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Ring-closing metathesis of α-ester-substituted enol ethers: application to the shortest synthesis of KDO

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This paper is dedicated to our inspirator Professor K. C. Nicolaou

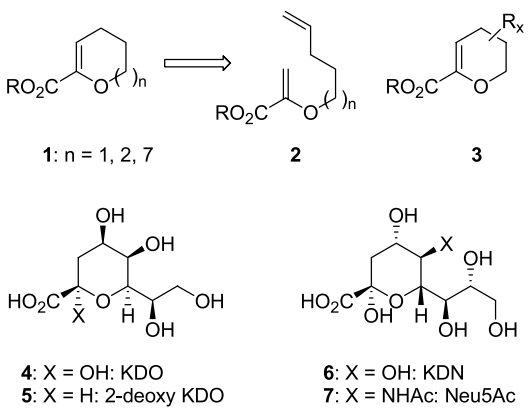
Abstract—Ring-closing metathesis reactions of α-ester-substituted enol ethers are described. In the case of unsubstituted terminal olefins, isomerization prior to cyclization was observed as an undesired side reaction, which could not be completely inhibited. Furthermore, this methodology was applied to a formal synthesis of KDO, which now represents the shortest synthetic pathway to KDO and its deoxy analogue. Interestingly, in this route olefin isomerization was not observed, presumably due to the increased steric environment of the double bond. Finally, an efficient two-step conversion to transform an alcohol into an α-alkoxy acrylate is also described.

1. Introduction

In the past decade, ring-closing metathesis (RCM) has emerged as a powerful tool for the synthetic organic chemist.[1] During this period, the scope of this type of reaction has been continuously increased starting from regular terminal olefins to olefins that are substituted with very different electron-withdrawing or electron-donating substituents. Many examples nowadays exist where electron-poor olefins have been cyclized in high yields,[2] including results from our own group.[3] On the other hand, RCM of electron-rich olefins—substituted with heteroatoms such as oxygen or nitrogen—is also encountered. Early examples of electron-rich olefins involve Ti-mediated cyclization reactions of enol ethers,[4] followed by other examples where either Mo-catalysts[5] or Ru-catalysts have been used.[6] In addition, our group was the first to demonstrate that electron-rich enamide double bonds could be efficiently cyclized into their cyclic counterparts,[7] which was later also shown by others in the synthesis of indoles.[8] Considering these reactions, we realized that there are virtually no RCM examples of olefins substituted with both electron-withdrawing and electron-donating substituents (e.g. olefin **2**, Scheme 1). Notwithstanding, we anticipated that such a transformation would hold a considerable potential since cyclic ethers **1** are formed, which may be synthetically useful building blocks. We also envisaged that if such cyclizations are successful, more elaborated cyclic ethers **3** could be synthesized, which might eventually provide practical pathways to biologically relevant natural products such as the ulosonic acids KDO (**4**, 3-deoxy-D-manno-2-octulosonic acid) and 2-deoxy KDO (**5**),[9] and the sialic acids KDN (**6**, 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid) and *N*-acetylneuraminic acid (Neu5Ac (**7**), 5-acetamido-3,5-dideoxy-D-glycero-D-galacto-2-nonulosonic acid).[10,11]

2. RCM of ester-substituted enol ethers

Initially, we set out to investigate the potential of the RCM reaction for the generation of unsaturated oxygen heterocycles **1** as shown in Scheme 1. We thereby focused on the generation of small six- and seven-membered ring systems as well as on a twelve-membered ring oxacycle.



Scheme 1. RCM of α-ester-substituted enol ethers.

Keywords: α-alkoxy acrylate; ring-closing metathesis; cross-metathesis.
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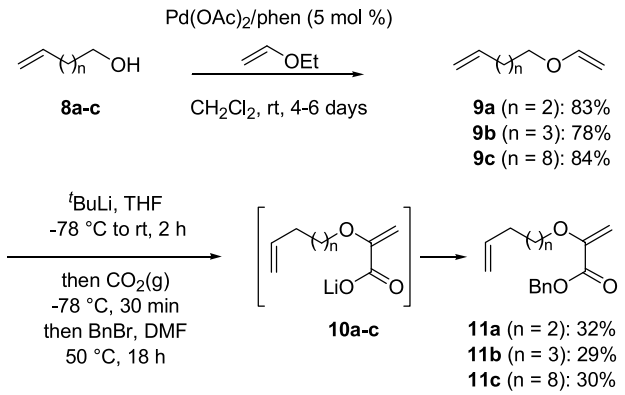


Scheme 2. Synthesis of the RCM precursors; phen=1,10-phenanthroline.

2.1. Synthesis of the precursors

The precursors **11a–c** for the formation of six-, seven- and twelve-membered rings, respectively, were prepared from the corresponding unsaturated alcohols **8** as shown in Scheme 2. First, the alcohol functions were efficiently vinylated in good yields according to a recently reported procedure, using a $Pd(OAc)_2$/phenanthroline catalyst and ethyl vinyl ether.[12] Next, the resulting vinyl ethers **9** were lithiated using *tert*-butyllithium, followed by reaction with CO_2 at low temperature, resulting in the corresponding lithium carboxylate salts **10**. Subsequent addition of an excess of benzyl bromide produced the desired benzyl esters **11** in moderate yields.

2.2. Ring-closing metathesis

Subjection of compound **11a** to the first generation Grubbs' catalyst **A** (Figure 1) at either 70°C or 95°C in toluene did not result in any cyclization, but instead in the slow formation of the homodimeric cross-metathesis product **13a** (Table 1, entries 1 and 2). The more reactive catalyst **B**, on the other hand, showed cyclic products with a conversion of 85% at 70°C within 2 h. Surprisingly, GC–MS analysis of the products showed the presence of an almost equal amount of the five-membered heterocycle **12d** together with the anticipated six-membered ring **12a** (entry 3), both of which could not be separated by column chromatography. Isomerization of the terminal double bond to the more stable internal one prior to the cyclization reaction must be the reason for this observation. This undesired side reaction has very recently also been reported in a number of other publications.[7,13] In most cases, the isomerization has been attributed to the presence of a ruthenium-hydride species, although the exact nature and source of this catalyst impurity is still unknown. More specifically, Grubbs has reported that a Fischer–carbene complex, resulting from reaction of the Ru-catalyst with a vinyl ether moiety, could be converted into a Ru-H species upon prolonged heating.[14] However, in the proposed mechanism it is the α-vinyl ether hydrogen, which is effectively transferred to the Ru.[15] This can obviously not occur with compounds **11a–c**, which all lack such a hydrogen atom.

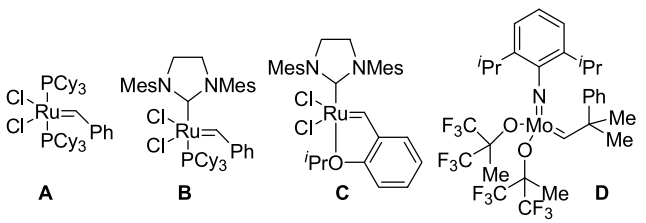
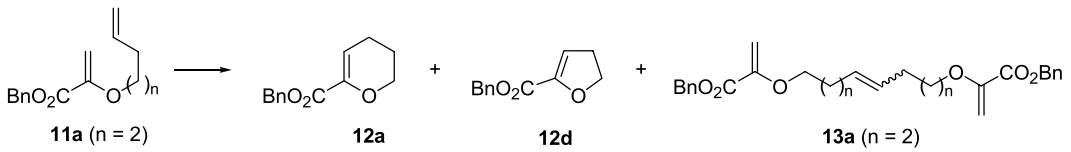


Figure 1. Different RCM catalysts.

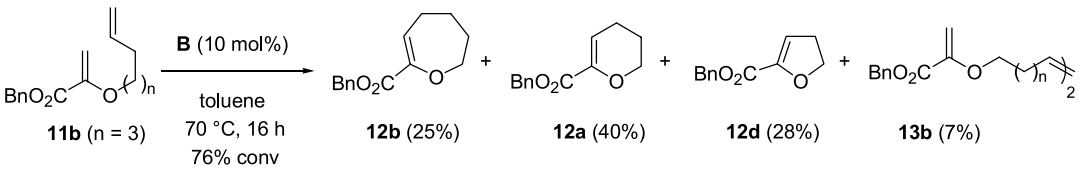
Column chromatographic purification of catalyst **B** immediately before use, as suggested by Snapper and co-workers,[16] significantly decreased the amount of isomerization (entry 4). In contrast, the addition of tricyclohexylphosphine oxide was reported by Nolan and co-workers to slow down the catalysis and thereby inhibit isomerization.[13a] Unfortunately, we found this not to be the case for compound **11a**. A slower reaction was indeed observed, but this only resulted in formation of a substantial amount of the homodimeric cross-metathesis product **13a** (entry 5). The use of catalysts **C** and **D** did not improve the

Table 1. RCM results of **11a** using catalysts **A–D**



Entry	Catalyst (mol%)/additive (mol%)	Temperature (°C)	Solvent	Time (h)	**12a**[a]	**12d**[b]	**13a**[a]	**11a**[a]
1	**A** (20)	70	Toluene	40	–	–	56[b]	n.d.
2	**A** (20)	95	Toluene	18	–	–	65[b]	n.d.
3	**B** (10)	70	Toluene	2	45	40	–	15
4	**B** (10)[c]	70	Toluene	2	51	28	–	21
5	**B** (10)/Cy_3PO (10)	60	Toluene	20	40	28	23	9
6	**B** (10)	40–60	$(ClCH_2)_2$	48	32	29	–	39
7	**C** (10)	50	Toluene	48	42	22	9	27
8	**C** (10)	85	Toluene	3	40	56	–	4
9	**D** (15)	50	Toluene	3	–	–	59[b]	n.d.
10	**D** (15)	85	Toluene	2	12	2	47	39

Reactions were performed under a nitrogen atmosphere, in approximately 0.03 M solutions. n.d.=not determined.
[a] GC yields, unless noted otherwise.
[b] Isolated yield.
[c] Catalyst was purified by column chromatography directly before use.

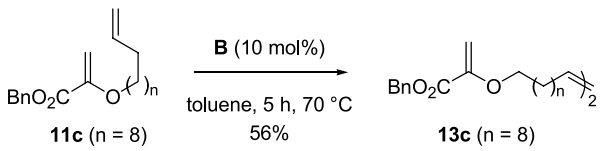


Scheme 3. Ring-closing metathesis of **11b**.

outcome of the reaction either. The Hoveyda catalyst **C** produced results similar to those obtained with **B** (entries 7 and 8), whereas the Schrock catalyst **D** hardly yielded any cyclized product (entries 9 and 10). In conclusion, only catalysts **B** and **C** were able to readily react in the desired fashion with the acrylic double bond of **11a**. The optimal temperature for the RCM reaction was approximately 70°C, since higher temperatures appeared to promote isomerization and lower temperatures resulted in significant amounts of the cross-metathesis product.

When the homologue **11b** was reacted under the optimized conditions with catalyst **B**, a similar double bond migration prior to RCM was observed (Scheme 3). Besides the expected seven-membered ring **12b**, the corresponding six- and five-membered ring systems **12a** and **12d** were encountered in comparable yields. Especially the formation of the latter product is remarkable, since the terminal double bond must have isomerized twice before cyclization to the five-membered ring can take place.

Finally, we did not succeed in generating a twelve-membered ring. Reaction of **11c** with catalyst **B** at 70°C gave exclusively the dimer **13c**, resulting from cross-metathesis of the starting material, in 56% isolated yield (Scheme 4). Despite these somewhat disappointing results, it is obvious that ester-substituted enol ethers indeed can undergo RCM, although isomerization could never be completely suppressed. Because of these isomerization problems, we decided to abandon the model systems and look into applications of this approach involving substituted olefins, where the substituents as a result of steric hindrance might efficiently retard such isomerization processes.[16]

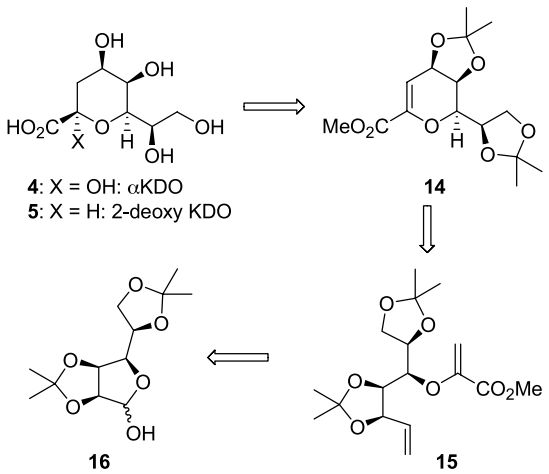


Scheme 4. Reaction of **11c** with catalyst **B**.

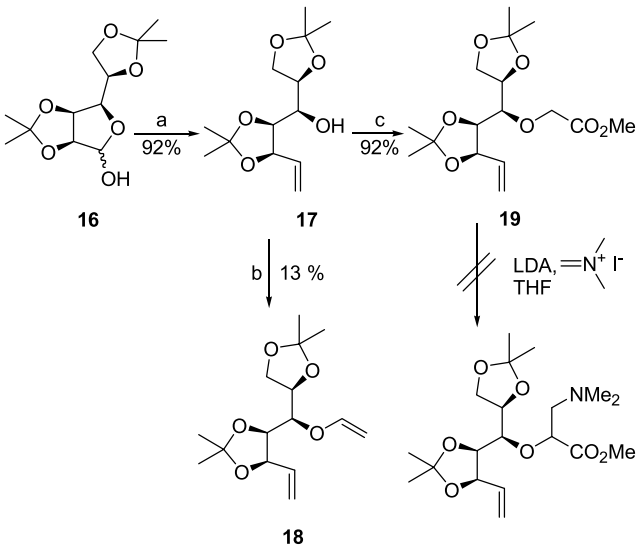
3. Synthesis of KDO

The monosaccharide 3-deoxy-D-manno-2-octulosonic acid (**4**, KDO) is an important component of lipopolysaccharides (LPS) that are present in the outer membrane in Gram-negative bacteria.[9] For this reason, KDO-containing oligosaccharides present promising lead compounds for the development of vaccines. Moreover, KDO has been used as a lead molecule for potentially new antibiotics, because of its likely involvement in the growth of bacteria. As a consequence, the development of efficient synthetic routes to KDO and analogues thereof has been an important subject of investigation over the past decades. Several syntheses of KDO have already been reported, including enzymatic approaches,[17] de novo syntheses[18] and routes using carbohydrates as starting materials.[19]

Our approach to the synthesis of KDO involves the RCM methodology discussed in the previous section as the key step (Scheme 5), which may result in the olefin **14**, a known intermediate in the synthesis of KDO,[20] and more importantly, a crucial starting point for the synthesis of derivatives of KDO.[21] The required precursor would then be the sugar-derived enol ester **15**, which might be accessible from readily available di-*O*-isopropylidene-protected D-mannose (**16**).[22]



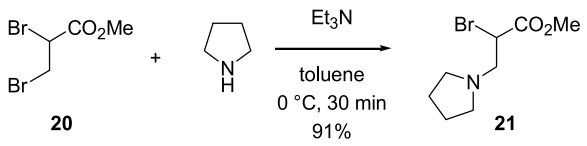
Scheme 5. Retrosynthetic approach towards KDO and 2-deoxy KDO.



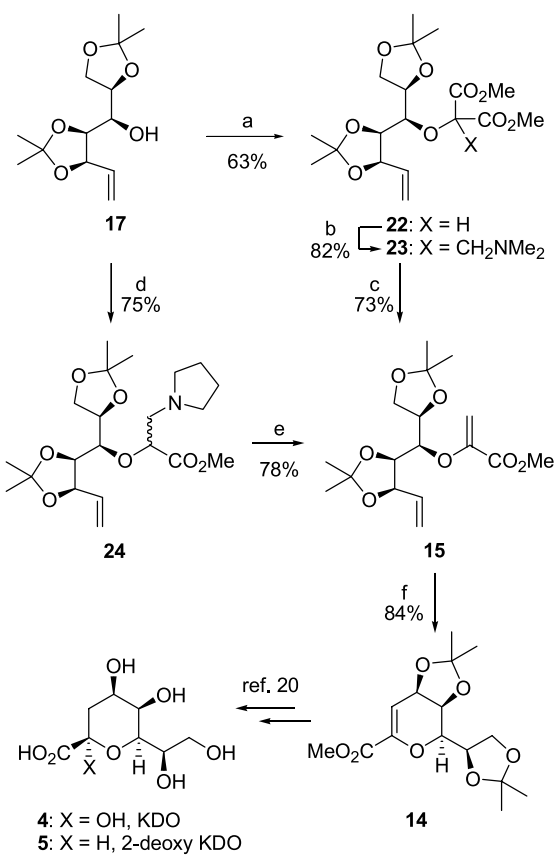
Scheme 6. Unsuccessful routes; (a) Ph_3PCH_2Br, *n*BuLi, THF, rt; (b) $[Ir(cod)Cl_2]$, vinyl acetate, Na_2CO_3, toluene, 100°C, 24 h; (c) $BrCH_2CO_2Me$, NaH, THF, rt, 17 h.

Thus, compound **16** was reacted with the appropriate Wittig reagent under literature conditions to give the olefin **17**.[23] The approach that was used to prepare the enol ester fragments in model compounds **11a–c** proved not to be successful for the preparation of compound **15** (Scheme 6) The palladium-catalyzed vinylation method gave no conversion at all, while a different recently reported method, using $[Ir(cod)Cl]_2$ as the catalyst,[24] yielded only a small amount (13%) of the desired vinyl ether **18**. In a different approach, alcohol **17** was first reacted with an α-bromo ester resulting in the formation of **19**. Unfortunately, attempts to react **19** with Eschenmoser's salt to introduce the double bond, were also unsuccessful.

A route that finally led to success is shown in Scheme 8. Following a procedure of Ganem,[25] alcohol **17** was reacted with dimethyl diazomalonate[26] in the presence of a catalytic amount of $Rh_2(OAc)_4$ to give the corresponding product **22** in 63% yield. Reaction with Eschenmoser's salt under mildly basic conditions then gave compound **23** in good yield. Treatment with an excess of methyl iodide in refluxing acetonitrile led to the formation of the quaternary ammonium salt, followed by elimination and iodide-induced decarboxylation to produce the desired RCM-precursor **15** in 73% yield.



Scheme 7. Synthesis of pyrrolidine-substituted α-bromo ester **21**.



Scheme 8. *Reagents and conditions*: (a) dimethyl diazomalonate, $Rh_2(OAc)_4$, benzene, 55°C, 3 h; (b) $CH_2{=}NMe_2I$, Et_3N, CH_2Cl_2, 40°C, 48 h; (c) MeI, MeCN, reflux, 48 h; (d) **21**, NaH, THF/DMF, 0°C→rt, 18 h; (e) MeI, Na_2CO_3, MeOH, reflux, 16 h; (f) B, toluene, 70°C, 1 h.

In addition to this route, which consists of essentially known conversions, we also discovered a shorter route to prepare the α-alkoxy acrylate fragment of **15**. For this purpose, bromide **21** was prepared by reacting commercially available 2,3-dibromopropionic acid methyl ester (**20**) with pyrrolidine and Et_3N in toluene at 0°C for 30 min. This reaction, which probably proceeds via an elimination/conjugate addition mechanism, was directly used for the next step without further purification (Scheme 7). Treatment of alcohol **17** with bromide **21** in the presence of NaH led to a clean conversion into ester **24** in 75% yield. Reaction of **24** with MeI and Na_2CO_3 in refluxing methanol resulted in methylation of the pyrrolidine-nitrogen and subsequent base-induced elimination to give the desired precursor **15** in good yield. Hence, an efficient procedure has been developed to convert alcohols into the corresponding α-enol esters in good yields. Further investigation of the synthetic potential of this sequence is currently being carried out.

Gratifyingly, subjection of precursor **15** to catalyst **B** under the optimized conditions led at 70°C to a smooth conversion to give the functionalized oxacycle **14** in 84% isolated yield within 1 h. Indeed, no isomerization of the mono-substituted double bond was observed, which sharply contrasts with the results obtained with the model systems **11a–c**. This underlines the assumption that the observed double bond isomerization is strongly dependent on steric hindrance.

Reduction of the double bond,[20a] followed by oxidation with MoOPH and deprotection[20b] have been previously reported to give KDO in three steps from **14**. More significant, however, is the fact that **14** is an important and useful building block for the preparation of oligosaccharides containing KDO fragments.[21] Thus, we efficiently prepared **14** in only four steps from readily available starting materials in an overall yield of 45%. To the best of our knowledge, this sequence now represents the shortest synthesis of KDO and its crucial intermediate **14**.

4. Conclusions

In summary, application of RCM on ester-substituted enol-ethers showed that the six- and seven-membered oxygen heterocycles could be efficiently generated by this method. A drawback, however, was that isomerization of the unhindered terminal olefin occurred as an undesired side-reaction, which could not be completely inhibited. Nonetheless, this methodology was applied in a formal synthesis of KDO, where due to the increased steric environment of the terminal olefin, isomerization was not observed. Finally, preliminary results were described involving a novel two-step transformation to efficiently convert an alcohol into the corresponding α-alkoxy acrylate function. Implementation of this novel reaction allowed us to carry out a formal synthesis of KDO in only seven steps starting from protected D-mannose.

5. Experimental

5.1. General

All reactions were performed under a nitrogen atmosphere, unless stated otherwise. Nitrogen was dried over SICAPENT® (Merck), $CaCl_2$ and KOH. CH_2Cl_2 was distilled over CaH_2. THF was distilled over Na. Acetonitrile was distilled and stored on molecular sieves (4Å). Benzene was dried on molecular sieves (4Å). Toluene was deoxygenated using the freeze-pump-thaw method. Et_3N was distilled and stored over KOH. All other chemicals were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 or a Bruker DMX 300 spectrometer. IR measurements were performed on an ATI Mattson Genesis Series FTIP spectrometer. Mass spectra were measured on a Fisons (VG) Micromass 7070E apparatus or a Finnigan MAT 900S apparatus. Optical rotations were determined with a Perkin–Elmer 241 polarimeter.

5.2. General procedure for preparation of vinyl ethers

To a solution of the alcohol in ethyl vinyl ether (0.3 M) was added a solution of $Pd(OAc)_2$ (5 mol%) and 1,10-phenanthroline (5.5 mol%) in a small amount of CH_2Cl_2. The mixture was stirred in air for 4–6 days, filtered over Celite and carefully concentrated in vacuo. The resulting crude product was filtered over a short silica gel column (100% pentane) to remove any starting alcohol. The vinyl ethers were further purified by column chromatography (100% pentane) or directly used in the next steps.

5.2.1. 5-Vinyloxypent-1-ene[27] **(9a).** ^1H NMR ($CDCl_3$, 300 MHz): δ 6.45 (dd, J=6.6, 14.3 Hz, 1H, OC*H*=CH_2), 5.81 (m, 1H, CH_2CH=CH_2), 5.03 (m, 2H, CH_2CH=C*H*$_2$), 4.16 (dd, J=1.8, 14.3 Hz, 1H, OCH=C*H*$_2$), 3.96 (dd, J=1.8, 6.9 Hz, 1H, OCH=C*H*$_2$), 3.68 (t, J=6.4 Hz, 2H, CH_2CH_2O), 2.15 (m, CH_2=CHC*H*$_2$), 1.74 (m, CH_2CH_2O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.6, 137.6, 114.9, 86.2, 67.3, 30.3, 28.4.

5.2.2. 6-Vinyloxyhex-1-ene (9b). ^1H NMR ($CDCl_3$, 200 MHz): δ 6.46 (dd, J=6.7, 14.5 Hz, 1H, OC*H*=CH_2), 5.80 (m, 1H, CH_2CH=CH_2), 4.99 (m, 2H, CH_2CH=C*H*$_2$), 4.15 (dd, J=2.0, 14.3 Hz, 1H, OCH=C*H*$_2$), 3.96 (dd, J=2.0, 6.7 Hz, 1H, OCH=C*H*$_2$), 3.67 (t, J=6.3 Hz, 2H, CH_2CH_2O), 2.08 (m, 2H, CH_2=CHC*H*$_2$), 1.70–1.43 (m, 4H, $CH_2CH_2CH_2O$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.6, 138.2, 114.4, 86.1, 67.9, 33.6, 28.7, 25.5.

5.2.3. 11-Vinyloxyundec-1-ene (9c). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.45 (dd, J=6.9, 14.3 Hz, 1H, OC*H*=CH_2), 5.80 (m, 1H, CH_2CH=CH_2), 4.95 (m, 2H, 2H, CH_2CH=C*H*$_2$), 4.16 (dd, J=1.9, 14.4 Hz, 1H, OCH=C*H*$_2$), 3.95 (dd, J=1.9, 6.8 Hz, 1H, OCH=C*H*$_2$), 3.66 (t, J=6.6 Hz, 2H, CH_2CH_2O), 2.03 (m, 2H, CH_2=CHC*H*$_2$), 1.64 (m, 2H, CH_2=CHCH_2C*H*$_2$), 0.86 (m, 12H, 6×C*H*$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.7, 138.9, 114.0, 86.1, 68.1, 34.0, 29.7, 29.6, 29.5, 29.3, 29.2. 29.1, 26.2.

5.3. General procedure for preparation of the enol esters

To a solution of the vinyl ether in THF (0.35 M) was added a 1.7 M pentane solution of ^{t}BuLi (1.7 equiv.) at −78°C. After stirring for 1 h, the cold bath was removed and the mixture was stirred for 1 h at room temperature. Next, the reaction was cooled again to −78°C and during 30 min a stream of CO_2 was led through the solution, followed by stirring for another hour upon gradually warming to room temperature. Benzyl bromide (1.7 equiv.) and DMF were then added and the reaction was stirred overnight at 50°C. After cooling to room temperature, H_2O was added and the resulting mixture was extracted three times with pentane. The organic layers were concentrated and the product purified by column chromatography (EtOAc/hexane/Et_3N 2:100:1).

5.3.1. Benzyl 2-(4-pentenyloxy)acrylate (11a). ^1H NMR (C_6D_6, 200 MHz): δ 7.06 (m, 5H, Ar-*H*), 5.69–5.52 (m, 1H, CH_2=C*H*), 5.44 (d, J=2.2 Hz, 1H, OC=C*H*$_2$), 5.04 (s, 2H, OC*H*$_2$Ph), 4.92 (m, 2H, CH=C*H*$_2$), 4.26 (d, J=2.2 Hz, 1H, OC=C*H*$_2$), 3.30 (t, J=6.4 Hz, 2H, OC*H*$_2$CH$_2$), 1.99 (m, 2H, CH_2=CHC*H*$_2$), 1.54 (m, 2H, CH_2=CHCH_2C*H*$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7, 151.0, 137.4, 135.5, 128.3, 128.0, 127.9, 115.1, 94.1, 67.8, 66.9, 30.2, 27.9. IR (film) 3066, 3034, 2946, 1734, 1618, 1165 cm^{-1}. HRMS: calcd for $(C_{15}H_{18}O_3)^+$: 246.1256, found: 246.1250.

5.3.2. Benzyl 2-(5-hexenyloxy)acrylate (11b). ^1H NMR (C_6D_6, 300 MHz): δ 7.05 (m, 5H, Ar-*H*), 5.74–5.60 (m, 1H, CH_2=C*H*), 5.45 (d, J=2.1 Hz, 1H, OC=C*H*$_2$), 5.05 (s, 2H, OC*H*$_2$Ph), 4.97 (m, 2H, CH=C*H*$_2$), 4.29 (d, J=2.3 Hz, 1H, OC=C*H*$_2$), 3.33 (t, J=6.0 Hz, 2H, OC*H*$_2$CH$_2$), 1.89 (m, 2H, CH_2=CHC*H*$_2$), 1.50 (m, 2H, CH_2=CHCH_2C*H*$_2$), 1.34 (m, 2H, CH_2CH_2O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7, 151.0, 138.1, 135.5, 128.3, 128.0, 127.9, 114.6, 93.9, 68.4, 66.8, 33.5, 28.1, 25.4. IR (film) 3066, 3033, 2959, 1735, 1618, 1166 cm^{-1}. HRMS: calcd for $(C_{16}H_{20}O_3)^+$: 260.1412, found: 246.1414.

5.3.3. Benzyl 2-(10-undecenyloxy)acrylate (11c). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.36 (m, 5H, Ar-*H*), 5.91–5.71 (m, 1H, CH_2=C*H*), 5.34 (d, J=2.2 Hz, 1H, OC=C*H*$_2$), 5.24 (s, 2H, OC*H*$_2$Ph), 4.96 (m, 2H, CH=C*H*$_2$), 4.60 (d, J=2.3 Hz, 1H, OC=C*H*$_2$), 3.73 (t, J=6.7 Hz, 2H, OC*H*$_2$CH$_2$), 2.03 (m, 2H, CH_2=CHC*H*$_2$), 1.75 (m, 2H, CH_2=CHCH_2C*H*$_2$), 1.28 (m, 12H, 6×C*H*$_2$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.8, 151.2, 139.2, 128.6, 128.5, 128.2, 128.1, 114.1, 94.0, 68.6, 66.8, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.5, 25.9. IR (film) 3066, 3033, 2924, 1734, 1617, 1166 cm^{-1}. HRMS: calcd for $(C_{21}H_{30}O_3)^+$: 330.2195, found: 330.2191.

5.4. General procedure for the ring-closing metathesis reactions of compounds 11a–c

A solution of the enol ester (0.03 M) and the catalyst in toluene was stirred and monitored by TLC or GC. When no further conversion was observed, the mixture was concentrated and the products isolated by column chromatography. The different products could not be separated by this method, but GC–MS allowed us to determine the nature and ratio of the compounds. With this knowledge we were able

to assign the ^{1}H NMR-signals of compounds **12a**, **b**, **d** (data are shown below).

5.4.1. Benzyl 3,4-dihydro-2*H*-6-pyrancarboxylate (12a). ^{1}H NMR (C_6D_6, 200 MHz): δ 7.20–7.03 (m, 5H, Ar-*H*), 5.71 (t, *J*=3.2 Hz, 1H, C*H*=C), 5.03 (s, 2H, OCH_2Ph), 3.91 (t, *J*=9.9 Hz, 2H, CH_2CHO), 1.98 (dt, *J*=3.2, 9.8 Hz, 2H, CH_2CH=C), 1.21 (m, 2H, CH_2CH_2O). LRMS: *m*/*z* 218 (M^+).

5.4.2. Benzyl 4,5,6,7-tetrahydro-2-oxepinecarboxylate (12b). ^{1}H NMR (C_6D_6, 300 MHz): δ 7.20–7.03 (m, 5H, Ar-*H*), 6.44 (t, *J*=6.0 Hz, 1H, C*H*=C), 5.06 (s, 2H, OCH_2Ph), 3.68 (m, 2H, CH_2CHO), 1.84 (m, 2H, CH_2-CH=C), 1.47 (m, 2H, $CH_2CH_2CH_2O$), 1.31 (m, 2H, CH_2CH_2O). LRMS: *m*/*z* 232 (M^+).

5.4.3. Benzyl 4,5-dihydro-2-furancarboxylate (12d). ^{1}H NMR (C_6D_6, 200 MHz): δ 7.20–7.03 (m, 5H, Ar-*H*), 6.06 (t, *J*=4.1 Hz, 1H, C*H*=C), 5.08 (s, 2H, OCH_2Ph), 3.60 (dd, *J*=4.8, 5.1 Hz, 2H, CH_2CHO), 1.56 (m, 2H, CH_2CH=C). LRMS: *m*/*z* 204 (M^+).

5.4.4. Benzyl 2-[(*E*)-8-(1-[(benzyloxy)carbonyl]-vinyloxy)-4-octenyl]oxyacrylate (13a). ^{1}H NMR (C_6D_6, 300 MHz): δ 7.17–7.03 (m, 10H, Ar-*H*), 5.45 (t, *J*=2.1 Hz, 2H, CH_2=C), 5.26 (m, 2H, C*H*=C*H*), 5.06 (m, 4H, OCH_2Ph), 4.31 (t, *J*=1.8 Hz, 2H, CH_2=C), 3.36 (t, *J*=6.3 Hz, 4H, OCH_2CH_2), 2.03 (m, 4H, CH=CHCH_2), 1.58 (m, 4H, OCH_2CH_2).

5.4.5. Benzyl 2-[(*E*)-20-(1-[(benzyloxy)carbonyl]-vinyloxy)-10-icosenyl]oxyacrylate (13c). ^{1}H NMR (C_6D_6, 300 MHz): δ 7.18–7.07 (m, 10H, Ar-*H*), 5.61 (m, 2H, C*H*=C*H*), 5.54 (d, *J*=2.2 Hz, 2H, CH_2=C), 5.13 (s, 4H, OCH_2Ph), 4.40 (d, *J*=2.2 Hz, 2H, CH_2=C), 3.46 (t, *J*=6.3 Hz, 4H, OCH_2CH_2), 2.16 (m, 4H, CH=CHCH_2), 1.61 (m, 4H, OCH_2CH_2), 1.51–1.28 (m, 24H, 12×CH_2).

5.5. KDO synthesis

5.5.1. (*R*)[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl][(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methanol (17). This compound was prepared according to a literature procedure.[23] The yield was 2.57 g (92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.09 (m, 1H, C*H*=CH_2), 5.37 (m, 2H, CH=CH_2), 4.69 (t, *J*=7.8 Hz, 1H, C*H*CH=CH_2), 4.38 (d, *J*=7.5 Hz, 1H, C*H*CHCH=CH_2), 4.09–3.96 (m, 3H, CH_2O and C*H*CH_2O), 3.45 (t, *J*=7.9 Hz, 1H, C*H*OH), 2.19 (d, *J*=8.1 Hz, 1H, O*H*), 1.52 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 1.34 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.0, 119.5, 109.2, 108.5, 79.1, 76.7, 76.0, 67.1, 27.0, 26.8, 25.5, 24.7.

5.5.2. (*R*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyl vinyl ether (18). To a solution of $[Ir(cod)Cl]_2$ (3.7 mg, 2 mol%), Na_2CO_3 (36 mg, 1.1 mol%) and vinyl acetate (56 μL, 0.57 mmol) in toluene (2 mL) was added **17** (81 mg, 0.31 mmol). The reaction was stirred at 100°C for 24 h, after which the mixture was concentrated in vacuo. Column chromatography (EtOAc/heptane, 1:5) gave the product in 13% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.26 (dd, *J*=6.4, 14.0 Hz, 1H, OC*H*=CH_2), 6.02–5.84 (m, 1H, CC*H*=CH_2), 5.33 (m, 2H, CCH=CH_2), 4.66 (t, *J*=7.3 Hz, 1H, C*H*CH=CH_2), 4.41–4.17 (m, 3H, OCH=CH_2 and C*H*CHCH=CH_2), 4.01 (m, 3H, CH_2O and C*H*CH_2O), 3.79 (dd, *J*=2.2, 4.9 Hz, 1H, C*H*OH), 1.52 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3).

5.5.3. Methyl 2-((*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyloxy)acetate (19). A solution of **17** (402 mg, 1.56 mmol) in THF (20 mL) was cooled to 0°C and NaH (60% dispersion in mineral oil, 154 mg, 3.84 mmol) was added. The resulting suspension was stirred at room temperature for 1 h, before it was cooled again to 0°C. Next, methyl 2-bromoacetate (644 mg, 4.21 mmol) was added and the reaction was stirred overnight upon warming to room temperature. Finally, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, after which the product was purified by column chromatography (EtOAc/heptane, 1:3). The yield was 475 mg (92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.96 (m, 1H, C*H*=CH_2), 5.30 (m, 2H, CH=CH_2), 4.57 (dd, *J*=6.6, 7.3 Hz, 1H, C*H*CH=CH_2), 4.42–4.03 (m, 6H, CH_2CO_2Me and CH_2O and C*H*CH_2O and C*H*CHCH=CH_2), 3.72 (s, 3H, OCH_3), 3.63 (m, 1H, C*H*OCH_2CO_2Me), 1.51 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 1.34 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 134.3, 118.6, 109.0, 108.6, 79.5, 78.9, 78.0, 76.9, 69.1, 66.1, 51.7, 27.4, 26.3, 25.9, 25.3.

5.5.4. Dimethyl 2-((*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyloxy)malonate (22). To a solution of **17** (184 mg, 0.71 mmol) and $Rh_2(OAc)_4$ (6.5 mg, 2.1 mol%) in benzene (4 mL) was added dimethyl diazomalonate[26] (213 mg, 1.35 mmol) over a period of 10 min. The mixture was stirred at 55°C for 3 h, cooled to room temperature and an additional 10 mL of benzene was added. The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (2×15 mL), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (EtOAc/heptane 1:4). The yield was 173 mg (63%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.85 (m, 1H, C*H*=CH_2), 5.29 (m, 2H, CH=CH_2), 4.98 (s, 1H, C*H*$(CO_2Me)_2$), 4.56 (dd, *J*=5.9, 7.0 Hz, 1H, C*H*CH=CH_2), 4.20–4.07 (m, 4H, CH_2O and C*H*CH_2O and C*H*CHCH=CH_2), 3.78 (m, 7H, OCH_3 and C*H*$OCH(CO_2Me)_2$), 1.50 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 166.7, 134.2, 118.7, 109.2, 108.5, 79.8, 79.4, 79.3, 78.7, 75.8, 66.7, 52.8, 52.6, 27.8, 26.1, 25.8, 25.1. IR (film) 2986, 1747, 1214, 1155, 1031 cm^{-1}. $[\alpha]_D^{25}$=+28.4 (*c*=0.40, CH_2Cl_2). HRMS: calcd for $(C_{18}H_{28}O_9)^+$: 388.1733, found: 388.1724.

5.5.5. Dimethyl 2-[(dimethylamino)methyl]-2-((*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyloxy)malonate (23). To a solution of **22** (75 mg, 0.19 mmol) and CH_2=NMe_2I (54 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (45 μL, 0.32 mmol). The mixture was stirred at reflux temperature for 48 h, cooled to room temperature and an additional 10 mL CH_2Cl_2 was added. The reaction

mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and the water layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, after which the product was purified by column chromatography (EtOAc/heptane, 1:2). The yield was 70 mg (82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.97 (m, 1H, C*H*=CH_2), 5.28 (m, 2H, CH=CH_2), 4.62 (t, J=5.9 Hz, 1H, C*H*CH=CH_2), 4.41 (m, 1H, C*H*CHCH=CH_2), 4.32–4.20 (m, 3H, CH_2O and C*H*CH_2O), 4.05 (m, 1H, C*H*OCH(CO_2Me)$_2$$NMe_2$), 3.75 (s, 3H, OC$H_3$), 3.72 (s, 3H, OC$H_3$), 3.10 (AB, J=14.1 Hz, 2H, C$H_2$$NMe_3$), 2.25 (s, 6H, NC$H_3$), 1.48 (s, 3H, CC$H_3$), 1.40 (s, 3H, CC$H_3$), 1.35 (s, 3H, CC$H_3$), 1.33 (s, 3H, CC$H_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.8, 135.1, 117.6, 109.1, 107.7, 79.4, 78.3, 77.3, 74.9, 68.2, 62.1, 52.7, 52.4, 46.7, 28.1, 26.2, 25.8, 25.3. IR (film) 2985, 2773, 1748, 1214, 1160, 1034 cm^{-1}. $[\alpha]_D^{25}$=+52.3 (c=0.30, CH_2Cl_2). HRMS: calcd for $(C_{21}H_{36}NO_9)^+$, [M$^+$+H]: 446.2390, found: 446.2386.

5.5.6. Methyl 2-bromo-3-pyrrolidin-1-ylpropanoate (21). A solution of methyl 2,3-dibromopropanoate **20** (853 mg, 3.47 mmol) in toluene (50 mL) was cooled to 0°C and pyrrolidine (0.28 mL, 3.39 mmol) and Et_3N (0.48 mL, 3.46 mmol) were added. After stirring at 0°C for 30 min, the resulting suspension was filtered over Celite, washed with H_2O (25 mL) and concentrated. The resulting crude product was >95% pure according to NMR and therefore directly used in the next step. The yield was 747 mg (91%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.33 (dd, J=6.0, 9.2 Hz, 1H, C*H*Br), 3.88 (s, H, OCH_3), 3.30 (dd, J=9.2, 12.9 Hz, 1H, CHCH_2N), 2.95 (dd, J=6.0, 12.9 Hz, 1H, CHCH_2N), 2.72 (m, 4H, NC$H_2$$CH_2$), 1.84 (m, 4H, NC$H_2CH_2$). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 169.5, 59.3, 58.2, 54.1, 43.0, 23.6.

5.5.7. Methyl 2-((*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyloxy)-3-pyrrolidin-1-ylpropanoate (24). A solution of **17** (66 mg, 0.26 mmol) in THF (6 mL) and DMF (2 mL) was cooled to 0°C and NaH (60% dispersion in mineral oil, 22 mg, 0.55 mmol) was added. The resulting suspension was stirred at room temperature for 1 h, before it was cooled again to 0°C. Next, **21** (200 mg, 0.84 mmol) was added and, upon warming to room temperature, the mixture was stirred for 18 h, followed by quenching with H_2O (5 mL). The mixture was extracted with pentane (4×15 mL) and the organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/heptane/Et_3N 66:33:1) yielded 80 mg (75%) of the desired product. Using the eluent above, both diastereomers could be separated.

First diastereomer. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.03 (m, 1H, C*H*=CH_2), 5.28 (m, 2H, CH=CH_2), 4.51 (dd, J=6.1, 7.1 Hz, 1H, C*H*CH=CH_2), 4.34 (m, 1H, C*H*CHCH=CH_2), 4.09 (m, 4H, CH_2O and C*H*CH_2O and C*H*OCH(CO_2Me)), 3.77 (m, 1H, OC*H*(CO_2Me)CH_2), 3.70 (s, 3H, OCH_3), 2.82–2.67 (m, 2H, CHCH_2N), 2.52 (m, 4H, NC$H_2$$CH_2$), 1.71 (m, 4H, NC$H_2CH_2$), 1.47 (s, 3H, CC$H_3$), 1.39 (s, 3H, CC$H_3$), 1.31 (s, 3H, CC$H_3$), 1.30 (s, 3H, CC$H_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 134.5, 118.7, 108.9, 108.4, 79.9, 79.6, 78.9, 78.8, 76.1, 66.4, 58.9, 54.6, 51.6, 27.9, 26.3, 25.9, 25.0, 23.9. R_f (EtOAc/heptane 4:1)=0.12.

Second diastereomer. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.92 (m, 1H, C*H*=CH_2), 5.27 (m, 2H, CH=CH_2), 4.64 (dd, J=5.2, 6.6 Hz, 1H, C*H*CH=CH_2), 4.54 (m, 1H, C*H*CHCH=CH_2), 4.17 (dd, J=5.8, 8.7 Hz, 1H, C*H*CH_2O), 4.05 (m, 3H, CH_2O and C*H*OCH(CO_2Me)), 3.71 (s, 3H, OCH_3), 3.63 (m, 1H, OC*H*(CO_2Me)CH_2), 2.94–2.76 (m, 2H, CHCH_2N), 2.58 (m, 4H, NC$H_2$$CH_2$), 1.71 (m, 4H, NC$H_2CH_2$), 1.49 (s, 3H, CC$H_3$), 1.35 (s, 3H, CC$H_3$), 1.33 (s, 3H, CC$H_3$), 1.29 (s, 3H, CC$H_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 134.6, 118.4, 109.1, 108.2, 80.5, 78.9, 78.2, 77.3, 76.2, 67.4, 57.8, 54.2, 51.8, 28.2, 26.3, 25.9, 25.4, 23.7. R_f (EtOAc/heptane 4:1)=0.07.

Mixture: IR (film) 2981, 2783, 1752, 1736, 1210, 1148, 1035 cm^{-1}. $[\alpha]_D^{25}$=+28.2 (c=0.30, CH_2Cl_2). HRMS: calcd for $(C_{21}H_{34}NO_7)^+$, [M$^+$−H]: 412.2335, found: 412.2331.

5.5.8. Methyl 2-((*R*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyloxy)acrylate (15). *From* **23**. A solution of **23** (30 mg, 68 μmol) and MeI (48 μL, 0.77 mmol) in MeCN (4 mL) was stirred at reflux temperature. After 48 h, the reaction mixture was concentrated in vacuo and the product was isolated by column chromatography (EtOAc/hexane 1:4). The yield was 17 mg (73%). *From* **24**: a solution of **24** (22 mg, 53 μmol), MeI (34 μL, 0.55 mmol) and Na_2CO_3 (26 mg, 0.25 mmol) in MeOH (6 mL) was stirred at reflux temperature. After 16 h, the reaction mixture was concentrated in vacuo and the product was isolated by column chromatography (EtOAc/hexane 1:4). The yield was 14 mg (78%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (m, 1H, C*H*=CH_2), 5.50 (d, J=3.0 Hz, 1H, OC=CH_2), 5.30 (m, 2H, CH=CH_2), 5.87 (d, J=2.4 Hz, 1H, OC=CH_2), 4.68 (dd, J=6.9, 7.5 Hz, 1H, C*H*CH=CH_2), 4.34–4.19 (m, 3H, CH_2 and OC*H*), 4.03 (m, 2H, OC*H*), 3.78 (s, 3H, OCH_3), 1.61 (s, 3H, CCH_3), 1.39 (s, 3H, CCH_3), 1.35 (s, 3H, CCH_3), 1.34 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.2, 150.3, 133.7, 119.4, 109.6, 108.8, 96.8, 78.9, 78.5, 76.7, 75.4, 65.6, 52.3, 26.7, 26.5, 25.9, 25.6. IR (film) 2984, 2935, 1734, 1623, 1199, 1165, 1057 cm^{-1}. $[\alpha]_D^{25}$=−44.7 (c=0.30, CH_2Cl_2). HRMS: calcd for $(C_{17}H_{26}O_7)^+$: 342.1679, found: 342.1675.

5.5.9. Methyl (3a*S*,4*R*,7a*R*)-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-6-carboxylate (14).[20a] A solution of **15** (24.1 mg, 70 μmol) and **B** (6.2 mg, 10.4 mol%) in toluene (4 mL) was stirred at 70°C. After 1 h, TLC indicated that the reaction was complete and the mixture was concentrated in vacuo. After purification by column chromatography (EtOAc/heptane 1:4) the product was obtained in a yield of 17.5 mg (84%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.99 (dd, J=1.5, 3.3 Hz, 1H, C*H*=C), 4.78 (dd, J=3.3, 6.0 Hz, 1H, C*H*CH=C), 4.45 (m, 2H, C*H*CH_2 and C*H*CHCH=C), 4.19 (m, 2H, CH_2), 3.82 (m, 1H, C*H*$CHCH_2$), 3.79 (s, 3H, OCH_3), 1.46 (s, 1H, CCH_3), 1.41 (s, 9H, CCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.2, 143.7, 110.9, 110.3, 109.5, 76.4, 73.8, 71.2, 68.8, 66.8, 52.4, 28.2, 27.1, 26.9, 25.5. $[\alpha]_D^{25}$=+31.9 (c=0.30, CH_2Cl_2). The data in all respect were congruent to those that were previously reported.[20a]

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