Stereoselective Synthesis of Heterocyclic Zinc Reagents via a Nickel-Catalyzed Radical Cyclization

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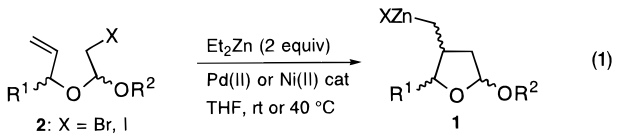
Unsaturated iodo or bromo acetals of type **2** undergo a smooth cyclization mediated by diethylzinc (2 equiv) and $Ni(acac)_2$ as catalyst (2−5 mol %). These cyclizations proceed via a radical mechanism affording a (tetrahydrofuranylmethyl)zinc halide of type **1**, which can be reacted with various electrophiles after a transmetalation with CuCN·2LiCl. High stereoselectivities are usually observed in the ring closures, especially if monocyclic cyclization precursors are used. In these cases, bicyclic products of the *endo*-configuration are obtained with over 94% diastereoselectivity. The synthetic method has been extended to the preparation of a nitrogen heterocycle and over 98% pure *trans*-4,5-disubstituted γ-butyrolactones. A short enantioselective synthesis of (−)-methylenolactocine (**3**) using the radical cyclization and a novel oxidation of α-silyl zinc peroxide as a key step is also described.

Introduction

Polyfunctional organozincs are versatile intermediates that react with various electrophiles in the presence of the appropriate transition metal catalyst.[1] These organometallics can be prepared by the direct insertion of zinc to an organic halide[2] or by a halogen−zinc exchange reaction mediated by diethylzinc.[3] This second preparation method could be improved by the addition of transition metal salts of Cu(I),[4] Pd(II),[5] or Mn(II).[6] These transition metal catalysts induce radical processes[7] that can be used to prepare substituted cyclopentanes from acyclic precursors with excellent stereoselectivity.[5] Herein, we wish to report the extension of this reaction to the stereoselective preparation of tetrahydrofurans of type **1** starting from the unsaturated iodo or bromo acetals **2** (eq 1). Application to a stereoselective synthesis of disubstituted butyrolactones and to a formal synthesis of antitumor antibiotic (−)-methylenolactocin (**3**) will also be described.[1,8]



(1)

Results

The synthesis of the cyclization precursors was readily achieved by reacting vinylic ethers **4** with allylic alcohols **5** in the presence of *N*-iodosuccinimide (NIS) (Scheme 1).[9] The resulting unsaturated iodo acetals **6a**−**c** were obtained in 70−85% yield. Cyclic alkenyl ethers like 2,3-dihydrofuran (**4d**) and 2,3-dihydro-2*H*-pyran (**4a**) afford the cyclic *trans*-iodo acetals **6d** and **6e** in, respectively, 61% and 75% yield with the NIS procedure. By using substituted allylic alcohols like **5b** or **5c**, substituted acetals like **6f**−**h** are obtained as 1:1 mixtures of diastereoisomers (Scheme 1). The iodo acetals **6** have a limited stability and decompose slowly at rt; therefore, the synthesis of more stable cyclization precursors like the corresponding bromo acetals **7** was envisioned. Thus, the treatment of alkenyl ethers with allylic alcohols in the presence of NBS[10] in CH_2Cl_2 (0 °C to rt) affords the desired unsaturated bromo acetals **7a**−**e** in good yields (Scheme 2).

The preparation of unsatured alkyl iodide **8** was performed by opening cyclohexene oxide[11] with the magnesium amide **9** (THF, rt, 4 h; 69% yield), affording the intermediate amino alcohol **10**, which was converted to the corresponding *cis*-alkyl iodide **8** using 2 DCC·MeI[12] (1.8 equiv, THF, 3d, 40 °C, 68% yield). The cyclization of 5-hexenyl iodides with Et_2Zn was best performed with dichloro (1,1′-bis(diphenylphosphino)ferrocene)palladium-(II) ($PdCl_2$(dppf))[13] as catalyst. We observed less effective reactions with substrates **6** and **7**, but a far better reaction was achieved with $Ni(acac)_2$ (2 mol %) as catalyst. Under these conditions, the cyclization of the iodo acetals **6** is completed within 1 h at rt furnishing

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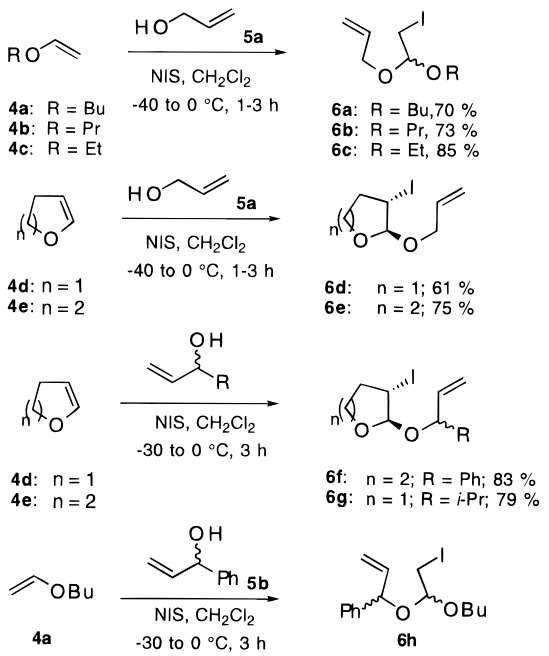
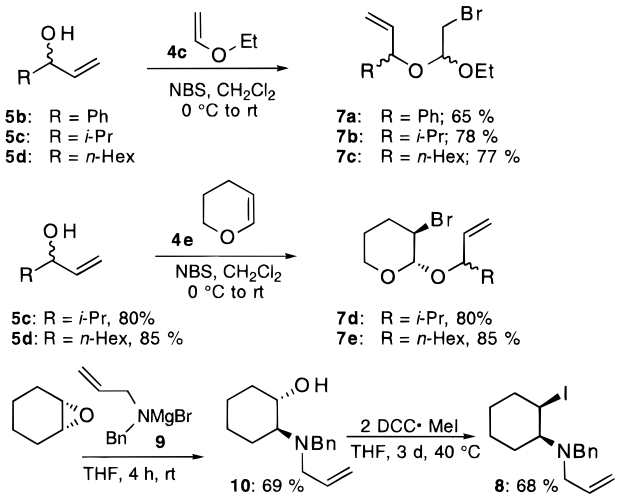
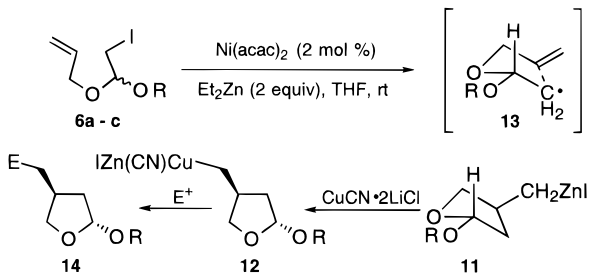
Scheme 1



Scheme 2



Scheme 3



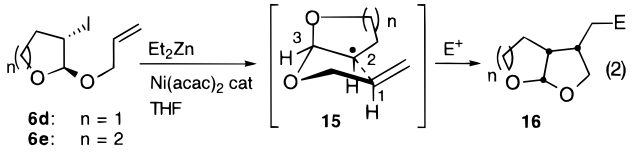
(tetrahydrofuranylmethyl)zinc iodides **11**, which after transmetalation with CuCN·2LiCl (1 equiv) leading to the zinc−copper reagent **12**, were reacted with various electrophiles to furnish the products **14** (Table 1 and Scheme 3). In the case of open-chain iodo acetals **6a**−**c**, a *cis*:*trans* ratio of 15:85 was obtained, which can be rationalized via the transition state conformation **13** in which all the substituents occupy pseudoequatorial positions according to the Beckwith model.[14] In the case of cyclic iodo acetals like **6d**−**e** higher stereoselectivities are observed and the *endo*-products **16** are obtained in ≥95:5

Table 1. Polyfunctional Tetrahydrofurans 14a−e and 16a−i Obtained by the Cyclization of the Unsaturated Iodo Acetals 6a−h with Et_2Zn

alkyl iodide	electrophile	product	stereoselectivity[b]	yield (%)[a]
4a		**14a**: R = Bu	15 : 85	70
4b		**14b**: R = Pr	15 : 85	64[c]
4c		**14c**: R = Et	15 : 85	69
4c		**14d**	15 : 85	63
4b		**14e**	15 : 85	62
6d		**16a**: n = 1	2 : 98	83
6e		**16b**: n = 2	4 : 96	66
6d	PhCOCl	**16d**	2 : 98	64
6e		**16e**	4 : 96	65
6f		**16f**: R = Ph; n = 2	4 : 96	75[d]
6g		**16g**: R = *i*-Pr; n = 1	2 : 98	67[d]
6h		**16h**	2 : 98	66
6h	PhCHO	**16i**	2 : 98	60

[a] All yields refer to analytically pure products. [b] *Cis*:*trans* or *exo*:*endo* ratio. [c] $PdCl_2$(dppf) was used as a catalyst. [d] Mixture of diastereomers at position 2.

ratio as shown by NMR spectroscopy ($^1H^1H$ NOESY spectra). This high selectivity can be explained by the intermediate pseudochair conformation **15** in which the alkyl substituents at C(1) and C(2) occupy equatorial positions and the alkoxy substituent at C(3) occupies the axial position (eq 2). This stereochemistry should be



further favored by an anomeric effect and has been observed for several cyclization reactions involving cyclic radicals.[15] This excellent *endo*-selectivity is also observed with cyclic acetals substituted on C(2) like **6f** and **6g** (*endo*:*exo* > 96:4). As seen from Table 1, the zinc−copper reagents have been trapped with ethyl (α-bromomethyl)-

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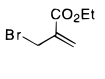
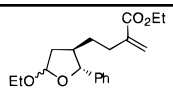
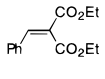
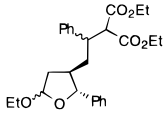
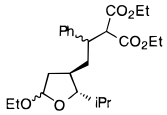
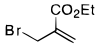
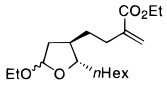
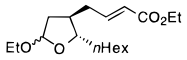
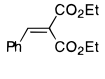
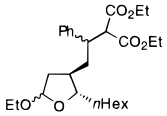
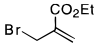
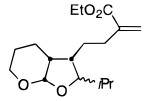
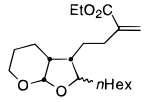
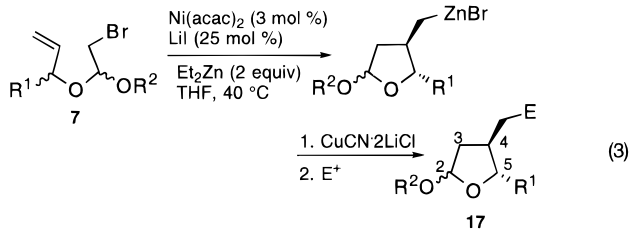
Table 2. Polyfunctional Tetrahydrofurans 17a−h Obtained by the Cyclization of Unsaturated Bromo Acetals 7a−e in the Presence of Ni(acac)$_2$ as Catalyst

alkyl bromide	electrophile	product		stereoselectivity (*cis*:*trans*)	yield (%)[a]
7a			**17a**	2 : 98	64
7a			**17b**	2 : 98	61
7b			**17c**	2 : 98	61
7c			**17d**	2 : 98	61
7c			**17e**	2 : 98	61
7c			**17f**	2 : 98	60
7d			**17g**	4 : 96[b]	66
7e			**17h**	4 : 96[b]	65

[a] All yields refer to analytically pure products. [b] *Exo*:*endo* ratio.

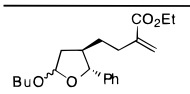
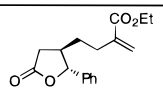
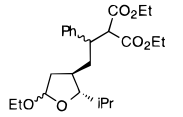
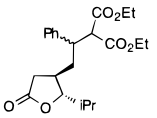
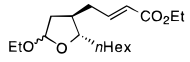
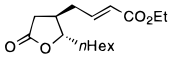
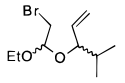
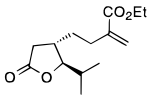
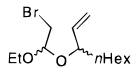
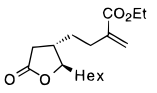
acrylate, acid chlorides, and ethyl propiolate in satisfactory yields.[16] As mentioned previously, bromo acetals of type **7** are more stable and more easy to prepare. Although the compounds **7** do not undergo the nickel-catalyzed cyclization, we found that a smooth reaction occurs if dry lithium iodide (25 mol %) is added to the reaction mixture and if the reaction is performed 40 °C (eq 3). Under these conditions, a range of unsaturated



(3)

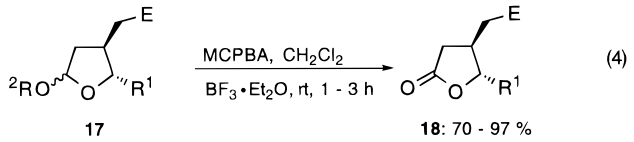
bromo acetals were cyclized (Table 2) and quenched with different electrophiles after a transmetalation with CuCN·2LiCl leading to the tetrahydrofurans **17**. The role of lithium iodide may be to generate *in situ* small amounts of the corresponding alkyl iodide, which may initiate the radical reaction. Whereas the relative stereochemistry of the anomeric carbon is not controlled, a high diastereocontrol is observed between C(4) and C(5), giving the *trans*-product in over 98% stereoselectivity (see Table 2). The monocyclic acetals **17** were oxidized to pure *trans*-

Table 3. *trans*-4,5-Disubstituted γ-Butyrolactones 18a−e Obtained by *m*-CPBA Oxidation

starting material	method	product		yield (%)[a]
	A		**18a**	70
	A		**18b**	87
	A		**18c**	98
	B		**18d**	53
	B		**18e**	50

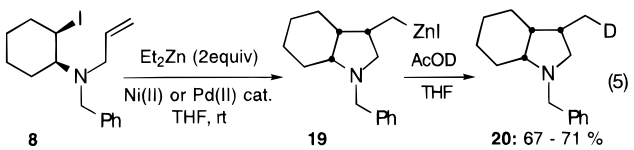
[a] All yields refer to analytically pure products.

γ-butyrolactones using a solution of *m*-CPBA[18] in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (0.4 equiv) at rt. This method affords the desired lactones **18** in 70−98% yield (method A; eq 4). It is also possible to perform a "one-



(4)

pot reaction" starting from the bromo acetals **7b**,**c**. The zinc reagent resulting from the cyclization procedure was transmetalated with CuCN·2LiCl and reacted with an electrophile. The crude mixture was filtered over a short column, and after evaporation of the solvent the crude product was submitted to the oxidation conditions described above to afford the lactones **18** in 50−53% overall yield (method B; Table 3). The relative stereochemistry of the products was established by two-dimensional ^{1}H-NMR experiments (^{1}H^{1}H NOESY) on the lactone **18a** (see the Experimental Section). The alkyl iodide **8** was also submitted to the cyclization conditions using either $PdCl_2$(dppf) (3 mol %) or Ni(acac)$_2$ (2 mol %) as a catalyst. In both cases, a rapid reaction was observed at rt, affording the intermediate zinc reagent **19** that could be trapped efficiently with AcOD to provide the *endo*-product **20** as the only stereoisomer. Attempts to quench **19** with other electrophiles were not successful, due to the low reactivity of the organozinc reagent due to the coordination of zinc to nitrogen (eq 5). As an application of this synthetic



(5)

method, we have developed a formal total synthesis of (−)-methylenolactocin (**3**), a molecule of biological interest for which two total syntheses have already been reported

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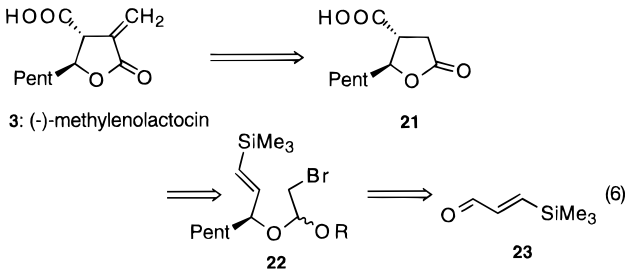
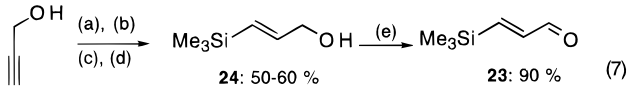
by Greene[8b] and Zhu.[8c,d] The target molecule is the lactone **21**, which has been converted in one step to (−)-methylenolactocin (**3**).[8b] This molecule was prepared by the diethylzinc-mediated cyclization of the unsaturated bromo acetal **22**, which was obtained in optically pure form from (*E*)-3-(trimethylsilyl)propenal (**23**) (eq 6). The



(6)

aldehyde **23** was prepared from propargylic alcohol in three steps. Thus, the metalation of propargylic alcohol with ethylmagnesium bromide and silylation affords after acidic workup 3-(trimethylsilyl)-2-propyn-1-ol, which was reduced stereoselectively with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to afford (*E*)-3-(trimethylsilyl)-2-propen-1-ol (**24**) in 50−60% overall yield.[19] The oxidation of **24** with MnO_2 in CH_2Cl_2 at 35 °C for 12 h provides the aldehyde **23** in 90% yield (eq 7).[20] The

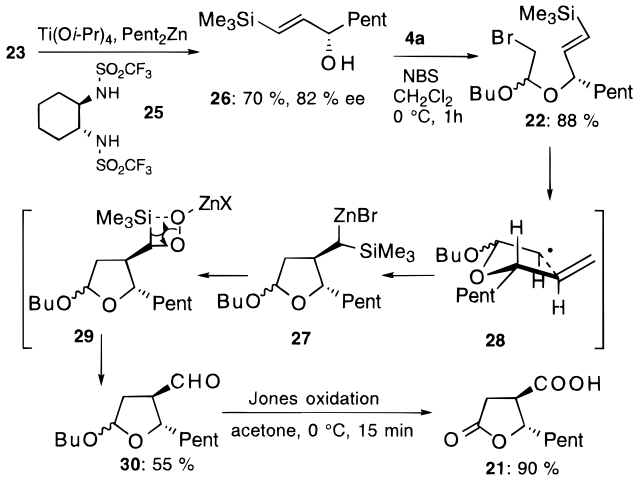


(7)

Conditions: (a) EtMgBr, THF, 0 °C; (b) Me_3SiCl, 70 °C; (c)1.4 M H_2SO_4, 45 °C; (d) $NaAlH_2(OCH_2CH_2OMe)_2$; (e) MnO_2, CH_2Cl_2, 35 °C, 8h

reaction of **23** with dipentylzinc in the presence of Ti(O-*i*-Pr)$_4$ and (1*R*,2*R*)-1,2-bis(trifluoromethanesulfonamido)-cyclohexane (**25**)[21] in toluene at −30 °C affords the allylic alcohol **26**[20,22] in 70% and 82% ee as determined by derivatization to the corresponding mandelic ester using (*S*)-(+)-*O*-acetylmandelic acid.[23] The treatment of **26** with butyl vinyl ether (**4a**) in the presence of NBS in CH_2Cl_2 (0 °C, 1 h) produces the expected cyclization precursor **22** in 88% yield (Scheme 4). The cyclization of **22** in the presence of diethylzinc (2 equiv), lithium iodide (0.25 equiv), and Ni(acac)$_2$ (5 mol %) affords the intermediate zinc organometallic **27** via the transition state conformation **28**. The organozinc bromide **27** could be directly oxidized with oxygen in the presence of TMSCl, leading to an intermediate zinc peroxide **29** that undergoes an oxy-Peterson elimination to furnish the *trans*-aldehyde **30** (100% *trans*) in 55% overall yield.[24] Jones oxidation

Scheme 4



of **30** gives the target carboxylic acid **21** (90% yield; Scheme 4). This crystalline product has a melting point of 104 °C (lit.[25] mp 105−107 °C) and a specific rotation of $[\alpha]_D = -50.5$ ($c = 0.41$, $CHCl_3$) (lit.[25] $[\alpha]_D = -54$ ($c = 0.4$, $CDCl_3$)).

In summary, we have developed a new efficient cyclization of unsaturated iodo and bromo acetals that affords substituted tetrahydrofurans and butyrolactones with good stereoselectivity. This method was applied to the enantioselective preparation of (−)-methylenolactocin (**3**) in four steps starting from (*E*)-3-(trimethylsilyl)-propenyl in 30% overall yield and ca. 90% ee.

Experimental Section

General Considerations. Unless otherwise indicated, all reactions were carried out under argon. Solvents (THF, toluene) were dried and freshly distilled over sodium/benzophenone. Dichloromethane was freshly distilled over CaH_2. Reactions were monitored by gas−liquid-phase chromatography (GC) or thin-layer chromatography (TLC) analysis of hydrolyzed aliquots.

Starting Materials. The following starting materials were prepared according to literature procedures: ethyl α-(bromomethyl)acrylate,[26] *N*-methyl-*N*,*N*′-dicyclohexylcarbodiimidium iodide (2 DCC·MeI),[12] dichloro (1,1′-bis(diphenylphosphino)-ferrocene)palladium(II),[13] 3-iodo-2-cyclohexen-1-one,[27] 1-phenyl-2-propen-1-ol,[28] 1-nonen-3-ol,[29] 4-methyl-1-penten-3-ol,[30] *N*-iodosuccinimide (NIS),[31] (*E*)-3-(trimethylsilyl)-2-propenal,[32] and (1*R*,2*R*)-1,2-bis(trifluoromethanesulfonamido)cyclohexane.[21a]

Preparation of Cyclization Precursors of Type 6, 7, and 8. Preparation of 2-Butoxy-1-iodo-3-oxa-5-hexene (6a). The preparation of the alkyl iodide **6a** was carried out according to the literature procedure[9] with butyl vinyl ether (**4a**) (2.0 g, 20 mmol, 1 equiv), 2-propen-1-ol (**5a**) (1.70 g, 20.0 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). Purification by silica gel chromatography (hexanes/ether 9:1) of the crude product afforded the iodo acetal **6a** (4.0 g, 14.5 mmol, 70% yield) as a colorless liquid.

IR (neat): 2910 (s), 2870 (s), 1110 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.86 (m, 1H), 5.19 (d, $J = 17.2$ Hz, 1H),

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5.10 (d, J = 10.3 Hz, 1H), 4.58 (t, J = 5.5 Hz, 1H), 4.05 (dd, J = 14.3, 5.3 Hz, 1H), 3.54 (m, 1H), 3.43 (m, 2H), 3.15 (d, J = 5.6 Hz, 2H), 1.49 (m, 2H), 1.37 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 134.0, 117.2, 101.7, 67.1, 66.2, 31.6, 19.1, 13.6, 5.0. MS (EI): 227 ($M^+ - C_4H_9$, 12), 211 (20), 87 (78), 41 (100). Anal. Calcd for $C_9H_{17}IO$ (283.19): C, 38.16; H, 6.01. Found: C, 38.24; H, 5.93.

Preparation of 1-Iodo-3-oxa-2-propoxy-5-hexene (6b). The literature procedure[9] was followed with propyl vinyl ether (**4b**) (2.10 g, 20 mmol), 2-propen-1-ol (**5a**) (1.70 g, 20.0 mmol), and NIS[31] (4.5 g, 20 mmol). Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) afforded the iodo acetal **6b** (3.90 g, 14.6 mmol, 73% yield) as a colorless liquid.

IR (neat): 2918 (vs), 1645 (w), 1410 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.91 (m, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.3 Hz, 1H), 4.62 (t, J = 5.5 Hz, 1H), 4.12 (dd, J = 12.7, 5.4 Hz, 1H), 4.06 (dd, 1H, J = 12.6, 5.4 Hz), 3.55 (m, 1H), 3.51 (m, 1H), 3.22 (d, 2H, J = 5.5 Hz), 1.60 (sextet, 2H, J = 7.4 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 134.2, 117.3, 101.3, 68.3, 67.3, 22.9, 10.7, 5.2. MS (EI): 227 (10), 143 (54), 87 (40), 57 (100). Anal. Calcd for $C_8H_{15}IO_2$ (269.18): C, 35.68; H, 5.57. Found: C, 35.58; H, 5.52.

Preparation of 2-Ethoxy-1-iodo-3-oxa-5-hexene (6c). The literature procedure[9] was followed with ethyl vinyl ether (**4c**) (1.70 g, 24.0 mmol, 1.2 equiv), 2-propen-1-ol (**5a**) (1.70 g, 20 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the crude product afforded the iodo acetal **6c** (4.33 g, 17.0 mmol, 85% yield) as a colorless liquid.

IR (neat): 2920 (s), 1710 (w), 1110 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.84 (m, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.59 (t, J = 5.5 Hz, 1H), 4.09 (dd, J = 16.5, 9.9 Hz, 1H), 3.95 (dd, J = 16.5, 9.9 Hz, 1H), 3.55 (m, 2H), 3.15 (d, J = 5.4 Hz, 2H), 1.80 (t, J = 7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 134.0, 117.1, 101.1, 67.2, 62.0, 15.0, 5.2. MS (EI): 213 ($M^+ - C_3H_5$, 9), 129 (68), 41 (100). Anal. Calcd for $C_7H_{13}IO_2$ (255.14): C, 32.94; H, 5.98. Found: C, 32.90; H, 5.93.

Preparation of *trans*-3-Iodo-2-(2-propenyloxy)tetrahydrofuran (6d). The literature procedure[9] was followed with 2,3-dihydrofuran (**4d**) (1.70 g, 24.0 mmol, 1.2 equiv), 2-propen-1-ol (**5a**) (1.40 mL, 20 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). After usual workup the residual oil was purified by bulb-to-bulb distillation (0.1 mmHg, 80 °C), affording the iodo acetal **6d** (3.1 g, 12.0 mmol, 61% yield) as a colorless oil.

IR (neat): 3040 (s), 1305 (s), 1220 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.82 (m, 2H), 5.14 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.08 (m, 5H), 2.61 (m, 1H), 2.16 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 134.2, 117.3, 109.8, 68.0, 67.1, 35.6, 24.8. MS (EI): 254 ($M^+ + 1$, 3), 168 (92), 70 (100). Anal. Calcd for $C_7H_{11}IO_2$ (253.14): C, 33.21; H, 4.35. Found: C, 33.23; H, 4.41.

Preparation of *trans*-3-Iodo-2-(2-propenyloxy)tetrahydropyran (6e). The literature procedure[9] was followed with 3,4-dihydro-2*H*-pyran (**4e**) (1.68 g, 20.0 mmol, 1 equiv), 2-propen-1-ol (**5a**) (1.70 mL, 20.0 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). Purification by silica gel chromatography (hexanes/ether 9:1) afforded the iodo acetal **6e** (4.1 g, 15.0 mmol, 75% yield) as a colorless oil.

IR (neat): 2799 (vs), 1715 (s), 1440 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.85 (ddd, J = 17.2, 9.1, 5.2 Hz, 1H), 5.15 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 9.3 Hz, 1H), 4.61 (d, J = 5.3 Hz, 1H), 4.17 (dd, J = 12.1, 5.2 Hz, 1H), 4.03 (m, 3H), 3.45 (m, 1H), 2.29 (m, 1H), 1.96 (m, 1H), 1.67 (m, 1H), 1.47 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 133.9, 117.4, 101.5, 68.9, 63.4, 32.7, 29.3, 25.5. MS (EI): 268 ($M^+ + 1$, 1), 154 (43), 142 (60), 84 (73), 41 (100). Anal. Calcd for $C_8H_{13}IO_2$ (267.15): C, 35.96; H, 4.87. Found: C, 36.09; H, 4.84.

Preparation of *trans*-3-Iodo-2-[(1-phenyl-2-propenyl)oxy]tetrahydropyran (6f). The literature procedure[9] was followed with 3,4-dihydro-2*H*-pyran (**4e**) (2.5 g, 30 mmol, 1.5 equiv), 1-phenyl-2-propen-1-ol[28] (**5b**) (2.68 g, 20.0 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). The crude product was purified by flash chromatography (hexanes/ether 4:1), affording a 1:1 mixture of diastereomers of the iodo acetal **6f** (5.7 g, 16.6 mmol, 83% yield) as a yellow oil.

IR (neat): 3050 (vs), 2950 (s), 1450 (m), 1440 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 6.02 (ddd, J = 17.1, 8.1, 5.6 Hz, 1H), 5.32 (m, 2H), 4.53 (d, J = 5.1 Hz, 1H), 4.13 (m, 1H), 4.02 (m, 1H), 3.55 (m, 1H), 2.41 (m, 1H), 1.98 (m, 2H), 1.76 (m, 1H), 1.57 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 140.7, 138.6, 129.4, 128.3, 127.9, 118.3, 100.0, 79.2, 63.5, 32.4, 29.5, 25.3 (first diastereomer); δ 139.3, 137.3, 128.4, 127.7, 127.5, 115.3, 98.8, 78.8, 63.2, 32.3, 29.1, 25.2 (second diastereomer). MS (EI): 211 (12), 117 (100), 84 (25). Anal. Calcd for $C_{14}H_{17}IO_2$ (343.25): C, 48.98; H, 4.97. Found: C, 48.80; H, 4.73.

Preparation of *trans*-3-Iodo-2-[(3-isopropyl-2-propenyl)oxy]tetrahydrofuran (6g). The literature procedure[9] was followed with 2,3-dihydrofuran (**4e**) (2.1 g, 30 mmol, 1.5 equiv), 4-methyl-1-penten-3-ol[30] (**5c**) (2.0 g, 20.0 mmol, 1 equiv), and NIS[31] (4.5 g, 20 mmol, 1 equiv). After usual workup the crude product was purified by bulb-to-bulb distillation (80 °C, 0.1 mmHg), affording a 1:1 mixture of diastereomers of the iodo acetal **6g** (4.7 g, 15.8 mmol, 79% yield) as a yellow oil.

IR (neat): 2950 (vs), 1195 (m), 910 (vs), 810 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.62 (m, 1H), 5.30 (d, J = 19.5 Hz, 1H), 5.13 (m, 2H), 4.05 (m, 3H), 3.60 (m, 1H), 2.57 (m, 1H), 2.12 (m, 1H), 1.61 (m, 1H), 0.83 (m, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 137.4, 118.6, 110.0, 84.3, 67.0, 35.8, 32.5, 25.3, 18.5, 18.3 (first diastereomer); δ 136.4, 116.6, 107.1, 82.1, 66.6, 35.5, 32.3, 25.3, 18.3, 18.1 (second diastereomer). MS (EI): 197 (100), 70 (81), 55 (34). Anal. Calcd for $C_{10}H_{17}IO_2$ (295.22): C, 40.68; H, 5.76. Found: C, 40.59; H, 5.80.

Preparation of 2-Butoxy-1-iodo-3-oxa-4-phenyl-5-hexene (6h). The literature procedure[9] was followed with *n*-butyl vinyl ether (**4a**) (0.71 g, 10.0 mmol, 1 equiv), 1-phenyl-2-propen-1-ol[28] (**5b**) (1.3 g, 10.0 mmol, 1 equiv), and NIS[31] (2.2 g, 10 mmol, 1 equiv). The reaction mixture was allowed to warm from −40 to 0 °C within 1 h. After usual workup, the crude residue was filtered (hexanes/ether 9:1) over a short plug of silica gel, affording the alkyl iodide **6h** (2.57 g, 7.2 mmol, 72% yield) as a yellow oil that was directly submitted to further transformations.

Preparation of 1-Bromo-2-ethoxy-4-phenyl-3-oxa-5-hexene (7a). A 100 mL three-necked flask with argon inlet, septum cap, and internal thermometer was charged with a suspension of NBS (3.45 g, 20 mmol, 1 equiv) in 1-phenyl-2-propen-1-ol[28] (**5b**) (4.0 mL, 29.8 mmol, 1.5 equiv) and dichloromethane (4 mL). The suspension was cooled to 0 °C, and ethyl vinyl ether (**4c**) (1.34 g, 20.0 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred for 12 h at 0 °C, diluted with ether (50 mL), and poured on ice−water (100 mL). After filtration and separation of the organic layer the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. Purification by silica gel chromatography (hexanes) of the residual oil afforded a 1:1 diastereomeric mixture of the alkyl bromide **7a** (4.5 g, 15.4 mmol, 77% yield) as a colorless liquid.

IR (neat): 2980 (s), 1120 (s), 1030 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.39 (m, 5H), 5.96 (m, 1H), 5.29 (m, 3H), 4.92 (t, J = 5.7 Hz, 1H), 3.64 (m, 2H), 3.40 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 140.5, 138.9, 128.6, 128.1, 127.4, 117.4, 99.7, 79.7, 62.0, 32.2, 15.3 (first diastereomer); δ 140.1, 138.1, 128.5, 128.0, 126.8, 115.9, 99.5, 79.4, 61.7, 32.1, 15.2 (second diastereomer). MS (EI): 159 (11), 117 (100), 72 (15). Anal. Calcd for $C_{13}H_{17}BrO_2$ (284.14): C, 54.93; H, 6.02. Found: C, 54.89; H, 5.97.

Preparation of 1-Bromo-2-ethoxy-4-isopropyl-3-oxa-5-hexene (7b). The procedure described above for the preparation of **7a** was followed with ethyl vinyl ether (**4c**) (1.34 g, 20.0 mmol, 1 equiv), 4-methyl-1-penten-3-ol[30] (**5c**) (4.0 mL, 40 mmol, 2 equiv), and NBS (3.45 g, 20 mmol, 1 equiv) in dichloromethane (4 mL). The reaction mixture was stirred for 1 h at 0 °C and then for 4 h at rt. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the residual oil afforded a 1:1 mixture of diastereoisomers

of the alkyl bromide **7b** (3.9 g, 15.6 mmol, 78% yield) as a colorless liquid.

IR (neat): 2975 (vs), 1115 (s), 950 (vs), 925 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.64 (ddd, J = 17.2, 10.4, 8.1 Hz, 1H), 5.13 (m, 2H), 4.60 (m, 1H), 3.55 (m, 3H), 3.29 (m, 2H), 1.72 (m, 1H), 1.14 (t, J = 6.0 Hz, 3H), 0.85 (2d, J = 6.8 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 137.4, 118.8, 100.8, 85.0, 62.6, 32.7, 32.6, 18.6, 15.4 (first diastereomer); δ 136.7, 117.7, 98.9, 83.7, 61.3, 32.5, 32.3, 18.3, 15.3 (second diastereomer). MS (EI): 153 (94), 83 (100), 55 (67). Anal. Calcd for $C_{10}H_{19}BrO_2$ (250.23): C, 47.99; H, 7.64. Found: C, 47.65; H, 7.51.

Preparation of 1-Bromo-2-ethoxy-4-hexyl-3-oxa-5-hexene (7c). The procedure for the preparation of **7a** was followed with ethyl vinyl ether (**4c**) (1.34 g, 20.0 mmol, 1 equiv), 1-nonen-3-ol[29] (**5d**) (4.0 g, 27.7 mmol, 1.4 equiv), and NBS (3.6 g, 20.0 mmol, 1 equiv). Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the residual oil afforded the alkyl bromide **7c** (4.5 g, 15.4 mmol, 77% yield) as a colorless liquid.

IR (film): 2820 (vs), 1120 (s), 920 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.65 (m, 1H), 5.10 (m, 2H), 4.61 (m, 1H), 3.89 (m, 1H), 3.59 (m, 2H), 3.42 (m, 1H), 3.28 (m, 2H), 1.54 (m, 1H), 1.23 (m, 8H), 1.13 (t, 3H, J = 7.6 Hz), 0.80 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.3, 116.6, 100.5, 79.6, 76.6, 62.5, 35.5, 35.4, 32.2, 29.2, 25.2, 22.6, 14.0 (first diastereomer); δ 138.5, 116.5, 98.9, 78.6, 77.6, 61.2, 35.5, 31.7, 29.1, 25.0, 15.2 (second diastereomer). MS (EI): 153 (95), 151 (100), 125 (32), 123 (33), 83 (31). Anal. Calcd for $C_{13}H_{25}BrO_2$ (292.28): C, 53.42; H, 8.56. Found: C, 53.44; H, 8.52.

Preparation of *trans*-3-Bromo-2-[(1-isopropyl-2-propenyl)oxy]tetrahydropyran (7d). The procedure described above for the preparation of **7a** was followed with 3,4-dihydro-2*H*-pyran (**4e**) (2.5 g, 30 mmol, 1 equiv), 4-methyl-1-penten-3-ol[30] (**5c**) (5.4 g, 54 mmol, 1.8 equiv), and NBS (5.2 g, 30 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h at 0 °C and for 1 h at rt. Usual workup and purification by silica gel chromatography of the residual oil afforded a 1:1 diastereomeric mixture of the alkyl bromide **7d** (4.2 g, 16.0 mmol, 80% yield) as a colorless liquid.

IR (neat): 2950 (vs), 1205 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.52 (ddd, J = 17.1, 10.3, 8.5 Hz, 1H), 5.19 (d, J = 10.3 Hz, 1H), 5.10 (d, J = 17.1 Hz, 1H), 4.57 (d, J = 3.9 Hz, 1H), 3.84 (m, 2H), 3.71 (t, J = 7.1 Hz, 1H), 3.50 (m, 1H), 2.29 (m, 1H), 1.86 (m, 2H), 1.81 (m, 1H), 1.45 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 135.9, 119.2, 97.0, 82.4, 49.7, 32.3, 29.7, 22.9, 18.3, 18.2 (first diastereomer); δ 136.9, 116.5, 100.9, 85.6, 63.1, 49.9, 31.9, 30.9, 23.8, 18.1, 17.6 (second diastereomer). MS (EI): 165 (49), 83 (100), 55 (99). Anal. Calcd for $C_{11}H_{19}BrO_2$ (262.24): C, 50.38; H, 7.25. Found: C, 50.20; H, 7.39.

Preparation of *trans*-3-Bromo-2-[(1-hexyl-2-propenyl)oxy]tetrahydropyran (7e). The procedure described above for the preparation of **7a** was followed with 3,4-dihydro-2*H*-pyran (**4e**) (2.5 g, 30 mmol, 1 equiv), 1-nonen-3-ol[29] (**5d**) (2.5 g, 20.0 mmol, 0.6 equiv), and NBS (5.2 g, 30 mmol, 1 equiv). The reaction mixture was stirred for 1 h at 0 °C and for 1 h at rt. After usual workup, the crude product was purified by flash chromatography (hexanes/ether 4:1) to afford a 1:1 diastereomeric mixture of the alkyl bromide **7e** (5.0 g, 17.0 mmol, 85% yield) as a colorless liquid.

IR (neat): 2815 (vs), 2780 (s), 1205 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.58 (m, 1H), 5.14 (d, J = 11.6 Hz, 1H), 5.11 (d, J = 5.0 Hz, 1H), 4.58 (d, J = 4.3 Hz, 1H), 4.00 (q, J = 6.7 Hz, 1H), 3.83 (m, 2H), 3.46 (m, 1H), 2.32 (m, 1H), 1.85 (m, 2H), 1.54 (m, 1H), 1.47 (m, 2H), 1.32 (m, 8H), 0.80 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 138.0, 117.8, 97.4, 77.7, 62.2, 49.6, 35.3, 31.6, 29.9, 29.1, 25.2, 23.1, 22.5, 13.9. MS (EI): 221 (1), 165 (74), 163 (88), 83 (64), 69 (100). Anal. Calcd for $C_{14}H_{25}BrO_2$ (304.29): C, 55.26; H, 8.22. Found: C, 55.06; H, 8.34.

Preparation of *cis*-*N*-Benzyl-*N*-(2-propenyl)-2-amino-1-iodocyclohexane (8). A 250 mL three-necked flask equipped with an argon inlet, magnetic stirring bar, and internal thermometer was charged with a solution of the amino alcohol **10** (4.40 g, 18.0 mmol) in THF (140 mL). 2 DCC·MeI[12] (10.0 g, 32 mmol, 1.8 equiv) was added in small portions at rt. The reaction mixture was then stirred for 3 days at 35 °C. The solvent was distilled off, and the residual oil was dissolved in hexanes (150 mL). The resulting solution was washed with MeOH/H_2O (4:1) (3 × 100 mL). The combined aqueous phase was extracted with hexanes (3 × 200 mL). The combined organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The crude residue was purified by flash chromatography (hexanes/ether 9:1) to afford alkyl iodide **8** (4.3 g, 12.2 mmol, 68% yield) as a yellow oil.

IR (neat): 2933 (vs), 2846 (m), 2805 (w), 1145 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H), 5.98 (m, 1H), 5.20 (d, J = 17.3 Hz, 1H), 5.11 (d, J = 10.0 Hz, 1H), 4.26 (td, J = 11.6, 4.2 Hz, 1H), 3.86 (d, J = 13.7 Hz, 1H), 3.42 (d, J = 13.7 Hz, 1H), 3.26 (d, J = 14.2 Hz, 1H), 2.96 (dd, J = 14.2, 8.3 Hz, 1H), 2.66 (m, 2H), 2.08 (m, 3H), 1.57 (m, 1H), 1.27 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.8, 137.4, 129.1, 127.9, 126.7, 116.5, 64.4, 53.7, 52.7, 41.0, 38.5, 29.2, 25.8, 25.2. MS (EI): 355 (M^+ + 1, 7), 187 (35), 91 (100). Anal. Calcd for $C_{16}H_{22}IN$ (354.31): C, 54.31; H, 6.21; N, 3.95. Found: C, 54.20; H, 6.37; N, 3.94.

Preparation of *trans*-2-[*N*-Benzyl-*N*-(2-propenyl)amino]cyclohexan-1-ol (10). A 250 mL three-necked flash equipped with an argon inlet, magnetic stirring bar, and internal thermometer was charged with a 0.86 M solution of EtMgBr (68 mL, 60 mmol) in THF. The magnesium amide was generated by dropwise addition of a solution of *N*-benzyl-3-amino-1-propene (19.8 g, 60.0 mmol) in THF (15 mL) at rt. After completion of the addition the reaction mixture was stirred for 1 h at 35 °C. It was allowed to cool again to rt, and cyclohexene oxide (5.0 mL, 50.0 mmol, 0.83 equiv) was added dropwise. After being stirred for 4 h at rt, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl solution (300 mL). Ether (300 mL) was added, and the organic layer was separated. The aqueous layer was washed twice with ether (300 mL), the combined organic layer was dried ($MgSO_4$) and filtrated, and the solvent was evaporated. Purification by silica gel chromatography of the residual oil (hexanes/ether 9:1) afforded the product **10** (8.5 g, 34.6 mmol, 69% yield) as a colorless oil.

IR (film): 3466 (s, br), 2933 (vs), 1445 (s), 1076 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.28 (m, 5H), 5.73 (m, 1H), 5.12 (d, J = 15.2 Hz, 1H), 5.06 (d, J = 9.3 Hz, 1H), 3.82 (d, J = 13.6 Hz, 1H), 3.80 (d, J = 3.6 Hz, 1H), 3.40 (m, 1H), 3.31 (d, J = 16.9 Hz, 2H), 2.38 (m, 1H), 2.06 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 1.58 (m, 1H), 1.15 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.5, 136.7, 128.7, 128.3, 126.9, 69.0, 64.9, 53.4, 52.6, 33.1, 25.4, 24.0, 22.4. MS (EI): 245 (M^+, 10), 186 (50), 91 (100). Anal. Calcd for $C_{16}H_{23}NO$ (245.32): C, 78.36; H, 9.38; N, 5.71. Found: C, 78.23; H, 9.45; N, 5.71.

Typical Procedure for the Cyclization of Iodo Acetals of Type 4 and 6. Preparation of *trans*-2-Butoxy-4-(3-carbethoxy-3-butenyl)tetrahydrofuran (14a). A 50 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar, an internal thermometer, and a septum cap was charged with $Ni(acac)_2$ (15 mg, 0.06 mmol, 2 mol %), and a solution of the alkyl iodide **6a** (0.85 g, 3.0 mmol, 1 equiv) in THF (5 mL) was added. The resulting green suspension was cooled to −78 °C, and Et_2Zn (0.6 mL, 6.0 mmol, 2 equiv) was added dropwise. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature for 2 h. The excess of Et_2Zn and the solvent were removed *in vacuo* (rt, 2 h). After addition of THF (5 mL) and cooling to −50 °C, CuCN·2LiCl (CuCN: 0.27 g, 3.0 mmol; LiCl: 0.25 g, 6.0 mmol) in THF (5 mL) was added. The reaction mixture was warmed to 0 °C (10 min) and cooled to −78 °C. Ethyl (α-bromomethyl)-acrylate[26] (1.78 g, 9.0 mmol, 3 equiv) was added. The reaction mixture was allowed to warm to 0 °C within 12 h and was quenched by addition of saturated aqueous NH_4Cl solution (15 mL). Precipitated copper salts were dissolved by addition of small portions of an aqueous NH_3 solution. The aqueous phase was extracted with ether (3 × 30 mL). The combined organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/ether 6:1), affording the product **14a** (0.56 g, 2.1 mmol, 70% yield) as a colorless oil.

IR (neat): 2920 (s), 2850 (s), 1730 (s), 1720 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.15 (s, 1H), 5.52 (s, 1H), 5.10 (dd,

J = 5.6, 3.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.96 (m, 1H), 3.64 (m, 1H), 3.45 (dd, J = 8.4, 2.4 Hz, 1H), 3.38 (m, 1H), 2.27 (m, 4H), 1.57 (m, 4H), 1.34 (m, 3H), 1.32 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.0, 140.7, 124.5, 104.4, 71.6, 67.3, 60.6, 38.9, 38.1, 32.2, 31.9, 30.9, 19.4, 14.2, 13.9 (first diastereomer); δ 140.6, 124.4, 104.1, 72.2, 66.9, 39.2, 36.7, 33.1, 30.8 (second diastereomer). MS (EI): 211 (4), 183 (58), 69 (100), 41 (48). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.66; H, 9.63. Found: C, 66.51; H, 9.60.

Preparation of *trans*-4-(3-Carbethoxy-3-butenyl)-2-propoxytetrahydrofuran (14b). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6b** (1.34 g, 5.0 mmol) and $PdCl_2$(dppf)[13] (100 mg, 0.15 mmol, 3 mol %) as a catalyst. Ethyl (α-bromomethyl)acrylate[26] (1.98 g, 10.0 mmol, 2 equiv) was used as an electrophile. Reaction conditions: −78 to 0 °C, 1 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the crude product afforded the acetal **14b** (0.82 g, 3.2 mmol, 64% yield) as a colorless oil.

IR (neat): 2923 (vs), 2885 (s), 1715 (vs), 1635 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.08 (s, 1H), 5.45 (s, 1H), 5.04 (dd, J = 5.6, 3.1 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.90 (d, J = 7.4 Hz, 1H), 3.59 (dt, J = 16.2, 6.9 Hz, 1H), 3.39 (d, J = 8.9 Hz, 1H), 3.27 (dt, J = 16.2, 6.7 Hz, 1H), 2.18 (m, 4H), 1.52 (m, 5H), 1.42 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.1, 140.7, 124.5, 104.4, 71.6, 69.3, 60.6, 38.9, 38.1, 32.1, 10.9, 23.0, 14.3, 10.7 (first diastereomer); δ 104.1, 72.2, 68.9, 39.2, 36.7, 33.0, 30.8 (second diastereomer). MS (EI): 168 (29), 123 (35), 82 (40), 69 (100). Anal. Calcd for $C_{14}H_{24}O_4$ (256.30): C, 65.62; H, 9.37. Found: C, 65.93; H, 9.13.

Preparation of *trans*-4-(3-Carbethoxy-3-butenyl)-2-ethoxytetrahydrofuran (14c). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6c** (1.27 g, 5.0 mmol). Ethyl (α-bromomethyl)acrylate[26] (2.97 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 2 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1 to 4:1) of the crude product afforded the acetal **14c** (0.83 g, 3.4 mmol, 69% yield) as a colorless oil.

IR (neat): 2920 (vs), 1710 (vs), 1635 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.07 (s, 1H), 5.48 (s, 1H), 5.04 (dd, J = 5.0, 3.2 Hz, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.89 (m, 1H), 3.63 (m, 1H), 3.42 (q, J = 8.6 Hz, 2H), 3.33 (m, 1H), 2.15 (m, 3H), 1.58 (q, J = 7.5 Hz, 2H), 1.43 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.1, 140.5, 124.5, 104.2, 71.5, 63.0, 60.6, 39.0, 38.1, 31.9, 30.9, 15.3, 14.2 (first diastereomer); δ 124.6, 103.9, 72.2, 62.5, 39.2, 36.6, 32.9, 30.8, 15.2 (second diastereomer). MS (EI): 241 (M^+ − 1, 6), 95 (50), 69 (100). Anal. Calcd for $C_{13}H_{22}O_4$ (240.23): C, 64.99; H, 8.38. Found: C, 64.92; H, 8.40.

Preparation of *trans*-4-((*E*)-3-Carbethoxy-2-propenyl)-2-ethoxytetrahydrofuran (14d). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6c** (1.27 g, 5.0 mmol), and ethyl propiolate (1.47 g, 15.0 mmol, 3 equiv) was used as electrophile. Reaction conditions: −78 to 0 °C, 12 h. Usual workup and purification by silica gel chromatography of the crude residue (hexanes/ether 9:1 to 4:1) afforded an 85:15 mixture of diastereomers of the product **14d** (0.71 g, 3.1 mmol, 63%) as a colorless oil.

IR (neat): 2900 (vs), 1715 (vs), 1650 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.85 (m, 1H), 5.75 (d, J = 15.6 Hz, 1H), 5.05 (dd, J = 8.1, 5.3 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.88 (m, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 3.35 (m, 1H), 2.29 (m, 2H), 2.17 (m, 2H), 1.52 (m, 1H), 1.21 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 166.4, 146.9, 122.4, 104.1, 71.4, 62.9, 60.2, 38.5, 36.8, 36.0, 15.2, 14.2 (first diastereomer); δ 166.3, 146.5, 122.7, 103.7, 62.6, 38.9, 36.5, 15.2 (second diastereomer). MS (EI): 227 (M^+ − 1, 2), 183 (18), 109 (14), 85 (20), 81 (39), 69 (100), 57 (26), 41 (38). Anal. Calcd for $C_{12}H_{20}O_4$ (228.25): C, 63.16; H, 8.77. Found: C, 63.16; H, 8.77.

Preparation of *trans*-3-[(2-Propoxytetrahydrofuranyl-)methyl]-2-cyclohexen-1-one (14e). The procedure described for the preparation of **14a** was followed with Ni(acac)$_2$ (15 mg, 0.06 mmol, 2 mol %) and a solution of the alkyl iodide **6b** (0.81 g, 3.0 mmol, 1 equiv) in THF (5 mL). 3-Iodo-2-cyclohexen-1-one[27] (1.35 g, 6.0 mmol, 2 equiv) was used as an electrophile. Reaction conditions: −78 to 0 °C, 12 h. After usual workup the crude product was purified by flash chromatography (hexanes/ether 6:1), affording the ketone **14e** (0.45 g, 1.7 mmol, 62% yield) as a colorless oil.

IR (neat): 2920 (vs), 2880 (s), 1687 (vs), 1630 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.80 (s, 1H), 5.04 (dd, J = 5.4, 2.0 Hz, 1H), 3.90 (t, J = 8.5 Hz, 1H), 3.43 (t, J = 8.5 Hz, 1H), 3.23 (td, J = 9.4, 2.1 Hz, 1H), 3.51 (td, J = 9.4, 2.1 Hz, 1H), 2.26 (m, 8H), 1.92 (m, 2H), 1.48 (m, 3H), 0.84 (t, J = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 199.3, 164.2, 126.2, 103.9, 71.2, 68.9, 41.8, 58.4. 37.1, 35.1, 29.7, 22.7, 22.5, 10.6 (first diastereomer); δ 163.9, 126.5, 71.5, 68.8, 67.2, 42.3, 38.9, 34.6, 31.7, 29.6, 22.8, 19.3, 13.7, 10.5 (second diastereomer). MS (EI): 210 (1), 179 (23), 110 (60), 69 (100). Anal. Calcd for $C_{14}H_{22}O_3$ (238.26): C, 70.29; H, 9.20. Found: C, 69.96; H, 9.20.

Preparation of *endo*-4-(3-Carbethoxy-3-butenyl)-2,8-dioxabicyclo[3.3.0]octane (16a). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6d** (1.35 g, 5.0 mmol) and ethyl α-(bromomethyl)-acrylate[26] (2.97 g, 15.0 mmol, 3 equiv) as an electrophile. Reaction conditions: −78 °C to rt, 2 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the residue afforded the product **16a** (1.00 g, 4.2 mmol, 80% yield) as a colorless oil.

IR (neat): 2830 (vs), 1620 (s), 1430 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.10 (s, 1H), 5.66 (d, J = 5.0 Hz, 1H, 1-H), 5.49 (s, 1H), 3.96 (q, J = 7.2 Hz, 2H), 3.90 (m, 1H), 3.80 (dd, J = 7.5, 6.3 Hz, 2H), 3.36 (dd, J = 11.4, 8.4 Hz, 2H), 2.79−2.74 (m, 1H, 5-H), 2.28−2.23 (m, 3H, 4-H), 1.83 (m, 1H), 1.52 (m, 2H), 1.24 (t, J = 7.3 Hz, 3H). ^{1}H-NMR-NOE ($CDCl_3$, 500 MHz) irradiation in the resonance frequency of 1-H increased the intensity of the signal of 5-H; irradiation in the resonance frequency of 4-H increased the intensity of the signal of 4-H. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.8, 140.2, 124.9, 109.6, 72.3, 69.0, 60.6, 45.1, 41.7, 30.9, 27.1, 24.9, 14.1. MS (EI): 222 (15), 167 (11), 149 (12), 97 (100). Anal. Calcd for $C_{13}H_{20}O_4$ (240.23): C, 64.99; H, 8.33. Found: C, 64.89; H, 8.32.

Preparation of *endo*-7-(3-Carbethoxy-3-butenyl)-2,9-dioxabicyclo[4.3.0]nonane (16b). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6e** (0.81 g, 3.0 mmol) and $PdCl_2$(dppf)[13] (76 mg, 0.1 mmol, 3.3 mol %) as a catalyst. Ethyl (α-bromomethyl)-acrylate[26] (1.18 g, 6.0 mmol, 2 equiv) was used as an electrophile. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the crude residue afforded the cyclic acetal **16b** (0.50 g, 2.0 mmol, 66% yield) as a yellow oil.

IR (film): 2915 (s), 2860 (s), 1710 (vs), 1630 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.09 (s, 1H), 5.47 (s, 1H), 5.17 (d, J = 3.7 Hz, 1H), 3.92 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 7.0 Hz, 1H), 3.59 (m, 3H), 2.24 (m, 3H), 1.92 (m, 1H), 1.64 (m, 2H), 1.52 (m, 2H), 1.40 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.8, 140.3, 124.6, 101.8, 69.6, 60.8, 60.5, 40.5, 36.2, 36.6, 26.1, 23.0, 19.0, 14.0. MS (EI): 239 (14), 127 (24), 97 (79), 81 (100). Anal. Calcd for $C_{14}H_{22}O_4$ (254.25): C, 66.14; H, 8.66. Found: C, 66.12; H, 8.69.

Preparation of *endo*-4-(2-Oxo-2-phenylethyl)-2,8-dioxabicyclo[3.3.0]octane (16d). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6d** (1.30 g, 5.0 mmol) and benzoyl chloride (2.12 g, 15.0 mmol, 3 equiv) as an electrophile. Reaction conditions: −78 to −20 °C, 12 h. After usual workup the crude product was purified by bulb-to-bulb distillation (0.1 mmHg, 170 °C), affording the ketone **16d** (0.73 g, 3.2 mmol, 63% yield) as a colorless oil.

IR (neat): 2880 (m), 1685 (s), 1600 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.19 (m, 2H), 7.51 (m, 1H), 7.43 (m, 2H), 5.70 (d, J = 4.5 Hz, 1H), 4.05 (dd, J = 8.3, 7.3 Hz, 1H), 3.80 (m, 2H), 3.44 (dd, J = 11.1, 8.4 Hz, 1H), 3.15−2.99 (m, 3H), 2.86 (m, 1H), 1.80 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 198.1, 136.5, 133.4, 128.7, 127.9, 109.5, 71.8, 69.0, 45.2, 37.3, 36.6, 25.6. MS (EI): 232 (M^+, 4), 162 (19), 105 (100). Anal. Calcd for $C_{14}H_{16}O_3$ (232.25): C, 72.41; H, 6.89. Found: C, 72.38; H, 6.89.

Preparation of *endo*-7-[2-Oxo-2-(1,1-dimethylethyl)]-2,9-dioxabicyclo[4.3.0]nonane. The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6e** (1.33 g, 5.0 mmol) and pivaloyl chloride (1.80 g, 15.0 mmol, 3 equiv) as an electrophile. Reaction conditions: −78 °C to 0 °C, 12 h. After usual workup the residue was purified by flash chromatography (hexanes/ether 4:1 to 100% ether), affording the title ketone (0.72 g, 3.2 mmol, 64% yield) as a colorless oil.

IR (neat): 2830 (s), 1710 (vs), 1145 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.52 (d, J = 3.8 Hz, 1H), 4.03 (d, J = 8.5 Hz, 1H), 3.74 (m, 1H), 3.62 (m, 1H), 3.59 (d, J = 8.3 Hz, 1H), 2.55 (m, 4H), 2.08 (m, 1H), 1.54 (m, 2H), 1.35 (m, 1H), 1.15 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 214.5, 101.8, 70.0, 61.1, 44.1, 36.3, 35.9, 34.7, 27.1, 23.1, 19.8 (first diastereomer); δ 101.5, 73.9, 64.3, 44.1, 27.2, 26.4, 22.5, 20.6 (second diastereomer). MS (EI): 226 (M^+, 4), 127 (30), 111 (11), 85 (29), 57 (100). Anal. Calcd for $C_{13}H_{22}O_3$ (226.28): C, 69.03; H, 9.73. Found: C, 69.10; H, 9.91.

Preparation of *endo*-7-((*E*)-3-Carbethoxy-2-propenyl)-2,9-dioxabicyclo[4.3.0]nonane (16e). The procedure described for the preparation of **14a** was followed with the alkyl iodide **6e** (813 mg, 3.0 mmol) and ethyl propiolate (580 mg, 6.0 mmol, 2 equiv) as an electrophile. Reaction conditions: −78 to 0°C, 12 h. Purification by silica gel chromatography (hexanes/ether 4:1) of the crude product afforded the cyclic acetal **16e** (468 mg, 1.9 mmol, 65% yield) as a yellow oil.

IR (neat): 2985 (vs), 1700 (s), 1655 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.29 (m, 5H), 6.69 (dt, J = 15.8, 7.4 Hz, 1H), 5.77 (d, J = 15.5 Hz, 1H), 5.60 (d, J = 3.5 Hz, 1H), 4.73 (d, J = 8.5 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.75 (m, 1H), 3.66 (m, 1H), 2.19 (m, 4H), 1.71 (m, 1H), 1.58 (m, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.1, 145.9, 141.8 (first diasteromer); 128.4, 127.7, 126.1, 122.7, 101.8, 82.9, 60.8, 60.2, 49.5, 36.9, 28.5, 22.9, 20.6, 14.1 (second diastereomer). MS (EI): 316 (M^+, 20), 129 (20), 117 (34), 97 (100), 41 (17). Anal. Calcd for $C_{19}H_{24}O_4$ (316.33): C, 72.15; H, 7.59. Found: C, 72.30; H, 7.54.

Preparation of *endo*-7-(3-Carbethoxy-3-butenyl)-8-phenyl-2,9-dioxabicyclo[4.3.0]nonane (16f). The procedure described for the preparation of **14a** was followed with the alkyl iodide **6f** (1.72 g, 5.0 mmol) and ethyl (α-bromomethyl)acrylate[26] (2.97 g, 15.0 mmol, 3 equiv) as an electrophile. Reaction conditions: −78 °C to rt, 2 h. Purification by silica gel chromatography (hexanes/ether 4:1) of the crude product afforded a 1:1 diastereomeric mixture of the ester **16f** (1.22 g, 3.7 mmol, 75% yield) as a yellow oil.

IR (neat): 2930 (vs), 1710 (vs), 1630 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.27 (m, 5H), 6.01 (s, 1H), 5.62 (s, 1H), 5.33 (s, 1H), 4.68 (d, J = 9.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.78 (m, 1H), 3.65 (m, 1H), 2.24 (m, 1H), 2.13 (m, 1H), 2.05 (m, 2H), 1.81 (m, 1H), 1.57 (m, 3H), 1.47 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.9, 142.6, 140.3, 128.3, 127.7, 126.3, 124.8, 101.9, 83.3, 60.9, 60.6, 50.3, 37.1, 30.5, 24.7, 23.2, 19.6, 14.1. MS (EI): 330 (M^+, 2), 224 (28), 110 (67), 97 (100). Anal. Calcd for $C_{20}H_{26}O_4$ (330.37): C, 72.73; H, 7.88. Found: C, 72.71; H, 7.81.

Preparation of *endo*-4-(3-Carbethoxy-2-propenyl)-3-isopropyl-2,8-dioxabicyclo[3.3.0]octane (16g). The procedure described above for the preparation of **14a** was followed with the alkyl iodide **6g** (1.47 g, 5.0 mmol) and ethyl propiolate as an electrophile. Reaction conditions: −78 to 0 °C, 1.5 h. Purification by silica gel chromatography (hexanes/ether 9:1 to 4:1) of the crude product afforded a 1:1 mixture of diastereomers of the ester **16g** (0.93 g, 3.4 mmol, 67% yield) as a yellow oil.

IR (film): 2850 (s), 1615 (vs), 1525 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.15 (s, 1H), 5.62 (d, J = 4.9 Hz, 1H), 5.53 (s, 1H), 3.88 (q, J = 7.1 Hz, 2H), 3.89 (m, 2H), 3.52 (dd, J = 10.3, 2.7 Hz, 1H), 2.42 (m, 2H), 2.30 (m, 1H), 1.88 (m, 3H), 1.73−1.44 (m, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.00 (m, 1H), 0.85 (d, J = 6.7 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.9, 140.6, 124.8, 108.4, 87.0, 68.7, 66.6, 45.8, 42.9, 31.5, 30.8, 29.1, 25.0, 20.5, 15.4, 14.2 (first diasteromer); δ 140.5, 124.5, 108.0, 89.2, 50.1, 46.5, 33.1, 32.9, 30.3, 19.8, 17.1 (second diastereomer). MS (EI): 240 (6), 239 (38), 221 (19), 97 (100). Anal. Calcd for $C_{16}H_{26}O_4$ (282.30): C, 68.09; H, 9.22. Found: C, 67.93; H, 9.16.

Preparation of 2-Butoxy-4-(3-carbethoxy-3-butenyl)-5-phenyltetrahydrofuran (16h). The procedure described for the preparation of **14a** was followed with the iodo acetal **6h** (1.63 g, 5.0 mmol) and ethyl (α-bromomethyl)acrylate[26] (2.97 g, 15.0 mmol, 3 equiv) as electrophile. Reaction conditions: −78 °C to rt, 1 h). Usual workup and purification by silica gel chromatography of the residual oil afforded the product **16h** (1.10 g, 3.3 mmol, 66% yield) as a colorless oil.

IR (neat): 2830 (vs), 1715 (vs), 1645 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 5H), 6.11 (s, 1H), 5.42 (s, 1H), 5.35 (dd, J = 5.7, 3.0 Hz, 1H), 4.61 (d, J = 8.7 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.80 (td, J = 9.7, 6.8 Hz, 1H), 3.46 (td, J = 9.7, 6.7 Hz, 1H), 2.53 (m, 1H), 2.33 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.81−1.58 (m, 5H), 1.50−1.36 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.0, 141.0, 140.6, 128.4, 126.8, 124.5, 104.0, 84.7, 67.6, 60.5, 47.0, 39.4, 31.9, 31.0, 30.6, 19.4, 14.1, 13.9. MS (EI): 272 (5), 127 (44), 91 (100), 71 (76), 57 (98), 41 (63). Anal. Calcd for $C_{21}H_{30}O_4$ (346.38): C, 72.83; H, 8.67. Found: C, 72.90; H, 8.70.

Preparation of 2-Butoxy-4-(2-hydroxy-2-phenylethyl)-5-phenyltetrahydrofuran (16i). The procedure described for the preparation of **14a** was followed with the iodo acetal **6h** (1.63 g, 5.0 mmol). After completion of the cyclization reaction the reaction mixture was cooled to −78 °C, and BF_3•-Et_2O (4.23 g, 30.0 mmol) was added followed by dropwise addition of benzaldehyde (1.59 g, 15.0 mmol, 3 equiv). The reaction mixture was allowed to warm to −20 °C within 12 h, was diluted with ether (30 mL), and was poured into cold saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. Purification by silica gel chromatography (hexanes/ether 4:1) of the residual oil afforded the alcohol **16i** (1.01 g, 3.0 mmol, 60% yield) as a colorless oil.

IR (neat): 3350 (s), 2850 (vs), 1330 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 10H), 5.26 (m, 1H), 4.56 (m, 2H), 3.75 (dt, J = 8.7, 6.7 Hz, 1H), 3.40 (dt, J = 8.6, 6.7 Hz, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 1.89 (m, 2H), 1.80-1.76 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.6, 140.5, 128.4, 127.8, 127.5, 126.8, 125.7, 104.0, 84.7, 73.3, 67.6, 43.9, 41.3, 39.4, 31.8, 19.3, 13.8 (first diastereomer); δ 144.2, 140.4, 127.5, 126.7, 125.6, 103.9, 73.1, 43.8, 41.0, 39.2 (second diastereomer). MS (EI): 218 (35), 160 (100), 107 (83), 104 (98), 57 (74). Anal. Calcd for $C_{22}H_{28}O_3$ (340.39): C, 77.65; H, 8.24. Found: C, 77.46; H, 8.22.

Typical Procedure for the Cyclization Reaction of Bromo Acetals of Type 7. Preparation of 4-(3-Carbethoxy-3-butenyl)-2-ethoxy-5-phenyltetrahydrofuran (17a). A 50 mL three-necked flask equipped with an argon inlet, an internal thermometer, a magnetic stirring bar, and a septum cap was charged with $Ni(acac)_2$ (66 mg, 0.25 mmol, 5 mol %) and dry LiI (160 mg, 1.25 mmol, 25 mol %). A solution of the bromo acetal **7a** (1.42 g, 5.0 mmol) in THF (5 mL) was added, and the mixture was cooled to −78 °C. At this temperature Et_2Zn (1.0 mL, 10.0 mL, 2 equiv) was added dropwise, and after completion of the addition the reaction mixture was gradually warmed to 40 °C. It was stirred at this temperature for 12 h. The solvent and excess of Et_2Zn was removed *in vacuo*, and the further preparation was carried out as described for **14a**. Ethyl (α-bromomethyl)acrylate[26] (2.79 g, 15.0 mmol, 3 equiv) was added at −78 °C, and the reaction mixture was warmed to 0 °C and stirred for 1 h. Usual workup and purification by silica gel chromatography of the residual oil afforded the product **17a** (0.97 g, 3.2 mmol, 64% yield) as a yellow oil.

IR (neat): 2820 (s), 1725 (vs), 1645 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 5H), 6.22 (s, 1H), 6.05 (s, 1H), 5.28 (dd, J = 5.7, 3.2 Hz, 1H), 4.53 (d, J = 8.7 Hz, 1H), 4.11 (m, 3H), 3.76 (m, 1H), 3.43 (m, 1H), 2.49 (m, 1H), 2.24 (m, 2H), 1.62 (m, 3H), 1.20 (m, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.8, 142.2, 140.4, 128.2, 127.4, 126.4, 103.6, 84.6, 66.8, 63.1

(first diastereomer); δ 165.7, 140.6, 137.8, 127.7, 125.2, 124.3, 81.9, 37.6, 31.5, 13.9 (second diasteromer). MS (EI): 159 (11), 117 (100), 72 (15). Anal. Calcd for $C_{19}H_{26}O_4$ (306.35): C, 70.59; H, 8.49. Found: C, 70.31; H, 8.36.

Preparation of 4-(3,3-Dicarbethoxy-2-phenylpropyl)-2-ethoxy-5-phenyltetrahydrofuran (17b). The procedure described for the preparation of **17a** was followed with the bromo acetal **7a** (1.42 g, 5.0 mmol). Diethyl benzylidenemalonate (3.72 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 12 h. After usual workup, the residual oil was purified by flash chromatography (hexanes/ether 9:1 to 4:1), affording the product **17b** (1.30 g, 3.1 mmol, 61% yield).

IR (neat): 2990 (s), 2940 (s), 1715 (vs), 1455 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.28 (m, 10H), 5.24 (dd, J = 5.8, 3.4 Hz, 1H), 4.70 (d, J = 7.8 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.82 (m, 3H), 3.50 (m, 3H), 2.49 (m, 1H), 1.84 (m, 4H), 1.27 (m, 6H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 168.1, 141.2, 139.9, 128.5, 128.3, 127.9, 127.1, 126.8, 103.8, 85.3, 63.5, 61.6, 59.3, 44.9, 44.4, 40.7, 38.7, 35.2, 15.3, 14.2, 13.7 (first diasteromer); δ 167.7, 140.4, 140.4, 139.8, 128.5, 128.4, 128.1, 127.5, 127.0, 103.7, 84.4, 63.2, 61.1, 59.2, 44.4, 14.1 (second diastereomer). MS (EI): 409 ($M^+ - OC_2H_5$, 5), 188 (100), 45 (12). Anal. Calcd for $C_{27}H_{34}O_6$ (454.50): C, 71.37; H, 7.49. Found: C, 71.31; H, 7.28.

Preparation of 4-(3,3-Dicarbethoxy-2-phenylpropyl)-2-ethoxy-5-isopropyltetrahydrofuran (17c). The procedure described for the preparation of **17a** was followed with the bromo acetal **7b** (1.25 g, 5.0 mmol). Diethyl benzylidenemalonate (3.72 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 12 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1 to 4:1) of the residual oil afforded the product **17c** (1.30 g, 3.1 mmol, 61% yield) as a pale yellow oil.

IR (neat): 2850 (s), 1810 (s), 2790 (m), 1760 (vs), 1740 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 5H), 4.94 (dd, J = 5.3, 2.8 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.79 (q, J = 7.1 Hz, 2H), 3.25 (m, 3H), 3.32 (m, 2H), 1.99 (m, 1H), 1.69 (m, 3H), 1.49 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H), 1.09 (m, 4H), 0.88 (m, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 168.1, 167.6, 140.8, 140.6, 128.6, 128.5, 128.2, 127.0, 103.3, 103.2, 102.9, 90.7, 87.9, 87.6, 65.7, 62.2 (2C), 61.4 (2C), 60.9, 59.1, 45.5, 44.5, 40.6, 40.0, 38.9, 38.7, 38.1, 37.8, 37.0, 32.8, 31.5, 31.3 (2 C), 19.9, 19.5, 18.5, 18.0 (2C), 17.7, 16.8, 15.3, 14.9, 13.9, 13.6. 1. MS (EI): 420 (M^+, 19), 331 (97), 229 (56), 171 (100). Anal. Calcd for $C_{24}H_{36}O_6$ (420.43): C, 68.57; H, 8.57. Found: C, 68.72; H, 8.44.

Preparation of 4-(3-Carbethoxy-3-butenyl)-2-ethoxy-5-hexyltetrahydrofuran (17d). The procedure described above for the preparation of **17a** was followed with the bromo acetal **7c** (1.50 g, 5.0 mmol). Ethyl (α-bromomethyl)acrylate[26] (2.97 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 1 h. After usual workup the residual oil was purified by flash chromatography (hexanes/ether 95:5), affording the product **17d** (970 mg, 3.1 mmol, 61% yield) as a colorless oil.

IR (neat): 2930 (vs), 1990 (m), 1720 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.25 (s, 1H), 5.44 (s, 1H), 5.02 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.64 (m, 2H), 3.38 (m, 1H), 3.32 (m, 1H), 2.23 (m, 3H), 1.60 (m, 2H), 1.45 (m, 2H), 1.45−1.32 (m, 6H), 1.29−1.15 (m, 7H), 1.13 (t, J = 7.1 Hz, 3H), 0.81 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.9, 140.7, 124.2, 103.1, 82.5, 62.5, 60.4, 43.3, 39.1, 34.3, 31.9, 31.7, 30.7, 29.3, 26.2, 22.5, 15.2, 14.1, 13.9. MS (EI): 280 (6), 153 (100), 96 (35), 55 (38), 43 (52). Anal. Calcd for $C_{19}H_{34}O_4$ (326.38): C, 69.93; H, 10.43. Found: C, 69.90; H, 10.40.

Preparation of 4-((*E*)-3-Carbethoxy-2-propenyl)-2-ethoxy-5-hexyltetrahydrofuran (17e). The procedure described for the preparation of **17a** was followed with the bromo acetal **7c** (1.46 g, 5.0 mmol). Ethyl propiolate (1.45 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions −78 to −10 °C, 12 h. Usual workup and purification by silica gel chromatography (hexanes/ether 4:1) of the residual oil afforded the product **17e** (940 mg, 3.1 mmol, 61% yield) as a colorless oil.

IR (neat): 2830 (s), 1720 (vs), 1650 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.84 (dt, J = 15.6, 7.2 Hz, 1H), 5.77 (d, J = 15.6 Hz, 1H), 5.00 (d, J = 5.5 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H) 3.64 (m, 2H), 3.35 (m, 1H), 2.30 (m, 1H), 2.19 (m, 2H), 1.80 (m, 1H), 1.52−1.40 (m, 8H), 1.21 (2t, J = 7.1 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H), 0.81 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.5, 147.1, 122.6, 103.2, 82.5, 62.7, 60.2, 42.3, 38.9, 36.1, 34.4, 31.8, 29.4, 26.2, 22.6, 15.4, 14.3, 14.1. MS (EI): 227 (38), 85 (100), 57 (29). Anal. Calcd for $C_{18}H_{32}O_4$ (312.36): C, 69.32; H, 10.26. Found: C, 69.39; H, 10.30.

Preparation of 4-(3,3-Dicarbethoxy-2-phenylpropyl)-2-ethoxy-5-hexyltetrahydrofuran (17f). The procedure described above for the preparation of **17a** was followed with the bromo acetal **7c** (1.46 g, 5.0 mmol). Diethyl benzylidenemalonate (3.72 g, 15.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 to 10 °C, 12 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the residual oil afforded the product **17f** (1.30 g, 3.0 mmol, 60% yield) as a colorless oil.

IR (neat): 2840 (vs), 1640 (vs), 1350 (s), 1260 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.21 (m, 5H), 4.85 (dd, J = 5.5, 2.2 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.64-3.41 (m, 4H), 3.30 (m, 2H), 1.93 (m, 1H), 1.72 (m, 2H), 1.48 (m, 2H), 1.24 (12H), 1.08 (t, J = 7.1 Hz, 3H), 0.84 (m, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 168.2, 167.7, 140.6, 128.7, 128.4, 127.1, 103.2, 82.8, 62.5, 61.5, 61.1, 59.2, 45.2, 41.4, 40.2, 38.3, 34.7, 31.8, 29.4, 26.0, 22.6, 15.3, 14.1, 14.0, 13.6 (first diastereomer); δ 140.3, 129.4, 128.3, 103.3, 82.3, 62,7, 44.5, 40.8, 37.1, 33.6, 22.5 (second diastereomer). MS (EI): 371 (2), 203 (19), 153 (47), 45 (100). Anal. Calcd for $C_{27}H_{42}O_6$ (462.50): C, 70.11; H, 9.14. Found: C, 69.91; H, 9.25.

Preparation of *endo*-7-(3-Carbethoxy-3-butenyl)-8-isopropyl-2,9-dioxabicyclo[4.3.0]nonane (17g). The procedure described for the preparation of **17a** was followed with the bromo acetal **7d** (1.0 g, 3.5 mmol). Ethyl (α-bromomethyl)-acrylate[26] (1.38 g, 7.0 mmol, 2 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 1 h. Usual workup and purification by silica gel chromatography of the residual oil afforded the product **17g** (0.68 g, 2.3 mmol, 66% yield) as a colorless oil.

IR (neat): 2950 (s), 1710 (vs), 1660 (w) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.13 (s, 1H), 5.36 (s, 1H), 5.14 (s, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.72 (m, 1H), 3.56 (m, 2H), 2.20 (m, 1H), 1.97 (m, 1H), 1.66 (m, 4H), 1.55 (m, 4H), 1.49 (m, 7H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.9, 140.6, 124.5, 101.1, 85.3, 60.9, 60.6, 43.0, 37.1, 31.6, 30.9, 26.5, 23.4, 20.3, 19.8, 16.6, 14.2. MS (EI): 254 ($M^+ - CH_3$, 16), 253 (100), 97 (31). Anal. Calcd for $C_{17}H_{28}O_4$ (269.36): C, 68.91; H, 9.45. Found: C, 68.95; H, 9.57.

Preparation of *endo*-7-(3-Carbethoxy-3-butenyl)-8-hexyl-2,9-dioxabicyclo[4.3.0]nonane (17h). The procedure described for the preparation of **17a** was followed with the bromo acetal **7e** (1.30 g, 4.0 mmol). Ethyl (α-bromomethyl)-acrylate[26] (2.37 g, 12.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 to 0 °C, 1 h. Usual workup and purification by silica gel chromatography (hexanes/ether 9:1) of the residual oil afforded the product **17h** (0.87 g, 2.6 mmol, 65% yield) as a colorless oil.

IR (neat): 2921 (vs), 1709 (vs), 1640 (w) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.13 (s, 1H), 5.46 (s, 1H), 5.19 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.69 (m, 2H), 3.54 (m, 1H), 2.29 (m, 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 1H), 1.29 (m, 10H), 1.13 (t, J = 7.2 Hz, 3H), 0.80 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.9, 140.6, 124.5, 100.7, 80.8, 60.8, 60.5, 46.3, 36.9, 35.5, 31.7, 30.8, 29.4, 26.2, 25.8, 23.3, 22.5, 19.7, 14.1, 13.9. MS (EI): 338 (M^+, 2), 253 (100), 97 (40), 55 (31). Anal. Calcd for $C_{20}H_{34}O_4$ (338.44): C, 70.97; H, 10.11. Found: C, 70.84; H, 10.35.

Typical Procedure for the Oxidation of Cyclic Acetals to γ-Butyrolactones (Method A).[18] Preparation of *trans*-4-(3-Carbethoxy-3-butenyl)-5-phenyltetrahydrofuran-2-one (18a). A 25 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar, and a septum cap was charged with *m*-CPBA (50% by weight (Aldrich), 1.0 g, 2.4 mmol, 1.2 equiv), CH_2Cl_2 (9 mL), and $MgSO_4$ (0.5 g). The suspension was stirred at rt for 0.5 h, and the magnesium salt

was removed by filtration. $BF_3 \cdot Et_2O$ (0.12 mL, 0.8 mmol, 0.4 equiv) was added to the clear solution of the peracid, followed by the acetal **16h** (0.68 g, 2.0 mmol) dissolved in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 1.5 h at rt. It was diluted with ether (50 mL) and washed successively with aqueous $Na_2S_2O_3$ solution (10%, 30 mL), saturated aqueous Na_2CO_3 solution (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residual oil was purified by flash chromatography (hexanes/ether 1:1), affording the lactone **18a** (0.40 g, 1.4 mmol, 70% yield) as a colorless oil.

IR (neat): 2820 (s), 1770 (vs), 1705 (vs), 1630 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 6.06 (s, 1H), 5.38 (s, 1H), 5.97 (d, J = 8.8 Hz, 1H, 5-H), 4.10 (q, J = 7.1 Hz, 2H), 2.76 (dd, J = 14.4, 6.3 Hz, 1H), 2.42−2.20 (m, 1H, 4-H), 1.73 (m, 1H, 4-H), 1.61 (m, 1H, 4-H), 1.21 (t, J = 7.1 Hz, 3H). ^{1}H-NMR-NOE (500 MHz, $CDCl_3$): irradiation on the resonance frequency of 5-H increases the intensity of 4-H. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 175.9, 166.6, 139.5, 138.1, 128.8, 128.7, 126.1, 125.3, 86.6, 60.8, 44.4, 35.2, 31.0, 30.1, 14.2. MS (EI): 288 (M^+, 3), 174 (100), 105 (77), 81 (65), 41 (54). Anal. Calcd for $C_{17}H_{20}O_4$ (288.27): C, 70.82; H, 6.98. Found: C, 70.51; H, 6.86.

Preparation of *trans*-4-(3,3-Dicarbethoxy-2-phenylpropyl)-5-isopropyltetrahydrofuran-2-one (18b). The procedure described for the preparation of **18a** was followed with the acetal **17c** (294 mg, 0.70 mmol, 1 equiv). The oxidation was complete after 3 h of stirring at rt. Usual workup and purification by silica gel chromatography of the residual oil afforded the lactone **18b** (240 mg, 0.61 mmol, 87% yield) as a colorless oil.

IR (neat): 2980 (vs), 2950 (vs), 2890 (s), 1780 (vs), 1750 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.21 (m, 5H), 4.17 (m, 2H), 3.80 (m, 3H), 3.53 (dd, J = 10.6, 2.7 Hz, 1H), 3.28 (m, 1H) 2.08−1.56 (m, 7H), 1.18 (t, J = 5.3 Hz, 3H), 0.83 (m, 6H), 0.68 (dd, J = 11.9, 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 176.3, 168.0, 167.5, 139.6, 128.6, 128.0, 127.6, 89.9, 61.6, 58.6, 44.3, 38.8, 36.1, 35.3, 34.5, 31.5, 18.3, 16.9, 13.9, 13.5 (first diastereomer); δ 175.9, 167.9, 139.2, 128.3, 127.5, 89.6, 61.4, 58.4, 43.8, 39.7, 35.8, 31.8, 18.9, 16.8, 13.6 (second diastereomer). MS (EI): 390 ($M^+ - 1$, 8), 249 (15), 189 (100), 171 (19). Anal. Calcd for $C_{22}H_{31}O_6$ (391.37): C, 67.52; H,7.93. Found: C, 67.40; H, 7.93.

Preparation of *trans*-4-((*E*)-3-Carbethoxy-2-propenyl)-5-hexyltetrahydrofuran-2-one (18c). The procedure described above for the preparation of **18a** was followed with the acetal **17e** (178 mg, 0.57 mmol, 1 equiv). The oxidation was complete after 1.5 h of stirring at rt. After usual workup the residual oil was purified by flash chromatography (hexanes/ether 4:1), affording the lactone **18c** (160 mg, 0.56 mmol, 98% yield) as a colorless oil.

IR (neat): 2920 (vs), 1780 (vs), 1720 (vs), 1660 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.76 (dt, J = 8.6, 7.0 Hz, 1H), 5.81 (d, J = 5.5 Hz, 1H), 3.94 (q, J = 7.1 Hz, 2H), 3.88 (m, 1H), 2.64 (m, 2H), 2.31 (m, 2H), 2.19 (m, 3H), 1.57 (m, 3H), 1.41 (m, 1H), 1.23 (m, 7H), 0.81 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 175.6, 165.8, 144.0, 124.1, 85.0, 60.4, 39.7, 35.4, 34.5, 34.5, 31.5, 28.8, 25.8, 22.4, 14.2, 14.0. MS (EI): 282 (M^+, 3), 197 (80), 151 (100), 123 (84), 41 (86). Anal. Calcd for $C_{16}H_{26}O_4$ (282.30): C, 68.09; H, 9.22. Found: C, 68.09; H, 8.97.

Typical Procedure for the Preparation of γ-Butyrolactones from Bromo Acetals of Type 7 (Method B). Preparation of *trans*-4-(3-Carbethoxy-3-butenyl)-5-isopropyltetrahydrofuran-2-one (18d). First the procedure described for the preparation of **17a** was followed with the bromo acetal **7b** (0.75 g, 3.0 mmol). Ethyl (α-bromomethyl)-acrylate[26] (1.77 g, 9.0 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 2 h. After usual workup the residual oil was filtered over a short plug of silica gel. After evaporation of the solvents the residual oil was directly submitted to the oxidation procedure described for the preparation of **18a**. The oxidation was complete after 1.5 h at rt. Usual workup and purification by silica gel chromatography (hexanes/ether 4:1) afforded the lactone **18d** (0.30 g, 1.5 mmol, 53% yield) as a colorless oil.

IR (neat): 2830 (s), 1760 (vs), 1710 (vs), 1630 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.10 (s, 1H), 5.47 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 5.4 Hz, 1H), 2.62 (dd, J = 19.8, 11.2 Hz, 1H), 2.18 (m, 5H), 1.76 (m, 1H), 1.67 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.5 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 176.3, 166.6, 139.8, 125.1, 90.0, 60.6, 37.2, 34.9, 33.4, 32.1, 29.9, 18.6, 17.0, 14.1. MS (EI): 211 (57), 165 (100), 137 (97), 81 (58). Anal. Calcd for $C_{14}H_{22}O_4$ (206.28): C, 66.14; H, 8.66. Found: C, 66.16; H, 8.92.

Preparation of *trans*-4-(3-Carbethoxy-3-butenyl)-5-hexyltetrahydrofuran-2-one (18e). The procedure described above for the preparation of **18d** was followed with the bromo acetal **7c** (420 mg, 1.42 mmol, 1 equiv). Ethyl (α-bromomethyl)acrylate[26] (820 mg, 4.2 mmol, 3 equiv) was used as an electrophile. Reaction conditions: −78 °C to rt, 1 h. After usual workup volatile components were distilled off, and the residual oil was submitted to the oxidation procedure. The oxidation was complete after 1 h at rt. Usual workup and purification by silica gel chromatography (hexanes/ether 4:1) afforded the lactone **18e** (220 mg, 0.73 mmol, 50% yield) as a colorless oil.

IR (film): 2910 (vs), 2870 (m), 1780 (vs), 1710 (vs) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.10 (s, 1H), 5.48 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.04 (dt, J = 10.4, 4.3 Hz, 1H), 2.40 (dd, J = 17.0, 8.2 Hz, 1H), 2.10 (m, 3H), 2.05 (m, 1H), 1.84 (m, 1H), 1.80 (m, 2H), 1.76 (m, 3H), 1.25 (m, 10H), 0.82 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 176.3, 166.8, 139.4, 125.2, 85.8, 60.8, 40.9, 35.1, 34.7, 32.2, 311.7, 30.2, 29.1, 25.6, 22.5, 14.2, 14.0. MS (EI): 296 ($M^+ - 1$, 19), 137 (77), 81 (69), 41 (100). Anal. Calcd for $C_{17}H_{29}O_4$ (297.33): C, 68.69; H, 9.76. Found: C, 68.42; H, 9.64.

Preparation of *endo*-4-(Deuteriomethyl)-2-azabicyclo-[4.3.0]nonane (20). The procedure described for the preparation of **14a** was followed with the alkyl iodide **8** (1.06 g, 3.0 mmol). The cyclization was performed in the presence of Ni(acac)$_2$ (15 mg, 0.06 mmol, 2 mol %) as well as in the presence of $PdCl_2$(dppf)[13] (76 mg, 0.09 mmol, 3 mol %) as a catalyst. The resulting alkylzinc species were quenched by addition of a solution of AcOD (D_2O: 1.0 mL, 50 mmol; AcCl: 1.7 mL, 25 mmol) in THF (2 mL) at −78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to rt and was diluted with ether (15 mL) and saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residual oil was purified by flash chromatography (hexanes/ether 9:1), affording the monodeuterated product **20** (490 mg, 2.13 mmol, 71% yield) as a colorless oil.

IR (neat): 3300 (s), 2955 (m), 2890 (w) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H), 4.00 (d, J = 13.8 Hz, 1H), 3.29 (d, J = 13.7 Hz, 1H), 2.85 (m, 1H), 2.64 (d, J = 9.4 Hz, 1H), 2.49 (dd, J = 9.8 Hz, 1H), 2.20 (m, 1H), 1.87 (d, J = 9.8 Hz, 1H), 1.81−1.76 (m, 2H), 1.66−1.61 (m, 1H), 1.48−1.20 (m, 5H), 0.87 (d, J = 5.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 141.3, 128.2, 128.0, 126.3, 63.9, 59.1, 58.2, 42.7, 34.5, 27.1, 25.6, 22.9, 20.7, 13.2 (t). MS (EI): 231 ($M^+ + 1$, 7), 230 (M^+, 45), 91 (100). Anal. Calcd for $C_{16}H_{22}DN$ (230.31): C, 83.48; H, 10.43; N, 6.08. Found: C, 83.34; H, 10.29; N, 6.30.

Formal Synthesis of (−)-Methylenolactocin (3). Preparation of (*E*)-(*S*)-(+)-(Trimethylsilyl)-1-octen-3-ol (26).[32] A 50 mL three-necked flask equipped with a magnetic stirring bar, a septum cap, and an argon inlet was charged with (1*R*,2*R*)-1,2-bis(trifluoromethanesulfonamido)cyclohexane[33] (**25**) (316 mg, 0.8 mmol, 8 mol %) and Ti(O-*i*-Pr)$_4$ (6.0 mL, 20.0 mmol, 2 equiv) in toluene (5 mL). The reaction mixture was stirred for 45 min at 45 °C. It was cooled to −40 °C, $Pent_2Zn$ (4.2 mL, 20.0 mmol, 2 equiv) was added, and the resulting deep red solution was stirred for 10 min followed by dropwise addition of (*E*)-3-(trimethylsilyl)-2-propenal[32] (**23**) (1.28 g, 10.0 mmol, 1 equiv). After 1 h of stirring at −40 °C the reaction was complete, the reaction mixture was quenched with an aqueous HCl solution (10%), ether (60 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 60 mL), and the combined organic layer was washed with saturated $NaHCO_3$ solution (60 mL)

and brine (60 mL). It was dried ($MgSO_4$) and filtered, and after evaporation of the solvents the crude residue was purified by flash chromatography (hexanes/ether 9:1), affording the alcohol **26** (1.42 g, 7.1 mmol, 71% yield) as a colorless oil.

$[\alpha]^{25}_{589}$: 9.22 (c = 6.00, benzene). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.99 (dd, J = 17.6, 3.7 Hz, 1H), 5.75, (d, J = 17.6 Hz, 1H), 4.00 (td, J = 6.3, 6.2 Hz, 1H), 1.77 (s, 1H), 1.47−1.36 (m, 2H), 1.35−1.17 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H), 0.01 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 148.8, 129.1, 74.7, 36.9, 31.8, 25.1, 22.6, 14.0, −1.4.

Preparation of (*E*)-(4*S*)-(−)-1-Bromo-2-butoxy-6-(trimethylsilyl)-3-oxa-4-pentyl-5-hexene (22). A 50 mL three-necked flask equipped with a gas inlet, a septum cap, and a magnetic stirring bar was charged with (*E*)-(*S*)-(+)-(trimethylsilyl)-1-octen-3-ol (**26**) (1.60 g, 8.0 mmol, 1 equiv) dissolved in dichloromethane (3 mL). NBS (2.4 g, 13.3 mmol, 1.6 equiv) was added, and the resulting suspension was cooled to 0 °C. Butyl vinyl ether (**4a**) (1.76 mL, 13.3 mmol, 1.6 equiv) was added dropwise at this temperature. After 1 h of stirring, the reaction mixture was diluted with ether (30 mL) and poured on ice-cooled brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$), and the solvents were evaporated. Purification by silica gel chromatography (hexanes/ether 9:1) afforded the alkyl bromide **22** (2.48 g, 7.1 mmol, 88% yield) as a colorless liquid.

$[\alpha]^{25}_{589}$: −30.46 (c = 5.36, $CHCl_3$). IR (neat): 2940 (s), 2920 (s), 1250 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.86 (d, J = 6.9 Hz, 1H), 5.73 (d, J = 3.2 Hz, 1H), 4.56 (q, J = 5.4 Hz, 2H), 3.85 (m, 1H), 3.47 (m, 2H), 3.31 (m, 2H), 1.51 (m, 4H), 1.46 (m, 7H), 0.85 (m, 6H), 0.00 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.9, 133.6, 101.1, 81.7, 67.1, 65.7, 35.3, 32.5, 31.9 (2 C), 24.9, 22.5, 19.3, 13.9, −1.4 (first diastereomer); δ 146.1, 132.0, 99.4, 80.7, 65.7, 35.2, 32.3, 31.7 (2 C), 19.2, 13.8 (second diastereomer). MS (EI): 181 (30), 179 (30), 73 (34), 57 (100). Anal. Calcd for $C_{17}H_{35}BrO_2Si$ (378.41): C, 53.95; H, 9.31. Found: C, 53.68; H, 9.58.

Preparation of *trans*-(4*R*,5*S*)-5-Pentyl-2-butoxytetrahydrofuran-4-carbaldehyde (30). A 25 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar, a septum cap, and an internal thermometer was charged with $Ni(acac)_2$ (11.6 mg, 0.05 mmol, 5 mol %) and LiI (31.0 mg, 0.25 mmol, 25 mol %). A solution of the bromo acetal **22** (0.35 g, 1.0 mmol) in THF (1.5 mL) was added, and the resulting suspension was cooled to −78 °C. At this temperature Et_2Zn (0.25 mL, 2.5 mmol, 2.5 equiv) was added. The cooling bath was removed, and the reaction mixture was gradually warmed to 40 °C. It was stirred for 12 h at this temperature, and the excess of Et_2Zn was removed *in vacuo* (6 h, rt, 0.1 mmHg). The solid residue was dissolved in THF (3 mL) and cooled to −15 °C. At this temperature TMSCl (0.25 mL, 2.0 mmol, 2 equiv) was added, and the argon supply was replaced by oxygen. The reaction mixture was allowed to warm to −5 °C and stirred vigorously for 4 h. It was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL), ether (5 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 15 mL). The combined organic layer was dried ($MgSO_4$), the solvent was evaporated, and the crude residue was purified by flash chromatography (hexanes/ether 95:5), affording the aldehyde **30** (133 mg, 0.55 mmol, 55% yield) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.56 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 3.9 Hz, 1H), 4.13 (dd, J = 12.9, 7.4 Hz, 1H), 3.60 (m, 1H), 3.26 (m, 1H), 2.91 (m, 1H), 2.11 (m, 3H), 1.46 (m, 6H), 1.30 (m, 9H), 1.22 (t, J = 7.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 200.3, 103.5, 79.7, 66.9, 55.7, 37.2, 34.6, 32.0, 31.6, 25.6, 22.4, 19.2, 13.8, 13.7 (major diastereomer); δ 66.7, 54.7, 31.5, 26.5 (minor diastereomer).

Preparation of *trans*-(4*R*,5*S*)-(−)-2-Oxo-5-pentyltetrahydrofuran-4-carboxylic Acid (21). A 10 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar, and a septum cap was charged with a solution of the aldehyde **30** (120 mg, 0.5 mmol) in acetone (1 mL). This solution was cooled to 0 °C, and the Jones reagent (3.0 mL) was added dropwise. After being stirred for 5 min at 0 °C, the excess of the oxidizing agent was quenched by addition of 2-propanol (1 mL). The reaction mixture was diluted with ether (5 mL), and the precipitated chromium salts were dissolved by addition of a saturated aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried ($MgSO_4$). After filtration and evaporation of the solvents, the solid residue was purified by recrystallization (dichloromethane/hexanes), affording the carboxylic acid **21** (90 mg, 0.45 mmol, 90% yield) as a white crystalline solid, mp 104 °C (lit.[8b] mp = 105 −106 °C).

$[\alpha]^{25}_{589}$: −50.3 (c = 0.41, $CHCl_3$) (lit.[8b] $[\alpha]^{25}_{589}$: −50.5 (c = 0.40, $CHCl_3$)). IR (KBr): 3438 (s, br), 2956 (s), 2929 (s), 1749 (vs), 1241 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.93 (s, 1H), 4.56 (dt, J = 7.3, 4.9 Hz, 1H), 3.10 (ddd, J = 9.3, 8.3, 7.3 Hz, 1H), 2.89 (dd, J = 17.8, 9.7 Hz, 1H), 2.79 (dd, J = 17.9, 9.7 Hz, 1H), 1.75 (m, 2H), 1.25 (m, 6H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 176.3, 174.6, 81.9, 45.4, 35.3, 31.9, 31.3, 24.8, 22.4, 13.9. MS (EI): 199 (M^+ − 1, 14), 180 (44), 179 (46), 129 (55), 57 (100). Anal. Calcd for $C_{10}H_{16}O_4$ (200.17): C, 59.99; H, 8.05. Found: C, 59.91; H, 8.19.

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