Formal Total Synthesis of Ascidiatrienolide A and the Didemnilactones

Alois Fürstner,* Monika Schlede

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany
Fax: (+49)-208-306-2994, e-mail: fuerstner@mpi-muelheim.mpg.de

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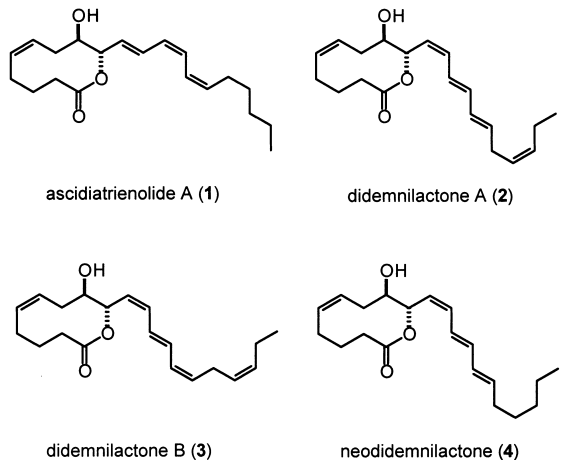
Abstract: A concise synthesis of the ten-membered lactone **26** is described which constitutes the key intermediate of a previous total synthesis of the marine natural product ascidiatrienolide **1** and can also be elaborated into the closely related didemnilactones **2** – **4**. The *E/Z*-ratio obtained in the ring-closing metathesis (RCM) reaction forging such non-enolide structures is found to be dependent on the relative configuration of the cyclization precursor as well as on the chosen catalyst. Specifically, it is shown that the ruthenium indenylidene complex **12** and the "second generation" Grubbs type catalyst **13** bearing an *N*-heterocyclic carbene ligand lead to opposite stereochemical results when applied to the *syn*-configured diene **21**, but to the identical outcome with the *anti*-configured analogue **10**.

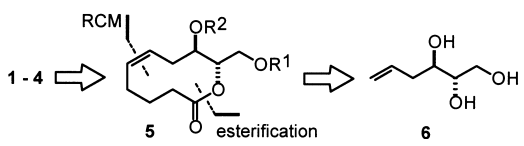
Keywords: medium-sized rings; metathesis; natural products; ruthenium; stereochemistry

Introduction

Crude extracts of the marine ascidian *Didemnum candidum* exhibit strong *in vitro* inhibitory activity against phospholipase A_2. A search for the active principle led to the discovery of ascidiatrienolide A (**1**) which was assumed to incorporate a nine membered lactone.[1,2,3] During an elegant synthetic study directed towards this eicosanoid, however, Holmes et al. found that the original structural assignment was incorrect. They have established the constitution and stereochemistry of ascidiatrienolide A as it appears in **1**,[4] showing that this secondary metabolite is a close relative of the didemnilactones **2** – **4**.[5] This family of complex fatty acid derivatives isolated from the tunicate *Didemnum moseleyi* is known for its affinity to the leukotriene B_4 receptor of human polymorphonuclear leucocyte membrane fractions and has been subject of total synthesis in the past.[5]



Described below is a complementary synthesis of the common lactone core segment of **1** – **4** that can be elaborated into any of these marine lipids[6,7] by adopting the chain elongation protocol developed by Holmes. As shown in Scheme 1, ring closing olefin metathesis (RCM)[8] allows us to deconvolute this target (**5**) into a simple, *anti*-configured triol **6** derived from the chiral pool. Although this approach promises to be straightforward,[9] it bears the non-negligible risk associated with the formation of medium-sized rings by RCM.[8,10] Since the inherent ring strain predisposes such compounds to ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP), the number of successful applications in this series – in particular to ten-membered cycloalkenes[11,12] – is still rather limited. Moreover, RCM reactions tend to provide mixtures of (*E*)- and (*Z*)-configured products and a reliable and general method to control the geometry of the newly formed double bond has yet to be found.[13] Therefore, lactone **5** provides an excellent testing ground to study which parameters influence the effi-



Scheme 1.

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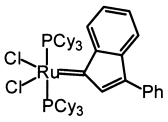
ciency and/or the stereochemical course of RCM as applied to medium-sized rings.

Results and Discussion

Our exploratory study (Scheme 2)[14] starts from 2-deoxy-D-ribose **7** which reacts without need for protecting groups with an excess of methylenetriphenylphosphorane to afford the acyclic triol **8** in 88% yield.[15] Treatment of the latter with *p*-methoxybenzaldehyde dimethyl acetal in the presence of catalytic amounts of camphorsulfonic acid affords product **9** in line with the known preference of aldehyde derivatives to react with polyols to 1,3-dioxane rings under equilibrating conditions.[16] Esterification of the remaining secondary hydroxy group in **9** with 5-hexenoic acid delivers diene **10** and sets the stage for the envisaged RCM event. Assuming that the pre-existing ring orients the olefinic side chains in a cyclization friendly conformation, we were not surprised to find that substrate **10** readily cyclizes to the ten-membered lactone **11** in 67% yield on exposure to catalytic amounts of the ruthenium indenylidene complex **12**[17] in refluxing CH_2Cl_2 as the preferred solvent.[18] This catalyst has recently been shown to be equipotent or even superior to the more popular Grubbs carbene $(PCy_3)_2Cl_2Ru{=}CHPh$[19] and is particularly easy to make on a large scale.[17,20] The observed isomer distribution of $E{:}Z = 8{:}1$, however, is highly unfavorable for the envisaged total synthesis of **1** – **4** which invariably contain a (*Z*)-alkene in their core structure. It is important to note that the use of the "second generation" catalyst **13**[21] bearing an *N*-heterocyclic carbene ligand leads to essentially the same outcome (71%, $E{:}Z = 8.4{:}1$).[22]



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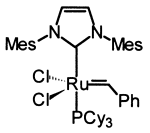
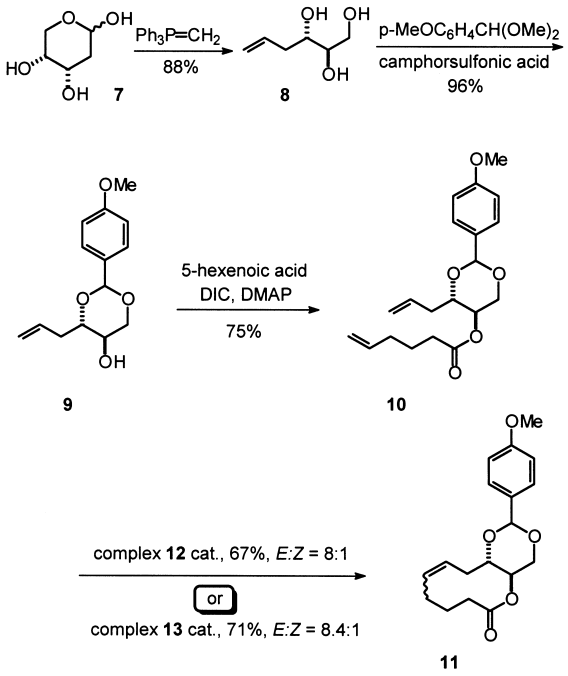
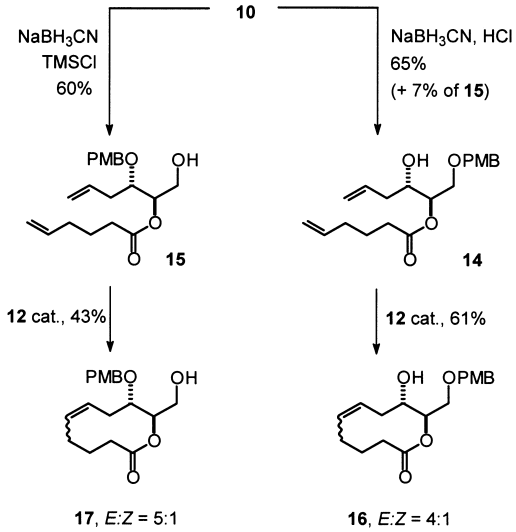


13

Therefore, we investigated to what extent the constraints imposed by the pre-existing acetal unit in **10** on the transition state of RCM account for the efficiency of cyclization and/or for the observed stereochemical preference (Scheme 3). For this purpose, reductive cleavage of the acetal ring was performed with $NaBH_3CN$ in the presence of ethereal HCl providing product **14** in 65% yield carrying the resulting PMB ether at the terminal position.[23] If the reduction is performed with $NaBH_3CN$ in MeCN in the presence of TMSCl as the promotor,[24] the isomeric PMB-ether derivative **15** is formed as the only product. Though acyclic, both dienes convert into the corresponding cycloalkenes **16** and **17** in 61% and 43% yield, respectively, on exposure to catalytic amounts of complex **12**;[17] the (*E*)-isomer is



Scheme 2.



Scheme 3.

again favored in either case. This result shows that the presence of the acetal ring in **10** is neither necessary to ensure an efficient closure of the medium-sized ring nor does it determine the stereochemical course of the reaction.

Next we probed if changes in the relative configuration of the triol segment affect the cyclization reaction. For this purpose, the *syn*-configured substrate **21** was prepared as depicted in Scheme 4 using a tin-mediated, ultrasound-promoted addition of allyl bromide to unprotected glyceraldehyde **18**.[25] The resulting mixture of isomers is carried through to compound **21** by acetalization and subsequent esterification as described

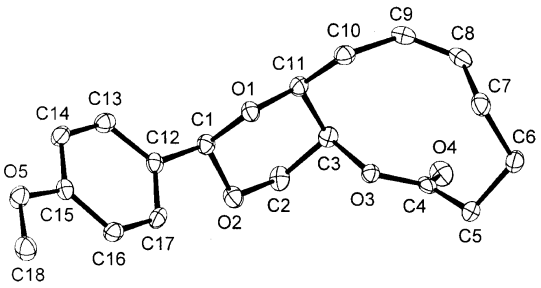


Figure 1. Molecular structure of (*Z*)-**22.** Anisotropic displacement parameters are shown at 50% probability level, hydrogen atoms have been omitted for clarity.

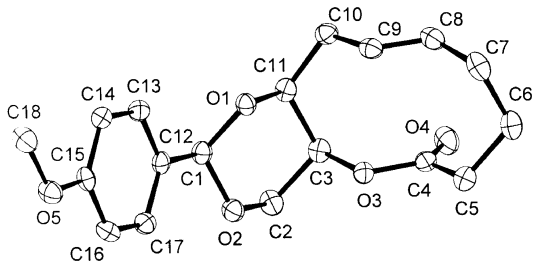
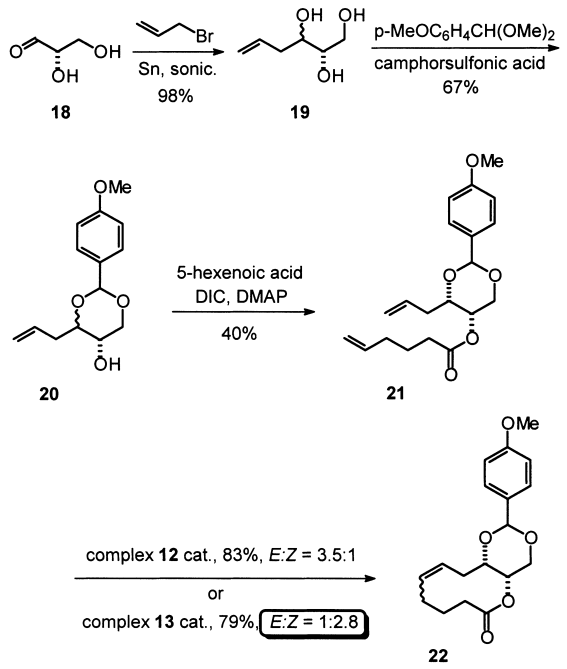
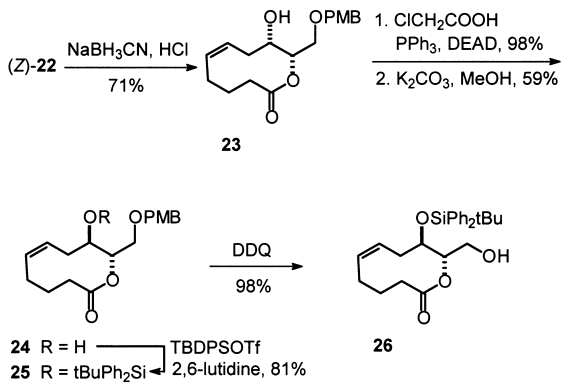


Figure 2. Molecular structure of (*E*)-**22.** Anisotropic displacement parameters are shown at 50% probability level, hydrogen atoms have been omitted for clarity.



Scheme 4.



Scheme 5.

above. At that stage, the major *syn* isomer can be conveniently purified by conventional flash chromatography. Exposure of diene **21** to a refluxing solution of the indenylidene complex **12** affords cycloalkene **22** in excellent yield with an *E:Z* ratio of 3.5:1 as determined by GC. A comparison of this result with the isomer distribution obtained for the corresponding *anti*-configured substrate **10** under otherwise identical conditions (*E:Z* = 8:1, *vide supra*) illustrates the subtle influence of remote substituents on the stereochemical outcome of RCM in the macrocyclic series.[26]

Since the replacement of the indenylidene catalyst **12** by the NHC-containing complex **13** has essentially no effect on either the productivity or the *E/Z*-ratio in the cyclization of the *anti*-configured substrate **10**, it was surprising to find that changing the catalyst has a very profound implication in the *syn* series.[22] Specifically, RCM of diene **21** in the presence of **13** delivers the (*Z*)-alkene as the major product in good overall yield (*E:Z* = 1:2.8). The structures of both geometrical isomers of **22** in the solid state are depicted in Figures 1 and 2.

The favorable outcome obtained with complex **13** paves the way to the common core of ascidiatrienolide and the didemnilactones (Scheme 5). Specifically, reductive opening of the acetal ring of (*Z*)-**22** with $NaBH_3CN$ in the presence of ethereal HCl affords product **23** in good yield which is subjected to a Mitsunobu reaction[27] with chloroacetate to install the proper configuration at C-8 (ascidiatrienolide numbering). Cleavage of the chloroacetate with K_2CO_3 in MeOH, protection of the resulting secondary OH group in **24** as a *t*-$BuPh_2Si$ ether followed by oxidative cleavage of the PMB group readily affords compound **26**. This product is identical in all respects with the key intermediate prepared by Holmes and therefore completes a formal total synthesis of ascidiatrienolide A **1**.[4] As the didemnilactones are isomers of **1** in the polyunsaturated domain (with or without an additional double bond) they should be accessible from the same intermediate by adopting the established chain elongation protocol.

In summary, this study witnesses the efficiency of RCM even when applied to the least favorable ring sizes. It also reveals, however, the very subtle and cooperative influence of different parameters on the stereochemical course of metathesis which are difficult to rationalize and predict at our present level of mechanistic understanding. Strategies for the stereoselective and reagent-controlled formation of cycloalkenes by metathetic

routes are therefore urgently called for and are subject of ongoing investigations in this laboratory.[28]

Experimental Section

General Remarks

All reactions were carried out under Ar. The solvents used were purified by distillation over the indicated drying agents prior to use and were transferred under Ar: THF, Et_2O (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), pyridine (KOH, then CaH_2). Flash chromatography: Merck silica gel 60 (230 – 400 mesh). NMR: Spectra were recorded on DPX 300 or DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR: Nicolet Magna 750 FT-IR, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95. All commercially available chemicals (Lancaster, Aldrich) were used as received.

(2*R*,3*S*)-Hex-5-ene-1,2,3-triol (8)

A suspension of $NaNH_2$ (2.07 g, 53.0 mmol) and methyl(triphenyl)phosphonium bromide (9.46 g, 27.0 mmol) in THF (100 mL) was refluxed for 4 h and then stirred at ambient temperature overnight. The precipitated ylide was filtered off and added in portions to a suspension of 2-deoxy-D-ribose **7** (1.77 g, 13.0 mmol) in THF (50 mL) at –78 °C. The resulting mixture was allowed to warm to ambient temperature over a period of 9 h and stirring was continued for another 12 h. For work-up, the reaction was quenched by carefully adding EtOH (5 mL), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (EtOH/CH_2Cl_2, 1:4) to afford product **8** as colorless crystals; yield: 1.54 g (88%); mp 54 – 55 °C; $[\alpha]_D^{20}$: 9.1 (*c* 1.1, H_2O). ^{1}H NMR (300 MHz, CD_3OD): δ = 5.82 (tdd, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.12 – 4.91 (m, 2H), 3.64 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.50 – 3.42 (m, 2H), 3.40 – 3.33 (m, 1H), 2.40 – 2.31 (m, 1H), 2.16 – 2.04 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 136.9, 117.6, 76.1, 73.4, 64.9, 39.1; IR (film): ν = 3313, 3231, 2901, 1643, 1464, 1066, 1030, 982, 915, 870 cm^{-1}. MS: *m*/*z* (rel. intensity) = 101 (3), 91 (55), 83 (13), 71 (67), 70 (43), 61 (100), 60 (13), 55 (25), 45 (41), 44 (89), 43 (83), 42 (19), 41 (42), 39 (26), 31 (35), 29 (26), 27 (24); HRMS: calcd. for ($C_6H_{12}O_3$ + H): 133.086469; found: 133.086172. The analytical and spectroscopic data are in agreement with those reported in the literature.[29]

(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-[1,3]dioxan-5-ol (9)

A solution of triol **8** (1.13 g, 8.55 mmol), *p*-methoxybenzaldehyde dimethyl acetal (3.12 g, 17.1 mmol) and camphorsulfonic acid (0.20 g, 0.86 mmol) in CH_2Cl_2 (30 mL) was stirred at ambient temperature for 18 h. The reaction was then neutralized by careful addition of Et_3N, all volatiles were removed under vacuum and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford product **9** as a colorless solid; yield: 2.07 g (96%); mp 96 – 97 °C; $[\alpha]_D^{20}$: – 24.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.37 (dd, *J* = 6.7, 1.7 Hz, 2H), 6.87 (dd, *J* = 6.7, 2.1 Hz, 2H), 5.98 (tdd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.42 (s, 1H), 5.18 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.14 – 5.09 (m, 1H), 4.23 – 4.18 (m, 1H), 3.79 (s, 3H), 3.63 – 3.50 (m, 3H), 2.69 – 2.59 (m, 1H), 2.47 – 2.35 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 160.1, 134.6, 130.6, 127.5, 117.1, 113.5, 100.9, 81.2, 71.1, 65.5, 55.3, 36.4; IR (film): ν = 3415, 3078, 3002, 2935, 2909, 1642, 1614, 1518, 1251, 1173, 1081, 1034, 832, 563 cm^{-1}; MS: *m*/*z* (rel. intensity) = 250 ([M^+], 25), 249 (18), 209 (17), 179 (15), 137 (88), 136 (42), 135 (100), 121 (23), 109 (17), 108 (16), 77 (21), 43 (11), 41 (13); anal. calcd. for $C_{14}H_{18}O_4$ (250.29): C 67.18, H 7.25; found: C 67.24, H, 7.34.

(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)[1,3]dioxan-5-yl Hex-5-enoate (10)

A solution of compound **9** (1.55 g, 6.20 mmol) in CH_2Cl_2 (100 mL) was added to a solution of 5-hexenoic acid (1.42 g, 12.4 mmol), diisopropylcarbodiimide (0.86 g, 6.80 mmol) and 4-dimethylaminopyridine (*ca.* 20 mg) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 24 h before the solvent was removed in vacuum and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to give product **10** as a colorless syrup; yield: 1.62 g (75%); $[\alpha]_D^{20}$: –27.9 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.41 (dd, *J* = 6.7, 2.0 Hz, 2H), 6.90 (dd, *J* = 6.7, 2.0 Hz, 2H), 5.94 (tdd, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.83 (tdd, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.47 (s, 1H), 5.17 – 5.00 (m, 4H), 4.79 (dt, *J* = 10.0, 5.3 Hz, 1H), 4.33 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.85 (ddd, *J* = 9.6, 7.4, 3.7 Hz, 1H), 3.81 (s, 3H), 3.60 (t, *J* = 10.3 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.41 – 2.30 (m, 3H), 2.16 – 2.08 (m, 2H), 1.79 – 1.69 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 172.3, 160.2, 137.8, 133.8, 130.3, 127.5, 117.1, 115.2, 113.5, 101.1, 78.6, 68.0, 66.2, 55.3, 36.3, 33.3, 33.0, 24.0; IR (film): ν = 3077, 2936, 2858, 1742, 1641, 1616, 1518, 1250, 1170, 1035, 995, 917, 828 cm^{-1}; MS: *m*/*z* (rel. intensity) = 346 ([M^+], 17), 303 (10), 169 (28), 137 (30), 136 (24), 135 (100), 127 (13), 121 (12), 97 (26), 80 (29), 79 (10), 69 (36), 55 (29), 41 (47); anal. calcd. for $C_{20}H_{26}O_5$ (346.42): C 69.34, H 7.56; found: C 69.48, H 7.63.

(2*R*,4a*R*,12a*S*)-2-(4-Methoxyphenyl)-4a,7,8,9,12,12a-hexahydrooxecino[10,9-*e*]-1,3-dioxin-6-one (11)

A solution of diene **10** (91 mg, 0.262 mmol) and the ruthenium indenylidene complex **12** (48 mg, 0.052 mmol) in CH_2Cl_2 (130 mL) was refluxed until TLC showed complete conversion. The solvent was evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford cycloalkene **11** as a colorless solid; yield: 56 mg (67%): *E*:*Z* = 8:1 (GC). Characteristic data of the major isomer: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.32 – 7.27 (m, 2H), 6.80 – 6.77 (m, 2H), 5.45 – 5.39 (m 1H), 5.35 (s, 1H), 5.29 – 5.24 (m, 1H), 4.92 (ddt, *J* = 14.3, 5.6, 1.0 Hz, 1H), 4.02 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.69 (s, 3H), 3.54 (t, *J* = 10.6 Hz, 1H), 2.50 – 2.46 (m, 1H), 2.26 – 2.12 (m, 3H), 1.97 – 1.65 (m, 4H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 174.9, 160.2, 130.4, 128.3, 127.5, 113.5, 101.3, 77.3, 68.2, 67.2, 55.3, 38.7, 34.3, 33.7, 25.2. IR (film): ν = 3061, 2929, 2863, 1729, 1614, 1516, 1241, 1113, 1085, 1022, 973, 842, 816 cm^{-1}. MS: *m*/*z* (rel. intensity) = 318 ([M^+], 43), 182 (14), 139 (15), 137 (27), 136 (22), 135 (37), 127 (100), 121 (12),

114 (12), 84 (13), 77 (10), 67 (13), 55 (30), 41 (12); anal. calcd. for $C_{18}H_{22}O_5$ (318.36): C 67.91, H 6.97; found: C 67.82, H 7.02.

(1*R*,2*S*)-1-(4-Methoxybenzyloxymethyl)-2-hydroxypent-4-enyl Hex-5-enoate (14)

To a solution of acetal **10** (166 mg, 0.479 mmol), $NaBH_3CN$ (301 mg, 4.79 mmol) and powdered molecular sieves 3 Å (172 mg) in THF (8 mL) was added a solution of HCl in Et_2O (0.8 M) at 0 °C until the evolution of gas had ceased. After stirring for another 30 min at ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), the aqueous layer was extracted with *tert*-butyl methyl ether (3 × 20 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford alcohol **14** as a colorless syrup; yield: 109 mg (65%). A second fraction contained the isomeric product **15** (*ca.* 7%). Analytical and spectroscopic data of **14**: $[\alpha]_D^{20}$: –20.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 – 7.21 (m, 2H), 6.93 – 6.85 (m, 2H), 5.90 – 5.70 (m, 2H), 5.14 – 4.92 (m, 5H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 5.0, 10.8 Hz, 1H), 3.64 (dd, *J* = 3.9, 10.8 Hz, 1H), 2.54 (br s, 1H), 2.38 – 2.22 (m, 1H), 2.32 – 2.15 (m, 3H), 2.13 – 2.04 (m, 2H), 1.78 – 1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 159.4, 137.9, 134.2, 130.3, 129.6, 117.4, 115.1, 113.7, 78.1, 75.0, 72.1, 61.7, 55.2, 35.5, 33.6, 33.0, 24.1.; IR (film): ν = 3469, 3076, 3000, 2935, 2865, 1734, 1641, 1612, 1514, 1457, 1441, 1249, 1173, 1101, 1036, 995, 916, 821 cm^{-1}; MS: *m*/*z* (rel. intensity) = 348 ([M$^+$], 1), 251 (1), 234 (1), 216 (1), 191 (3), 164 (2), 137 (33), 121 (100), 97 (5), 80 (5), 69 (7), 55 (5) 41 (8); anal. calcd. for $C_{20}H_{28}O_5$ (348.43): C 68.94, H 8.10; found: C 69.10, H 8.08.

(1*R*,2*S*)-1-Hydroxymethyl-2-(4-methoxybenzyloxy)-pent-4-enyl Hex-5-enoate (15)

A solution of TMSCl (706 mg, 6.50 mmol) in MeCN (10 mL) was added to a suspension of acetal **10** (351 mg, 1.01 mmol), $NaBH_3CN$ (409 mg, 6.51 mmol) and MS 3 Å in MeCN (15 mL) at 0 °C and the resulting mixture was stirred for 6 d at ambient temperature. For work-up, all insoluble residues were filtered off, the filtrate was stirred with chilled saturated aqueous $NaHCO_3$ (10 mL) for 10 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give alcohol **15** as a colorless syrup; yield: 213 mg (60%); $[\alpha]_D^{20}$: –37.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 – 7.24 (m, 2H), 6.90 – 6.86 (m, 2H), 5.86 (ddt, *J* = 17.2, 10.0, 7.0 Hz, 1H), 5.81 (ddt, *J* = 17.2, 10.4, 6.6 Hz, 1H), 5.12 (ddt, *J* = 17.2, 2.0, 1.4 Hz, 1H), 5.10 (ddt, *J* = 10.2, 2.0, 1.6 Hz, 1H), 5.04 (ddt, *J* = 17.2, 2.0, 1.6 Hz, 1H), 4.91 (dt, *J* = 5.0, 4.0 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.72 (dt, *J* = 11.1, 5.9 Hz, 1H), 2.40 – 2.30 (m, 4H), 2.14 – 2.08 (m, 2H), 1.77 – 1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 159.8, 138.0, 134.6, 130.6, 129.9, 117.7, 115.4, 114.0, 78.9, 75.4, 72.9, 62.1, 55.6, 35.8, 34.0, 33.4, 24.5; IR (film): ν = 3462, 2935, 1736, 1641, 1613, 1514, 1461, 1441, 1302, 1249, 1174, 1094, 1036, 915, 822 cm^{-1}. MS: *m*/*z* (rel. intensity) = 348 ([M$^+$], 1), 191 (4), 157 (2), 122 (12), 121 (100), 97 (4), 69 (5), 41 (7); anal. calcd. for $C_{20}H_{28}O_5$ (348.43): C 68.94, H 8.10; found: C 69.03, H 8.06.

(9*S*,10*R*)-9-Hydroxy-10-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydrooxecin-2-one (16)

A solution containing diene **14** (37 mg, 0.106 mmol) and complex **12** (19 mg, 0.021 mmol) in CH_2Cl_2 (100 mL) was refluxed for 48 h. The solvent was evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc, 2:1) to afford cycloalkene **16** as a colorless syrup; yield: 21 mg (61%); *E*:*Z* = 4:1 (GC). Characteristic data of the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 – 7.21 (m, 2H), 6.92 – 6.84 (m, 2H), 5.51 – 5.41 (m, 1H), 5.39 – 5.18 (m, 1H), 4.97 (dt, *J* = 9.4, 4.3 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 3.92 –3.79 (m, 1H), 3.78 (s, 3H), 3.72 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.54 (dd, *J* = 10.5, 4.4 Hz, 1H), 2.58 –2.46 (m, 1H), 2.37 – 2.23 (m, 2H), 2.19 – 2.05 (m, 1H), 1.89 – 1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 159.4, 129.5, 129.3, 129.0, 113.9, 113.9, 74.9, 73.1, 70.1, 69.1, 55.3, 40.8, 34.5, 33.6, 24.9; IR (film): ν = 3455, 3059, 2929, 2857, 1734, 1612, 1514, 1250, 1179, 1038, 820 cm^{-1}. MS: *m*/*z* (rel. intensity) = 310 (9), 205 (3), 183 (1), 166 (1), 137 (21), 121 (100), 109 (2), 91 (2), 77 (3), 67 (2), 55 (5), 41 (3); HRMS: calcd. for $C_{18}H_{24}O_5$: 320.162372, found: 320.162646.

(9*S*,10*R*)-10-Hydroxy-9-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydrooxecin-2-one (17)

A solution containing diene **15** (50 mg, 0.143 mmol) and complex **12** (26 mg, 0.028 mmol) in CH_2Cl_2 (100 mL) was refluxed for 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc, 2:1) to afford cycloalkene **17** as a colorless syrup; yield: 20 mg (43%); *E*:*Z* = 5:1 (GC). Characteristic data of the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 – 7.23 (m, 2H), 6.91 – 6.86 (m, 2H), 5.44 (dddd, *J* = 15.2, 11.2, 3.1, 1.0 Hz, 1H), 5.23 (dddd, *J* = 15.3, 10.3, 3.8, 1.9 Hz, 1H), 4.92 (dt, *J* = 9.5, 4.1 Hz, 1H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 3.79 (s, 3H), 3.71 (br s, 2H), 3.60 (ddd, *J* = 11.0, 9.6, 3.7 Hz, 1H), 2.80 – 2.74 (m, 1H), 2.35 – 2.25 (m, 2H), 2.13 – 1.97 (m, 2H), 1.93 – 1.68 (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 175.0, 159.5, 130.1, 129.6, 129.2, 113.8, 75.7, 75.0, 71.2, 63.0, 55.3, 37.3, 34.5, 33.7, 24.7; IR (film): ν = 3525, 2960, 2931, 1718, 1611, 1511, 1246, 1218, 1072, 1034, 831, 815 cm^{-1}; MS: *m*/*z* (rel. intensity) = 320 ([M$^+$], 2), 184 (1), 166 (4), 137 (4), 121 (100), 106 (1), 91 (2), 77 (4), 67 (2), 55 (3), 41 (3); anal. calcd. for $C_{18}H_{24}O_5$ (320.38): C 67.48, H 7.55; found: C 67.57, H 7.49.

(±)-4-Allyl-2-(4-methoxyphenyl)-[1,3]dioxane-5-ol (20)

A solution of triol **19** (204 mg, 1.54 mmol), *p*-methoxybenzaldehyde dimethyl acetal (562 mg, 3.08 mmol) and camphorsulfonic acid (35 mg, 0.15 mmol) in CH_2Cl_2 (30 mL) was stirred for 18 h. For work-up, the reaction was neutralized with Et_3N, all volatiles were evaporated and the crude product was

purified by flash chromatography (hexanes/EtOAc, 2:1) to afford acetal **20** as a colorless syrup; yield: 215 mg (67%); mixture of diastereoisomers ≈ 1.8:1 (NMR). Characteristic signals: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 5.51 (s, 1H), 5.42 (1 H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 134.6, 133.9, 130.7, 127.4, 127.3, 117.4, 117.1, 113.5, 113.4, 101.4, 100.8, 81.2, 79.6, 72.8, 71.1, 65.6, 64.8, 55.3, 55.3, 36.5, 35.7; IR (film): ν = 3445, 3076, 2961, 2935, 2911, 2855, 2839, 1642, 1615, 1518, 1250, 1084, 1033, 955, 922, 828 cm^{-1}; MS: *m*/*z* (rel. intensity) = 250 ([M$^+$], 28), 232 (1), 219 (3), 209 (17), 179 (6), 166 (2), 152 (4), 135 (100), 121 (13), 109 (20), 94 (7), 77 (18), 65 (5), 55 (6), 41 (10), 29 (6); anal. calcd. for $C_{14}H_{18}O_4$ (250.29): C 67.18, H 7.25; found: C 67.25, H 7.21.

(±)-(2*R*,4*S*,5*S*)-4-Allyl-2-(4-methoxyphenyl)[1,3]dioxane-5-yl Hex-5-enoate (21)

A solution of alcohol **20** (mixture of diastereoisomers, 3.13 g, 12.50 mmol) in CH_2Cl_2 (100 mL) was added to a solution of 5-hexenoic acid (1.57 g, 13.70 mmol), diisopropylcarbodiimide (1.73 g, 13.70 mmol) and DMAP (*ca.* 4 mg) in CH_2Cl_2 (50 mL) and the resulting mixture was stirred for 20 h. For work-up, all insoluble residues were filtered off through a short pad of silica, the filtrate was evaporated and the crude product was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford diene **21** as a colorless syrup; yield: 1.74 g (40%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.43 – 7.39 (m, 2H), 6.93 – 6.87 (m, 2H), 5.90 – 5.76 (m, 2H), 5.33 (s, 1H), 5.17 – 4.98 (m, 4H), 4.72 (q, *J* = 1.6 Hz, 1H), 4.25 (dd, *J* = 12.9, 1.6 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.80 (s, 3H), 2.51 – 2.41 (m, 3H), 2.38 – 2.28 (m, 1H), 2.18 – 2.11 (m, 2H), 1.83 – 1.73 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 173.2, 160.1, 137.9, 133.4, 130.8, 127.4, 117.6, 115.2, 113.4, 100.9, 77.4, 69.6, 66.4, 55.3, 35.7, 33.5, 33.1, 24.2; IR (film): ν = 3077, 2977, 2936, 2854, 1732, 1642, 1616, 1518, 1249, 1171, 1097, 1035, 917, 829 cm^{-1}. MS: *m*/*z* (rel. intensity) = 346 ([M$^+$], 42), 305 (3), 233 (7), 210 (7), 169 (57), 156 (6), 137 (62), 135 (100), 127 (29), 121 (11), 108 (13), 97 (48), 80 (19), 69 (57), 55 (37), 41 (65); anal. calcd. for $C_{20}H_{26}O_5$ (346.42): C 69.34, H 7.56; found: C 69.40, H 7.55.

(±)-(2*R*,4a*S*,12a*S*)-2-(4-Methoxyphenyl)-4a,7,8,9,12,12a – hexahydrooxecino[10,9-*e*]-1,3-dioxin-6-one (22)

Method A: A solution of diene **21** (341 mg, 0.984 mmol) and the indenylidene complex **12** (18 mg, 0.019 mmol) in CH_2Cl_2 (400 mL) was refluxed for 42 h until TLC showed complete conversion of the substrate. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) delivering product **22** as a colorless solid; yield: 263 mg (83%); *E*:*Z* = 3.5:1).

Method B: A solution of diene **21** (91.3 mg, 0.263 mmol) and complex **13** (5.0 mg, 0.005 mmol) in CH_2Cl_2 (105 mL) was refluxed for 24 h until TLC showed complete conversion of the substrate. Work-up as described above provided the title compound as a colorless solid; 66.6 mg (79%); *E*:*Z* = 1:2.8). The isomers can be separated by preparative HPLC.

(*Z*)-isomer: mp 111 – 112 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.43 – 7.39 (m, 2H), 6.93 – 6.87 (m, 2H), 5.51 (s, 1H), 5.46 (ddt, *J* = 11.2, 4.6, 1.5 Hz, 1H), 5.33 – 5.24 (m, 1H), 4.51 (br. s, 1H), 4.23 – 4.13 (m, 3H), 3.80 (s, 3H), 2.82 (dt, *J* = 12.6, 10.3 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.60 – 2.47 (m, 1H), 2.45 – 2.36 (m, 1H), 2.33 – 2.24 (m, 1H), 2.19 – 2.10 (m, 1H), 2.04 – 1.94 (m, 1H), 1.76 – 1.62 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 174.4, 160.1, 133.9, 130.8, 127.3, 122.8, 113.6, 113.5, 100.5, 75.4, 69.9, 66.5, 55.3, 35.6, 29.6, 26.8, 25.8; IR (KBr): ν = 3012, 2975, 2939, 2852, 1732, 1616, 1518, 1448, 1251, 1154, 1094, 1032, 826, 708 cm^{-1}; MS: *m*/*z* (rel. intensity) = 318 ([M$^+$], 34), 287 (1), 207 (1), 182 (17), 166 (4), 135 (43), 127 (100), 121 (11), 95 (4), 84 (10), 67 (11), 55 (25), 41 (13); anal. calcd. for $C_{18}H_{22}O_5$ (318.36): C 67.91, H 6.97; found: C 68.06, H 6.91.

(*E*)-isomer: mp 105 – 106 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.50 – 7.45 (m, 2H), 6.95 – 6.90 (m, 2H), 5.88 – 5.79 (m, 1H), 5.57 (s, 1H), 5.31 – 5.22 (m, 1H), 5.12 – 5.10 (m, 1H), 4.09 (dd, *J* = 12.5, 1.6 Hz, 1H), 4.02 (m, 1H), 4.01 (dd, *J* = 12.5, 1.8 Hz, 1H), 3.82 (s, 3H), 2.64 (m, 1H), 2.39 – 2.19 (m, 4H), 2.07 – 1.86 (m, 2H), 1.82 – 1.75 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 175.1, 160.1, 130.9, 130.7, 127.8, 127.4, 113.4, 101.4, 75.9, 70.7, 66.0, 55.3, 36.9, 34.6, 33.7, 26.2; IR (KBr): ν = 2964, 2929, 2903, 2856, 1729, 1614, 1517, 1246, 1199, 1123, 1057, 828 cm^{-1}. MS: *m*/*z* (rel. intensity) = 318 ([M$^+$], 37), 182 (11), 153 (2), 135 (30), 127 (100), 114 (10), 95 (3), 84 (7), 67 (8), 55 (18), 41 (8); anal. calcd. for $C_{18}H_{22}O_5$ (318.36): C 67.91, H 6.97; found: C 67.88, H 6.91.

(±)-(9*S*,10*S*)-9-Hydroxy-10-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydrooxecin-2-one (23)

To a suspension of compound (*Z*)-**22** (170 mg, 0.532 mmol), $NaBH_3CN$ (335 mg, 5.33 mmol) and powdered molecular sieves 3 Å in THF (25 mL) was added a saturated solution of HCl in Et_2O at 0 °C until the evolution of gas had ceased. Stirring was continued for 50 min before the reaction mixture was filtered and quenched with aqueous saturated $NaHCO_3$, the aqueous phase was repeatedly extracted with CH_2Cl_2 (60 mL), the combined organic layers were dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give alcohol **23** as a colorless syrup; yield: 121 mg (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 – 7.22 (m, 2H), 6.90 – 6.85 (m, 2H), 5.39 (ddt, *J* = 10.8, 4.9, 1.3 Hz, 1H), 5.33 – 5.24 (m, 1H), 4.72 (dt, *J* = 5.5, 2.8 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.17 – 4.11 (m, 1H), 3.80 (s, 3H), 3.75 (d, *J* = 5.5 Hz, 2H), 2.71 – 2.59 (m, 1H), 2.51 – 2.25 (m, 3H), 2.18 – 2.08 (m, 1H), 1.98 – 1.85 (m 1H), 1.79 – 1.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 159.4, 132.4, 129.5, 129.4, 124.2, 113.9, 73.3, 72.9, 70.1, 68.7, 55.3, 35.2, 31.7, 26.5, 25.8; IR (film): ν = 3452, 3064, 3003, 2934, 1737, 1612, 1514, 1449, 1249, 1220, 1148, 1091, 1035, 820, 716 cm^{-1}. MS: *m*/*z* (rel. intensity) = 320 ([M$^+$], 7), 205 (2), 166 (3), 137 (40), 121 (100), 109 (3), 91 (3), 77 (5), 67 (4), 55 (7), 41 (5); HRMS: calcd. for $C_{18}H_{24}O_5$: 320.162373; found: 320.162759.

(±)-(9*R*,10*S*)-9-Hydroxy-10-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydrooxecin-2-one (24)

To a solution of (*Z*)-**23** (33 mg, 0.101 mmol), chloroacetic acid (39 mg, 0.407 mmol) and PPh_3 (107 mg, 0.407 mmol) in THF (5 mL) was slowly added DEAD (71 mg, 0.407 mmol) via syringe. The resulting mixture was stirred for 18 h before the

solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford (±)-(9*S*,10*S*)-9-chloroacetyl-10-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydrooxecin-2-one [R=C(O)CH_2Cl] as a colorless syrup; yield: 39 mg (98%). This ester derivative shows the following spectroscopic properties: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.24 – 7.19 (m, 2H), 6.89 – 6.84 (m, 2H), 5.49 – 5.45 (m, 2H), 5.38 (dt, *J* = 10.7, 3.5 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 4.36 – 4.28 (m, 1H), 4.04 (d, *J* = 15.0 Hz, 1H), 3.93 (d, *J* = 14.8 Hz, 1H), 3.79 (s, 3H), 3.52 (dd, *J* = 3.4, 2.3 Hz, 2H), 2.78 (br s, 1H), 2.39 – 1.48 (m, 7H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 173.4, 165.3, 159.5, 133.2, 130.0, 129.6, 123.4, 113.7, 72.9, 71.8, 71.2, 68.2, 55.3, 41.2, 34.9, 29.2, 26.3, 25.5; IR (KBr): ν = 3006, 2936, 2866, 1740, 1612, 1514, 1447, 1303, 1248, 1140, 1033, 816, 790 cm^{-1}; MS: *m*/*z* (rel. intensity) = 396 ([M$^+$], 8), 303 (1), 259 (4), 224 (5), 188 (1), 175 (3), 166 (6), 151 (3), 137 (66), 121 (100), 106 (5), 91 (4), 77 (13), 55 (10), 41 (5). HRMS: calcd. for $C_{20}H_{25}ClO_6$: 396.133966; found: 396.134246.

To a solution of this compound (47 mg, 0.117 mmol) in MeOH (4 mL) was added K_2CO_3 (49 mg, 0.351 mmol). After stirring for 5 min, the reaction mixture was diluted with water (2 mL) and neutralized with aqueous HCl (2 M), the aqueous layer was extracted with CH_2Cl_2 (15 mL in several portions), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) furnishing the title compound **24** as a colorless syrup; yield: 22 mg (59%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.26 – 7.22 (m, 2H), 6.90 – 6.85 (m, 2H), 5.61 (dt, *J* = 4.9, 10.9 Hz, 1H), 5.42 (dt, *J* = 5.9, 10.4 Hz, 1H), 4.72 – 4.65 (m, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.13 – 4.07 (m, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.54 (dd, *J* = 6.7, 9.7 Hz, 1H), 2.74 – 2.66 (m, 2H), 2.37 – 2.04 (m, 5H), 1.92 – 1.72 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 173.6, 159.4, 131.7, 129.5, 129.4, 124.8, 113.9, 73.3, 72.7, 70.7, 70.1, 55.3, 34.8, 32.0, 26.2, 25.5; IR (film): ν = 3450, 3007, 2936, 2864, 1737, 1612, 1514, 1448, 1249, 1145, 1038, 821, 731 cm^{-1}. MS: *m*/*z* (rel. intensity) = 320 ([M$^+$], 7), 205 (3), 184 (2), 166 (2), 137 (38), 121 (100), 109 (2), 91 (2), 77 (4), 67 (3), 55 (7), 41 (4); HRMS: calcd. for $C_{18}H_{24}O_5$: 320.162373; found: 320.162599.

(±)-(9*R*,10*S*)-9-*tert*-Butyldiphenylsilyloxy-10-(4-methoxybenzyloxy)-3,4,5,8,9,10-hexahydro-oxecin-2-one (25)

To a solution of (*Z*)-**24** (12.0 mg, 0.037 mmol) and 2,6-lutidine (46 mg, 0.429 mmol) in CH_2Cl_2 (1.5 mL) was added a stock solution of *t*-BuPh_2SiOTf (0.05 M in CH_2Cl_2, 1.5 mL) at 0 °C. The mixture was stirred for 24 h at ambient temperature, the solvent was removed in vacuum and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford silyl ether **25** as a colorless syrup; yield: 17 mg (81%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.69 – 7.67 (m, 4H), 7.45 – 7.33 (m, 6H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.59 (m, 1H), 5.39 – 5.33 (m, 1H), 4.81 (m, 1H), 4.29 – 4.19 (m, 3H), 3.79 (s, 3H), 3.67 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.58 (dd, *J* = 1.8, 11.0 Hz, 1H), 2.48 (m, 1H), 2.32 – 2.10 (m, 2H), 2.09 – 1.92 (m, 2H), 1.82 – 1.74 (m, 2H), 1.56 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 173.6, 159.3, 136.1, 136.0, 134.0, 133.5, 132.1, 130.4, 129.9, 129.8, 129.4, 127.7, 127.6, 124.9, 113.6, 74.7, 72.7, 69.7, 69.1, 55.3, 35.1, 32.9, 26.8, 26.4, 25.6, 19.3; IR (film): ν = 3070, 3047, 3010, 2955, 2858, 1738, 1658, 1613, 1514, 1428, 1249, 1143, 1111, 1067, 823, 741, 704, 611 cm^{-1}; MS: *m*/*z* (rel. intensity) = 558 ([M$^+$], 0.3), 501 (2), 367 (1), 333 (1), 295 (1), 253 (2), 241 (1), 199 (4), 183 (1), 139 (1), 121 (100), 77 (2), 55 (1); HRMS: calcd. for $C_{34}H_{42}O_5Si$: 559.2880; found: 559.2881.

(±)-(9*R*,10*S*)-9-*tert*-Butyldiphenylsilyloxy-10-(hydroxymethyl)-3,4,5,8,9,10-hexahydrooxecin-2-one (26)

A solution of (*Z*)-**25** (8.0 mg, 0.014 mmol) and DDQ (5.0 mg, 0.020 mmol) in CH_2Cl_2 (0.7 mL) and water (40 μL) was stirred for 4 h at ambient temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ (0.5 mL), the aqueous layer was extracted with CH_2Cl_2 (5 mL), the organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **26** as a colorless oil; yield: 6 mg (98%); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.72 – 7.67 (m, 4H), 7.50 – 7.02 (m, 6H), 5.64 – 5.58 (m, 1H), 5.42 – 5.37 (m, 1H), 4.70 – 4.67 (m, 1H), 4.13 – 4.09 (m, 1H), 3.75 (dd, *J* = 12.2, 2.3 Hz, 1H), 3.59 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.30 (dt, *J* = 11.8, 4.0 Hz, 1H), 2.24 – 2.19 (m, 1H), 2.18 (ddd, *J* = 13.0, 11.9, 5.0 Hz, 1H), 2.09 – 2.01 (2H), 1.87 – 1.83 (1H), 1.76 – 1.69 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2): δ = 174.6, 136.3, 134.2, 133.6, 132.2, 130.3, 130.2, 128.2, 128.0, 125.2, 77.2, 69.8, 62.6, 35.5, 32.3, 27.1, 26.8, 25.9, 19.6; IR (film): ν = 3453, 3071, 3048, 3011, 2957, 2932, 1737, 1658, 1589, 1567, 1428, 1266, 1111, 1079, 822, 741, 704, 612 cm^{-1}; MS: *m*/*z* (rel. intensity) = 438 ([M$^+$], 2), 381 (51), 363 (5), 285 (12), 241 (13), 199 (100), 181 (15), 163 (20), 135 (38), 91 (19), 77 (12), 55 (18), 41 (9); HRMS: calcd. for $C_{26}H_{34}O_4Si$: 439.2305; found: 439.2306. The analytical data are in full agreement with those reported in the literature.[4]

X-Ray Crystallographic Study

The structure determinations of (*Z*)-**22** and (*E*)-**22** were carried out on an Enraf-Nonius Kappa CCD diffractometer, using graphite-monochromated Mo-K_α-radiation (λ = 0.71073 Å). The crystal was mounted in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97[30]) and refined by full-matrix least-squares techniques against F^2 (SHELXL-97[31]). For (*Z*)-**22** the hydrogen atoms were included at calculated positions with fixed thermal parameters, for (*E*)-**22** the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All non-hydrogen atoms were refined anisotropically. The crystal and intensity data are given below.

Crystal and intensity data for (*Z*)-**22:** $C_{18}H_{22}O_5$, M_r = 318.36 g·mol^{-1}, colorless blocks, size 0.60 × 0.23 × 0.14 mm^3, orthorhombic, space group $P2_12_12_1$, *a* = 6.5970(2) Å, *b* = 13.1429(4) Å, *c* = 18.1690(6) Å, *V* = 1575.32(9) Å^3, T = 100 K, ρ_{calc} = 1.311 g × cm^{-3}, *Z* = 4, μ (Mo-K_α) = 0.097 mm^{-1}, F(000) = 680 e, θ limit 1.91 – 33.68°, 16996 refl. measured, 5651 independent reflections, 3785 obs. refl. with I > 2σ(I), 208 parameters, S = 0.915, R_1 = 0.044, wR^2 = 0.077, largest diff. peak and hole = 0.3/–0.2 e × Å^{-3}.

Crystal and intensity data for (*E*)-**22**: $C_{18}H_{22}O_5$, M_r = 318.36 g·mol^{-1}, colorless blocks, size 0.53 × 0.33 × 0.11 mm^3,

orthorhombic, space group $P2_12_12_1$, $a = 10.1674(3)$ Å, $b = 11.8663(3)$ Å, $c = 13.3721(4)$ Å, $V = 1613.34(8)$ Å^3, T = 100 K, $\rho_{calc} = 1.311$ g × cm^{-3}, $Z = 4$, μ (Mo-K_α) = 0.095 mm^{-1}, F(000) = 680 e, θ limit 2.29 – 33.15°, 17444 refl. measured, 6104 independent reflections, 4181 obs. refl. with $I > 2\sigma(I)$, 296 parameters, $S = 1.065$, $R_1 = 0.041$, $wR^2 = 0.073$, largest diff. peak and hole = 0.2/–0.2 e × Å^{-3}.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-177659 [(*Z*)-**22**] and CCDC-177660 [(*E*)-**22**]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]

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