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$AuCl_3$-Catalyzed Hydroalkoxylation of Conjugated Alkynoates: Synthesis of Five- and Six-Membered Cyclic Acetals

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Dedicated to Professor Alain Krief

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The $AuCl_3$-catalyzed double hydroalkoxylation of conjugated 7-hydroxyheptynoates offers a convenient route for the synthesis of six-membered cyclic acetals, which are common substructures of polyketide natural products. When conjugated 6-hydroxyhexynoates are used as starting materials, either five-membered cyclic *E*-enol ethers or the corresponding acetals can be obtained by simply choosing the appropriate reaction solvent. NMR spectroscopic studies were carried out to determine the kinetics and pathway of the latter domino 5-*exo* cyclization–hydroalkoxylation reaction.
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Introduction

Pyran rings are substructures contained in numerous polyketide natural products, some of which display useful biological activities, such as (+)-acutiphycin or the callipeltoside family (Figure 1).[1] The embedded β-pyranoacetal ester unit **2** (Scheme 1) in these compounds has been synthesized by a variety of methods including acid-catalyzed cyclization of δ-hydroxyketones,[1] addition of acetic ester enolates to δ-lactones,[2] or more recently, Pd-catalyzed alkoxycarbonylation of δ-alkynols.[3]

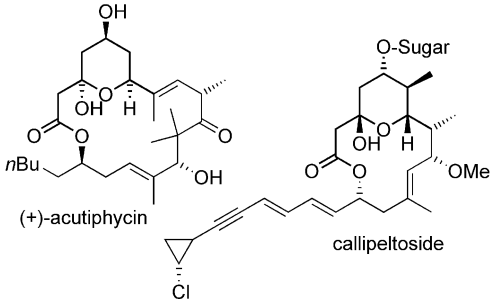
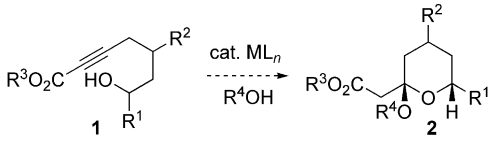


Figure 1. Pyran-containing polyketide natural products.

As an alternative disconnection, we investigated a double hydroalkoxylation reaction of 7-hydroxy-2-alkynoate derivatives **1** as a new method for the preparation of β-pyranoacetal esters **2** by a metal-mediated process (Scheme 1).



Scheme 1. Synthetic plan.

The conjugate addition of oxygen nucleophiles to α,β-unsaturated ketones and esters has generally suffered from reversibility and low reactivity, especially in the second step of the hydroalkoxylation process. Only recently has an increasing number of catalytic systems for oxy-Michael reactions emerged.[4] Nevertheless, examples of additions to triple bonds remain sparse and are largely limited to ynones[5] or dimethyl acetylene dicarboxylate (DMAD).[6] In contrast, the thiol double conjugate addition to a wide variety of propargylic carbonyl-containing compounds has been exploited more extensively.[7]

Although transition-metal-catalyzed activation of terminal alkynes towards hydroalkoxylation is well precedented,[8] the use of alkynoates in these reactions has only been described in a few isolated examples.[9] This might be due to the fact that electron-deficient alkynes are less prone to coordinate to electrophilic transition metals and, thus, are less readily activated towards nucleophilic attack.

Recently, we reported the $PtCl_4$-catalyzed formation of fused bicyclic acetals from enantiopure 1,2-heptynediols or directly from the corresponding butane-2,3-diacetal (BDA) derivatives.[10] Whereas electron-rich aryl-substituted triple bonds led to 7-*endo* cyclization, substitution with electron-poor aromatic rings decreased the reactivity and favored

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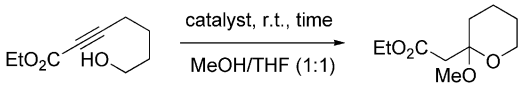
initial 6-*exo* cyclization (conjugate addition relating to the aromatic ring). Following a similar concept, we reasoned that transition-metal-catalyzed hydroalkoxylation of electron-deficient alkynes, particularly 7-hydroxyheptynoate derivatives **2**, would allow rapid access to desired cyclic acetals **1**.

Results and Discussion

Initially, we investigated the cyclization of ethyl 7-hydroxyhept-2-ynoate (**1a**; R^1, R^2 = H, R^3 = Et) with different catalytic systems in methanol/THF (1:1) at room temperature (Table 1). A catalyst screen revealed that $AuCl_3$ or [$AuCl(PPh_3)$] combined with $AgSbF_6$ led to complete conversion to desired six-membered cyclic acetal **2a** within less than 4 h at room temperature (Table 1, Entries 16 and 10). In the absence of the Ag^I salt, [$AuCl(PPh_3)$] showed no activity (Table 1, Entry 9). Although Pt^{II}-, Pt^{IV}-, and Pd^{II}-based catalysts also gave quantitative conversion, significantly longer reaction times were required (Table 1, Entries 12, 14, and 15). In contrast, DABCO[5c] or TBAF did not effect any conversion to the desired product (Table 1, Entries 1 and 2). Brønsted or Lewis acids such as TfOH, HCl, TFA, CSA, and $FeCl_3$[11] were likewise ineffective under these reaction conditions (Table 1, Entries 3–7). Reported conditions for the Ir^{IV}-catalyzed hydroalkoxylation of methyl 2-butynoate[9e] led to the formation of desired product **2a** but in only 20% after 5 days (!) (Table 1, Entry 8).

Table 1. Optimization of the double hydroalkoxylation of ethyl 7-hydroxyhept-2-ynoate (**1a**).



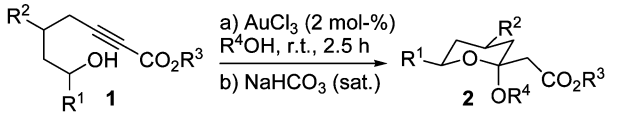
1a **2a**

Entry	Catalyst	Time [h]	Yield[a] [%]
1	10 mol-% DABCO	120	0
2	100 mol-% TBAF	120	0
3	10 mol-% TMSOTf[b]	120	0
4	10 mol-% TMSCl[c]	120	0
5	10 mol-% TFA	120	0
6	10 mol-% CSA	120	0
7	5 mol-% $FeCl_3$	120	0
8	5 mol-% $[Na(18\text{-}C6)]_2[IrCl_6]$	144	20
9	2 mol-% [$AuCl(PPh_3)$]	25	0
10	2 mol-% [$AuCl(PPh_3)$], 2 mol-% $AgSbF_6$	4	98
11	2 mol-% $[PdCl_2(CH_3CN)_2]$	26	60
12	2 mol-% $[PdCl_2(CH_3CN)_2]$, 2 mol-% $AgSbF_6$	26	98
13	2 mol-% $AgSbF_6$	26	3
14	2 mol-% $PtCl_4$	26	99
15	1 mol-% $[PtCl_2(CH_2CH_2)]_2$	4	99
16	2 mol-% $AuCl_3$	1	96

[a] Yield determined by GC–MS vs. $nC_{14}H_{30}$. [b] Formation of TfOH is assumed under the reaction conditions. [c] Formation of HCl is assumed under the reaction conditions. Tf = trifluoromethanesulfonyl.

On the basis of these results, $AuCl_3$ (2 mol-%) was selected as the best catalyst to explore the scope of the double hydroalkoxylation reaction of 7-hydroxyhept-2-ynoate derivatives **1** (Table 2). In general, good to excellent isolated

Table 2. Double oxy-Michael addition to 7-hydroxyalkynoates **1**.



1 **2**

Entry	1	2	Yield[a] [%]
1	**1a**	**2a**	96
2	**1b**	**2b**	85
3	**1c**	**2c**	93
4	**1d**	**2d**	99
5	**1e**	**2e**	87
6	**1f**	**2f**	88
7	**1g**	**2g**	99
8	**1h**	**2h**	82
9	**1b**	**2i**	75[b,c]
10	**1b**	**2j**	79[b,d]
11	**1i**	**2k**	98

[a] Yield of isolated product based on ω-hydroxyalkynoate **1**. [b] THF instead of MeOH was used as solvent. [c] 2.5 equiv. of AllylOH was used. [d] 5 equiv. of AcOH was used. Bn = benzyl; PMB = *p*-methoxybenzyl.

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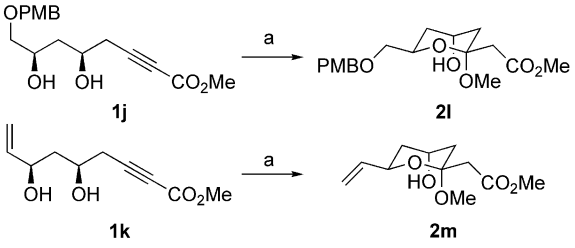
yields of products were obtained as single diastereoisomers.[12] Notably, alkynoates **1** bearing substituents R^1 such as vinyl, phenyl, or benzyl gave excellent conversion to the desired product (Table 2, Entries 6–8).[13] It is also noteworthy that transesterification was not observed and PMB ether cleavage did not occur under the reaction conditions (Table 2, Entry 11).

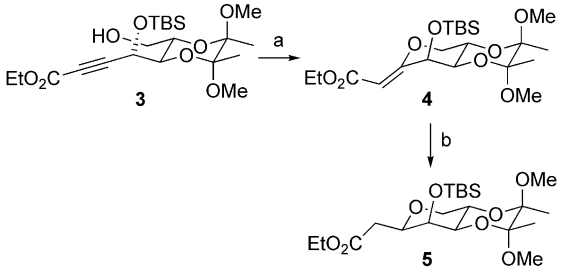
We then investigated reducing the amount of R^4OH in order to vary the acetal formed and make the process more economic. Accordingly, hydroalkoxylation of **1b** in THF as solvent by using allyl alcohol (2.5 equiv.) was studied (Table 2, Entry 9). The corresponding 2-allyloxytetrahydropyran **2i** was obtained in good yield; however, further reduction of the amount of alcohol in these reactions led to mixtures of cyclic acetal **2i** and hemiacetal **2j**. The latter could be isolated as the exclusive product in the presence of AcOH (5 equiv.) in THF as solvent (Table 2, Entry 10). The formation of the hemiacetal in this example probably occurred during the aqueous workup.

Taking into account the above results, we anticipated that the use of enantiopure 1,3-diols as starting materials should afford natural-product-like compounds (Scheme 2). Pleasingly, the corresponding cyclic acetals **2l** and **2m** were obtained in high yield and as single diastereoisomers under the reaction conditions described previously. As before, the vinyl group did not participate in any side reactions and the PMB protecting group was stable under the reaction conditions.



Scheme 2. Reagents and conditions: (a) $AuCl_3$ (2 mol-%), MeOH, r.t., 3 h, then sat. $NaHCO_3$, **2l**, 88%; **2m**, 82%.

By applying the same protocol, BDA-protected ethyl 7-hydroxyheptynoate **3**[14] gave exclusively *Z*-exocyclic enol ether **4**, which could be stereoselectively hydrogenated to pyran derivative **5** (Scheme 3).[15]



Scheme 3. Reagents and conditions: (a) $AuCl_3$ (2 mol-%), MeOH, r.t., 4 h, then sat. $NaHCO_3$, 88%; (b) H_2, Pd/C, EtOAc, r.t., 12 h, 99%.

Remarkably, the secondary silyl ether was not cleaved during the hydroalkoxylation reaction, which further illustrates the mild conditions of this method. The structure of **5** was unambiguously established by X-ray crystallography (Figure 2).[16]

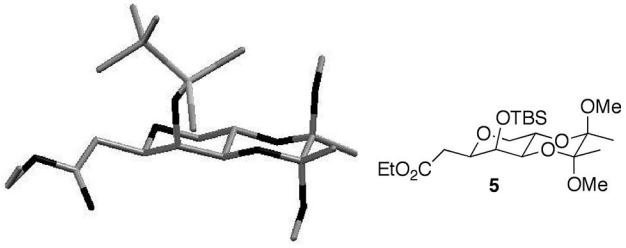
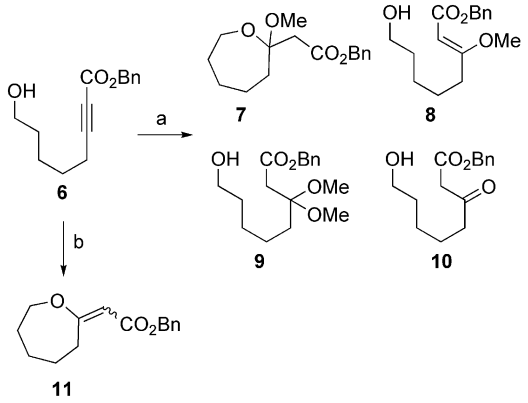


Figure 2. X-ray structure of BDA-derivative **5**.

Although the hydroalkoxylation of **3** did not give the corresponding acetal, this result suggests the intermediacy of cyclic (*Z*)-β-alkoxyenoates in the formation of alkoxytetrahydropyrans **2**. Moreover, this observation is in agreement with the commonly accepted mechanism for the Au-catalyzed hydroalkoxylation of triple bonds.[8p,10a]

We briefly investigated the formation of seven-membered cyclic acetals. From the reaction of benzyl 8-hydroxy-2-octynoate (**6**) in methanol, cyclic acetal **7** was isolated in 18% yield along with 15% of acyclic enol ether **8**, 35% of dimethylacetal **9**, and a small amount of ketone **10** (Scheme 4). This result clearly illustrates the thermodynamic instability of **7** in comparison to that of the acyclic products. The yield of cyclic acetal **7** could be improved to 34% when the reaction was performed in THF in the presence of MeOH (1.1 equiv.). When the reaction was carried out in pure THF as the solvent, exocyclic enol ether **11** was isolated as a 1.6:1 mixture of isomers in 60% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) $AuCl_3$ (2 mol-%), MeOH, r.t., 2.5 h, then sat. $NaHCO_3$, **7**, 18%; **8**, 15%; **9**, 35%, **10**, 5%; or (a) $AuCl_3$ (2 mol-%), MeOH (1.1 equiv.), r.t., 2.5 h, then sat. $NaHCO_3$, **11**, 34%; (b) $AuCl_3$ (2 mol-%), THF, r.t., 2.5 h, then sat. $NaHCO_3$, 60% (1:1.6).

We next turned our attention to the synthesis of the five-membered cyclic acetals. When we applied the previously optimized reaction conditions, $AuCl_3$ (2 mol-%) in MeOH, to benzyl 6-hydroxy-2-hexynoate (**12a**), cyclic acetal **13a**

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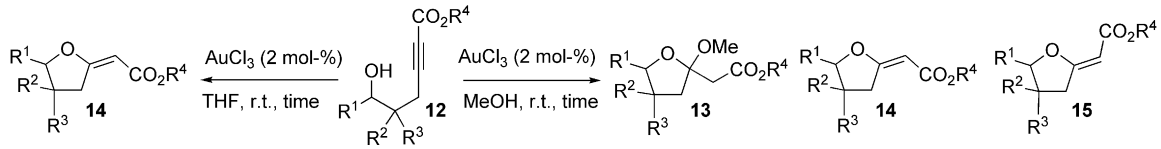
Table 3. Hydroalkoxylation of 6-hydroxy-2-hexynoate derivatives **12**.



Entry	**12**	R^1	R^2	R^3	R^4	Solvent	Time [min]	Product	Yield[a] [%]
1	**12a**	H	H	H	Bn	MeOH	150	**13a** + **14a**	80 + 7
2	**12b**	Tol	H	H	Et	MeOH	150	**13b**[b]	92
3	**12c**	H	$-(CH_2)_4-$		Et	MeOH	150	**13c**	86
4	**12d**	$-(CH_2)_4-$[c]		H	Bn	MeOH	120	**13d**[d]	82
5	**12d**	$-(CH_2)_4-$[c]		H	Bn	MeOH	20	**15d**[e] + **13d**	47 + 30[d]
6	**12a**	H	H	H	Bn	THF	150	**14a**	80
7	**12b**	Tol	H	H	Et	THF	150	**14b**	82
8	**12c**	H	$-(CH_2)_4-$		Et	THF	150	**14c**	93
9	**12d**	$-(CH_2)_4-$[d]		H	Bn	THF	15	**14d**[e]	91

[a] Yield of isolated product based on alkynoate **12**. [b] 1:1.75 mixture of epimers. [c] (*R**,*S**) isomer. [d] 1:1.6 mixture of epimers. [e] Structure unambiguously established by X-ray crystallography. Tol = *p*-MeC_6H_4.

was isolated in good yield together with a small amount of *E*-enol ether **14a** (Table 3, Entry 1). Noteworthy, the *E*-double bond geometry of **14a** is unexpected in view of the commonly accepted mechanism for the Au-catalyzed hydroalkoxylation of triple bonds.[8p,10a] Similarly, other 6-hydroxy-2-hexynoate derivatives **12** gave the corresponding cyclic acetals **13** in good isolated yields as mixtures of epimers at the acetal carbon atom (Table 3, Entries 2–4). Moreover, when we conducted the reaction in THF, corresponding *E*-enol ether **14** was obtained as the major product and as single isomer in good yield (Table 3, Entries 6–9). Interestingly, when we treated **12d** with $AuCl_3$ (2 mol-%) in MeOH for 20 min, *Z*-enol ether **15d** was isolated as the major product along with an epimeric mixture of the corresponding cyclic acetal **13d** (Table 3, Entry 5). This result indicates that expected *Z*-enol ether **15d** is initially formed as the kinetic product, which, depending on the reaction conditions, evolves into thermodynamically more-stable *E*-enol ether **14d** and/or cyclic acetal **13d**. The structures of both enol ethers **14d** and **15d** were confirmed by single-crystal X-ray diffraction analysis (Figure 3).[16]

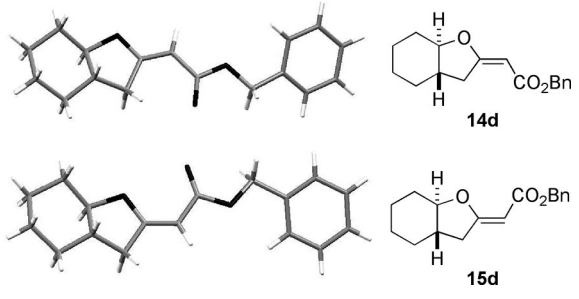


Figure 3. X-ray structure of *E*- and *Z*-enol ethers **14d** and **15d**.

In order to clarify the mechanism of these transformations, we monitored the Au^{III}-catalyzed hydroalkoxylation of **12a** by ^1H NMR spectroscopy by using CD_3OD and $[D_8]$THF as solvents. In CD_3OD we observed rapid consumption of the starting material, by a first-order decay, and formation of *Z*-enol ether **15a** (Figure 4). The concentration of **15a** reached a maximum approximately 5 min after the beginning of the reaction. At this time, only a small amount of cyclic acetal **13a** and *E*-enol ether **14a** had been formed. Intermediate *Z*-enol ether **15a** evolved slowly, following first-order kinetics, to an 8:1 equilibrium mixture of **13a** and **14a**. Analysis of the NMR spectroscopic data showed that the first step of the reaction (formation of **15a**) is approximately 10 times faster than the second step (formation of **13a** and **14a**).

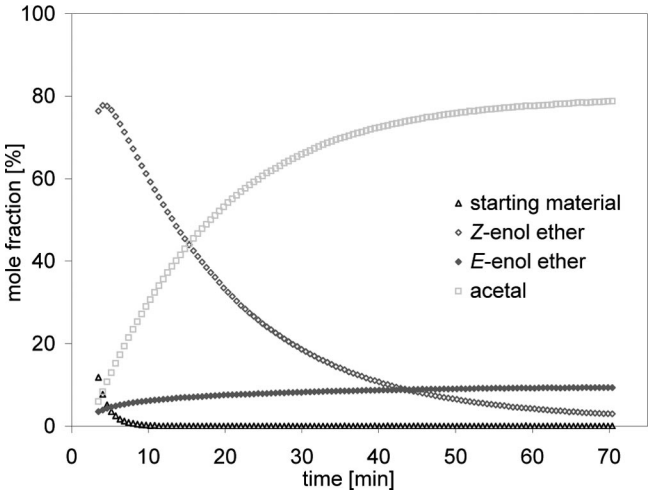


Figure 4. Hydroalkoxylation of **12a** in CD_3OD. Concentration versus reaction time.

In $[D_8]$THF the reaction displayed different kinetic behavior. After an induction period, exclusive formation of *E*-enol ether **14a** was detected. In comparison to the reaction in CD_3OD the rate of reaction is smaller and does not follow first-order kinetics.

These results are in agreement with the following mechanistic proposal (Scheme 5).[17] Coordination of the Au^{III} species to the triple bond (A) promotes the intramolecular *trans* addition of the hydroxy group and leads to *Z*-enol

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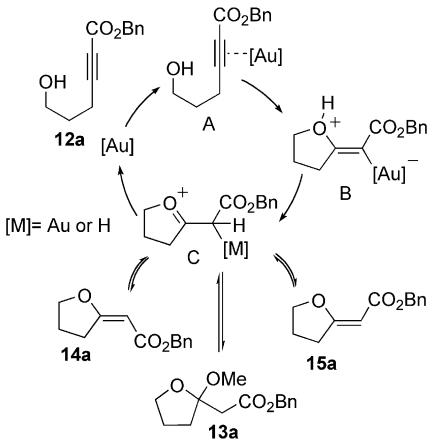
ether **15** after protodemetalation of B. Subsequent formation of acetal **13** and equilibration with enol ethers **14** and **15** might be Au^{III}- or proton-catalyzed (via C).[18]



Scheme 5. Proposed mechanism for the hydroalkoxylation of **12a** in MeOH.

In THF, the situation is less clear as there are at least three mechanistic scenarios that can account for the experimental observation: (a) The initial cyclization occurs with *trans* addition but more slowly and becomes the rate-determining step, which prevents accumulation of *Z*-enol ether **15**. (b) Protodemetalation occurs through a different mechanism, which directly forms *E*-enol ether **14**. (c) The initial cyclization proceeds by *cis* alkoxymetalation.[8j]

Conclusions

In conclusion, the Au^{III}-catalyzed intramolecular hydroalkoxylation of acetylenic esters offers a convenient route for the synthesis of five- and six-membered cyclic acetals, which are common substructures of polyketide natural products. In the case of five-membered rings, exocyclic enol ethers can be accessed selectively by changing the reaction solvent from MeOH to THF. Ongoing work in our laboratory is focused on the application of this new method towards the synthesis of complex pyran-containing polyketide natural products.

Experimental Section

General Procedure for the Synthesis of Cyclic Acetals 2 and 13: A freshly prepared 0.01 M solution of $AuCl_3$ (0.02 equiv. relative to the ω-hydroxyalkynoate) in anhydrous MeOH was added to the substrate, and the reaction mixture was stirred at room temperature until TLC analysis indicated complete conversion of the starting material. The resulting mixture was diluted with petroleum ether (PE) 30–40 and Et_2O (8:2), and quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with water (2×) and brine (2×) and dried with Na_2SO_4. Solvents were removed by rotary evaporation, and the resultant residue was filtered through a small pad of silica gel (previously deactivated with PE 30–40/Et_2O/Et_3N, 7.5:1.5:1) by using a mixture of PE 30–40/Et_2O (8:2) as eluent. Concentration in vacuo afforded the desired cyclic acetal.

Ethyl (2-Methoxytetrahydro-2*H*-pyran-2-yl)acetate (2a): Colorless oil. R_f = 0.52 (PE 40–60/EtOAc, 2:1). IR (neat): $\tilde{\nu}$ = 1031, 1200, 1734 (C=O), 2943 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.18–4.10 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.64–3.59 (m, 2 H, 6′-H), 3.28 (s, 3 H, OCH_3), 2.70 (d, J = 13.5 Hz, 1 H, 2-Hb), 2.52 (d, J = 13.5 Hz, 1 H, 2-Ha), 1.92–1.47 (m, 6 H, 3′,4′,5′-H), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 97.4, 61.6, 60.5, 47.9, 42.4, 33.5, 24.8, 18.5, 14.2 ppm. HRMS (ESI): calcd. for $C_{10}H_{18}O_4Na$ $[M + Na]^+$ 225.1103; found 225.1098.

Benzyl (2-Methoxytetrahydro-2*H*-pyran-2-yl)acetate (2b): Colorless oil. R_f = 0.66 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 697, 737, 1031, 1090, 1198, 1735 (C=O), 2943 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 5 H, Ar-H), 5.16 (d, J = 12.4 Hz, 1 H, C*H*HPh), 5.12 (d, J = 12.4 Hz, 1 H, CH*H*Ph), 3.64–3.61 (m, 2 H, 6′-H), 3.28 (s, 3 H, OCH_3), 2.76 (d, J = 13.5 Hz, 1 H, 2-Hb), 2.61 (d, J = 13.5 Hz, 1 H, 2-Ha), 1.92–1.47 (m, 6 H, 3′,4′,5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 135.9, 128.5, 128.2, 97.5, 66.4, 61.6, 48.0, 42.4, 33.5, 24.8, 18.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1262; found 287.1259.

Ethyl [(2*S,6*S**)-2-Methoxy-6-methyltetrahydro-2*H*-pyran-2-yl]-acetate (2c):** Colorless oil. R_f = 0.29 (PE 40–60/EtOAc, 10:1). IR (neat): $\tilde{\nu}$ = 1003, 1032, 1082, 1735 (C=O), 2937 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.71–3.63 (m, 1 H, 6′-H), 3.26 (s, 3 H, OCH_3), 2.74 (d, J = 13.5 Hz, 1 H, 2-Hb), 2.49 (d, J = 13.5 Hz, 1 H, 2-Ha), 1.91–1.52 (m, 6 H, 3′,4′,5′-H), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.12 (d, J = 6.2 Hz, 3 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 98.0, 66.7, 60.4, 47.8, 42.6, 33.0, 32.2, 21.7, 18.85, 14.17 ppm. HRMS (ESI): calcd. for $C_{11}H_{20}O_4Na$ $[M + Na]^+$ 239.1257; found 239.1254.

Ethyl [(2*S,6*S**)-6-Ethyl-2-methoxytetrahydro-2*H*-pyran-2-yl]-acetate (2d):** Colorless oil. R_f = 0.36 (PE 40–60/EtOAc, 10:1). IR (neat): $\tilde{\nu}$ = 1028, 1086, 1201, 1736 (C=O), 2939 cm^{-1}. ^1H NMR: δ = (400 MHz, $CDCl_3$) 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.50–3.38 (m, 1 H, 6′-H), 3.26 (s, 3 H, OCH_3), 2.75 (d, J = 13.5 Hz, 1 H, 2-Hb), 2.50 (d, J = 13.5 Hz, 1 H, 2-Ha), 1.93–1.39 (m, 8 H, 4,5,6,8-H), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.92 (t, J = 7.5 Hz, 3 H, 8′-H) ppm. ^{13}C NMR: δ = (100 MHz, $CDCl_3$) 170.0, 98.3, 72.3, 60.8, 48.2, 43.1, 33.8, 30.5, 29.4, 19.3, 14.6, 10.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{22}O_4Na$[M + Na]$^+$ 253.1412; found 253.1410.

Ethyl [(2*S,6*R**)-6-Isopropyl-2-methoxytetrahydro-2*H*-pyran-2-yl]-acetate (2e):** Colorless oil. R_f = 0.52 (PE 40–60/EtOAc, 8:2). IR (neat): $\tilde{\nu}$ = 1029, 1095, 1205, 1234, 1309, 1737 (C=O), 2946 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.25 (s, 3 H, OCH_3), 3.25–3.20 (m, 1 H, 6′-H), 2.70 (d, J = 13.5 Hz, 1 H, 2-Hb), 2.52 (d, J = 13.5 Hz, 1 H, 2-Ha), 1.89–1.55 (m, 7 H, 3′,4′,5′,7′-H), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.93 (d, J = 6.6 Hz, 3 H, 8′-H), 0.89 (d, J = 6.9 Hz, 3 H, 9′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 97.9, 75.3, 60.4, 47.8, 42.6, 33.4, 32.9, 27.1, 18.9, 18.5, 18.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{24}O_4Na$ $[M + Na]^+$ 267.1563; found 267.1567.

Ethyl [(2*S,6*R**)-6-Benzyl-2-methoxytetrahydro-2*H*-pyran-2-yl]-acetate (2f):** Colorless oil. R_f = 0.71 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 700, 1030, 1079, 1198, 1234, 1736 (C=O), 2942 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.17 (m, 5 H, Ar-H), 4.14 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.74–3.67 (m, 1 H, 6′-H), 3.04 (s, 3 H, OCH_3), 2.78 (dd, J = 13.4, 7.5 Hz, 1 H, 7′-Ha), 2.69 (d, J =

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13.5 Hz, 1 H, 2-Hb), 2.65 (dd, *J* = 13.9, 6.2 Hz, 1 H, 7′-Hb) 2.52 (d, *J* = 13.9 Hz, 1 H, 2a-H), 1.91–1.56 (m, 6 H, 3′,4′,5′-H), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): *δ* = 169.5, 138.8, 129.5, 128.0, 126.0, 98.1, 71.8, 60.3, 47.7, 42.6, 42.5, 33.2, 30.1, 18.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{24}O_4Na$ [M + Na]$^+$ 315.1570; found 315.1570.

Ethyl [(2*S,6*R**)-2-Methoxy-6-vinyltetrahydro-2*H*-pyran-2-yl]acetate (2g):** Colorless oil. R_f = 0.64 (PE 30–40/Et$_2$O, 1:1). IR (neat): ṽ = 1021, 1092, 1201, 1311, 1735 (C=O), 2943 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 5.82 (ddd, *J* = 17.1, 10.7, 6.1 Hz, 1 H, 7′-H), 5.24 (d, *J* = 17.2 Hz, 1 H, 8-H$_{trans'}$), 5.09 (d, *J* = 10.6 Hz, 1 H, 8-H$_{cis'}$), 4.14 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 4.06–4.01 (m, 1 H, 6-H′), 3.28 (s, 3 H, OCH$_3$), 2.78 (d, *J* = 13.5 Hz, 1 H, 2-Hb), 2.54 (d, *J* = 13.5 Hz, 1 H, 2-Ha), 1.95–1.62 (m, 6 H, 3′,4′,5′-H), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): *δ* = 169.5, 138.9, 114.9, 98.1, 71.4, 60.5, 48.0, 42.5, 33.0, 30.4, 18.6, 14.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{20}O_4Na$ [M + Na]$^+$ 251.1256; found 251.1254.

Ethyl [(2*S,6*R**)-2-Methoxy-6-phenyltetrahydro-2*H*-pyran-2-yl]-acetate (2h):** Colorless oil. R_f = 0.61 (PE 30–40/Et$_2$O, 1:1). IR (neat): ṽ = 698, 1026, 1091, 1206, 1234, 1734 (C=O), 2943 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 7.37–7.25 (m, 5 H, Ar-H), 4.61 (dd, *J* = 11.7, 2.2 Hz, 1 H, 6′-H), 4.18 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 3.32 (s, 3 H, OCH$_3$), 2.80 (d, *J* = 13.9 Hz, 1 H, 2-Hb), 2.67 (d, *J* = 13.5 Hz, 1 H, 2-Ha), 2.06–1.45 (m, 6 H, 3′,4′,5′-H), 1.29 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): *δ* = 169.6, 142.7, 128.3, 127.4, 126.0, 98.5, 72.8, 60.5, 48.1, 42.5, 33.0, 32.8, 19.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_4Na$ [M + Na]$^+$ 301.1415; found 301.1410.

Benzyl (2-Allyloxytetrahydro-2*H*-pyran-2-yl)acetate (2i): Colorless oil. R_f = 0.69 (PE 40–60/EtOAc, 1:1). IR (neat): ṽ = 697, 737, 1025, 1084, 1197, 1225, 1736 (C=O), 2943 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 7.36–7.31 (m, 5 H, Ar-H), 5.92 (ddd, *J* = 17.2, 10.4, 5.1 Hz, 1 H, C*H*=), 5.30 (dd, *J* = 17.2, 1.5 Hz, 1 H, =CH*H*), 5.17–5.10 (m, 3 H, =C*H*H, CH$_2$Ph), 4.06 (d, *J* = 5.1 Hz, 2 H, C*H*$_2$-Allyl), 3.66–3.63 (m, 2 H, H-6′), 2.75 (d, *J* = 13.9 Hz, 1 H, H-2a), 2.65 (d, *J* = 13.9 Hz, 1 H, H-2b), 1.98–1.47 (m, 6 H, H-3′,4′,5′) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) = 169.2, 135.9, 134.8, 128.4, 128.1, 115.8, 97.6, 66.3, 61.8, 61.2, 43.3, 33.6, 24.8, 18.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{22}O_4Na$ [M + Na]$^+$ 313.1421; found 313.1410.

Benzyl (2-Hydroxytetrahydro-2*H*-pyran-2-yl)acetate (2j): Colorless oil. R_f = 0.48 (PE 40–60/EtOAc, 1:1). IR (neat): ṽ = 698, 1014, 1157, 1204, 1717 (C=O), 2945, 3478 (OH) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) = 7.38–7.30 (m, 5 H, Ar-H), 5.22 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 5.15 (d, *J* = 12.4 Hz, 1 H, CH*H*Ph), 4.68 (d, *J* = 2.2 Hz, 1 H, OH), 3.98 (td, *J* = 10.9, 4.1 Hz, 1 H, H-6′a), 3.64–3.60 (m, 1 H, H-6′b), 2.70 (d, *J* = 15.7 Hz, 1 H, H-2b), 2.59 (d, *J* = 15.4 Hz, 1 H, H-2a), 1.96–1.85 (m, 1 H, H-5′a), 1.79–1.74 (m, 1 H, H-5′b), 1.70–1.42 (m, 4 H, H-3′,4′) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) = 172.1, 135.4, 128.6, 128.3, 128.2, 94.6, 66.6, 61.3, 45.2, 34.7, 25.0, 18.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_4Na$ [M + Na]$^+$ 273.1103; found 273.1108. The spectroscopic data match those reported previously.[19]

Ethyl [2-Methoxy-4-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-2-yl]acetate (2k): Colorless oil. R_f = 0.43 (PE 40–60/EtOAc, 7:3). IR (neat): ṽ = 2940 (w), 1733 (s), 1612 (m), 1513 (s), 1464 (m), 1364 (s), 1315 (m), 1303 (m), 1246 (s), 1172 (m), 1142 (m), 1098 (s), 1072 (s), 1032 (s), 980 (m), 816 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* = 7.25 (2 H, ArH), 6.82 (2 H, ArH), 4.48 (d, *J* = 11.3 Hz, 1 H, C*H*H-4-MeOC$_6$H$_4$), 4.46 (d, *J* = 11.3 Hz, 1 H, CH*H*-4-MeOC$_6$H$_4$), 4.16 (m, 2 H, OC*H*$_2$CH$_3$), 3.88–3.72 (m, 2 H, H-4′, H-6′), 3.79 (s, 3 H, CH$_3$O), 3.62–3.53 (m, 1 H, H-6′), 3.23 (s, 3 H, CH$_3$O), 2.76 (d, *J* = 13.9 Hz, 1 H, H-2), 2.59 (d, *J* = 13.5 Hz, 1 H, H-2), 2.43 (ddd, *J* = 12.8, 4.4, 1.8 Hz, 1 H, H-3′), 1.94 (ddd, *J* = 12.8, 4.2, 2.0 Hz, 1 H, H-5′), 1.65–1.49 (m, 2 H, H-3′, H-5′), 1.27 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* = 169.5, 159.5, 131.2, 129.6, 114.2, 99.8, 71.5, 70.0, 61.0, 60.2, 55.7, 48.3, 42.5, 40.5, 32.2, 14.6. HRMS (ESI): calcd. [M + Na]$^+$ calculated for $C_{18}H_{26}O_6Na$: 361.1651; found 361.1660.

Methyl {4-Hydroxy-2-methoxy-6-[(4-methoxybenzyloxy)methyl]-tetrahydro-2*H*-pyran-2-yl}acetate (2l): Colorless oil. R_f = 0.50 (PE 40–60/EtOAc, 1:1). $[a]_D^{25}$ = –42 (*c* = 11, CHCl$_3$). ^{1}H NMR (500 MHz, C$_6$D$_6$): *δ* = 7.30 (d, *J* = 6.6 Hz, 2 H, ArH), 6.89 (d, *J* = 6.6 Hz, 2 H, ArH), 4.46 (s, 2 H, H-9), 4.25–4.18 (m, 1 H, H-6′), 4.15–4.08 (m, 1 H, H-4′), 3.92 (d, *J* = 9.6 Hz, 1 H, OH), 3.49 (dd, *J* = 10.2, 6.2 Hz, 1 H, H-7a′), 3.39 (s, 3 H, ArOMe), 3.37 (dd, *J* = 10.2, 3.8 Hz, 1 H, H-7b′), 3.34 (s, 3 H, CO$_2$Me), 3.11 (s, 3 H, OMe), 2.68 (d, *J* = 13.9 Hz, 1 H, H-2a), 2.47 (d, *J* = 13.9 Hz, 1 H, H-2b), 2.32 (dt, *J* = 14.4, 2.5 Hz, 1 H, H-3ax′), 1.88 (dd, *J* = 14.4, 3.6 Hz, 1 H, H-3eq′), 1.82 (dq, *J* = 13.4, 3.1 Hz, 1 H, H-5eq′), 1.41 (td, *J* = 13.4, 2.8 Hz, 1 H, H-5ax′) ppm. ^{13}C NMR (125 MHz, C$_6$D$_6$): *δ* = 168.8, 159.7, 131.0, 129.3, 114.0, 100.1, 73.2, 73.1, 65.6, 64.1, 54.7, 51.2, 47.7, 42.1, 38.6, 34.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}O_7Na$ [M + Na]$^+$ 377.1576; found 377.1593.

Methyl (4-Hydroxy-2-methoxy-6-vinyltetrahydro-2*H*-pyran-2-yl)-acetate (2m): Colorless oil. R_f = 0.48 (PE 40–60/EtOAc, 1:1). $[a]_D^{25}$ = –41 (*c* = 9, CHCl$_3$). ^{1}H NMR (400 MHz, C$_6$D$_6$): *δ* = 5.85 (ddd, *J* = 17.0, 10.5, 5.3 Hz, 1 H, H-8′), 5.30 (d, *J* = 17.0 Hz, 1 H, H-7a′), 5.07 (d, *J* = 10.5 Hz, 1 H, H-7b′), 4.45–4.41 (m, 1 H, H-6′), 4.09–4.06 (m, 1 H, H-4′), 3.89 (d, *J* = 9.4 Hz, 1 H, OH), 3.36 (s, 3 H, CO$_2$Me), 3.02 (s, 3 H, OMe), 2.64 (d, *J* = 13.9 Hz, 1 H, H-2a), 2.46 (d, *J* = 13.9 Hz, 1 H, H-2b), 2.29 (dt, *J* = 14.5, 2.3 Hz, 1 H, H-3ax′), 1.87 (dd, *J* = 14.5, 3.7 Hz, 1 H, H-3eq′), 1.88–1.86 (m, 1 H, H-5eq′), 1.37 (td, *J* = 13.7, 2.5 Hz, 1 H, H-5ax′) ppm. ^{13}C NMR (125 MHz, C$_6$D$_6$): *δ* = 168.5, 138.6, 114.2, 99.9, 66.1, 63.9, 50.9, 47.4, 41.9, 38.2, 37.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{18}O_5Na$ [M + Na]$^+$ 253.1052; found 253.1056.

(*Z*)-Ethyl {8-(*tert*-Butyldimethylsilyloxy)-2,3-dimethoxy-2,3-dimethyldihydro-2*H*-pyrano[4,3-*b*][1,4]dioxin-7(3*H*,8*H*,8a*H*)-ylidene}-ethanoate (4): White solid. M.p. 99–102 °C. R_f = 0.43 (PE 40–60/EtOAc, 4:1). $[a]_D^{25}$ = –205 (*c* = 6.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) = 5.09 (s, 1 H, CH=), 4.46 (td, *J* = 10.6, 5.6 Hz, 1 H, H-4a), 4.35 (dd, *J* = 10.3, 5.6 Hz, 1 H, H-5$_{eq}$), 4.17–4.10 (m, 3 H, OCH$_2$, H-8), 3.69 (t, *J* = 10.6 Hz, 1 H, H-5$_{ax}$), 3.58 (dd, *J* = 10.2, 2.7 Hz, 1 H, H-8a), 3.24 (s, 3 H, OCH$_3$), 3.22 (s, 3 H, OCH$_3$), 1.27 (s, 3 H, CH$_3$), 1.26 (s, 3 H, CH$_3$), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 0.87 (s, 9 H, *t*BuSi), 0.11 [s, 3 H, Si(CH$_3$)$_2$], 0.05 [s, 3 H, Si(CH$_3$)$_2$] ppm. ^{13}C NMR (125 MHz, CDCl$_3$) = 166.1, 165.2, 101.8, 100.3, 99.7, 71.9, 70.6, 70.1, 61.3, 60.2, 48.3, 48.1, 25.9, 18.6, 18.1, 18.0, 14.7, –4.8, –4.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{39}O_8Si$ [M + H]$^+$ 447.2330; found 447.2327. $C_{21}H_{38}O_8Si$ (446.62): calcd. C 56.48, H 8.58; found C 56.09, H 8.66.

Ethyl 2-{(2*R*,3*R*,4a*S*,7*R*,8*S*,8a*R*)-8-(*tert*-Butyldimethylsilyloxy)-2,3-dimethoxy-2,3-dimethylhexahydro-2*H*-pyrano[4,3-*b*][1,4]dioxin-7-yl}ethanoate (5): White solid. M.p. 92–95 °C. R_f = 0.35 (PE 40–60/EtOAc, 4:1). $[a]_D^{25}$ = –81 (*c* = 6.5, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) = 4.16–4.10 (m, 2 H, OC*H*$_2$CH$_3$), 4.06 (td, *J* = 10.3, 5.0 Hz, 1 H, H-4a), 3.93 (dd, *J* = 2.6, 0.7 Hz, 1 H, H-8), 3.89 (dd, *J* = 10.6, 5.0 Hz, 1 H, H-5$_{eq}$), 3.82 (ddd, *J* = 7.0, 6.3, 0.7 Hz, 1 H, H-7), 3.58 (dd, *J* = 10.3, 2.6 Hz, 1 H, H-8a), 3.33 (t, *J* = 10.6 Hz, 1 H, H-5$_{ax}$), 3.24 (s, 3 H, OCH$_3$), 3.18 (s, 3 H, OCH$_3$), 2.62 (dd, *J* = 16.2, 7.1 Hz, 1 H, C*H*$_2$CO$_2$), 2.55 (dd, *J* = 16.2, 6.1 Hz, 1 H, C*H*$_2$CO$_2$), 1.27 (s, 3 H, CH$_3$), 1.25 (t, *J* = 16.2, 7.1 Hz, 3 H,

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OCH_2CH_3), 1.23 (s, 3 H, CH_3), 0.91 (s, 9 H, *t*BuSi), 0.14 [s, 3 H, $Si(CH_3)_2$], 0.04 [s, 3 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 170.3, 99.0, 98.2, 75.3, 71.4, 69.4, 67.2, 61.7, 59.5, 46.8, 46.4, 35.6, 25.0, 17.5, 16.7, 16.6, 13.2, –5.3, –5.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{41}O_8Si$ $[M + H]^+$ 449.2571; found 449.2564. $C_{21}H_{40}O_8Si$ (448.63): calcd. C 56.22, H 8.99; found C 56.17, H 8.62.

Benzyl 2-(2-Methoxyoxepan-2-yl)acetate (7): Colorless oil. R_f = 0.68 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 1065, 1099, 1187, 1736 (C=O), 2929 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.31 (m, 5 H, Ar-H), 5.13 (s, 2 H, OCH_2Ph), 3.76–3.69 (m, 1 H, H-7′a), 3.59–3.54 (m, 1 H, H-7′b), 3.25 (s, 3 H, OCH_3), 2.76 (d, *J* = 13.5 Hz, 1 H, H-2a), 2.65 (d, *J* = 13.9 Hz, 1 H, H-2b), 2.43 (dd, *J* = 15.2, 8.2 Hz, 1 H, H-3′a), 1.83–1.79 (m, 1 H, H-3′b), 1.70–1.27 (m, 6 H, H-4′,5′,6′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 169.4, 135.9, 128.5, 128.2, 128.1, 102.6, 66.3, 62.0, 48.5, 40.7, 37.8, 30.5, 29.7, 22.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_4Na$ $[M + Na]^+$ 301.1412; found 301.1410.

(*Z*)-Benzyl 8-Hydroxy-3-methoxyoct-2-enoate (8): Colorless oil. R_f = 0.34 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 1048, 1131, 1616 (C=C), 1710 (C=O), 2937, 3378 (OH) cm^{-1}. ^1H NMR = (400 MHz, $CDCl_3$) 7.37–7.31 (m, 5 H, Ar-H), 5.13 (s, 2 H, OCH_2Ph), 5.05 (s, 1 H, H-2), 3.63–3.61 (m, 5 H, H-8, OCH_3), 2.77 (t, *J* = 7.7 Hz, 2 H, H-4), 1.63–1.56 (m, 4 H, H-5, H-7), 1.44–1.36 (m, 2 H, H-6), 1.26 (br. s, 1 H, OH) ppm. ^{13}C NMR = (100 MHz, $CDCl_3$) 171.5, 168.4, 137.1, 128.5, 128.1, 128.0, 90.3, 65.3, 62.9, 55.5, 32.5, 31.9, 27.6, 25.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_4Na$ $[M + Na]^+$ 301.1421; found 301.1410.

Benzyl 8-Hydroxy-3,3-dimethoxyoctanoate (9): Colorless oil. R_f = 0.32 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 697, 746, 1047, 1173, 1736 (C=O), 2938, 3436 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.36–7.33 (m, 5 H, Ar-H), 5.13 (s, 2 H, OCH_2Ph), 3.60(t, 2 H, *J* = 6.2 Hz, H-8), 3.20 (m, 6 H, 2 × OCH_3), 2.71 (s, 2 H, H-2), 1.75–1.72 (m, 2 H), 1.54–1.52 (m, 2 H), 1.41–1.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 169.2, 135.8, 128.5, 128.2, 128.2, 101.8, 66.4, 62.8, 48.1, 38.6, 33.5, 32.5, 25.8, 23.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{26}O_5Na$ $[M + Na]^+$ 333.1674; found 333.1672.

Benzyl 8-Hydroxy-3-oxooctanoate (10): Colorless oil. R_f = 0.31 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 699, 1057, 1263, 1316, 1713 (C=O), 1741 (C=O), 2936, 3442 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.33 (m, 5 H, Ar-H), 5.18 (s, 2 H, OCH_2Ph), 3.65–3.60 (m, 2 H, H-8), 3.48 (s, 2 H, H-2), 2.53 (t, *J* = 7.1 Hz, 2 H, H-4), 1.65–1.52 (m, 4 H, H-5,7), 1.38–1.31 (m, 2 H, H-6), 1.25 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 202.3, 160.9, 131.1, 128.6, 128.5, 128.4, 67.1, 62.6, 49.3, 42.9, 37.4, 25.1, 23.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1258; found 287.1254.

Benzyl (2-Methoxytetrahydrofuran-2-yl)acetate (13a): Colorless oil. R_f = 0.57 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 697, 737, 1041, 1204, 1735 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.32 (m, 5 H, Ar-H), 5.14 (d, *J* = 2.6 Hz, 2 H, CH_2Ph), 3.87 (m, 2 H, H-5′), 3.24 (s, 3 H, OCH_3), 3.02 (d, *J* = 14.3 Hz, 1 H, H-2a), 2.70 (d, *J* = 14.3 Hz, 1 H, H-2b), 2.13–2.07 (m, 2 H, H-3′), 2.04 (m, 1 H, H-4′a), 1.88 (m, 1 H, H-4′b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 169.5, 135.9, 128.5, 128.2, 106.8, 67.8, 66.4, 48.6, 40.2, 36.2, 24.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_4Na$ $[M + Na]^+$ 273.1096; found 273.1097.

Benzyl (2-Methoxy-5-*p*-tolyltetrahydrofuran-2-yl)acetate (13b): Colorless oil. R_f = 0.44 (PE 40–60/Et_2O, 8:2). IR (neat): $\tilde{\nu}$ = 816, 1032, 1111, 1212, 1735 (C=O), 2978 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.28–7.14 (m, 10 H, ArH), 5.05–4.99 (m, 2 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 3.04 (d, *J* = 13.9 Hz, 1 H), 3.03 (d, *J* = 14.3 Hz, 1 H), 2.81 (d, *J* = 14.3 Hz, 1 H), 2.72 (d, *J* = 14.6 Hz, 1 H), 2.20–2.12 (m, 8 H), 2.34 (br. s, 6 H), 1.89–1.80 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 169.7, 169.6, 139.3, 139.1, 137.2, 137.1, 129.0, 126.5, 125.8, 107.3, 107.1, 83.3, 80.1, 60.5, 49.0, 48.8, 40.8, 40.3, 38.0, 36.6, 33.6, 21.1, 14.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_4Na$ $[M + Na]^+$ 301.1416; found 301.1425.

Ethyl (3-Methoxy-2-oxaspiro[4.5]decan-3-yl)acetate (13c): Colorless oil. R_f = 0.37 (PE 40–60/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1034, 1119, 1225, 1641, 1703, 1737 (C=O), 2925 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 4.14 (q, *J* = 7.5 Hz, 2 H, OCH_2CH_3), 3.67 (d, *J* = 8.4 Hz, 1 H, H-1′a), 3.55 (d, *J* = 8.4 Hz, 1 H, H-1′b), 3.22 (s, 3 H, OCH_3), 2.93 (d, *J* = 13.9 Hz, 1 H, H-2a), 2.57 (d, *J* = 14.0 Hz, 1 H, H-2b), 2.06 (d, *J* = 13.5 Hz, 1 H, H-4′a), 1.93 (d, *J* = 13.5 Hz, 1 H, H-4′a), 1.58–1.31 (m, 10 H), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 169.6, 107.3, 77.8, 60.5, 48.2, 43.2, 40.6, 37.9, 36.6, 25.7, 24.2, 23.6, 23.4, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1572; found 279.1567.

Benzyl [(3a*R,7a*S**)-2-Methoxyoctahydrobenzofuran-2-yl]acetate (13d):** Colorless oil. R_f = 0.62 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 698, 980, 1034, 1073, 1215, 1456, 1736 (C=O), 2936 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.32 (m, 5 H, Ar-H), 5.16 (d, 1 H, *J* = 12.4 Hz, OCH_2Ph), 5.12 (d, 1 H, *J* = 12.1 Hz, OCH_2Ph), 3.32–3.29 (m, 1 H, H-7a′), 3.31 (s, 3 H, OCH_3), 2.90 (d, 1 H, *J* = 13.5 Hz, H-2a), 2.72 (d, *J* = 13.5 Hz, 1 H, H-2b), 2.55 (dd, *J* = 12.8, 7.7 Hz, 1 H, H-3′a), 2.07–2.03 (m, 1 H, H-3′b), 1.83–1.78 (m, 2 H), 1.68–1.59 (m, 3 H), 1.37–1.10 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 169.5, 135.8, 128.5, 128.3, 128.2, 106.6, 82.2, 66.4, 49.3, 45.4, 42.1, 41.5, 30.6, 28.6, 25.6, 24.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_4Na$ $[M + Na]^+$ 327.1572; found 327.1568.

General Procedure for the Synthesis of Cyclic Enol Ethers: For the synthesis of cyclic enol ethers **11**, **14**, and **15** THF was used as solvent following the same procedure described above.

(*E*/*Z*)-Benzyl (Oxepan-2-ylidene)acetate (11): Colorless oil. R_f = 0.66 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 696, 734, 1053, 1116, 1621 (C=C), 1706 (C=O), 2929 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.29 (m, 10 H), 5.30 (s, 1 H), 5.13–5.10 (m, 4 H), 5.09 (s, 1 H), 4.14 (m, 2 H), 3.79 (m, 2 H), 3.17 (m, 2 H), 2.94 (m, 2 H), 1.75–1.44 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 177.9, 175.5, 168.1, 167.6, 136.9, 136.7, 128.5, 128.4, 128.2, 95.5, 91.4, 69.2, 66.1, 65.2, 65.0, 30.5, 29.9, 29.2, 27.8, 26.9, 26.3, 24.6, 23.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 296.1154; found 269.1159.

(*E*)-Benzyl Dihydrofuran-2(3*H*)-ylideneacetate (14a): Colorless oil. R_f = 0.54 (PE 40–60/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 1043, 1107, 1641, 1702 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.38–7.27 (m, 5 H, Ar-H), 5.38 (s, 1 H, H-2), 5.14 (s, 2 H, CH_2Ph), 4.23 (t, *J* = 7.0 Hz, 2 H, H-5′), 3.12 (td, *J* = 7.8, 1.7 Hz, 2 H, H-3′), 2.09 (quint, *J* = 7.3 Hz, 2 H, H-4′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 177.2, 168.4, 136.9, 128.5, 128.0, 127.8, 89.3, 71.9, 65.1, 30.3, 23.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{14}O_3Na$ $[M + Na]^+$ 241.0847; found 241.0835.

(*E*)-Ethyl [5-(4-Tolyl)dihydrofuran-2(3*H*)-ylidene]acetate (14b): Colorless oil. R_f = 0.44 (PE 40–60/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 816, 1045, 1103, 1349, 1371, 1638 (C=C), 1700 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.20 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.17 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.41 (br. s, 1 H, H-2), 5.35 (t, *J* = 7.5 Hz, 1 H, H-5′), 4.16 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 3.41 (1 H, *J* = 18.3, 8.7, 4.3, 1.2 Hz, dddd, H-3′a), 3.08 (1 H, *J* = 18.3, 9.2, 2.0 Hz, dtd, H-3′b), 2.53–2.45 (m, 1 H, H-4′a), 2.35 (s, 3 H, Ar-CH_3), 2.03 (dq,

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J = 12.6, 8.7 Hz, 1 H, H-4′b), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 176.1, 168.6, 138.1, 136.8, 129.3, 125.6, 89.9, 86.9, 59.2, 32.3, 30.6, 21.1, 14.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 269.1154; found 269.1160.

(*E*)-Ethyl (2-Oxaspiro[4.5]decan-3-ylidene)acetate (14c): Colorless oil. R_f = 0.38 (PE 40–60/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 821, 1049, 1083, 1097, 1118, 1639 (C=C), 1701 (C=O), 2927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 5.24 (br. s, 1 H, H-2), 4.10 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.91 (s, 2 H, H-1′), 2.92 (d, *J* = 1.5 Hz, 2 H, H-4′), 1.54–1.40 (m, 10 H), 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 177.6, 168.6, 90.4, 80.9, 59.1, 42.4, 41.8, 34.6, 25.7, 23.3, 14.5 (OCH_2CH_3) ppm. HRMS (ESI): calcd. for $C_{13}H_{21}O_3$ $[M + H]^+$ 225.1491; found 225.1492.

(*E*)-Benzyl [(3a*R,7a*R**)-Hexahydro-1-benzofuran-2(3*H*)-ylidene]-acetate (14d):** White solid. M.p. 70–72 °C. R_f = 0.42 (PE 40–60/Et_2O, 8:2). IR (neat): $\tilde{\nu}$ = 1040, 1075, 1109, 1138, 1346, 1637 (C=C), 1705 (C=O), 2936 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.37–7.28 (m, 5 H, Ar-H), 5.39 (d, 1 H, *J* = 1.1 Hz, H-2), 5.13 (s, 2 H, CH_2Ph), 3.55–3.51 (m, 1 H, H-7a′), 2.73 (ddd, *J* = 17.4, 12.8, 2.3 Hz, 1 H, H-3′a), 2.24–2.20 (m, 1 H, H-3′b), 2.02–2.00 (m, 1 H), 1.91–1.89 (m, 1 H), 1.78–1.71 (m, 2 H), 1.63–1.54 (m, 1 H), 1.46 (ddd, *J* = 23.7, 11.7, 3.7 Hz, 1 H), 1.36–1.19 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) = 176.3, 168.2, 136.8, 128.5, 127.9, 127.8, 90.6, 86.9, 65.1, 44.3, 36.4, 30.3, 28.3, 25.3, 24.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{20}O_3Na$ $[M + Na]^+$ 295.1310; found 295.1299.

(*Z*)-Benzyl [(3a*R,7a*R**)-Hexahydro-1-benzofuran-2(3*H*)-ylidene]-acetate (15d):** White solid. M.p. 101–103 °C. R_f = 0.42 (PE 40–60/Et_2O, 8:2). IR (neat): $\tilde{\nu}$ = 731, 1028, 1039, 1197, 1213, 1648 (C=C), 1717 (C=O), 2935 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.39–7.26 (m, 5 H, Ar-H), 5.16 (d, *J* = 12.4 Hz, 1 H, OC*H*HPh), 5.12 (d, *J* = 12.8 Hz, 1 H, OCH*H*Ph), 4.97 (d, *J* = 1.5 Hz, 1 H, H-2), 3.72 (td, *J* = 11.0, 3.7 Hz, 1 H, H-7a′), 2.64 (dd, *J* = 15.7, 6.2 Hz, 1 H, H-3′a), 2.40–2.33 (m, 2 H, H3′b, H-3a′), 2.00–1.89 (m, 2 H). 1.78–1.75 (m, 1 H), 1.69–1.53 (m, 2 H), 1.39–1.15 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.1, 165.4, 136.9, 128.3, 128.0, 127.7, 89.3, 88.9, 65.0, 43.9, 38.2, 30.5, 28.3, 25.2, 24.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{20}O_3Na$ $[M + Na]^+$ 295.1310; found 295.1319.

NMR Spectroscopic Experiments: Compound **4b** (70.0 mg, 0.321 mmol) was dissolved in $[D_4]$MeOH (892 μL) resulting in a 0.333 M solution. Of this solution, a 750 μL aliquot was transferred to a dry NMR tube and an initial ^1H NMR spectrum was recorded. A 0.02 M solution of $AuCl_3$ in $[D_4]$MeOH (250 μL; prepared from 15.3 mg of $AuCl_3$ and 2.52 mL of $[D_4]$MeOH) was added and the NMR tube was inverted repeatedly to achieve mixing. The NMR tube was returned to the spectrometer and spectra (single pulse) were recorded in 33.7 s intervals over a period of approx. 60 min. Well-resolved resonances of the starting material and the products were integrated and normalized relative to the integral of all aromatic signals (the absolute value of this integral changed less than 3% between the first and last spectrum). The thus derived concentrations of the components of the reaction mixture were plotted against time for visualization. The experiment in $[D_8]$THF was carried out as described above, except that $[D_8]$THF was used as the solvent: 750 μL of 0.333 M benzyl 6-hydroxyhex-2-ynoate (60.3 mg in 769 μL $[D_8]$THF), 250 μL of 0.02 M $AuCl_3$ (4.4 mg in 725 μL $[D_8]$THF).

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