HETEROCYCLES, Vol. 81, No. 1, 2010, pp. 149 - 161. © The Japan Institute of Heterocyclic Chemistry
Received, 20th September, 2009, Accepted, 26th October, 2009, Published online, 27th October, 2009
DOI: 10.3987/COM-09-11835

A SYNTHETIC STUDY OF DIBENZO-AROMATIC MACROLACTAMS

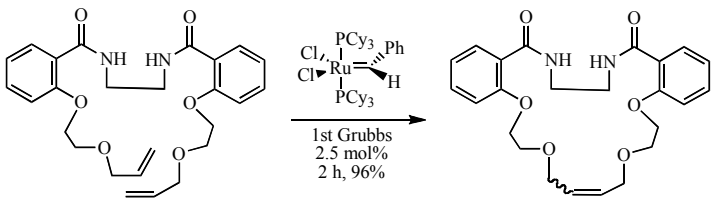
David P. Brown* and Thomas Wong

Department of Chemistry, St. John's College of Liberal Arts and Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, New York 11439, USA
E-mail: brownd@stjohns.edu

Abstract – Efforts to generate benzenoid macrolactams in the development of hybrid molecules as New Chemical Entities are described. The olefin metathesis protocol was adopted in facilitating the cyclization process.

Among the plethora of naturally occurring biologically active systems that have engaged the intellectual curiosity of synthetic chemists are those compounds containing an aromatic macrocyclic lactam skeleton.[1] These compounds are known for their varied properties which include potent antibiotic and anti-tumor activities.[2] An attractive feature of the macrocyclic skeletal system is the increased permeability of the macromolecules to membranous barriers. They are also less prone to standard routes of *in vivo* degradation. Accordingly, orally bioavailable macrocycles have been developed which include enzyme inhibitors of HIV protease, ACE, and matrix metalloproteinases.[3]

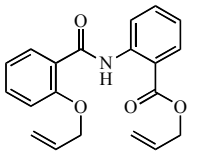
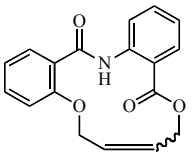
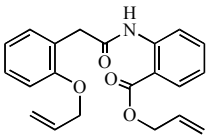
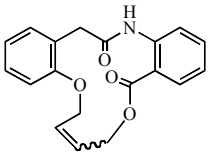
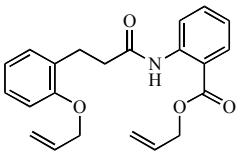
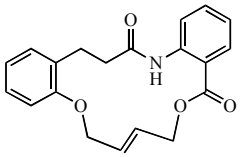
Current investigative efforts in the design and synthesis of novel natural product hybrids[4] required that we explored the generation of macrolactams incorporating two or more independent benzenoid structural units. Of particular interest were the effects of atom connectivity across the aromatic rings, and ring size on product yields. Ibrahim and John have demonstrated the synthesis of some structurally related systems; specifically, a series of macrocyclic ployoxadi- and polyoxatetramides[5] employing ring closing metathesis (RCM) methodology,[6] Scheme 1. In a previous study, we have similarly applied the RCM protocol in the synthesis some novel macrolactones in good to excellent yields.[7]

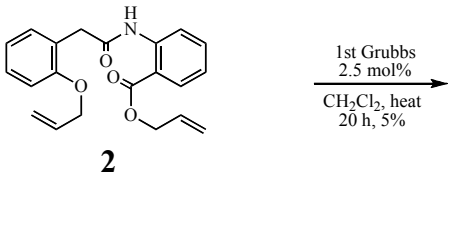


Scheme 1. Poyloxadiamide Synthesis

Synthesis of the RCM substrates **1** through **12** were accomplished through nucleophilic acyl substitution reactions as were reported for the macrolactones previously synthesized.[7] With the preliminary findings that, in addition to ring size, the macrocyclization process in the case of the lactones was affected by atom connectivity across the benzene rings, we initially explored the generality of this effect, observing the outcomes of dienes **1**, **2** and **3**. Table 1 summarizes the results from high dilution studies, employing the first generation Grubbs catalyst in CH_2Cl_2 under reflux for 8 h. The expected progressive increase in product yields was observed, with all three macrocycles isolated as inseparable mixtures of stereoisomers. For diene **2**, extending the reaction time to about 20 h yielded the cyclic dimer **14a** as the exclusive product in a low 5% yield, Scheme 2. The proton NMR spectrum of compound **14a** gave distinct chemical shifts of δ 9.35 and 9.45 for the amide protons suggesting a head-to-tail dimerization outcome.

Table 1. RCM Reactions of Substrates **1** – **3**.

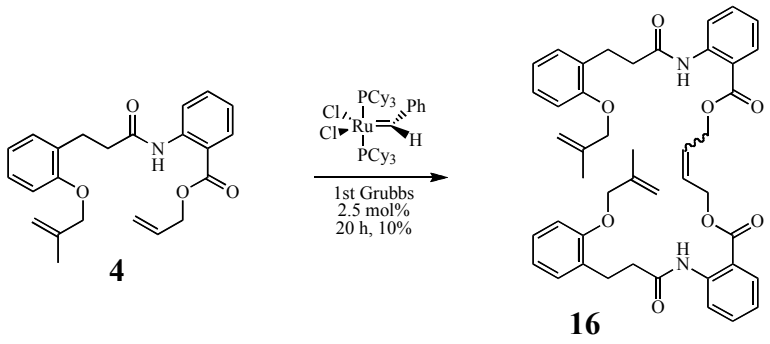
Entry	Diene	Isolated Product	Yields (%)
(1)	 **1**	 **13**	15
(2)	 **2**	 **14**	20
(3)	 **3**	 **15**	70



2 **14a**

Scheme 2. RCM Reaction of Substrate **2**

In the case of substrate **4**, only the acyclic dimer **16,** Scheme 3, and un-reacted starting material were isolated.



Scheme 3. Olefin Metathesis of Substrate **4**

Attempted RCM cyclization of the mixed 1,2-di- and 1,3-disubstituted benzene derivatives **5** through **9** proved futile. Except for substrate **7**, the starting diene and un-characterizable polymeric materials were recovered. For diene **7**, trace amounts of the acyclic dimer **17** was isolated along with starting material.

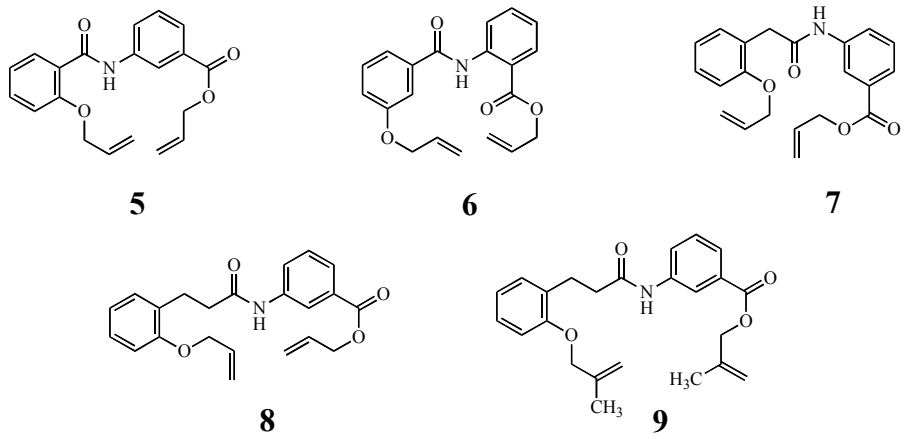
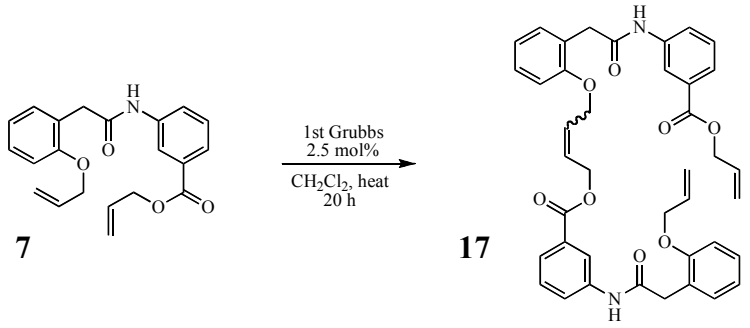
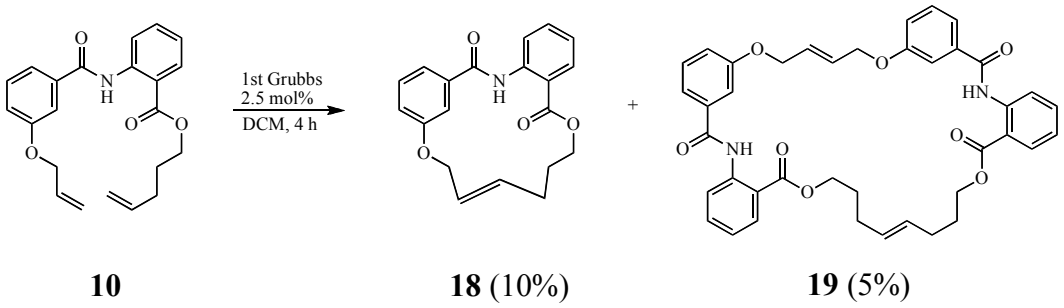


Figure 1. RCM Substrates **5** – **9**



Scheme 4. Olefin Metathesis of Substrate **7**

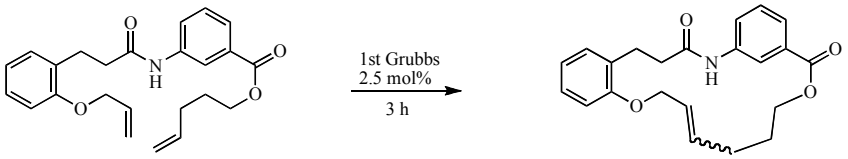
The pentenyl esters **10**, **11** and **12** were subjected to the RCM conditions with the expectation that increasing the ring size would assist in combating the apparent negative enthalpy factors during cyclization. Diene **10** afforded the expected product **18** along with the cyclic dimer **19**, Scheme 5.



10 **18** (10%) **19** (5%)

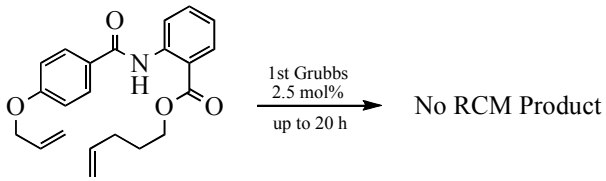
Scheme 5. RCM Reaction of Substrate **10**

After about 3 h, the macrolactam **20** was isolated in about 15% yield from the RCM reaction on diene **11**, Scheme 6. Extending the reaction time up to 20 h failed to improve on the product yield. As expected, the diene **12** failed to undergo cyclization under the reaction conditions investigated. Significant compound decomposition was observed on prolonged heating with the catalyst.



11 **20**

Scheme 6. RCM Reaction of Substrate **11**



12

Figure 2. RCM Substrates **12**

In summary, we have further elucidated the application of the first generation Grubbs catalyst in the synthesis of dibenzo-aromatic macrolactams, with our findings alluding to the necessity of using a more

active catalyst system such as the second generation or the Schrock catalyst[6] for mixed 1,2- and 1,3-disubstituted derivatives. Albeit, for the applied catalyst, the RCM approach appears to be more amenable to 1,2-disubstituted macrolactone and macrolactam precursors, with more encouraging yields resulting from substrates possessing four or more covalent bonds connecting the two aromatic rings.[7]

EXPERIMENTAL

Infrared spectra were obtained on a Perkin Elmer 1000 Spectrometer as neat samples or CCl_4 solutions. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX 400 MHz spectrometer, with chemical shifts reported as parts per million (δ ppm) downfield of the internal standard TMS. Gas Chromatography Mass Spectrometry (GC/MS) analyses were performed using the Shimadzu GCMS-QP5050A system. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. All required compounds for the outlined syntheses were obtained from Aldrich Chemical Company. High purity DMF was used without further purification. Dichloromethane (DCM) and THF were distilled from CaH_2 and stored over 4 angstrom molecular sieves under nitrogen. Flash chromatographic purification was performed using silica gel, 200 – 400 mesh, purchased from Aldrich.

General Synthetic Procedure for the RCM Substrates 1 – 12.

A three-necked round-bottomed flask (RBF) fitted with a pressure-equalizing dropping funnel and a magnetic stir bar was flame-dried under a positive atmosphere of dry nitrogen for 5 min. After cooling to rt, a solution of the required amine (1.0 equiv.) in dichloromethane (DCM) was added *via* syringe through a pierced rubber septum. A separate RBF, equipped for magnetic stirring was similarly flame-dried, cooled to rt, and charged with the reacting acid (1.00 equiv.) and 5.0 equiv. $SOCl_2$. The mixture was stirred for 2 h, after which the excess $SOCl_2$ was evaporated *in vacuo*. The resulting acid chloride was re-dissolved in dry DCM and transferred via syringe to the dropping funnel, which was then added drop-wise with stirring to the amine solution at 0 ^oC. The mixture was stirred at the cooling temperature for 1 h after which the solvent was evaporated under reduced pressure. Ether was then added to extract the product, with the organic phase being washed with brine and dried over anhydrous $MgSO_4$. Chromatographic purification was done with hexane-EtOAc (5:1 v/v) as eluent.

Allyl 2-[(2-allyloxybenzoyl)amino] benzoate, (1).

Compound **1** was isolated as a clear oil, (45%); IR: 754, 1074, 1123, 1253, 1297, 1446, 1518, 1583, 1667, 1703, 2939, 3070, 3268 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 4.77 (d, J = 5.4 Hz, 2H), 4.82 (d, J = 4.0 Hz, 2H), 5.24 (d, J = 9.1 Hz, 1H), 5.26 (d, J = 9.1 Hz, 1H), 5.37 (d, J = 17.2 Hz, 2H), 6.04 (m, 2H), 6.96 (d, J

= 8.3 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.94 (d, *J* = 8.3 Hz, 1H), 12.1 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 65.9, 69.9, 113.4, 116.0, 118.4, 118.9, 121.5, 122.4, 123.0, 124.0, 131.2, 132.4, 132.6, 133.3, 134.6, 141.8, 156.8, 165.1, 167.8; MS: (EI, m/z): 337(M^+), 279, 264, 234, 207, 177, 119, 105, 77, 51, 45. *Anal*. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.14. Found: C, 71.31; H, 5.67; N, 4.08.

Allyl 2-([2-allyloxyphenyl]acetyl)amino benzoate, (2).

Compound **2** was obtained as a pale yellow oil, (38%); IR: 753, 1084, 1142, 1254, 1294, 1449, 1492, 1524, 1587, 1649, 1688, 2866, 2943, 2982, 3025, 3077, 3275, 3301 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 3.79 (s, 2H), 4.56 (d, *J* = 3.7 Hz, 2H), 4.70 (d, *J* = 4.9 Hz, 2H), 5.16 (d, *J* = 10.6 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 17.0 Hz, 1H), 5.37 (d, *J* = 14.1 Hz, 1H), 5.98 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 10.94 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): δ 66.2, 68.9, 112.9, 117.0, 117.4, 119.2, 121.3, 121.4, 123.7, 124.1, 129.5, 131.4, 132.2, 133.1, 134.4 (2C's), 135.1, 141.2, 157.0, 167.5, 170.4; MS: (EI, m/z): 351(M^+), 177, 160, 146, 119, 105, 91, 77, 65. *Anal*. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.74; H, 6.08; N, 4.01.

Allyl 2-{3-[2-(allyloxy)phenyl]propanoyl}amino benzoate, (3).

Compound **3** was isolated as a clear oil, (45%); IR: 753, 930, 1162, 1253, 1526, 1588, 1602, 1688, 2846, 2917, 3010, 3076, 3312 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 2.78 (t, *J* = 8.1 Hz, 2H), 3.13 (t, *J* = 7.5 Hz, 2H), 4.60 (d, *J* = 4.8 Hz, 2H), 4.83 (d, *J* = 5.5 Hz, 2H), 5.29 (dd, *J* = 0.6, 10.6 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 5.44 (d, *J* = 17.0 Hz, 1H), 5.46 (dd, *J* = 1.1, 17.3 Hz, 1H), 6.04 (ddt, *J* = 5.7, 10.6, 15.7 Hz, 1H), 6.13 (ddt, *J* = 5.1, 10.7, 16.9 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.77 (d, *J* = 8.5 Hz, 1H), 11.05 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 27.1, 39.0, 66.1, 69.0, 111.9, 115.2, 117.5, 119.1, 120.8, 121.1, 122.7, 127.9, 129.6, 130.5, 131.2, 132.1, 133.9, 135.1, 142.2, 156.9, 168.2, 172.2; MS: (EI, m/z): 365(M^+), 307, 288, 177, 161, 147, 131, 119, 105, 91, 77, 65, 55, 41. *Anal*. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.29; H, 6.46; N, 4.00.

Allyl 2-[3-({2-methyl}allyloxyphenyl)propanoyl]amino benzoate, (4).

Subtrate **4** was obtained as a pale yellow oil, (56%); IR: 751, 935, 1158, 1532, 1587, 1600, 1687, 2845, 2920, 3011, 3079, 3316 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 1.85 (s, 3H), 2.77 (t, *J* = 4.7 Hz, 2H), 3.11 (m,

2H), 4.45 (s, 2H), 4.79 (m, 2H), 4.98 (s, 1H), 5.13 (s, 1H), 5.29 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.39 (dd, *J* = 1.5, 17.2 Hz, 1H), 6.02 (m, 1H), 6.84 (m, 2H), 7.05 (m, 1H), 7.20 (m, 2H), 7.53 (m, 1H), 8.04 (m, 1H), 8.76 (dd, *J* = 4.0, 8.3 Hz, 1H), 11.03 s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 20.0, 27.1, 39.0, 65.2, 71.9, 111.8, 112.7, 115.2, 119.1, 120.8, 121.0, 122.7, 127.9, 129.5, 130.5, 131.2, 132.2, 135.1, 141.4, 142.2, 156.0, 168.2, 172.1; MS: (EI, m/z): 379(M^+), 322, 218, 204, 177, 161, 105, 90, 77, 57. *Anal*. Calcd for $C_{23}H_{25}NO_4$ (379.45): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.69; H, 6.59; N, 3.71.

Allyl 3-[(2-allyloxybenzoyl)amino] benzoate, (5).

Substrate **5** was isolated as a yellow oil, (52%); IR: 751, 1069, 1124, 1258, 1460, 1520, 1588, 1667, 1706, 2939, 3071, 3265 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 4.82 (m, 4H), 5.30 (dd, *J* = 1.1, 10.3 Hz, 1H), 5.42 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.50 (d, *J* = 10.4 Hz, 1H), 5.56 (d, *J* = 17.2 Hz, 1H), 6.06 (m, 1H), 6.23 (m, 1H), 7.04 (t, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.46 (m, 2H), 7.81 (dd, *J* = 0.9, 7.6 Hz, 1H), 8.14 (m, 2H), 8.30 (dd, *J* = 1.6, 7.8 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 66.1, 70.7, 113.3, 118.7, 120.9, 121.4, 122.1, 122.4, 125.1, 125.6, 129.6, 131.3, 132.1, 132.6, 133.0, 133.8, 139.2, 156.8, 163.7, 166.4; MS: (EI, m/z): 337(M^+), 280, 204, 177, 162, 105, 77, 57. *Anal*. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.21; H, 5.67; N, 4.16.

Allyl 2-[(3-allyloxybenzoyl)amino] benzoate, (6).

Compound **6** was obtained as a clear syrup, (42%); IR: 757, 1082, 1144, 1269, 1301, 1449, 1490, 1531, 1647, 1589, 1677, 2944, 3077, 3271, 3306 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 4.61 (d, *J* = 5.0 Hz, 2H), 4.83 (d, *J* = 5.5 Hz, 2H), 5.31 (d, *J* = 10.2 Hz, 2H), 5.42 (d, *J* = 16.8 Hz, 1H), 5.44 (d, *J* = 16.8 Hz, 1H), 6.05 (ddt, *J* = 5.6, 10.5, 16.2 Hz, 2H), 7.10 (d, *J* = 6.2 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.58 (m, 3H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.92 (d, *J* = 8.4 Hz, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 66.3, 69.3, 113.8, 115.5, 118.3, 119.2, 119.5, 119.8, 120.8, 123.0, 130.2, 131.4, 132.1, 133.4, 135.2, 136.7, 142.3, 159.4, 165.8, 168.5; MS: (EI, m/z): 337(M^+), 177, 160, 133, 119, 105, 77, 55. *Anal*. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.19; H, 5.64; N, 4.20.

Allyl 3-([2-allyloxyphenyl]acetyl)amino benzoate, (7).

Compound **7** was isolated as a clear syrup, (54%); IR: 753, 1084, 1142, 1254, 1298, 1492, 1524, 1587, 1649, 1688, 2943, 2982, 3025, 3078, 3275, 3307 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 3.74 (s, 2H), 4.64 (m, 2H), 4.79 (m, 2H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.35 (d, *J* = 11.1 Hz, 1H), 5.40 (dd, *J* = 1.4, 17.3 Hz, 1H), 5.48 (d, *J* = 17.3 Hz, 1H), 6.06 (m, 2H), 6.94 (m, 2H), 7.26 (m, 3H), 7.74 (d, *J* = 6.6 Hz, 1H), 7.90 (m, 2H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 40.7, 66.1, 69.5, 112.4, 118.7, 119.0, 120.8, 122.0, 123.4,

123.8, 124.7, 125.4, 129.4, 129.5, 131.1, 131.9, 132.5, 133.1, 156.2, 166.3, 170.2; MS: (EI, m/z): 351(M^+), 177, 160, 146, 119, 105, 91, 77, 65. *Anal*. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.77; H, 6.01; N, 3.96.

Allyl 3-[3-((2-allyloxyphenyl)propanoyl)amino] benzoate, (8).

Compound **8** was isolated as a yellow syrup, (45%); IR: 750, 930, 1162, 1253, 1526, 1588, 1602, 1690, 2846, 2917, 3010, 3076, 3314 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 2.73 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 4.60 (d, *J* = 4.3 Hz, 2H), 4.84 (d, *J* = 5.5 Hz, 2H), 5.32 (d, *J* = 10.4 Hz, 2H), 5.43 (dd, *J* = 1.4, 17.1 Hz, 1H), 5.46 (dd, *J* = 1.3, 13.0 Hz, 1H), 6.08 (ddt, *J* = 5.6, 10.5, 17.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 7.22 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.91 (s, 1H), 7.92 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 27.3, 39.5, 66.0, 69.1, 111.9, 115.2, 117.4, 119.1, 120.8, 121.1, 122.6, 127.8, 129.6, 130.4, 131.2, 132.1, 134.0, 135.1, 142.1, 156.9, 168.2, 172.3; MS: (EI, m/z): 365(M^+), 307, 288, 177, 161, 147, 131, 119, 105, 91, 77, 65, 55. *Anal*. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.33; H, 6.38; N, 3.89.

2-Methylallyl 3-[3-(({2-methyl}allyloxyphenyl)propanoyl)amino] benzoate, (9).

Substrate **9** was obtained as a pale yellow syrup, (52%); IR: 755, 930, 1162, 1255, 1526, 1588, 1608, 1697, 2845, 2917, 3010, 3076, 3328 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 1.86 (s, 3H), 1.88 (s, 3H), 2.72 (t, *J* = 7.4 Hz, 2H), 3.11 (t, *J* = 7.5 Hz, 2H), 4.49 (s, 2H), 4.76 (s, 2H), 5.01 (s, 1H), 5.04 (s, 1H), 5.09 (s, 1H), 5.15 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.92 (t, *J* = 7.1 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 3H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 19.7, 19.9, 27.3, 39.5, 66.0, 69.1, 111.7, 115.2, 117.3, 119.1, 120.8, 121.1, 122.6, 127.8, 129.6, 130.3, 131.2, 132.1, 134.1, 135.1, 142.3, 156.9, 168.1, 172.5; MS: (EI, m/z): 393(M^+), 322, 232, 203, 177, 161, 105, 91, 77, 55. *Anal*. Calcd for $C_{24}H_{27}NO_4$ (393.48): C, 73.26; H, 6.92; N, 3.56. Found: C, 73.31; H, 6.78; N, 3.58.

Pent-4-en-1-yl 2-{[3-(allyloxy)phenyl]carbonyl}amino benzoate, (10).

Compound **10** was obtained as a clear oil, (58%); IR: 757, 956, 1162, 1253, 1526, 1586, 1602, 1678, 2846, 2917, 3013, 3077, 3324 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 1.89 (q, J = 6.7 Hz, 2H), 2.23 (dt, *J* = 7.0. 7.1 Hz, 2H), 4.36 (t, *J* = 6.6 Hz, 2H), 4.62 (d, *J* = 5.3 Hz, 2H), 5.03 (d, *J* = 10.2 Hz, 1H), 5.08 (dd, *J* = 1.6, 17.1 Hz, 1H), 5.31 (dd, *J* = 1.2, 10.5 Hz, 1H), 5.45 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.84 (ddt, *J* = 6.6, 10.3, 17.0 Hz, 1H), 6.08 (ddt, *J* = 5.3, 10.5, 17.2 Hz, 1H), 7.11 (dt, *J* = 1.2, 8.4 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.61 (m, 3H), 8.08 (dd, *J* = 1.4, 8.0 Hz, 1H), 8.92 (d, *J* = 8.2 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR ($CDCl_3$,

ppm): δ 29.6, 38.7, 66.7, 69.1, 113.9, 115.7, 118.2, 119.2, 119.7, 119.9, 120.8, 123.1, 130.2, 131.4, 132.4, 133.4, 135.0, 136.7, 142.5, 159.4, 165.8, 168.7; MS: (EI, m/z): 365(M^+), 280, 204, 177, 161, 113, 105, 85, 77, 41. *Anal*. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.29; H, 6.28; N, 3.78.

Pent-4-en-1-yl 3-{3-[2-(allyloxy)phenyl]propanoyl}amino benzoate, (11).

Substrate **11** was isolated as a clear syrup, (56%); IR: 748, 928, 1256, 1529, 1588, 1602, 1690, 2849, 2918, 3013, 3077, 3321 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) δ 1.83 (q, *J* = 6.8 Hz, 2H), 2.18 (dt, *J* = 7.0. 7.2 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 3.07 (t, *J* = 7.4 Hz, 2H), 4.29 (t, *J* = 6.6 Hz, 2H), 4.53 (d, *J* = 4.9 Hz, 2H), 5.00 (d, *J* = 10.2 Hz, 1H), 5.05 (dd, *J* = 1.3, 17.1 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 5.43 (d, *J* = 17.3 Hz, 1H), 5.83 (ddt, *J* = 6.6, 10.3, 17.0 Hz, 1H), 6.05 (ddt, *J* = 5.1, 10.7, 17.1 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.87 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.91 (s, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 26.6, 27.8, 30.1, 37.7, 64.6, 68.7, 111.7, 115.5, 117.4, 120.6, 120.9, 124.5, 125.1, 127.8, 129.0, 129.1, 130.2, 130.9, 133.3, 137.4, 138.3, 156.3, 166.4, 171.4; MS: (EI, m/z): 393(M^+), 308, 246, 204, 190, 177, 147, 105, 91, 77. *Anal*. Calcd for $C_{24}H_{27}NO_4$ (393.48): C, 73.26; H, 6.92; N, 3.56. Found: C, 73.29; H, 6.88; N, 3.58.

Pent-4-en-1-yl 2-{[4-(allyloxy)phenyl]carbonyl}amino benzoate, (12).

Compound **12** was obtained as a yellow oil, (57%); IR: 756, 956, 1163, 1253, 1526, 1586, 1607, 1678, 2849, 2920, 3013, 3075, 3326 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) δ 1.88 (q, *J* = 6.9 Hz, 2H), 2.21 (dt, *J* = 6.8, 7.7 Hz, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 4.56 (dd, *J* = 1.4, 5.3 Hz, 2H), 5.01 (dd, *J* = 1.7, 10.2 Hz, 1H), 5.07 (dd, *J* = 1.7, 15.4 Hz, 1H), 5.29 (dd, *J* = 1.4, 10.6 Hz, 1H), 5.42 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.85 (ddt, *J* = 6.6, 10.3, 17.1 Hz, 1H), 6.03 (ddt, *J* = 5.2, 12.0, 17.3 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.06 (dt, *J* = 1.1, 6.9 Hz, 1H), 7.55 (dt, *J* = 1.3, 7.1 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 8.04 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.93 (d, *J* = 8.5 Hz, 1H), 11.98 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 27.7, 30.1, 64.8, 68.8, 114.7 (2 C's), 115.1, 115.6, 118.0, 120.3, 122.3, 127.3, 129.3 (2 C's), 130.8, 132.7, 134.7, 137.2, 142.2, 161.6, 165.1, 168.6; MS: (EI, m/z): 365(M^+), 280, 204, 177, 161, 113, 105, 85, 77, 41. *Anal*. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.30; H, 6.27; N, 3.81.

General Procedure for the RCM Reaction

A 100 mL round-bottomed flask fitted with a reflux condenser, a calcium chloride guard tube, and equipped for magnetic stirring, was flame dried under a positive atmosphere of dry nitrogen. After

cooling to room temperature, the flask was charged with a solution of the RCM substrate in DCM (2 mM). To this solution was added the Grubbs catalyst (2 – 2.5 mol%) dissolved in 20 mL DCM with stirring. The reaction mixture was stirred under reflux (40 ^{o}C) for up to 20 h, cooled to rt, then filtered through a short silica gel column, after which the solvent was evaporated *in vacuo*. The desired product was then extracted by stirring with diethyl ether, evaporated to dryness, and the crude product purified by flash chromatography.

Dibenzo[*b,f*]-1,6,12-dioxazacyclotridec-3-en-7,13-dione, (13).

Compound **13** was obtained after 6 h as a clear syrup, (15%); IR: 746, 1049, 1122, 1137, 1243, 1312, 1359, 1453, 1533, 1585, 1600, 1666, 1718, 3025, 3068, 3340 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 4.79 (d, *J* = 6.4 Hz, 2H), 4.94 (d, *J* = 7.6 Hz, 2H), 6.35 (m, 1H), 6.52 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 6.9 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.0 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 8.25 (d, *J* = 7.3 Hz, 1H), 8.90 (d, *J* = 8.4 Hz, 1H), 11.5 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 59.4, 63.1, 110.0, 112.7, 118.6, 122.3, 122.4, 122.5, 123.7, 132.1, 132.6, 133.0, 133.5, 133.6, 134.5, 144.0, 161.0, 165.0; MS: (EI, m/z): 309(M^+), 281, 239, 207, 189, 146, 119, 92, 65, 53, 45. *Anal*. Calcd for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53. Found: C, 69.74; H, 4.91; N, 4.49.

Dibenzo[*b,g*]-1,6,12-dioxazacyclotetradec-3-en-7,13-dione, (14).

Macrolactam **14** was obtained after 8 hours as a yellow syrup, (20%); IR: 753, 1082, 1092, 1140, 1230, 1294, 1367, 1443, 1494, 1522, 1587, 1604, 1688, 1737, 3025, 3064, 3275 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 3.74 (s, 2H), 4.32 (s, 2H), 4.81 (s, 2H), 5.74 (m, 1H), 5.90 (m, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 10.93 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 31.0, 65.6, 111.7, 112.1, 115.1, 118.5, 120.5, 121.7, 122.1, 122.4, 123.2, 128.9, 130.1, 131.3, 131.5, 133.2, 133.4, 167.5, 170.8; MS: (EI, m/z): 323(M^+), 204, 119, 105, 90, 77. *Anal*. Calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.60; H, 5.28; N, 4.39.

Macrocyclic Dilactam 14a

Compound **14a** was obtained as a dark brown syrup (5%), IR: 763, 1082, 1140, 1230, 1294, 1367, 1443, 1494, 1522, 1587, 1610, 1688, 1743, 3025, 3064, 3280 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 3.69 (s, 2H), 3.75 (s, 2H), 4.56 (d, *J* = 6.5 Hz, 2H), 4.72 (d, *J* = 7.2 Hz, 2H), 4.81 (s, 2H), 4.97 (d, *J* = 8.3 Hz, 2H), 5.84 (m, 2H), 6.27 (dt, *J* = 8.3, 16.9 Hz, 1H), 6.44 (dt, *J* = 7.0, 17.3 Hz, 1H), 7.06 (m, 6H), 7.40 (m, 6H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 9.35 (s,

1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 66.2, 67.5, 68.9, 70.1, 112.7, 112.9, 117.0, 117.2, 117.4, 117.8, 119.2, 119.4, 121.3, 121.4, 121.5, 122.6, 123.7, 123.9, 124.1, 124.3, 129.5, 129.6, 131.4, 132.2, 133.1, 133.4, 134.2 (2C's), 134.6, 134.9, 135.1, 141.2, 157.0, 157.1, 167.5, 168.0, 170.3, 170.6; MS: (EI, m/z): 646(M^+), 323, 204, 188, 135, 119, 105, 90, 77. *Anal*. Calcd for $C_{38}H_{34}N_2O_8$ (646.23): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.54; H, 5.29; N, 4.30.

Dibenzo[*b,h*]-1,6-12-dioxazacyclopentadec-3-en-7,13-dione, (15).

Macrolactam **15** was isolated as a clear solid, (70%); MP 92 ^{o}C; IR: 751, 973, 1244, 1447, 1552, 1583, 1604, 1668, 1681, 1714, 2846, 2919, 3021, 3060, 3335, 3384 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 2.63 (dt, *J* = 3.5, 8.6 Hz, 2H), 3.04 (t, *J* = 8.0 Hz, 2H), 4.63 (d, *J* = 5.1 Hz, 2H), 4.94 (d, *J* = 6.0 Hz, 2H), 6.34 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 7.15 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.25 (m 2H), 7.57 (dt, *J* = 1.5, 8.7 Hz, 1H), 8.04 (dd, *J* = 1.5, 7.9 Hz, 1H), 8.60 (d, *J* = 7.7 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 29.2, 40.0, 65.4, 67.3, 113.4, 118.3, 121.7, 122.1, 123.7, 128.4, 128.8, 130.0, 131.1, 132.4, 134.1, 134.5, 139.3, 157.1, 166.2, 171.6; MS: (EI, m/z): 337 (M^+), 279, 264, 234, 207, 190, 175, 159, 145, 131, 120 (100%), 92, 77, 65, 55. *Anal*. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.20; H, 5.61; N, 4.18.

Acyclic Dimer 16

Compound **16** was isolated as a brown syrup, (10%); IR: 759, 945, 1536, 1578, 1617, 1687, 2845, 2923, 3011, 3079, 3328 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 1.18 (s, 6H), 2.77 (t, *J* = 7.9 Hz, 4H), 3.10 (t, *J* = 7.1 Hz, 4H), 4.45 (s, 4H), 4.84 (m, 2H), 4.97 (m, 4H), 5.12 (s, 2H), 6.06 (m, 2H), 6.83 (t, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 7.2 Hz, 2H), 7.15 (m, 6H), 7.54 (t, *J* = 7.0 Hz, 2H), 8.05 (d, *J* = 7.9 Hz, 2H), 8.75 (d, *J* = 8.1 Hz, 2H), 11.00 (s, 2H); ^{13}C NMR ($CDCl_3$, ppm, 2 C's per signal): δ 20.0, 27.1, 32.5, 39.0, 64.8, 71.9, 111.8, 112.7, 115.0, 121.0, 122.7, 127.9, 128.5, 129.4, 130.5, 132.5, 135.3, 141.4, 142.2, 145.3, 156.8, 168.1, 172.2; MS: (EI, m/z): 730 (M^+), 378, 322, 218, 204, 177, 161, 105, 90, 77, 57. *Anal*. Calcd for $C_{44}H_{46}N_2O_8$ (730.84): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.28; H, 6.41; N, 3.78.

Acyclic Dimer 17

Compound **17** was obtained as a brown syrup, (5%); IR: 761, 1067, 1072, 1251, 1298, 1492, 1524, 1587, 1649, 1688, 2943, 2986, 3025, 3068, 3275, 3348 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): δ 3.75 (s, 4H), 4.74 (m, 8H), 5.36 (m, 4H), 6.12 (m, 4H), 6.95 (d, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 6.1 Hz, 2H), 7.29 (m, 6H), 7.80 (m, 6H), 8.00 (s, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 40.7, 66.1, 67.9, 69.5, 109.9, 111.1, 112.0, 112.4, 118.4, 118.7, 119.0, 120.8, 121.7, 122.0, 123.3, 123.4, 123.8, 124.1, 124.3, 124.7, 125.1, 125.4,

129.0, 129.1, 129.4, 129.5, 131.0, 131.1, 131.5, 131.9, 132.5, 132.6, 133.1, 138.5, 155.8, 156.7, 166.0, 166.3, 170.2, 179.3; MS: (EI, m/z): 674 (M^+), 617, 498, 350, 294, 177, 160, 146, 119, 105, 91, 77, 65.

Macrolactam 18

Compound **18** was obtained as yellow syrup, (10%); IR: 760, 956, 1162, 1526, 1586, 1610, 1658, 2846, 2927, 3013, 3078, 3348 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 1.97 (m, 2H), 2.23 (m, 2H), 4.56 (t, *J* = 5.6 Hz, 2H), 4.77 (d, *J* = 5.6 Hz, 2H), 5.71 (dt, *J* = 5.7, 15.7 Hz, 1H), 6.15 (dt, *J* = 6.7, 15.6 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.62 (dt, *J* = 1.6, 8.4 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 8.06 (dd, *J* = 1.4, 7.9 Hz, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 29.7, 39.0, 66.7, 69.1, 113.9, 115.7, 119.2, 119.7, 120.7, 123.1, 130.1, 131.4, 132.9, 133.1, 134.9, 136.7, 142.5, 159.4, 166.3, 167.6; MS: (EI, m/z): 337 (M^+), 293, 202, 177, 105, 91, 77. *Anal*. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.18; H, 5.41; N, 4.28.

Macrocyclic Dilactam 19

Compound **19** was obtained as brown syrup, (5%); IR: 789, 948, 1202, 1536, 1634, 1639, 2843, 2930, 3015, 3067, 3337 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 1.95 (q, *J* = 6.7 Hz, 4H), 2.80 (dt, *J* = 6.3, 6.6 Hz, 4H), 4.23 (t, *J* = 7.2 Hz, 4H), 4.67 (d, *J* = 5.6 Hz, 4H), 5.73 (dt, *J* = 5.9, 15.5 Hz, 2H), 5.91 (dt, *J* = 6.8, 15.5 Hz, 2H), 7.02 (dt, *J* = 1.0, 8.1 Hz, 2H), 7.09 (dd, *J* = 1.2, 8.8 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 2H), 7.43 (dt, *J* = 1.5, 8.6 Hz, 2H), 7.57 (m, 4H), 8.01 (dd, *J* = 1.4, 8.0 Hz, 2H), 8.73 (d, *J* = 7.9 Hz, 2H), 12.01 (s, 2H); ^{13}C NMR ($CDCl_3$, ppm): δ 21.1, 22.7, 23.7, 24.4, 28.1, 28.3, 28.5, 28.9, 31.6, 34.7, 60.4, 63.3, 63.6, 64.9, 68.7, 96.2, 104.9, 110.9, 113.4, 115.4, 116.2, 116.6, 119.2, 120.5, 122.6, 125.5, 129.7, 129.8, 130.2, 130.8, 131.1, 134.7, 136.4, 141.9, 150.5, 159.0, 165.5, 168.1, 168.6, 171.1; MS: (EI, m/z): 674 (M^+), 532, 413, 294, 174, 120, 104, 91.

Macrolactam 20

Compound **20** was isolated as a yellow syrup, (15%); IR: 749, 975, 1244, 1452, 1552, 1583, 1604, 1668, 1681, 1714, 2846, 2925, 3032, 3060, 3335, 3378 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ 2.00 (m, 2H), 2.43 (m, 2H), 2.80 (m, 2H), 3.10 (m, 2H), 4.50 (m, 2H), 4.70 (m, 1H), 4.90 (m, 1H), 5.70 (m, 1H), 6.00 (m, 1H), 6.90 (m, 2H), 7.25 (m, 2H), 7.37 (m, 1H), 7.55 (s, 1H), 7.68 (m, 1H), 8.10 (s, 1H), 8.40 (m, 1H); ^{13}C NMR ($CDCl_3$, ppm): δ 24.1, 27.0, 28.2, 29.7, 30.1, 36.9, 66.1, 71.8, 113.7, 115.8, 118.1, 121.2, 124.4, 124.9, 126.6, 128.2, 130.3, 133.5, 136.0, 137.9, 156.5, 166.3; MS: (EI, m/z): 365 (M^+), 202, 148, 119, 105, 91, 77. *Anal*. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.36; H, 6.29; N, 3.76.

ACKNOWLEDGEMENTS

The authors thank the College of Liberal Arts and Sciences of St. John's University for financial support.

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