Titanium Isopropoxide Promoted Tandem Self-Cross and Ring-Closing Metathesis Approach for the Synthesis of Macrotetralides

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Dedicated to Professor Goverdhan Mehta on the occasion of his 70th birthday

A new approach is demonstrated for the synthesis of macrotetralides through an olefin metathesis reaction using Grubbs' second-generation catalyst with titanium isopropoxide as a cocatalyst. This study demonstrates a tandem self-cross and ring-closing metathesis approach to form macrocyclic ring systems with excellent (*E*) selectivity. The reaction was optimized with regard to functional group, catalyst, solvent, Lewis acid, concentration, and temperature.

Introduction

Olefin metathesis methods continue to be a subject of considerable interest and intensive investigation in synthetic organic chemistry to prepare structures such as carbocycles, heterocycles, and fused-ring frameworks.[1] Olefin metathesis reactions have important applications to natural products, materials chemistry, chemical biology, and to fine chemicals, which include their large-scale production.[2] Exemplary approaches to perform the reaction can involve two alkenes that are conformationally inaccessible for a simple cyclization into monomers to the formation of a macrocycle from dimerization and trimerization reactions through olefin metathesis.[3] This process involves both the cleavage and formation of C–C bonds. Efforts to control the stereochemistry of the resulting olefin in the preparation of macrocyclic compounds through a ring-closing metathesis (RCM) reaction are often difficult.[4] A variety of factors can affect the stereochemistry to give products with either the (*E*) or (*Z*) configuration or as a regioisomeric mixture of olefinic products, and this remains a significant challenge.

Most of the transition metal complexes such as WCl_6/Bu_4Sn,[5] MoO_3/SiO_2,[6] Cr^0,[7] and $Re_2O_7/N_2O_3Cl_2$[8] have been used as catalysts for olefin metathesis. The advantages and limitations of homogeneous and heterogeneous catalysts have depended on the employed catalyst. Among these, molybdenum and ruthenium complexes have played an important role in olefin metathesis. In fact, a Ru-catalyzed ring-closing metathesis (RCM) has proven to be highly efficient and is becoming recognized as one of the straightforward and reliable methods to synthesize larger rings.[9] The fascinating attributes of ruthenium over molybdenum catalysts include their functional-group tolerance, their stability in the atmosphere, and their quality of being easily handled. It has been observed that the outcome of a ring-closing metathesis depends on a combination of the substrate structure and the nature of the catalyst as well as the type of transformation.[10] Grubbs' first- and second-generation catalysts are exceedingly useful for olefin metathesis (see Figure 1). However, the presence of the more basic and bulkier N-heterocyclic carbene (NHC) in place of the PCy_3 group has also led to fundamental changes that arise from a greater tendency toward equilibrium processes. Thermodynamic control is particularly relevant in the RCM synthesis of many medium-sized or macrocyclic targets.[11] The second-generation catalysts have a better lifetime, provide good enantioselectivity, and are reusable.
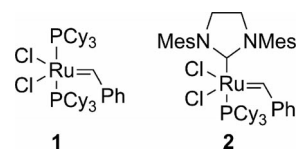

Figure 1. Grubbs' catalysts (Mes = 2,4,6-trimethylphenyl).

Grubbs' catalyst is an active catalyst that is used for the formation of tri- and tetrasubstituted cycloalkenes, cyclophane derivatives, and macrocycles.[12] Template-directed olefin metathesis is a useful approach that is employed for linear substrates to generate favorable conformations and facilitate the formation[13a] of various macrocycles. A five-membered chelate between the carbonyl moiety of an ester

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301239.

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and a Lewis acid metal was formed by an [Ru]-carbene complex in the presence of a catalytic amount of Ti-(O*i*Pr)$_4$. We have also reported[13b] that the [Ru] catalyst exhibits a higher activity in a RCM to form a sequence of symmetrical diolefins in the presence of CsCl as an additive.

Because of their biological and ion-selective properties as well as their applications in the perfume industry, the synthesis and study of the macrocyclic lactones[13] and azamacrocycles[14,15] are impressive in organic chemistry. To the best our knowledge, the synthesis of macrotetralides with different ring sizes through olefin dimerization and ring-closing metathesis reactions has not been investigated. We, herein, report the synthesis of macrotetralides by sequential self-cross (homodimerization)/ring-closing metathesis reactions in the presence of Grubbs' and Ti(O*i*Pr)$_4$ catalysts. The most interesting features of Ti(O*i*Pr)$_4$ are: (i) its inhibition of chelate formation between the substrate and catalyst, (ii) its use of chelation to acquire a suitable conformation of the substrate for cyclization, and (iii) its addition should not destroy the catalyst and should coordinate to the polar functional group. A study of the optimization of the reaction conditions with regard to catalyst, solvent, Lewis acid, temperature, and concentration as well as a control experiment has also been performed.

Results and Discussion

With the objective to develop a new and efficient method for the synthesis of macrotetralides, the required dicarboxylic acid derivatives **4** were assembled by using a literature method.[16] The dialkylation reaction of dicarboxylic acid **3a** (see Figure 2) was carried out with an excess amount of allyl bromide, potassium carbonate, and a catalytic amount of tetrabutylammonium iodide (TBAI) at room temperature to afford the respective symmetrical dialkylated prod-

uct **4a** in 89% yield (see Scheme 1 and Table 1, Entry 1) as a colorless, viscous oil. Other dialkylated products **4b–4k**
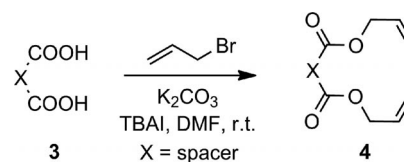
Scheme 1. Alkylation of diacids (DMF = *N,N*-dimethylformamide).

Table 1. Alkylation of diacids **3**.

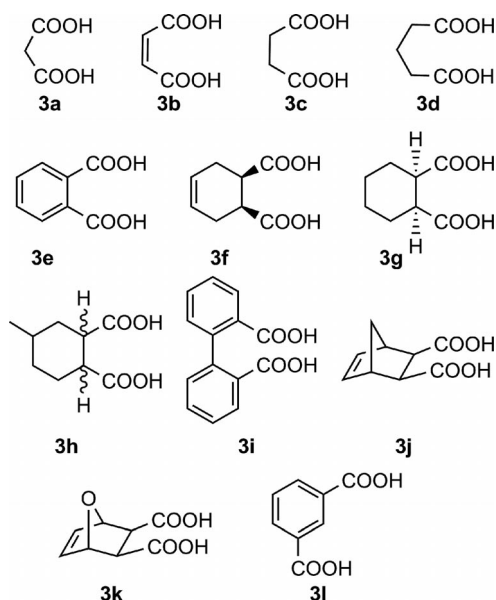| Entry	Dicarboxylic acids 3	Diolefins 4		Yields [%][a]
1	**3a**		**4a**	89
2	**3b**		**4b**	85
3	**3c**		**4c**	88
4	**3d**		**4d**	85
5	**3e**		**4e**	91
6	**3f**		**4f**	90
7	**3g**		**4g**	85
8	**3h**		**4h**	87
9	**3i**		**4i**	92
10	**3j**		**4j**	90
11	**3k**		**4k**	93

[a] Isolated yield.

Figure 2. Dicarboxylic acids utilized for this study.

(see Table 1, Entries 2–11) were also synthesized in a similar manner from the appropriate dicarboxylic acids **3b–3k**.

As the solvent plays an important role in the product distribution,[17] the olefin metathesis reactions of diolefins **4** were examined in various organic solvents. It is well known that a polar solvent disrupts the hydrogen bonding through its coordinating action within a molecular network or between two molecules. Thus, the metathesis reaction of diolefin **4a** using 5 mol-% of catalyst **1** in dichloromethane (DCM) was performed at reflux to furnish macrotetralide **5a** in 23% yield (see Scheme 2 and Table 2, Entry 1). The reaction conditions were optimized by using other solvents to afford **5a** (see Table 2). A marginal improvement in the yield (36%) was observed when the reaction was performed in toluene (see Table 2, Entry 5). In all the cases, the starting material **4a** was recovered in a range of 45–60% yield, but the catalyst decomposed. The same reaction that was conducted with catalyst **2** in toluene provided **5a** in 53% yield. From this study, the macrotetralide formation appears to be dependent not only on the activity of the catalyst but also on the solvent.
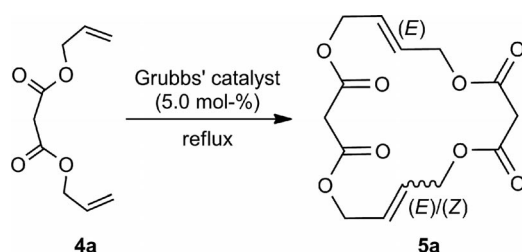
Scheme 2. Olefin metathesis reaction.

Table 2. Effect of catalyst and solvent on the synthesis of macrotetralide **5a**.[a]

Entry	Catalyst	Solvent	Yield [%][b]	Time [h]
1	**1**	DCM	23	36
2	**1**	DCE[c]	20	36
3	**1**	chloroform	26	36
4	**1**	carbon tetrachloride	23	36
5	**1**	toluene	36	36
6	**1**	*o*-xylene	33	36
7	**1**	benzene	30	36
8	**1**	hexane	0	40
9	**2**	DCM	37	24
10	**2**	DCE	39	24
11	**2**	chloroform	37	24
12	**2**	carbon tetrachloride	33	24
13	**2**	toluene	53	24
14	**2**	*o*-xylene	51	24
15	**2**	benzene	49	24
16	**2**	hexane	10	36

[a] Reagents and conditions: Grubbs' catalyst **1** or **2** (5.0 mol-%), reflux. [b] Isolated yield. [c] DCE = dichloroethane.

Lewis acid catalyzed synthetic reactions are favored because of the good coordinating ability of the metal atom. We envisioned, in principle, that if some metal complex or Lewis acid was introduced into the reaction system to compete or prevent the coordination of the O atom to the ruthenium–carbene intermediate, then the olefin metathesis re-

action of dialkylated compound **4** should occur. Furthermore, a few reports have demonstrated RCM reactions in the presence of a metal complex or Lewis acid as a binary catalyst system.[17] Therefore, the model reaction in the presence of a Lewis acid was examined to determine the feasibility of this idea. Thus, diallyl compound **4a** was subjected to the olefin metathesis reaction using Grubbs' second-generation catalyst (**2**) to furnish 17-membered macrotetralide **5a** in 53% yield (see Scheme 2). To achieve complete conversion and improve the yield of macrotetralide **5**, the reaction was carried out with different metal ions such as TiCl$_4$, CsCl, Ti(O*i*Pr)$_4$, LiI, La(OTf)$_3$ (OTf = trifluoromethanesulfonate), AlCl$_3$, and so forth (see Table 3). Diolefin **4a** was subjected to the olefin metathesis reaction using Grubbs' second-generation catalyst (**2**) in the presence of CsCl for 12 h to furnish product **5a** in 86% yield. A similar reaction was examined in the presence of Ti(O*i*Pr)$_4$ to yield the product in a shorter duration time (6 h) in 96% yield.

Table 3. Effect of metal ion on the synthesis of macrotetralide **5a**.[a]

Entry	Metal ion	Yield [%][b]	Time [h]
1	–	53	24
2	CsCl	86	12
3	Ti(O*i*Pr)$_4$	96	6
4	ZnCl$_2$	83	12
5	LiCl	76	12
6	LiI	78	12
7	Zn(OTf)$_2$	73	24
8	La(OTf)$_3$	59	24
9	In(OTf)$_3$	60	24
10	Sc(OTf)$_3$	60	24
11	Yb(OTf)$_3$	58	24
12	TiCl$_4$	–	24
13	AlCl$_3$	–	24
14	BF$_3$	–	24

[a] Reagents and conditions: **4a** (0.3 mmol), catalyst **2** (5.0 mol-%), toluene, reflux. [b] Isolated yield.

The olefin metathesis protocol for the synthesis of the macrotetralide using Ti(O*i*Pr)$_4$ was further optimized with regard to mol-% and temperature. The use of mild reaction conditions is essential with substrates that contain thermally unstable functional groups, and, therefore, the development of reaction systems that are active at low temperature is of great relevance. The metathesis reaction of **4a** in the presence of Grubbs' second-generation catalyst (**2**) and

Table 4. Effect of mol-% of Ti(O*i*Pr)$_4$ and temperature on the synthesis of macrotetralide **5a**.[a]
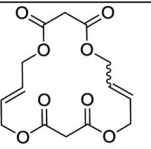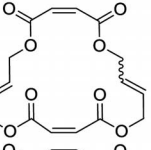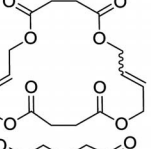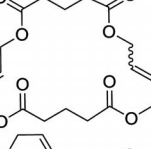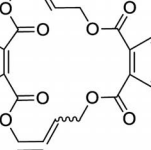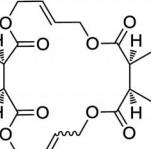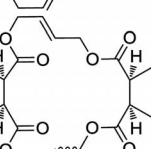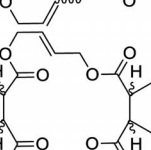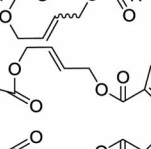
Entry	Ti(O*i*Pr)$_4$ [mol-%]	Temperature [°C]	Yield [%][b]	Time [h]
1	10	25	–	12
2	20	25	–	12
3	10	80	56	12
4	20	80	96	6
5	20	110	96	6
6	50	80	96	6
7	50	110	96	6
8	100	110	96	6

[a] Reagents and conditions: catalyst **2** (5.0 mol-%), toluene. [b] Isolated yield.

Ti(O*i*Pr)$_4$ at room temperature was unsuccessful (see Table 4). The reaction at 80 °C with 10 mol-% of Ti(O*i*Pr)$_4$ afforded **5a** in 56% yield (see Table 4, Entry 3). The optimized reaction conditions employed 20 mol-% of Ti(O*i*Pr)$_4$ to afford **5a** in 96% yield (see Table 4, Entry 4).

On the basis of the optimized procedure, compound **4a** was stirred with 5 mol-% of Grubbs' second-generation catalyst (**2**) and 20 mol-% of Ti(O*i*Pr)$_4$ under an inert gas in toluene, and the reaction was monitored by TLC and ^{1}H NMR spectroscopy.[18] The crude reaction mixture was

Table 5. Synthesized macrotetralide **5** using olefin metatheis method.[a]

Entry	Diolefin 4	Macrotetralide 5	Ring size	Time [h]	Yield [%][b]	(E)/(Z)[c]
1	4a	5a	18	6	96	4:1
2	4b	5b	20	6	90	4:1
3	4c	5c	20	6	87	4:1
4	4d	5d	22	7	85	4:1
5	4e	5e	20	9	90	3:1
6	4f	5f	20	8	88	3:1
7	4g	5g	20	8	89	3:1
8	4h	5h	20	8	86	3:1
9	4i	5i	25	9	94	3:1
10	4j	polymerized product	–	–	12	–	–
11	4k	polymerized product	–	–	12	–	–

[a] Reagents and conditions: Grubbs' catalyst **2** (5.0 mol-%), Ti(O*i*Pr)$_4$ (20 mol-%), toluene, reflux. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR analysis.

purified using column chromatography to furnish **5a** in 96% yield as a mixture of (*E*)/(*Z*) isomers in a ratio of 4:1 (see Table 5, Entry 1). Dimer **5a** was clearly distinguished by the absence of the olefinic CH$_2$ proton signals that appeared at δ = 5.27 and 5.19 ppm in the ^{1}H NMR spectra of diolefin **4a**. The high-resolution mass spectrum of macrotetralide **5a** showed the required *m/z* peak at 335.0752 for [M + Na]$^+$, which clearly indicated a sequential self-cross metathesis (homodimerization process) followed by a ring-closing metathesis reaction. The structure and stereochemistry of crystallized macrotetralide **5a** were further
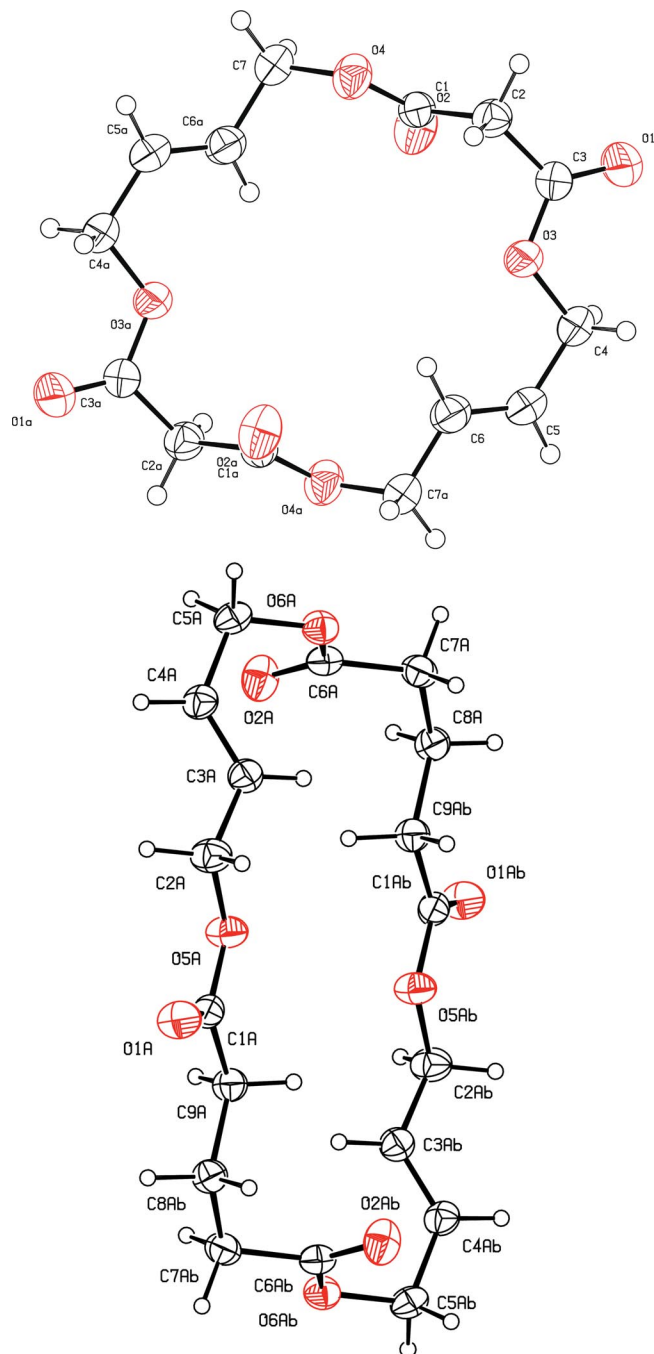
confirmed by using single-crystal X-ray analysis,[19] which displayed both double bonds in the (*E*) configuration (see Figure 3, top).

The reaction of the other dialkylated compounds **4b**–**4d** under similar olefin metathesis reaction conditions afforded macrotetralides **5b**–**5d** in good yields as a mixture of (*E*)/(*Z*) isomers in a ratio of 4:1. The stereochemistry of the representative product **5d** was also confirmed[19] by using single-crystal X-ray analysis (see Figure 3, bottom). Dialkylated compounds **4e**–**4i** furnished **5e**–**5i** (Table 5) as a mixture of (*E*)/(*Z*) isomers in a ratio of 3:1. Obviously, side products such as intramolecular ring-closing metathesis product **9** (see Scheme 5), oligomers, and polymerized compounds were not observed under these reaction conditions. However, under the olefin metathesis conditions, diolefinic compounds **4j** and **4k** with a norbornane ring system produced polymerized products, which may be a result of a ring-opening metathesis reaction with the norbornane ring system.

The 1,3-disubstituted aromatic derivative **6** was prepared by the alkylation reaction of the corresponding acid **3l** with allyl bromide (see Scheme 3). Compound **6** was subjected to similar olefin metathesis reaction conditions in toluene at 80 °C to afford macrocyclic product **7** in 82% yield. An intramolecular product of type **9** was not observed.
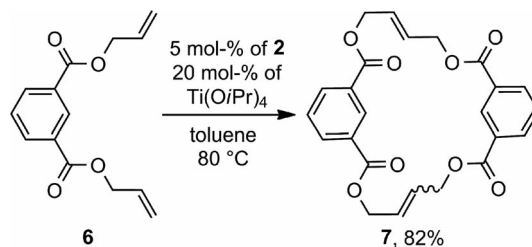
Scheme 3. Olefin metathesis on isophthalic derivative **6**.

Next, we intended to examine a cross-metathesis reaction in the above process. In regard to this, the reaction of a mixture of equimolar amounts of **4a** and **4e** was performed in the presence of catalyst **2** in toluene under similar conditions to furnish metathesis products **5a** and **5e** (see Scheme 4). No products from the cross-metathesis reaction were observed.
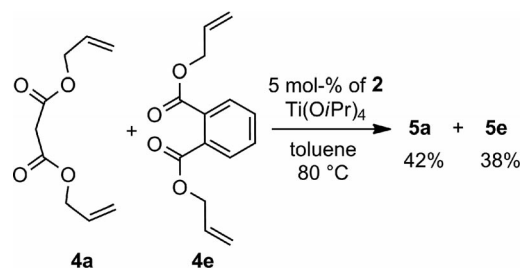
Scheme 4. Cross-metathesis reaction.

Figure 3. ORTEP views of compounds **5a** (top) and **5d** (bottom).

To obtain some insight into the mechanism, the representative reaction was carefully monitored. The reaction of **4e**

was carried out in the presence of catalyst **2** and titanium isopropoxide in toluene to furnish the interesting homodimerized product **8**, which was produced after 45 min of reaction time through a self-cross metathesis reaction (see Scheme 5). The isolated dimerized product **8** was further subjected to Grubbs' second-generation catalyst (**2**) and titanium isopropoxide for 4 h to afford macrotetralide **5e** through a ring-closing metathesis reaction. Notably, the intramolecular ring-closing metathesis reaction of **4e** to give conventional macrodiolide **9** was not observed (see Scheme 5). Efforts were made[13c] to obtain conventional macrodiolide **9** through an olefin metathesis by performing the reaction at different concentration levels,[18] but these attempts failed to afford product **9**. This observation indicates that the formation of metathesis product **5** is independent of concentration but may depend[9b] on the length of the olefin tether.
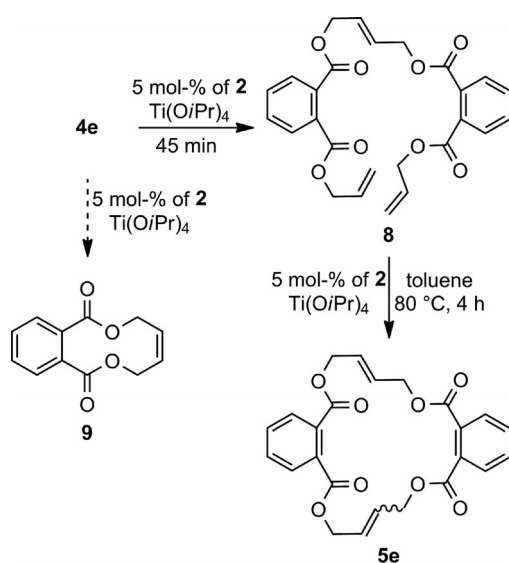
Scheme 5. Controlled self-cross metathesis and ring-closing metathesis reactions.

Conclusions

The present work describes a simple and convenient method to synthesize macrotetralides in good yields through an olefin metathesis reaction that employs easily available diolefins, Grubbs' catalyst, and titanium isopropoxide as a cocatalyst in toluene. Interestingly, this reaction provides an example of sequential self-cross metathesis and ring-closing metathesis reactions to afford macrotetralides in good yields with stereoselectivity.

Experimental Section

The Alkylation of Diacid 3: An oven-dried flask under an inert gas was charged with dicarboxylic acid **3** (2.0 mmol) and anhydrous powdered K_2CO_3 (6.0 mmol) in dry DMF, and the reaction mixture was stirred at room temperature for 10 min. Alkenyl bromide (5.0 mmol) and a catalytic amount of tetrabutylammonium iodide

were added, and the reaction mixture was stirred at room temperature for 6 h. To the reaction mixture was added water (200 mL), and the resulting solution was extracted with dichloromethane (4 × 50 mL). The combined organic layers were washed with water (3 × 200 mL) and dried with Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography using silica gel (100–200 mesh) afforded the respective dialkylated product **4** as a colorless oil.

Diprop-2-en-1-yl Propanedioate (4a): Colorless viscous oil (315 mg, 89%). IR (neat): $\tilde{v}_{max}$ = 2958, 1733, 1462, 1416, 1258, 1162, 1089, 936 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.89–5.80 (m, 2 H, =CH$_2$), 5.27 (dd, ^1J = 17 Hz, ^2J = 1.2 Hz, 2 H, OCH$_2$), 5.19 (dd, ^1J = 17 Hz, ^2J = 1.2 Hz, 2 H, OCH$_2$), 4.59 (d, J = 6 Hz, 4 H, CH$_2$), 3.37 (s, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 165.8 (C=O), 131.6 (=CH), 118.3 (=CH$_2$), 65.8 (CH$_2$), 41.2 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_9H_{12}O_4Na$ [M + Na]$^+$ 207.0633; found 207.0645.

Diprop-2-en-1-yl (2Z)-But-2-enedioate (4b): Colorless viscous oil (280 mg, 85%). IR (neat): $\tilde{v}_{max}$ = 3054, 1733, 1421, 1379, 1264, 1159, 1127, 947 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.22 (s, 2 H, =CH), 5.92–5.82 (m, 2 H, =CH), 5.32–5.17 (m, 4 H, CH$_2$), 4.61–4.59 (m, 4 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.7 (C=O), 131.6 (=CH), 129.7 (=CH), 118.7 (CH$_2$), 65.7 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{10}H_{12}O_4Na$ [M + Na]$^+$ 219.0633; found 219.0625.

Diprop-2-en-1-yl Butanedioate (4c): Colorless viscous oil (290 mg, 88%). IR (neat): $\tilde{v}_{max}$ = 3061, 1713, 1648, 1598, 1474, 1360, 1244, 1076, 935 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.85–5.75 (m, 2 H, =CH), 5.22–5.10 (m, 4 H, CH$_2$), 4.48–4.47 (m, 4 H, OCH$_2$), 2.55 (s, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.7 (C=O), 132.0 (=CH), 118.0 (=CH$_2$), 65.2 (CH$_2$), 28.9 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{10}H_{14}O_4Na$ [M + Na]$^+$ 221.0790; found 221.0782.

Diprop-2-en-1-yl Pentanedioate (4d): Colorless viscous oil (270 mg, 85%). IR (neat): $\tilde{v}_{max}$ = 2986, 1715, 1648, 1442, 1379, 1358, 1283, 1249, 1195, 1005, 969 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.85–5.77 (m, 2 H, =CH), 5.23–5.11 (m, 4 H, =CH$_2$), 4.48–4.47 (m, 4 H, OCH$_2$), 2.31 (t, J = 7.2 Hz, 4 H, CH$_2$), 1.89–1.85 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.3 (C=O), 132.1 (=CH), 118.0 (CH$_2$), 64.9 (CH$_2$), 33.0 (CH$_2$), 20.0 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{11}H_{16}O_4Na$ [M + Na]$^+$ 235.0946; found 235.0958.

Diprop-2-en-1-yl Benzene-1,2-dicarboxylate (4e): Colorless viscous oil (280 mg, 91%). IR (neat): $\tilde{v}_{max}$ = 3061, 2984, 2939, 1737, 1685, 1495, 1367, 1264, 1126, 1078, 998 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.66 (dd, ^1J = 5.6 Hz, ^2J = 3.2 Hz, 2 H, Ar), 7.46 (dd, ^1J = 5.6 Hz, ^2J = 3.2 Hz, 2 H, Ar), 5.96–5.86 (m, 2 H, =CH), 5.33–518 (m, 4 H, =CH), 4.72–4.70 (m, 4 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.2 (C=O), 132.0 (Ar), 131.8 (=CH), 131.1 (=CH), 129.0 (=CH), 118.7 (=CH$_2$), 66.3 (OCH$_2$) ppm. HRMS (ESI+): calcd. for $C_{14}H_{14}O_4Na$ [M + Na]$^+$ 269.0790; found 269.0784.

Diprop-2-en-1-yl (1R,2S)-Cyclohex-4-ene-1,2-dicarboxylate (4f): Colorless viscous oil (265 mg, 90%). IR (neat): $\tilde{v}_{max}$ = 3031, 2926, 2358, 1730, 1445, 1379, 1248, 1185, 1078, 979 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.87–5.77 (m, 2 H, =CH), 5.61 (s, 2 H, =CH), 5.25–5.20 (m, 4 H, =CH$_2$), 4.59 (d, J = 6 Hz, 4 H, OCH$_2$), 3.03–3.00 (m, 2 H), 2.55–2.47 (m, 2 H), 2.33–2.28 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.8 (C=O), 132.1 (=CH), 125.1 (=CH), 118.0 (=CH$_2$), 65.2 (OCH$_2$), 39.8 (CH), 39.5 (CH), 25.8 (CH$_2$) ppm. HRMS (ESI+): calcd. for $C_{14}H_{18}O_4Na$ [M + Na]$^+$ 273.1103; found 273.1109.

Diprop-2-en-1-yl (1R,2S)-Cyclohexane-1,2-dicarboxylate (4g): Colorless viscous oil (250 mg, 85%). IR (neat): $\tilde{\nu}_{max}$ = 3056, 2940, 1728, 1650, 1450, 1378, 1349, 1245, 1243, 1193, 1028, 937 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.89–5.79 (m, 2 H, =CH), 5.27–5.14 (m, 4 H, =CH$_2$), 4.52 (m, 4 H, OCH$_2$), 2.82 (s, 2 H), 1.97–1.72 (m, 4 H), 1.49–1.36 (m, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.2 (C=O), 132.2 (=CH), 118.9 (=CH$_2$), 65.0 (OCH$_2$), 42.6 (CH), 26.2 (CH$_2$), 23.7 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{14}$H$_{20}$O$_4$Na [M + Na]$^+$ 275.1259; found 275.1248.

Diprop-2-en-1-yl 4-Methylcyclohexane-1,2-dicarboxylate (4h): Colorless viscous oil (250 mg, 87%). IR (neat): $\tilde{\nu}_{max}$ = 2955, 2870, 1734, 1648, 1522, 1376, 1255, 1092, 866 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.85–5.77 (m, 2 H, =CH), 5.20–5.13 (m, 2 H, =CH$_2$), 5.11–5.10 (m, 2 H, =CH$_2$), 4.50–4.47 (m, 4 H, OCH$_2$), 3.20–3.18 (m, 1 H, CH), 2.43–1.88 (m, 6 H, CH$_2$), 1.96–1.92 (m, 2 H, CH), 0.87–0.80 (m, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.8 (C=O), 172.5 (C=O), 132.3 (=CH), 117.7 (=CH$_2$), 117.4 (=CH$_2$), 64.7 (OCH$_2$), 64.6 (OCH$_2$), 43.4 (CH), 41.5 (CH), 40.7 (CH), 36.1 (CH$_2$), 31.8 (CH$_2$), 30.4 (CH$_2$), 27.9 (CH$_2$), 22.1 (CH$_3$) ppm. HRMS (ESI+): calcd. for C$_{15}$H$_{22}$O$_4$Na [M + Na]$^+$ 289.1416; found 289.1429.

Diprop-2-en-1-yl Biphenyl-2,2′-dicarboxylate (4i): Semisolid (240 mg, 92%). IR (neat): $\tilde{\nu}_{max}$ = 3005, 2957, 1734, 1625, 1438, 1412, 1339, 1279, 1149, 1024, 953 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.55–7.51 (m, 2 H, Ar), 7.46–7.42 (m, 4 H, Ar), 7.24–7.22 (m, 4 H, Ar), 5.74–5.64 (m, 2 H, =CH), 5.18–5.11 (m, 2 H, =CH), 5.10–5.00 (m, 2 H, =CH), 4.53–4.51 (m, 4 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.7 (C=O), 143.3 (Ar), 131.9 (=CH), 131.5 (=CH), 130.3 (=CH), 130.0 (=CH), 129.5 (Ar), 118.0 (=CH$_2$), 65.4 (OCH$_2$) ppm. HRMS (ESI+): calcd. for C$_{20}$H$_{18}$O$_4$Na [M + Na]$^+$ 345.1103; found 345.1116.

Diprop-2-en-1-yl Benzene-1,3-dicarboxylate (6): Semisolid (270 mg, 87%). IR (neat): $\tilde{\nu}_{max}$ = 3033, 2950, 2882, 1728, 1428, 1450, 1373, 1278, 1126, 1071, 967 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.61 (s, 1 H, Ar), 8.60–8.11 (m, 2 H, Ar), 7.42 (t, J = 7 Hz, 1 H, Ar), 5.99–5.89 (m, 2 H, =CH), 5.34–5.18 (m, 4 H, =CH), 4.75–4.73 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 165.2 (C=O), 133.8 (=CH), 132.0 (=CH), 131.5 (=CH), 130.7 (=CH), 130.6 (Ar), 129.0 (=CH), 118.5 (=CH$_2$), 65.8 (OCH$_2$) ppm. HRMS (ESI+): calcd. for C$_{14}$H$_{14}$O$_4$Na [M + Na]$^+$ 269.0790; found 269.0798.

Tandem Self-Cross and Ring-Closing Metathesis Reactions of Compounds 4: In an oven-dried round-bottom flask, diolefin **4** (0.3 mmol) and Ti(OiPr)$_4$ (20 mol-%) were dissolved in dry toluene (100 mL) under an inert gas, and the reaction mixture was then warmed to 80 °C. To this warm solution was slowly added Grubbs' second-generation catalyst (5 mol-%) in dry toluene (5 mL) by a syringe pump over 30 min, and the reaction mixture was stirred for the appropriate time at 80 °C. The reaction was monitored by TLC. Then, the mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography using silica gel (100–200 mesh, EtOAc/hexane) to furnish the respective macrotetralide **5**.

Macrotetralide 5a: Colorless solid (82 mg, 96%); m.p. 159 °C. IR (neat): $\tilde{\nu}_{max}$ = 2926, 1730, 1455, 1383, 1274, 1249, 1148, 1072, 978 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.80–5.74 (m, 4 H, =CH$_2$), 4.70–4.59 (m, 8 H, CH$_2$), 3.37 (s, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.9 (C=O), 164.6 (C=O), 126.7 (=CH), 125.9 (=CH), 125.8 (=CH), 63.5 (CH$_2$), 59.4 (CH$_2$), 40.9 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{14}$H$_{16}$O$_8$Na [M + Na]$^+$ 335.0743; found 335.0752.

Macrotetralide 5b: Semisolid (77 mg, 90%). IR (neat): $\tilde{\nu}_{max}$ = 2921, 2852, 1732, 1625, 1527, 1376, 1255, 1092, 866 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.21–6.20 (m, 4 H, =CH), 5.89–5.74 (m, 4 H, =CH), 4.73–4.60 (m, 8 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.7 (C=O), 164.6 (C=O), 129.8 (=CH), 129.7 (=CH), 129.6 (=CH), 128.06 (=CH), 65.8 (CH$_2$), 64.5 (CH$_2$), 29.7 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{16}$H$_{16}$O$_8$Na [M + Na]$^+$ 359.0743; found 359.0749.

Macrotetralide 5c: Semisolid (75 mg, 87%). IR (neat): $\tilde{\nu}_{max}$ = 2929, 1735, 1415, 1382, 1272, 1252, 1081, 972 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.77–5.64 (m, 4 H, =CH), 4.66–4.52 (m, 8 H, CH$_2$), 2.63–2.58 (m, 8 H, OCH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.6 (C=O), 171.5 (C=O), 171.4 (C=O), 127.8 (=CH), 127.4 (=CH), 127.2 (=CH), 64.0 (CH$_2$), 60.4 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 22.5 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{16}$H$_{20}$O$_8$Na [M + Na]$^+$ 363.1056; found 363.1063.

Macrotetralide 5d: Colorless solid (74 mg, 85%); m.p. 182 °C. IR (neat): $\tilde{\nu}_{max}$ = 2920, 1732, 1641, 1440, 1390, 1351, 1295, 1246, 1195, 1041, 947 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.78–5.66 (m, 4 H, =CH), 4.63–4.50 (m, 8 H, OCH$_2$), 2.36–2.30 (m, 8 H, CH$_2$), 1.94–1.97 (m, 4 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.5 (C=O), 172.4 (C=O), 172.3 (C=O), 128.1 (=CH), 128.0 (=CH), 127.6 (=CH), 65.1 (CH$_2$), 63.8 (CH$_2$), 63.7 (CH$_2$), 63.5 (CH$_2$), 33.2 (CH$_2$), 33.1 (CH$_2$), 29.6 (CH$_2$), 20.3 (CH$_2$), 20.0 (CH$_2$), 19.9 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{18}$H$_{24}$O$_8$Na [M + Na]$^+$ 391.1369; found 391.1357.

Macrotetralide 5e: Semisolid (80 mg, 90%). IR (neat): $\tilde{\nu}_{max}$ = 3064, 2942, 1724, 1648, 1600, 1448, 1362, 1274, 1122, 966 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.71–7.63 (m, 4 H, Ar), 7.51–7.47 (m, 4 H, Ar), 5.93–5.80 (m, 4 H, =CH), 4.84–4.82 (m, 4 H, OCH$_2$), 4.75–4.37 (m, 4 H, OCH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.4 (C=O), 166.2 (C=O), 131.9 (Ar), 130.7 (Ar), 130.6 (Ar), 130.4 (=CH), 130.3 (=CH), 130.3 (=CH), 130.2 (=CH), 128.4 (=CH), 128.0 (=CH), 127.9 (=CH), 126.9 (=CH), 126.8 (=CH), 126.0 (Ar), 64.1 (OCH$_2$), 63.9 (OCH$_2$), 60.6 (OCH$_2$), 60.4 (OCH$_2$) ppm. HRMS (ESI+): calcd. for C$_{24}$H$_{20}$O$_8$Na [M + Na]$^+$ 459.1056; found 459.1043.

Macrotetralide 5f: Semisolid (78 mg, 88%). IR (neat): $\tilde{\nu}_{max}$ = 2929, 1733, 1654, 1439, 1377, 1273, 1247, 1188, 1028, 937 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.76–5.72 (m, 4 H, =CH), 5.62 (s, 4 H, =CH), 4.60–4.43 (m, 8 H), 3.07–3.04 (m, 4 H), 2.49–2.26 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.8 (C=O), 172.7 (C=O), 127.6 (=CH), 127.5 (=CH), 125.1 (=CH), 125.0 (=CH), 64.1 (OCH$_2$), 63.9 (OCH$_2$), 39.1 (CH), 39.0 (CH), 25.8 (CH$_2$), 25.7 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{24}$H$_{28}$O$_8$Na [M + Na]$^+$ 467.1682; found 467.1695.

Macrotetralide 5g: Semisolid (79 mg, 89%). IR (neat): $\tilde{\nu}_{max}$ = 2951, 2887, 1728, 1448, 1281, 1124, 1078, 738 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.90–5.79 (m, 4 H, =CH), 4.73–4.37 (m, 8 H, OCH$_2$), 2.93 (s, 4 H, CH), 1.97–1.71 (m, 4 H, CH$_2$), 1.49–1.35 (m, 4 H, CH$_2$), 0.81–0.78 (m, 8 H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.2 (C=O), 172.1 (C=O), 126.4 (=CH), 126.2 (=CH), 62.9 (OCH$_2$), 62.7 (OCH$_2$), 52.4 (CH$_2$), 41.7 (CH), 41.6 (CH), 28.7 (CH$_2$), 25.3 (CH$_2$), 25.2 (CH$_2$), 22.6 (CH$_2$) ppm. HRMS (ESI+): calcd. for C$_{24}$H$_{32}$O$_8$Na [M + Na]$^+$ 471.1995; found 471.1988.

Macrotetralide 5h: Semisolid (77 mg, 86%). IR (neat): $\tilde{\nu}_{max}$ = 2925, 1728, 1650, 1455, 1371, 1349, 1294, 1243, 1193, 1036, 937 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.77–5.23 (m, 4 H, =CH), 4.62–4.33 (m, 8 H, =CH$_2$), 3.29–3.23 (m, 2 H, OCH$_2$), 2.47–2.17 (m, 4 H, CH$_2$), 2.15–2.13 (m, 4 H, CH), 1.96–1.71 (m, 4 H), 0.88–0.77 (m, 6 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.3 (C=O), 172.2 (C=O), 171.8 (C=O), 126.7 (=CH), 126.4 (=CH), 126.3 (=CH),

125.9 (=CH), 62.9 (OCH_2), 42.7 (CH), 42.4 (CH), 42.3 (CH), 40.3 (CH), 32.8 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 30.0 (CH_2), 27.9 (CH_2), 20.9 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{26}H_{36}O_8Na$ $[M + Na]^+$ 499.2308; found 499.2319.

Macrotetralide 5i: Semisolid (86 mg, 94%). IR (neat): $\tilde{\nu}_{max}$ = 2928, 1710, 1598, 1574, 1441, 1370, 1279, 1240, 1074, 961 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 4 H, Ar), 7.49–7.41 (m, 8 H, Ar), 7.39–7.12 (m, 4 H, Ar), 5.45–5.27 (m, 4 H, =CH), 4.41–4.34 (m, 8 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (C=O), 165.5 (C=O), 142.3 (Ar), 142.1 (Ar), 130.6 (=CH), 129.3 (=CH), 129.2 (=CH), 129.2 (Ar), 129.0 (Ar), 128.9 (Ar), 128.8 (=CH), 128.7 (=CH), 128.4 (Ar), 128.3 (Ar), 126.6 (=CH), 126.5 (=CH), 126.4 (=CH), 126.3 (=CH), 126.2 (=CH), 126.1 (=CH), 63.1 (=CH), 63.0 (=CH_2), 62.9 (=CH_2), 59.2 (=CH_2), 59.8 (=CH_2) ppm. HRMS (ESI+): calcd. for $C_{36}H_{28}O_8Na$ $[M + Na]^+$ 611.1682; found 611.1674.

Macrotetralide 7: Semisolid (73 mg, 82%). IR (neat): $\tilde{\nu}_{max}$ = 2936, 2916, 1754, 1481, 1257, 1305, 1053, 918 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.65–8.63 (m, 2 H, Ar), 8.26–8.21 (m, 4 H, Ar), 7.56–7.50 (m, 2 H, Ar), 6.05–5.90 (m, 4 H, =CH), 5.00–4.84 (m, 4 H, OCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (C=O), 134.6 (=CH), 134.4 (=CH), 134.3 (=CH), 130.4 (Ar), 130.3 (=CH), 129.8 (Ar), 129.0 (=CH), 128.9 (=CH), 128.6 (=CH), 127.6 (=CH), 127.52 (=CH), 64.6 (OCH_2), 64.4 (OCH_2), 59.7 (OCH_2) 59.4 (OCH_2) ppm. HRMS (ESI+): calcd. for $C_{24}H_{20}O_8Na$ $[M + Na]^+$ 459.1056; found 459.1063.

Homodimerized Product 8: Semisolid (83 mg, 91%). IR (neat): $\tilde{\nu}_{max}$ = 3022, 1725, 1435, 1281, 1116, 738, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 4 H, Ar), 7.51–7.19 (m, 4 H, Ar), 5.97–5.89 (m, 4 H, =CH), 5.34–5.19 (m, 4 H, OCH_2), 4.84–4.70 (m, 8 H, OCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (C=O), 164.1 (C=O), 148.3 (Ar), 138.2 (=CH), 131.6 (Ar), 128.4 (=CH), 128.0 (=CH), 119.4 (=CH), 66.8 (OCH_2), 65.5 (OCH_2) ppm. HRMS (ESI+): calcd. for $C_{26}H_{24}O_8Na$ $[M + Na]^+$ 487.1369; found 487.1377.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of selected compounds **4** and **5**, X-ray crystal data of **5a** and **5d**.

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[18] See the Supporting Information.

[19] CCDC-943124 (for **5a**) and -943125 (for **5d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.