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Synthesis of Perhydrofuro[2,3-*b*]furans from Isopentenyl Alcohol through Carbonyl-Ene and Wacker-Type Reactions

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Dedicated to Professor K. C. Nicolaou on the occasion of his 65th birthday

Keywords: Natural products / Synthetic methods / Oxygen heterocycles / Ene reaction / Wacker reaction / Perhydrofurofurans

A range of 2-substituted perhydrofuro[2,3-*b*]furans have been synthesized in a stereoselective manner through a sequence involving the Lewis-acid catalyzed carbonyl-ene reaction of a protected isopentenyl alcohol with a variety of enophiles, deprotection of the corresponding monoprotected diols, and palladium-catalyzed intramolecular acetalization under Wacker-type reaction conditions.

Introduction

Perhydrofuro[2,3-*b*]furans possess an interesting bicyclic acetal structure which is present in many natural products.[1] In particular, those with substituents at the 2-position can be found as substructures in neoclerodane diterpenes which are especially abundant in *Ajuga*[2] and *Scutellaria*[3] species. Lupulin C (**I**),[2a] scutecolumnin C (**II**),[3a] and areptin A (**III**)[2c] are some representative examples of this family of natural products (Figure 1) which exhibit notable insect antifeedant activity.[4] Compounds **IV** and **V** are synthetic analogs with the latter displaying the above-mentioned activity in laboratory bioassays.[5] The reported synthetic routes for these types of compounds are, however, rather long.[4–6] Therefore, the design of alternative approaches to attain 2-substituted perhydrofuro[2,3-*b*]furans in a straightforward manner would be welcome.

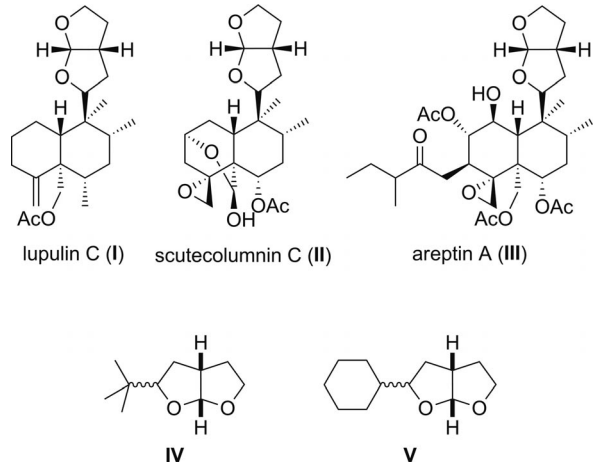

Figure 1. Natural and synthetic 2-substituted perhydrofuro[2,3-*b*]-furans.

Our continuous interest in the synthesis of fused bicyclic[7] and spirocyclic[8] polyether skeletons led us to discover a new and highly efficient synthesis of 2,5-substituted perhydrofuro[2,3-*b*]furans. The strategy consisted of the arene-catalyzed lithiation of allylic chlorinated substrates and subsequent reaction with carbonyl compounds, followed by an intramolecular acetalization of the resulting 3-methylidene-1,5-diols under Wacker-type reaction conditions.[9] More recently, we developed a new synthesis of 2-substituted perhydrofuro[2,3-*b*]furans based on the ultrasound-promoted generation of the dianion of isopentenyl alcohol and reaction with carbonyl compounds, followed by the aforementioned intramolecular acetalization.[10] This methodology was applied to both ketones and aldehydes with the perhydrofuro[2,3-*b*]furans obtained stereoselectively from the latter (Scheme 1). Although the overall yields were modest, this approach represents hitherto, to the best of our knowledge, the most direct route to these compounds. In addition, their transformation into the corresponding lactones was easily accomplished by ruthenium-catalyzed oxidation.

Notwithstanding the advantages of this methodology, all the perhydrofurofurans synthesized bore hydrocarbon substituents because of the incompatibility of the dianion of isopentenyl alcohol with many functional groups. We sought to synthesize more functionalized methylidenic 1,5-diols, and we identified the carbonyl-ene reaction as a po-

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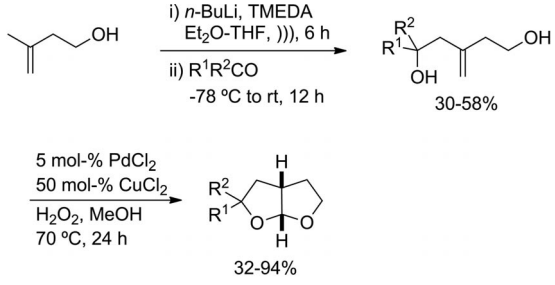


Scheme 1. Straightforward synthesis of perhydrofuro[2,3-*b*]furans through the isopentenyl alcohol dianion and Wacker-type reaction.

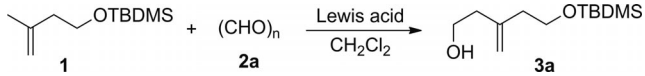
tential solution. An alternative to the carbonyl addition of allylmetals, this is an atom-efficient carbon–carbon bond-forming reaction, in which an alkene bearing an allylic hydrogen (the ene) is treated with a carbonyl compound (the enophile), accompanied by migration of the double bond and a 1,5-hydrogen shift.[11] The intermolecular version of this reaction is entropically disfavored in comparison to the intramolecular counterpart, and, hence, the carbonyl group needs to be highly activated. Lewis acid promoters, such as aluminium halides, and catalysts, such as $SnCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, or $Yb(OTf)_3$, enable the ene reactions to proceed at room or low temperature. Most of the research concerning the intermolecular processes is focused on non-functionalized hydrocarbon-based enes.[12] A few reports deal with protected methallyl alcohol as the ene component,[13] whereas the carbonyl-ene reaction with isopentenyl alcohol has seldom been studied.[14] We wish to present herein a new and straightforward route towards the synthesis of functionalized 2-substituted perhydrofuro[2,3-*b*]furans involving the carbonyl-ene reaction of protected isopentenyl alcohol with activated enophiles, followed by deprotection and an oxidation–acetalization reaction under Wacker-type[15] conditions.

Results and Discussion

Initial attempts for a direct reaction between isopentenol and either paraformaldehyde or ethyl glyoxylate, in the presence of variable amounts of different Lewis acids, led to complex mixtures and/or starting material. A maximum 20% conversion to the desired homoallylic diol was recorded for the reaction with ethyl glyoxylate promoted by $SnCl_4$ (1 equiv.) at –78 °C after 72 h. Therefore, we decided it was more convenient to carry out all the ene reactions with isopentenol protected as the *tert*-butyldimethylsilyl (TBDMS) ether **1**. Unfortunately, we were unable to find a Lewis acid that could be generally applied in the reactions with a range of enophiles. Consequently, selection of the Lewis acid and optimization of the reaction conditions were mandatory for every enophile.

Paraformaldehyde has been one of the most studied enophiles with hydrocarbon enes, generally giving modest yields of the homoallylic alcohols.[16] To the best of our knowledge, there is only one example reported of its reaction with isopentenyl alcohol which, in the presence of Me_2AlCl, led to a mixture of three products.[17] We observed that $BF_3{\cdot}Et_2O$ at 0 °C gave the expected product in moderate conversion, although substantial amounts of byproducts were present irrespective of the reaction conditions (Table 1, Entries 1–3). Catalytic amounts of $Cu(OTf)_2$ and $TiCl_4$ or stoichiometric amounts of $SnCl_4$ and $AlCl_3$ exerted very little effect, albeit approximately a 25% conversion was observed with the latter (Table 1, Entries 4–7). We were delighted with the performance of the organoaluminium Lewis acid Me_2AlCl which provided high conversion to and good isolated yield of the desired product (Table 1, Entry 8).

Table 1. Carbonyl-ene reaction of **1** with paraformaldehyde (**2a**).



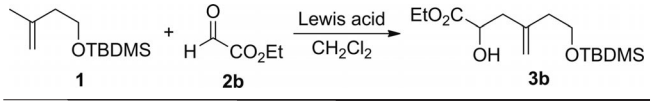
Entry	Lewis acid [mol-%]	**1**/**2a** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	$BF_3{\cdot}Et_2O$ [119]	1:1	–10	3.5	**1** [56][b]
2	$BF_3{\cdot}Et_2O$ [119]	1:1	–10	5	**1** [9], **3a** [13][b]
3	$BF_3{\cdot}Et_2O$ [119]	1:1	0	3	**3a** [46][b]
4	$Cu(OTf)_2$ [10]	1:10	r.t.	24	**1** [95]
5	$TiCl_4$ [10]	1:1	–70 to –30	48	**1** [94], **3a** [6]
6	$SnCl_4$ [100]	2:1	–78	16	**1** [79], **3a** [2]
7	$AlCl_3$ [150]	1:1	0	24	**1** [73], **3a** [26]
8	Me_2AlCl [220]	1:1	0 to r.t.	16	**3a** [91] (72)

[a] Determined from the GLC (gas–liquid chromatography) peak area. The isolated yield is in parentheses. [b] Substantial amounts of byproducts were obtained.

Next, we studied the behavior of 2-oxoesters as the enophiles, starting with ethyl glyoxylate (**2b**). In this case, both $TiCl_4$ and Me_2AlCl gave low conversions to **3b** (Table 2, Entries 1 and 2). The $AgSbF_6$/*rac*-BINAP-$PdCl_2$ combination [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], which proved to be effective in the asymmetric version of the glyoxylate- and phenylglyoxal-ene reaction with hydrocarbon enes,[18] furnished the expected product in moderate conversion independent of the temperature and reaction time (Table 2, Entries 3 and 4). In contrast, $SnCl_4$ gave more satisfactory results, and catalytic amounts of this Lewis acid led to moderate conversions and byproduct formation (Table 2, Entries 5 and 6). However, the outcome of the reaction was especially good at low temperature with stoichiometric amounts of the Lewis acid and a prolonged reaction time (Table 2, Entries 7 and 8).

A stoichiometric amount of $SnCl_4$ was also chosen to promote the carbonyl-ene reaction of **1** with ethyl pyruvate (**2c**) (Table 3, Entry 3). It is noteworthy that, under the reaction conditions, partial deprotection towards the corresponding diol **4c** was observed. Rather than being a problem, this fact was somewhat advantageous as compounds **3** were later subjected to protodesilylation. Upon scaling the reaction to >1 mmol, carbon–carbon double-bond isomer-

Table 2. Carbonyl-ene reaction of **1** with ethyl glyoxylate (**2b**).

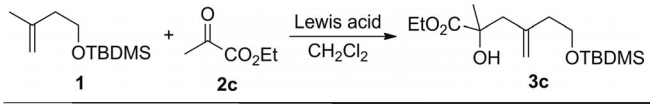


Entry	Lewis acid [mol-%]	**1/2b** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	$TiCl_4$ [10]	1:1	–70 to –30	24	**1** [89], **3b** [11]
2	Me_2AlCl [220]	1:1	0 to r.t.	27	**1** [65], **3b** [35]
3	$AgSbF_6$ [11], BINAP-$PdCl_2$ [5]	1:2.2	–78	3.5	**1** [42], **3b** [58]
4	$AgSbF_6$ [11], BINAP-$PdCl_2$ [5]	1:1	r.t.	31	**1** [60], **3b** [40]
5	$SnCl_4$ [10]	1:1	r.t.	32	**3b** [60][b]
6	$SnCl_4$ [10]	1:1	0	48	**3b** [71][b] (10)
7	$SnCl_4$ [50]	2:1	–78	16	**1** [90], **3b** [10]
8	$SnCl_4$ [100]	1:1	–78	72	**3b** [96] (66)

[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Substantial amounts of a byproduct were obtained.

ization occurred giving rise to approximately a 3:1 mixture of **3c** and (*E*)-ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-2,4-dimethylhex-4-enoate.

Table 3. Carbonyl-ene reaction of **1** with ethyl pyruvate (**2c**).



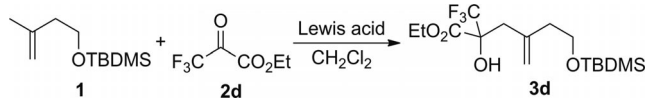
Entry	Lewis acid [mol-%]	**1/2c** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	Me_2AlCl [220]	1:1	0 to r.t.	22	**1** [93], **3c** [7]
2	$EtAlCl_2$ [220]	1:1	0 to r.t.	24	**3c** [24], **4c** [10][b]
3	$SnCl_4$ [100]	1:1	–78	21	**3c** [64] (40), **4c** [15] (14)[b]

[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Deprotected **3c**.

Despite being more activated than ethyl pyruvate (**2c**), ethyl 3,3,3-trifluoropyruvate (**2d**) was a rather problematic enophile. For instance, a stoichiometric amount of $SnCl_4$ afforded a near equimolar ratio of **1** and deprotected product **4d** together with multiple byproducts (Table 4, Entry 1). The $AgSbF_6$/*rac*-BINAP-$PdCl_2$ combination was shown to be somewhat effective, but only with long reaction times at low temperature (Table 4, Entries 2–4). $EtAlCl_2$ gave low conversion to **3d** together with 22% of the double-bond isomerization product (*E*)-ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-4-methyl-2-(trifluoromethyl)-hex-4-enoate (Table 4, Entry 5). The conversion was improved with Me_2AlCl, though minor amounts of both the deprotected and isomerized **3d** were also obtained (Table 4, Entry 6).

Little has been studied about diethyl 2-oxomalonate (**2e**) as an enophile in comparison with $(CHO)_n$ or the other 2-oxoesters.[19] The resulting α-hydroxymalonic esters, once hydrolyzed, can undergo oxidative bis(decarboxylation), the entire sequence being synthetically equivalent to an ene reaction of carbon dioxide. Very low conversions were noted

Table 4. Carbonyl-ene reaction of **1** with ethyl 3,3,3-trifluoropyruvate (**2d**).

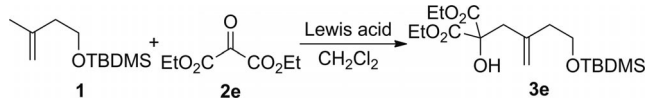


Entry	Lewis acid [mol-%]	**1/2d** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	$SnCl_4$ [100]	1:1	0	24	**1** [35], **4d** [40][b]
2	$AgSbF_6$ [11], BINAP-$PdCl_2$ [5]	1:2.2	–78	4	**1** [>99]
3	$AgSbF_6$ [11], BINAP-$PdCl_2$ [5]	1:2.2	–78	67	**1** [65], **3d** [35]
4	$AgSbF_6$ [11], BINAP-$PdCl_2$ [5]	1:1	–30	44	**1** [27], **3d** [42]
5	$EtAlCl_2$ [220]	1:1	0 to r.t.	20	**1** [54], **3d** [23][c]
6	Me_2AlCl [220]	1:1	0 to r.t.	27	**1** [44], **3d** [50] (12)[d], **4d** [6] (6)[b]

[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Deprotected **3d**. [c] 22% of the double-bond isomerization product was obtained. [d] 6% of the double-bond isomerization product was obtained.

with the aluminium Lewis acids as well as with $SnCl_4$ at 0 °C or room temperature (Table 5, Entries 1–5). Very modest conversion and isolated yield were only achieved with $SnCl_4$ at low temperature, though it was fortunate that the reaction was scalable to 10 mmol (Table 5, Entry 6).

Table 5. Carbonyl-ene reaction of **1** with diethyl oxomalonate (**2e**).



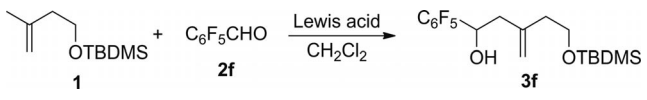
Entry	Lewis acid [mol-%]	**1/2e** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	Me_2AlCl [220]	1:1	0 to r.t.	24	**1** [33], **3e** [12]
2	$EtAlCl_2$ [220]	1:1	0 to r.t.	22	**3e** [4]
3	$SnCl_4$ [10]	1:1	0	24	**3e** [6][b]
4	$SnCl_4$ [10]	1:1	r.t.	24	**3e** [14][b]
5	$SnCl_4$ [100]	1:1	0 or r.t.	72	**3e** [0]
6	$SnCl_4$ [100]	1:1	–78	44	**3e** [38] (18)

[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Complex mixture.

Next, we focused our attention on some enophiles possessing a neat formyl group. The reaction of aliphatic and aromatic aldehydes with alkenes could be promoted by Me_2AlCl.[17] We also found out that the reaction of **1** with 2,3,4,5,6-pentafluorobenzaldehyde (**2f**) was better effected with $EtAlCl_2$ or Me_2AlCl than with $SnCl_4$ (Table 6). Among the former two, Me_2AlCl provided a moderate combined yield of the methylidenic alcohol **3f** and deprotected diol **4f** (Table 6, Entry 3). It is also worth mentioning that this reaction could easily be scaled to 5 mmol.

A similar trend to that mentioned above for **2f** was observed when using 6-nitropiperonal (**2g**) as the enophile, although an intractable crude reaction mixture was obtained with $SnCl_4$ (Table 7, Entry 1). In this case, $EtAlCl_2$ provided slightly better results than Me_2AlCl, with the in situ depro-

Table 6. Carbonyl-ene reaction of **1** with 2,3,4,5,6-pentafluorobenzaldehyde (**2f**).

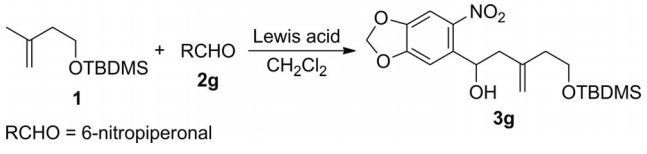


Entry	Lewis acid [mol-%]	**1**/**2f** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	$SnCl_4$ [100]	1:1	0	24	**1** [46], **3f** [20], **4f** [24][b]
2	$EtAlCl_2$ [220]	1:1	0 to r.t.	1.5	**1** [8], **3f** [64] (38), **4f** [10] (8)[b]
3	Me_2AlCl [220]	1:1	0 to r.t.	27	**1** [11], **3f** [64] (55), **4f** [25] (10)[b]

[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Deprotected **3f**.

tection to the corresponding diol giving the highest recorded conversions amongst all the enophiles presently tested (Table 7, Entries 2 and 3).

Table 7. Carbonyl-ene reaction of **1** with 6-nitropiperonal (**2g**).



RCHO = 6-nitropiperonal

Entry	Lewis acid [mol-%]	**1**/**2g** [mmol]	*T* [°C]	*t* [h]	Product[a] [%]
1	$SnCl_4$ [100]	1:1	–78	44	complex mixture
2	Me_2AlCl [220]	1:1	0 to r.t.	24	**1** [10], **3g** [21], **4g** [69][b]
3	$EtAlCl_2$ [220]	1:1	0 to r.t.	1	**3g** [31] (18), **4g** [69] (30)[b]

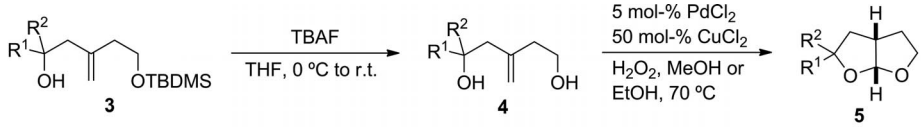
[a] Determined from the GLC peak area. The isolated yield is in parentheses. [b] Deprotected **3g**.

The next step of the synthetic sequence was to submit all compounds **3** to deprotection. Using mild conditions and distinct reaction times, tetra-*n*-butylammonium fluoride (TBAF) in THF (tetrahydrofuran) was used for this purpose (Table 8).[20] Conversion to homoallylic alcohols **4** was quantitative with the exception of compound **3e** (60%). The isolated yields of **4** ranged from modest to good (47–71%) as a result of the loss of mass during workup and/or purification (Table 8). With a series of methylidenic diols **4** in hand, we studied their palladium-catalyzed intramolecular acetalization reactions under Wacker-type conditions which we previously developed.[9,10] The simplest diol, 3-methylenepentane-1,5-diol (**4a**), was transformed to the unsubstituted perhydrofuro[2,3-*b*]furan **5a** in high conversion (Table 8, Entry 1). The low isolated yield attained was attributed to the compound's high volatility. This represents the third synthesis of **5a**. Previous ones involved the reaction of α-litioacetonitrile with protected 2-bromoethanol followed by deprotection and acetalization,[5a] and the rhodium-catalyzed hydroformylation–acetalization reaction of alkenediols.[21] It must be noted that the reactions with ethyl oxoester derivatives **4b**–**4e** were carried out in ethanol instead of in methanol to prevent transesterification (Table 8, Entries 2–5). Perhydrofurofurans **5b**–**5d** were obtained in moderate yields and stereoselectivity favoring the (2*R**,3a*S**,6a*R**)-**5b**, (2*S**,3a*S**,6a*R**)-**5c**, and (2*S**,3a*S**,6a*R**)-**5d** diastereomers (Table 8, Entries 2–4). In these examples, the differences in their moderate stereoselectivities follow similarly to the trend of the differences in steric contribution of the two substituents at the 2-position of the bicycle, that is, CO_2Et versus H in **5b** gave higher a diastereomeric ratio than CO_2Et versus Me or CF_3 in **5c** and **5d**, respectively. Perhydrofurofuran-2,2-dicarboxylate (**5e**) was also successfully prepared in moderate yield from the diol (**4e**) derived from diethyl 2-oxomalonate (Table 8, Entry 5). The more sterically demanding pentafluorophenyl and 6-nitrobenzo[*d*][1,3]dioxol-5-yl groups imparted a higher diastereoselectivity to perhydrofurofurans **5f** and **5g**, respectively, with the latter achieving a maximum ratio of 87:13 also in favor of the (2*R**,3a*S**,6a*R**) diastereomer (Table 8, Entries 6 and 7). In general, equal or longer reaction times were needed to get high conversions, in comparison to the hydrocarbon-substituted analogs previously synthesized by us.[9,10]

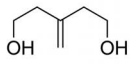
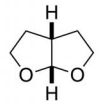
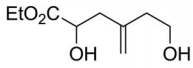
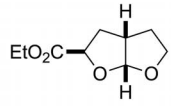
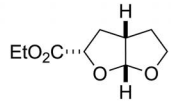
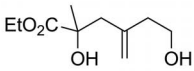
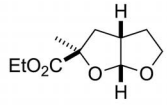
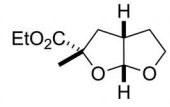
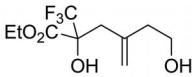
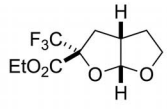
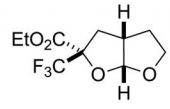
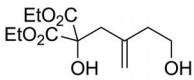
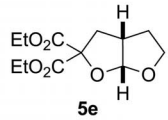
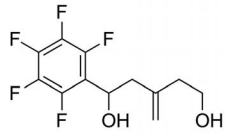
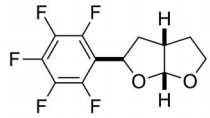
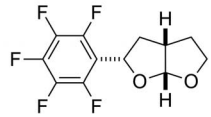
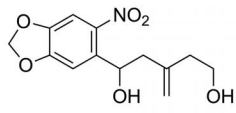
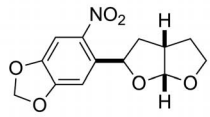
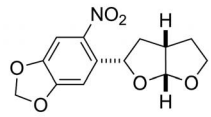
The major relative configuration (2*R**,3a*S**,6a*R**) observed for **5b**, **5f**, and **5g** is in agreement with what we reported for 2,5-disubstituted and 2-monosubstituted perhydrofuro[2,3-*b*]furans [9,10] and was confirmed by NOE experiments conducted on both diastereomers of compound **5b** (Figure 2). A small NOE was observed for 2-H and 3a-H in both diastereomers, whereas the NOE between 2-H and 5-H was manifested in only the major diastereomer. Analogous to the perhydrofurofuran bearing a phenyl group at the 2-position,[10] the 2-H and 5-H in (2*R**,3a*S**,6a*R**)-**5b** are believed to be in closer proximity than those in (2*S**,3a*S**,6a*R**)-**5b**, which would explain the shown NOE (Figure 2). As shown earlier, we reported that the opposite stereoselectivity was exhibited by **5c** and **5d**, favoring the (2*S**,3a*S**,6a*R**) diastereomer. Similarly, the stereochemistry was established on the basis of NOE experiments performed on compound **5c**. As depicted in Figure 3, the NOE between the 5-H and 2-Me in (2*R**,3a*S**,6a*R**)-**5c** is in accordance with the short interatomic distance measured in its geometry-optimized model (PM3 semiempirical method was applied).[22] In contrast, this particular NOE was not detected for the major diastereomer (2*S**,3a*S**,6a*R**)-**5c**, where the mentioned nuclei are further apart. The stereochemistry of **5d** with the bulkier trifluoromethyl group could be rationalized likewise.

It is worth mentioning that the relative stereochemistry of compounds **5** could be correlated with the ^1H NMR chemical shift of acetal hydrogen 6a-H (Table 9). In all cases, 6a-H appeared more deshielded in (2*R**,3a*S**,6a*R**)-**5** than in (2*S**,3a*S**,6a*R**)-**5**, with chemical shift ranges of 5.87–6.02 and 5.75–5.95 ppm, respectively. Furthermore, the differences in chemical shifts were larger (approximately double $\Delta\delta$) in the 2-monosubstituted series (Table 9, Entries 1, 4, and 5) than in the 2,2-disubstituted derivatives (Table 9, Entries 2 and 3). Indeed, this seems to be a direct and reliable method to assign the relative stereochemistry

Table 8. Synthesis of methylidenic diols **4** and perhydrofuro[2,3-*b*]furans **5**.[a]



3 **4** **5**

Entry	3	*t* [h]	4	Yield [%][b]	*t* [h]	5	Yield [%][c]
1	**3a**	3	 **4a**	69	24	 **5a**	93 (20)[b]
2	**3b**	1.5	 **4b**	48	24	 (2*R**,3a*S**,6a*R**)-**5b** 76:24  (2*S**,3a*S**,6a*R**)-**5b**	87 (64)
3	**3c**	21	 **4c**	63	48	 (2*R**,3a*S**,6a*R**)-**5c** 40:60  (2*S**,3a*S**,6a*R**)-**5c**	70 (53)
4	**3d**	20	 **4d**	58	72	 (2*R**,3a*S**,6a*R**)-**5d** 34:67  (2*S**,3a*S**,6a*R**)-**5d**	75 (45)[d]
5	**3e**	0.5	 **4e**	47	48	 **5e**	71 (53)
6	**3f**	27	 **4f**	71	48	 (2*R**,3a*S**,6a*R**)-**5f** 82:18  (2*S**,3a*S**,6a*R**)-**5f**	94 (60)
7	**3g**	1	 **4g**	51	48	 (2*R**,3a*S**,6a*R**)-**5g** 87:13  (2*S**,3a*S**,6a*R**)-**5g**	80 (48)

[a] Reagents and conditions: **3** (1 mmol), TBAF (1.58 mmol), THF, 0 °C to r.t.; **4** (1 mmol), $PdCl_2$ (5 mol-%), $CuCl_2$ (50 mol-%), 35% H_2O_2 (10 mmol), MeOH (10 mL, Entries 1, 6, and 7) or EtOH (10 mL, Entries 2–5). [b] Isolated yield. [c] Conversion into **5** determined by GLC. The GLC yield is in parentheses. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] The yield was determined by ^{1}H NMR spectroscopy.

of 2-substituted perhydrofuro[2,3-*b*]furans (whenever both diastereomers are available), as the same trend was observed for perhydrofuro[2,3-*b*]furans with a hydrocarbon substituent at the 2-position[10] and 2,5-positions.[7d]

A reaction mechanism for this palladium-catalyzed intramolecular acetalization was proposed in our original contribution,[9] in terms of oxypalladation–dehydropalladation reactions.[23] We rationalized the differences in the dia-

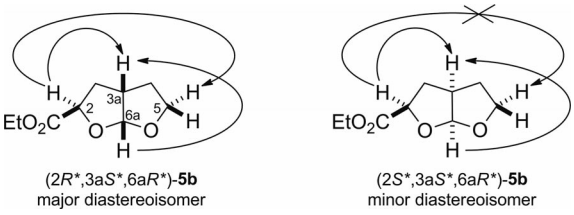


Figure 2. NOE experiments for the diastereomers of **5b**.

Table 9. ^{1}H NMR chemical shifts of 6a-H in (2*R**,3a*S**,6a*R**)-**5** and (2*S**,3a*S**,6a*R**)-**5**.[a]

Entry	Compound **5**	δ(2*R**,3a*S**,6a*R**) [ppm]	δ(2*S**,3a*S**,6a*R**) [ppm]	$\Delta\delta$ [ppm]
1	**5b**	5.91	5.77	0.14
2	**5c**	5.87	5.79	0.08
3	**5d**	6.02	5.95	0.07
4	**5f**	5.91	5.75	0.16
5	**5g**	5.97	5.82	0.15

[a] Chemical shifts were recorded at 400 MHz using $CDCl_3$ as the solvent and TMS as the internal standard.

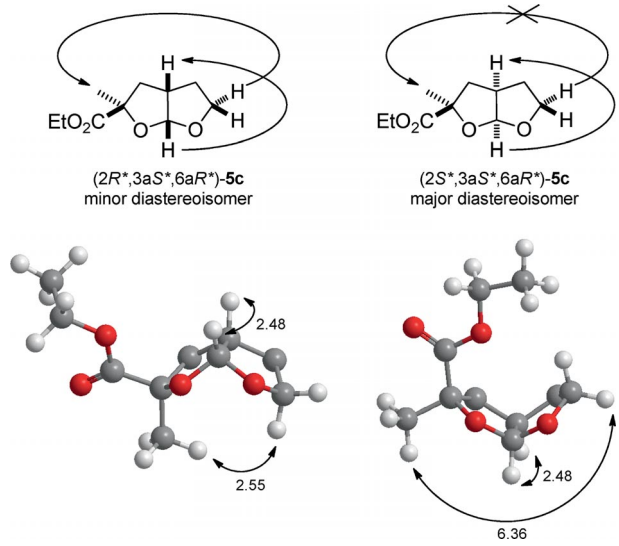
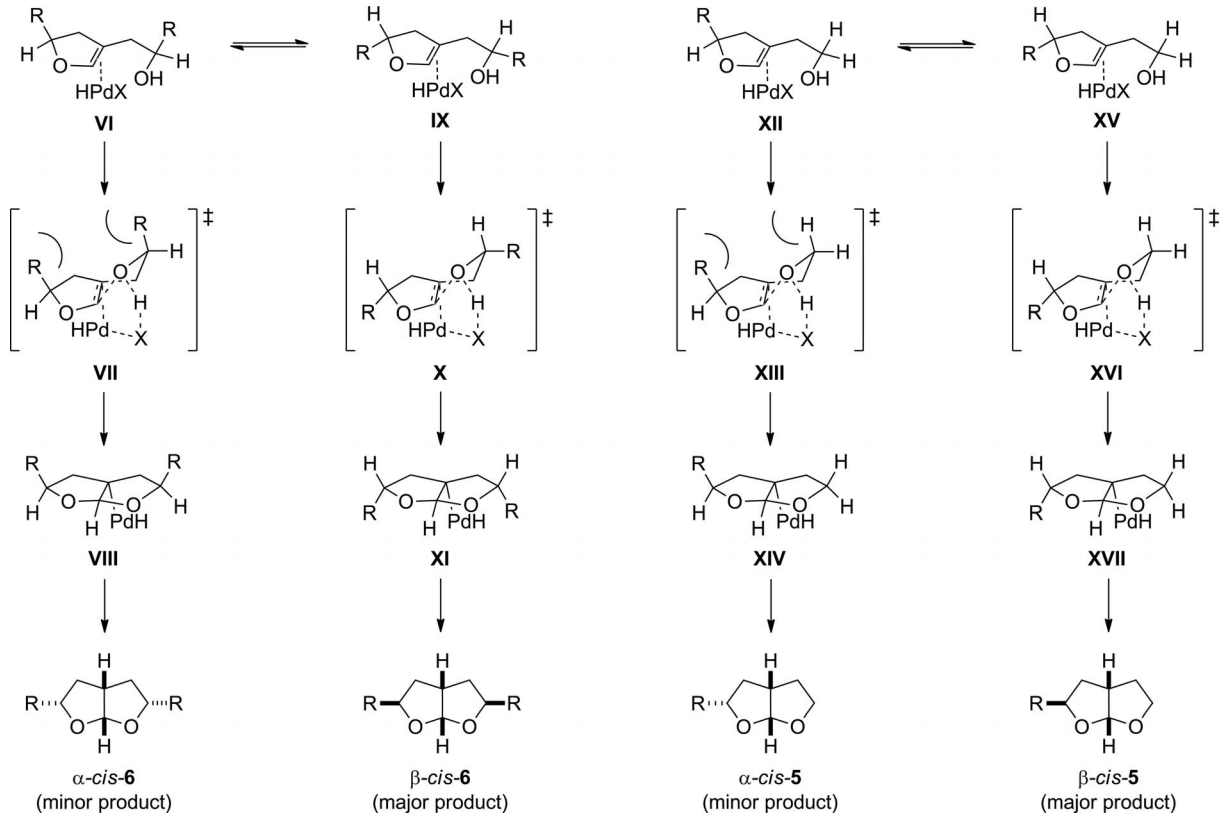


Figure 3. NOE experiments and optimized-geometry models for the diastereomers of **5c**. Numbers on the arrows refer to interatomic distances in Å. Some hydrogen atoms have been omitted for clarity.

stereoselectivity observed between the 2-monosubstituted and 2,5-disubstituted perhydrofurofurans. The diastereomeric ratios of the former with hydrocarbon substituents (85:15–93:7)[10] were akin to those reported here (76:24–87:13), but in both cases lower than those obtained for the 2,5-disubstituted derivatives (94:6–99:1).[9] In the latter case, two plausible π-palladium hydride complexes **VI** and **IX**, resulting from the first cyclization, were proposed followed by the corresponding hypothetical transition states **VII** and **X**, suggested for the second cyclization (Scheme 2). Unfavorable steric interactions involving the two R groups in transition state **VII**, which are absent in **X**, could account



Scheme 2. Intermediates and transition states proposed to explain the diastereoselectivity in the synthesis of 2,5-disubstituted and 2-monosubstituted perhydrofuro[2,3-*b*]furans.

for the preferential formation of perhydrofurofuran β-*cis*-**6** through intermediate **XI**. A similar argument was invoked to explain that β-*cis*-**5** was the major diastereomer in the 2-substituted perhydrofurofuran series. However, in this case the energy difference between the hypothetical transition states **XIII** and **XVI** must be lower than between those for **VII** and **X**, and thus, there is a decrease in the diastereoselectivity.

Conclusions

We have devised a new route toward the synthesis of perhydrofuro[2,3-*b*]furans consisting of: (1) protection of isopentenyl alcohol, (b) carbonyl-ene reaction with paraformaldehyde and various activated enophiles, (c) alcohol deprotection, and (d) palladium-catalyzed intramolecular acetalization under Wacker-type reaction conditions. In the ene reaction, tin(IV) chloride was the Lewis acid of choice for ethyl glyoxylate, ethyl pyruvate, and ethyl 2-oxomalonate, whereas dimethylaluminium chloride worked better for paraformaldehyde, ethyl trifluoropyruvate, and pentafluorobenzaldehyde, and ethylaluminium dichloride was best for 6-nitropiperonal. The resulting homoallylic diols were transformed into the corresponding perhydrofurofurans in modest yields and variable diastereoselectivities which were lower than those found for the 2,5-disubstituted analogs. The relative stereochemistry of the perhydrofurofurans was unequivocally established on the basis of NOE experiments.

Experimental Section

General Comments: Dimethylaluminium chloride (1.0 M solution in hexane) and ethylaluminium dichloride (1.0 M solution in hexane) were purchased from Aldrich. Tin(IV) chloride, 3-methylbut-3-en-1-ol, paraformaldehyde, ethyl pyruvate, ethyl 3,3,3-trifluoropyruvate, diethyl oxomalonate, 2,3,4,5,6-pentafluorobenzaldehyde, and 6-nitropiperonal were commercially available as the best grade (Aldrich and Alfa Aesar) and were used without further purification. Ethyl glyoxylate (50% in toluene, Aldrich) was distilled prior to use. Dry THF and dichloromethane were dried in a Sharlab PS-400–3MD solvent purification system using an alumina column. Tetra-*n*-butylammonium fluoride (1.0 M solution in THF) was purchased from Alfa Aesar. Infrared analysis was performed with a FTIR Nicolet Impact 400D and Jasco 4100LE (Pike MIRacle ATR) spectrophotometers, and wavenumbers are given in cm^{-1}. NMR spectroscopic data were recorded with Bruker Avance 300 and 400 spectrometers (300 and 400 MHz for ^1H NMR, 75 and 100 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are given in parts per million (δ), and coupling constants are given in Hertz (J). Mass spectra (EI) were obtained at 70 eV with an Agilent 5973 spectrometer, and fragment ions are given in *m*/*z* with relative intensities (%) in parenthesis. HRMS analyses were carried out with a Finnigan MAT95S spectrometer. The purity of volatile compounds and the chromatographic analyses (GLC) were determined with a Hewlett–Packard HP-6890 instrument equipped with a flame ionization detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness) using nitrogen (2 mL/min) as the carrier gas [$T_{injector}$ = 275 °C, T_{column} = 60 °C (3 min) and then 60–270 °C (15 °C/min)]. Retention times (t_R) are given in min. Flash column chromatography was performed using silica gel 60 (40–60 microns).

General Procedures for the Carbonyl-Ene Reaction

Method A:[17] The Lewis acid solution (Me_2AlCl or $EtAlCl_2$, 2.2 mmol) was added, using a syringe and under nitrogen, to a solution of the enophile (**2**, 1 mmol) and the protected isopentenyl alcohol (**1**, 0.2 g, 1 mmol) in dry CH_2Cl_2 (5 mL) cooled in an ice bath. After the addition, the ice bath was removed, and the solution was stirred and monitored by GLC and/or TLC. Workup was performed by slowly adding a saturated aqueous solution of NaH_2PO_4 (5 mL) and of Et_2O (10 mL) to the reaction mixture. The dropwise addition of 10% HCl dissolved the precipitated alumina. The organic layer was separated by decantation, the aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried with anhydrous $MgSO_4$. The solvents were evaporated in vacuo, and the residue obtained was subjected to flash chromatography (silica gel, hexane/EtOAc) to yield the corresponding ene adducts **3**.

Method B:[24] In a dropwise manner, $SnCl_4$ (0.12 mL, 1 mmol) was added to a stirred solution of the appropriate enophile (**2**, 1 mmol) and protected isopentenyl alcohol (**1**, 0.2 g, 1 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C. The mixture was stirred at this temperature for the time indicated in Tables 1, 2, 3, 4, 5, 6, and 7. Saturated aqueous $NaHCO_3$ (3 mL) was then added, and the mixture was warmed to room temperature before being partitioned between CH_2Cl_2 and water. The organic extract was washed with brine and dried with anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, hexane/EtOAc) yielded the corresponding ene adducts **3**.

5-(*tert*-Butyldimethylsilyloxy)-3-methylenepentan-1-ol (3a): Following Method A (Table 1, Entry 8), compound **3a** (166 mg, 72%) was obtained as a colorless oil. R_f = 0.28 (hexane/EtOAc, 10:1); t_R = 11.89 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.92 (s, 2 H, CH_2=C), 3.76 (t, J = 6.7 Hz, 2 H, CH_2OH), 3.73 (t, J = 6.2 Hz, 2 H, CH_2OTBDMS), 2.33 (t, J = 6.2 Hz, 2 H, CH_2CH$_2$OTBDMS), 2.28 (t, J = 6.7 Hz, 2 H, CH_2CH$_2$OH), 0.90 [s, 9 H, $(CH_3)_3$C], 0.07 [s, 6 H, $(CH_3)_2$Si] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.6 (*C*=CH$_2$), 113.7 (*C*H$_2$=C), 62.4 (CH$_2$OH), 60.6 (*C*H$_2$OTBDMS), 39.6 (*C*H$_2$CH$_2$OH), 38.8 (*C*H$_2$CH$_2$OTBDMS), 25.9 [(*C*H$_3$)$_3$C], 18.3 [*C*(CH$_3$)$_3$], –5.4 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3362, 1256, 1047, 870, 836 cm^{-1}. MS (EI): *m*/*z* (%) = 229 (<1%) [M – H]$^+$, 144 (13), 143 (100), 105 (13), 101 (36), 89 (11), 75 (46), 73 (19). HRMS (EI): calcd. for $C_{12}H_{25}SiO_2$ [M – H]$^+$ 229.1624; found 229.1624.

Ethyl 6-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-4-methylenehexanoate (3b): Following Method B (Table 2, Entry 8), compound **3b** (200 mg, 66%) was obtained as a colorless oil. R_f = 0.25 (hexane/EtOAc, 10:1); t_R = 14.84 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.94 (s, 2 H, CH_2=C), 4.34 (ddd, J = 8.4, 5.2, 3.9 Hz, 1 H, C*H*OH), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 3.76 (t, J = 6.7 Hz, 2 H, CH_2OTBDMS), 2.95 (d, J = 5.2 Hz, 1 H, OH), 2.61 (dd, J = 14.2, 3.9 Hz, 1 H, C*H*HCH), 2.38 (dd, J = 14.2, 8.4 Hz, 1 H, CH*H*CH), 2.32 (t, J = 6.7 Hz, 2 H, CH_2CH$_2$O), 1.31 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O), 0.90 [s, 9 H, $(CH_3)_3$C], 0.07 [s, 6 H, $(CH_3)_2$Si] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5 (CO_2), 142.4 (*C*=CH$_2$), 114.8 (*C*H$_2$=C), 69.5 (*C*HCH$_2$), 62.4 (O*C*H$_2$CH$_3$), 61.6 (*C*H$_2$OTBDMS), 41.4 (*C*H$_2$CH), 39.0 (*C*H$_2$CH$_2$O), 25.9 [(*C*H$_3$)$_3$C], 18.3 [*C*(CH$_3$)$_3$], 14.2 (*C*H$_3$CH$_2$O), –5.4 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3415, 1738, 1259, 1099 cm^{-1}. MS (EI): *m*/*z* (%) = 257 (4) [M – C_2H_5O]$^+$, 227 (15), 215 (100), 171 (69), 143 (41), 141 (39), 131 (26), 103 (20), 101 (19), 97 (20), 89 (23), 75 (86), 73 (42). HRMS (EI): calcd. for $C_{13}H_{25}SiO_3$ [M – C_2H_5O]$^+$ 257.1573; found 257.1589.

Ethyl 6-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-2-methyl-4-methylenehexanoate (3c): Following Method B (Table 3, Entry 3), compound **3c** (130 mg, 40%) was obtained with **4c** (28 mg, 14%) as a colorless oil. R_f = 0.35 (hexane/EtOAc, 15:1); t_R = 14.83 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87, 4.81 (2 s, 2 H, CH_2=C), 4.17, 4.15 (2 dq, J = 10.5, 7.1 Hz, 2 H, OCH_2CH$_3$), 3.66 (t, J = 6.8 Hz, 2 H, CH_2OTBDMS), 2.53, 2.33 (2 d, J = 13.8 Hz, 2 H, CCH_2C), 2.28, 2.22 (2 dt, J = 14.7, 6.8 Hz, 2 H, CH_2CH$_2$O), 1.37 (s, 3 H, CCH$_3$), 1.25 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O), 0.84 [s, 9 H, (CH_3)$_3$C], 0.01 [s, 6 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6 (CO_2), 142.4 (C=CH$_2$), 115.7 (CH_2=C), 74.8 (COH), 62.3 (OCH_2CH$_3$), 61.6 (CH_2OTBDMS), 46.2 (CCH_2C), 40.0 (CH_2CH_2O), 26.4 (CH_3C), 25.9 [(CH_3)$_3$C], 18.3 [C(CH$_3$)$_3$], 14.2 (CH_3CH_2O), –5.3 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3435, 1733, 1698, 1255, 1205, 1109, 837 cm^{-1}. MS (EI): m/z (%) = 316 (<1%) [M]$^+$, 229 (32), 185 (96), 183 (33), 145 (32), 111 (53), 89 (33), 75 (100), 73 (61). HRMS (EI): calcd. for $C_{14}H_{27}SiO_3$ [M – C_2H_5O]$^+$ 271.1729; found 271.1717.

Ethyl 6-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-4-methylene-2-(trifluoromethyl)hexanoate (3d): Following Method A (Table 4, Entry 6), compound **3d** (44 mg, 12%) was obtained with **4d** (15 mg, 6%) as a colorless oil. R_f = 0.28 (hexane/EtOAc, 10:1); t_R = 14.09 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.97, 4.94 (2 s, 2 H, CH_2=C), 4.36, 4.32 (2 dq, J = 10.6, 7.1 Hz, 2 H, OCH_2CH$_3$), 3.74 (td, J = 6.4, 2.0 Hz, 2 H, CH_2OTBDMS), 2.80, 2.69 (2 d, J = 14.1 Hz, 2 H, CCH_2C), 2.42, 2.29 (2 dt, J = 14.6, 6.4 Hz, 2 H, CH_2CH$_2$O), 1.35 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O), 0.91 [s, 9 H, (CH$_3$)$_3$C], 0.08 [s, 6 H, (CH$_3$)$_2$Si] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (CO_2), 140.3 (C=CH$_2$), 123.3 (q, $^1J_{C,F}$ = 287.0 Hz, CF_3), 116.9 (CH_2=C), 78.4 (q, $^2J_{C,F}$ = 28.6 Hz, CCF_3), 63.4 (OCH_2CH$_3$), 62.4 (CH_2OTBDMS), 39.9 (CCH_2C), 37.4 (CH_2CH_2O), 25.9 [(CH_3)$_3$C], 18.3 [C(CH$_3$)$_3$], 14.0 (CH_3CH_2O), –5.4 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3494, 1742, 1310, 1251, 1128, 1099, 836, 776, 697 cm^{-1}. MS (EI): m/z (%) = 325 (4) [M – C_2H_5O]$^+$, 295 (22), 283 (100), 255 (25), 107 (25), 99 (26), 97 (21), 95 (23), 89 (52), 80 (25), 77 (81), 75 (54), 73 (85), 67 (24). HRMS (EI): calcd. for $C_{14}H_{24}SiO_3F_3$ [M – C_2H_5O]$^+$ 325.1447; found 325.1452.

Diethyl 2-[4-(*tert*-Butyldimethylsilyloxy)-2-methylenebutyl]-2-hydroxymalonate (3e): Following Method B (Table 5, Entry 6), compound **3e** (67 mg, 18%) was obtained as a colorless oil. R_f = 0.27 (hexane/EtOAc, 15:1); t_R = 15.45 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (s, 2 H, CH_2=C), 4.24 (q, J = 7.1 Hz, 4 H, 2 CH_2CH$_3$), 3.70 (t, J = 6.7 Hz, 2 H, CH_2OTBDMS), 2.82 (s, 2 H, CCH_2C), 2.32 (t, J = 6.7 Hz, 2 H, CH_2CH$_2$O), 1.28 (t, J = 7.1 Hz, 6 H, 2 CH_3CH$_2$), 0.88 [s, 9 H, (CH$_3$)$_3$C], 0.04 [s, 6 H, (CH$_3$)$_2$Si] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (2 CO_2), 141.2 (C=CH$_2$), 115.9 (CH_2=C), 79.3 (COH), 62.3 (2 CH_2CH$_3$), 62.1 (CH_2OTBDMS), 40.2 (CCH_2C), 40.1 (CH_2CH_2O), 25.8 [(CH_3)$_3$C], 18.2 [C(CH$_3$)$_3$], 14.0 (2 CH_3CH$_2$), –5.4 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3495, 2857, 1740, 1255, 1214, 1081, 837 cm^{-1}. MS (EI): m/z (%) = 374 (<1%) [M]$^+$, 287 (56), 243 (33), 215 (54), 189 (87), 95 (42), 89 (32), 75 (100). HRMS (EI): calcd. for $C_{16}H_{29}SiO_5$ [M – C_2H_5O]$^+$ 329.1784; found 329.1783.

5-(*tert*-Butyldimethylsilyloxy)-3-methylene-1-(pentafluorophenyl)-pentan-1-ol (3f): Following Method A (Table 6, Entry 3), compound **3f** (218 mg, 55%) was obtained with **4f** (28 mg, 10%) as a colorless oil. R_f = 0.35 (hexane/EtOAc, 10:1); t_R = 15.85 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (dd, J = 9.5, 4.9 Hz, 1 H, CHOH), 4.99, 4.98 (2 s, 2 H, CH_2=C), 3.82 (t, J = 6.2 Hz, 2 H, CH_2OTBDMS), 3.15 (br. s, 1 H, OH), 2.82 (dd, J = 13.8, 9.5 Hz, 1 H, CHHCH), 2.53 (dd, J = 13.8, 4.9 Hz, 1 H, CHHCH), 2.34 (t, J = 6.2 Hz, 2 H, CH_2CH$_2$O), 0.91 [s, 9 H, (CH$_3$)$_3$C], 0.09 [s, 6 H, (CH$_3$)$_2$Si] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8 (d, $^1J_{C,F}$ = 251.0 Hz, ArCF), 142.7 (C=CH$_2$), 140.5 (d, $^1J_{C,F}$ = 253.5 Hz, ArCF), 137.5 (d, $^1J_{C,F}$ = 253.5 Hz, ArCF), 116.7 (ArC), 115.7 (CH_2=C), 64.8 ($CHCH_2$), 62.5 (CH_2OTBDMS), 43.8 (CH_2CH), 38.6 (CH_2CH_2O), 25.9 [(CH_3)$_3$C], 18.3 [C(CH$_3$)$_3$], –5.4 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3405, 1652, 1304, 1257, 1121, 837, 778 cm^{-1}. MS (EI): m/z (%) = 396 (<1%) [M]$^+$, 339 (11), 337 (11), 321 (31), 247 (13), 219 (21), 197 (43), 181 (43), 167 (7), 143 (17), 127 (13), 105 (100), 101 (19), 75 (84). HRMS (EI): calcd. for $C_{14}H_{16}SiO_2F_5$ [M – C_4H_9]$^+$ 339.0840; found 339.0843.

5-(*tert*-Butyldimethylsilyloxy)-3-methylene-1-(6-nitrobenzo[*d*][1,3]-dioxol-5-yl)pentan-1-ol (3g): Following Method A (Table 7, Entry 3), compound **3g** (71 mg, 18%) was obtained with **4g** (84 mg, 30%) as an orange oil; R_f = 0.27 (hexane/EtOAc, 5:1). ^{1}H NMR δ = (300 MHz, $CDCl_3$): 7.50, 7.34 (2 s, 2 H, 2 ArH), 6.11 (s, 2 H, OCH_2O), 5.43 (dd, J = 9.8, 2.4 Hz, 1 H, CHOH), 5.09, 5.06 (2 s, 2 H, CH_2=C), 3.86 (td, J = 6.3, 2.8 Hz, 2 H, CH_2OTBDMS), 2.72 (d, J = 13.7 Hz, 1 H, CHHCH), 2.41 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 2.19 (dd, J = 13.7, 9.8 Hz, 1 H, CHHCH), 0.90 [s, 9 H, (CH$_3$)$_3$C], 0.08 [s, 6 H, (CH$_3$)$_2$Si] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 146.7, 143.5, 137.9 (4 ArC), 141.1 (C=CH$_2$), 115.9 (CH_2=C), 106.9, 105.1 (2 ArCH), 102.8 (OCH_2O), 67.6 (CHOH), 62.2 (CH_2OTBDMS), 46.3 (CH_2CH), 38.3 (CH_2CH_2O), 25.9 [(CH_3)$_3$C], 18.4 [C(CH$_3$)$_3$], –5.3 [(CH$_3$)$_2$Si] ppm. IR (CCl_4): $\tilde{\nu}$ = 3411, 1618, 1483, 1332, 1256, 1097, 1038, 933, 836 cm^{-1}. MS [EI-DIP (direct insertion probe)]: m/z (%) = 395 (<1%) [M]$^+$, 278 (16), 220 (23), 196 (32), 143 (50), 131 (31), 75 (60), 69 (100). HRMS (EI-DIP): calcd. for $C_{19}H_{29}NSiO_6$ [M]$^+$ 395.1764; found 395.1795.

General Procedure for the Deprotection of Homoallylic Alcohols 3:[20] TBAF (1.58 mmol) was added to a stirred solution of diol **3** (1 mmol) in dry THF (33 mL) previously cooled in an ice bath. The ice bath was removed, and the reaction solution was stirred and monitored by GLC or TLC. Silica gel was added to the resulting mixture followed by solvent evaporation and flash chromatography (silica gel, hexane/EtOAc).

3-Methylidenepentane-1,5-diol (4a):[17] Colorless liquid; R_f = 0.23 (hexane/EtOAc, 1:4); t_R = 7.86 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.00 (s, 2 H, CH_2=C), 3.78 (t, J = 6.2 Hz, 4 H, 2 CH_2OH), 2.35 (t, J = 6.2 Hz, 4 H, 2 CH_2CH_2OH), 1.64 (br. s, 2 H, 2 OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3 (C=CH$_2$), 113.3 (CH_2=C), 60.4 (2 CH_2OH), 38.8 (2 CH_2CH_2OH) ppm. IR (CCl_4): $\tilde{\nu}$ = 3362, 3077, 1645, 1046, 897 cm^{-1}. MS (EI): m/z (%) = 116 (<1%) [M]$^+$, 98 (5), 86 (32), 69 (28), 68 (87), 67 (100), 56 (44), 53 (36). HRMS (EI): calcd. for $C_6H_{10}O$ [M – H_2O]$^+$ 98.0732; found 98.0731.

Ethyl 2,6-Dihydroxy-4-methylidenehexanoate (4b): Colorless oil; R_f = 0.38 (hexane/EtOAc, 1:4); t_R = 11.11 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.01 (s, 2 H, CH_2=C), 4.35 (dd, J = 8.4, 4.1 Hz, 1 H, CHOH), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 3.76 (t, J = 6.2 Hz, 2 H, CH_2OH), 2.60 (dd, J = 14.5, 4.1 Hz, 1 H, CHHCH), 2.38 (dd, J = 14.5, 8.4 Hz, 1 H, CHHCH), 2.37 (t, J = 6.2 Hz, 2 H, CH_2CH_2O), 1.31 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5 (CO_2), 141.7 (C=CH$_2$), 115.5 (CH_2=C), 69.7 ($CHCH_2$), 61.8 (OCH_2CH$_3$), 60.6 (CH_2OH), 40.5 (CH_2CH), 39.1 (CH_2CH_2O), 14.1 (CH_3CH_2O) ppm. IR [ATR, (attenuated total reflectance)]: $\tilde{\nu}$ = 3403, 1735, 1647, 1269, 1100, 1041 cm^{-1}. MS (EI): m/z (%) = 188 (<1%) [M]$^+$, 170 (3), 158 (20), 140 (53), 113 (22), 112 (40), 111 (24), 97 (61), 96 (34), 95 (24), 85 (25), 79 (21), 75 (24), 69 (100), 57 (27), 56 (33), 55 (38), 53 (27). HRMS (EI): calcd. for $C_9H_{15}O_3$ [M – OH]$^+$ 171.1021; found 171.1002.

Ethyl 2,6-Dihydroxy-2-methyl-4-methylidenehexanoate (4c): Colorless oil; R_f = 0.40 (hexane/EtOAc, 1:2); t_R = 11.03 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.97, 4.91 (2 s, 2 H, CH_2=C), 4.17, 4.15 (2 dq, J = 10.5, 7.1 Hz, 2 H, OCH_2CH$_3$), 3.71 (t, J = 6.1 Hz, 2 H, CH_2OH), 3.54 (s, 1 H, OH), 2.57, 2.41 (2 d, J = 14.0 Hz, 2 H, CCH$_2$C), 2.39, 2.32 (2 dt, J = 14.4, 6.1 Hz, 2 H, CH_2CH$_2$O), 2.08 (br. s, 1 H, OH), 1.42 (s, 3 H, CCH$_3$), 1.30 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6 (CO_2), 142.0 (C=CH$_2$), 116.2 (CH_2=C), 75.0 (COH), 61.8 (OCH_2CH$_3$), 60.7 (CH_2OH), 45.3 (CCH_2C), 39.9 (CH_2CH$_2$O), 26.6 (CCH_3), 14.1 (CH_3CH$_2$O) ppm. IR (CCl_4): $\tilde{\nu}$ = 3384, 1731, 1644, 1206, 1021 cm^{-1}. MS (EI): m/z (%) = 202 (<1%) [M]$^+$, 117 (100), 111 (75), 69 (38), 68 (33), 67 (48). HRMS (EI): calcd. for $C_{10}H_{18}O_4$ [M]$^+$ 202.1205; found 202.1189.

Ethyl 2,6-Dihydroxy-4-methylidene-2-(trifluoromethyl)hexanoate (4d): Colorless oil; R_f = 0.40 (hexane/EtOAc, 1:1); t_R = 11.19 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.99, 4.97 (2 s, 2 H, CH_2=C), 4.52 (s, 1 H, OH), 4.35, 4.28 (2 dq, J = 10.7, 7.1 Hz, 2 H, OCH_2CH$_3$), 3.72 (t, J = 6.3 Hz, 2 H, CH_2OH), 2.77, 2.64 (2 d, J = 14.2 Hz, 2 H, CCH$_2$C), 2.41, 2.32 (2 dt, J = 15.2, 6.3 Hz, 2 H, CH_2CH$_2$O), 1.32 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2 (CO_2), 139.6 (C=CH$_2$), 123.2 (q, $^1J_{C,F}$ = 287.0 Hz, CF_3), 117.4 (CH_2=C), 78.4 (q, $^2J_{C,F}$ = 28.6 Hz, CCF$_3$), 63.7 (OCH_2CH$_3$), 60.6 (CH_2OH), 39.8 (CCH_2C), 36.8 (CH_2CH$_2$O), 13.9 (CH_3CH$_2$O) ppm. IR (CCl_4): $\tilde{\nu}$ = 3479, 1744, 1311, 1224, 1132, 699 cm^{-1}. MS (EI): m/z (%) = 238 (5) [M – H_2O]$^+$, 208 (55), 180 (100), 165 (48), 117 (29), 97 (28), 95 (37), 83 (28), 69 (43), 55 (48). HRMS (EI): calcd. for $C_{10}H_{13}O_3F_3$ [M – H_2O]$^+$ 238.0817; found 238.0825.

Diethyl Hydroxy(4-hydroxy-2-methylidenebutyl)propanedioate (4e): Colorless oil; R_f = 0.29 (hexane/EtOAc, 1:1); t_R = 13.39 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (s, 2 H, CH_2=C), 4.27 (q, J = 7.1 Hz, 4 H, 2 CH_2CH$_3$), 3.75 (t, J = 6.0 Hz, 2 H, CH_2OH), 2.84 (s, 2 H, CCH$_2$C), 2.39 (t, J = 6.0 Hz, 2 H, CH_2CH$_2$O), 1.30 (t, J = 7.1 Hz, 6 H, 2 CH_3CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (2 CO_2), 140.8 (C=CH$_2$), 116.8 (CH_2=C), 79.4 (COH), 62.5 (2 CH_2CH$_3$), 60.5 (CH_2OH), 40.1 (CCH_2C), 39.4 (CH_2CH$_2$O), 14.0 (2 CH_3CH$_2$) ppm. IR (CCl_4): $\tilde{\nu}$ = 3496, 1739, 1266, 1210 cm^{-1}. MS (EI): m/z (%) = 260 (<1%) [M]$^+$, 242 (3) [M – H_2O]$^+$, 212 (72), 184 (42), 175 (28), 169 (82), 168 (34), 150 (29), 141 (21), 138 (45), 123 (39), 113 (35), 97 (24), 95 (100), 83 (90), 82 (27), 71 (21), 69 (27), 68 (23), 67 (85), 55 (61), 54 (21). HRMS (EI): calcd. for $C_{12}H_{18}O_5$ [M – H_2O]$^+$ 242.1154; found 242.1129.

3-Methylidene-1-(pentafluorophenyl)pentane-1,5-diol (4f): Colorless oil; R_f = 0.23 (hexane/EtOAc, 1:1); t_R = 13.79 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.23 (dd, J = 9.0, 5.3 Hz, 1 H, CHOH), 5.01, 5.00 (2 s, 2 H, CH_2=C), 3.79 (t, J = 6.1 Hz, 2 H, CH_2OH), 3.35 (br. s, 1 H, OH), 2.79 (dd, J = 14.0, 9.0 Hz, 1 H, CHHCH), 2.52 (dd, J = 14.0, 5.3 Hz, 1 H, CHHCH), 2.37, 2.34 (2 dt, J = 14.9, 6.1 Hz, 2 H, CH_2CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7 (d, $^1J_{C,F}$ = 248.2 Hz, ArCF), 141.8 (C=CH$_2$), 140.5 (d, $^1J_{C,F}$ = 253.8 Hz, ArCF), 137.5 (d, $^1J_{C,F}$ = 253.2 Hz, ArCF), 116.6 (ArC), 115.9 (CH_2=C), 64.6 (CHCH$_2$), 60.7 (CH_2OH), 43.1 (CH_2CH), 38.3 (CH_2CH$_2$O) ppm. IR (CCl_4): $\tilde{\nu}$ = 3400, 1681, 1304, 1146, 1124 cm^{-1}. MS (EI): m/z (%) = 282 (<1%) [M]$^+$, 264 (4), 246 (38), 234 (24), 197 (100), 181 (37), 169 (29), 68 (30), 67 (30). HRMS (EI): calcd. for $C_{12}H_9OF_5$ [M – H_2O]$^+$ 264.0574; found 264.0574.

3-Methylidene-1-(6-nitro-1,3-benzodioxol-5-yl)pentane-1,5-diol (4g): Yellow oil; R_f = 0.26 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49, 7.32 (2 s, 2 H, 2 ArH), 6.12, 6.11 (2 d, J = 1.2 Hz, 2 H, OCH$_2$O), 5.45 (dd, J = 9.9, 2.4 Hz, 1 H, CHOH), 5.12, 5.09 (2 s, 2 H, CH_2=C), 3.84 (t, J = 6.1 Hz, 2 H, CH_2OH), 2.68 (d, J = 13.9 Hz, 1 H, CHHCH), 2.45 (t, J = 6.1 Hz, 2 H, CH_2CH$_2$OH), 2.19 (dd, J = 13.9, 9.9 Hz, 1 H, CHHCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 146.8, 143.0, 138.1 (4 ArC), 140.9 (C=CH$_2$), 115.8 (CH_2=C), 106.7, 105.1 (2 ArCH), 102.9 (OCH$_2$O), 67.7 (CHOH), 60.7 (CH_2OH), 45.4 (CH$_2$CH), 38.2 (CH$_2$CH$_2$OH) ppm. IR (CCl_4): $\tilde{\nu}$ = 3373, 1519, 1330, 1120, 930, 760 cm^{-1}. MS (EI-DIP): m/z (%) = 263 (<1%) [M – H_2O]$^+$, 230 (15), 195 (36), 187 (20), 165 (87), 148 (37), 134 (14), 127 (15), 120 (98), 119 (58), 107 (90), 103 (20), 79 (79), 63 (100), 62 (39). HRMS (EI-DIP): calcd. for $C_{13}H_{15}NO_6$ [M]$^+$ 281.0899; found 281.0915.

General Procedure for the Intramolecular Acetalization of Homoallylic Diols 4: A solution of $PdCl_2$ (8.9 mg, 0.05 mmol), $CuCl_2$ (67.2 mg), and the corresponding methylidenic diol **4** (1 mmol) in MeOH (10 mL, for **4a**, **4f**, and **4g**) or EtOH (10 mL, for **4b**–**4e**) was prepared in a tube equipped with a screw top followed by the addition of a 35% H_2O_2 solution (0.86 mL, 10 mmol). The top was airtight on the reaction tube which was heated at 70 °C for 24 h. After that time, the reaction progress was monitored by TLC and GLC. One additional portion of the 35% H_2O_2 solution (0.86 mL, 10 mmol) along with heating (70 °C for 24 h) was required for **4c**, **4e**–**4g** (Table 8, Entries 3, 5, 6, and 7), and two portions were needed for **4d** (Table 8, Entry 5).

Workup for 5c, 5d, 5f, 5g: The solvent was evaporated to dryness followed by the addition of EtOAc (20 mL) and filtration of the resulting mixture through Celite. The filtrate was washed with brine (2 × 5 mL), the organic phase was dried with anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. **Workup for 5a, 5b, 5e:** Brine (10 mL) was added to the reaction mixture followed by extraction with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with water (2 × 10 mL) and filtered through Celite. The solvent was evaporated under vacuum at 15 °C. All compounds **5**, except **5a**, were purified by column chromatography (silica gel, hexane/EtOAc).

***cis*-Perhydrofuro[2,3-*b*]furan (5a):**[5a] Colorless oil; R_f = 0.33 (hexane/EtOAc, 7:3); t_R = 6.89 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.68 (d, J = 5.1 Hz, 1 H, OCHO), 3.86 (dd, J = 9.0, 5.1 Hz, 4 H, 2 CH_2O), 2.88–2.79 (m, 1 H, CH_2CHCH$_2$), 2.12–2.04, 1.73–1.69 (2 m, 4 H, CH_2CHCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.5 (OCHO), 68.1 (2 CH_2O), 42.4 (CH_2CHCH$_2$), 32.5 (CH$_2$CHCH$_2$) ppm. IR (film): $\tilde{\nu}$ = 1055, 1026 cm^{-1}. MS (EI): m/z (%) = 114 (12) [M]$^+$, 113 (30), 84 (95), 83 (32), 69 (49), 68 (68), 67 (68), 57 (13), 56 (46), 55 (100), 54 (26), 53 (25). HRMS (EI): calcd. for $C_6H_{10}O_2$ [M]$^+$ 114.0681; found 114.0687.

(2*R,3a*S**,6a*R**)-Ethyl Perhydrofuro[2,3-*b*]furan-2-carboxylate (5b):** Colorless oil; R_f = 0.59 (hexane/EtOAc, 1:1); t_R = 12.18 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (d, J = 5.0 Hz, 1 H, OCHO), 4.62 (t, J = 7.2 Hz, 1 H, OCHCO$_2$), 4.18 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.95–3.84 (m, 2 H, OCH_2CH$_2$), 2.98–2.84 (m, 1 H, CH_2CHCH$_2$), 2.25–2.14, 2.14–2.00, 1.76–1.68 (3 m, 4 H, CH_2CHCH_2), 1.26 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (CO_2), 110.2 (OCHO), 77.3 (OCHCO$_2$), 61.3 (OCH_2CH$_3$), 67.7 (OCH_2CH$_2$), 41.8 (CH_2CHCH$_2$), 35.9, 32.2 (CH$_2$CHCH$_2$), 14.2 (CH_3CH$_2$O) ppm. IR (film): $\tilde{\nu}$ = 1750, 1278, 1203, 1113, 1063, 1036 cm^{-1}. MS (EI): m/z (%) = 186 (<1%) [M]$^+$, 113 (100), 69 (89), 66 (17), 55 (30). HRMS (EI): calcd. for $C_9H_{14}O_4$ [M]$^+$ 186.0892; found 186.0895. Selected data for the minor diastereomer (2*S**,3a*S**,6a*R**)-**5b**: t_R = 11.98 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (d, J = 5.2 Hz, 1 H, OCHO), 4.44 (dd, J = 8.3, 6.7 Hz, 1 H, OCHCO$_2$), 2.55–2.44, 2.14–2.00, 1.99–1.89, 1.76–1.68 (4 m, 4 H, CH_2CHCH_2) ppm. MS (EI): m/z (%) = 186 (<1%) [M]$^+$, 113 (100), 69 (91), 67 (17), 55 (31).

(2*S,3a*S**,6a*R**)-Ethyl 2-Methylperhydrofuro[2,3-*b*]furan-2-carboxylate (5c):** Colorless oil; R_f = 0.54 (hexane/EtOAc, 1:1); t_R = 11.68 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (d, J = 5.1 Hz, 1 H, OCHO), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 3.91–3.78 (m, 2 H, OCH_2CH$_2$), 3.01–2.86 (m, 1 H, CH$_2$CHCH$_2$), 2.42–2.33, 2.11–1.99, 1.76–1.67 (3 m, 4 H, CH_2CHCH_2), 1.45 (s, 3 H, CH$_3$C), 1.30 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (CO_2), 110.4 (OCHO), 84.7 (CCH$_3$), 67.2 (OCH$_2$CH$_2$), 61.4 (OCH$_2$CH$_3$), 42.9 (CH$_2$$CHCH_2$), 41.1, 32.0 ($CH_2CHCH_2$), 23.9 ($CH_3$C), 14.3 ($CH_3CH_2$O) ppm. IR (film): $\tilde{\nu}$ = 1731, 1286, 1184, 1129, 1017 cm^{-1}. MS (EI): *m*/*z* (%) = 156 (1) [M – CO_2]$^+$, 127 (100), 85 (15), 83 (11), 81 (9). HRMS (EI): calcd. for $C_{10}H_{16}O_4$ [M]$^+$ 200.1049; found 200.1048. Selected data for the minor diastereomer (2*R**,3a*S**,6a*R**)-**5c**: t_R = 11.82 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (d, J = 5.3 Hz, 1 H, OCHO), 4.18 (q, J = 6.8 Hz, 2 H, OCH_2CH$_3$), 2.57–2.49, 2.08–1.89, 1.76–1.67 (3 m, 4 H, CH$_2$CHCH$_2$), 1.55 (s, 3 H, CH$_3$C) ppm. MS (EI): *m*/*z* (%) = 156 (1) [M – CO_2]$^+$, 127 (100), 85 (15), 83 (9), 81 (10).

(2*S,3a*S**,6a*R**)-Ethyl 2-(Trifluoromethyl)perhydrofuro[2,3-*b*]furan-2-carboxylate (5d):** Colorless oil; R_f = 0.55 (hexane/EtOAc, 3:1); t_R = 10.48 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (d, J = 5.0 Hz, 1 H, OCHO), 4.32 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 4.04–3.92 (m, 2 H, OCH_2CH$_2$), 3.10–2.97 (m, 1 H, CH$_2$CHCH$_2$), 2.73–2.65, 2.30–1.99, 1.77–1.68 (3 m, 4 H, CH_2CHCH_2), 1.33 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (CO_2), 127.2 (CF_3), 112.9 (OCHO), 84.7 (CCF$_3$), 67.1 (OCH$_2$CH$_2$), 62.9 (OCH$_2$CH$_3$), 42.6 (CH$_2$$CHCH_2$), 36.1, 32.6 ($CH_2CHCH_2$), 14.1 ($CH_3CH_2$O) ppm. IR (film): $\tilde{\nu}$ = 1745, 1244, 1177 cm^{-1}. MS (EI): *m*/*z* (%) = 254 (<1%) [M]$^+$, 182 (8), 181 (100), 164 (5), 135 (7), 115 (10), 83 (5), 69 (7), 55 (7). HRMS (EI): calcd. for $C_{10}H_{13}O_4F_3$ [M]$^+$ 254.0766; found 254.0767. Selected data for the minor diastereomer (2*R**,3a*S**,6a*R**)-**5d**: t_R = 10.74 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (d, J = 4.9 Hz, 1 H, OCHO) ppm. MS (EI): *m*/*z* (%) = 254 (<1%) [M]$^+$, 182 (7), 181 (100), 135 (6), 115 (8), 69 (5).

(3a*S,6a*R**)-Diethyl Perhydrofuro[2,3-*b*]furan-2,2-dicarboxylate (5e):** Colorless oil; R_f = 0.48 (hexane/EtOAc, 8:2); t_R = 14.68 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (d, J = 5.2 Hz, 1 H, OCHO), 4.38–4.14 (m, 4 H, 2 OCH_2CH$_3$), 4.02–3.83 (m, 2 H, OCH_2CH$_2$), 3.07–2.88 (m, 1 H, CH$_2$CHCH$_2$), 2.60 (dd, J = 13.8, 9.6 Hz, 1 H, CHHC), 2.42 (dd, J = 13.8, 6.6 Hz, 1 H, CHHC), 2.02 (ddt, J = 12.6, 10.8, 8.3 Hz, 1 H, CHHCH$_2$O), 1.77 (ddt, J = 12.6, 5.4, 1.6 Hz, 1 H, CHHCH$_2$O), 1.28 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O), 1.26 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 168.4 (2 CO_2), 111.7 (OCHO), 87.2 (CCO$_2$), 67.1 (OCH$_2$CH$_2$), 62.3, 62.2 (2 CH$_2$CH$_3$), 42.3 (CH$_2$$CHCH_2$), 37.6, 32.2 ($CH_2CHCH_2$), 14.2, 14.1 (2 C$H_3CH_2$) ppm. IR (film): $\tilde{\nu}$ = 1742, 1283, 1238, 1118, 1064, 1027 cm^{-1}. MS (EI): *m*/*z* (%) = 258 (<1%) [M]$^+$, 186 (11), 185 (100), 139 (11), 129 (12), 111 (15), 83 (44), 55 (12). HRMS (EI): calcd. for $C_{12}H_{18}O_6$ [M]$^+$ 258.1103; found 258.1073.

(2*R,3a*S**,6a*R**)-2-(Pentafluorophenyl)perhydrofuro[2,3-*b*]furan (5f):** Colorless oil; R_f = 0.62 (hexane/EtOAc, 1:1); t_R = 13.33 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (d, J = 4.9 Hz, 1 H, OCHO), 5.47 (dd, J = 9.5, 6.9 Hz, 1 H, OCHAr), 4.09–3.95 (m, 2 H, OCH_2CH$_2$), 3.19–3.09 (m, 1 H, CH$_2$CHCH$_2$), 2.48–2.33, 2.27–2.11, 1.88–1.79 (3 m, 4 H, CH_2CHCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4 (d, $^1J_{C,F}$ = 253.6 Hz, ArCF), 141.1 (d, $^1J_{C,F}$ = 260.7 Hz, ArCF), 137.8 (d, $^1J_{C,F}$ = 254.0 Hz, ArCF), 114.8 (ArC), 110.0 (OCHO), 71.6 (OCHAr), 68.2 (OCH$_2$CH$_2$), 43.3 (CH$_2$$CHCH_2$), 38.4, 32.5 ($CH_2CHCH_2$) ppm. IR (film): $\tilde{\nu}$ = 1737, 1655, 1524, 1506, 1132, 1020 cm^{-1}. MS (EI): *m*/*z* (%) = 280 (3) [M]$^+$, 235 (12), 234 (43), 233 (11), 219 (83), 214 (11), 207 (15), 195 (33), 194 (66), 193 (10), 187 (23), 181 (73), 169 (17), 167 (11), 143 (11), 84 (100), 83 (24), 69 (20), 56 (22), 55 (36), 54 (12). HRMS (EI): calcd. for $C_{12}H_9F_5O_2$ [M]$^+$ 280.0523; found 280.0519. Selected data for the minor diastereomer (2*S**,3a*S**,6a*R**)-**5f**: t_R = 13.43 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, J = 5.5 Hz, 1 H, OCHO), 5.10 (dd, J = 11.2, 5.8 Hz, 1 H, OCHAr), 3.08–2.98 (m, 1 H, CH$_2$CHCH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3 (OCHO), 70.7 (OCHAr), 66.5 (OCH$_2$CH$_2$), 43.4 (CH$_2$$CHCH_2$), 36.2, 32.6 ($CH_2CHCH_2$) ppm. MS (EI): *m*/*z* (%) = 280 (<1%) [M]$^+$, 234 (15), 219 (43), 195 (27), 194 (42), 187 (15), 181 (47), 169 (11), 84 (100), 83 (22), 69 (16), 56 (19), 55 (31), 54 (11).

5-[(2*R,3a*S**,6a*R**)-Perhydrofuro[2,3-*b*]furan-2-yl]-6-nitro-1,3-benzo[*d*][1,3]dioxole (5g):** Yellow oil; R_f = 0.64 (hexane/EtOAc, 1:1); t_R = 20.46 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52, 7.25 (2 s, 2 H, 2 ArH), 6.11 (d, J = 3.0 Hz, 2 H, OCH$_2$O), 5.97 (d, J = 5.0 Hz, 1 H, OCHO), 5.65 (dd, J = 9.6, 5.6 Hz, 1 H, OCHAr), 4.08–3.94 (m, 2 H, OCH_2CH$_2$), 3.05–2.95 (m, 1 H, CH$_2$CHCH$_2$), 2.60–2.51, 2.25–2.13, 1.96–1.88, 1.88–1.78 (4 m, 4 H, CH_2CHCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 147.1, 141.3, 136.2 (4 ArC), 109.5 (OCHO), 106.3, 105.4 (2 ArCH), 103.1 (OCH$_2$O), 77.5 (OCHAr), 68.1 (OCH$_2$CH$_2$), 43.1 (CH$_2$$CHCH_2$), 41.0, 32.4 ($CH_2CHCH_2$) ppm. IR (ATR): $\tilde{\nu}$ = 3018, 2853, 1512, 1482, 1257, 1150, 1019 cm^{-1}. MS (EI): *m*/*z* (%) = 262 (6) [M – OH]$^+$, 216 (28), 206 (12), 190 (10), 187 (12), 178 (11), 177 (10), 176 (17), 174 (11), 164 (15), 163 (12), 149 (14), 148 (21), 136 (22), 135 (16), 120 (22), 119 (11), 115 (10), 84 (17), 83 (100), 79 (13), 77 (13), 70 (12), 69 (20), 65 (12), 63 (19), 62 (12), 56 (17), 55 (45), 54 (11), 53 (15), 51 (10). HRMS (EI): calcd. for $C_{13}H_{13}NO_6$ [M]$^+$ 279.0743; found 279.0765. Selected data for the minor diastereomer (2*S**,3a*S**,6a*R**)-**5g**: t_R = 20.14 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (d, J = 4.9 Hz, 1 H, OCHO), 5.50 (dd, J = 9.2, 6.2 Hz, 1 H, OCHAr) ppm. MS (EI): *m*/*z* (%) = 262 (5) [M – OH]$^+$, 217 (10), 216 (23), 206 (10), 191 (11), 190 (11), 188 (11), 187 (11), 178 (11), 177 (10), 176 (19), 174 (12), 165 (11), 149 (15), 148 (17), 136 (20), 135 (23), 121 (10), 120 (18), 115 (12), 89 (11), 84 (31), 83 (100), 77 (15), 70 (11), 69 (18), 65 (13), 63 (18), 62 (15), 56 (15), 55 (37), 54 (10), 53 (14), 51 (10).

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