Unexpected Lewis Acid Mediated Reactions of 1-Arylbut-3-en-1-ols with Trimethyl Orthoformate – A New Synthesis of Homoallyl Ethers and Chlorides

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Abstract: 1-Arylbut-3-en-1-ols react with trimethyl orthoformate in the presence of Lewis acids like $InCl_3$, $BiCl_3$, $TiCl_4$, or $BF_3{\cdot}OEt_2$ providing homoallyl ethers or homoallyl chlorides in high yields.

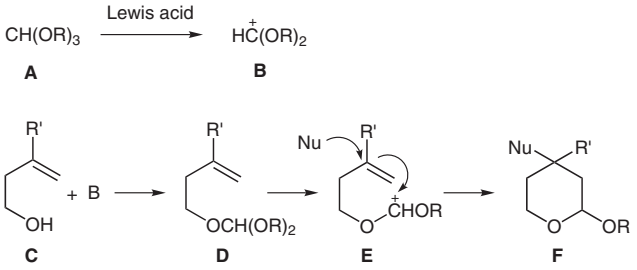
Key words: alcohols, ethers, indium, halides, Lewis acids

Relatively little is known about reactions between ortho esters and alcohols.[1] Among the best known transformations of this kind is the acid-catalyzed transesterification of simple ortho esters with an excess of a less volatile alcohol. The resulting products are higher ortho esters with three identical OR groups. More difficult to achieve is the selective access to mixed ortho esters as no general preparation method is known. Albizati et al. could demonstrate that the synthesis of mono-exchanged products can be achieved by reacting an alcohol with a large excess of an ortho ester in the presence of $MgCl_2$.[2] This method has also been applied to the synthesis of a mixed ortho ester of a homoallyl alcohol. Using the substrates in almost equimolar amounts leads, of course, to mixtures of products derived from mono-, bis- and tris-exchange.

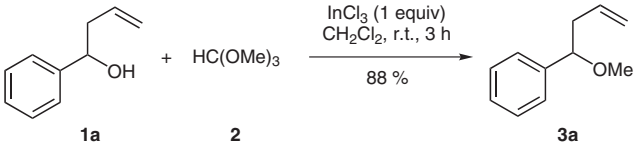
When the reaction of the homoallyl alcohol with the orthoformate is not performed with $MgCl_2$, but in the presence of other Lewis acids like $SnCl_4$,[3a,b] $SnBr_4$,[3a,b] $ZnBr_2$,[3a,b] MgI_2[3b] or $Mg(CO_2CF_3)_2$,[3b] the stereoselective formation of tetrahydropyrans is observed. It can be assumed that the reaction sequence starts with the Lewis acid mediated transformation of the orthoformate **A** into the electrophilic dioxenium cation **B**,[4] which in turn is attacked by the allyl alcohol **C** as a nucleophile to yield the mixed ortho ester **D**. The latter is transformed into the dioxenium ion **E** – again in a Lewis acid mediated reaction. The sequence is completed by the intramolecular cationic olefin cyclization of **E** to give the tetrahydropyran **F** (Scheme 1).[3,5]

Such intramolecular Prins reactions have been developed into an efficient method for the synthesis of tetrahydropyrans.[6] In particular, allylsilanes and related compounds have been employed as intramolecular traps for oxocarbenium ions which are generated in various ways.[7]

During the course of our studies towards the construction of pyrans and pyrones by means of cationic cyclizations[8]



Scheme 1 Synthesis of tetrahydropyrans by reaction of homoallyl alcohols and orthoformates



Scheme 2 Reaction of **1a** and **2** with $InCl_3$

we focused on the development of a general method for the use of ortho esters as precursors for dioxenium ions in intramolecular olefin cyclizations. For this purpose, we chose the reactions between 1-arylbut-3-en-1-ols and orthoformates. To start with, 1-phenylbut-3-en-1-ol (**1a**) was prepared in 90% yield by reacting benzaldehyde with allylmagnesium bromide in Et_2O.[9] Subsequently, one equivalent **1a** was reacted with one equivalent trimethyl orthoformate (TMOF, **2**) in the presence of one equivalent of $InCl_3$ at room temperature (Scheme 2). $InCl_3$ is a reagent that has proved to be an efficient Lewis acid in a number of Prins reactions.[10] The transformation proceeded cleanly and without any side reactions. Surprisingly, instead of the expected tetrahydropyran or a mixed ortho ester we isolated the homoallyl ether **3a** with 88% yield upon workup.[11]

Homoallyl ethers are important and versatile building blocks amenable to further transformations so that several synthetic methods can be found in the literature,[12] most of them based on the allylation of acetals.

Several reagents have been used to effect this transformation. These include $TiCl_4$,[13a] $AlCl_3$,[13b] $BF_3{\cdot}OEt_2$,[13b] Me_3SiOTf,[13c] Me_3SiI,[13d] $TrClO_4$,[13e] Ph_2BOTf,[13e] montmorillonite,[13f] $PbBr_2$/Al/$AlBr_3$,[13g] $TMSN(SO_2F)_2$,[13h] $TiCp_2(CF_3SO_3)_2$,[13i] $BiBr_3$,[13j] $TMSNTf_2$,[13k] $Sc(OTf)_3$,[13l] $Bi(OTf)_3$,[13m] and TMSOTf in ionic liquids.[13n] In addition to the very popular allyltrimethylsilane,[13a–f] allyl bromide,[13g] and allylborates[14] have served as allylating re-

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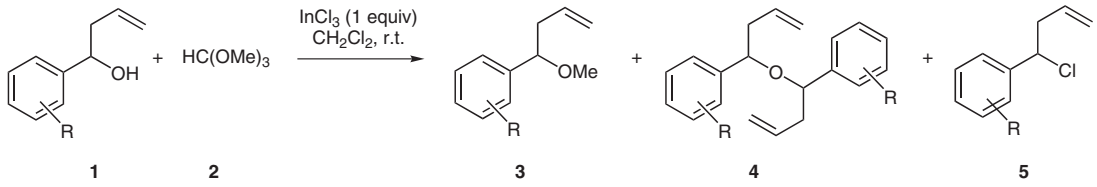


Scheme 3 $InCl_3$-mediated reaction of homoallyl alcohols **1** with TMOF (**2**)

Table 1 Results of the $InCl_3$-Mediated Reactions between **1** and **2**

Entry	1	R	Time (h)	3	Yield (%)	4	Yield (%)	5	Yield (%)
1	**1a**	H	3	**3a**	88	–	–	–	–
2	**1b**	2-Me	2	**3b**	86	–	–	–	–
3	**1c**	3-Me	2	**3c**	84	–	–	–	–
4	**1d**	4-Me	2	**3d**	92	–	–	–	–
5	**1e**	2,5-dimethyl	2	**3e**	90	–	–	–	–
6	**1f**	4-F	2	**3f**	72	**4f**	9	–	–
7	**1g**	4-Cl	3	**3g**	63	**4g**	14	–	–
8	**1h**	4-Br	3	**3h**	61	**4h**	14	–	–
9	**1i**	4-CF_3	3	**3i**	–	–	–	**5i**	82
10	**1j**	pentafluoro	3	**3j**	–	–	–	**5j**	83
11	**1k**	4-CN	3	**3k**	–	–	–	**5k**	88
12	**1l**	4-O_2N	3	**3l**	–	–	–	**5l**	67

agents. As the reaction shown in Scheme 2 promised a new approach to homoallyl ethers, which benefits from very cheap and easily available substrates as well as the use of a particular mild Lewis acid under mild reaction conditions, we decided to investigate scope and limitation of the new reaction.

For these studies a number of aryl-substituted homoallyl alcohols **1** were prepared. Apart from compounds having aryl groups with *+I*,*+M*-substituents **1b**−**e** compounds with *–I*,*+M*-substituents (**1f**–**h**,**j**) and *–I*,*–M*-substituents (**1i**,**k**,**l**) were also synthesized. Most of the homoallyl alcohols were obtained according to the simple method that had already been employed for the preparation of **1a** in high yield. Reaction of the correspondingly substituted aldehydes with allylmagnesium bromide in Et_2O delivered the homoallyl alcohols **1b**–**j** with yields ranging from 70% to 99%. Only the alcohols **1k**,**l** with cyano or nitro groups as substituents on the aromatic ring were prepared according to the method of Baba.[15]

Then each of the alcohols **1b**–**l** was reacted with TMOF (**2**) in the presence of $InCl_3$ in CH_2Cl_2 at room temperature (Scheme 3, Table 1).[16] Progress of the reactions was monitored by TLC. The reactions were stopped by adding water according to the reaction times specified in Table 1. After extractive workup followed by purification of the crude products by means of Kugelrohr distillation (**3b**–**e**) and flash chromatography (**3f**–**h**, **4f**–**h**, **5i**–**l**), respectively, the products **3**–**5** were obtained analytically pure. The structures of all products were established unambiguously.

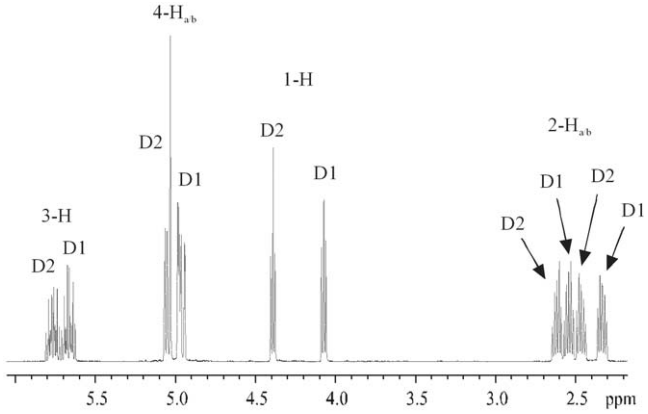
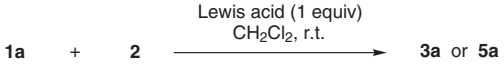


Figure 1 Part of ^1H NMR spectrum of **4f** in $CDCl_3$, displaying the signals for selected protons of the two diastereomers D_1 and D_2



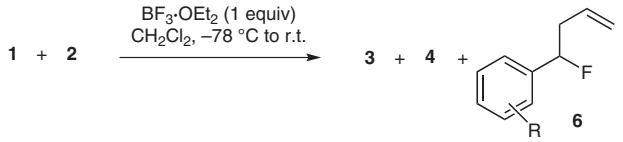
Scheme 4 Reactions of **1a** and **2** with different Lewis acids

Quite remarkably, the result of the transformations is crucially dependent on the nature of the substituent R of the aryl ring of **1**. In the case of *+I*,*+M*-substituents, the homoallyl ethers **3**[17] were isolated exclusively with yields ranging from 84% to 92% (Table 1, entries 2–5). With halogen atoms as the substituents R, the homoallyl ethers **3f**–**h** (61–72%) were accompanied by bishomoallyl ethers **4f**–**h**[18] (9–14%) as side products (Table 1, entries 6–8). If the aryl groups of the homoallyl alcohols **1** carry several halogen atoms or a *–I*,*–M*-substituent, the homoallyl chlorides **5i**–**l**[19] were exclusively formed in yields of between 67% and 88% (Table 1, entries 9–12).

The structures of all products **3**–**5** were established unambiguously. In the case of the bishomoallyl ethers **4** separate signals can be observed for two diastereomers (Figure 1). For example, the ^1H NMR spectrum of **4f** exhibits two signals for the olefinic proton 3-H at $\delta = 5.67$ ppm and $\delta = 5.77$ ppm in a 1:1 ratio, indicating a 1:1 mixture of two diastereomers D_1 and D_2.[20] Complete proton assignment for both diastereomers has been achieved using 1D NMR (^1H, ^{13}C) and 2D NMR (gCOSY, decoupling experiments, gHSQC, gHMBC, gHSQCAD, gHMBCAD).

Table 2 Results of the Reactions of **1a** and **2** with Different Lewis Acids

Entry	Lewis acid	Temp (°C)	Time (h)	Yield of **3a** (%)	Yield of **5a** (%)
1	$InCl_3$	r.t.	3	88	–
2	$BiCl_3$	r.t.	2	80	–
3	$BF_3{\cdot}OEt_2$	–78 °C	2	86	–
4	$TiCl_4$	–78 °C	2	–	92



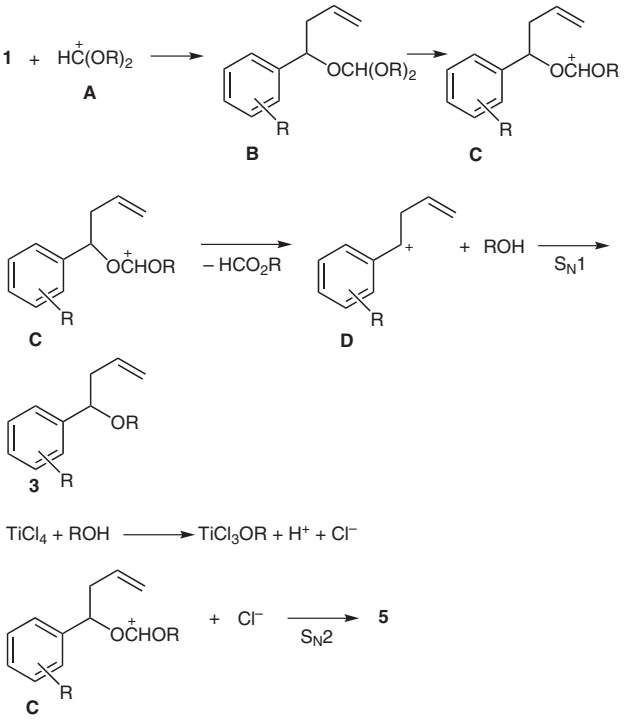
Scheme 5 Reactions of **1** and **2** with $BF_3{\cdot}OEt_2$

Table 3 Results of the $BF_3{\cdot}OEt_2$-Mediated Reactions between **1** and **2**

Entry	**1**	R	Time (h)	**3**	Yield (%)	**4**	Yield (%)	**6**	Yield (%)
1	**1a**	H	2	**3a**	86	–	–	–	–
2	**1b**	2-Me	1	**3b**	70	–	–	–	–
3	**1c**	3-Me	1	**3c**	71	–	–	–	–
4	**1d**	4-Me	1	**3d**	70	–	–	–	–
5	**1e**	2,5-dimethyl	1	**3e**	71	–	–	–	–
6	**1f**	4-F	2	**3f**	77	**4f**	3	–	–
7	**1g**	4-Cl	2	**3g**	72	**4g**	10	–	–
8	**1h**	4-Br	2	**3h**	68	**4h**	12	–	–
9	**1j**	pentafluoro	6	–	–	–	–	**6j**	21

In the face of the exceptional dependence of product distribution on the nature of the aryl substituents the influence of the Lewis acid on the reactions was briefly studied (Scheme 4, Table 2). It was found that transformations with $BiCl_3$ could also be performed at room temperature. The reaction of equimolar amounts of **1a**, TMOF (**2**) and $BiCl_3$ in CH_2Cl_2 delivered the homoallyl ether **3a** in high yield (80%) as expected (Table 2, entry 2). With strong Lewis acids like $BF_3{\cdot}OEt_2$ and $TiCl_4$, however, the reactions could be performed at low temperatures. Employing $BF_3{\cdot}OEt_2$ as the Lewis acid the homoallyl ether **3a** could again be isolated exclusively and in high yield (86%, Table 2, entry 3), whereas the reaction with $TiCl_4$ provided an unexpected result, namely the exclusive formation of the homoallyl chloride **5a** in 92% yield (Table 2, entry 4). These results definitely prove that product distribution can also be controlled by choosing the appropriate Lewis acid.

Compared to $InCl_3$ and $BiCl_3$, $BF_3{\cdot}OEt_2$ is a very cheap Lewis acid. This is why the entire range of 1-arylbut-3-en-1-ols **1a–l** was reacted with TMOF (**2**) in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Scheme 5). The results summarized in Table 3 clearly demonstrate that the reactions with $BF_3{\cdot}OEt_2$ largely resemble the $InCl_3$-mediated transformations. For example, the transformations of **1a–e** also led to the exclusive formation of homoallyl ethers **3a–e** (Table 3, entries 1–5), though with somewhat lower yields. The reactions of **1f–h** are also similar to the corresponding $InCl_3$-mediated transformations. The homoallyl ethers **3f–h** were the main products accompanied by small amounts of the bishomoallyl ethers **4f–h** (Table 3, entries 6–8). The $BF_3{\cdot}OEt_2$-mediated reactions with **1j–l** were unsatisfactory as in all but one case, a multitude of products of unknown structure was formed. Only with the pentafluorophenyl-substituted butenol **1j** as the substrate could the homoallyl fluoride **6j** be isolated in analytically pure form (Table 3, entry 9).



Scheme 6 A plausible reaction mechanism for the formation of different products

Mechanistic considerations accounting for the formation of the products **3–5** rely on the carbenium ion **C** as the central intermediate (Scheme 6). If the aryl ring of **C** carries *+I*,*+M*- or *–I*,*+M*-substituents, an S_N1 process is favored and the formation of the carbenium ion **D**, which is both an allyl cation and a benzyl cation, occurs. If $InCl_3$, $BiCl_3$, or $BF_3{\cdot}OEt_2$ are used as Lewis acids, the carbenium ion **D** is subsequently trapped with the alcohol ROH as the nucleophile to yield the homoallyl ether **3**. If the homoallyl alcohol **1** itself acts as the nucleophile, the formation of a bishomoallyl ether **4** takes place. If $TiCl_4$ is used, the alcohol ROH undergoes an irreversible reaction with the Lewis acid, and thus, the carbenium ion **D** reacts with the remaining chloride ion to afford the allyl halide **5**. If the aryl ring of **C** carries several halogen atoms or a *–I*,*–M*-

substituent, it is supposed that an S_N2 reaction takes place. In this case, **C** reacts with the chloride ion as the best nucleophile available under the reaction conditions and affords the allyl halide **5**.

In summary, this is the first report on the Lewis acid mediated transformation of 1-arylbut-3-en-1-ols and trimethyl orthoformates into their corresponding homoallyl ethers and homoallyl halides.

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(16) **General Procedure for $InCl_3$-Mediated Reactions of Homoallyl Alcohols 1 with TMOF (2)**
$InCl_3$ (3 mmol) was added to a stirred solution of homoallyl alcohol **1** (3 mmol) and TMOF (**2**, 3 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at r.t. under Ar until **1** had been completely consumed (TLC). Then H_2O (25 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (75 mL). The extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by Kugelrohr distillation or flash chromatography on silica gel.
(17) Selected data for **3e**: R_f = 0.20 (PE–CH_2Cl_2, 7:3). UV/Vis (MeCN): λ_{max} (log ε) = 269 (3.17), 277 (3.18) nm. IR (ATR): 3090, 2927, 2819, 1641 (C=C), 1500, 1448, 1357, 1189, 1156, 1108 (C–O–C), 1091, 974, 912, 808, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, 2′-CH_3), 2.38 (s, 3 H, 5′-CH_3), 2.44 (br ddd, 1 H, $^2J_{gem}$ = 14.5 Hz, ^3J = ca. 7.4 Hz, ^3J = ca. 7.4 Hz, 2-H), 2.53 (br ddd, 1 H, $^2J_{gem}$ = 14.5 Hz, ^3J = ca. 7.0 Hz, ^3J = ca. 7.0 Hz, 2-H), 3.27 (s, 3 H, 1-OCH_3), 4.48 (br dd, ^3J = 7.9 Hz, ^3J = 8.0 Hz, 1 H, 1-H), 5.11 (ddt, 1 H, $^3J_{cis}$ = 9.8 Hz, ^2J = 1.3 Hz, 4-H), 5.17 (dq, 1 H, $^3J_{trans}$ = 17.2 Hz, ^2J = 1.3 Hz, 4-H), 5.87 (dddd, 1 H, $^3J_{cis}$ = 10.1, $^3J_{trans}$ = 17.1 Hz, ^3J = ca. 7.0 Hz, ^3J = ca. 7.0 Hz, 3-H), 7.04 (br d, ^3J = 7.5 Hz, 1 H, 3′-H), 7.08 (br d, ^3J = 7.8 Hz, 1 H, 4′-H), 7.24 (s, 1 H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (2′-CH_3), 21.1 (5′-CH_3), 41.6 (C-2), 56.6 (1-OCH_3), 80.0 (C-1), 116.6 (C-4), 126.4 (C-6′), 127.8 (C-4′), 130.2 (C-3′), 132.2 (C-1′), 135.2 (C-3), 135.6 (C-5′), 139.5 (C-1′). MS (EI, 70 eV): *m/z* (%) = 149 (100) [M^+ – 41], 143 (12), 133 (45), 119 (59), 105 (65), 103 (15), 91 (31), 77 (32), 65 (8), 51 (10). HRMS (EI): *m/z* calcd for $C_{13}H_{18}O$: 190.1357; found: 190.1316 [M^+]. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.05; H, 9.58.
(18) Selected data for **4f**: R_f = 0.62 (PE–CH_2Cl_2, 7:3). UV/Vis (MeCN): λ_{max} (log ε) = 271 (3.01), 265 (3.05) nm. IR (ATR): 3077, 2980, 2905, 1641 (C=C), 1604, 1508, 1431, 1343, 1295, 1220, 1156, 1073 (C–O–C), 1013, 991, 915, 831, 785, 722 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 273 (4) [M^+ – 41], 150 (20), 149 (100), 109 (35), 95 (3), 53 (2). HRMS (EI): *m/z* calcd for the fragment [$C_{10}H_{10}F^+$]: 149.0761; found: 149.0750.
(19) Selected data for **5j**: R_f = 0.50 (PE). UV/Vis (MeCN): λ_{max} (log ε) = 266 (1.97) nm. IR (ATR): 3080, 2980, 1654 (C=C), 1523, 1501, 1449, 1424, 1359, 1316, 1148, 1130, 1042, 991, 955, 928, 802, 761, 741, 684 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.96 (br ddd, 1 H, ^2J = 14.3 Hz, ^3J = ca. 7.8 Hz, ^3J = ca. 7.8 Hz, 2-H), 3.05 (br ddd, 1 H, ^2J = 14.3 Hz, ^3J = ca. 7.1 Hz, ^3J = ca. 7.1 Hz, 2-H), 5.15 (ddt, 1 H, ^3J = 10.1 Hz, ^2J = 1.4 Hz, ^4J = 1.2 Hz, 4-H), 5.19 (dq, 1 H, ^2J = 1.4 Hz, $^3J_{trans}$ = 17.1 Hz, 4-H), 5.22 (br dd, 1 H, ^3J = ca. 8.0 Hz, ^3J = ca. 8.0 Hz, 1-H), 5.73 (dddd, 1 H, $^3J_{trans}$ = 17.2 Hz, $^3J_{cis}$ = 10.1 Hz, ^3J = ca. 7.0 Hz, ^3J = ca. 7.0 Hz, 3-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.1 (C-2), 49.5 (C-1), 114.5 (C-1′), 119.5 (C-4), 132.5 (C-3) 138.7 (d, C-4′), 141.2 (d, C-

3′and C-5′), 144.75 (d, C-2′and C-6′). MS (EI, 70 eV): *m/z* (%) = 256 (33) [M$^+$], 215 (100) [M$^+$ – 41], 207 (57), 194 (35), 181 (45), 151 (12), 143 (11), 123 (7), 105 (3), 99 (6), 75 (5), 51 (5). HRMS (EI): *m/z* calcd for $C_{10}H_6ClF_5$: 256.0078; found: 256.0076 [M$^+$].

(20) Compound **4f** (D_1): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (dddq, 1 H, ^2J = 13.9 Hz, ^3J = ca. 6.5 Hz, ^3J = ca. 6.5 Hz, ^4J = 1.1 Hz, 2-H), 2.55 (br dddt, 1 H, ^2J = 14.0 Hz, ^3J = ca. 7.2 Hz, ^3J = ca. 7.2 Hz, ^4J = 1.3 Hz, 2-H), 4.08 (dd, 1 H, ^3J = 7.3 Hz, ^3J = 6.6 Hz, 1-H), 4.96 (dddd, 1 H, $^3J_{trans}$ = 17.2 Hz, ^2J = ca. 1.6 Hz, ^4J = ca. 1.6 Hz, ^4J = ca. 1.6 Hz, 4-H), 4.98 (br d, 1 H, $^3J_{cis}$ = 10.4 Hz, 4-H), 5.67 (dddd, 2 H, $^3J_{trans}$ = 17.1 Hz, $^3J_{cis}$ = 10.2 Hz, ^3J = ca. 6.9 Hz, ^3J = ca. 6.9 Hz, 3-H), 7.06 (br dd, 2 H, ^3J = 8.7 Hz, $^3J_{H–F}$ = 8.0 Hz, 3′-H and 5′-H), 7.23 (br dd, 2 H, ^3J = 8.7 Hz, $^4J_{H–F}$ = 5.5 Hz, 2′-H and 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.05 (C-2), 77.85 (C-1), 115.44 (d, $^2J_{C–F}$ = 21.4 Hz, C-3′ and C-5′), 117.28 (C-4), 128.88 (d, $^3J_{C–F}$ = 8.5 Hz, C-2′ and C-6′), 134.7 (C-3), 137.70 (d, $^4J_{C–F}$ = 2.9 Hz, C-1′), 162.5 (d, $^1J_{C–F}$ = 245.5 Hz, C-4′).
Compound **4f** (D_2): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (dddq, 1 H, ^2J = 14.1 Hz, ^3J = ca. 7.1 Hz, ^3J = ca. 7.1 Hz, ^4J = 1.1 Hz, 2-H), 2.62 (dddt, 1 H, ^2J = 14.1 Hz, ^3J = ca. 7.1 Hz, ^3J = ca. 7.1 Hz, ^4J = 1.2 Hz, 2-H), 4.39 (dd, 1 H, ^3J = ca. 6.4 Hz, ^3J = ca. 6.4 Hz, 1-H), 5.04 (br d, 1 H, $^3J_{cis}$ = 10.0 Hz, 4-H), 5.05 (dddd, 1 H, $^3J_{trans}$ = 17.5 Hz, ^2J = ca. 1.6 Hz, ^4J = ca. 1.6 Hz, ^2J = ca. 1.6 Hz, 4-H), 5.77 (dddd, 2 H, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = ca. 7.2 Hz, ^3J = ca. 7.2 Hz, 3-H), 6.94 (br dd, 2 H, ^3J = ca. 8.8 Hz, $^3J_{H–F}$ = ca. 8.8 Hz, 3′-H and 5′-H), 7.14 (br dd, 2 H, ^3J = 8.6 Hz, $^4J_{H–F}$ = 5.5 Hz, 2′-H and 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.96 (C-2), 79.4 (C-1), 115.06 (d, $^2J_{C–F}$ = 21.3 Hz, C-3′and C-5′), 117.54 (C-4), 128.51 (d, $^3J_{C–F}$ = 7.5 Hz, C-2′ and C-6′), 134.5 (C-3), 137.19 (d, $^4J_{C–F}$ = 3.7 Hz, C-1′), 162.20 (d, $^1J_{C–F}$ = 244.7 Hz, C-4′).