1.2	1.1	1.1	4		33.8		33.6
3′,5′			1.2	1.5	4′				33.8
3,6	[a]	0.4	0.5	[a]	5		3.6		3.6
3′,6′			0.3	[a]	5′				3.6
4,5	[b]		[a]		10		273.8		273.9
4′,5′			[a]		10′				273.9
4,6	1.7		1.7						
4′,6′			1.8						
5,6	7.9	8.2	7.8	8.1					
5′,6′			7.9	8.4					

[a] Not determined. [b] 7.6–8.0 Hz.

Table 5. Hydrolytic data.

	4a	4b	4c	4d	4e	4f	4g	4h	4i	6	10	11
$t_{1/2}$/min	114	210	868	422	103	36	35	540	<5	<5	<5	<5
% aspirin	0	0	0	0	15	0	0	0[a,b]	100[a]	100	100[c]	100[c]

[a] Hydrolysis carried out in buffer with 1 % acetonitrile. [b] The half-lives in 10 % and 50 % buffered human plasma at 37 °C were 273 min and 92 min, respectively. [c] The product of the hydrolysis is triflusal **9**.

The half-lives of the hydrolyses were calculated and the product distribution between **2** and **3** measured. The results are shown in Table 5. A single compound, i.e., **4h**, was hydrolyzed in 10 % and 50 % buffered human plasma to study the influence of esterases on the half-life and hydrolytic product distribution. As can be seen from Table 5 the product remained the same as in the non-enzymatic experiments, namely salicylic acid, while the half-life, not surprisingly, had decreased. The half-life of **4h** is relatively long compared with other substituted-phenol derivatives of **4**.[8] Most of the compounds are hydrolyzed to salicylic acid, except **4e**, which gave 15 % acetylsalicylic acid, and **4i** which was hydrolyzed to 100 % acetylsalicylic acid. The rapid breakdown of **4i**, which is the first aspirin-derived ortho ester with an enolic alcohol component, can be explained by the vinylogous pseudo-anhydride nature of the compound. The stereochemistry of the two diastereomers **4c** and **4d** is obviously important for the hydrolytic half-lives which differ by a factor of two.

While the potential aspirin prodrugs **4** by necessity also form the by-product ROH upon hydrolysis which in the general case 'dilutes' their effective aspirin contents, **6** would, given a reasonably long hydrolytic half-life, constitute an ideal prodrug, capable of forming only **2** and **3**. Unfortunately, while indeed forming 100 % aspirin upon hydrolysis, **6** is hydrolyzed with a half-life of less than 5 min. The corresponding hydrolytic half-lives of **10** and **11** are likewise of the order of minutes and triflusal is formed as the only product.

Conclusions

Unfortunately, the substituents chosen for the present series of **4**, while increasing overall hydrophilicity, led to compounds which failed to furnish significant amounts of aspirin upon hydrolysis and thus cannot be regarded as potential aspirin prodrugs. On the other hand the remarkably long hydrolytic half-life of **4h** surpasses that of the experimental aspirin prodrug 2-(2-methoxyphenoxy)-2-methyl-4*H*-1,3-benzodioxin-2-one ($t_{1/2}$ = 139 min, 88 % aspirin)[8,10] and thus a combination of the two substitution patterns of 2-aryloxy-2-methyl-4*H*-1,3-benzodioxin-2-one might well lead to new potential aspirin produgs with increased hydrolytic half-lives. Experiments along these lines are in progress in our laboratory.

The hydrolytic half-life of **6** which was measured by HPLC may be compared with that of the classical anhydride **7**, 8 min at pH 7.4 and 25 °C.[18] Bundgaard and de Weck have shown that traces of **7** give rise to hypersensitivity toward commercial aspirin preparations.[19] This hypersensitivity is due to *N*-acetylsalicyloylation of proteins.[19–22] It is likely that **6**, because of its reactivity, shares the immunogenic properties of **7** and that possible small amounts of **6** in commercial aspirin preparations may have gone undetected in the past. The symmetrical aspirin anhydride **8** has not been observed yet.

Experimental

Identification. The identification of the compounds was carried out by ^{1}H and ^{13}C NMR spectroscopy including two-dimensional COSY and HETCOR NMR experiments (Varian Gemini 200). ^{1}H NMR chemical shifts refer to $CHCl_3$ ($\delta = 7.3$ ppm) and ^{13}C chemical shifts refer to $CDCl_3$ ($\delta = 77.0$ ppm). The IR data mentioned in the experimental section refer to C=O stretching frequencies (Nicolet MX-S) Elemental analyses were carried out by *Løvens Kemiske Fabrik*, DK-2750 Ballerup, Denmark.

High-performance liquid chromatography equipment. The HPLC studies were carried out with a Kontron pump 420, an ACS 750 UV detector (215 nm) and a Rheodyne 7125 injection valve with a 20 µl loop. A reversed-phase Chrompack column (100 × 3 mm) packed with Chromspher C_{18} (5 µm particles), initially connected to a Chromguard column (10 × 3 mm), was used.

Hydrolysis. The hydrolyses of **4a-i**, **6**, **10** and **11** were carried out in 100 % 0.01 M aqueous phosphate buffer [pH 7.4, adjusted with 2 M NaOH; ionic strength (µ) 0.5 M, adjusted with KCl]. Throughout the hydrolysis, the temperature was kept at 37 °C by means of a water bath.

The progress of the hydrolysis was followed by reversed-phase HPLC procedures. The kinetics (i.e., the detection of **4a-i**, **6**, **10** or **11**, for the calculation of the half-lives) was run in CH_3OH–CH_3CN–H_2O–H_3PO_4 (45 : 10 : 45 : 1 v/v) for **4a**, **4c-f**, **4h**, **6**, **10** and **11**, and in CH_3OH–CH_3CN–H_2O–H_3PO_4 (30 : 10 : 60 : 1 v/v) for **4b**, **4g** and **4i**. The flow rate was 0.3 ml min^{-1}. The hydrolysis was initiated by filtering a saturated solution of the ortho ester or anhydride, and a trace of benzoic acid, used as the internal standard, into preheated buffer. This solution was chromatographed.

(R,S)-*2-Methyl-2-(2-oxopropoxy)-4*H-*1,3-benzodioxin-4-one* (**4a**). To a suspension of acetylsalicylic acid (3.2 g, 18 mmol) in 50 ml toluene was added trifluoroacetic

anhydride (4.2 g, 20 mmol) at 40 °C. Stirring was continued until the acetylsalicylic acid was dissolved. A solution of hydroxypropanone (1.3 g, 18 mmol) in 25 ml toluene was added over 10 min at room temperature. Stirring was continued for another 10 min before work-up with saturated aqueous sodium hydrogen carbonate (2 × 15 ml). The organic phase consisted of 3.1 g **4a** (72%). Recrystallization from ether–petroleum ether–chloroform 1 : 1 : 1 gave 1.0 g (23.8%), m.p. 75.1–75.8 °C. ^{1}H NMR: δ 2.12 (3 H, s, CH_3), 4.31 (2 H, s, CH_2). ^{13}C NMR: δ 69.1 (CH_2), 204.7 (CO), 26.4 (CH_3). IR (KBr): 1734 (s), 1748 (s) cm^{-1}. Anal. Found: C 60.76; H 5.28. Calc. for $C_{12}H_{12}O_5$: C 61.02; H 5.28.

(R,S)-*2-(5-Hydroxy-4-oxo-4*H*-pyran-2-ylmethoxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4b**). As for **4a** except that the neat alcohol component 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one is not dissolved before its addition to the solution of acetylsalicylic acid and trifluoroacetic anhydride. After recrystallization from ether–petroleum ether–chloroform 1 : 1 : 1 a yield of 25.3% **4b** was obtained, m.p. 179.4–179.8 °C. The alcohol component as well as the ortho ester gave a positive color reaction with aqueous acetonic Fe^{3+}, indicating that **4b** still contained an enol group. ^{1}H NMR: δ 6.46 (1 H, s, H-3′), 7.81 (1 H, s, H-6′), 4.70 (1 H, d, J = 13.9 Hz, H_A, H-1′), 4.62 (1 H, d, J = 13.9 Hz, H_B, H-1′). ^{13}C NMR: δ 61.9 (CH_2), 163.7 (C-2′), 110.8 (C-3′), 174.1 (C-4′), 145.9 (C-5′), 137.7 (C-6′). IR (KBr): 1748 (s) cm^{-1}. Anal. Found C 58.72; H 3.97. Calc. for $C_{15}H_{12}O_7$: C 59.21; H 3.98.

(S*,R*)-*2-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4c**) *and* (R*,R*)-*2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4d**). Procedure as for **4a**. The crude product contained a mixture of the two diastereomeric compounds in a ratio 1 : 2 corresponding to a yield of 15.5% and 31.1%, respectively. Compound **4c** crystallized from chloroform–petroleum ether 10 : 1 and **4d** was purified on a silica gel (Merck silica gel 60, 70–230 mesh ASTM, pH 7.0) column with ether–petroleum ether 2 : 1 as the eluent.

Isomer **4c**: m.p. 197.2 °C. ^{1}H NMR: δ 4.45 (1 H, s, H-3′), 0.95 (6 H, s, 2 CH_3), 3.92 (1 H, d, J = 9.0 Hz, H_A, H-5′), 3.98 (1 H, d, J = 9.0 Hz, H_B, H-5′). ^{13}C NMR: δ 76.8 (C-3′), 173.5 (C-2′), 75.8 (C-5′), 40.0 (C-4′), 19.0 and 22.7 (2 CH_3). IR (KBr): 1738 (s), 1798 (s) cm^{-1}. Anal. $C_{15}H_{16}O_6$: C, H.

Isomer **4d**: m.p. 199.2–200.2 °C. ^{1}H NMR: δ 4.43 (1 H, s, H-3′), 0.87 (3 H, s, CH_3) and 1.13 (3 H, s, CH_3), 3.95 (2 H, s, CH_2). ^{13}C NMR: δ 76.9 (C-3′), 173.6 (C-2′), 75.8 (C-5′), 40.1 (C-4′), 19.0 (CH_3) and 22.8 (CH_3). IR (KBr): 1760 (s), 1781 (m), 1797 (m) cm^{-1}. Anal. Found: C 61.64; H 5.57. Calc. for $C_{15}H_{16}O_6$: C 61.64; H 5.52.

(R,S)-*2-Methyl-2-(2-methyl-2-nitropropoxy)-4*H*-1,3-benzodioxin-4-one* (**4e**). Procedure as for **4a**. The crude product contained practically pure **4e** (yield 72.2%). Recrystallization from ether–petroleum ether–chloroform 1 : 1 : 1 gave 51.2% **4e**, m.p. 89.1–89.7 °C. ^{1}H NMR: δ 4.13 (1 H, d, J = 10.01 Hz, H_A, CH_2), 3.97 (1 H, d, J = 10.01 Hz, H_B, CH_2), 1.52 (3 H, s, CH_3) and 1.50 (3 H, s, CH_3). ^{13}C NMR: δ 68.8 (CH_2), 86.2 (CNO_2), 22.7 (CH_3) and 22.9 (CH_3). IR (KBr): 1748 (s) cm^{-1}. Anal. Found: C 55.47; H 5.43. Calc. for $C_{13}H_{15}NO_6$: C 55.51; H 5.38.

(2RS,4′RS)-*2-(2,2-Dimethyl-1,3-dioxolan-4-ylmethoxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4f**). Procedure as for **4a**. The crude product contained a mixture of four stereoisomers (total yield 79.9%). It was not possible to separate the diastereomers, therefore the NMR data are not assigned in detail. ^{1}H NMR: δ 3.50–4.50 (5 H, m, H-4′, H-5′, H-6′), 1.31, (1.34, 1.36) (6 H, s, d, 2 CH_3). ^{13}C NMR: δ 109.6 (C-2′), 64.7, 64.9, 66.4, 73.6 (C-4′, C-5′, C-6′), 25.0, 26.4 (2 CH_3). IR (film): 1755 (s) cm^{-1}.

(R,S)-*2-(2-Chloroethoxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4g**). Procedure as for **4a**. Yield 91.4%. ^{1}H NMR: δ 3.87–4.07 (2 H, m, CH_2O), 3.54 (2 H, J = 5.9 Hz, CH_2Cl). ^{13}C NMR: δ 64.1 (CH_2O), 41.5 (CH_2Cl). IR (film): 1753 (s) cm^{-1}.

(R,S)-*2-[4-Acetamidophenoxy]-2-methyl-4*H*-1,3-benzodioxin-4-one* (**4h**).[16] Procedure as for **4b**. The crude product corresponded to a yield of 82.7% of practically pure **4h**. ^{1}H NMR: δ 8.20 (1 H, br s, NH), 7.00 (1 H, d, J = 8.8 Hz, H-2′), 7.48 (1 H, d, J = 8.8 Hz, H-3′), 2.15 (3 H, s, CH_3-9). ^{13}C NMR: δ 148.4 (C-1′), 122.3 (C-2′), 121.0 (C-3′), 135.5 (C-4′), 169.1 (C-5′), 24.0 (C-6′).

(R,S)-*2-Methyl-2-(2-oxo-2,5-dihydrofuran-4-yloxy)-4*H*-1,3-benzodioxin-4-one* (**4i**). M.p. 105.5–106.0 °C. ^{1}H NMR: δ 4.49 (1 H, dd, J = 16.4, 1.4 Hz, H_A, CH_2), 4.60 (1 H, dd, J = 16.4, 1.37 Hz, H_B, CH_2), 5.66 (1 H, t, J = 1.4 Hz, H-2′). ^{13}C NMR: δ 172.9 and 171.6 (C-1′ and C-3′), 95.3 (C-2′), 68.0 (C-4′). Anal. $C_{13}H_{10}O_6$: C, H.

(R,S)-*2-(2-Acetoxybenzoyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one* (**6**). A mixture of 3.6 g (0.020 mol) **2** and 2.5 g (0.012 mol) trifluoroacetic anhydride in 100 ml toluene was stirred at 40 °C until dissolution was complete. Stirring was continued for another 15 min at room temperature. To this reaction mixture was added a solution of 2.0 g (0.020 mol) triethylamine in 25 ml toluene over a period of 10 min. After 10 min the solution was worked up with 2 × 20 ml saturated aqueous sodium hydrogen carbonate and 20 ml water. This crude product contained **6** and **7** in the ratio 2 : 1. The solution was filtered through 10 g Al_2O_3 (Merck alumina 90, activity grade II–III, standardized according to Brockmann, pH 9.0) and concentrated *in vacuo* to give a yellow oil which solidified upon trituration with diethyl ether to yield 0.51 g (15%) **6** after recrystallization which was carried out in diethyl ether–chloroform 4 : 1. The crude product could, alternatively, be purified on a short silica gel (Merck silica gel 60, 70–230 mesh ASTM, pH 7.0)

column with diethyl ether–petroleum ether 1 : 1 as the eluent. R_f(TLC) = 0.62 (Merck silica gel 60, pH = 7.0; eluent ether–petroleum ether 1 : 2). M.p. 111.5–111.7 °C. IR (KBr): 1745 (s), 1767 (s) cm^{-1}. Anal. Found: C 62.71; H 4.30. Calc. for $C_{18}H_{14}O_7$: C 63.16; H 4.12.

(R,S)-*2-(2-Acetoxy-4-trifluoromethylbenzoyloxy)-2-methyl-7-trifluoromethyl-4*H-*1,3-benzodioxin-4-one* (**10**). A mixture of 5.0 g (0.020 mol) **9** and 2.5 g (0.012 mol) trifluoroacetic anhydride in 100 ml toluene was stirred at 50 °C for 15 min. To this mixture was added a solution of 2.0 g (0.020 mol) triethylamine in 25 ml toluene over a period of 10 min. After another 10 min the solution was worked up with 2 × 20 ml saturated aqueous sodium hydrogen carbonate and 20 ml water. The crude product containing a mixture of **10** and **11** in the ratio 1 : 3 was chromatographed on a short silica gel (Merck silica gel 60, 70–230 mesh ASTM, pH 7.0) column with diethyl ether–petroleum ether 1 : 2 as the eluent to furnish 0.80 g of **10** (16.7% yield). R_f(TLC) = 0.91 (Merck silica gel 60, pH = 7.0; eluent ether–petroleum ether 1 : 2). M.p. 140.7–141.2 °C. IR (KBr): 1742 (s), 1769 (s) cm^{-1}. Anal. Found: C 50.24; H 2.56. Calc. for $C_{20}H_{12}F_6O_7$: C 50.22; H 2.53.

Acetylsalicylic anhydride (**7**). Procedure described by Bundgaard and Bundgaard.[23] R_f(TLC) = 0.46 (Merck silica gel 60, pH = 7.0; eluent ether–petroleum ether 1 : 2). M.p. 83–86 °C. IR (KBr): 1761 (s), 1788 (s) cm^{-1}.

2,2'-Diacetoxy-4,4'-bis(trifluoromethyl)benzoic anhydride (**11**). To a solution of 4.96 g (0.020 mol) **9** in 40 ml chloroform was added 2.06 g (0.010 mol) *N,N'*-dicyclohexylcarbodiimide, dissolved in 15 ml chloroform, and the mixture was stirred for 10 min at room temperature. *N,N'*-Dicyclohexylurea was filtered off and the filtrate concentrated *in vacuo* to a white solid consisting of 3.52 g **11** (74% yield). It could be recrystallized from ether–chloroform 4 : 1. Compound **11** decomposed on TLC (Merck silica gel 60, pH = 7.0; eluent ether–petroleum ether 1 : 2). M.p. 109 °C. IR (KBr): 1775 (s), 1798 (s) cm^{-1}. Anal. Found: C 50.33; H 2.65. Calc. for $C_{20}H_{12}F_6O_7$: C 50.22; H 2.53.

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