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Sequential Staudinger Ketene−Imine Cycloaddition, RCM Approach to Highly Rigid Macrocrocyclic Bisazetidinones

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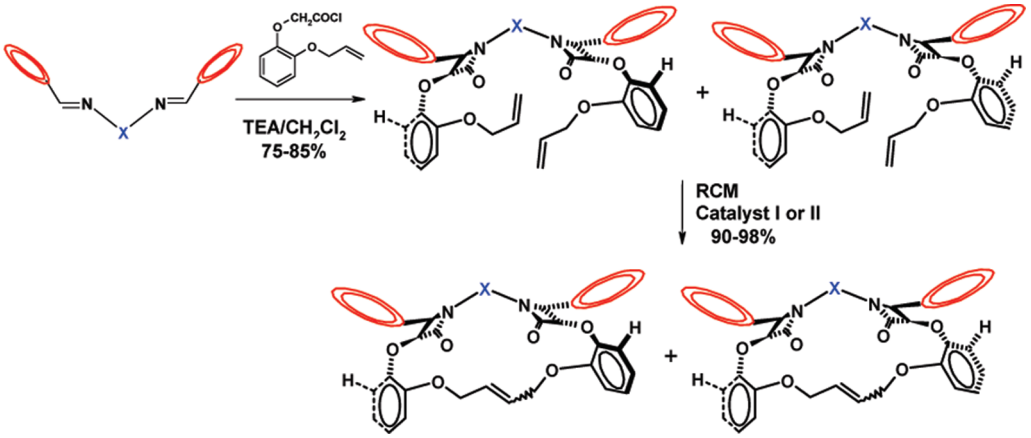

An efficient approach to highly rigid macrocyclic bisazetidinones with interesting structural feature was achieved via sequential Staudinger ketene−imine cycloaddition of *o*-allyloxyphenoxyketene and bis-arylidenediamines followed by RCM. The ketene−imine cycloaddition afforded the corresponding bis-*o*-allyloxyphenoxyazetidinones as the *cis-cis* diastereomers, exclusively obtained as a mixture of *cis-syn-cis* and *cis-anti-cis*. RCM of the latter using Grubbs' catalysts afforded good yields of the corresponding novel macrocyclic bisazetidinones. The *cis-anti-cis* bisazetidinones are readily identified by ^{1}H NMR using Eu(hfc)$_3$ chiral shift reagent. ^{1}H NMR indicated the high shielding effect of the aryl substituents on one of the *ortho*-H's of the condensed phenylene ring, and VT ^{1}H NMR indicates the highly restricted rotation of the aryl groups, thus offering a highly rigid system.

Introduction

Crown compounds, azacrown compounds, and crown ethers incorporating amide groups find many interesting applications in diverse fields of supramolecular chemistry.[1] During our recent interest in the synthesis of macrocyclic polyethers moiety, we and others successfully applied the ring-closing metathesis (RCM) technique to efficiently synthesize a large number of macrocycles of variable ring sizes.[1]

The Staudinger [2 + 2] ketene−imine cycloaddition reaction is considered as one of the most important synthetic approaches to β-lactams (2-azetidinones), which have important applications in pharmaceutical and synthetic chemistry.[2−4]

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(2) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51–123.

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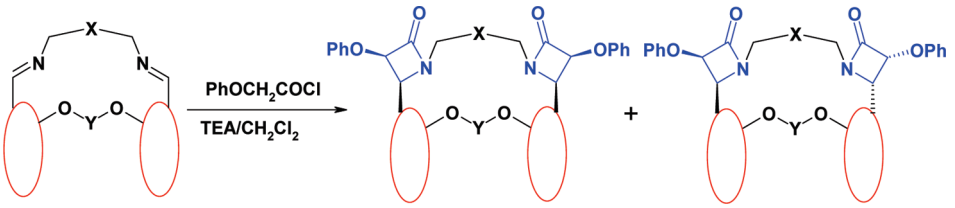
SCHEME 1



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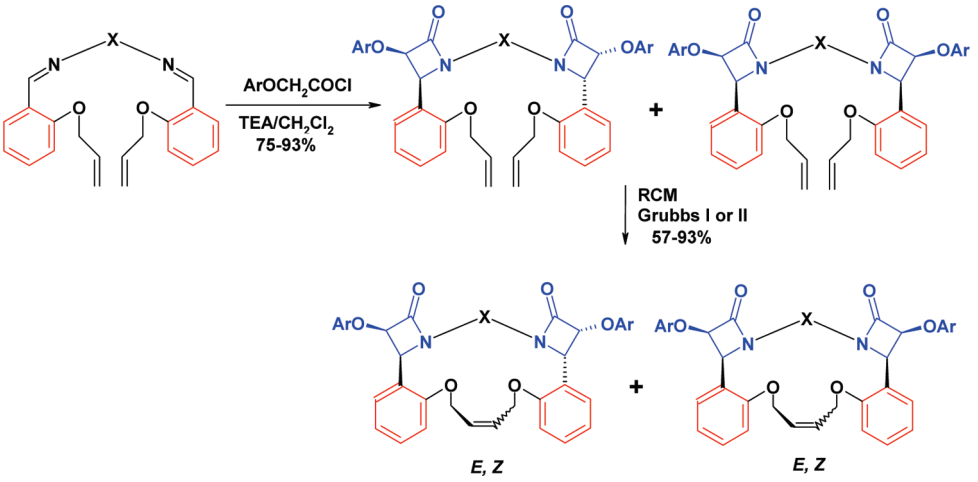

This reaction has been used to construct macrocyclic bisazetidinone polyethers by the reaction of the appropriate ketene precursors with macrocyclic diimines (Scheme 1).[4,5]

Recently, we reported the sequential application of Staudinger [2 + 2] ketene−imine cycloaddition followed by RCM to construct macrocyclic bisazetidinone polyethers (Scheme 2).[6] Subsequently the same procedure has then been applied for the synthesis of macrocyclic bisazetidinone polyethers incorporating ferrocene moiety inside the macrocycles.[7] Moreover, bis-β-lactams were macrocyclized via Cu-catalyzed alkyne−azide cycloadditions[8a] or via M−C or M−N (M = Pd or Pt) bonds.[8b]

The obtained macrocyclic bisazetidinones are potenial starting materials for the synthesis of highly functionalized macrocycles through the chemical transformation of the azetidinone ring moiety,[4] thus leading to macrocyclic crown compounds containing suitable functionalities of potential applications in supramolecular chemistry. This includes the transformation to macrocyclic azacrown ethers, macrocyclic bisamides, and macrocyclic β-aminoacids.[4,7]

Results and Discussion

In the present work we describe an alternative sequential application of Staudinger [2 + 2] ketene−imine cycloaddition followed by RCM reactions as a route to novel macrocyclic azacrown ethers incorporating the azetidinone ring fused to the macrocycle through the 1,3-positions of the azetidinone ring (Scheme 3). Thus, treatment of *N*,*N*′-bis-aryliden-1,2-ethanediamines **1a**, **2a**, **3a**, **4a**, and **5a** with *o*-allyloxyphenoxyacetyl chloride in CH_2Cl_2 in the presence of triethylamine gave a mixture of *cis-anti-cis* (*racemic*) **6a**, **7a**, **8a**, **9a**, and **10a** and *cis-syn-cis* (*meso*) **11a**, **12a**, **13a**, **14a**, and **15a** diastereomers. These stereoisomers were successfully separated by column chromatography. On the other hand, similar treatment of *N*,*N*′-bis-arylidene-3,6-dioxaoctane-1,8-diamines **1b**, **3b**, and **4b** gave inseparable mixtures of the corresponding *cis-anti-cis* (*racemic*) **6b**, **8b**, and **9b** and *cis-syn-cis* (*meso*) **11b**, **13b**, and **14b** diastereomers. Table 1 shows the diastereomeric ratio obtained and the characteristic ^{1}H and ^{13}C NMR signals of these novel acyclic isomeric bisazetidinone derivatives.

RCM of **6a**−**15a** was succefully achieved with Grubbs' catalyst I to give a mixture of the corresponding *E*,*Z* isomers at the olefinic double bond, which were readily characterized from their ^{1}H and ^{13}C NMR (Table 2, entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20). On the other hand RCM with Grubbs' catalyst II gave only the corresponding *E* isomers (Table 2, entries 1, 3, 5, 7, 9, 11, 13, 15, 17, 19). The *E*,*Z* isomers of the olefinic double bonds were readily assigned, and their ratios were determined from the ^{1}H NMR and ^{13}C NMR spectra. The *E* isomers show the characteristic ^{13}C signal of the OCH_2 (of the $OCH_2CH{=}CHCH_2O$) at frequency lower than that for the corresponding *Z* isomer (cf. the experimental data in Supporting Information).

Similar RCM results were obtained when the mixture of each of the enatiomers **6b**, **11b** and **8b**, **13b** and **9b**, **14b** were treated with either Grubbs' I or Grubbs' II catalysts. However, because of the complexity of the four products mixtures obtained in each case with Grubbs' I catalyst, results

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SCHEME 3

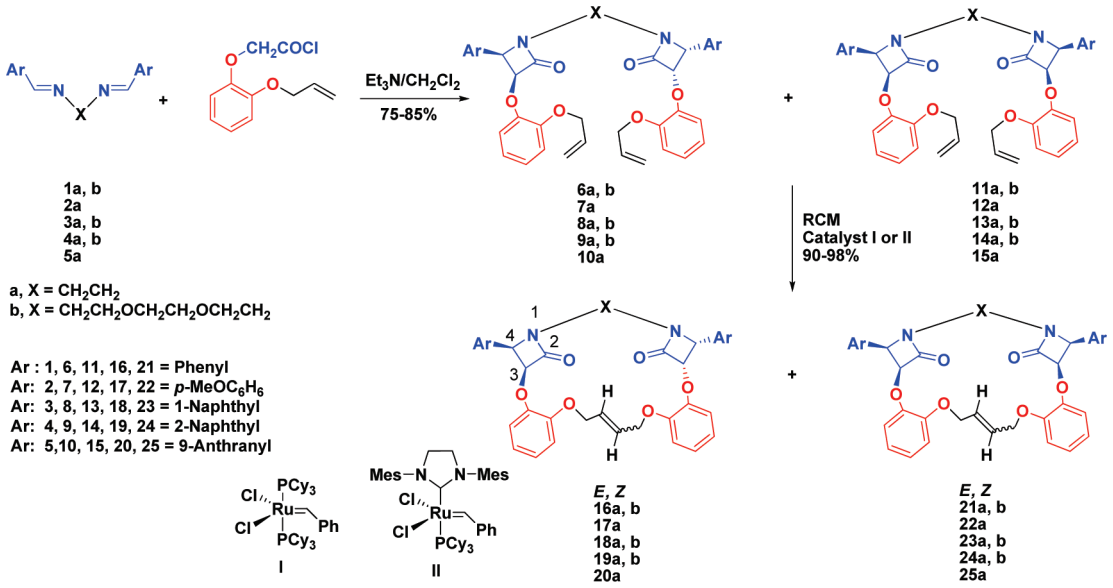

TABLE 1. Products 6−15 Obtained by the Reaction of *o*-Allyloxyphenoxyketene with 1−5[a]

entry	substrates	products	yield,[b] *anti*:*syn*	δ H3 (C3)	δ H4 (C4)
1	**1a**	**6a**	85%	5.44 (83.7)	5.20 (61.1)
		11a	47:53	5.26 (83.4)	4.77 (62.1)
2	**2a**	**7a**	80%	5.40 (83.6)	5.16 (60.8)
		12a	35:45	5.24 (83.4)	4.76 (61.6)
3	**3a**	**8a**	80%	5.71 (84.4)	6.08 (57.4)
		13a	50:50	5.03 (83.7)	5.51 (57.9)
4	**4a**	**9a**	75%	5.52 (83.9)	5.39 (61.4)
		14a	44:56	5.28 (83.6)	4.93 (62.3)
5	**5a**	**10a**	75%	5.96 (85.9)	6.89 (58.1)
		15a	40:35	4.79 (84.9)	5.65 (58.2)
6	**1b**	**6b**	75%	5.47 (83.4)	5.00 (63.0)
		11b	49:51	5.45 (83.3)	4.98 (63.0)
7	**3b**	**8b**	80%	5.71 (83.9)	5.79 (59.1)
		13b	45:55	5.57 (83.9)	5.64 (59.1)
8	**4b**	**9b**	85%	5.48 (83.43)	5.11 (63.1)
		14b	34:66	5.44 (83.40)	5.08 (63.1)

[a]Reaction conditions: substrate (1 mmol) in DCM (5 mL) was added to a solution of *o*-allyloxyphenoxyketene [prepared from *o*-allyloxyphenoxyacetyl chloride, (4 mmol)] at −78 °C and stirred overnight at room temperature (cf. the experimental data in Supporting Information). The crude product was separated (for entries 1−5) and purified as a mixture (for entries 6−8) by chromatography. [b]Yields were determined by ^{1}H NMR and agree with the isolated yields within ±5% (cf. the experimental data in Supporting Information).

obtained only from Grubbs' II catalyst were recorded in Table 3 and in the Experimental Section.

NMR of the Products. The *cis* stereochemistry of all of these new bis-β-lactams **6**−**15** and their corresponding macrocycles **16**−**25** were established on the basis of the azetidinones ^3J(H3,H4) coupling constant of 4.4−4.9 Hz as reported previously.[6,8,9] Generally, the H-3 signal of the azetidinone ring appears at lower frequency than the H-4 signal in all of the present new acyclic and macrocyclic derivatives except in cases of 1-naphthyl and 9-anthracenyl derivatives where the opposite occurs (Table 1, entries 3, 5, 7; Table 2, entries 9−12, 17−20; Table 3, entry 2). This is clearly attributed to the more anisotropic effect of the 1-naphthyl and 9-anthracenyl substituents. All H-3 and H-4 signals have been assigned on the basis of their cross correlation with their respective carbon signals in HSQC-NMR experiments where the C-3 signal appears at δ = 83−87 and the C-4 signal appears at δ = 59−64.

The ^{1}H NMR spectra of the *anti* isomers **6a**−**10a** and the corresponding *syn* isomers **11a**−**15a** showed the diastereotopic NCH_2CH_2N proton signals at two δ values. The $\Delta\delta$ in the former are larger ($\Delta\delta \approx 1$ except for **10a** $\Delta\delta$ = 1.34) than in the latter ($\Delta\delta \approx 0.6$ except for **15a** $\Delta\delta$ = 1.02). Similarly, all *anti* macrocycles isomers **16a**−**20a** whether *E* or *Z* showed the NCH_2CH_2N proton signals at two δ values with $\Delta\delta \approx 1.1$ except for **20a** with $\Delta\delta$ = 1.38, 1.34 for the *E* and *Z* isomers, respectively. On the other hand, the corresponding macrocyclic *syn* isomers **21a**−**25a** showed the NCH_2CH_2N proton signals at two δ values with $\Delta\delta \approx 0.34-0.7$ except for **25a** with $\Delta\delta$ = 1.30, 1.38 for *E* and *Z* isomers, respectively. Although these findings are characteristic for the *anti* and *syn* isomers in the present study, they are opposite to what has been reported recently by Pellico et al.[8a] In addition to our previous work[6] this $\Delta\delta$ of the diastereotopic NCH_2 signals cannot be taken as a generalization for assigning the *anti* and *syn* bis-azetidinones. Additionally in all of the *cis-anti-cis* the two diastereotopic NCH_2 signals have significantly different appearance than the *cis-syn-cis* derivatives (cf. Figure 1 and ^{1}H NMR spectra in Supporting Information).

As reported previously,[6] the chiral shift reagent Eu(hfc)$_3$ was used to confirm the assignment of the *cis-anti-cis* and *cis-syn-cis* isomers of compounds **6a** and **11a** from NMR spectral analysis. The two methylene CH_2N bridge and azetidinone H-3 and H-4 proton signals appear at δ 2.85,

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TABLE 2. RCM Products of 6a−15a with Grubbs' I and Grubbs' II Catalysts[a]

			δ H3 (C3)		δ H4 (C4)		^{1}H NMR of Z/E product ArH[c]	
entry	substrate product	yield,[b] Z:E ratio	Z	E	Z	E	Z	E
1	**6a**	97%		5.78		5.07		5.49
	16a	0:1		85.1		61.4		
2	**6a**	98%	5.41	5.78	5.05	5.07	5.86	5.49
	16a	1:4.9	85.6	85.1	61.3	61.4		
3	**11a**	98%		5.77		4.98		6.29
	21a	0:1		84.4		63.3		
4	**11a**	98%	5.60	5.77	4.96	4.98	6.48	6.29
	21a	1:7.3	84.3	84.4	63.2	63.3		
5	**7a**	98%		5.72		5.01		5.63
	17d	0:1		85.0		60.9		
6	**7a**	97%	5.39	5.72	4.98	5.01	5.94	5.63
	17d	1:2.7	85.5	85.0	60.8	60.9		
7	**12a**	97%		5.73		4.97		6.35
	22a	0:1		84.3		62.8		
8	**12a**	90%	5.54	5.73	4.93	4.97	6.50	6.35
	22a	1:3.0	84.2	84.3	62.7	62.8		
9	**8a**	92%		5.97		6.11		4.95
	18a	0:1		85.8		58.5		
10	**8a**	90%	5.76	5.97	5.94	6.11	5.43	4.95
	18a	1:2.8	86.2	85.8	58.2	58.5		
11	**13a**	97%		5.84		6.05		5.92
	23a	0:1		85.1		59.70		
12	**13a**	98%	5.82	5.84	5.90	6.05	6.07	5.92
	23a	1:4.3	85.0	85.1	59.74	59.70		
13	**9a**	96%		5.89		5.26		5.43
	19a	0:1		85.4		63.5		
14	**9a**	97%	5.53	5.89	5.23	5.26	5.84	5.43
	19a	1:3.8	85.8	85.4	61.55	61.62		
15	**14a**	97%		5.86		5.19		6.26
	24a	0:1		84.71		63.5		
16	**14a**	97%	5.68	5.86	5.19	5.19	6.47	6.26
	24a	1:6.7	84.74	84.71	63.4	63.5		
17	**10a**	98%		6.33		6.66		5.01
	20a	0:1		86.8		59.4		
18	**10a**	98%	6.02	6.33	6.66	6.66	5.54	5.01
	20a	1:2.6	87.1	86.8	58.9	59.4		
19	**15a**	95%		6.22		6.58		6.05
	25a	0:1		86.5		60.6		
20	**15a**	95%	6.35	6.22	6.68	6.58	6.03	6.05
	25a	1:6.6	86.8	86.5	59.4	60.6		

[a]Reaction conditions: substrate (0.03 mmol) in DCM (10 mL) and Grubbs' II (1.2 mg, 5 mol % for entries 1, 3, 5, 7, 9, 11, 13, 15, 17, 19) or Grubbs' I (1.3 mg, 5 mol % for entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20) were heated under reflux for 1 h. [b]Identified from their characteristic ^{1}H NMR; with Grubbs' II, only the *E* isomers were obtained in 90−98% yield. Yields were determined by ^{1}H NMR and agree with the isolated yields within ±5% (cf. the experimental data in Supporting Information). [c]This ArH is the highest frequency proton signals ortho to the azetidinone ring of the condensed benzene ring.

TABLE 3. RCM Product of 6b, 11b, 8b, 13b, 9b, 14b with Grubbs' II Catalyst[a]

				NMR of products		
entry	substrate (*anti*:*syn*)	product	yield,[b] *anti*:*syn*	δ H3 (C3)	δ H4 (C4)	δ $OCH_2\underline{CH}=$
1	**6b**, **11b** (49:51)	**16b**	95%, 49:51	5.07	5.48	5.86
				84.5	63.2	
		21b		5.07	5.51	5.85
				84.3	63.1	
2	**8b**, **13b** (45:55)	**18b**	90%, 47:53	5.84	5.93	5.88
				85.1	59.8	
		23b		5.90	5.93	6.00
				84.8	59.1	
3	**9b**, **14b** (34:66)	**19b**	80%, 53:47	5.25	5.55	5.56
				83.8	63.3	
		24b		5.28	5.60	5.68
				84.8	63.5	

[a]Reaction conditions: substrate (0.03 mmol) in DCM (10 mL) and Grubbs' II (1.2 mg, 5 mol %) were heated under reflux for 1 h. [b]Only *E* isomers were formed under these conditions as identified from their characteristic ^{1}H NMR. Yields were determined by ^{1}H NMR and agree with the isolated yields within ±5% (cf. the experimental data in Supporting Information).

3.84, 5.20, 5.44, respectively, in the ^{1}H NMR spectrum of the *anti* isomer **6a** (see Supporting Information). After the addition of the chiral shift reagent the two signals of the diastereotopic methylene (CH_2N) bridge and azetidinone H-3 and H-4 proton signals shifted to lower frequency, and each proton signal splits resulting in eight signals at δ 2.97, 3.02, 4.01, 4.09, 5.47, 5.45, 5.71, and 5.77, which confirms that **6a** is a racemic mixture. As for compound **11a**, after the addition of the chiral shift reagent the two H-3 and H-4 proton signals of the azetidinone appear at δ 4.77 and 5.26 shifted to lower frequency without splitting, which indicates that **11a** is the *meso* isomer.

Another significant difference between the *syn* and the *anti* isomers is that one of the aromatic proton signals appears at high frequency at δ 5.49 for the *anti* isomer **16a** and shows at δ 6.29 for the *syn* isomer **21a** (See Figure 1). This is due to the diamagnetic anisotropic shielding caused by the phenyl ring alignment to the aromatic proton in the macrocyclic system of the *anti* isomer **16a**. NOE-difference spectroscopy confirmed further the assignment of this high-frequency aromatic proton signal. Thus, irradiation of this proton enhanced the two *ortho* phenyl proton signals in compounds ***E*-16a** and ***E*-17a** (cf. Supporting Information). Replacing the phenyl ring in the azetidinone system by a 1-naphthyl or 9-anthracenyl ring in *anti* isomers **18a**, **20a** increases the diamagnetic anisotropic shielding effect, which resulted in further shielding of the aromatic proton to δ 4.95, 5.01, respectively (Table 2, entries 9, 17, Figure 1). The 2-naphthyl derivatives do not affect markedly the position of this high frequency aromatic proton signal.

Interestingly, the aromatic proton signal of the macrocyclic *anti Z* isomers are shifted to lower frequency compared to their *anti E* isomer counterparts (Table 2). Apparently these systems are highly rigid as evidenced from the ^{1}H NMR experiments preformed at different temperatures in pyridine-d_6 for the *anti* isomer **16a** (see Supporting Information). At 298 K the aromatic proton signal in the macrocyclic system shows at δ 5.87, upon increasing the temperature to 378.4 K the aromatic proton signal shifted to lower frequency at δ 6.09. When the temperature was lowered to 232.5 K, the proton signal shifted to high frequency at δ 5.69. The differences in aromatic proton signal shift of approximately ±0.2 ppm from the experiment carried out at room temperature indicate that there is no significant conformational rearrangement in the macrocyclic system. It also indicates that there is some flexibility in the phenyl ring rotation, which may be only swinging. At higher temperature this swinging has a larger amplitude so that, on average, its position for an effective shielding is somewhat diluted.

On subjecting the anthracenyl derivative ***E*-20a** to cycloaddition reaction with *N*-phenylmaleimide, an almost quantitative yield of the corresponding cycloadduct **26** was obtained. The ^{1}H NMR of **26** shows the high frequency

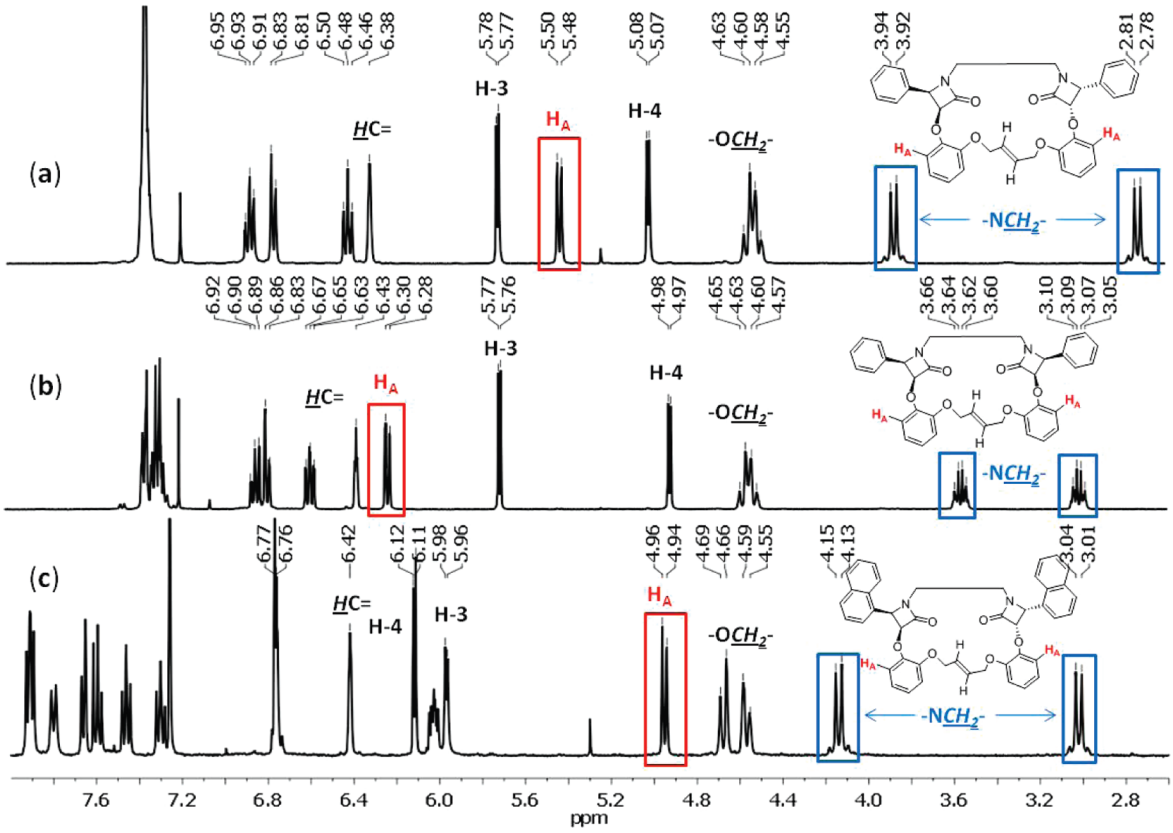
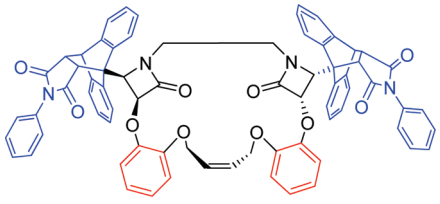


FIGURE 1. ^{1}H NMR (400 MHz, $CDCl_3$) spectra: (a) *cis-anti-cis* isomer of compound **16a**; (b) *cis-syn-cis* isomer of compound **21a**; (c) *cis-anti-cis* isomer of compound **18a**.

aromatic proton signal at δ 5.16, which has not been affected significantly by such structural modification.



26

Conclusion

The present study offers alternative synthetic routes toward macrocyclic azacrown ethers condensed with bisazetidinones via bridgehead (ring junction) nitrogens through the sequential application of Staudinger [2 + 2] ketene−imine cycloaddition followed by RCM reactions in an overall yield of these two steps amounting to 83%. The new macrocyclic bisazetidinones were proved to be conformationaly rigid systems and also are not expected to be efficiently otherwise accessible using other synthetic approaches.

Experimental Section

The starting compounds **1a**,[10] **2a**,[10] **3a**,[11] **4a**,[11] **5a**,[12] **1b**,[13] **3b**,[13] **4b**,[14] and *o*-allyloxyphenol[1e] were prepared as reported in the literature. Cycloaddition of *N*-phenylmaleimide and ***E*-20a** were done following literature procedure.[15]

Synthesis of *β*-Lactams 6−15 by Staudinger Reaction: General Procedure. A solution of *o*-allyloxyphenoxyacetyl chloride (4 mmol) in dry CH_2Cl_2 (5 mL) was purged with nitrogen and cooled to −78 °C, and then a solution of Et_3N (8 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise with a syringe. The mixture was stirred for 30 min, and a solution of the corresponding diimine **1**−**5** (1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 2 h. The reaction mixture was then stirred overnight at room temperature. The organic layer was washed with water and Na_2CO_3 solution (10%) until no effervescence and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The crude product was separated or purified by chromatography. All *anti* products **6a**, **7a**, **8a**, **9a**, and **10a** were readily separated from their corresponding *syn* isomers **11a**, **12a**, **13a**, **14a**, and **15a**.

Compound 6a. Yield 0.30 g (40%); yellow oil, R_f = 0.36 (pet. ether/EtOAc 2:1). MS: m/z = 616 (M^+, 5%). IR: 3065, 3033, 2973, 2925, 1755, 1499, 1455, 1406, 1354, 1256, 1209, 747, 700. ^{1}H NMR ($CDCl_3$): δ 2.85 (d, 2H, J 11.0), 3.84 (d, 2H, J 11.0), 4.30 (dt, 4H, J 5.2, 1.5), 5.13 (ddd, 2H, J 10.5, 2.8, 1.5), 5.20 (d, 2H, J 4.8), 5.22 (ddd, 2H, J 17.2, 3.2, 1.5), 5.44 (d, 2H, J 4.8), 5.88 (m, 2H), 6.74 (m, 6H), 6.83 (m, 2H), 7.31 (m, 6H), 7.38 (dd, 4H, J 8.0, 1.6). ^{13}C NMR ($CDCl_3$): δ 37.2, 61.1, 69.8, 83.7, 115.2, 116.9, 117.1, 121.2, 122.8, 128.3, 128.4, 128.5, 133.1, 133.2,

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147.1, 148.4, 167.3. ^{15}N NMR ($CDCl_3$): δ 139.6. HRMS = 616.2565 ($C_{38}H_{36}N_2O_6$ requires 616.2567).

Compound 11a. Yield 0.33 g (45%); colorless crystals, mp 149 °C, R_f = 0.23 (pet. Ether/EtOAc 2:1). MS: m/z = 616 (M^+, 5%). IR: 3065, 3034, 2984, 2922, 2860, 1759, 1500, 1455, 1407, 1357, 1258, 1212, 744, 702. ^{1}H NMR ($CDCl_3$): δ 3.10 (m 2H), 3.71 (m, 2H), 4.30 (dt, 4H, J 5.1, 1.6), 4.77 (d, 2H, J 4.6), 5.15 (ddd, 2H, J 10.6, 2.8, 1.6), 5.21 (ddd, 2H, J 17.2, 3.2, 1.6), 5.26 (d, 2H, J 4.6), 5.87 (m, 2H), 6.66 (dd, 2H, J 8.5, 1.6), 6.75 (m, 4H), 6.84 (dt, 2H, J 1.5, 7.2), 7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 37.9, 62.1, 70.0, 83.4, 115.4, 117.1, 117.2, 121.3, 123.0, 128.5, 128.6, 128.9, 133.0, 133.3, 147.2, 148.5, 166.4. ^{15}N NMR ($CDCl_3$): δ 139.3. HRMS = 616.2567 ($C_{38}H_{36}N_2O_6$ requires 616.2567).

General Procedures of the RCM. (Condition A) To a solution of each of the appropriate β-lactams **6**−**15** (0.03 mmol) in DCM (10 mL) was added Grubb's catalyst II (1.2 mg, 5 mol %). The reaction mixture was heated under reflux for 1 h, the solvent was removed in vacuo, and the product was purified by column chromatography with eluent DCM/pet. ether (60−80)/EtOAc to give the corresponding E isomers **16**−**25**. (Condition B) To a solution of each of the appropriate β-lactams **6**−**15** (0.03 mmol) in DCM (10 mL) was added Grubb's catalyst I (1.2 mg, 5 mol %). The reaction mixture was heated under reflux for 1 h, the solvent was removed in vacuo, and the product was purified by column chromatography with eluent DCM/pet. ether (60−80)/EtOAc to give mixture of the coresponding E and Z isomer. ^{1}H NMR and ^{13}C NMR data of the Z isomer were extracted from the mixed spectra by comparison with the pure E isomer.

Compound 16a-*E*. Yield 0.57 g (97%) (Condition A), 0.48 g (83%) (Condition B), colorless oil, R_f = 0.41 (DCM/pet. ether/EtOAc 1:1:1). MS: m/z = 588 (M^+, 25%). HRMS = 588.2253 ($C_{36}H_{32}N_2O_6$ requires 588.2254). IR: 3061, 3029, 2926, 2852, 1764, 1751, 1597, 1496, 1453, 1410, 1257, 1213, 1114, 1040, 745, 700. ^{1}H NMR ($CDCl_3$): δ 2.80 (d, 2H, J 11.2), 3.93 (d, 2H, J 11.2), 4.56 (d, 2H, J 10.8), 4.61 (d, 2H, J 10.8), 5.07 (d, 2H, J 4.5), 5.49 (dd, 2H, J 7.9, 1.6), 5.78 (d, 2H, J 4.5), 6.38 (t, 2H, J 2.4), 6.48 (td, 2H, J 7.7, 1.4), 6.83 (dd, 2H, 8.1, 1.3), 6.93 (td, 2H, J 7.6, 1.6), 7.43 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 37.4, 61.4, 67.6, 85.1, 112.4, 120.4, 122.9, 124.8, 127.4, 128.5, 128.7(2C), 134.2, 145.1, 150.4, 168.0. ^{15}N NMR ($CDCl_3$): δ 138.5.

Compound 16a-*Z*. Formed in 17% as mixture with **4a-*E*** (Condition B), ^{1}H NMR ($CDCl_3$): δ 2.78 (d, 2H, J 10.8), 3.88 (d, 2H, J 10.8), 4.70 (d, 2H, J 9.6), 4.74 (d, 2H, J 9.6), 5.05 (d, 2H, J 4.6), 5.41 (d, 2H, J 4.6), 5.86 (dd, 2H, J 7.8, 1.6), 6.22 (t, 2H, J 4.7), 6.58 (td, 2H, J 7.6, 1.3), 6.90 (dd, 2H, J 8.0, 1.3), 6.98 (td, 2H, J 7.8, 1.6), 7.41 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 36.8, 61.3, 62.2, 85.6, 112.6, 120.7, 122.8, 124.9, 128.2, 128.3, 128.5, 128.7, 131.2, 146.2, 150.0, 167.7.

Compound 21a-*E*. Yield 0.58 g (98%) (Condition **A**), 0.52 g (88%) (Condition **B**), colorless oil, R_f = 0.46 (DCM/pet. ether/EtOAc 1:1:1). MS: m/z = 588 (M^+, 25%). HRMS = 588.2254 ($C_{36}H_{32}N_2O_6$ requires 588.2254). IR: 3064, 2957, 2928, 2860, 1762, 1729, 1497, 1460, 1381, 1272, 1124, 1072, 745, 702. ^{1}H NMR ($CDCl_3$): δ 3.10 (m, 2H), 3.63 (m, 2H), 4.63 (m, 4H), 4.98 (d, 2H, J 4.6), 5.77 (d, 2H, J 4.6), 6.29 (dd, 2H, J 8.0, 1.5), 6.44 (t, 2H, J 2.5), 6.65 (td, 2H, J 7.7, 1.5), 6.85 (dd, 2H, J 8.2, 1.7), 6.90 (td, 2H, J 8.0, 1.5), 7.31−7.38 (m, 6H), 7.42 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 38.9, 63.3, 68.4, 84.4, 113.8, 120.1, 121.1, 123.7, 128.1, 128.4, 128.7, 128.8, 133.7, 146.4, 149.2, 167.3. ^{15}N NMR ($CDCl_3$): δ 138.6.

Compound 21a-*Z*. Formed in 12% with **21a-*E*** (Condition **B**), ^{1}H NMR ($CDCl_3$): δ 3.16 (m, 2H), 3.50 (m, 2H), 4.73 (dd, 2H, J 11.0, 4.3), 4.76 (dd, 2H, J 11.0, 4.3), 4.96 (d, 2H, J 4.8), 5.60 (d, 2H, J 4.8), 6.18 (t, 2H, J 4.3), 6.48 (dd, 2H, J 8.2, 1.6), 6.71 (td, 2H, J 7.8, 2.0), 6.90 (dd, 2H, J 8.0, 1.5), 6.92 (td, 2H, J 7.8, 2.0), 7.31−7.38 (m, 6H), 7.42 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 38.8, 63.2, 64.4, 84.3, 114.8, 119.8, 121.5, 123.8, 128.3, 128.5, 128.8, 128.9, 134.3, 147.1, 149.2, 167.0.

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Supporting Information Available: General experimental methods and full experimental details for all reactions; characterization data for all products; ^{1}H NMR (600 MHz, $CDCl_3$) spectra of *cis-anti-cis* compound **6a** (*racemic*) and *cis-syn-cis* compound **11a** (*meso*) (a) before addition of chiral shift reagent, Eu(hfc)$_3$ and (b) after addition of chiral shift reagent, Eu(hfc)$_3$; ^{1}H, ^{13}C NMR and ^{15}N full spectral assignment of **6a** and **11a** and copies of ^{1}H NMR and ^{13}C NMR spectra and some representative 2D NMR. This material is available free of charge via the Internet at http://pubs.acs.org.