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Synthesis of the proposed structure of queenslandon

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ABSTRACT

The proposed structure of the benzolactone queenslandon (**6**) was synthesized utilizing a triol containing building block prepared from D-ribose. While a ring-closing metathesis approach did not lead to the macrocycle, alkylation of a benzyl(phenyl)selane, elimination to generate the styrene double bond, followed by Mitsunobu macrolactonization proved to be successful. Spectral data suggest that the structure of queenslandon should be revised, probably to the C11 epimer.

1. Introduction

Natural polyketides cover an enormous structural space, even though simple building blocks like acetate and propionate are being used. Among the polyketides resorcylic acid lactones represent a unique family of privileged structures.[1] These 14-membered lactones are mycotoxins and are produced by fungal strains. Besides the resorcylic acid part, which results from an intramolecular aldol condensation, typical structural features include a double bond or ketomethylene function next to the aryl ring. In addition, the aliphatic part can be functionalized with keto or hydroxyl groups. The discovery, that radicicol (**1**) is a potent and selective Hsp90 inhibitor renewed interest in the RALs (Fig. 1). One of the most simple RAL, zearalenone (**2**) shows estrogenic activity. Its binding to Hsp90 and kinases is low.[2] Then there are several RALs, which are characterized by a *cis*-enone in the macrocyclic ring. These macrolactones like LL-Z1640–2 (**3**),[3] radicicol A (**4**) or L-783,277 (**5**)[4,5] are potent kinase inhibitors.[6] Among the RALs, queenslandon (**6**) is unique since it features a dihydroxyacetone subunit and a highly oxidized benzoic acid.[7] It was isolated from the strain *Chrysosporium queenslandicum* IFM51121. According to the original report queenslandon showed activity against several fungal strains but not bacteria. In order to further delineate its biological properties a synthetic route to queenslandon seemed highly desirable.

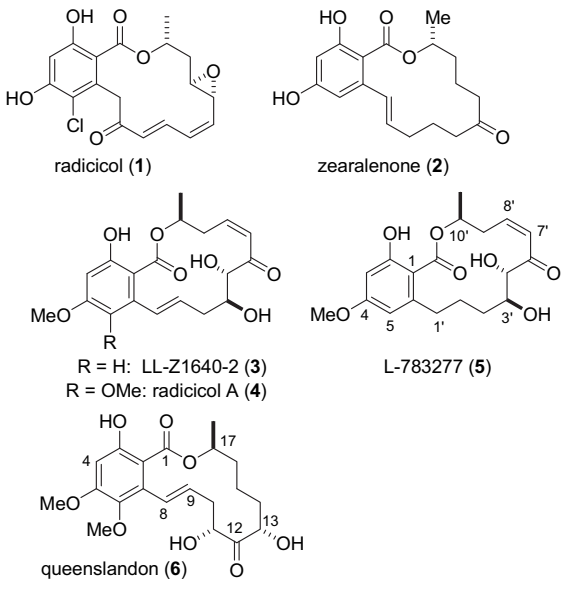

Figure 1. Structures of some representatives resorcylic acid lactones (RALs).

We previously described a strategy toward the core structure **12** of queenslandon using a chiral glycolate for construction of the dihydroxyacetone region (Fig. 2).[8] Thus, an aldol reaction on one side and a Tebbe olefination followed by a hydroboration and a Suzuki cross-coupling stitched the glycolate between the vinylbenzoic acid and the aliphatic part. However, this strategy could not be extended to the real system due to problems in the late stage oxidative cleavage of the dioxane.

Therefore, a different strategy was chosen where the dihydroxyacetone part was fashioned from D-(+)-ribose (Fig. 3). In

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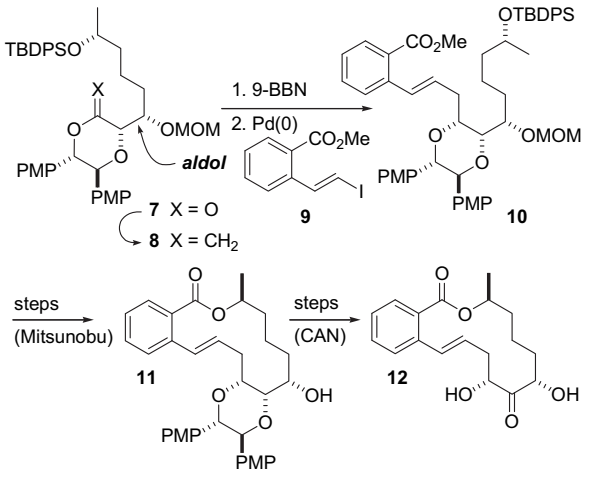


Figure 2. Previous strategy toward the core structure **12** of queenslandon.

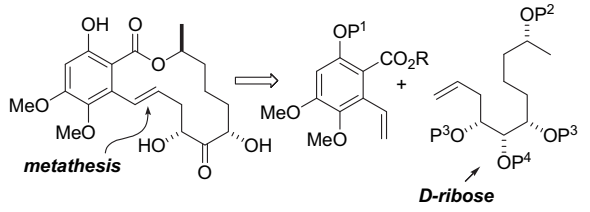


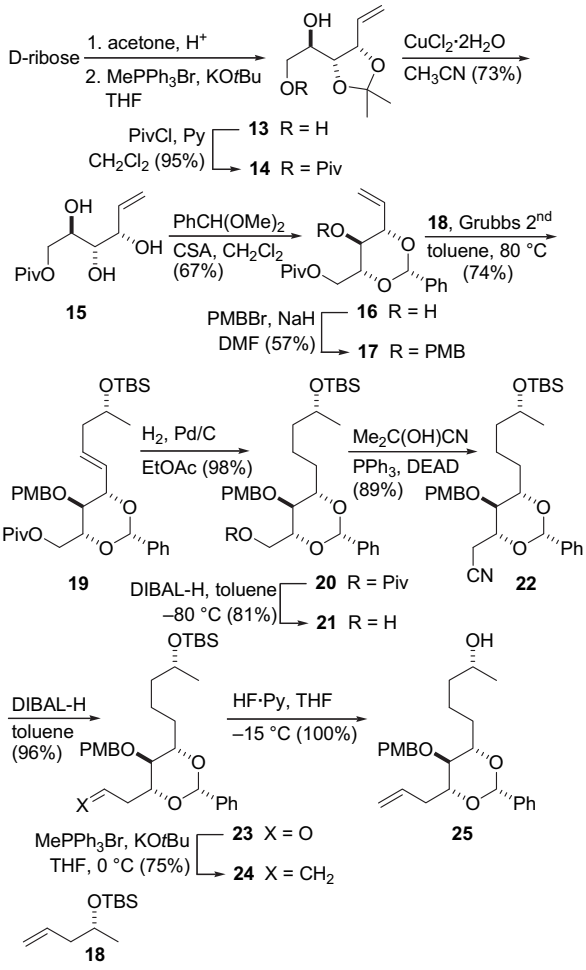
Figure 3. Plan for the synthesis of queenslandon via a metathesis strategy.

addition, we planned to form the styrene double bond either by intramolecular or intermolecular metathesis.

2. Results and discussion

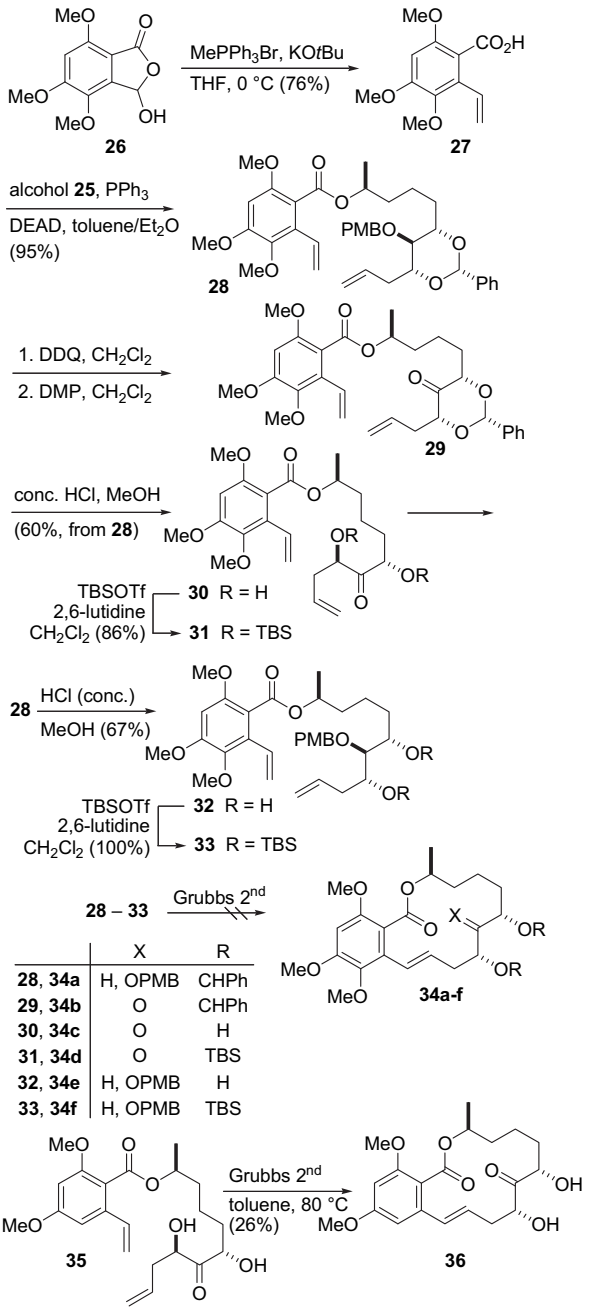
The synthesis of the aliphatic sector was started with D-(+)-ribose, which was converted via acetonide formation and Wittig reaction to alkenol **13** (Scheme 1).[9] A subsequent pivaoylation followed by hydrolysis of the acetal, mediated by $CuCl_2 \cdot 2H_2O$[10] led to triol **15** in good yield. A transacetalization reaction on benzaldehyde dimethylacetal produced 1,3-dioxane **16** thereby exposing the central hydroxyl function. This group was then protected as PMB ether. In the next step a cross-metathesis reaction[11] between alkene **17** and pent-4-en-2-ol derivative[12] **18** (1 equiv) using Grubbs second generation catalyst (5 mol%) at 80 °C in toluene provided an excellent yield of alkene **19**. A subsequent catalytic hydrogenation of the double bond furnished the differently protected pentaol **20**. Reductive cleavage of the pivalate group was followed by chain extension of alcohol **21** to nitrile **22** using Mitsunobu conditions.[13] Reduction of nitrile **22** to the corresponding aldehyde and Wittig reaction furnished terminal alkene **24**. Removal of the silyl protecting group provided alkenol **25**.

The aromatic fragment of the metathesis route toward the styrene double bond was prepared from known hydroxyphthalide[14] **26** via Wittig olefination. Acid **27** and alkenol **25** were then combined via Mitsunobu esterification to provide benzoic ester **28** in excellent yield.[15] Based on previous experience, a clean inversion could be assumed.[16] Ester **28** served as precursor for various substrates **28**–**33** that were intended for RCM. Thus, oxidative cleavage of the PMB ether followed by oxidation provided ketone **29**. Treatment of acetal **29** with conc. HCl in MeOH removed the benzylidene acetal generating dihydroxy ketone **30**. We also prepared the derivatives **31**–**33**. Unfortunately, none of the substrates **28**–**33** could be cyclized with the Grubbs second generation catalyst (5 mol%, toluene, 80 °C, 0.002–0.004 M). With the Grubbs–Hoveyda catalyst (5 mol%, CH_2Cl_2, room temperature, 0.002 M) substrate **30** dimerized (45% yield). The fact that the nor-methoxy substrate **35** gave macrolactone **36** (26%) in presence of Grubbs second generation catalyst (5 mol%, toluene, 80 °C, 0.004 M) points to steric or electronic interference by the 4-methoxy group (Scheme 2).



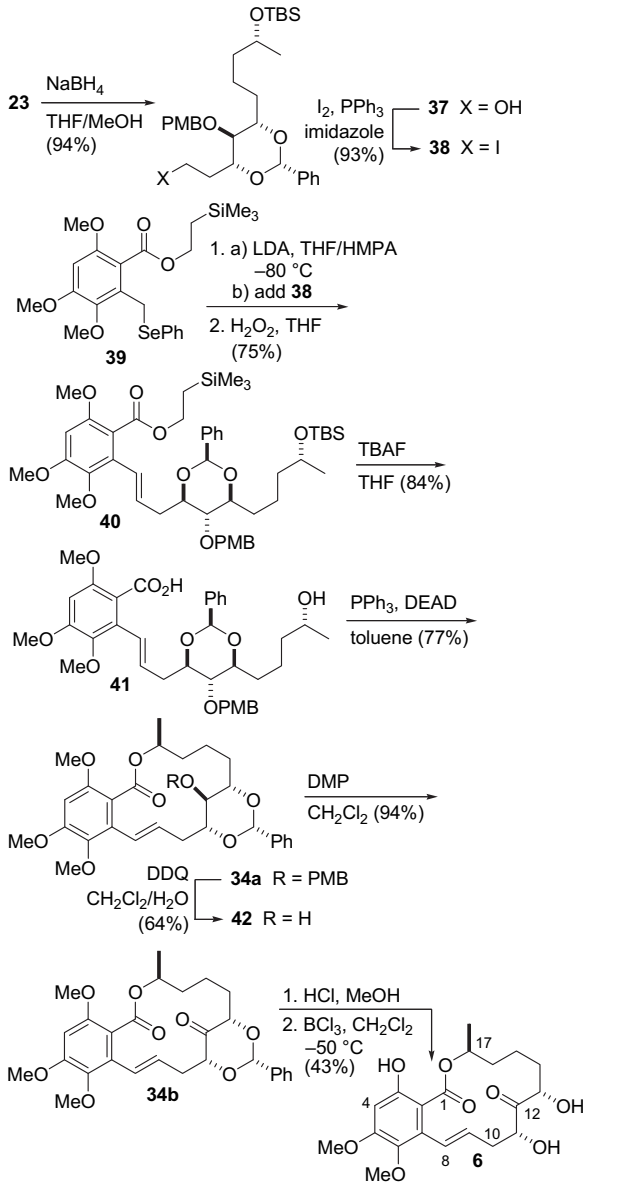
Scheme 1. Synthesis of alkenol **25** from D-ribose.

Therefore, we turned to a strategy pioneered by Winssinger et al.[6,5] for the synthesis of other resorcylic acid lactones. This is characterized by alkylation of a 2-(phenylselanylmethyl)benzoate with an alkyl iodide followed by elimination of the derived phenylselenoxide. Accordingly, aldehyde **23** was reduced to primary alcohol **37** (Scheme 3). Reaction of alcohol **37** with iodine and PPh_3 gave iodide **38**. Alkylation of the lithium anion of benzyl (phenyl)-selane[6,17–19] **39** in THF/HMPA afforded crude selenoether. The crude selenide was oxidized leading after elimination to *E*-alkene **40** in 75% yield. Simultaneous cleavage of the trimethylsilylethanyl (TMSE) ester and the silyl ether furnished hydroxy acid **41**. Somewhat to our surprise the cyclization of hydroxy acid **41** under Mitsunobu conditions went quite well and gave macrolactone **34a** in 77% yield.[20] MacroModel calculations on a model compound (PMB and Ph replaced by methyl group) showed an all equatorial orientation of the substituents in the dioxane ring (see Supplementary data). Thus, the cyclic acetal seems to favor macrolactonization by imposing conformational constraint on the aliphatic region. Selective removal of the PMB protecting group with DDQ was followed by oxidation of alcohol **42** to ketone **34b**. Finally, the benzylidene acetal was cleaved by acid-catalyzed transacetalization. Treatment of the crude dihydroxy ketone with BCl_3 (4.0 equiv) at −50 °C, gave rise to the proposed structure **6** of queenslandon. The chemoselective ether



	X	R
28, **34a**	H, OPMB	CHPh
29, **34b**	O	CHPh
30, **34c**	O	H
31, **34d**	O	TBS
32, **34e**	H, OPMB	H
33, **34f**	H, OPMB	TBS

Scheme 2. Synthesis of various substrates for the RCM approach.



Scheme 3. Synthesis of the proposed structure of queenslandon via Mitsunobu lactonization.

cleavage next to a carboxylic group is well known.[1,21] However, this is also evident from the NOESY spectrum where the phenolic OH (3-OH) showed correlations to 17-H and 17-CH_3. In addition, the HMBC spectrum displays the expected correlations (5-OCH_3/C-5 and 6-OCH_3/C-6). Macrolactone **6** shows moderate cytostatic activity with an IC_{50} of 33 μg mL^{-1} (84 μM) against the mouse fibroblast cell line L929.

The ^1H NMR signatures of **6** matched nicely the ones published for the simple model compound **12**. In particular, a NOESY cross peak between 11-H (4.60–4.67) and 13-H (4.36–4.41) suggests the *cis*-orientation at these methine carbons. However, with regard to the published data for queenslandon we observed some distinct discrepancies. For example, there are big differences (δ ppm>3) for C12 (keto function), C9 (alkene carbon), and C11 (δ ppm=6.4). Thus, one might conclude that something is wrong with C11 since both C9 and C12 are in the vicinity to C11. Further support for this hypothesis comes from a comparison of the queenslandon structure **6** with the related compounds **3**—**5**. In these macrolides C11 (or C3′) have opposite configuration. The measured optical rotations for **6** are $[\alpha]_D^{20}=-41.0$ (*c* 0.5, CH_2Cl_2), $[\alpha]_D^{20}=-51.0$ (*c* 0.1, CH_3OH). The literature value for the isolated queenslandon[7] amounts to $[\alpha]_D^{20}=+24.4$ (*c* 0.028, CH_3OH). Efforts are now underway to prepare the C11 epimer of **6**.

3. Conclusion

In conclusion, we accomplished the synthesis of the proposed structure of the macrolactone queenslandon (**6**). The structural challenges of this natural product include a highly substituted electron-rich benzoic acid part and an aliphatic region featuring a dihydroxy ketone subunit. This subunit was fashioned from D-ribose via triol **15**. Via formation of a benzylidene acetal the hydroxyl functions could be differentiated. Thereafter, this central fragment was extended via cross-metathesis at the alkene and substitution of the primary alcohol by cyanide. Several substrates that were intended for a ring-closing metathesis reaction failed to cyclize to

the corresponding macrolactone. The only ester that cyclized with moderate yield was the 6-nor-methoxy compound **35**. Finally, iodide **38** was used to alkylate the trimethylsilylethyl 2-methylbenzoate derivative **39**. This led after elimination of phenylselanol to seco acid **41**. This substrate underwent a clean Mitsunobu lactonization, probably facilitated by conformational constraint imposed through the benzylidene acetal. The spectral data showed that the prepared lactone **6** does not correspond to queenslandon. Since the biggest differences are observed for the chemical shifts around C11 it is likely that the configuration of C11 should be inverted. This work highlights the role of organic synthesis in detecting errors in structure elucidation of natural products.[22]

4. Experimental section

4.1. (*R*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethyl pivalate (14)

To an ice-cooled solution of diol[9] **13** (16.65 g, 88.6 mmol) and DMAP (1.07 g, 8.8 mmol) in a CH_2Cl_2/pyridine mixture (120 mL, 5:1) was added PivCl (11.0 mL, 106.3 mmol) in a dropwise fashion. After the addition, the reaction mixture was allowed to warm to room temperature. Stirring was continued for 2 h before the reaction mixture was washed with 1 N HCl (5×100 mL) and satd. NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude pivaloate **14** (22.8 g, 95%) was pure enough to be introduced to the next step without additional purification. R_f (petroleum ether/EtOAc, 5:1): 0.25; $[\alpha]_D^{20}$ +9.7 (*c* 2.2, CH_2Cl_2); d_H (400 MHz $CDCl_3$) 1.21 (s, 9H, $C(CH_3)_3$), 1.34 (s, 3H, CH_3C), 1.46 (s, 3H, CH_3C), 3.84 (dd, *J*=7.9, 5.3 Hz, 1H, CH_2CHOH), 4.04–4.17 (m, 2H, CH_2OPiv), 4.36 (ddd, *J*=7.9, 4.3, 3.8 Hz, 1H, *CH*OH), 4.69 (t, *J*=6.6 Hz, 1H, CH_2=CHCHOR), 5.30–5.43 (m, 2H, CH_2=CH), 5.98 (ddd, *J*=17.3, 10.4, 6.9 Hz, 1H, CH_2=CH); d_C (150 MHz $CDCl_3$) 25.3 ($C(CH_3)_3$), 27.2 (CH_3), 27.7 (CH_3), 38.9 ($C(CH_3)_3$), 66.6 ($PivOCH_2$), 68.8 (CH_2CHOH), 77.5 (CHOH), 78.5 (CH_2=CHCHOR), 109.0 ($C(CH_3)_2$), 118.3 (CH_2=CH), 133.7 (CH=CH_2), 179.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{24}O_5Na$ 295.15159, found 295.15162.

4.2. (2*R*,3*S*,4*S*)-2,3,4-Trihydroxyhex-5-enyl pivalate (15)

To an ice-cooled solution of acetonide **14** (10.56 g, 38.8 mmol) in acetonitrile (100 mL) was added $CuCl_2 \cdot 2H_2O$ (46.0 g, 271.6 mmol) portionwise within 1 h and then the reaction mixture was allowed to warm to room temperature. After being stirred for 12 h at room temperature, inorganic solids were filtered off, and the filter cake washed with acetonitrile (100 mL). The combined filtrates were washed with satd. NH_4Cl (3×100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give triol **3** (6.59 g, 73%) as a white amorphous solid. R_f (petroleum ether/EtOAc, 1:1) 0.26; $[\alpha]_D^{20}$ −6.7 (*c* 1.0, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.22 (s, 9H, $C(CH_3)_3$), 2.54 (br s, 3H, 3×OH), 3.55 (dd, *J*=7.9, 5.3 Hz, 1H, CH_2CHOH), 3.84 (ddd, *J*=7.9, 4.3, 3.8 Hz, 1H, *CH*OH), 4.32–4.35 (m, 3H, $PivOCH_2$ and H_2C=CHCHOH), 5.98 (m, 2H, CH_2=CH), 5.99 (ddd, *J*=17.2, 10.5, 6.6 Hz, 1H, CH_2=CH); d_C (150 MHz, $CDCl_3$): 27.2 ($C(CH_3)_3$), 39.0 ($C(CH_3)_3$), 66.3 ($PivOCH_2$), 72.4 (CH_2CHOH), 72.8 (CHOH), 74.7 (CH_2=CHCHOH), 118.3 (CH_2=CH), 136.3 (CH=CH_2), 179.8 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{20}O_5Na$ 255.12029, found 255.12023.

4.3. ((2*S*,4*R*,5*S*,6*S*)-5-Hydroxy-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (16)

To a solution of triol **15** (6.59 g, 28.0 mmol) in CH_2Cl_2 (80 mL) was added CSA (1.29 g, 5.6 mmol) followed by the dropwise addition of benzaldehydedimethylacetal (5.1 mL, 33.6 mmol) at room temp. After being stirred for 1 h the reaction mixture was washed with satd. $NaHCO_3$ (100 mL), satd. NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give hydroxydioxane **16** (8.3 g, 91%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.17; $[\alpha]_D^{20}$ −31.3 (*c* 0.9, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.23 (s, 9H, $C(CH_3)_3$), 3.30 (t, *J*=9.2 Hz, 1H, *CH*OH), 3.82–3.86 (m, 1H, $PivOCH_2CH$), 4.07–4.11 (m, 1H, H_2C=CHCHOH), 4.34 (dd, *J*=12.2, 4.1 Hz, 1H, $PivOCH_2$), 4.56 (dd, *J*=12.2, 4.1 Hz, 1H, $PivOCH_2$), 5.32 (m, 2H, CH_2=CH), 5.63 (s, 1H, *CH*Ph), 6.00 (ddd, *J*=17.0, 10.7, 6.4, 1H, CH_2=CH), 7.34–7.37 (m, 3H, H aryl), 7.48–7.50 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) 27.2 ($C(CH_3)_3$), 39.0 ($C(CH_3)_3$), 63.5 ($PivOCH_2$), 66.2 (CHOH), 79.4 ($PivOCH_2CH$), 81.8 (CH_2=CHCHOH), 100.6 (*C*HPh), 118.9 (CH_2=CH), 126.2, 128.2, 129.0, 134.5 (C aryl), 137.4 (CH=CH_2), 179.5 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{24}O_5Na$ 343.15159, found 343.15164.

4.4. ((2*S*,4*R*,5*S*,6*S*)-5-(4-Methoxybenzyloxy)-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (17)

To a cooled (−5 °C) suspension of NaH (0.54 g, 13.4 mmol, 60% in mineral oil) in anhydrous DMF (40 mL) was added dropwise a solution of alcohol **16** (1.23 g, 3.8 mmol) in DMF (5 mL) at the same temperature. After complete addition, the reaction mixture was stirred for 1 h at −5 °C before a solution of freshly prepared PMBBr[8] (1.28 g, 6.4 mmol) in DMF (5 mL) was added. After being stirred for additional 2 h at −5 °C the reaction was quenched with satd. NH_4Cl (10 mL) and the product extracted with EtOAc (3×100 mL). The combined organic layers were washed with water, satd. NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give PMB ether **17** (0.97 g, 57%) as a colorless oil. R_f (petroleum ether/EtOAc, 10:1) 0.26; $[\alpha]_D^{20}$=+5.5 (*c* 0.8, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.26 (s, 9H, $C(CH_3)_3$), 3.40 (t, *J*=9.4 Hz, 1H, CHOPMB), 3.83 (s, 3H, OCH_3), 3.91–3.94 (m, 1H, $PivOCH_2CH$), 4.19–4.23 (m, 1H, H_2C=CHCHOH), 4.34 (m, 1H, CH_2Ar), 4.44–4.52 (m, 2H, CH_2Ar, $PivOCH_2$), 4.63 (d, *J*=10.2 Hz, 1H, $PivOCH_2$), 5.39 (d, *J*=10.4 Hz, 1H, CH_2=CH), 5.58 (d, *J*=10.4 Hz, 1H, CH_2=CH), 5.63 (s, 1H, CHPh), 6.09 (ddd, *J*=17.3, 10.7, 6.6, 1H, CH_2=CH), 6.90–6.92 (m, 2H, PMB), 7.25–7.29 (m, 2H, PMB), 7.35–7.39 (m, 3H, H aryl), 7.50–7.52 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) 27.2 ($C(CH_3)_3$), 38.9 ($C(CH_3)_3$), 55.3 (OCH_3), 62.9 ($ArCH_2$), 73.8 (CHOPMB), 74.4 ($PivOCH_2$), 78.4 ($PivOCH_2CH$), 81.6 (CH_2=CHCHOH), 100.3 (CHPh), 114.0 (C aryl), 118.8 (CH_2=CH), 126.2, 128.2, 128.9, 129.4, 129.8 (C aryl), 135.1 (CH=CH_2), 137.5 (C aryl), 159.6 (C aryl), 178.2 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{32}O_6Na$ 463.20911, found 463.20878.

4.5. ((2*S*,4*R*,5*S*,6*S*)-6-((*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-pent-1-enyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl pivalate (19)

Alkene **17** (1.76 g, 4.0 mmol) was dissolved in degassed toluene (17.6 mL) and then alkene[12] **18** (0.8 g, 4.0 mmol) was added. The reaction mixture was slightly warmed (to around 40–50 °C) and Grubbs second catalyst (170 mg, 5 mol %) was added. The temperature was brought to 80 °C and maintained for 2 h. After that air was bubbled through the reaction (for approx. 5 min) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give metathesis product **19** (1.80 g, 74%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.34; $[\alpha]_D^{20}$ −9.8 (*c* 0.4, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.14 (d, *J*=6.1 Hz, 3H, $TBSOCHCH_3$), 1.23 (s, 9H, $C(CH_3)_3$), 2.04–2.27 (m, 2H, CH_2), 3.34 (t, *J*=9.2 Hz, 1H, CHOPMB), 3.79 (s, 3H, OCH_3), 3.84–3.89 (m, 2H, $PivOCH_2CH$OR, TBSO*CH*), 4.11–4.15 (m, 1H, CH=CHCHOR), 4.27–4.31 (m, 1H, $PivOCH_2$), 4.41–4.47 (m, 3H, $PivOCH_2$, CH_2 of PMB), 4.58 (d,

J=10.3 Hz, 1H, PivOCH_2), 5.58 (s, 1H, CHPh), 5.64–5.70 (m, 1H, CH=CHCH$_2$), 5.94–6.02 (m, 1H, CH=CHCH$_2$), 6.86–6.88 (m, 2H, PMB), 7.18–7.22 (m, 2H, PMB), 7.32–7.34 (m, 3H, H aryl), 7.46–7.48 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.5 (Si(CH_3)$_2$), 18.1 (CH_2), 23.6 (CHCH_3), 25.9 (SiC(CH_3)$_3$), 27.2 (C(CH_3)$_3$), 38.9 (C(CH_3)$_3$), 42.9 (SiC(CH_3)$_3$), 55.3 (OCH_3), 63.0 (CH_2 of PMB), 68.4 ($CHCH_3$), 73.9 (CHOPMB), 74.3 (PivOCH_2), 78.4 (PivOCH$_2$CHOR), 81.5 (CH_2CHOR), 100.3 (CHPh), 114.0, 126.2, 128.2, 128.8, 128.9, 129.5 (C aryl), 129.7 (CH=CHCH$_2$), 132.4 (CH=CHCH$_2$), 137.6, 159.6 (C aryl), 178.2 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{35}H_{52}O_7SiNa$ 635.35310, found 635.34213.

4.6. ((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-butyldimethylsilyloxy)-pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl pivalate (20)

Metathesis product **19** (1.64 g, 2.67 mmol) was dissolved in EtOAc (5 mL), Pd/C (10% wt) was added and a balloon filled with hydrogen was attached through a rubber septum. The reaction mixture was stirred for 5 h at room temperature and then the palladium catalyst was filtered off through a pad of Celite®, washed with EtOAc (2×10 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give protected polyol **20** (1.60 g, 98%) as colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.34; $[\alpha]_D^{20}$ −0.1 (*c* 4.4, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.04 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.13 (d, J=6.1 Hz, 3H, TBSOCHCH_3), 1.25 (s, 9H, C(CH_3)$_3$), 1.39–1.62 (m, 4H, 2×CH_2), 1.85–1.90 (m, 2H, CH_2), 3.32 (t, J=9.1 Hz, 1H, HCOPMB), 3.64–3.68 (m, 1H, CH_2CHOR), 3.77–3.80 (m, 4H, OCH_3, HCOTBS), 3.84–3.87 (m, 1H, PivOCH$_2$CHOR), 4.28–4.32 (m, 1H, PivOCH_2), 4.50–4.57 (m, 3H, PivOCH_2, CH_2 of PMB), 5.54 (s, 1H, CHPh), 6.88–6.91 (m, 2H, PMB), 7.25–7.27 (m, 2H, PMB), 7.33–7.36 (m, 3H, H aryl), 7.46–7.48 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.4 (Si(CH_3)$_2$), 18.1, 21.3 (CH_2), 23.8 ($CHCH_3$), 25.9 (SiC(CH_3)$_3$), 27.2 (C(CH_3)$_3$), 32.1 (CH_2), 38.9 (SiC(CH_3)$_3$), 39.6 (C(CH_3)$_3$), 55.3 (OCH_3), 63.0 (CH_2 of PMB), 68.5 ($CHCH_3$), 74.1 (CHOPMB), 74.7 (PivOCH_2), 78.5 (PivOCH$_2$CHOR), 80.4 (CH_2CHOR), 100.2 (CHPh), 114.0, 126.0, 128.1, 128.6, 129.5, 129.7, 137.8, 159.6 (C aryl), 178.2 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{35}H_{54}O_7SiNa$ 637.35310, found 637.35287.

4.7. ((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)-pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methanol (21)

A solution of pivaloate **20** (1.18 g, 1.92 mmol) in CH_2Cl_2 (15 mL) was cooled to −80 °C and then DIBAL-H (11.52 mL, 11.5 mmol, 1 M in hexane) was added over 1 h at the same temperature. The reaction mixture was stirred for an additional 1 h before satd. NH_4Cl (5 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with satd. NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **21** (0.82 g, 81%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.17; $[\alpha]_D^{20}$ −22.4 (*c* 1.4, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.04 (s, 6H, Si(CH_3)$_2$), 0.87 (s, 9H, Si(CH_3)$_3$), 1.12 (d, J=6.1 Hz, 3H, CHCH_3), 1.36–1.60 (m, 4H, 2×CH_2), 1.82–1.88 (m, 2H, CH_2), 1.95 (br s, 1H, OH), 3.38 (t, J=9.2 Hz, 1H, CHOPMB), 3.62–3.71 (m, 1H, CH_2CHOCHPh), 3.73–3.77 (m, 1H, TBSOCHCH$_3$), 3.77–3.80 (m, 4H, OCH_3, HOCH_2), 3.93–3.96 (m, 1H, HOCH_2), 4.58 (s, CH_2 of PMB), 5.56 (s, 1H, CHPh), 6.88–6.90 (m, 2H, PMB), 7.25–7.28 (m, 2H, PMB), 7.34–7.38 (m, 3H, H aryl), 7.47–7.49 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.4 (Si(CH_3)$_2$), 18.1, 21.3 (CH_2), 23.8 (CHCH_3), 25.9 (SiC(CH_3)$_3$), 32.0 (CH_2), 39.7 (SiC(CH_3)$_3$), 55.3 (OCH_3), 62.2 (CH_2 of PMB), 68.5 ($CHCH_3$), 73.3 (HCOPMB), 74.7 (PivOCH_2), 80.4 (HOCH$_2$CHOR), 80.7 (CH_2CHOR), 100.3 (CHPh), 114.0, 126.1, 128.2, 128.8, 129.8, 137.8, 159.5 (C aryl); HRMS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{46}O_6SiNa$ 553.29559, found 553.29557.

4.8. 2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)-pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetonitrile (22)

To a stirred solution of alcohol **21** (0.54 g, 1.0 mmol) in diethyl ether (3.4 mL) was added PPh_3 (0.59 g, 2.2 mmol) at −5 °C. The mixture was stirred at the same temperature for 15 min before DEAD (0.98 mL, 2.2 mmol) was added dropwise. The reaction mixture became like a white paste. After 20 min acetone cyanohydrine (0.21 mL, 2.2 mmol) was added dropwise and the solids dissolved. The mixture was stirred at −5 °C for 6 h and for additional 12 h at room temperature. After that the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give nitrile **22** (0.487 g, 89%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.42; $[\alpha]_D^{20}$ −1.0 (*c* 1.4, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.03 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 1.12 (d, J=6.1 Hz, 3H, TBSOCHCH_3), 1.37–1.65 (m, 4H, 2×CH_2), 1.86–1.88 (m, 2H, CH_2), 2.54–2.75 (m, 2H, NCCH_2), 3.23 (t, J=9.2 Hz, CHOPMB), 3.63–3.68 (m, 1H, CH_2CH_2CH), 3.76–3.85 (m, 5H, OCH_3, NCCH$_2$CH and TBSOCHCH$_3$), 4.50–4.69 (dd, J=17.9, 10.9 Hz, 2H, CH_2 of PMB), 5.54 (s, 1H, CHPh), 6.89–6.92 (m, 2H, H of PMB), 7.25–7.27 (m, 2H, H of PMB), 7.34–7.35 (m, 3H, H aryl), 7.47–7.49 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.4 (Si(CH_3)$_2$), 18.1, 21.4 (CH_2), 23.8 ($CHCH_3$), 25.9 (SiC(CH_3)$_3$), 29.3 (NCCH_2), 32.1 (CH_2), 39.6 (SiC(CH_3)$_3$), 55.3 (OCH_3), 68.4 ($CHCH_3$), 75.0 (CH_2 of PMB), 75.6 (CH_2CH_2CH), 76.8 (CHOPMB), 80.6 (HOCH_2CHO), 100.4 (CHPh), 114.0 (C aryl), 116.9 (NC), 126.1, 128.2, 128.9, 129.2, 129.9, 137.1, 159.8 (C aryl); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{45}NO_5SiNa$ 562.29592, found 562.29624.

4.9. 2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)-pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (23)

A solution of nitrile **22** (0.49 g, 0.90 mmol) in CH_2Cl_2 (10 mL) was cooled to −80 °C followed by slow addition of DIBAL-H (5.4 mL, 1 M in hexane, 5.4 mmol). After being stirred for 1 h at −80 °C satd. NH_4Cl solution was added and the mixture allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give aldehyde **23** (469 mg, 96%) as a colorless oil. R_f (petroleum ether/EtOAc, 5:1) 0.42; $[\alpha]_D^{20}$ −7.8 (*c* 1.7, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.06 (s, 6H, Si(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 1.16 (d, J=6.1 Hz, 3H, TBSOCHCH_3), 1.41–1.65 (m, 4H, 2×CH_2), 1.87–1.91 (m, 2H, CH_2), 2.65–2.83 (m, 2H, CHOCH_2), 3.14 (t, J=9.2 Hz, 1H, CHOPMB), 3.68–3.73 (m, 1H, CH_2CH_2CH), 3.80–3.84 (m, 4H, OCH_3, TBSOCHCH$_3$), 4.18–4.24 (m, 1H, CHOCH$_2$CH), 4.49–4.62 (dd, J=17.8, 10.9 Hz, 2H, CH_2 of PMB), 5.59 (s, 1H, CHPh), 6.90–6.92 (m, 2H, PMB), 7.25–7.27 (m, 2H, PMB), 7.34–7.36 (m, 3H, H aryl), 7.46–7.48 (m, 2H, H aryl), 9.82 (t, J=2.3 Hz, 1H, CHO); d_C (150 MHz, $CDCl_3$) −4.7, −4.4 (Si(CH_3)$_2$), 18.1, 21.3 (CH_2), 23.8 ($CHCH_3$), 25.9 (SiC(CH_3)$_3$), 32.1 (CH_2), 39.6 (SiC(CH_3)$_3$), 46.3 (CHOCH_2), 55.3 (OCH_3), 68.5 ($CHCH_3$), 74.7 (CH_2 of PMB), 75.9 (CH_2CH_2CH), 77.4 (CHOPMB), 80.8 (O=CCH$_2$CH), 100.3 (CHPh), 114.0, 126.0, 128.1, 128.8, 129.3, 129.8, 137.5, 159.7 (C aryl), 200.2 (CHO); HRMS (ESI): $[M+CH_3OH+Na]^+$ calcd for $C_{32}H_{50}O_7SiNa$ 597.32180, found 597.32221.

4.10. 3,4,6-Trimethoxy-2-vinyl-benzoic acid (27)

KO*t*Bu (0.41 g, 3.34 mmol) was added in one portion to a stirred suspension of PPh_3MeBr (1.22 g, 3.34 mmol) in THF (12 mL) at 0 °C.

After 0.5 h hydroxyphthalide[14] **26** (0.10 g, 0.42 mmol) was added in one portion and the mixture was allowed to warm to rt. After 2 h, water (2 mL) was added followed by addition of 1 N HCl until the pH of a reaction mixture was approx. 2. The organic layer was separated and the aqueous phase extracted with EtOAc (2×10 mL). The combined organic extracts were washed with satd. NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:4) to give styrene **27** (76 mg, 76%) as a white crystalline solid. R_f (petroleum ether/EtOAc, 1:4) 0.56; d_H (400 MHz, $CDCl_3$) 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.49 (dd, *J*=11.7, 1.3 Hz, 1H, C*H*$_2$=CH), 7.75 (dd, *J*=17.8, 1.3 Hz, 1H, C*H*$_2$=CH), 6.46 (s, 1H, H aryl), 6.84 (dd, *J*=17.8, 11.5 Hz, 1H, CH_2=C*H*); d_C (150 MHz, $CDCl_3$) 56.0, 56.7, 60.4 (OCH_3), 96.3 (CH aryl), 113.7 (*C*H$_2$=CH), 120.4, 130.4 (C aryl), 132.0 (CH_2=*C*H), 141.0, 153.6, 154.8 (C aryl), 171.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{14}O_5Na$ 261.07390, found 261.07378.

4.11. 2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)-pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)ethanol (37)

A solution of aldehyde **23** (107 mg, 0.20 mmol) in a THF/MeOH mixture (3.3 mL, 10:1) was cooled in an ice/salt bath and $NaBH_4$ (17.1 mg, 0.24 mmol) was added in one portion. The reaction mixture was stirred in an ice bath for 1 h followed by the addition of satd. NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with satd. NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **37** (102 mg, 94%) as a colorless oil. R_f (petroleum ether/EtOAc, 1:1) 0.77; $[\alpha]_D^{20}$ −2.3 (*c* 1.3, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.04 (s, 6H, $SiC(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, *J*=6.1 Hz, 3H, CHC*H*$_3$), 1.37–1.47 (m, 2H, CH_2), 1.58–1.73 (m, 2H, CH_2), 1.83–1.91 (m, 2H, CH_2), 2.13–2.18 (m, 2H, $HOCH_2CH_2CH$), 3.12 (m, 1H, CHOPMB), 3.61–3.66 (m, 1H, CH_2CH_2CH), 3.77–3.88 (m, 7H, OCH_3, TBSOCH, $HOCH_2$, $HOCH_2CH_2CH$), 4.56 (dd, *J*=19.0, 10.4 Hz, 2H, CH_2 of PMB), 5.53 (s, 1H, CHPh), 6.88–6.90 (m, 2H, PMB), 7.24–7.26 (m, 2H, PMB), 7.33–7.36 (m, 3H, H aryl), 7.44–7.46 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.3 ($Si(CH_3)_2$), 18.1, 21.5 (CH_2), 23.8 (*C*HCH$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 32.2 (CH_2), 34.3 ($HOCH_2CH_2$) 39.7 ($SiC(CH_3)_3$), 55.3 (OCH_3), 60.7 ($HOCH_2$), 68.5 (*C*HCH$_3$), 74.9 (CH_2 of PMB), 77.8 ($CH_2CH_2CH_2CH$), 80.2 (HCOPMB), 80.7 ($HOCH_2CH_2CH$), 100.2 (CHPh), 114.0, 125.9, 128.2, 128.7, 129.7, 137.8, 159.6 (C aryl); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{48}O_6SiNa$ 567.31124, found 567.31077.

4.12. (2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)-pentyl)-4-(2-iodoethyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxane (38)

Iodine (407 mg, 1.60 mmol) was added to a cooled solution (ice bath) of PPh_3 (392 mg, 1.49 mmol) and imidazole (131 mg, 1.91 mmol) in CH_2Cl_2 (3 mL). The resulting yellow suspension was stirred for 20 min at the same temperature before a solution of alcohol **37** (584 mg, 1.07 mmol) in CH_2Cl_2 (1 mL) was added. The cooling bath was removed and the resulting yellowish suspension was stirred for additional 12 h at ambient temperature. After that, the CH_2Cl_2 was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give primary iodide **38** (655 mg, 93%) as a slightly yellow oil. R_f (petroleum ether/EtOAc, 10:1) 0.59; $[\alpha]_D^{20}$ +19.2 (*c* 0.9, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.13 (d, *J*=6.1 Hz, 3H, CHC*H*$_3$), 1.37–1.47 (m, 2H, CH_2), 1.57–1.43 (m, 2H, CH_2), 1.86–2.04 (m, 2H, CH_2), 2.35–2.39 (m, 2H, ICH_2CH_2), 3.07 (t, *J*=9.2 Hz, 1H, CHOPMB), 3.29–3.34 (m, 2H, ICH_2CH_2CH, CH_2CH_2CH), 3.62–3.74 (m, 2H, ICH_2), 3.77–3.81 (m, 4H, OCH_3, TBSOCH), 4.50–4.60 (m, 2H, CH_2 of PMB), 5.52 (s, 1H, CHPh), 6.89–6.91 (m, 2H, PMB), 7.25–7.27 (m, 2H, PMB), 7.25–7.27 (m, 3H, H aryl), 7.46–7.48 8 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.3, ($Si(CH_3)_2$), 1.6 (CH_2I), 18.1, 21.5 (CH_2), 23.8 (*C*HCH$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 32.2 (CH_2), 36.3 ($HOCH_2CH_2$) 39.7 ($SiC(CH_3)_3$), 55.3 (OCH_3), 68.5 (*C*HCH$_3$), 74.8 (CH_2 of PMB), 77.6 (CH_2CH_2CH), 80.0 (HCOPMB), 80.6 (ICH_2CH_2CH), 100.0 (CHPh), 114.0, 126.0, 128.1, 128.7, 129.6, 129.7, 137.9, 159.6 (C aryl); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{47}IO_5SiNa$ 677.21297, found 677.21222.

4.13. 2-(Trimethylsilyl)ethyl 2-((*E*)-3-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoate (40)

(a) *Alkylation*: To a solution of phenylbenzyl selenoether[17] **39** (65.4 mg, 0.14 mmol) in a THF/HMPA mixture (3.3 mL, 10:1) was added dropwise a preformed solution of LDA (0.22 mmol) in THF (0.54 mL) whereby the reaction mixture turned red. After 20 min, a precooled (−40 °C) solution of alkyl iodide **38** (89.2 mg, 0.1 mmol) in THF (0.5 mL) was added slowly and the resulting reaction mixture was stirred for 2 h at −80 °C before satd. NH_4Cl solution (5 mL) was added. The reaction mixture was allowed to warm to room temperature, then the layers were separated and the aqueous phase extracted with EtOAc (2×10 mL). The combined organic layers were washed with satd. NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of around 2 mL. This solution was filtered through a short pad of Celite® and the Celite washed with EtOAc (2×10 mL). The combined organic washings were evaporated to give crude alkylation product (118.9 mg), which was directly introduced to the next step. R_f (petroleum ether/EtOAc, 3:1) 0.43.
(b) *Elimination*: The crude alkylation product (119 mg, 0.1 mmol) was dissolved in THF (2 mL) and H_2O_2 (0.026 mL, 0.25 mmol, 30%) was added at rt. After being stirred for 2 h, the reaction was quenched with satd. $Na_2S_2O_8$ solution (2 mL), and the mixture extracted with EtOAc (2×10 mL). The combined organic layers were washed with satd. NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to give styrene **40** (85.5 mg, 75% over 2 steps) as a colorless oil. R_f (petroleum ether/EtOAc, 3:1) 0.41; $[\alpha]_D^{20}$ +10.4 (*c* 0.5, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) −0.04 (s, 9H, $Si(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, *J*=6.1 Hz, 3H, CHC*H*$_3$), 1.40–1.88 (m, 8H, 3×CH_2, CH_2TMS), 2.53–2.63 (m, 1H, CH=CHC*H*$_2$), 2.76–2.79 (m, 1H, CH=CHC*H*$_2$), 3.14 (t, *J*=9.2 Hz, 1H, C*H*OPMB), 3.58–3.62 (m, 4H, OCH_3, TBSOCH), 3.71–3.80 (m, 8H, 2×OCH_3, HC=CHCH$_2$C*H*, CH_2CH_2CH), 3.87 (s, 3H, OCH_3), 4.20–4.35 (m, 2H, OC*H*$_2$CH$_2$TMS), 4.56–4.65 (m, 2H, CH_2 of PMB), 5.49 (s, 1H, CHPh), 6.34–6.41 (m, 2H, H_2CCH=CH, H aryl), 6.55 (d, *J*=16.3 Hz, 1H, H_2CCH=C*H*), 6.87–6.89 (m, 2H, H aryl), 7.25–7.32 (m, 6H, H aryl), 7.47–7.49 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) −4.7, −4.4 ($Si(CH_3)_2$), −1.6 ($Si(CH_3)_3$), 17.3 (CH_2TMS), 18.1 (SiC(*C*H$_3$)$_3$), 21.6 (CH_2), 23.8 (*C*HCH$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 32.8 (*C*H$_2$), 36.2 (CH=CHCH$_2$), 39.7 (*C*H$_2$), 55.3, 56.1, 56.5, 60.4 (OCH_3), 63.5 (*C*H$_2$CH$_2$TMS), 68.6 (*C*HCH$_3$), 74.8 (CH_2 of PMB), 77.5 (CH_2CH_2CH), 80.0 (CHOPMB), 80.7 (CH=CHCH$_2$*C*H), 96.1 (CH aryl), 100.0 (CHPh), 113.9, 116.1, 125.6, 126.1, 128.0 (C aryl), 128.4 (CH=*C*HCH$_2$), 129.5, 130.0 (C aryl), 130.5 (*C*H=CHCH$_2$), 132.5, 138.3, 140.7, 153.1, 153.8, 159.4 (C aryl), 168.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{47}H_{70}O_{10}Si_2Na$ 873.43997, found 873.43955.

4.14. 2-((*E*)-3-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-Hydroxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoic acid (41)

To a cooled (ice bath) solution of ester **40** (85.5 mg, 0.1 mmol) in THF (1.5 mL) was added TBAF (0.6 mL, 0.8 mmol, 1 M in THF) and the mixture was allowed to warm to room temperature. After being

stirred overnight satd. NH_4Cl solution (3 mL) was added to the mixture. The layers were separated and the aqueous phase extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/EtOAc, 1:2) to give hydroxy acid **41** (53.5 mg, 84%) as a white amorphous solid. R_f (petroleum ether/EtOAc, 1:5) 0.68; $[\alpha]_D^{20}$ +8.0 (*c* 0.2, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.13 (d, *J*=6.1 Hz, 3H, CHC*H*$_3$), 1.50–1.82 (m, 6H, 3×CH_2), 2.63–2.64 (m, 1H, CH=CHC*H*$_2$), 2.78–2.82 (m, 1H, CH=CHC*H*$_2$), 3.23–3.27 (dd, *J*=9.2, 9.2 Hz, 1H, CHOPMB), 3.62–3.65 (m, 4H, OCH_3, HOC*H*CH_3), 3.75–3.81 (m, 8H, 2×OCH_3, CH=CHCH$_2$C*H*, CH_2CH_2C*H*), 3.86 (s, 3H, OCH_3), 4.55–4.66 (m, 2H, CH_2 of PMB), 5.48 (s, 1H, CHPh), 6.37–6.42 (m, 2H, H aryl, CH=C*H*CH_2), 6.61–6.65 (d, *J*=16.3 Hz, *H*C=CHCH$_2$), 6.85–6.87 (m, 2H, PMB), 7.25–7.33 (m, 6H, H aryl), 7.46–7.48 (m, 2H, H aryl), 8.58 (br s, 1H, CO_2H); d_C (150 MHz, $CDCl_3$) 20.8 (*C*H$_2$), 23.2 (HOCH*C*H$_3$), 31.5 (CH_2), 35.8 (CH=CH*C*H$_2$), 38.8 (CH_2), 55.2, 56.0, 56.5 (OCH_3), 68.1 (HOCHCH$_3$), 74.6 (CH_2 of PMB), 75.7 (CH_2CH_2*C*H), 79.8 (CH=CHCH$_2$*C*H), 80.6 (CHOPMB), 96.0 (C aryl), 100.5 (CHPh), 113.9 (C aryl), 126.0 (CH=*C*HCH$_2$), 126.2, 128.1, 128.6, 129.5, 130.1, 131.1 (C aryl), 132.4 (*C*H=CHCH$_2$), 138.0, 140.6, 153.2, 154.2, 159.3 (C aryl), 176.8 (C=O) (very small); HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{44}O_{10}Na$ 659.28267, found 659.28274.

4.15. Macrolactone 34a

To a solution of acid **41** (60.2 mg, 0.095 mmol) in toluene (9.5 mL) was added PPh_3 (55.6 mg, 0.19 mmol) at 0 °C. After being stirred for 15 min at 0 °C, DEAD (0.097 mL, 0.19 mmol) was added dropwise and the resulting mixture allowed to warm to room temperature. After 12 h the toluene was evaporated and the crude material purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give macrolactone **34a** (45.3 mg, 77%) as a colorless oil. R_f (petroleum ether/EtOAc, 1:1) 0.41; $[\alpha]_D^{20}$ +52.4 (*c* 1.3, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.31 (d, *J*=6.3 Hz, 3H, CHC*H*$_3$), 1.54–1.81 (m, 2H, CH_2), 1.98–2.00 (m, 2H, $CH_3CHCH_2CH_2$), 2.24–2.30 (m, 2H, CH_2CH_2CHOCHPh), 2.67–2.74 (m, 1H, CH=CHC*H*$_2$), 2.80–2.84 (m, 1H, CH=CHC*H*$_2$), 3.69 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.80–3.85 (m, 4H, OCH_3, HCOPMB), 3.88–3.91 (m, 4H, OCH_3, CH_2CH_2C*H*OCHPh), 4.54–4.64 (m, 2H, CH_2 of PMB), 5.35–5.39 (m, 1H, CH_3C*H*), 5.50 (s, 1H, CHPh), 6.46 (s, 1H, H aryl), 6.53–6.60 (m, 1H, CH=C*H*CH_2), 6.66–6.70 (d, *J*=16.7 Hz, 1H, C*H*=CHCH$_2$), 6.82–6.84 (m, 2H, H aryl), 7.21–7.24 (m, 3H, H aryl), 7.34–7.41 (m, 3H, H aryl), 7.64–7.66 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) 17.9 (CH_2), 18.9 (*C*H$_3$CH), 30.0, 34.1 (CH_2), 36.4 (CH=CH*C*H$_2$), 55.2, 56.1, 56.5, 60.5 (OCH_3), 70.1 (CH_2 of PMB), 73.0 (CH_3*C*H), 73.2 (CH_2CH_2*C*HOCHPh), 77.8 (CH=CHCH$_2$*C*H), 78.9 (CHOPMB), 96.3 (C aryl), 101.3 (CHPh), 113.9, 116.8 (C aryl), 126.8 (*C*H=CHCH$_2$), 127.0, 128.4, 129.0, 129.1, 129.2, 130.3 (C aryl), 132.4 (CH=*C*HCH$_2$), 138.5, 140.6, 153.0, 153.5, 159.3 (C aryl), 167.9 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{42}O_9Na$ 657.24604, found 657.24650.

4.16. Macrolactone 42

Macrolactone **34a** (12.7 mg, 0.021 mmol) was dissolved in CH_2Cl_2 (0.5 mL), then water was added (0.25 mL) followed by DDQ (5.7 mg, 0.025 mmol). The resulting mixture was stirred for 1 h at room temperature and then satd. $NaHCO_3$ solution was added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with satd. $NaHCO_3$ solution (5 mL), satd. NaCl solution, dried over $MgSO_4$, and filtered. The solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give alcohol **42** (6.6 mg, 64%) as a white amorphous solid. R_f (petroleum ether/EtOAc, 1:1) 0.28; $[\alpha]_D^{20}$ +55.7 (*c* 0.6, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.30 (d, *J*=6.4 Hz, 3H, CHC*H*$_3$), 1.50–1.75 (m, 4H, 2×CH_2), 2.08–2.22 (m, 2H, CH_2), 2.64–2.77 (m, 2H, HC=CHC*H*$_2$), 3.71 (s, 3H, OCH_3), 3.74–3.72 (m, 5H, OCH_3, C*H*OH, CH_2C*H*OCHPh), 3.86–3.91 (m, 4H, OCH_3, CH=CHCH$_2$C*H*), 5.34–5.38 (m, 1H, CH_3C*H*), 5.46 (s, 1H, CHPh), 6.38–6.45 (m, 2H, H aryl, CH=C*H*CH_2), 6.69 (d, *J*=16.5 Hz, 1H, C*H*=CHCH$_2$), 7.32–7.41 (m, 3H, H aryl), 7.65–7.67 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) 17.2 (CH_2), 19.0 (*C*H$_3$CH), 29.4, 34.5 (CH_2), 35.1 (CH=CH*C*H$_2$), 56.1, 56.5, 60.7 (OCH_3), 62.9 (CH_3*C*H), 73.6 (CH_2CH_2*C*HOCHPh), 78.8 (CH=CHCH$_2$*C*H), 79.1 (CHOH), 96.4 (C aryl), 102.1 (CHPh), 116.8 (C aryl), 126.6 (*C*H=CHCH$_2$), 127.0, 129.1, 129.7 (C aryl), 132.0 (CH=*C*HCH$_2$), 138.2, 140.4, 153.1, 153.3 (C aryl), 167.8 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{34}O_8Na$ 521.21459, found 521.21456.

4.17. Ketone 34b

Dess–Martin periodinane (0.063 mL, 0.03 mmol, sol 15wt% in CH_2Cl_2) was added dropwise to a cooled (ice bath) solution of alcohol **42** (9.8 mg, 0.02 mmol) in CH_2Cl_2 (1 mL). Then the reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. After that, the resulting suspension was loaded directly on a flash column. Elution (petroleum ether/EtOAc, 1:1) gave ketone **34b** (9.2 mg, 94%) as a white amorphous solid. R_f (petroleum ether/EtOAc, 1:1) 0.34; $[\alpha]_D^{20}$ +25.4 (*c* 0.5, CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.28 (d, *J*=6.4 Hz, 3H, CHC*H*$_3$), 1.41–1.64 (m, 4H, 2×CH_2), 1.88–1.93 (m, 1H, CH_2C*H*$_2$CH), 2.10–2.14 (m, 1H, CH_2C*H*$_2$CH), 2.72–2.80 (m, 1H, CH=CHC*H*$_2$), 3.09–3.15 (m, 1H, CH=CHC*H*$_2$), 3.68 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.50–4.55 (m, 2H, CH=CHCH$_2$C*H* and CH_2CH_2C*H*OCHPh), 5.13–5.17 (m, 1H, CH_3C*H*), 5.94 (s, 1H, CHPh), 6.30 (ddd, *J*=16.3, 14.0, 6.9 Hz, 1H, CH=C*H*CH_2), 6.41 (s, 1H, H aryl), 6.47 (d, *J*=16.3 Hz, 1H, C*H*=CHCH$_2$), 7.35–7.44 (m, 3H, H aryl), 7.62–7.64 (m, 2H, H aryl); d_C (150 MHz, $CDCl_3$) 19.9 (CH_2), 20.4 (*C*H$_3$CH), 30.1, 36.6 (CH_2), 36.4 (CH=CH*C*H$_2$), 56.1, 56.5, 60.3 (OCH_3), 72.0 (CH_3*C*H), 81.7 (CH_2CH_2*C*HOCHPh), 82.8 (CH=CHCH$_2$*C*H), 96.5 (C aryl), 99.9 (CHPh), 116.2 (C aryl), 126.5, 126.8 (*C*H=CHCH$_2$), 128.5 (C aryl), 129.1 (C aryl), 129.3 (CH=*C*HCH$_2$), 129.5, 138.0 (C aryl), 140.8, 152.7, 153.8 (C aryl), 167.4 (C=O), 207.5 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{32}O_8Na$ 519.19894, found 519.19936.

4.18. (3*S*,7*S*,9*R*,*E*)-7,9,16-Trihydroxy-13,14-dimethoxy-3-methyl-4,5,6,7,9,10-hexahydro-3*H*-benzo[*c*][1]oxacyclotetradecine-1,8-dione (6)

(a) *Acetal cleavage:* Ketone **34b** (15.5 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and then a solution of MeOH/HCl conc. (1.05 mL, 20:1) was added dropwise at room temperature. After being stirred for 0.5 h, the solution was neutralized with satd. $NaHCO_3$ and the mixture extracted with EtOAc (2×10 mL). The combined organic layers were washed with satd. NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide the dihydroxy ketone (8.0 mg) as a yellow oil. The compound was directly introduced to the next step.

(b) *OMe cleavage:* To a solution of crude dihydroxy ketone (8.0 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was added BCl_3 (0.08 mL, 0.08 mmol, 1 M sol in CH_2Cl_2) dropwise at −50 °C. After 20 min the reaction was quenched with satd. NaOAc (3 mL). The layers were separated and aqueous phase extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with satd. NaCl solution, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified via flash chromatography (CH_2Cl_2/MeOH, 40:1) to give compound **22** (5.2 mg, 43% over 2 steps) as a colorless crystalline solid. R_f (petroleum ether/EtOAc, 1:5) 0.47; $[\alpha]_D^{20}$ −41.0 (*c* 0.5, CH_2Cl_2), $[\alpha]_D^{20}$ −51.0 (*c* 0.1, CH_3OH); d_H (400 MHz, $CDCl_3$) 1.18–1.33 (m, 2H, CH_2), 1.37 (d, *J*=6.1 Hz, 3H, C*H*$_3$CH), 1.45–1.75 (m, 3H, CH_2), 2.12–2.20 (m, 1H, CH_2), 2.70–2.76 (m, 1H, CH=CHC*H*$_2$), 3.03–3.09 (m, 2H, CH=CHC*H*$_2$, CH_2CH_2CHOH), 3.44–3.49 (m, 1H, CH=CHCH$_2$CHO*H*),

3.58 (s, 3H, OCH_3), 3.86 (s, 3H. OCH_3), 4.36–4.41 (m, 1H, CH_2CH_2CHOH), 4.60–4.67 (m, 1H, $CH{=}CHCH_2CHOH$), 5.00–5.06 (m, 1H, CH_3CH), 5.84 (ddd, J=15.3, 8.9, 3.3 Hz, 1H, $CH{=}CHCH_2$), 6.40 (s, 1H, H aryl), 6.65 (d, J=15.3 Hz, 1H, $CH{=}CHCH_2$), 11.56 (br s, 1H, OH aromatic); d_C (150 MHz, $CDCl_3$) 20.5 (CH_2), 20.7 ($CHCH_3$), 32.5 (CH_2), 35.6 (CH_2), 37.0 ($CH{=}CHCH_2$), 55.9, 60.6 (OCH_3), 73.2 (CH_3CH), 73.4 ($CH{=}CHCH_2CH$), 75.0 (CH_2CH_2CHOH), 99.7 (CH aryl), 103.7 (C aryl), 126.6 ($CH{=}CHCH_2$), 127.3 ($CH{=}CHCH_2$), 133.5, 140.3, 158.7, 160.9 (C aryl), 170.7 (C=O ester), 213.0 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{26}O_8Na$ 417.15199, found 417.15197.

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Supplementary data

Supplementary data associated with this article (remaining procedures for Scheme 1 and 2, copies of NMR spectra) can be found in the online version, at doi:10.1016/j.tet.2009.11.024.

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