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Synthesis of Macrocyclic Lactams and Lactones via Ring-Closing Olefin Metathesis

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***Abstract*:** Lactones and lactams **4-6** were synthesized from a series of acyclic dienes **1-3** via ring-closing olefin metathesis, as shown in equation 1. The geometry of the resulting double bond was determined, and the *E/Z* ratios compared to values from molecular mechanics calculations.

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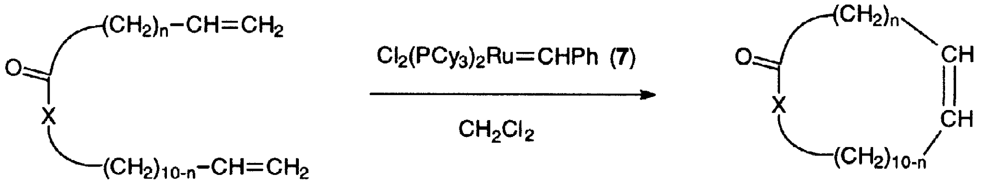
Recently the ring-closing metathesis (RCM) reaction has been applied in the synthesis of such macrocyclic natural products as manzamine A,[1,2] the epothilones,[3,4] and Sch 38516 (Fluvirucin B_1).[5] In addition to these natural product syntheses, various studies on the synthesis of unsaturated macrocyclic lactams and lactones by the RCM reaction have been conducted.[6-8] These studies have shown that the RCM reaction can be used to synthesize several different ring sizes, but no systematic study of a single ring size has been carried out yet. Herein we report such a study on the use of the RCM reaction to synthesize a series of unsaturated 14-membered ring lactones and lactams as shown in Equation 1.



(1)

1, X = O
2, X = NH
3, X = NBOC

4, X = O
5, X = NH
6, X = NBOC

Diene esters **1** were prepared by coupling the corresponding carboxylic acids and alcohols; the diene amides **2** were prepared from the corresponding carboxylic acids and amines, or by alkylation of the corresponding primary amides. A CH_2Cl_2 solution of $Cl_2(PCy_3)_2Ru{=}CHPh$ (**7**)[9,10] was added to a CH_2Cl_2 solution of **1**, or separate CH_2Cl_2 solutions of **2** and **7** were added to CH_2Cl_2 to

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form the corresponding lactones **4** or lactams **5** in poor to good yields (Table 1).[11] The number n represents the number of methylene units separating the carbonyl group and the double bond in the macrocyclic ring.

Table 1. Formation of 14-Membered Macrocyclic Lactones and Lactams by Ring-Closing Metathesis of Dienes **1**-**3**.

Substrate	X	n	Product	Conditions	Time (h)	Yield (%)[d]	*E*/*Z*[e]	Calculated *E*/*Z*[f]
1a	O	1	**4a**	a	30	11 (41)	50:50	96:4
1b	O	2	**4b**	a	31	45 (30)	82:18	99:1
1c	O	3	**4c**	a	20	47 (26)	23:77	35:65
1d	O	4	**4d**	a	6	75 (5)	56:44	65:35
1e	O	5	**4e**	a	30	62 (11)	>99:1	96:4
1f	O	6	**4f**	a	20	31 (28)	59:41	64:36
1g	O	7	**4g**	a	1.5	63 (9)	73:27	59:41
1h	O	8	**4h**	a	31	70 (5)	87:13	95:5
1i	O	9	**4i**	a	30	0 (66)		65:35
2a	NH	1	**5a**	b	24	0 (82)		99:1
2b	NH	2	**5b**	b	24	11 (75)	80:20	99:1
2c	NH	3	**5c**	b	25	39 (32)	11:89	17:83
2d	NH	4	**5d**	b	4	74 (9)	58:42	57:43
2e	NH	5	**5e**	b	1	87 (12)	>99:1	97:3
2f	NH	6	**5f**	b	7	86 (0)	54:46	48:52
2g	NH	7	**5g**	b	22	47 (39)	16:84	16:84
2h	NH	8	**5h**	b	20	32 (60)	72:28	95:5
2i	NH	9	**5i**	b	26.5	7 (83)	>99:1	63:37
3a	NBOC	1	**5a**	c	24	0 (93)		99:1
3b	NBOC	2	**5b**	c	24	31 (41)	82:18	99:1
3c	NBOC	3	**5c**	c	10	71 (8)	20:80	17:83
3g	NBOC	7	**5g**	c	8	62 (11)	13:87	16:84
3h	NBOC	8	**5h**	c	17	57 (5)	64:36	95:5
3i	NBOC	9	**5i**	c	24	20 (67)	>99:1	63:37

[a] A solution of 2 mol % **7**, 2.0 mM in CH_2Cl_2, was added to a solution of **1** in CH_2Cl_2. An additional 3 mol % of **7** was added to **1a** and **1i** after 18 hours.

[b] CH_2Cl_2 solutions of **2** and 5 mol % of **7**, 2.0 mM, were added over 3 hours, with the exception of **2e** where the substrate and the catalyst were added immediately.

[c] Same as b and the crude product was treated with CF_3COOH:CH_2Cl_2 (1:1) to cleave the BOC group.

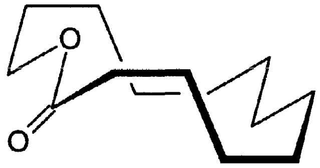
[d] Isolated yield of analytically pure material after chromatography, and recovered starting material in parenthesis.

[e] Ratio of isomers was determined by GC or ^1H NMR, or by chromatographic isolation.

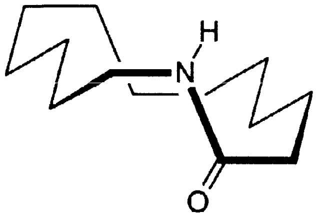
[f] Caculated using MacroModel 4.5 (see reference 17).

These results illustrate that the proximity of the terminal double bonds to the carbonyl oxygen or the heteroatom affects the cyclization. Earlier studies indicated when three bonds or less separate the terminal double bond from the carbonyl, unproductive metal complexes can result.[12,13] The poor yields of **4a**, **4i**, **5a**, **5b**, and **5i** and the general trend in yield can be explained in these terms. Amides **2a**-**2c** and **2g**-**2i** were protected with the BOC group to reduce the Lewis basicity of the carbonyl oxygen and the amide nitrogen atoms, and to sterically hinder the carbonyl oxygen. These *N*-BOC diene-amides **3** were treated under the same RCM conditions, and then with trifluoroacetic acid prior to purification, to yield the corresponding lactams **5** in improved yields (Table 1). These results with the *N*-protected diene-amides are consistent with previous studies indicating that the RCM reaction proceeds more smoothly when the nitrogen of diene-amides are protected.[14]

The observed *E/Z* ratios from the RCM reactions are also given in Table 1.[15] Comparing the series X=O, NH or BOC, suggested that, except for **1g** and **2g**, the heteroatom or its substituent had little effect on these ratios. Equilibrium studies on (*Z*)-**5g** and (*E*)-**5f** using active form of the catalyst **7**, $Cl_2(PCy_3)_2Ru{=}CH_2$, in CH_2Cl_2 showed little isomerization after 24 hours. In fact treatment of (*E*)-**5f** with **7** and excess ethylene converted the lactam back to starting amide **2f** (24%), 14% cyclic dimer and 60% recovered (*E*)-**5f**. Next we considered that the relative transition state energies for formation of the *E* and *Z* might be reflected in the relative strain of the isomeric products. The global minimum energy conformations[16] of 13-tridecanolide (**8**) and 2-azacyclotetradecanone (**9**) are shown below. The dihedral angles from these structures and the observed E/Z ratios for the corresponding bond positions suggested that the conformation of the transition state for ring formation is similar to these structures and controls the stereochemistry of the resulting double bond. MM3* calculations[17] were performed on each of the macrocyclic lactones and lactams. The calculated E/Z ratios (Table 1) are comparable with those observed for each series.



8



9

Diene esters and amides, with the terminal double bonds far removed from the functionality, can be used to form 14-membered ring lactones or lactams by RCM. The yields of lactams were improved by BOC protection of the amide nitrogen. The observed *E/Z* ratios were comparable to those from MM3* calculations, making molecular mechanics a predictive tool on the preferred stereochemistry of the resulting alkene. This constitutes the first systematic study of the RCM of a single ring size, exploring all logical double bond positions within the macrocyclic ring, and the first which displayed predictable double bond geometry. Further work is in progress to study the synthesis, conformation, and reactivity of these macrocyclic systems.

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