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A domino ring-closing metathesis as a key-step in the synthesis of chiral lactones from D-mannitol

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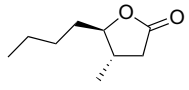
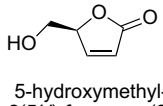
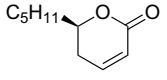
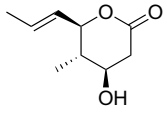
Abstract—Chiral lactones were synthesized in six steps from D-mannitol. The key-step was a domino ring-closing metathesis reaction leading to the symmetric cleavage of a D-mannitol triene derivative and to the formation of two molecules of the desired lactone.

Lactones hold an important place in the natural product field and are widely spread allover the biogenetic categories. Particularly, there are numerous examples of five- and six-membered chiral lactones, which often exhibit pheromonal, medicinal, flavoring, or olfactive properties: the whisky lactone (**1**) is an oak-derived flavor found in wines;[1] the skin-irritant massoialactone (**3**), which also produces systolic standstill in frog heart muscle has been isolated from the bark of *Cryptocarya massoia* and in the defense secretions of *Camponotus* ants,[2] while prelactones such as **4** are metabolites produced by some polyketide-producing *Streptomyces* species.[3] Furthermore, simple lactones such as furanone **2** have been used as starting materials in the total synthesis of natural products or medicines.[4] To this end we needed to make use of the butenolide **2** as an asymmetric dienophile in Diels–Alder reactions and we explored an original and practicable strategy toward this precursor.


whisky lactone (**1**)

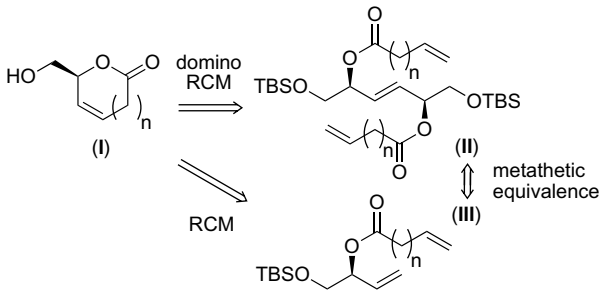

5-hydroxymethyl-2(5*H*)-furanone (**2**)


(-)-massoialactone (**3**)


prelactone C (**4**)

Ring-closing metathesis[5] (RCM) has provided an important route to lactone synthesis and the involvement of unsaturated esters as metathesis substrates has often been reported in the last few years either in the furanone[6] or in the pyranone[7] series. Some tandem processes have been used, especially RCM coupled to cross metathesis to form α-alkenyl lactones.[7a] We now report an original strategy leading to 5- or 6-membered chiral lactones (**I**) via domino RCM performed on C_2-symmetric trienes (**II**) synthesized from D-mannitol (Scheme 1).

Alkenes **II** were derived from intermediate (2*S*,5*S*)-3-hexene-1,2,5,6-tetraol, which was regarded as a synthetic equivalent of (*S*)-3-buten-1,2-diol, which is commercially but expensively available although it can be



Scheme 1. Synthetic plan for the lactones and evidence for 'metathetic equivalence' of the intermediates **II** and **III**.

Keywords: Domino metathesis; Chiral pool; Lactones.
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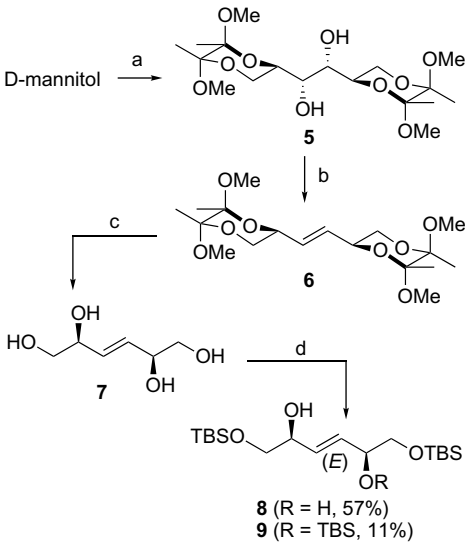


Scheme 2. Synthesis of the intermediate diol **8**: (a) butanedione, $BF_3{\cdot}OEt_2$, $H(OMe)_3$, methanol (52% after recrystallization from hexane); (b) PPh_3, imidazole, I_2, toluene, reflux (82%); (c) TFA/H_2O/CH_3OH 25:65:10, rt (quant.); (d) TBSCl (1.9 equiv), NEt_3 (2 equiv), DMAP (0.1 equiv), DCM/DMF 9:1, 0 °C → rt.

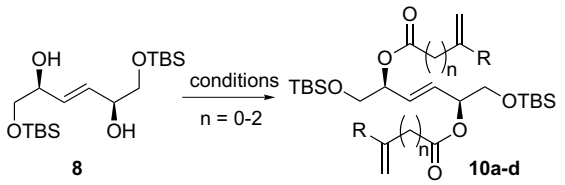
synthesized from D-mannitol. From a metathetic point of view the C_2-symmetric intermediates **II** were indeed equivalent to intermediates **III**, but clearly allowed for symmetric domino processes. With regard to the use of an internal double bond as a metal-directing relay, the strategy can be related to 'relay ring-closing metathesis', which has also been used to synthesized, α,β-disubstituted butenolides.[6b]

A five step synthesis of the (*E*)-alkene **8** (Scheme 2) from D-mannitol has been described,[8] but the compound was herein obtained by sequential butanediacetal diprotection,[9] dihydroxy-elimination,[10] deprotection and then silylation[11] reactions. The (*E*)-stereochemistry of the double bond was firstly assigned on the basis of the dihydroxy-elimination mechanism[10] (diol **5** to alkene **6**, step b) and was confirmed by NMR analysis of the desymmetrized side-product **9**. A characteristic coupling constant of 15.7 Hz between the two ethylenic protons was indeed observed. The metathesis substrates **10a–d** were then obtained after esterification of the diol **8** (Table 1).

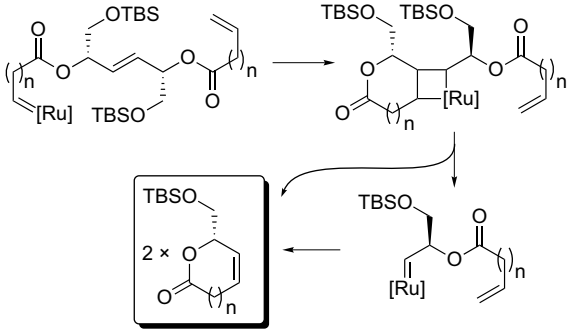
The metathesis step was performed on the trienes **10a–d**. It was expected to involve two RCM in a domino process (Scheme 3). A symmetric cleavage of the relaying internal double bond would then allow the formation of 2 equiv of the expected lactone.

Preliminary trials (Table 2, entries 1 and 2) were successively performed on the diacrylate **10a** in the presence of 10 mol % of the first or the second generation Grubbs' catalysts (**G1** and **G2**, respectively). Previous reports by Grubbs and co-workers[12] had shown that α,β-unsaturated carbonyl compounds were poorly incorporated by **G1** and that **G2** was more active thanks to its *N*-heterocyclic ligand. Indeed, the catalyst **G2** was more efficient (entry 2) and was used systematically in the next experiments.

Table 1. Conditions for the esterification of diol **8**



n (R)	Reagents and conditions	Products	Yields (%)
0 (H)	Acryloyl chloride, NEt_3, DCM, 0 °C	**10a**	71
1 (H)	Vinylacetic acid, DCC, DMAP, DCM, rt	**10b**	82
2 (H)	4-Pentenoyl chloride, py, DCM, 0 °C	**10c**	80
0 (Me)	Methacryloyl chloride, NEt_3, DCM, 0 °C	**10d**	56

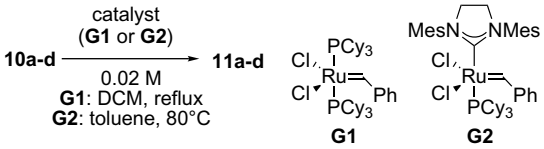


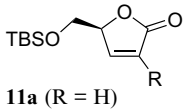
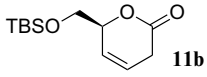
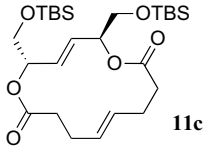
Scheme 3. Supposed pathway for the domino metathesis reaction (initial incorporation of the catalyst at one of the terminal olefins).

The synthesis of furanone **11a**, which started at low catalyst loading (5 mol %) required regular additions of **G2** (up to 30 mol % over 96 h) to be completed (entry 3). The enantiomeric purity was checked by NMR in the presence of the chiral chemical shift reagent[13] (+)-Eu(hfc)$_3$. A dramatic loss of ee was observed, due to partial racemization at the stereogenic center (ee = 0.38) in these conditions. This problem was readily circumvented by using directly a 30 mol % loading of the Grubbs' catalyst **G2** in toluene at 80 °C, thus greatly shortening the time of the reaction, which was completed in 2 h (entry 4). No racemization was observed under these conditions and the product **11a** was obtained in 71% yield and >0.99 enantiomeric excess.[14,15]

The methacrylate **10d** gave no reaction at all, the starting material being recovered (Table 2, entry 5). Obviously, the use of this electron-poor 1,1-disubstituted terminal olefin was detrimental to reaction initiation. It also showed that the ruthenium catalyst could not be incorporated through the internal double bond, thus supporting the reaction pathway of Scheme 3. When the vinylacetate **10b** was used in the presence of 10 mol % **G2** (entry 6), the enantiomerically pure β,

Table 2. Results of the metathesis step



	Substrate	Catalyst (equiv)	Time (h)	Product	Yield (%)
1	**10a**	**G1** (10)	48		6[a]
2	**10a**	**G2** (10)	48		34[a]
3	**10a**	**G2** (30)[b]	96		75[c]
4	**10a**	**G2** (30)	2	**11a** (R = H)	71[d]
5	**10d**	**G2** (30)	24	**11d** (R = Me)	—[a,e]
6	**10b**	**G2** (10)	4	 **11b**	80[f]
7	**10c**	**G2** (5)	1.5	 **11c**	81

[a] Starting material recovered.
[b] 6 × 5 mol % over 96 h.
[c] Ee = 0.38.
[d] Ee > 0.99.
[e] No reaction.
[f] 56% yield after 12 h with 5 mol % of **G2**.

γ-unsaturated δ-lactone **11b** was obtained in 80% yield after 4 h.[16] Considering the possibility to synthesize larger lactones ($n > 1$, Schemes 1 and 3), the reaction was applied to the 4-pentenoate diester **10c**. Instead of the expected hexenolide, the 14-membered macrodiolide **11c** was obtained in 81% yield after 1.5 h and in the presence of 5 mol % of **G2** (entry 7). The structure of this macrocyclic compound was unambiguously established by 2D NMR and mass spectrometry.[17] It displayed a C_2-symmetry axis passing over both double bonds and making the olefinic protons of the newly formed double bond chemically equivalent. No (*E*)- or (*Z*)-type coupling constant could therefore be observed and the trans stereochemistry was determined on the basis of NOE experiments and IR spectroscopy. This configuration is in accordance with the observations concerning the thermodynamically favored formation of (*E*)-olefins in macrocycles in the presence of **G2**.[18] Furthermore the exposition of compound **11c** to hydrolytic conditions gave back the diol **8** and thus supported the structural assignment. During these metathesis steps, the competition between both types of ring closing (lactone vs macrodiolide) thus appeared to favor the 5- and 6-membered lactones while the [14]-macrocycle was preferred to the seven-membered lactone.

This work brings some new examples in the domino metathesis field with an application to the synthesis of asymmetric lactones. The originality of the method consisted in the use of chiral trienes (**10**) derived from D-mannitol and thus having a C_2-symmetry axis. They were used as metathetic equivalents of (*S*)-3-buten-1,2-diol esters (see Scheme 1). The reaction will be of interest in the synthesis of lactone containing natural products. Studies will be pursued to enlarge the applications of the strategy (synthesis of cyclic ethers) and to reach the opposite enantiomeric series (that could be done via Mitsunobu esterification of the diol **8**).

Acknowledgments

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14. Data for compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ and 0.07 (2s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.80 (dd, $J = 6.3$, 10.7 Hz, 1H, $TBSOCH_2$), 3.93 (dd, $J = 4.5$, 10.7 Hz, 1H, $TBSOCH_2$), 5.05 (m, 1H, $CH_2CHCH{=}CH$), 6.16 (dd, $J = 2.0$, 5.7 Hz, 1H, $HC{=}CHC{=}O$), 7.50 (dd, $J = 1.5$, 5.7 Hz, 1H, $HC{=}CHC{=}O$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.1$, 18.3, 25.8, 63.0, 83.4, 122.6, 154.4, 173.0. IR (film, NaCl): $\nu = 1765\ cm^{-1}$. HR-MS (CI+, CH_4): *m/z* calculated for $C_{11}H_{21}O_3Si$ (MH+): 229.1260; observed: 229.1257. $[\alpha]_D^{20}$ −136 (*c* 0.85, $CHCl_3$) (Ref. 15a: $[\alpha]_D^{20}$ −136, *c* 1.13, $CHCl_3$; Ref. 15b: $[\alpha]_D^{20}$ −146, *c* 0.20, $CHCl_3$). Ee >0.99. Colorless syrup. $R_f = 0.13$ (heptane/Et_2O 7:3).
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16. Data for compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ and 0.07 (2s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 3.07 (m, 2H, $CH_2C{=}O$), 3.76 (dd, $J = 3.3$, 10.7 Hz, 1H, $TBSOCH_2$), 3.87 (dd, $J = 4.4$, 10.7 Hz, 1H, $TBSOCH_2$), 4.95 (m, 1H, $CH_2CHCH{=}CH$), 5.86 and 5.93 (2m, 2H, $HC{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.4$, 18.4, 25.9, 30.5, 65.0, 80.0, 123.2, 123.7, 169.0. IR (film, NaCl): $\nu = 1734\ cm^{-1}$. HR-MS (CI+, CH_4): *m/z* calculated for $C_{12}H_{23}O_3Si$ (MH+): 243.1416; observed: 243.1413. $[\alpha]_D^{20}$ −159 (*c* 1, CH_3OH). Ee >0.99. Colorless syrup. $R_f = 0.4$ (DCM/MeOH 99:1).
17. Data for compound **11c**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.05$ 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, $CH_2{-}C{=}O$), 3.69 (dd, $J = 4.8$, 11.1 Hz, 1H, $TBSOCH_aH_b$), 3.75 (dd, $J = 7.0$, 11.1 Hz, 1H, $TBSOCH_aH_b$), 5.24 (ddt, $J = 2.5$, 4.8, 4.8, 7.0 Hz, 2H, $=CHCH$), 5.36 (m, 2H, $=CHCH_2$), 5.74 (dd, $J = 2.5$, 4.8 Hz, 2H, $=CHCH$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.2$, 18.3, 25.9, 28.0, 33.3, 63.9, 74.6, 129.6, 131.6, 172.4. IR (film, NaCl): $\nu = 1751\ cm^{-1}$. HR-MS (CI+, CH_4): *m/z* calculated for $C_{26}H_{49}O_6Si_2$ (MH+): 513.3068; observed: 513.3064. $[\alpha]_D^{20}$ +61 (*c* 2.5, CH_2Cl_2). Colorless solid, mp = 38 °C. $R_f = 0.5$ (DCM).
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