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Staudinger Ketene−Imine Cycloaddition, RCM Approach to Macrocrocyclic Bisazetidinones

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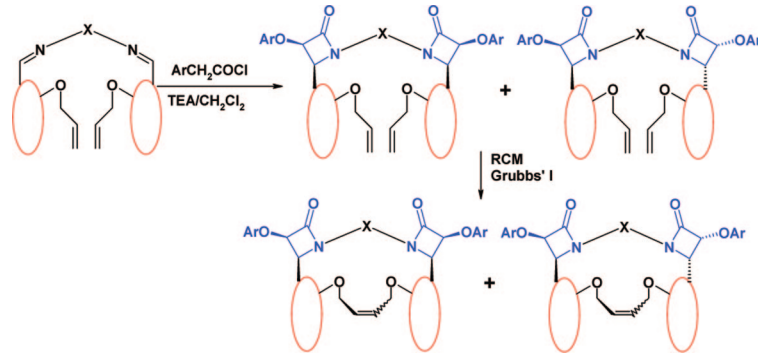

Application of Staudinger ketene−imine cycloaddition reaction to bis-*o*-allyloxyarylideneamines afforded the corresponding bisallyloxyazetidinones as the *cis-cis* diastereomers, exclusively obtained as a mixture of *cis-syn-cis* and *cis-anti-cis*. RCM of the latter using Grubbs' catalysts afforded the corresponding macrocyclic bisazetidinones in good yields. The *cis-anti-cis* bisazetidinones are readily identified by ^{1}H NMR using Eu(hfc)$_3$ chiral shift reagent.

Introduction

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 application in pharmaceutical and synthetic chemistry.[1−3] Recently, 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] 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 aza-crown ethers, macrocyclic bisamides, and macrocyclic β-amino acids.[4]

Crown compounds, aza-crown compounds, and crown ethers incorporating amide groups find many interesting applications in diverse fields of supramolecular chemistry.[6] During our recent studies of the synthesis of macrocyclic polyether moiety, we and others successfully applied the RCM technique to efficiently synthesize a large number of macrocycles of variable ring sizes.[6]

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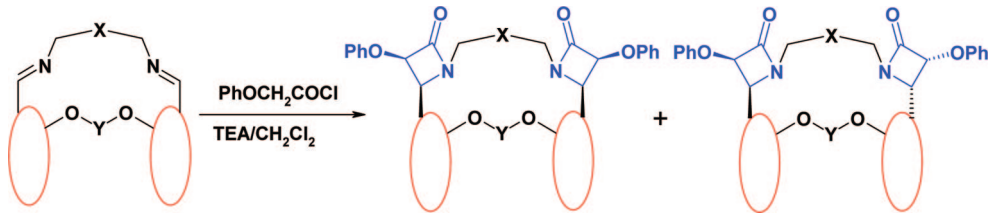
SCHEME 1



SCHEME 2

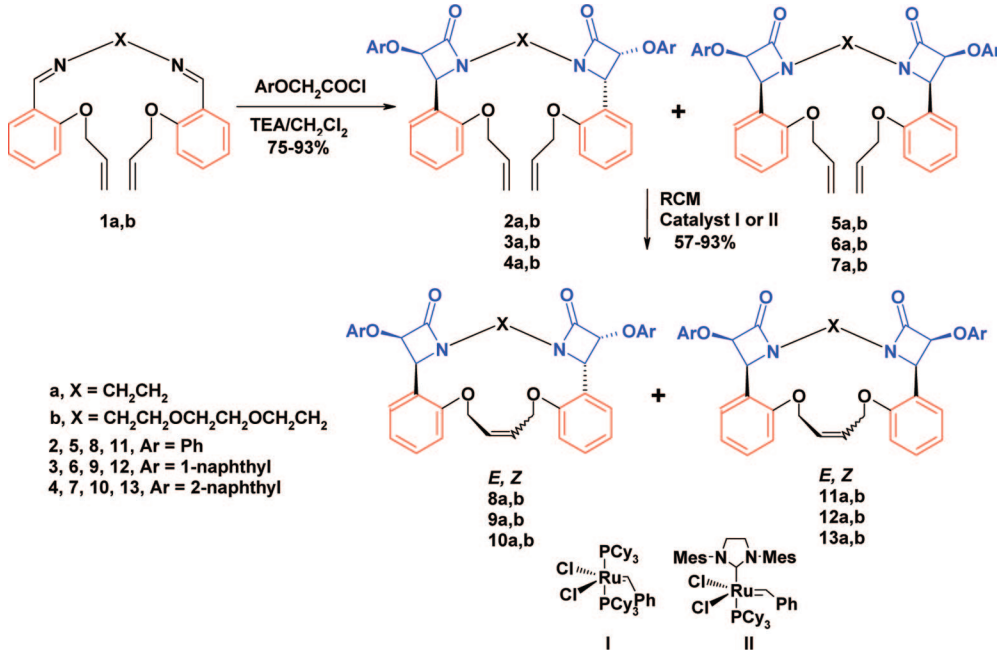


TABLE 1. Ketene−Imine Cycloaddition Products, Isolated Yield, Ratio of Anti and Syn, and Characteristic Azetidinone ^{1}H and ^{13}C NMR Signals

substrates	products	yield (%), anti/syn	δ H^3 (C^3)	δ H^4 (C^4)	J (H^3, H^4)
1a + PhOCH$_2$COCl	**2a**, **5a**	85, 53:47	5.51 (82.5), 5.32 (81.9)	5.84 (55.5), 5.44 (55.8)	4.4, 4.2
1a + α-NaphOCH$_2$COCl	**3a**, **6a**	91, 51:49	5.74 (82.8), 5.50 (82.4)	5.95 (55.6), 5.54 (56.1)	4.4, 4.6
1a + β-NaphOCH$_2$COCl	**4a**, **7a**	93, 51:49	5.68 (82.4), 5.48 (82.0)	5.98 (55.4), 5.58 (55.8)	4.4, 4.4
1b + PhOCH$_2$COCl	**2b**, **5b**	75, 52:48	5.44 (81.8), 5.41 (81.8)	5.58 (56.6), 5.57 (56.6)	4.2, 4.8
1b + α-NaphOCH$_2$COCl	**3b**, **6b**	90, 50:50	5.65 (82.1), 5.62 (82.1)	5.68 (56.9), 5.67 (56.9)	4.8, 4.8
1b + β-NaphOCH$_2$COCl	**4b**, **7b**	80, 50:50	5.60 (82.0), 5.57 (81.9)	5.71 (56.7), 5.71 (56.7)	4.2, 4.2

Results and Discussion

In the present work, we describe the sequential application of Staudinger 2 + 2 ketene−imine cycloaddition followed by RCM reactions as a route to functionalized macrocycles of possible use as starting materials for further functionalization of macrocyclic aza-crown ethers (Scheme 2). Thus, treatment of 1,2-bis-*o*-allyloxybenzylideneamines **1a**,**b** with aryloxyacetyl chloride in CH_2Cl_2 in the presence of triethylamine gave a mixture of *cis-anti-cis* (*racemic*) **2a**,**b**, **3a**,**b**, and **4a**,**b** and *cis-syn-cis* (*meso*) **5a**,**b**, **6a**,**b**, and **7a**,**b** diastereomers. These two isomers were separated by chromatography for all products isolated from **1a**. However, the isomeric mixtures synthesized from **1b** could not be isolated and were used as such in the next RCM reactions. 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 **2a** was investigated using each of Grubbs' catalysts **I** and **II** in dichloromethane at reflux. Table 2 shows the results obtained using different ratios of catalysts **I** and **II**. With catalyst **I** (1%), the reaction proceeds for 1 h and stops to give 32% of the product **8a** as an *E*/*Z* mixture. Increasing the ratio of **I** to 2%, 3%, 4%, and 5% led to an increased yield of the RCM products to 60%, 73%, 83%, and 98%, respectively, as an *E*/*Z* (70−83:30−17) mixture (Table 2). On the other hand, similar

TABLE 2. RCM of 2a with Different Ratios of Grubbs' Catalysts I and II

entry	substrate/catalyst (%)	yield (%) (*Z*/*E*)[a]
1	**2a**/**I** (1)	32 (30:70)
2	**2a**/**I** (2)	60 (27:73)
3	**2a**/**I** (3)	72 (25:75)
4	**2a**/**I** (4)	83 (23:77)
5	**2a**/**I** (5)	98 (17:83)
6	**2a**/**II** (1)	67 (30:70)
7	**2a**/**II** (2)	72 (21:79)
8	**2a**/**II** (3)	75 (24:76)
9	**2a**/**II** (4)	88 (18:82)

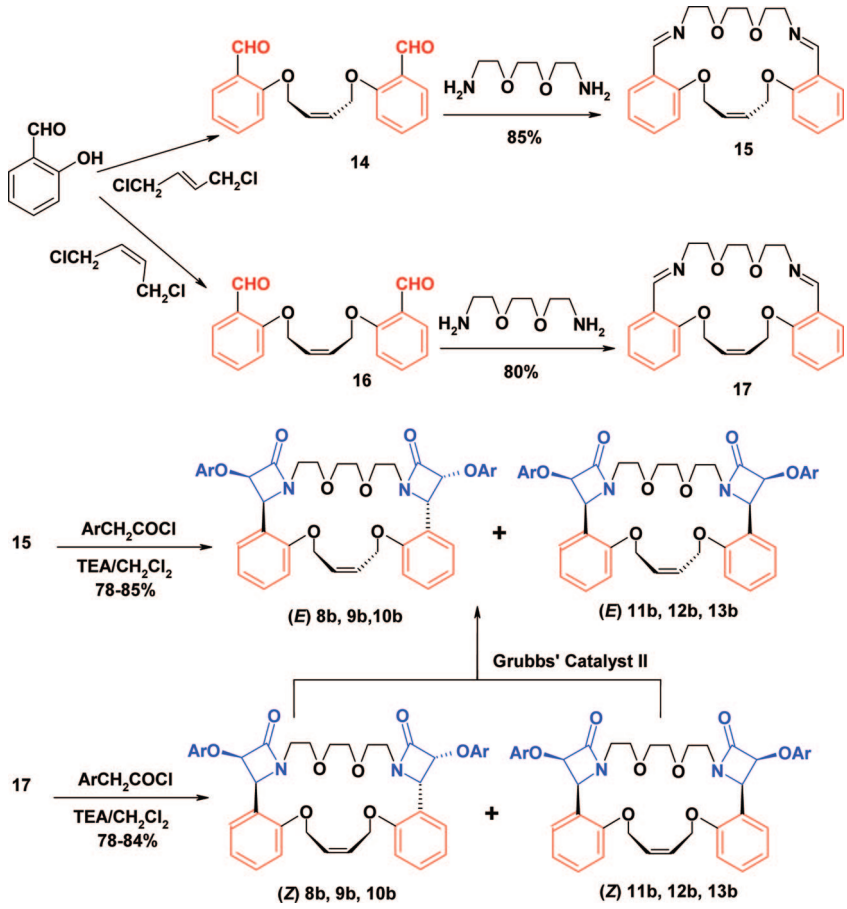
[a] No more product was detected after 1−2 h, and the remaining percent is a recovered unreacted starting material **2a**. Yield of product, percent of unreacted **2a**, and *E*/*Z* ratio were determined by ^{1}H NMR.

TABLE 3. RCM Products, Yield, Ratio of *Z* and *E* Isomers, and Characteristic ^{1}H, ^{13}C NMR of Azetidinones and ^{1}H NMR of CH=

			δ H^3/C^3		δ H^4/C^4		^{1}H NMR OCH$_2$C*H*=	
entry[a]	substrate/ product	yield (%), *Z*/*E* ratio	*Z*	*E*	*Z*	*E*	*Z*	*E*
1	**2a/8a**	98, 1:5	4.73/81.4	5.17/81.5	5.42/56.0	5.36/55.7	6.18	5.97
2	**5a/11a**	98, 1:5	5.44/81.8	5.43/81.9	5.56/55.7	5.48/55.8	6.08	5.98
3	**3a/9a**	95, 1:3.85	4.92/81.5	5.35/81.6	5.56/55.9	5.50/55.9	6.19	6.02
4	**6a/12a**	98, 1:4.17	5.32/82.1	5.59/82.1	5.68/55.7	5.65/56.0	6.08	5.97
5	**4a/10a**	57, 1:2.94	4.85/81.4	5.32/81.5	5.54/56.1	5.48/55.7	6.33	6.01
6	**7a/13a**	60, 1:1.56	5.67/81.6	5.61/81.9	5.76/55.7	5.65/55.8	6.32	6.02
7[b]	**2b/8b**	82, 1:1.72	5.39/82.1	5.45/82.0	5.59/56.8	5.69/56.2	5.95	6.17
	5b/11b	1:1.89	5.48/82.1	5.48/82.1	5.68/56.6	5.70/56.6	5.87	6.08
8[b]	**3b/9b**	80, 1:2.17	5.55/82.3	5.54/82.2	5.66/56.8	5.67/56.2	5.89	5.97
	6b/12b	1:1.54	5.65/82.4	5.56/82.3	5.74/56.6	5.68/56.6	5.81	5.91
9[b]	**4b/10b**	75, 1:1.79	5.45/82.0	5.60/81.9	5.62/56.7	5.83/56.3	5.63	6.21
	7b/13b	1:1.4	5.45/82.1	5.63/82.1	5.62/56.5	5.85/56.5	5.63	6.09

[a] Reaction conditions: substrate (0.03 mmol) in DCM (10 mL) and catalyst **I** (1.2 mg, 5 mol % for entries 1−9) or **II** (1.3 mg, 5 mol % for entries 10−12) were heated under reflux for 1 h. [b] Identified from their characteristic ^{1}H NMR and compared with their samples prepared as shown in Scheme 3; with catalyst **II**, only the *E* isomers were obtained in 90−94% yield. Yields were determined by ^{1}H NMR and agree with the isolated yields within ±5% (cf. the experimental data in the Supporting Information).

SCHEME 3



RCM of **2a** with different ratios (1−4%) of catalyst **II** was found to lead to the formation of the corresponding product **8a** in 67−88% yield with a better *trans* stereoselectivity (*E*/*Z* ≈ 80:20 ratio) (Table 2), after which the catalyst showed no further activity and the remainder was unreacted starting material **2a**.

From the results obtained in Table 2, RCM reactions of the other derivatives **2**−**7** were successfully accomplished to give 57−98% yields of the corresponding macrocycles **8**−**13** using catalyst **I** (5%) (Scheme 2). Table 3 illustrates the RCM products obtained by Grubbs' catalyst **I** together with *Z*/*E* ratio of the formed double bond and the characteristic ^{1}H and ^{13}C NMR of the azetidinone ring and olefinic protons. Interestingly, RCM of **2b**−**7b** with Grubbs' catalyst **II** (5%) led to complete disappearance of the starting materials and formation of the corresponding 22 membered macrocyclic bisazetidinones **8b**−**13b** in over 90% yield with only *E* stereochemistry.

The stereochemistry of the formed ethylenic double bond in the RCM reaction was proved by preparing samples of **8b**, **9b**, **10b**, **11b**, **12b**, and **13b** by the reaction sequence illustrated in Scheme 3. Thus, reacting (*E*)-1,4-bis(*o*-formylphenoxy)-2-butene **14** with 1,8-diamino-3,6-dioxaoctane gave the corresponding macrocyclic (*E*)-bisimine **15**. The latter was reacted

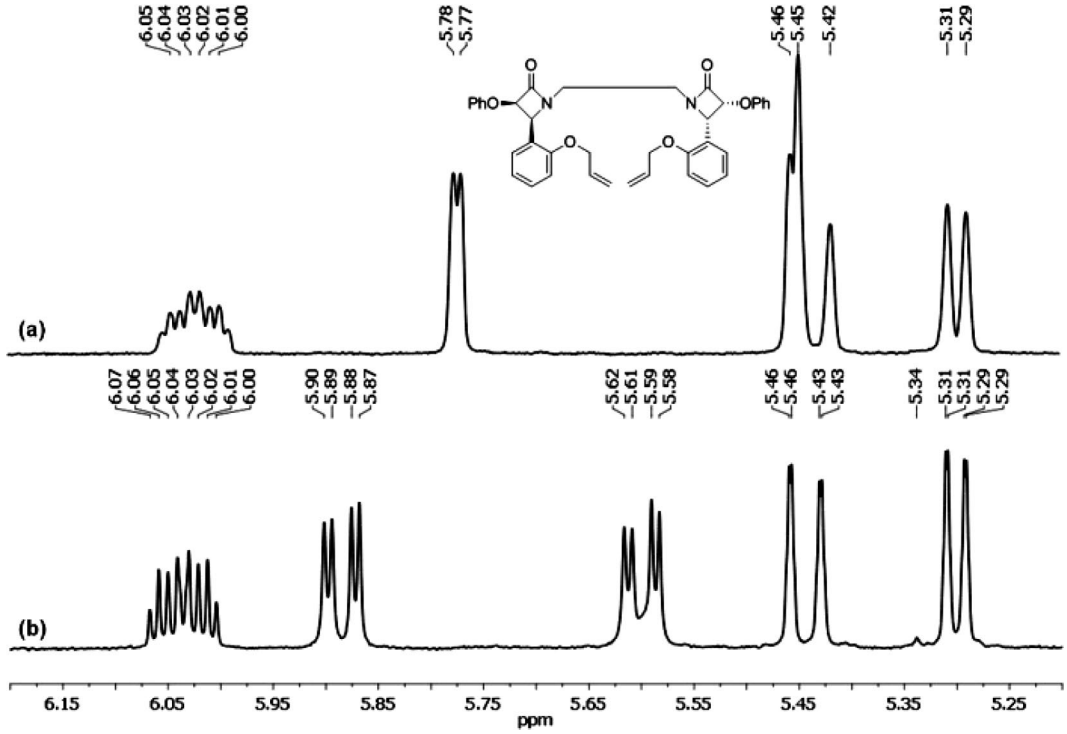


FIGURE 1. ^{1}H NMR (600 MHz, $CDCl_3$) spectra of *cis-anti-cis* compound **2a** (*racemic*): (a) before and (b) after addition of chiral shift reagent $Eu(hfc)_3$.

TABLE 4. Isomerization of *Z*-8b, *Z*-11b into *E*-8b, *E*-11b

entry[a]	catalyst (%)	overall yield (%) (***E*-8b**:***E*-11b**)
1	I (1)	0
2	II (1)	54 (29:25)
3	II (3)	95 (52:48)

[a] A solution of ***Z*-8b**, **Z-11b** mixture (0.03 mmol) in DCM (10 mL) and Grubb's catalyst (1−3 mol %) was heated under reflux for 1 h (no change in yield or percent distribution of all isomers after this time).

with the appropriate aryloxyketene generated in the reaction medium from the corresponding aryloxyacetyl chloride to give a mixture of the corresponding *anti-E*-bisazetidinones **8b**, **9b**, and **10b** together with their corresponding *syn-E*-isomers **11b**, **12b**, and **13b**, respectively. The corresponding *Z*-isomers were also prepared by reacting (*Z*)-1,4-bis(*o*-formylphenoxy)-2-butene **16** with 1,8-diamino-3,6-dioxaoctane to give the corresponding macrocyclic (*Z*)-bisimine **17**. Reaction of the latter with the appropriate aryloxyketene gave a mixture of the corresponding *anti*-(*Z*)-bisazetidinones **8b**, **9b**, and **10b** together with their corresponding *syn-Z*-isomers **11b**, **12b**, and **13b**, respectively (Scheme 3). The ***Z*-8b** and ***Z*-11b** isomers were readily isomerized to the corresponding ***E*-8b** and ***E*-11b** isomers upon refluxing in CH_2Cl_2 with Grubbs' catalyst **II**. This isomerization was complete using 3 mol % of the catalyst; however, using 1 mol % of the catalyst led only to 54% isomerization.

Attempted isomerization of the *Z* isomeric mixture **8b**, **11b** to the *E* isomers using Grubbs' catalyst **I** failed and led to complete recovery of the starting *Z*-isomers (Table 4). Similar observations were reported[6h] and were attributed to the higher tolerance of Grubbs' catalyst **II** to the steric effect of substituted alkenes. It was also observed during this isomerization reaction that the ratio of the *anti* isomer increases more in the product than in the reactant. Since this isomerization involves ring-opening/ring-closing metathesis, it is clear that the ring closure of the *anti* isomer is more favorable than that of the *syn* isomer for stereochemical reasons. Presumably, some of the *syn* isomers lead to the formation of polymer instead of the corresponding macrocycles, thus leading to loss of their relative abundances in the product mixture.

The structure and stereochemistry of **2a**, **5a**, **8a**, and **11a** were fully assigned using different NMR techniques (cf. the Supporting Information). It is found that azetidinone H-3 and H-4 appear more upfield in the *syn* (*meso*) isomer **5a** than in the corresponding *anti* isomer **2a**; in addition, the methylene CH_2N protons appear as two doublets for the *anti* isomer **2a** and as two multiplets for the *syn* isomer **5a**. To confirm the assignment of the *cis-anti-cis* and *cis-syn-cis* isomers (**2a**, **5a**) by NMR spectral analysis, a chiral shift reagent [$Eu(hfc)_3$] was added. ^{1}H NMR spectra for both isomers **2a** and **5a** before and after addition of $Eu(hfc)_3$ are shown in Figures 1 and 2. The azetidinone protons H-3 and H-4 of compound **2a** are shown as doublets at 5.45 and 5.77 ppm (Figure 1a); after the addition of the chiral shift reagent, the two protons are shifted downfield and each proton split into a doublet, resulting in four doublets at 5.58, 5.61, 5.87, and 5.89 ppm (Figure 1b), which confirms that the *cis-anti-cis* isomer **2a** is a racemic mixture. For compound **5a**, the two doublets at 5.29 and 5.42 ppm for the azetidinone protons H-3 and H-4 (Figure 2a) appeared downfield at 5.63 and 5.63 ppm after the addition of the chiral shift reagent without further splitting (Figure 2b), which indicates that *cis-syn-cis* **5a** is the *meso* isomer. The results are in agreement with the reported NMR data for acyclic bisazetidinones prepared from bisbenzylideneaminoethane where the stereochemistry is confirmed by X-ray crystallography.[7]

The opposite occurs with the corresponding macrocyclic bisazetidinones **8a** and **11a**, where H-3 and H-4 appear more downfield in the *syn* (*meso*) isomer **11a** than in the corresponding

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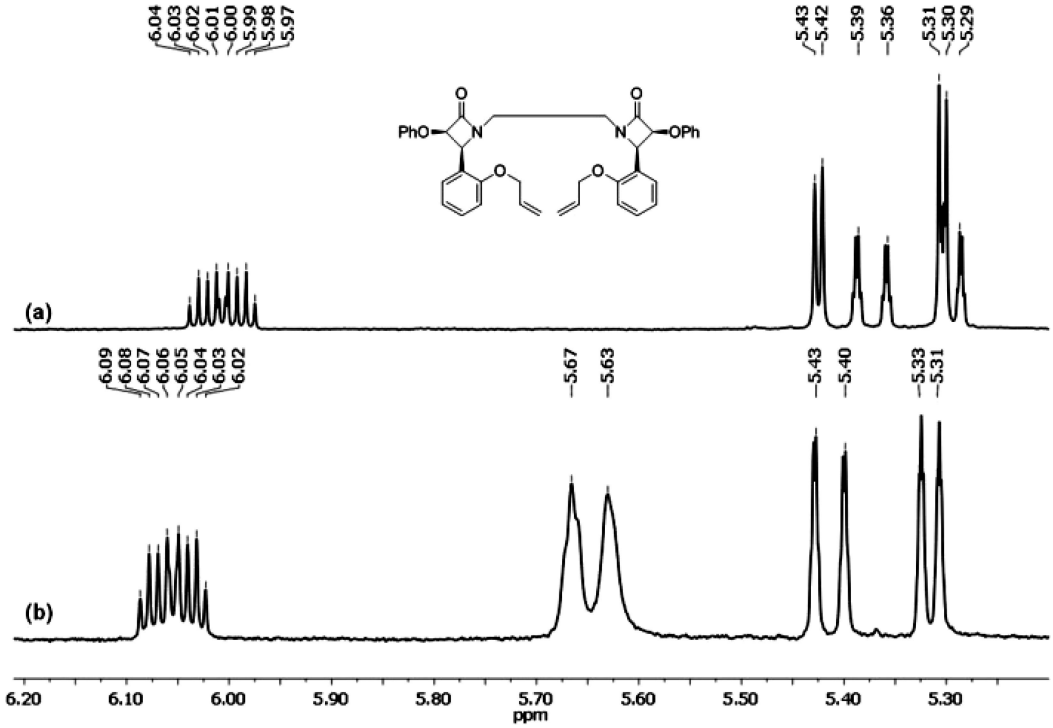

FIGURE 2. ^{1}H NMR (600 MHz, $CDCl_3$) spectra of *cis-syn-cis* compound **5a** (*meso*): (a) before and (b) after addition of chiral shift reagent $Eu(hfc)_3$.

anti isomer **8a**; in addition, the methylene CH_2N protons appear as two doublets for the *anti* isomer **8a** and as two multiplets for the *syn* isomer **11a**. Similar splitting of the racemic mixture of the macrocycle **8a** with the chiral shift reagent was observed (cf. the Supporting Information). Again, this is in agreement with the reported NMR data for cyclic bisazetidinones where the stereochemistry has been proved by X-ray crystallography.[4,5]

Conclusion

The present study offers synthetic routes toward macrocyclic aza-crown 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%, while the other approach in which the macrocyclic bis-imines **15** and **17** were prepared followed by Staudinger [2 + 2] ketene−imine cycloaddition gave the corresponding macrocyclic bisazetidinones **8b**−**13b** in an overall yield of these two steps amounting to 71%. Comparison of these two approaches clearly indicates that the Staudinger−RCM approach gave overall comparable or better yield of the desired macrocyclic bisazetidinones. Moreover, attempts to prepare the precursor cyclic bis-imines with X = CH_2CH_2 by reacting **14** and **16** with 1,2-ethylenediamine was completely impossible due to the formation of polymeric gummy material, which is a further advantage of the RCM technique. These macrocyclic bisazetidinones are potential starting materials useful for further functionalization of macrocyclic aza-crown ethers.

Experimental Section

Synthesis of β-Lactams 2−7 by Staudinger Reaction: General Procedure. A solution of aryloxyacetyl chloride (4 mmol) in dry CH_2Cl_2 (5 mL) was purged with nitrogen and cooled to 0 °C, and then a solution of triethylamine (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 **1a**,**b**, **15**, and **17** (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 occurred and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude product was separated by chromatography. All *anti* products **2a**, **3a**, **4a** were readily separated from their corresponding *syn* isomers **5a**, **6a**, **7a**. The other *anti and syn* isomers could not be separated and were identified as a mixture of each of these two isomers where ^{1}H NMR is almost completely identical except for the azetidinones ring, which is assigned for each isomer.

Compound 2a. Yield: 0.28 g (45%). Colorless crystals. Mp: 130−132 °C. R_f = 0.54 (petroleum ether/EtOAc 1:1). MS *m*/*z* = 616 (M^+, 5). IR: 3067, 3040, 2969, 2929, 1759, 1600, 1590, 1494, 1415, 1353, 12407, 1231, 1055, 1002, 926, 752, 691. ^{1}H NMR ($CDCl_3$): δ 2.90 (d, 2H, *J* 11.4), 3.90 (d, 2H, *J* 10.8), 4.34 (dd, 2H, *J* 13.2, 4.8), 4.50 (dd, 2H, *J* 13.2, 4.8), 5.34 (dd, 2H, *J* 10.8, 1.2), 5.48 (dd, 2H, *J* 17.7, 1.2), 5.51 (d, 2H, *J* 4.4), 5.84 (d, 2H, *J* 4.4), 6.06 (m, 2H), 6.73 (d, 2H, *J* 8.4), 6.80 (d, 4H, *J* 7.8), 6.87 (t, 2H, *J* 7.2), 6.94 (t, 2H, *J* 7.8), 7.11 (t, 4H, *J* 7.2), 7.20 (dt, 2H, *J* 7.8, 1.2), 7.32 (dd, 2H, *J* 7.8, 1.2). ^{13}C NMR ($CDCl_3$): δ 37.9, 55.5, 68.7, 82.5, 111.4, 115.6, 117.4, 120.4, 121.4, 121.7, 127.9, 128.9, 129.4, 133.0, 156.9, 157.0, 167.4. HRMS = 616.2568 ($C_{38}H_{36}N_2O_6$ requires 616.2567).

Compound 5a. Yield: 0.25 g (40%). Yellow oil. R_f = 0.39 (petroleum ether/EtOAc 1:1). MS: *m*/*z* = 616 (M^+, 5). IR: 3068, 3015, 2917, 2850, 1761, 1599, 1590, 1493, 1455, 1408, 1357, 1291, 1238, 997, 753, 691. ^{1}H NMR ($CDCl_3$): δ 3.11 (m, 2H), 3.85 (m, 2H), 4.28 (ddt, 2H, *J* 12.6, 5.4, 1.2), 4.44 (ddt, 2H, *J* 12.6, 5.4, 1.8), 5.29 (ddd, 2H, *J* 10.2, 2.0, 1.2), 5.32 (d, 2H, *J* 4.2), 5.38 (ddd, 2H, *J* 17.4, 2.4, 1.2), 5.44 (d, 2H, *J* 4.2), 6.00 (m, 2H), 6.71 (m, 6H), 6.86 (t, 2H, *J* 7.2), 6.98 (t, 2H, *J* 7.8), 7.09 (dt, 4H, *J* 7.2, 1.8), 7.22 (dt, 2H, *J* 8.4, 1.8), 7.30 (dd, 2H, *J* 7.8, 1.8). ^{13}C NMR ($CDCl_3$): δ 37.7, 55.8, 68.5, 81.9, 111.3, 115.2, 117.4, 120.4, 120.5, 121.5, 128.1, 128.7, 129.4, 132.7, 156.5, 156.6, 166.0. HRMS = 616.2568 ($C_{38}H_{36}N_2O_6$ requires 616.2567).

General Procedures of the RCM. To a solution of the appropriate β-lactam **2**−**7** (1 mmol) in DCM (10 mL) was added Grubbs' catalyst **I** or **II** (mol % indicated in Tables 2 and 3). The reaction mixture was heated under reflux (for the time indicated in Tables 2 and 3), and the solvent was removed in vacuo and the product was purified by column chromatography with eluent DCM/petroleum ether (60−80)/EtOAc.

Compound 8a. Yield: 0.56 g (95%) isolated as *cis*/*trans* (8:92) mixture after column chromatography [of RCM reaction with Grubbs' **I** (5 mol %)] as colorless crystals. Mp 123−125 °C. R_f = 0.61 (DCM/petroleum 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: 3065, 3041, 2922, 2853, 1764, 1599, 1590, 1492, 1456, 1404, 1355, 1237, 912, 752, 734. ***trans*-8a.** ^{1}H NMR ($CDCl_3$): δ 3.06 (d, 2H, *J* 9.6), 3.58 (d, 2H, *J* 9.6), 4.58 (dd, 2H, *J* 11.0, 2.8), 4.71 (dd, 2H, *J* 11.0, 2.8), 5.17 (d, 2H, *J* 4.6), 5.36 (d, 2H, *J* 4.6), 5.96 (t, 2H, *J* 2.8), 6.70 (d, 4H, *J* 7.8), 6.86 (m, 4H), 7.00 (t, 2H, *J* 7.2), 7.11 (m, 4H), 7.22 (td, 2H, *J* 8.4, 1.2), 7.39 (dd, 2H, *J* 7.8, 1.2). ***trans*-8a.** ^{13}C NMR ($CDCl_3$): δ 39.1, 55.7, 68.4, 81.5, 114.7, 115.3, 121.6, 121.7, 122.6, 129.1, 129.3, 129.75, 129.9, 156.6, 156.9, 166.6. ***cis*-8a.** ^{1}H NMR ($CDCl_3$): δ 3.32 (d, 2H, *J* 13.0), 3.73 (d, 2H, *J* 13.0), 4.63 (dd, 2H, *J* 11.0, 4.0), 4.67 (dd, 2H, *J* 11.0, 4.0), 4.73 (d, 2H, *J* 4.6), 5.42 (d, 2H, *J* 4.6), 6.18 (t, 2H, *J* 4.0), 6.64 (d, 4H, *J* 7.8), 6.86 (m, 4H), 7.06 (t, 2H, *J* 7.3), 7.12 (m, 4H), 7.27 (td, 2H, *J* 8.0, 2.0), 7.35 (dd, 2H, *J* 7.7, 1.6). ***cis*-8a.** ^{13}C NMR ($CDCl_3$): δ 39.4, 56.0, 64.6, 81.4, 111.9, 115.5, 121.4, 121.68, 121.8, 128.9, 129.2, 129.6, 129.8, 156.5, 156.7, 166.3.

Compound 11a. Yield: 0.55 g (94%) isolated as *cis/trans* (11:89) mixture after column chromatography [of RCM reaction with Grubbs' **I** (5 mol %)] as white crystals. Mp: 123−125 °C. R_f = 0.69 (DCM/petroleum ether/EtOAc 1:1:1). MS: m/z = 588 (M^+, 25). HRMS = 588.2256 ($C_{36}H_{32}N_2O_6$ requires 588.2261). IR: 3063, 3013, 2926, 1771, 1599, 1493, 1456, 1406, 1360, 1236, 1047, 866, 752, 690. ***trans*-11a.** ^{1}H NMR ($CDCl_3$): δ 2.95 (m, 2H), 3.78 (m, 2H), 4.62 (d, 2H, *J* 14.0), 4.75 (d, 2H, *J* 14.0), 5.43 (d, 2H, *J* 4.5), 5.48 (d, 2H, *J* 4.5), 5.95 (s, 2H), 6.78 (m, 6H), 6.89 (m, 4H), 7.15 (m, 6H), 7.28 (dd, 2H, *J* 7.6, 1.6). ***trans*-11a.** ^{13}C NMR ($CDCl_3$): δ 38.2, 55.8, 68.6, 81.9, 114.4, 115.5, 121.4, 121.9, 122.1, 128.9, 129.1, 129.4, 129.7, 156.6, 157.0, 166.2. ***cis*-11a.** ^{1}H NMR ($CDCl_3$): δ 2.93 (m, 2H), 3.97 (m, 2H), 4.46 (dd, 2H, *J* 10.4, 5.6), 4.64 (dd, 2H, *J* 10.4, 5.6), 5.44 (d, 2H, *J* 4.5), 5.56 (d, 2H, *J* 4.5), 6.22 (t, 2H, *J* 5.6), 6.78 (m, 6H), 6.89 (m, 4H), 7.15 (m, 6H), 7.28 (dd, 2H, *J* 7.6, 1.6). ***cis*-11a.** ^{13}C NMR ($CDCl_3$): δ 38.0, 55.7, 63.6, 81.8, 112.3, 115.6, 121.1, 121.6, 121.7, 128.8, 129.0, 129.8, 130.7, 156.9, 157.2, 166.5.

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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 **8a** (*racemic*) (a) before and (b) after addition of chiral shift reagent Eu(hfc)$_3$; ^{1}H, ^{13}C NMR, and ^{15}N full spectral assignment of **2a**, **5a**, **8a**, and **11a** and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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