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On the Importance of the Relative Stereochemistry of Substituents in the Formation of Nine-Membered Lactones by Ring-Closing Metathesis

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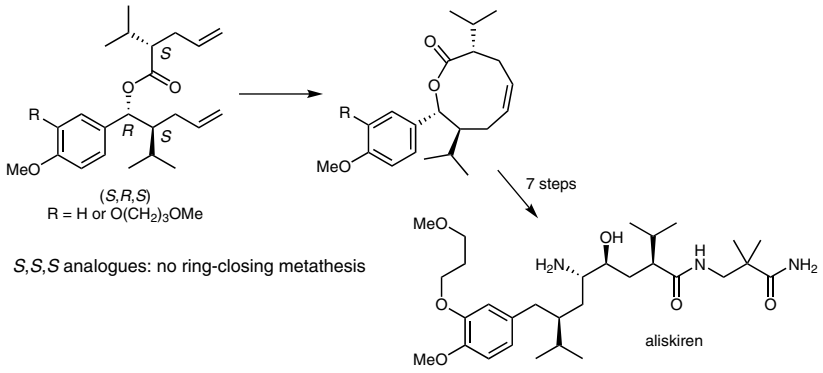

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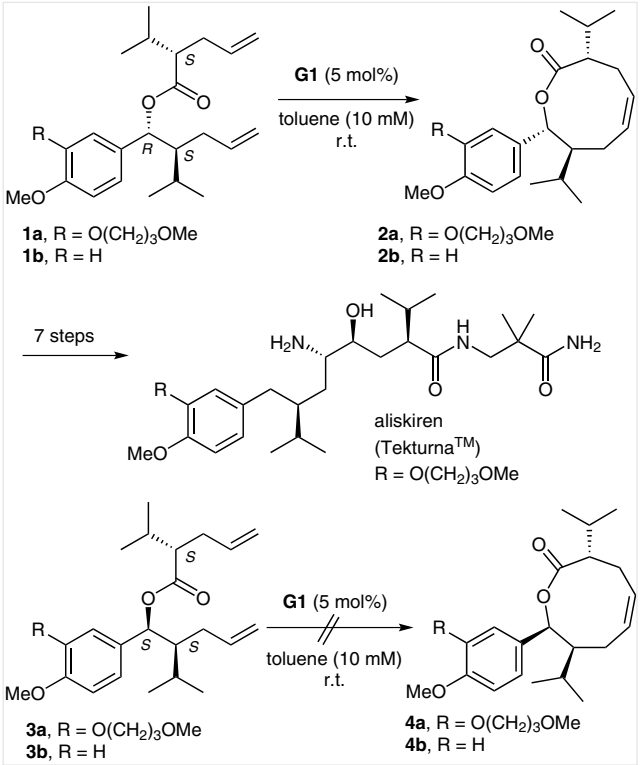
Abstract The effects of isopropyl substituents and molar concentration of diastereomeric esters toward the formation of nine-membered unsaturated lactones, in the context of the synthesis of the intermediates of the antihypertensive drug aliskiren, have been studied.

Key words lactone, metathesis, cyclization, macrocycle, dimerization

The now-venerable Grubbs olefin metathesis reaction[1] and its many recent variants[2] is an exceedingly useful and versatile method to construct internally unsaturated compounds of varying ring sizes.[3] Among these, the synthesis of nine-membered unsaturated lactones[4] and ethers[5] is of particular interest because of their limited occurrence in nature and their interesting biological activity.[6]

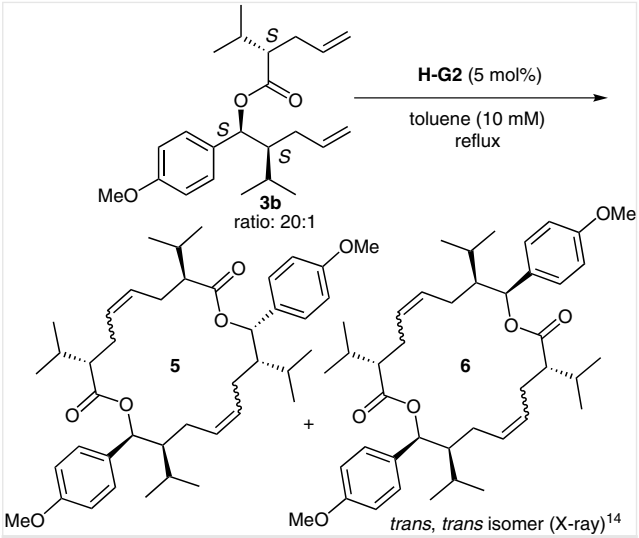
In a recent paper[7] on the total synthesis of the marketed antihypertensive drug aliskiren (Tekturna™)[8] we utilized a ring-closing metathesis reaction with the ester **1a** using Grubbs' 1st generation catalyst (**G1**)[9] to obtain a critical nine-membered unsaturated lactone intermediate **2a** that harbored two isopropyl groups in strategically pre-defined positions on an 8-aryloctanoic acid core unit (Scheme 1). The lactone **2a** was further elaborated to provide aliskiren in seven steps and 7% overall yield from readily available starting materials.[7] Compared to recent syntheses,[10] and a plethora of published patents,[11] our synthesis proved to be the shortest to date.

During the ring-closing metathesis reaction of a mixture of esters **1a** and diastereomeric **3a** with **G1** catalyst in refluxing toluene at a concentration of 10 mM, we observed that only the (*S*,*R*,*S*)-ester **1a** was converted into the lactone **2a**. The same observation was made with the (*S*,*R*,*S*)-ester of the corresponding *p*-methoxyphenyl analogue **1b**. The



Scheme 1 Synthetic route to aliskiren via a nine-membered lactone

diastereomeric ester **3b** did not give the expected lactone **4b** and remained unchanged. Further studies with Grubbs second-generation (**G2**)[12] and Hoveyda–Grubbs second-generation (**H-G2**)[2b] catalysts with a 4:1 diastereomeric mixture of *p*-methoxyphenyl analogue **1b** led to the lactone **2b** in excellent yield and in much shorter time. Under these conditions, the diastereomeric (*S*,*S*,*S*)-ester **3b**, obtained independently from a stereoselective reduction of the corre-



Scheme 2 Formation of dilactone dimers from ester **3b**

sponding ketone[13] led to an approximately 1:1 mixture of head-to-head and head-to-tail 18-membered dilactone dimers **5** and **6** as an inseparable mixture of olefin isomers. The structure of the C_2-symmetrical dilactone **6** was ascertained by X-ray crystallography (Scheme 2).[14]

In view of the continuing interest to develop viable synthetic routes to aliskiren, we focused on the key ring-closing metathesis step in our original synthesis.[7] In this paper, we report our qualitative observations pertaining to the reaction of the *p*-methoxyphenyl analogues **1b** and **3b** as well as their mono- and disubstituted diastereomeric esters in the presence of a variety of catalysts, in order to determine the influence of the isopropyl and vicinal aryl substituents and their relative stereochemistry on the nature of the products (Figure 1).

In the absence of any substituents, a mixture of racemic esters **7a** led to an inseparable mixture of dilactones **8a** and **9a** in excellent yield in presence of the **G1**, **G2**, and **H-G2** catalysts (Scheme 3, Table 1, entries 1–4). Compared to the **G1** catalyst, the dilactones were formed much faster with the **G2** catalyst. The reaction rate was slower in presence of **H-G2** catalyst in dichloromethane (entries 1–3). However, complete conversion occurred in refluxing toluene within 30 minutes (entry 4). No reaction occurred with the **G1** catalyst even in the presence of titanium(IV) isopropoxide[15] at room temperature in toluene. Hydrogenation of the double bonds was followed by treatment with triethylsilane/trifluoroacetic acid to give **11a** and **12a** in a quasi 1:1 ratio, which mirrored the amounts of the respective original dilactones **8a** and **9a** in the mixture (entries 1–4). The octanedioic acid was not isolated.

Treatment of the benzylic (*R*)-ester of **7b** with the **G1** catalyst resulted in the formation of the lactone **10b** in 33% yield, but only in the presence of titanium(IV) isopropoxide[15] and after repeated addition of catalyst (entry 5). In addition, dilactones **8b** and **9b** were formed in equal amounts as an inseparable mixture. The reaction rate was accelerated in the presence of the **G2** and **H-G2** catalysts (entries 6 and 7), but the yields were not improved. After completion of the reaction, lactone **10b** was isolated by chromatography and the mixture of the remaining dilactones was sub-

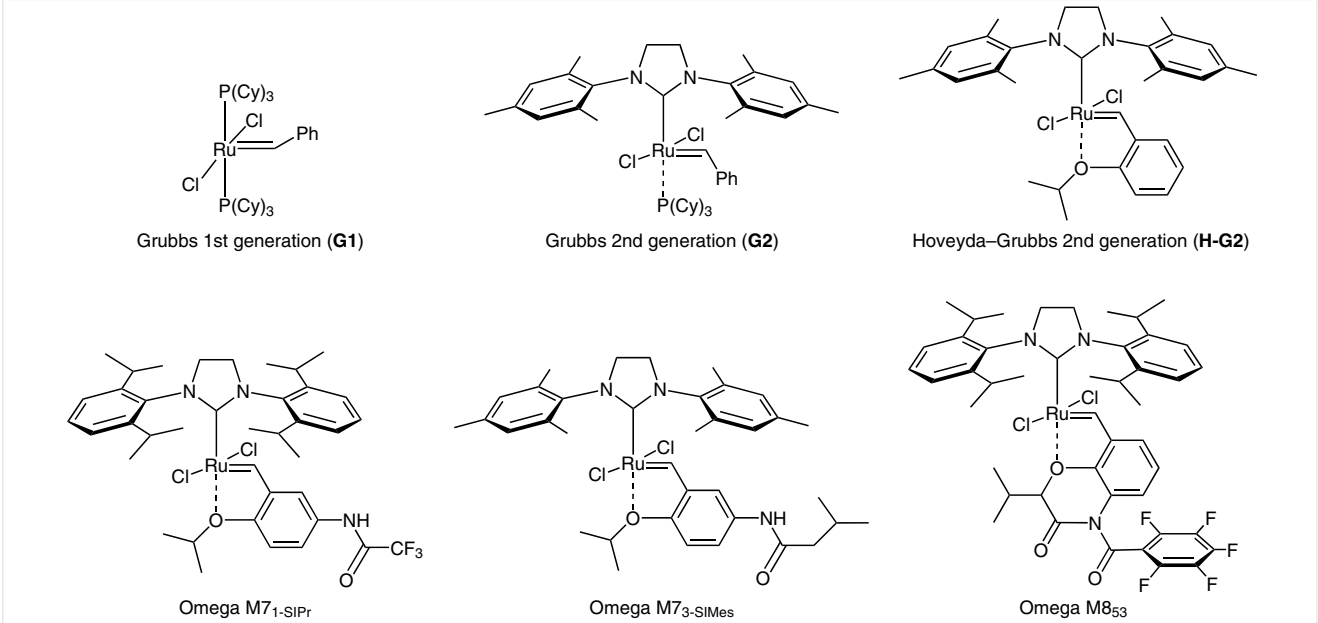


Figure 1 Structures of catalysts used for the ring-closing metathesis ($M7_{1\text{-SIPr}}$, $M7_{3\text{-SIMes}}$, and $M8_{53}$)[16]

mitted to hydrogenation then reductive cleavage of the benzylic ester functions to give the corresponding products **11b** and **12b** (Scheme 3).

In contrast, reaction of the benzylic (*S*)-ester of **7b** with the **G2** and **H-G2** catalysts led only to a mixture of the dilactones **8b** and **9b** which were converted into a 1:1 mixture of **11b** and **12b** as described above (entries 8 and 9). No reaction was observed with the **G1** catalyst.

Treatment of **7c** (as a mixture of benzylic ester diastereomers) with **G1**, **G2**, and **H-G2** gave dilactones **8c** and **9c** in a quasi 1:1 ratio with a distinct preference for the latter catalyst with regard to time. Hydrogenation and reductive cleavage led to **11c** and **12c** (entries 9–11). Trace amounts of the corresponding lactone **10c** were observed by MS.

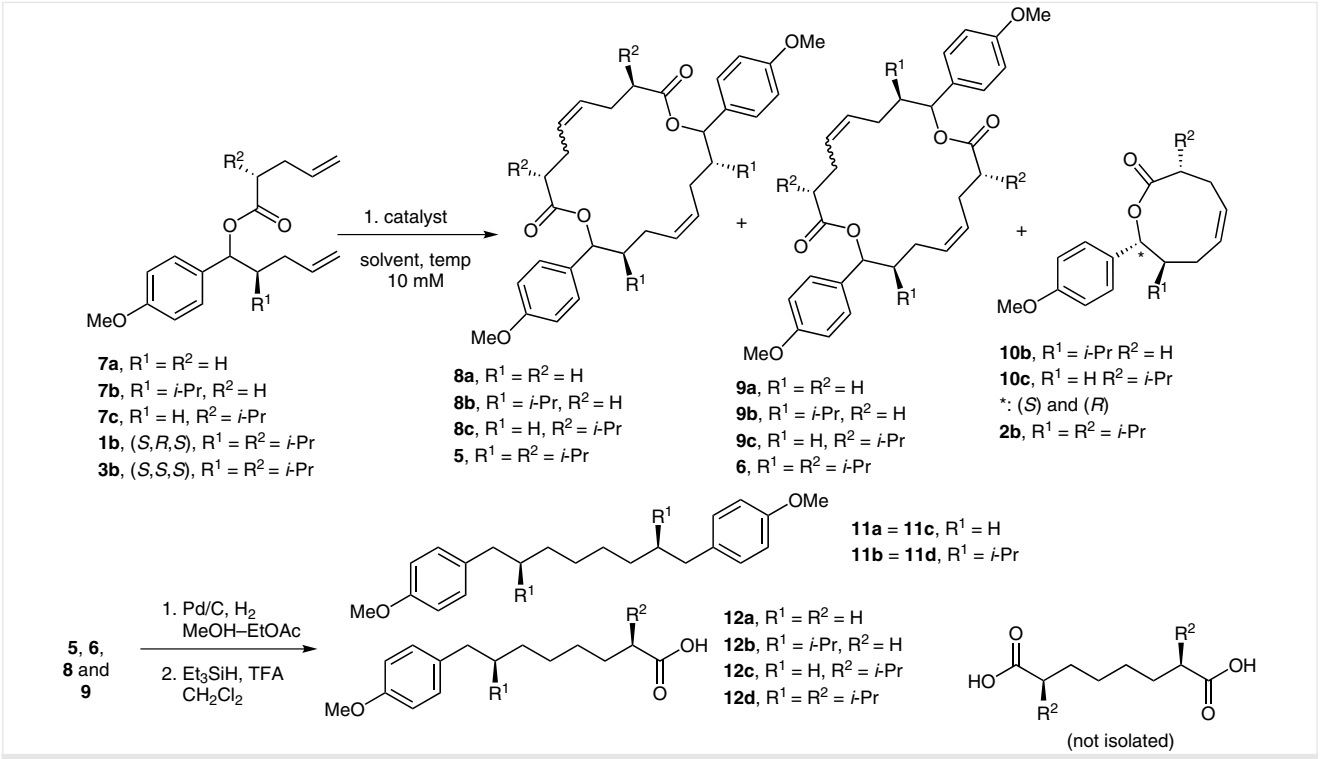
We then returned to the original disubstituted model (*S*,*R*,*S*)-ester **1b**, and studied the reaction in the presence of **G2** and then **H-G2** catalysts and the newer generation catalysts (Figure 1).[16] Using 5 mol% catalyst in refluxing toluene led to the nine-membered lactone **2b** in good yield, although the reaction was 2–3 times slower with the new generation catalysts (entries 13–17). Finally, the (*S*,*S*,*S*)-ester **3b** was subjected to the same reactions conditions, leading solely to the dilactones **5** and **6** as previously observed with the **G2** and **H-G2** catalysts (entries 18–22).[14] Hydrogenation of the double bonds and reductive cleavage in the presence of triethylsilane/trifluoroacetic acid led to **11d** and **12d** in a 1:1 ratio; 2,7-diisopropyloctanedioic acid was not isolated.

Since the formation of dilactone dimers prevailed in the case of the (*S*,*S*,*S*)-esters **3a** and **3b** (as well as other esters shown in Table 1), we considered running the reaction at higher dilution. Surprisingly, upon changing the concentration from 10 mM to 1 mM in refluxing toluene, ester **3b** gave the elusive lactone **4b** in 53% isolated yield, accompanied by 24% of the dimers **5** and **6** (Scheme 4, Table 2, entry 4). Extending the reaction time reduced the yield of lactone **4b** while favoring dilactone formation (entry 3). In contrast, dilution did not affect dilactone formation in the case of the

Table 1 Formation of Dilactones, Products from Cleavage Reactions, Reaction Parameters, and Ratio of Products with Different Catalyst (Scheme 3)

Entry	Ester	Ratio	Catalyst[a]	Solvent[b]	Temp (°C)	Time	Yield (%)		
							11	**12**	**2/10**
1	**7a** (*R*/*S*)	*rac*	**G1**	CH_2Cl_2	50	24 h	47	49	–
2	**7a** (*R*/*S*)	*rac*	**G2**	CH_2Cl_2	50	75 min	34	45	–
3	**7a** (*R*/*S*)	*rac*	**H-G2**	CH_2Cl_2	50	24 h	39	44	–
4	**7a** (*R*/*S*)	*rac*	**H-G2**	toluene	110	30 min	31	38	–
5	**7b** (*R*)	4:1	**G1**[c,d]	toluene	r.t.	5 d	17	20	33
6	**7b** (*R*)	4:1	**G2**[e]	toluene	110	40 min	16	17	30
7	**7b** (*R*)	4:1	**H-G2**	toluene	110	20 min	19	19	32
8	**7b** (*S*)	20:1	**G2**[e]	toluene	110	45 min	32	36	–
9	**7b** (*S*)	20:1	**H-G2**	toluene	110	45 min	36	37	–
10	**7c** (*R*/*S*)	*rac*	**G1**[c,d]	toluene	r.t.	5 d	40	35	–
11	**7c** (*R*/*S*)	*rac*	**G2**[e]	toluene	110	40 min	46	45	–
12	**7c** (*R*/*S*)	*rac*	**H-G2**	toluene	110	20 min	44	41	–
13	**1b** (*R*)	4:1	**G2**[e]	toluene	110	40 min	–	–	67
14	**1b** (*R*)	4:1	**H-G2**	toluene	110	20 min	–	–	64
15	**1b** (*R*)	4:1	$M7_{1\text{-}SIPr}$[e]	toluene	110	1 h	–	–	66
16	**1b** (*R*)	4:1	$M7_{3\text{-}SIMes}$[e]	toluene	110	1 h	–	–	63
17	**1b** (*R*)	4:1	$M8_{53}$[e]	toluene	110	1 h	–	–	61
18	**3b** (*S*)	20:1	**G2**[e]	toluene	110	40 min	39	40	–
19	**3b** (*S*)	20:1	**H-G2**	toluene	110	40 min	40	43	–
20	**3b** (*S*)	20:1	$M7_{1\text{-}SIPr}$[e]	toluene	110	1 h	37	38	–
21	**3b** (*S*)	20:1	$M7_{3\text{-}SIMes}$[e]	toluene	110	1 h	39	36	–
22	**3b** (*S*)	20:1	$M8_{53}$[e]	toluene	110	1 h	38	38	–

[a] Unless otherwise stated, 0.05 equiv (5 mol%).
[b] 0.01 M.
[c] $Ti(O\textit{i}\text{-}Pr)_4$ (1 equiv).
[d] Catalyst (5 mol%) was added every day.
[e] Catalyst (5 mol%) was added after 30 min.



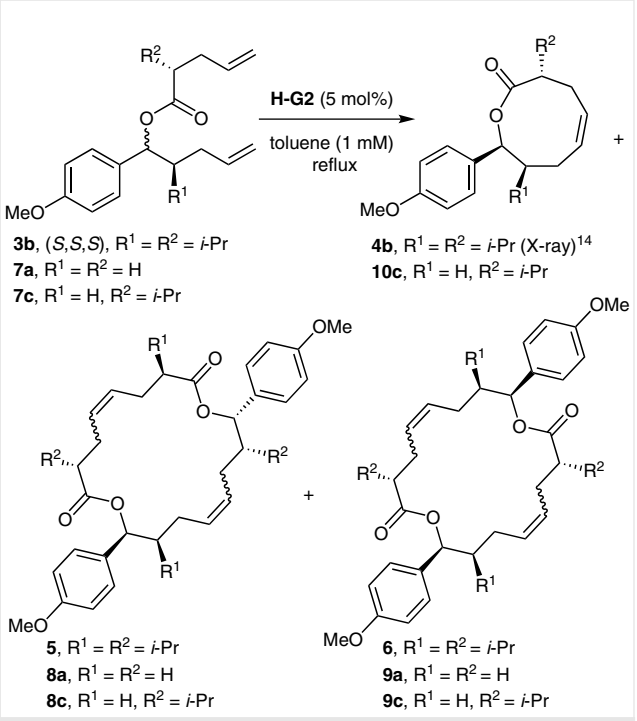
Scheme 3 Formation of dilactones and products from cleavage reactions (Table 1)

unsubstituted ester **7a**, since no monolactone was observed. The monosubstituted ester **7c** afforded 42% of the corresponding lactone **10c** and 37% yield of dilactones (entry 2). This was an improvement compared to the traces observed in 10 mM solution (Table 1, entries 10–12).

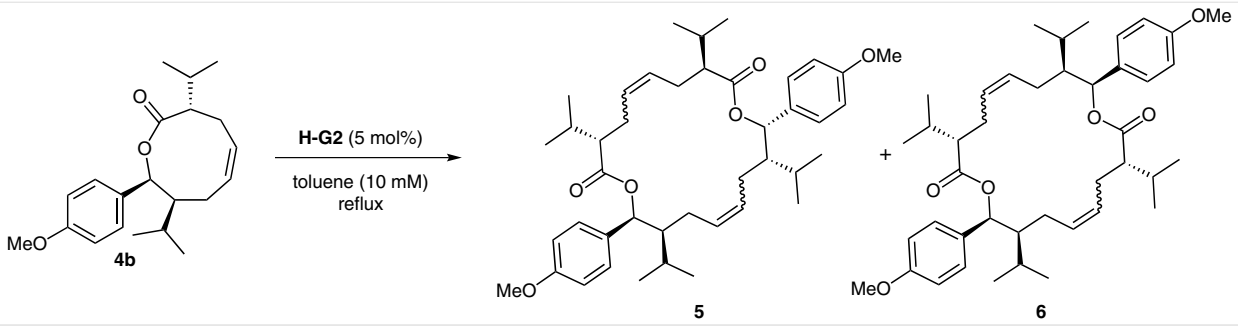
Table 2 Ring-Closing Metathesis of Diastereomeric Esters at 1 mM (Scheme 4)

Entry	Ester	Ratio	Time	Yield (%)	
				Monomer	Dimers
1	**7a** (*R*/*S*)	*rac*	overnight	–	81
2	**7c** (*R*/*S*)	*rac*	overnight	42	37
3	**3b** (*S*)	20:1	overnight	46	32
4	**3b** (*S*)	20:1	7 h	53	24

The somewhat diminished yield of nine-membered (*S*,*S*,*S*)-lactone **4b** when the reaction was run overnight as a 1 mM solution, led us to question whether once formed, it could undergo cycloreversion via alkylidene–ruthenium intermediates to the dilactones **5** and **6**. Indeed, submitting lactone **4b** to the reaction conditions at the original concentration of 10 mM in presence of **H-G2** catalyst yielded the corresponding dilactones **5** and **6** (Scheme 5). When a 1:1 mixture of (*S*,*S*,*S*)-lactones **4b** and **10c** was subjected to the ring-closing metathesis with the **H-G2** catalyst in 10 mM



Scheme 4 Ring-closing metathesis of diastereomeric esters at 1 mM (Table 2)

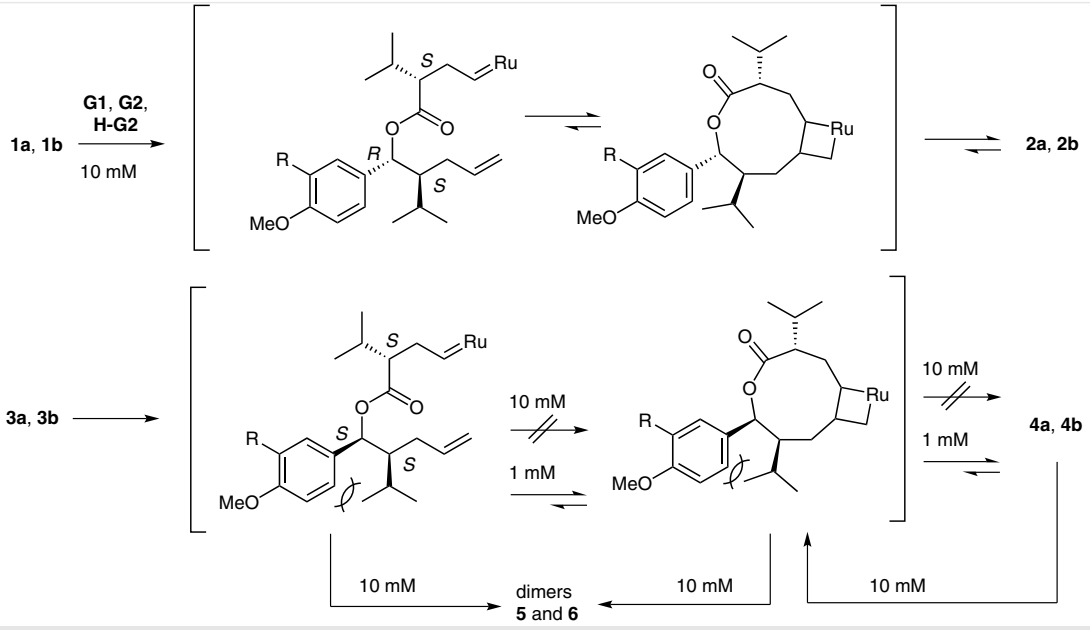


Scheme 5 Cycloreversion via ring-opening metathesis and cross-coupling reactions

solution, a mixture of all possible dilactones, including cross-over products was obtained, indicating that cycloreversion was possible in each case.

The existence of multiple coordination sites within each series of esters presents a major challenge with regard to the identity of the actual reactive intermediates and a preferred pathway. The outcome of ring-closing metathesis reactions leading to medium-sized rings is difficult to predict due to many intervening factors. For example, the nature of the catalyst, the solvent, the molarity, combined with conformational pre-organization, steric factors, as well as substituent and polar effects can have dramatic influences on the nature of the products (and byproducts) in a given reaction.[17] Nevertheless, it is clear that the ratio of nine-membered lactone formation compared to dilactones depends on the relative stereochemistry of the C7 isopropyl group and the adjacent C8 aryl moiety, and the concentration in the case of **1b** and **3b** (Scheme 3, Table 1, entries 14 and 19). This is evident from the results of reactions comprising the diastereomeric ester pairs (*S*,*R*,*S*)-**1b** and (*S*,*S*,*S*)-**3b**, and (*S*,*R*)-**7b** and (*S*,*S*)-**7b** (Scheme 3, Table 1, entries 13 and 18).

From our qualitative observations, it appears that the (*S*,*R*,*S*)-ester **1b** offers a less encumbered path to the ruthenium metallocycle, and eventually to the observed lactone **2b** (Scheme 6). A combination of stereochemical, conformational, and possibly stereoelectronic effects associated with a transoid ester configuration combine to favor the cyclization to give **2a** and **2b** as thermodynamically favored products. Reports concerned with the formation of nine-membered lactones using ring-closing metathesis are scarce. For example, cyclization of functionalized esters harboring terminal olefinic appendages, led to nine-membered unsaturated lactones with *cis*- and *trans*-geometries depending on the substituents.[18] However, no dimeric dilactones were reported or discussed in this study. The key steps in the total synthesis of the nine-membered unsaturated marine me-



Scheme 6 Ring-closing metathesis in 10 mM and 1 mM solutions; only one of the two possible alkylidene–ruthenium intermediates is shown

tabolite helicolactone, involved a ring-closing metathesis step achieved in the presence of **G1** catalyst in excellent yields.[4] The effect of substituents in the cyclization of larger rings has been reported.[18,19]

It can be presumed that the (*S*,*S*,*S*)-esters **3a** and **3b** experience substantial steric clash between the C7 isopropyl and the C8 aryl moiety so as to interfere with the proper alignment of the alkylidene–ruthenium intermediates en route to the ruthenium metallocycles. Thus, competitive intermolecular cross-coupling reactions predominate to give the corresponding dilactones irreversibly (Scheme 6). At lower molar concentration, the steric effect is overcome by the low rate of interactions of the alkylidene–ruthenium intermediates. This is reflected by the fact that the lactone **4b** may be kinetically formed at 10 mM concentrations, but rapidly undergoes cycloreversion to form the stable dilactones **5** and **6**. Although there appears to be a cooperative beneficial effect of having the two isopropyl groups present in addition to a stereochemical preference for the (*S*,*R*,*S*)-esters **1a** and **1b**, it is not clear why the monosubstituted or the unsubstituted substrates such as **7a** and **7c** have a preference for macrocyclic dilactone formation.

In earlier reports, Smith and co-workers[20] have discussed the potentially reversible nature of the metathesis reaction, while Fürstner and co-workers[21] exploited the reversibility of olefin metathesis in the formation of macrocyclic dilactones related to (–)-(*R*,*R*)-pyrenophorin.[22]

In conclusion, we have reported our observations regarding the effect of vicinal isopropyl and aryl substituents in diastereomeric esters with regard to their preference to give nine-membered unsaturated lactones. These have been recently utilized in the total synthesis of the antihypertensive drug aliskiren.[7]

Unfortunately, the involvement of multiple ruthenium-coordinated species and the dynamic nature of the ring-closing metathesis process do not allow a more detailed analysis beyond the qualitative observations reported in this paper. Further studies in this area are in progress.

All reactions were performed in oven-dried glassware under an argon atmosphere using anhydrous, deoxygenated solvents. CH_2Cl_2 and toluene were dried by passage through an activated alumina column under argon [Solvent Drying System (SDS)]. Reagents were purchased and used without further purification. Reactions were monitored by analytical TLC carried out on 0.25-mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde, and/or potassium permanganate solution. Flash column chromatography was performed using silica (particle size 40–63 μm, 230–400 mesh) at increased pressure. NMR spectra (^1H, ^{13}C) were recorded at either 300, 400, or 500 MHz relative to TMS (δ = 0.00) with the solvent resonance as the internal standard ($CHCl_3$, δ = 7.26); ^{13}C NMR spectra are recorded using the central peak of $CDCl_3$ (δ = 77.16) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm, using a 1-dm cell at r.t. and are reported in units of deg·cm^3·g^{-1}·dm^{-1}.

1-(4-Methoxyphenyl)pent-4-enyl Pent-4-enoate (7a); Typical Procedure

To a solution of the corresponding allylic acid (52 mg, 0.52 mmol, 1.0 equiv) in anhydrous toluene (4 mL) at 0 °C was added Et_3N (0.09 mL, 0.62 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.62 mmol, 1.2 equiv), and DMAP (76 mg, 0.62 mmol, 1.2 equiv). The resulting white slurry was stirred at 0 °C for 10 min. In a second dry round-bottomed flask a solution of corresponding benzylic alcohol (100 mg, 0.52 mmol, 1.0 equiv) in a minimum amount of anhydrous toluene was transferred to the reaction vessel containing the slurry in a dropwise manner at 0 °C then the reaction media was allowed to warm to r.t. The reaction was stirred at r.t. until TLC monitoring indicated no starting material remained. The solvent was removed and the resulting crude was taken up in EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were successively washed with 10% aq citric acid (10 mL) and sat. aq $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; CH_2Cl_2–hexanes, 3:7) to yield **7a** (134 mg, 94%) as a pale yellow oil; R_f = 0.55 (Et_2O–hexanes, 1:9).

IR (neat): 3077, 2979, 2935, 2837, 1735, 1641, 1613, 1515, 1253, 1169, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.89–6.84 (m, 2 H), 5.85–5.69 (m, 3 H), 5.06–4.95 (m, 4 H), 3.80 (s, 3 H), 2.45–2.31 (m, 4 H), 2.11–1.96 (m, 3 H), 1.89–1.79 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 159.4, 137.6, 136.8, 132.8, 128.1, 115.6, 115.3, 114.0, 75.4, 55.4, 35.4, 34.0, 29.9, 29.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}NaO_3$: 297.1461; found: 297.1468.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-enyl Pent-4-enoate (7b)

Following the typical procedure for **7a**; chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7b** (236 mg, 75%) as a pale yellow oil; R_f = 0.57 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +37 (*c* 0.5, $CDCl_3$).

IR (neat): 3077, 2958, 2874, 2837, 1736, 1640, 1612, 1514, 1464, 1369, 1250, 1171, 1036 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 6.87–6.82 (m, 2 H), 5.84–5.73 (m, 1 H), 5.69–5.66 (m, 1 H), 5.57–5.46 (m, 1 H), 5.05–4.94 (m, 2 H), 4.85 (s, 1 H), 4.81 (dd, *J* = 6.5, 1.8 Hz, 1 H), 3.79 (s, 3 H), 2.44–2.31 (m, 4 H), 2.04–1.93 (m, 2 H), 1.90–1.79 (m, 2 H), 0.93 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 159.2, 138.1, 136.8, 132.4, 128.6, 128.2, 115.6, 115.6, 113.7, 55.4, 48.8, 34.0, 31.1, 29.0, 27.3, 21.2, 18.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1919; found: 339.1931.

1-(4-Methoxyphenyl)pent-4-enyl (*S*)-2-Isopropylpent-4-enoate (7c)

Following the typical procedure for **7a**; chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7c** (771 mg, 94%) as a pale yellow oil; R_f = 0.57 (EtOAc–hexanes, 1:9).

IR (neat): 3077, 2960, 2926, 2875, 1735, 1640, 1613, 1514, 1465, 1248, 1167, 1107, 1035 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.87–6.83 (m, 2 H), 5.83–5.56 (m, 3 H), 5.03–4.95 (m, 3 H), 4.90 (ddd, *J* = 11.9, 8.7, 1.7 Hz, 1 H), 3.80 (s, 3 H), 2.35–2.17 (m, 3 H), 2.10–1.96 (m, 3 H), 1.91–1.78 (m, 2 H), 0.94 (d, *J* = 6.8 Hz, 1.5 H), 0.87 (d, *J* = 6.7 Hz, 1.5 H), 0.87 (d, *J* = 6.8 Hz, 1.5 H), 0.80 (d, *J* = 6.7 Hz, 1.5 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5, 174.5, 159.3, 137.7, 137.7, 136.1, 135.9, 132.9, 132.8, 128.3, 116.56, 116.47, 115.31, 115.28, 113.79, 75.17, 75.13, 55.38, 52.72, 52.63, 35.40, 35.37, 34.12, 33.99, 30.54, 30.31, 29.92, 20.50, 20.33, 20.23.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1918; found: 339.1935.

(8*S*,9*R*)-8-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydro-oxonin-2(3*H*)-one (10b)

Hoveyda–Grubbs 2nd generation catalyst (5 mg, 0.008 mmol, 0.05 equiv) was added to a solution of **7b** (50 mg, 0.16 mmol, 1.0 equiv) in anhydrous toluene (16 mL) and the mixture was stirred at reflux for 20 min. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc–hexanes, 1:50) to yield **10b** (17 mg, 38%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +37 (*c* 0.5, $CDCl_3$).

IR (neat): 2955, 2925, 2872, 1722, 1612, 1514, 1460, 1245, 1173, 1138, 1035 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2 H), 6.91–6.85 (m, 2 H), 5.84 (d, *J* = 10.6 Hz, 1 H), 5.72–5.63 (m, 1 H), 5.63–5.54 (m, 1 H), 3.80 (s, 3 H), 2.48 (dd, *J* = 20.3, 10.7 Hz, 1 H), 2.40–2.27 (m, 2 H), 2.17–2.08 (m, 1 H), 2.07–1.89 (m, 3 H), 1.47 (dtd, *J* = 13.7, 6.9, 2.4 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 159.6, 135.7, 132.1, 129.3, 125.5, 114.0, 79.8, 55.4, 52.6, 33.9, 27.8, 25.1, 24.8, 22.0, 16.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3765; found: 311.2605.

(3*S*,9*R*)-3-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydro-oxonin-2(3*H*)-one (10c)

Hoveyda–Grubbs 2nd generation catalyst (3 mg, 0.005 mmol, 0.05 equiv) was added to a solution of **7c** (30 mg, 0.095 mmol, 1.0 equiv) in anhydrous toluene (95 mL) and the mixture was stirred at reflux overnight. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc–hexanes, 1:50) to yield **10c** (12 mg, 42%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –32 (*c* 0.5, $CDCl_3$).

IR (neat): 2954, 2928, 2865, 1702, 1513, 1459, 1247, 1173, 1159, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H), 6.90–6.85 (m, 2 H), 5.84–5.73 (m, 1 H), 5.71–5.61 (m, 1 H), 5.61–5.51 (m, 1 H), 3.80 (s, 3 H), 2.62–2.50 (m, 2 H), 2.33–2.24 (m, 1 H), 2.21–2.09 (m, 2 H), 2.06–1.92 (m, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1, 164.8, 159.3, 137.5, 135.9, 135.1, 133.1, 131.0, 128.6, 127.9, 126.0, 114.0, 55.4, 51.5, 36.9, 29.9, 28.4, 23.8, 21.5, 19.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3766; found: 311.3772.

1,8-Bis(4-methoxyphenyl)octane (11a) and 8-(4-Methoxyphenyl)octanoic Acid (12a); Typical Procedure

Hoveyda–Grubbs 2nd generation catalyst (4 mg, 0.006 mmol, 0.05 equiv) was added to a solution of **7a** (30 mg, 0.11 mmol, 1.0 equiv) in anhydrous toluene (11 mL) and the mixture was stirred at reflux for 30 min. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated and the mixture was filtered through Celite to yield a crude mixture of dilactones **8a** and **9a**.

Pd/C (cat.) was added to a solution of dilactones **8a** and **9a** in MeOH (3 mL) and EtOAc (3 mL). The mixture was purged with H_2 and the mixture was stirred under a H_2 atmosphere (H_2 balloon). The reaction was monitored by LR-MS. When the reaction was complete, the mixture was filtered through Celite and concentrated to afford the crude dilactones.

TFA (3 drops) was added to a solution of the crude dilactones and Et_3SiH (0.1 mL) in CH_2Cl_2 (1 mL). The solution was stirred at r.t. for 10 min. Volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography [silica gel, 1.5 cm diameter × 20 cm height, hexanes (150 mL) then EtOAc–hexanes, 1:19] to yield alkane **11a** (6 mg, 31%) and acid **12a** (11 mg, 38%), both as clear oils.

Alkane 11a

R_f = 0.68 (EtOAc–hexanes, 1:4).

IR (neat): 2921, 2849, 1512, 1464, 1245, 1177, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.3 Hz, 4 H), 6.82 (d, *J* = 8.5 Hz, 4 H), 3.79 (s, 6 H), 2.59–2.48 (m, 4 H), 1.61–1.52 (m, 4 H), 1.36–1.28 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 135.2, 129.4, 113.8, 55.4, 35.2, 31.9, 29.6, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2328.

Acid 12a

R_f = 0.17 (EtOAc–hexanes, 1:4).

IR (neat): 2923, 2853, 1709, 1512, 1465, 1245, 1177, 1054, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.05 (m, 2 H), 6.85–6.79 (m, 2 H), 3.79 (s, 3 H), 2.61–2.48 (m, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 1.71–1.51 (m, 4 H), 1.35–1.29 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9, 157.7, 135.0, 129.4, 113.8, 55.4, 35.1, 34.1, 31.8, 29.2, 29.1, 29.1, 24.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_3$: 273.1461; found: 273.1472.

(3*R*,8*R*)-3,8-Bis(4-methoxybenzyl)-2,9-dimethyldecane (11b) and (*R*)-7-(4-Methoxybenzyl)-8-methylnonanoic Acid (12b)

Following the typical procedure for **11a** and **12a** gave **11b** (7 mg, 36%) and **12b** (10 mg, 37%), both as clear oils.

Alkane 11b

R_f = 0.64 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +21 (*c* 1.0, $CHCl_3$).

IR (neat): 2924, 2861, 1512, 1246, 1055, 1464, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.01 (m, 4 H), 6.84–6.78 (m, 4 H), 3.79 (s, 6 H), 2.49 (dd, *J* = 13.7, 6.8 Hz, 2 H), 2.35 (dd, *J* = 13.8, 7.6 Hz, 2 H), 1.67 (dtd, *J* = 13.7, 6.9, 3.5 Hz, 2 H), 1.44–1.33 (m, 2 H), 1.23–1.02 (m, 8 H), 0.86 (d, *J* = 13.9 Hz, 6 H), 0.83 (d, *J* = 13.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 134.5, 130.1, 113.6, 55.4, 46.1, 36.3, 29.7, 28.4, 28.0, 19.3, 18.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{43}O_2$: 411.3258; found: 411.3277.

Acid 12b

R_f = 0.12 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$).

IR (neat): 2938, 2866, 1709, 1512, 1455, 1346, 1321, 1059, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.6 Hz, 2 H), 6.84–6.78 (m, 2 H), 3.79 (s, 3 H), 2.53 (dt, *J* = 12.0, 5.6 Hz, 1 H), 2.38–2.34 (m, 1 H), 2.34–2.28 (m, 2 H), 1.74–1.65 (m, 1 H), 1.62–1.53 (m, 2 H), 1.46–1.38 (m, 1 H), 1.31–1.22 (m, 6 H), 1.14 (dd, *J* = 18.5, 11.4 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 157.7, 134.4, 130.0, 113.7, 55.4, 46.1, 36.3, 34.0, 29.6, 29.5, 28.6, 27.4, 24.8, 19.3, 18.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3277.

2-Isopropyl-8-(4-methoxybenzyl)octanoic Acid (12c)

Following the typical procedure for **11a** and **12a** gave **12c** (19 mg, 41%) as a clear oil; R_f = 0.11 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –5 (*c* 1.0, $CHCl_3$).

IR (neat): 2926, 2854, 1700, 1511, 1464, 1298, 1176, 1116, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.06 (m, 2 H), 6.86–6.79 (m, 2 H), 3.79 (s, 3 H), 2.58–2.50 (m, 2 H), 2.17–2.07 (m, 1 H), 1.88 (dq, *J* = 13.7, 6.7 Hz, 1 H), 1.67–1.45 (m, 4 H), 1.44–1.19 (m, 7 H), 0.97 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.4, 157.7, 135.0, 129.4, 113.8, 55.4, 52.7, 35.1, 31.8, 30.6, 29.6, 29.4, 29.2, 27.9, 20.6, 20.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3113.

2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic Acid (12d)

Following the typical procedure for **11a** and **12a** gave **12d** (11 mg, 40%). R_f = 0.12 (EtOAc–hexanes, 1:9) as a clear oil; $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$).

IR (neat): 2925, 2860, 1704, 1511, 1461, 1375, 1245, 1178, 1038 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.59 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 3.78 (s, 3 H), 2.51 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.36 (dd, *J* = 13.7, 7.8 Hz, 1 H), 2.13–2.05 (m, 1 H), 1.85 (dq, *J* = 13.7, 6.9 Hz, 1 H), 1.74–1.63 (m, 1 H), 1.60–1.49 (m, 1 H), 1.48–1.36 (m, 2 H), 1.29–1.14 (m, 6 H), 0.96–0.92 (m, 6 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{33}O_3$: 333.2435; found: 333.2440.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380130.

References

(1) (a) *Handbook of Metathesis*; Vols. 1–3; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(2) (a) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161. (b) Ung, T.; Hejl, A.; Grubbs, R. H.; Schrodi, Y. *Organometallics* **2004**, *23*, 5399. (c) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.
(3) (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(4) (a) Takahashi, T.; Wataqnabe, H.; Kitahara, T. *Heterocycles* **2002**, *58*, 99. (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81. (c) Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543.
(5) (a) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264. (b) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817. (c) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533. (d) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899.
(6) For an overview, see: Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.
(7) Hanessian, S.; Guesné, S.; Chénard, E. *Org. Lett.* **2010**, *12*, 1816.
(8) (a) Maibaum, J.; Feldman, D. L. *Annu. Rep. Med. Chem.* **2009**, *44*, 105. (b) Jensen, C.; Herold, P.; Brunner, H. R. *Nat. Rev. Drug Discovery* **2008**, *7*, 399. (c) Siragy, H. M.; Kar, S.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 779.
(9) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
(10) (a) Nam, G.; Ko, S. Y. *Helv. Chim. Acta* **2012**, *95*, 1937. (b) Slade, J.; Liu, H.; Prashad, M.; Prasad, K. *Tetrahedron Lett.* **2011**, *52*, 4349. (c) Dong, H.; Zhang, Z.-L.; Huang, J.-H.; Ma, R.; Chen, S.-H.; Li, G. *Tetrahedron Lett.* **2005**, *46*, 6337.
(11) For a summary, see: Yokokawa, F.; Maibaum, J. *Expert Opin. Ther. Pat.* **2008**, *18*, 581; and references cited therein.
(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(13) Hanessian, S.; Chénard, E. *Org. Lett.* **2012**, *14*, 3222.
(14) Hanessian, S.; Chénard, E.; Guesné, S.; Cusson, J.-P. *J. Org. Chem.* **2014**, *79*, 9531.
(15) For examples of the use of Ti(O*i*-Pr)$_4$ in metathesis reactions see ref. 4b and: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
(16) See the Supporting Information.
(17) For a concise review, see: Monfette, S.; Fogg, D. E. In *Green Metathesis Chemistry: Great Challenges in Synthesis, Catalysis and Nanotechnology*; Dragutan, I.; Finkelstein, E. S., Eds.; Springer Science: New York, **2010**.
(18) Ramírez-Fernández, J.; Collado, I. G.; Hernández-Galán, R. *Synlett* **2008**, 339.
(19) See for example: (a) Dai, W.-M.; Sun, L.; Feng, G.; Guan, Y.; Liu, Y.; Wu, J. *Synlett* **2009**, 2361. (b) Vassilikogiannakis, G.; Margaros, I.; Tofi, M. *Org. Lett.* **2004**, *6*, 205. (c) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155. (d) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731.
(20) Smith, A. B.; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984.
(21) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449.
(22) For selected reviews on using ring-closing metathesis in the synthesis of macrolactone natural products, see (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (c) Prunet, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 2826.