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New Approach to the Synthesis of Macrocyclic Tetralactones via Ring-Closing Metathesis Using Grubbs' First-Generation Catalyst

Sengodagounder Muthusamy,*,† Boopathy Gnanaprakasam,† and Eringathodi Suresh‡

School of Chemistry, Bharathidasan University, Tiruchirappalli, Tamilnadu 620 024, India, and Central Salt & Marine Chemicals Research Institute (CSIR), Bhavnagar, Gujarat 364 002, India

muthu@bdu.ac.in

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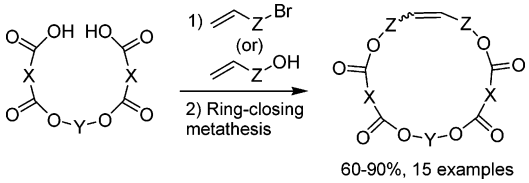
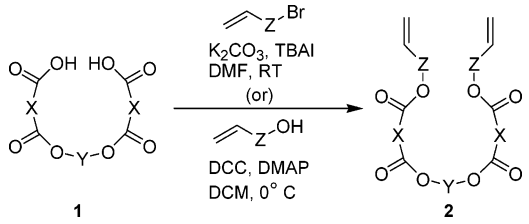


A facile and efficient route to synthesize macrocyclic tetralactones with different ring sizes having a wide variety of spacers is described. The application of ring-closing metathesis for the synthesis of macrocyclic tetralactones is demonstrated with many examples in excellent yield. The representative structure of macrocyclic tetralactones is characterized by X-ray crystallography.

Ring-closing metathesis (RCM) reactions have become one of the most versatile and efficient methods for constructing many carbo- and heterocyclic compounds.[1] They have been extensively used as a key step in a number of natural product syntheses to install a cyclic structure.[2] Olefin metathesis provides an efficient methodology for C═C bond formation and has received a great deal of attention for the synthesis of medium as well as large rings from acyclic diene precursors. Many macrolides have been ingeniously approached by RCM methods.[3] Synthesis[4] and studies[5] of the macrocyclic dilactones are impressive in organic chemistry due to their biological properties, complex formation, ion carriers, and application in the perfume industry. Even though literature methods provide a mixture of dilactones and tetralactones, the reactions give low yields and require drastic conditions. Recently, we have reported[6] the synthesis of macrocyclic tetralactones via DCC/DMAP cyclization of dicarboxylic acids. Since there has been no other literature report toward the synthesis of macrocyclic tetralactones, we herein report a successful method for macrocyclic tetralactones with different ring sizes via RCM reaction.

SCHEME 1. Esterification of Dicarboxylic Acids Using Alkenyl Bromide or Alcohol



With the objective to develop a new alternative efficient method for macrocyclic tetralactones, the required dicarboxylic acids **1** were assembled by the recently reported[6] method. The dicarboxylic acids **1** having different spacers were alkylated via two different methods. Method 1 involves the reaction of dicarboxylic acid **1**, alkenyl bromide, K_2CO_3, and a catalytic amount of tetrabutylammonium iodide (TBAI) at room temperature. The second method involves the reaction[6] of dicarboxylic acid **1** and alkenol in the presence of DCC/DMAP.

The dialkylation reaction of dicarboxylic acid **1a** and an excess amount of allyl bromide was carried out on the basis of

* To whom correspondence should be addressed. Fax: 91-431-2407053.
† Bharathidasan University.
‡ Central Salt & Marine Chemicals Research Institute (CSIR).

(1) (a) *Handbook of metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Trost, B. M.; Frederiksen, M. U.; Rudd, M. *T. Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (f) Arjona, O.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem*. **2003**, 611. (g) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (h) Walters, M. A. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Amsterdam, 2003; Vol. 15, pp 1−36. (i) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (j) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (k) Kotha, S.; Sreenivasachary, N. *Indian J. Chem.* **2001**, *40B*, 763. (l) Schmidt, B.; Hermanns, J. *Curr. Org. Chem.* **2006**, *10*, 1363.

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(5) (a) Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *Chem. Rev.* **1979**, *79*, 37. (b) Bogdanova, A.; Perkovic, M. W.; Popik, V. V. *J. Org. Chem.* **2005**, *70*, 9867. (c) Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261. (d) Masamune, S.; Bates, S. G.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (f) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

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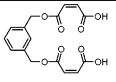
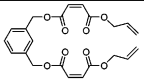
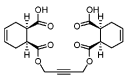
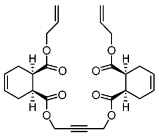
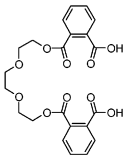
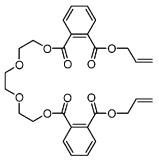
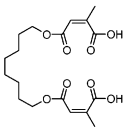
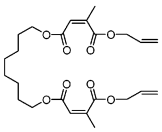
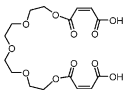
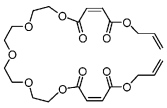
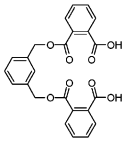
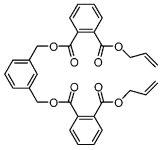
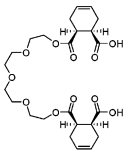
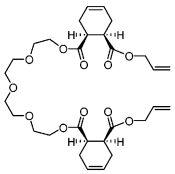
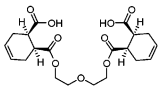
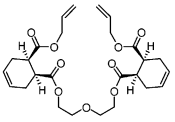
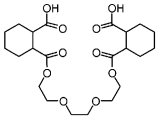
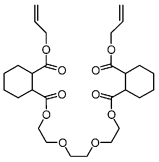
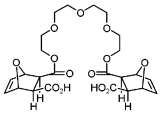
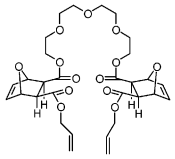
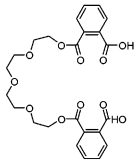
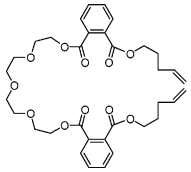
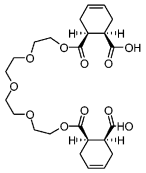
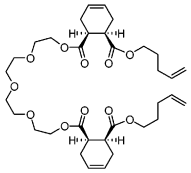
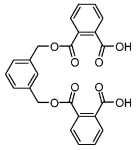
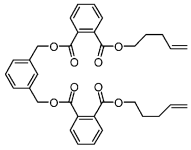
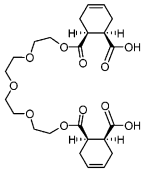
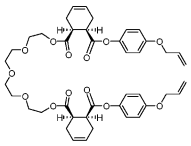
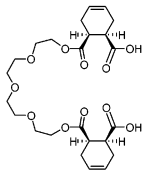
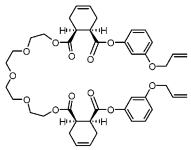
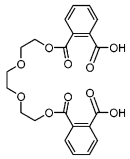
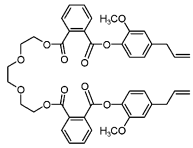
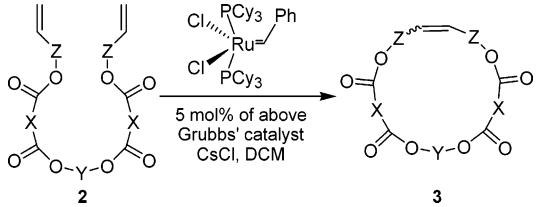
TABLE 1. Synthesis of the Dialkylated Compounds 2 via Scheme 1

entry	dicarboxylic acid	dialkylated product	yield[a] (%)
a			90 (**2a**)
b			96 (**2b**)
c			94 (**2c**)
d			94 (**2d**)
e			96 (**2e**)
f			90 (**2f**)
g			94 (**2g**)
h			94 (**2h**)
i			90 (**2i**)
j			82 (**2j**)
k			92 (**2k**)
l			92 (**2l**)
m			88 (**2m**)
n			88 (**2n**)
o			90 (**2o**)
p			76 (**2p**)

[a] Yield (unoptimized) refer to isolated and chromatographically pure compounds **2**.

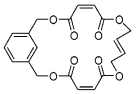
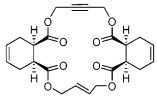
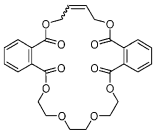
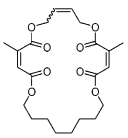
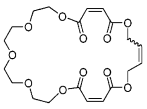
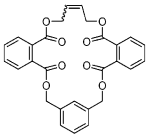
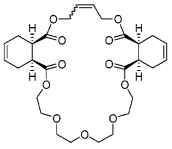
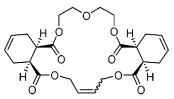
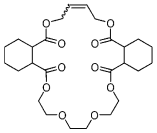
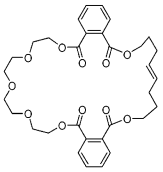
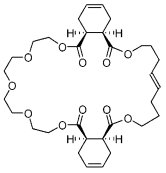
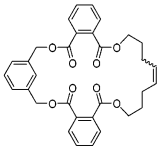
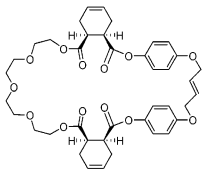
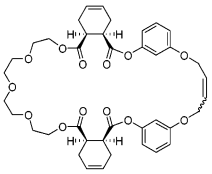
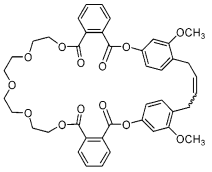
method 1 to furnish the respective symmetrical dialkylated product **2a** in 90% yield (Scheme 1, Table 1, entry a) as a colorless thick oil. Other dialkylated products **2b**−**j** (Table 1, entries b−j) were synthesized from the appropriate dicarboxylic acids **1**. The dialkylation reaction of dicarboxylic acids **1** was performed using 5-bromo-1-pentene to afford products **2k**−**m** (Table 1, entries k−m) having longer linkers between two olefin functional groups. The dialkylation reaction of dicarboxylic acid **1n** and an excess amount of 4-allyloxyphenol was carried out on the basis of method 2 to afford the respective dialkylated product **2n** in 88% yield (Table 1, entry n) having an aromatic spacer. Similar methodology was followed with 3-allyloxyphenol or 4-allyl-2-methoxyphenol to furnish the respective symmetrical diolefinic compounds **2o,p** (Table 1, entries o,p).

SCHEME 2. Ring-Closing Metathesis of Compounds 2



2 **3**

TABLE 2. Synthesis of the Macrocyclic Tetralactones 3 via Scheme 2

entry	olefin	reaction time (hr)	macrocyclic tetralactones (yield[a] %)	ratio of isomers[b] *E/Z*
a	**2a**	18	 **3a** (64)	1:0
b	**2b**	24	 **3b** (70)	1:0
c	**2c**	22	 **3c** (85)	3:1
d	**2d**	24	 **3d** (68)	2:1
e	**2e**	24	 **3e** (60)	2.5:1
f	**2f**	18	 **3f** (76)	3:1
g	**2g**	24	 **3g** (80)	3:1
h	**2h**	22	 **3h** (76)	2.2:1
i	**2i**	26	 **3i** (80)	3:1
j	**2k**	26	 **3k** (88)	1:0
k	**2l**	24	 **3l** (78)	1:0
l	**2m**	20	 **3m** (78)	-
m	**2n**	36	 **3n** (62)	1:0
n	**2o**	36	 **3o** (68)	3:1
o	**2p**	36	 **3p** (67)	2:1

[a] Yields (unoptimized) refer to isolated pure compounds **3**. [b] Ratio of isomers is determined by proton NMR spectroscopy.

We next performed the RCM reactions of the compounds **2** having a symmetrical diolefinic end using Grubbs' first-generation catalyst. Thus, compound **2a** was stirred with 5 mol % of Grubbs' catalyst and 2 equiv of CsCl under an inert atmosphere to afford 21-membered macrocyclic tetralactone **3a** in 64% yield (Scheme 2, Table 2, entry a). This reaction was performed in DCM under high dilution and monitored with the help of TLC. From the reaction mixture, 20% of the unreacted starting material was recovered, and the yield is almost 85% based on the recovery of the starting material. ^{1}H NMR showed the absence of olefinic CH_2 hydrogens. Mass spectrum clearly indicated that the molecular ion with a reduction of 28 atomic mass unit from the starting material. The product **3a** was obtained as a single isomer based on the spectral data, which is characterized as an *E*-isomer by the X-ray crystallography.[7]

To exploit this interesting result, the diallylated compound **2b** was also subjected to RCM reaction using 5 mol % of the Grubbs' catalyst to afford the tetralactone **3b** as a single isomer based on the proton NMR having 20 atoms in the cyclic core (Table 2, entry b). The unreacted starting material (20%) was also recovered from this reaction. Next, the diolefinic compounds **2c**−**i** having allyl units were subjected to the RCM reactions to afford the respective macrocycles **3c**−**i** as a mixture

(7) See the Supporting Information for the ORTEP view and crystal data of compounds **3a** and **3f**.

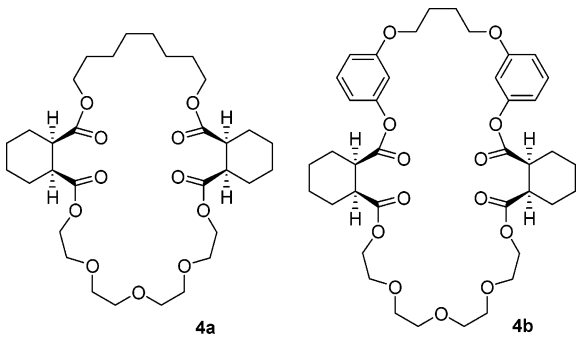


FIGURE 1. Macrocyclic tetralactones with C_2 symmetry.

of *E*/*Z* isomers (Table 2, entries c−i) comprising 21, 24, and 27 atoms in the cyclic core with different spacers in very good yield. The mixture of isomers **3f** was subjected for crystallization to furnish the single crystal, which was characterized[7] as an *E*-isomer on the basis of the X-ray crystallographic analysis. The RCM reaction of the compound **2j** having oxanorbornene ring system furnished a mixture of products **3j**. This may be due to the ring-opening metathesis reaction[1e] of the oxanorbornene ring system under these experimental conditions. The compound **2k** having the pentenyl ester was subjected under RCM conditions to afford the respective 31-membered macrocyclic tetralactone **3k** as a single isomer (entry j). During this reaction, 8% of the unreacted **2k** was isolated. The diolefinic esters **2l**,**m** were subjected under similar conditions to furnish the respective macrocyclic tetralactones **3l**,**m** as a single isomers (entries k,l) having 31 and 25 atoms in the cyclic core. The ratio of the isomer of **3m** could not be determined due to the complex nature of the ^{1}H NMR. The synthesis of a larger tethered compound **2n** leading to the formation of a single stereoisomer of the 37-membered oxa-heterocycle **3n** (entry m). Similarly, the diallylated compounds **2o**,**p** afforded the respective 35-membered tetralactones **3o**,**p** as a mixture of *E*/*Z*-isomers. The control reaction without CsCl reduces the yield in the range of 20−30% for the synthesis of **3** having oxyethylene spacers. This may be due to the close proximity[8] of the olefins resulting from the Cs complex formation with **2**. The crystal structure[7] of **3f** obtained from the mixture of isomers indicates that the structure of the major isomer present in **3** tentatively assigned as the *E*-isomer.

Subsequently, the representative isomerically pure tetralactone **3l** and *E*/*Z*-isomers of **3o** having olefin moiety were reduced in the presence of Pd−C/H_2 to furnish the respective macrocyclic compounds **4a**,**b** in an excellent yield with the complete C_2-symmetry (Figure 1). The structures of **4a**,**b** were consistent with the NMR and mass spectra, which also exhibited single sets of peaks due to the symmetry-related to protons and carbon atoms.

In conclusion, this work described the preparation of symmetrical bis-olefinic compounds by tethering several spacers and their RCM reactions providing an expedient strategy for the synthesis of symmetrical macrocyclic tetralactones. This methodology brings another application of Grubbs' catalyst for the synthesis of macrocyclic tetralactones having different ring sizes and spacers. These macrocyclic compounds are expected to be potentially important to the biologically significant materials and supramolecular chemistry.

Experimental Section

General Procedure for the Ring-Closing Metathesis of 2. To an oven dried flask, bis-olefin **2** (1 equiv) and cesium chloride (2 equiv) were charged in dry DCM (100 mL) under inert atmosphere and refluxed. To the above refluxed solution was added 5 mol % of Grubbs' first-generation catalyst in dry DCM (10 mL) slowly for 2 h and stirred for the appropriate time. The reaction was monitored by TLC. Finally, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was subjected to silica column (100−200 mesh) chromatography using EtOAc/hexane to furnish the respective macrocyclic tetralactone **3**.

Macrocyclic Tetralactone 3a. To the stirred solution of compound **2a** (0.200 g, 0.483 mmol) and cesium chloride (0.162 g, 0.966 mmol) in dry DCM (100 mL) under nitrogen atmosphere was slowly added 5 mol % of Grubbs' catalyst (19 mg) in dry DCM (10 mL) for 2 h and the mixture refluxed for 18 h. Purification of the reaction mixture using a silica gel column (30:70 EtOAc/hexane) afforded the tetralactone **3a** (0.119 g, 64%) as a single isomer. The unreacted compound **2a** (0.04 g, 20%) was recovered: white solid; mp 85−88 °C; ν_{max}(KBr)/cm^{-1} 3064, 2957, 2882, 1727, 1641, 1452, 1399, 1277, 1208, 1165, 988. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38 (m, 4H), 6.31−6.24 (m, 4H), 5.55 (d, 2H, J = 8 Hz), 5.18 (s, 4H), 4.40 (d, 4H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.1, 164.9, 164.8, 135.7, 135.6, 135.3, 130.1, 129.3, 129.1, 129.0, 128.7, 127.6, 127.3, 67.1, 67.0, 64.5, 60.9; HRMS (ESI+) calcd for $C_{20}H_{18}O_8Na$ $(M + Na)^+$ 409.0899, found 409.0865.

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Supporting Information Available: Experimental procedures, spectral data for the compounds **2a**−**p** and **3b**−**i**,**k**−**p,** ORTEP view with CIF files for **3a** and **3f**, and copies of spectra for the representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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