Tetrahedron 64 (2008) 10853–10859

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The use of D-mannitol-derived C_2-symmetric trienes in tandem metathesis reactions towards valuable lactones

Nassima Riache, Alain Blond, Bastien Nay *

Laboratoire de Chimie et Biochimie des Substances Naturelles, Muséum National d'Histoire Naturelle, CNRS, 57 rue Cuvier (CP 54), 75005 Paris, France

ARTICLE INFO

Article history:
Received 31 July 2008
Received in revised form 2 September 2008
Accepted 3 September 2008
Available online 17 September 2008

Keywords:
Tandem metathesis
Ring-closing metathesis
Chiral pool
Lactones
Macrodiolides

ABSTRACT

Chiral lactones were synthesized from D-mannitol. C_2-symmetric triene precursors were constructed with a central relay-olefin allowing the key domino ring-closing metathesis to be achieved. It led to the symmetrical cleavage of the substrate and to the formation of 2 mol of the desired 5- or 6-membered lactone. Attempts to form 7-membered lactones thus far only led to 14-membered macrodiolides instead.

1. Introduction

With the discovery of more and more efficient metathesis catalysts and since ring-closing metathesis (RCM) reactions are appropriate for tandem processes,[1] they have been strongly considered in synthetic strategies for atom economy.[2] Moreover we were convinced that in order to match with green synthetic strategies,[3] the use of the chiral pool in combination with this reaction would contribute to provide an elegant approach. RCM has been an important route to lactone construction and the involvement of unsaturated esters as metathesis substrates has often been reported either in the furanone[4] or in the pyranone[5] series. Sometime tandem processes were used, especially RCM coupled to cross metathesis to form α-alkenyl lactones.[5a] Previously, we reported that chiral lactones **I** could be obtained via domino RCM reactions performed on C_2-symmetric trienes derived from D-mannitol (Fig. 1).[6] There is indeed a 'metathetic equivalence' between both substrates **II** and **III**, derived from (2*S*,5*S*)-3-hexene-1,2,5,6-tetraol and (2*S*)-3-buten-1,2-diol, respectively. The strategy is close to 'relay ring-closing metathesis', which has also been used to synthesize α,β-disubstituted butenolides.[4b]

In this full paper, we wish to complete this work by describing significant improvements of the tandem RCM reaction applied to the synthesis of valuable lactones, especially by use of the second generation Hoveyda catalyst **H2**[1h] in comparison with the first and second generation Grubbs catalysts **G1** and **G2** (Fig. 2).[1a]

2. Results and discussion

The metathesis substrates were synthesized from D-mannitol (Scheme 1), which was protected as the butanediacetal **1** in 52% yield, according to the method of Ley and Michel.[7] Unlike the more common acetonide, it proved stable enough for dihydroxy-elimination carried out in the presence of iodine, triphenylphosphine and imidazole,[8] giving the alkene **2** in 83% yield. This allowed gaining one step compared to the already reported formation of the

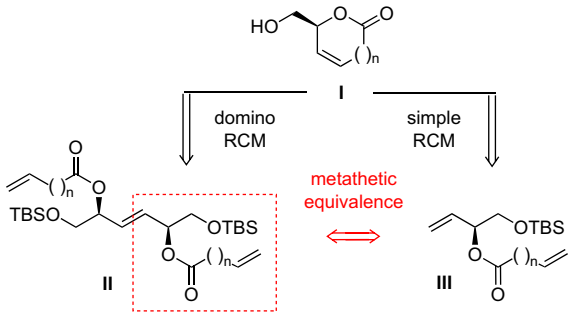


Figure 1. Synthetic plan for lactone synthesis and evidence for the 'metathetic equivalence' of intermediates **II** and **III**.

* Corresponding author. Tel.: +33 1 40 79 56 09; fax: +33 1 40 79 31 35.
E-mail address: bnay@mnhn.fr (B. Nay).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.09.012

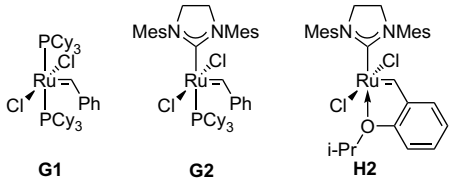
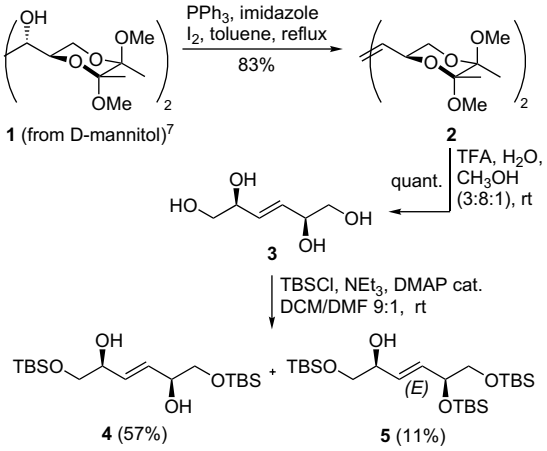


Figure 2. Metathesis catalysts used in this study.



Scheme 1. Synthesis of the intermediate diol **4**.

central double bond.[9] Then deprotection of both diols proceeded in aqueous acidic medium in the presence of TFA, affording quantitatively the tetrol compound **3**, which was regioselectively silylated at the primary alcohols (**4**) in 57% yield. The *E*-stereochemistry of the double bond was anticipated on the basis of the dihydroxy-elimination mechanism (diol **1** to alkene **2**).[8] It was confirmed by NMR analysis of the unsymmetrical trisilylated side-product **5**, showing a coupling constant of 15.7 Hz between both olefin protons.

To perform the tandem metathesis reaction, several trienes were synthesized by esterification of the diol **4** in the presence of an appropriate acyl source (Fig. 3). It provided unsaturated diesters with variable length: acrylate (**6**), methacrylate (**7**), 3-butenoate (**8**), 4-pentenoate (**9**), allylcarbonate (**10**). Alternatively, an acetylenic diester, bis(4-pentynoate) **11**, was synthesized, providing a C_2-symmetric enediyne. At last the unsymmetrical 4-pentynoate **12** was made from the trisilylated product **5** and provided an interesting substrate for testing tandem enyne metathesis then cross metathesis reactions.

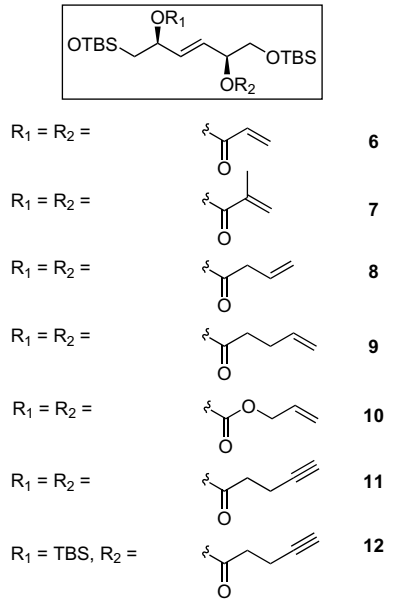


Figure 3. Structure of the metathesis substrates **6**–**12**.

Intermediates **6**–**12** were submitted to metathesis conditions in the presence of the ruthenium catalyst **G1**, **G2** or **H2**. The tandem metathesis mechanism from trienes **6**–**10** was expected to involve two successive RCM relayed by the symmetrical cleavage of the internal double bond (Fig. 4). This would allow the formation of 2 equiv of the expected lactone.

At first, we tried to perform the tandem metathesis reaction on the diacrylate **6** to obtain the silylated butenolide **13** (Table 1, entries 1–5). Compound **13** is a particularly important intermediate in organic synthesis[10] and thus the development of a preparation process with significant efficiency comparable to those existing[11] would have been interesting. Submitting triene **6** to 10 mol % of **G1** or **G2** only resulted in long reaction times (48 h) and poor to modest yields (entries 1 and 2). Many reports have indeed shown that α,β-unsaturated carbonyl compounds were poor substrates to **G1**.[12] This catalyst was excluded while further assays were performed in the presence of **G2** in toluene at 80 °C. Low catalyst loadings (5 mol % **G2**) were unable to complete the reaction and regular additions of **G2** (up to 30 mol % over 96 h) were required to get the respectable yield of 75% (entry 3). However a dramatic loss of enantiomeric excess was observed due to partial racemization of compound **13** (ee=0.38, checked by NMR in the presence of (+)-Eu[hfc]$_3$)[13] during the reaction. The problem was overcome by directly loading the reaction mixture with 30 mol % of catalyst **G2**, which resulted in great shortening of the reaction time to 2 h. No racemization was observed under these conditions and the furanone **13** was obtained in 71% yield and >0.99 enantiomeric excess (entry 4). Finally, the use of catalyst **H2** in toluene at 110 °C afforded the best improvement of the reaction since only 10 mol % of catalyst was needed to complete the reaction in only 2 h. A very good yield was obtained (88%) without any loss of enantiomeric excess (entry 5).

The methacrylate **7** did not give any reaction at all in the presence of 30 mol % of catalyst **G2** for 24 h, the starting material being recovered (Table 1, entry 6). Obviously, the use of this *gem*-disubstituted olefin was detrimental to the desired RCM. This showed

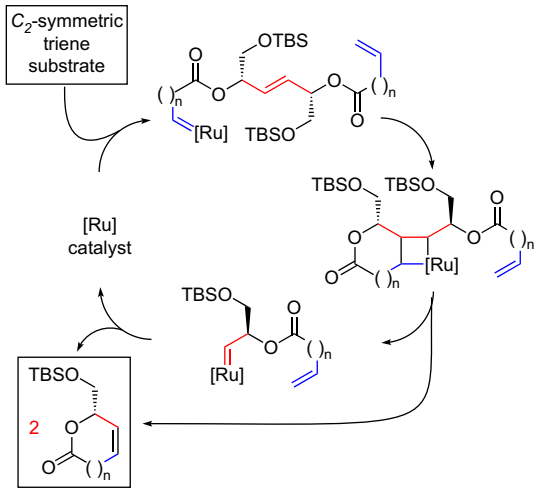
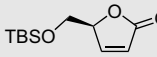
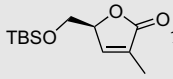
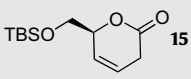
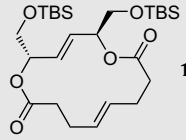
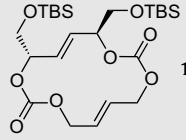
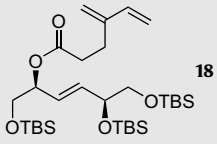


Figure 4. Mechanistic pathway for the domino metathesis reaction (initial incorporation of the catalyst at one of the terminal olefins).

Table 1
Metathesis reactions of substrates **6**–**12**

Entry	Substrate	Catalyst (equiv)	Temperature (°C)	Time (h)	Product (yield %)
1	**6**	**G1** (0.1)	40[a]	48	 **13** (6)
2	**6**	**G2** (0.1)	80[b]	48	**13** (34)
3	**6**	**G2** (0.3)[c]	80[b]	96	**13** (75)[d]
4	**6**	**G2** (0.3)	80[b]	2	**13** (71)[e]
5	**6**	**H2** (0.1)	110[b]	2	**13** (88)[e]
6	**7**	**G2** (0.3)	80[b]	24	No reaction
7	**7**	**H2** (0.1)	110[b]	24	 **14** (21)[e,f]
8	**8**	**G2** (0.1)	80[b]	4	 **15** (80)
9	**9**	**G2** (0.05)	80[b]	1.5	 **16** (81)
10	**9**	**H2** (0.05)	80[b]	1	**16** (75)
11	**10**	**G2** (0.06)	80[b]	2	 **17** (68)
12	**11**	—[g]	—[g]	—[g]	Degradation
13	**12**	**H2** (0.05)	80[b]	16	Degradation
14	**12**	**H2** (0.05)[h]	80[b]	1.5	 **18** (89)

[a] Reaction in dichloromethane.
[b] Reaction in toluene.
[c] Regular loading of 6×0.05 equiv over 96 h.
[d] ee=0.38.
[e] ee>99%.
[f] Corrected yield: 63%, based on 34% conversion.
[g] Catalyst **G1**, **G2** or **H2** under argon atmosphere, variable conditions.
[h] Reaction performed under an atmosphere of ethylene.

that the catalyst could not be incorporated through the internal double bond, thus supporting the reaction pathway of Figure 4. Nevertheless using only 10 mol % of **H2** in toluene at 110 °C for 24 h provided 63% of the butenolide **14** in >99% ee, based on recovered starting material (entry 7). As expected the use of the Hoveyda catalyst **H2** was thus crucial in the case of the α,β-unsaturated esters **6** and **7**.

With the 3-butenoyl derivative **8**, the reaction was performed in the presence of 10 mol % of the catalyst **G2**, yielding 80% of lactone **15** after 4 h (entry 8). Considering the possibility to synthesize larger lactones ($n>1$, Scheme 1), the same reaction was applied to the 4-pentenoate diester **9**. Instead of the desired 7-membered lactone, the 14-membered macrodiolide **16** was obtained in 81% yield after 1.5 h and in the presence of only 5 mol % of catalyst **G2** (entry 9), as observed in some preceding examples.[14] Similar results were obtained with catalyst **H2** (5 mol %) after slightly shorter

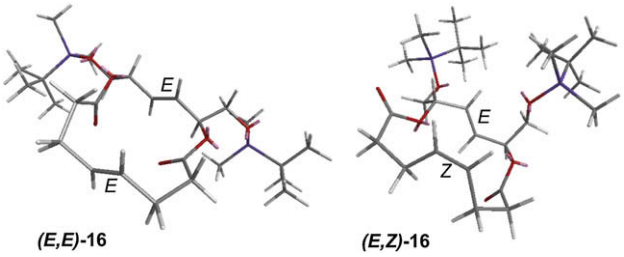


Figure 5. MM2 models of the *E* and *Z* isomers of the macrodiolide **16** (total energies of 27.4 and 75.5 kcal/mol, respectively).

reaction times (1 h, 75% yield, entry 10). The analogous carbonate **10** gave the 14-membered macrolactone **17** in 68% yields in the presence of **G2** (6 mol %, entry 11). The olefin configuration of macrolactones was in accordance with the thermodynamically favoured formation of *E*-olefins in macrocycles with the Grubbs catalyst.[14] Since metathesis reaction is reversible it was questionable if it could be run under conditions such that the monomers of **16** or **17** (7-membered rings) are formed.[15] Longer reaction times yet never promoted this transformation.

Total energy calculation (MM2) indeed favoured the *E* model with 27.4–75.5 kcal/mol for the *Z* compound. However, determining the configuration of the newly formed double bond was a puzzle task because of second order NMR multiplicities induced by the C_2-symmetry (crystals of the macrodiolide **16** or **17** could not be obtained for an X-ray analysis). 2D NMR experiments allowed assigning the complete skeleton and we first thought that NOESY spectra would be sufficient to distinguish both *Z* and *E* isomers. However, molecular modelling (MM2) showed that there were not much discriminating spatial differences between protons in both isomers (Fig. 5).

Finally compound **16** was rendered unsymmetrical by the selective hydrolysis of one of the esters in methanol in the presence of catalytic amounts of sodium cyanide (0.05 equiv),[16] affording the ester **19** in 33% yield (Fig. 6a).

Though the ^{1}H NMR spectra of **19** showed once again clearly the *E* configuration of the olefin of the alcohol moiety, the olefinic

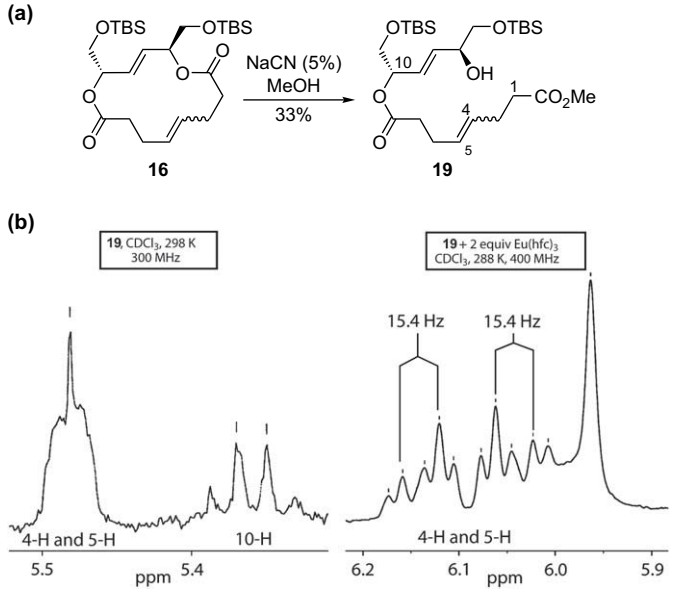
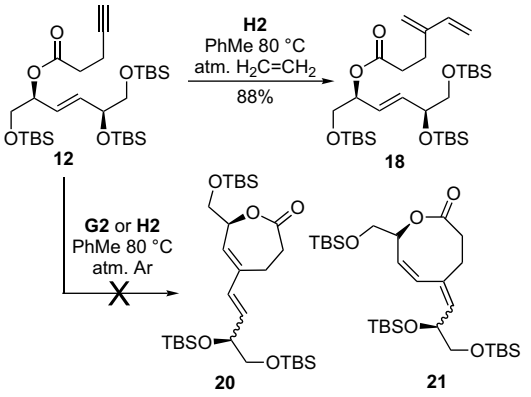


Figure 6. Determination of the newly formed olefin configuration of **16** (ester moiety): (a) Chemical desymmetrization of macrodiolide **16**; (b) ^{1}H NMR spectra of product **19** alone (left) and in the presence of (+)-Eu(hfc)$_3$ (right).

protons of the diester moiety still remained unresolved and not analyzable. The resolution was strongly improved by adding the chiral chemical shift reagent (+)-Eu(hfc)$_3$ (2 equiv) to the sample in $CDCl_3$. The NMR spectrum recorded at 15 °C showed this time two distinct doublet–triplet signals with the greater coupling constant of 15.4 Hz featuring for an *E* double bond.

Last attempts to carry on a tandem metathesis process were done with enynes **11** and **12**. Both compounds gave a complex mixture of unstable products when the reaction was performed under argon in the presence of **G2** or **H2** (entries 12 and 13). In the case of enyne **12** especially (entry 13) we had expected the formation of a cyclic diene (**20** or **21**) by an enyne metathesis mechanism followed by in situ cross metathesis (Scheme 2). These were not detected yet. Alternatively, when performed under an atmosphere of ethylene, only the diene **18** was obtained in 88% yield in the presence of 5 mol % of **H2** for 1.5 h at 80 °C. No more evolution of this reaction could be seen within longer reaction times.



Scheme 2. Reactivity of substrate **12** to various metathesis conditions.

3. Concluding remarks

Examples of domino metathesis reactions have been applied to the synthesis of valuable asymmetric lactones. The originality of the method consisted in the use of chiral trienes (**6**–**10**) derived from D-mannitol and thus having a C_2-symmetry axis and a central *E*-olefin. They were used as metathetic equivalents of (*S*)-3-buten-1,2-diol esters (Fig. 1). As expected the second generation Hoveyda catalyst **H2** gave the best results in the presence of α,β-unsaturated esters. Especially, it provides an alternative strategy to the synthetically useful (5*S*)-5-(hydroxymethyl)-5*H*-furan-2-one **13**.

When lengthened trienes were used (**9**, **10**) macrolactones (**16** and **17**) were formed and conserved the C_2-symmetry. Extensive NMR analyses were done to determine the structures of these compounds, especially by use of chemical shift reagents, which rendered interpretable the complex signals of olefinic protons.

4. Experimental part

4.1. General consideration

^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on a Bruker AC 300 or a Bruker Avance 400 spectrometer at 298 K. Chemical shifts (δ) for ^{1}H NMR were reported in parts per million (ppm) in deuterochloroform with residual chloroform as the internal standard (7.27 ppm) and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Chemical shifts for ^{13}C NMR were reported in parts per million relative to the triplet at 77.1 ppm for deuterochloroform. Infrared spectra (IR) were recorded on a Shimatzu FTIR 8400S spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra (MS) were obtained on a Biosystem API QSTAR Pulsar I spectrometer, in the ESI+ mode. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at room temperature (20 °C), using the sodium D-line. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Flash column chromatography separations were performed on Merck Geduran Silica Gel 60 (40–63 μm). Reactions were carried out in oven-dried glassware under a slight positive pressure of argon, unless otherwise mentioned. Toluene and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Triethylamine was dried over potassium hydroxide pellets. The bis(butanediacetal) **2** was synthesized according to Ley and Michel from D-mannitol.[7]

4.2. Experimental procedures

*4.2.1. (2S,5S)-1,2,5,6-Tetrahydroxy-3-hexene 1,2;5,6-bis(butanediacetal) (**2**)*

A mixture of diol **1** (1.51 g, 3.68 mmol), triphenylphosphine (3.86 g, 14.7 mmol) and imidazole (1 g, 14.7 mmol) in anhydrous toluene (130 mL) was heated at reflux while an iodine solution in toluene (0.55 M, 20 mL, 11 mmol) was added dropwise over 30 min. The reaction mixture was then left at reflux for 3.5 h before cooling at room temperature. Further solid iodine (0.93 g, 3.7 mmol) was added followed by a 1.6 N NaOH solution (20 mL). Stirring was continued until dissolution of tars. The toluene part was successively washed with water, a saturated solution of sodium thiosulfate, a saturated solution of sodium bicarbonate and brine (100 mL each). It was dried over $MgSO_4$ and concentrated. Silica gel column chromatography (heptane/AcOEt 7:3) gave 1.14 g of pure alkene **2** (83% yield) as an amorphous solid. R_f=0.35 (CH_2Cl_2/MeOH 98:2); mp: 96–97 °C; $[\alpha]_D^{20}$ −173 (*c* 1.1, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.27 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 3.40 (dd, *J*=11.2, 3.4 Hz, 1H, CH_aH$_b$), 3.58 (t-like dd, *J*=11.2 Hz, 1H, CH$_a$H$_b$), 4.38 (m, 1H, C*H*CH$_2$O), 5.68 (m, 1H, =C*H*–); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 17.6, 17.9, 48.1, 48.2, 62.9, 67.8, 97.9, 99.2, 129.2; IR (film) 1036, 1126, 1150, 1218, 1373, 1464, 2834, 2918, 2954, 2994 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}O_8Na$ $[M+Na]^+$: 399.1995, found: 399.1996.

*4.2.2. (2S,5S)-1,2,5,6-Tetrahydroxy-3-hexene (**3**)*

A solution of the alkene **2** (562 mg, 1.5 mmol) in the mixture H_2O/MeOH/TFA 8:1:3 (12 mL) was stirred at room temperature for 8 h. The resulting yellow solution was then concentrated in the rotatory evaporator at 40 °C. The residue was submitted to three more runs of co-evaporation with methanol in order to get rid of residual TFA. The crude mixture was purified by Sephadex LH20 chromatography (methanol), to give 230 mg of compound **3** as a colourless resin, which tended to solidify on standing (quantitative yield). R_f=0.25 (CH_2Cl_2/MeOH 8:2); mp: 50–52 °C; $[\alpha]_D^{20}$ −23 (*c* 1.16, methanol); ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 3.45 (dd, *J*=11.2, 6.6 Hz, 1H, CH_aH$_b$OH), 3.50 (dd, *J*=11.2, 5.0 Hz, 1H, CH$_a$H$_b$OH), 4.11 (m, 1H, C*H*OH), 5.76 (m, 1H, =C*H*–); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 67.2, 73.7, 132.7; IR (film) 1033, 1080, 1123, 1207, 1338, 1422, 1679, 2641, 2877, 2925, 3340 br cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_6H_{12}O_4Na$ $[M+Na]^+$: 171.0633, found: 171.0628.

*4.2.3. Silylation of compound **3***

A solution of compound **3** (50 mg, 0.338 mmol) in DMF (0.3 mL) was diluted in CH_2Cl_2 (3 mL) and was stirred at room temperature for 2 h in the presence of triethylamine (104 μL, 0.744 mmol), DMAP (2 mg, 0.02 mmol) and TBSCl (102 mg, 0.676 mmol). The

reaction mixture was diluted in ether (10 mL), washed with water (10 mL) and brine (10 mL), then dried over $MgSO_4$. The residue of evaporation was purified by silica gel chromatography (CH_2Cl_2/MeOH 98:2), thus affording the disilylated product **4** (white solid, 72 mg, 57% yield) and the trisilylated product **5** (colourless oil, 18 mg, 11% yield).

*4.2.3.1. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene (**4**).* R_f=0.22 (CH_2Cl_2/MeOH 98:2); mp: 89–90 °C; $[\alpha]_D^{20}$ −21 (*c* 0.45, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.08 (s, 6H, Si(CH_3)$_2$), 0.91 (s, 9H, SiC(CH_3)$_3$), 3.44 (dd, *J*=10.0, 7.9 Hz, 1H, CH_aH$_b$OTBS), 3.66 (dd, *J*=10.0, 3.7 Hz, 1H, CH$_a$$H_b$OTBS), 4.20 (m, 1H, C*H*OH), 5.78 (m, 1H, =C*H*–); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −4.5, 18.4, 25.9, 67.2, 72.2, 130.6; IR (CH_2Cl_2) 1109, 1271, 1327, 1365, 1402, 1477, 2859, 2890, 2933, 2958, 3568 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{41}O_4Si_2$ [M+H]$^+$: 377.2543, found: 377.2555.

*4.2.3.2. (2S,5S)-2-Hydroxy-1,5,6-tri(tert-butyldimethylsilyloxy)-3-hexene (**5**).* R_f=0.42 (CH_2Cl_2); $[\alpha]_D^{20}$ −17 (*c* 1.2, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05–0.09 (4s, 18H, 3Si(CH_3)$_2$), 0.90–0.92 (3s, 27H, 3SiC(CH_3)$_3$), 2.52 (d, *J*=3.1 Hz, 1H, O*H*), 3.43 (t-like dd, *J*=9.9 Hz, 1H, CH_aH$_b$OTBS), 3.45 (dd, *J*=9.9, 7.7 Hz, 1H, CH$_a$$H_b$OTBS), 3.53 (dd, *J*=10.0, 6.6 Hz, 1H, CH_aH$_b$OTBS), 3.64 (dd, *J*=10.0, 3.7 Hz, 1H, CH$_a$$H_b$OTBS), 4.19 (m, 2H, C*H*OH and C*H*OTBS), 5.68 (ddd, *J*=15.7, 5.7, 1.1 Hz, 1H, =C*H*–), 5.81 (ddd, *J*=15.7, 4.8, 0.8 Hz, 1H, =C*H*–); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.4, −4.6, 18.4, 25.9, 26.0, 67.2, 68.0, 72.3, 73.7, 129.0, 133.0; IR (film) 1113, 1253, 1369, 1399, 1478, 2850, 2895, 2937, 2955, 3569 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{55}O_4Si_3$ [M+H]$^+$: 491.3408, found: 491.3417.

*4.2.4. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(acrylate) (**6**)*

A solution of acryloyl chloride (35 μL, 0.425 mmol) in dichloromethane (0.9 mL) was added dropwise to a solution of diol **4** (40 mg, 0.106 mmol) and triethylamine (88 μL, 0.638 mmol) in dichloromethane (0.9 mL) at 0 °C. After 1 h stirring at 0 °C, the reaction mixture was warmed at room temperature and then quenched with water (5 mL). The mixture was extracted with diethyl ether (10 mL). The organic extract was washed with a saturated solution of $NaHCO_3$ (5 mL) and with brine (5 mL), then dried over $MgSO_4$. The crude extract was concentrated and purified by filtration on short silica gel column (CH_2Cl_2), furnishing the bis(acrylate) **6** as a yellowish oil (51 mg, 99% yield). R_f=0.44 (CH_2Cl_2); $[\alpha]_D^{20}$ +29 (*c* 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.03 and 0.04 (2s, 6H, Si(CH_3)$_2$), 0.86 (s, 9H, SiC(CH_3)$_3$), 3.70 (d, *J*=5.5 Hz, 2H, CH_2OTBS), 5.44 (m, 1H, C*H*OCO), 5.80 (m, 1H, =C*H*–), 5.83 (dd, *J*=10.4, 1.4 Hz, 1H, =CH^EH^Z), 6.14 (dd, *J*=17.3, 10.4 Hz, 1H, OCC*H*=), 6.42 (dd, *J*=17.3, 1.4 Hz, 1H, =C*H*^{E}H^Z); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −4.5, 18.3, 25.9, 64.7, 74.2, 128.7, 128.8, 130.9, 165.3 ppm; IR (film) 1054, 1131, 1196, 1266, 1296, 1365, 1410, 1470, 1624, 1639, 1738, 2856, 2931, 2956 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{44}O_6Si_2Na$ [M+Na]$^+$: 507.2574, found: 507.2577.

*4.2.5. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(methacrylate) (**7**)*

Methacryloyl chloride (51 μL, 0.532 mmol) was added dropwise to a solution of diol **4** (50 mg, 0.133 mmol) and triethylamine (110 μL, 0.798 mmol) in dichloromethane (1.3 mL) at 0 °C. After 30 min stirring at 0 °C, the reaction mixture was left 3 h at room temperature and then quenched with water (5 mL). The mixture was extracted with diethyl ether (10 mL). The organic extract was washed with a saturated solution of $NaHCO_3$ (5 mL) and with brine (5 mL), then dried over $MgSO_4$. The crude extract was concentrated and purified by silica gel column chromatography (cyclohexane/AcOEt 9:1), furnishing the bis(methacrylate) **7** as a yellowish oil (64 mg, 94% yield). R_f=0.83 (cyclohexane/AcOEt 8:2); $[\alpha]_D^{20}$ +5 (*c* 1.1, methanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03 and 0.04 (2s, 6H, Si(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 1.96 (m, 3H, CH_3C=CH_2), 3.71 (d, *J*=5.5 Hz, 2H, CH_2OTBS), 5.43 (m, 1H, C*H*OCO), 5.58 (m, 1H, =CH^EH^Z), 5.82 (m, 1H, =C*H*–), 6.14 (m, 1H, =C*H*^{E}H^Z); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.4, 18.2, 18.4, 25.8, 64.7, 74.3, 125.6, 128.7, 136.5, 166.5; IR (film) 1126, 1161, 1255, 1292, 1454, 1639, 1722, 2858, 2929, 2955 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{48}O_6Si_2Na$ [M+Na]$^+$: 535.2881, found: 535.2889.

*4.2.6. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(3-butenoate) (**8**)*

DCC (96 mg, 0.468 mmol) was added at room temperature to a solution of diol **4** (44 mg, 0.117 mmol), vinylacetic acid (40 μL, 0.468 mmol) and DMAP (1.5 mg, 0.012 mmol) in dichloromethane (1 mL). After 8 h stirring at room temperature, the mixture was filtered over Celite and concentrated. Purification by silica gel column chromatography (dichloromethane/hexane 9:1) furnished the bis(3-butenoate) **8** as a yellowish oil (49 mg, 82% yield). R_f=0.38 (dichloromethane); $[\alpha]_D^{20}$ +25 (*c* 1.8, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.04 (s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$) 3.11 (dt, *J*=6.9, 1.4 Hz, 2H, CH_2CH=CH_2), 3.66 (d, *J*=5.6 Hz, 2H, CH_2OTBS), 5.15 and 5.19 (2 m, 2H, CH_2CH=CH_2), 5.36 (m, 1H, C*H*OCO), 5.75 (m, 1H, =C*H*–), 5.93 (m, 1H, CH_2C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 25.8, 39.3, 64.6, 74.3, 118.6, 128.8, 130.3, 170.6 ppm; IR (film) 1124, 1173, 1257, 1326, 1646, 1739, 2709, 2743, 2857, 2965, 3088 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{48}O_6Si_2Na$ [M+Na]$^+$: 535.2881, found: 535.2887.

*4.2.7. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(4-pentenoate) (**9**)*

4-Pentenoyl chloride (26 μL, 0.234 mmol) was added dropwise at room temperature to a solution of diol **4** (40 mg, 0.106 mmol) and pyridine (43 μL, 0.532 mmol) in dichloromethane (1 mL). After 4 h stirring, diethyl ether (10 mL) was added. The solution was washed with a saturated solution of copper sulfate (5 mL), water (5 mL), a saturated solution of sodium bicarbonate (5 mL) and brine (5 mL), then dried over $MgSO_4$. The crude extract was concentrated and purified by silica gel column chromatography (cyclohexane/AcOEt 98:2), furnishing the bis(4-pentenoate) **9** as colourless oil (48 mg, 84% yield). R_f=0.44 (dichloromethane); $[\alpha]_D^{20}$ +28 (*c* 2.2, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05 (s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 2.39 (m, 4H, CH_2CH_2COO), 3.65 (d, *J*=5.6 Hz, 2H, CH_2OTBS), 5.00 and 5.06 (2m, 2H, CH_2CH=CH_2), 5.35 (m, 1H, C*H*OCO), 5.74 (m, 1H, =C*H*–), 5.83 (m, 1H, CH_2C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.0, 18.3, 25.8, 28.9, 33.8, 64.7, 74.0, 115.6, 128.9, 136.7, 172.1; IR (film) 1127, 1177, 1256, 1365, 1470, 1640, 1750, 2857, 2932, 2957, 3080 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{52}O_6Si_2Na$ [M+Na]$^+$: 563.3200, found: 563.3185.

*4.2.8. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(allylcarbonate) (**10**)*

Allyl chloroformate (90 μL, 0.862 mmol) was added dropwise at 0 °C to a solution of diol **4** (48 mg, 0.128 mmol) and pyridine (92 μL, 1.148 mmol) in dichloromethane (2 mL). After 5 h stirring at room temperature, diethyl ether (10 mL) was added. The solution was washed with a saturated solution of copper sulfate (5 mL), water (5 mL), a saturated solution of sodium bicarbonate (5 mL) and brine (5 mL), then dried over $MgSO_4$. The crude extract was concentrated and purified by silica gel column chromatography (dichloromethane/cyclohexane 8:2 then 1:0), furnishing the bis(allylcarbonate) **10** as colourless oil (34 mg, 49% yield) and some mono(allylcarbonate) derivative (14 mg, 24%). R_f=0.44 (dichloromethane); $[\alpha]_D^{20}$ +27 (*c* 0.21, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05 and 0.06 (2s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 3.70 (d, *J*=5.7 Hz, 2H, CH_2OTBS), 4.62 (m, 2H, CH_2CH=CH_2), 5.21 (m, 1H, C*H*OCO), 5.27 and 5.36 (2m, 2H, CH_2CH=CH_2), 5.82 (m, 1H, =C*H*–),

5.94 (m, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.3, 18.3, 25.9, 64.7, 68.5, 78.0, 118.8, 128.7, 131.7, 154.5; IR (film) 1126, 1255, 1369, 1388, 1464, 1749, 2858, 2929, 2955 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{48}O_8Si_2Na$ $[M+Na]^+$: 567.2785; found 567.2780.

4.2.9. (2S,5S)-2,5-Dihydroxy-1,6-di(tert-butyldimethylsilyloxy)-3-hexene bis(4-pentynoate) (**11**)

DCC (6.6 mg, 0.320 mmol) was added at room temperature to a solution of diol **4** (30 mg, 0.080 mmol), 4-pentynoic acid (31 mg, 0.320 mmol) and DMAP (1 mg, 0.008 mmol) in dichloromethane (1.2 mL). After 105 min stirring at room temperature, the mixture was quenched with water (6 mL) and then extracted with diethyl ether (3×12 mL). The organic extract was washed with brine (12 mL) and dried over $MgSO_4$. The crude extract was concentrated and purified by silica gel column chromatography (cyclohexane/AcOEt 75:25) furnishing the bis(4-pentynoate) **11** (43.7 mg, yellowish oil) in quantitative yield. R_f=0.82 (cyclohexane/AcOEt 7:3); $[\alpha]_D^{20}$ +25 (*c* 0.12, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.97 (s, 1H, C≡*CH*), 2.54 (m, 4H, CH_2CH_2COO), 3.66 (d, *J*=5.4 Hz, 2H, CH_2OTBS), 5.37 (m, 1H, *CH*OCO), 5.75 (m, 1H, =*CH*–); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.4, 14.3, 25.7, 29.7, 33.4, 64.6, 69.0, 74.3, 82.4, 128.8, 170.7; IR (film) 1124, 1165, 1254, 1362, 1373, 1464, 1472, 1742, 2857, 2928, 2953, 3312; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{48}O_6Si_2Na$ $[M+Na]^+$: 559.2887, found: 559.2887.

4.2.10. (2S,5S)-2-Hydroxy-1,5,6-tri(tert-butyldimethylsilyloxy)-3-hexene 4-pentynoate (**12**)

DCC (84 mg, 0.408 mmol) was added at room temperature to a solution of alcohol **5** (100 mg, 0.204 mmol), 4-pentynoic acid (40 mg, 0.408 mmol) and DMAP (3 mg, 0.024 mmol) in dichloromethane (2 mL). After 3 h stirring at room temperature, the mixture was filtered over Celite and concentrated. Purification by silica gel column chromatography (dichloromethane/cyclohexane 1:1) furnished the ester **12** as a colourless oil (86 mg, 74% yield). R_f=0.85 (CH_2Cl_2); $[\alpha]_D^{20}$ +14 (*c* 0.44, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05–0.07 (3s, 18H, $3Si(CH_3)_2$), 0.89–0.90 (3s, 27H, $3SiC(CH_3)_3$), 1.96 (t, *J*=2.6 Hz, 1H, C≡*CH*), 2.54 (m, 4H, CH_2CH_2COO), 3.43 (dd, *J*=9.9, 5.8 Hz, 1H, CH_2OTBS-a), 3.52 (dd, *J*=9.9, 6.4 Hz, 1H, CH_2OTBS-b), 3.66 (d, *J*=5.6 Hz, 2H, CH_2OTBS), 4.17 (q, *J*=5.6 Hz, 1H, *CH*OTBS), 5.39 (q, *J*=5.6 Hz, 1H, *CH*OCO), 5.70 (dd, *J*=15.7, 5.6 Hz, 1H, =*CH*–), 5.81 (dd, *J*=15.7, 4.8 Hz, 1H, =*CH*–); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.3, −5.2, −4.5, 14.4, 18.3, 25.9, 26.0, 33.7, 64.9, 67.9, 69.1, 73.6, 74.9, 82.6, 125.7, 134.7, 170.9; IR (film) 1124, 1256, 1361, 1464, 1470, 1744, 2858, 2930, 2955, 3315 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{58}O_5Si_3Na$ $[M+Na]^+$: 593.3484, found: 593.3487.

4.2.11. (5S)-5-((tert-Butyldimethylsilyloxy)methyl)furan-2(5H)-one (**13**)

The second generation Hoveyda catalyst **H2** (6 mg, 0.009 mmol) was added to a solution of the bis(acrylate) **6** (43 mg, 0.089 mmol) in toluene (0.9 mL). The mixture was stirred at 110 °C for 2 h, then cooled at room temperature and quenched with DMSO (31 μL, 0.445 mmol). After left at room temperature for 16 h, the solution was half evaporated and purified by silica gel chromatography (cyclohexane/AcOEt 9:1), giving the enantiomerically pure lactone **13** (38 mg, colourless oil) in 88% yield. R_f=0.18 (hexane/Et_2O 7:3); $[\alpha]_D^{20}$ −122 (*c* 0.85, $CHCl_3$) (Ref. 11a: $[\alpha]_D^{20}$ −136 (*c* 1.13, $CHCl_3$); Ref. 11b: $[\alpha]_D^{20}$ −143 (*c* 0.20, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.06 and 0.07 (2s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.80 (dd, *J*=10.7, 6.3 Hz, 1H, CH_aH_bOTBS), 3.93 (dd, *J*=10.7, 4.5 Hz, 1H, CH_aH_bOTBS), 5.05 (m, 1H, *CH*CH=CH), 6.16 (dd, *J*=5.7, 2.0 Hz, 1H, HC=*CH*CO), 7.50 (dd, *J*=5.7, 1.5 Hz, 1H, *HC*=CHCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.1, 18.3, 25.8, 63.0, 83.4, 122.6, 154.4, 173.0; IR (film) 1107, 1147, 1170, 1261, 1336, 1396, 1610, 1765 st, 2862, 2892, 2932, 2957 cm^{-1}; HRMS (CI, CH_4) *m*/*z* calcd for $C_{11}H_{21}O_3Si$ $[M+H]^+$: 229.1260, found: 229.1257.

4.2.12. (5S)-5-((tert-Butyldimethylsilyloxy)methyl)-3-methylfuran-2(5H)-one (**14**)

The second generation Hoveyda catalyst **H2** (6 mg, 0.009 mmol) was added to a solution of the bis(methacrylate) **7** (47 mg, 0.092 mmol) in toluene (1 mL). The mixture was stirred at 110 °C for 24 h, then cooled at room temperature and quenched with DMSO (31 μL, 0.445 mmol). After left at room temperature for 4 h, the solution was half evaporated and purified by silica gel chromatography (cyclohexane/AcOEt 9:1), affording recovered starting material **7** (31 mg, 66% yield) and the enantiomerically pure lactone **14** (10 mg, colourless oil) in 21% yield or 63% based on recovered starting material. R_f=0.2 (hexane/Et_2O 7:3); $[\alpha]_D^{20}$ −81 (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.07 and 0.08 (2s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.94 (t-like dd, *J*=1.8 Hz, 3H, HC=C(CH_3)CO), 3.75 (dd, *J*=10.7, 5.2 Hz, 1H, CH_aH_bOTBS), 3.87 (dd, *J*=10.7, 4.7 Hz, 1H, CH_aH_bOTBS), 4.91 (m, 1H, $TBSOCH_2CH$), 7.07 (m, 1H, *HC*=C(CH_3)CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.4, 10.7, 18.3, 25.8, 63.4, 81.2, 131.1, 146.5, 174.1; IR (film) 1062, 1122, 1205, 1257, 1342, 1384, 1464, 1759, 2858, 2930, 2955 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{23}O_3Si$ $[M+H]^+$: 243.1416, found: 243.1409.

4.2.13. (6S)-6-((tert-Butyldimethylsilyloxy)methyl)-pyran-2(3H,6H)-one (**15**)

The second generation Grubbs catalyst **G2** (8 mg, 0.01 mmol) was added to a solution of the bis(3-butenoate) **8** (48 mg, 0.096 mmol) in toluene (4 mL). The mixture was stirred at 80 °C for 4 h, then concentrated and purified by rapid filtration over silica gel column chromatography (dichloromethane/hexane 95:5), giving the enantiomerically pure lactone **15** as a colourless oil (36 mg) in 80% yield. R_f=0.28 (dichloromethane); $[\alpha]_D^{20}$ −159 (*c* 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.06 and 0.07 (2s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 3.07 (m, 2H, CH_2COO), 3.76 (dd, *J*=10.7, 3.3 Hz, 1H, CH_aH_bOTBS), 3.87 (dd, *J*=10.7, 4.4 Hz, 1H, CH_aH_bOTBS), 4.95 (m, 1H, $TBSOCH_2CH$), 5.86 and 5.93 (2m, 2H, *HC*=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, 18.4, 25.9, 30.5, 65.0, 80.0, 123.2, 123.7, 169.0; IR (film) 1101, 1165, 1238, 1388, 1468, 1733, 2860, 2934 cm^{-1}; HRMS (CI, CH_4) *m*/*z* calcd for $C_{12}H_{23}O_3Si$ $[M+H]^+$: 243.1416, found: 243.1413.

4.2.14. (5E,12E,11S,14S)-11,14-Di[(tert-butyldimethylsilyloxy)-methyl]-1,10-dioxacyclotetradeca-5,12-dien-2,9-dione **16**

The second generation Grubbs catalyst **G2** (2.5 mg, 0.003 mmol) was added to a solution of the bis(4-pentenoate) **9** (33 mg, 0.061 mmol) in toluene (3 mL). The mixture was stirred at 80 °C for 1.5 h, then concentrated and purified by silica gel column chromatography (dichloromethane/heptane 9:1), giving the macrodiolide **16** as a white solid (25 mg) in 81% yield. R_f=0.5 (dichloromethane); mp: 38–40 °C; $[\alpha]_D^{20}$ +61 (*c* 2.5, dichloromethane); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.05 and 0.06 (2s, 12H, $Si(CH_3)_2$), 0.88 (s, 18H, $SiC(CH_3)_3$), 2.20 and 2.45 (2m, 4H, =CH–CH_2), 2.36 (m, 4H, CH_2COO), 3.69 (dd, *J*=11.1, 4.8 Hz, 2H, CH_aH_bOTBS), 3.75 (dd, *J*=11.1, 7.0 Hz, 2H, CH_aH_bOTBS), 5.24 (m, 2H, *CH*OCO), 5.36 (m, 2H, =*CH*–CH_2), 5.74 (m, 2H, =*CH*–CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.2, 18.3, 25.9, 28.0, 33.3, 63.9, 74.6, 129.6, 131.6, 172.4; IR (film) 1115, 1142, 1179, 1237, 1260, 1370, 1435, 1470, 1750, 2853, 2927, 2953 cm^{-1}; HRMS (CI, CH_4) *m*/*z* calcd for $C_{26}H_{49}O_6Si_2$ $[M+H]^+$: 513.3068, found: 513.3064.

4.2.15. (5E,12E,11S,14S)-11,14-Di[(tert-butyldimethylsilyloxy)-methyl]-1,3,8,10-tetraoxacyclotetradeca-5,12-dien-2,9-dione **17**

The second generation Grubbs catalyst **G2** (1.5 mg, 0.002 mmol) was added to a solution of the bis(allylcarbonate) **10** (17 mg, 0.031 mmol) in toluene (3 mL). The mixture was stirred at 80 °C for 2 h. Then DMSO (7 μL, 1.5 mmol) was added at room temperature and the mixture was stirred for 16 h. It was concentrated and

purified by silica gel column chromatography (dichloromethane), giving the macrodiolide **17** (11 mg) in 68% yield and another product identified as its *Z* isomer according to ^{1}H NMR (3 mg, 19%). The products were hardly separated from the starting material. R_f=0.28 (dichloromethane); $[\alpha]_D^{20}$ +8 (*c* 0.12, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.06 and 0.07 (2s, 12H, Si(CH_3)$_2$), 0.89 (s, 18H, SiC(CH_3)$_3$), 3.70 (dd, *J*=11.3, 4.6 Hz, 2H, CH_aH$_b$OTBS), 3.80 (dd, *J*=11.3, 6.6 Hz, 2H, CH$_a$$H_b$OTBS), 4.28 (m, 2H, =CHC$H_2$O-a), 4.48 (m, 2H, =CHC$H_2$O-b), 4.96 (m, 2H, C*H*OCO), 5.80 (m, 2H, =C*H*–CH), 5.95 (m, 2H, =C*H*–CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.2, 18.4, 25.9, 63.8, 66.8, 79.4, 131.1, 132.8, 154.1; IR (film) 1105, 1255, 1369, 1452, 1751, 2856, 2930, 2955 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{44}O_8Si_2Na$ [M+Na]$^+$: 539.2472, found: 539.2472.

*4.2.16. (2S,5S)-2-Hydroxy-1,6,5-tri(tert-butyldimethylsilyloxy)-3-hexene 4-methylenehex-5-enoate (**18**)*

The second generation Hoveyda catalyst **H2** (1.3 mg, 0.002 mmol) was added to a solution of compound (**12**) in toluene (4.2 mL). The mixture was stirred at 80 °C under an ethylene atmosphere for 90 min, then cooled at room temperature and quenched with DMSO (7.5 μL, 0.105 mmol). After a night stirring at room temperature, the solution was concentrated and filtered through a pad of silica, then purified by silica gel column chromatography (cyclohexane/AcOEt 100:1), giving diene **18** (22 mg, colourless oil) in 89% yield. R_f=0.67 (heptane/Et$_2$O 7:3); $[\alpha]_D^{20}$ +15 (*c* 0.09, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.05–0.08 (6s, 18H, 3Si(CH_3)$_2$), 0.89–0.90 (3s, 27H, 3SiC(CH_3)$_3$), 2.54 (m, 4H, CH_2CH_2COO), 3.44 (dd, *J*=9.9, 5.8 Hz, 1H, CH_aH$_b$OTBS), 3.52 (dd, *J*=9.9, 6.5 Hz, 1H, CH$_a$$H_b$OTBS), 3.66 (d, *J*=5.6 Hz, 2H, CH_2OTBS), 4.17 (q, *J*=5.8 Hz, 1H, C*H*OTBS), 5.02 (s, 1H, C=CH_aH$_b$), 5.04 (s, 1H, C=CH$_a$$H_b$), 5.09 (d, *J*=10.9 Hz, 1H, HC=CH^ZH^E), 5.25 (d, *J*=17.6 Hz, 1H, HC=CH^ZH^E), 5.38 (m, 1H, C*H*OCO), 5.71 (dd, *J*=15.6, 5.8 Hz, 1H, H_aC=CH$_b$), 5.78 (dd, *J*=15.6, 4.9 Hz, 1H, H$_a$C=CH_b), 6.37 (dd, *J*=17.6, 10.9 Hz, 1H, *H*C=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −5.4, −5.3, −4.6, 18.2, 18.3, 18.4, 25.8, 25.9, 26.0, 26.5, 33.2, 64.9, 67.9, 73.6, 74.4, 113.5, 116.0, 125.9, 129.6, 134.4, 138.4, 144.8, 172.2; IR (film) 970, 1007, 1126, 1258, 1362, 1389, 1464, 1472, 1597, 1742, 2859, 2899, 2930, 2955, 3090; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{62}O_5Si_3Na$ [M+Na]$^+$: 621.3803, found: 621.3801.

Acknowledgements

N.R. acknowledges receipt of a scholarship from the MENRT.

References and notes

1. (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923; (d) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (e) Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129–5147; (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633; (g) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2; (h) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
2. (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.
3. Raston, C. *Green Chem.* **2005**, *7*, 57.
4. (a) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277–280; (b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211; (c) Langer, P.; Albrecht, U. *Synlett* **2002**, 1841–1842; (d) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143–4145; (e) Quinn, K. J.; Isaacs, A. K.; DeChristopher, B. A.; Szklarz, S. C.; Arvary, R. A. *Org. Lett.* **2005**, *7*, 1243–1245; (f) Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805–1808.
5. (a) Virolleaud, M.-A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081–8084; (b) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875–3878; (c) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547–7550; (d) Bouzbouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 1995–1997; (e) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967–3969; (f) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737–1739; (g) Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, *7*, 2225–2228.
6. Nay, B.; Gaboriaud-Kolar, N.; Bodo, B. *Tetrahedron Lett.* **2005**, *46*, 3867–3870.
7. (a) Michel, P.; Ley, S. V. *Synthesis* **2003**, 1598–1602; (b) Ley, S. V.; Michel, P. *Synthesis* **2004**, 147–150.
8. Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469–470.
9. Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829–4832.
10. (a) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3035–3038; (b) Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.* **1988**, *29*, 5349–5352; (c) Jeong, L. S.; Beach, J. W.; Chu, C. K. *J. Heterocycl. Chem.* **1993**, *30*, 1445–1452.
11. (a) Häfele, B.; Jäger, V. *Liebigs Ann. Chem.* **1987**, 85–87; (b) Mann, J.; Weymouth-Wilson, A. C. *Org. Synth.* **1998**, *75*, 139–145; (c) Tanigushi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547–3552; (d) Vigneron, J. P.; Méric, R.; Larchevêque, M.; Debal, A.; Lallemand, J. Y.; Kunesh, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521–3529; (e) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055–5072; (f) Ortuño, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1987**, *43*, 2199–2202; (g) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417–1419.
12. (a) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648–2649; (b) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418; (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
13. Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1970**, *92*, 6979–6980.
14. (a) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155–7158; (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147; (c) Macrocyclic lactone formation via RCM has also been well documented in Ref. 1b.
15. Conrad, J. C.; Eelman, M. D.; Silva, J. A. D.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.
16. Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727–730.