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Three-Step Metal-Promoted Allene-Based Preparation of Bis(heterocyclic) Cyclophanes from Carbonyl Compounds

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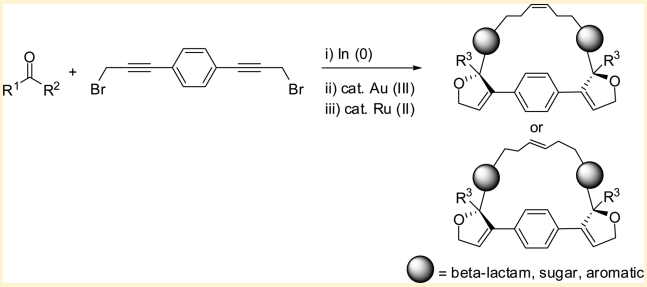
Supporting Information

ABSTRACT: A straightforward metal-mediated method for the synthesis of bis(dihydrofuryl) cyclophane scaffolds from carbonyl compounds has been developed. The combination of the dihydrofuran moiety with different heterocycles such as β-lactams and sugars allows high levels of skeletal diversity. The process comprises indium-promoted one-pot carbonyl bis(allenylation) and gold- or palladium-catalyzed double cyclization in the resulting bis(allenols), followed by selective ruthenium-catalyzed macrocyclization. In some cases, the method has been successfully applied to the synthesis of the challenging *Z*-isomers. The *E*- versus *Z*-stereochemistry of the metathesis-formed double bonds could not be assigned taking into consideration the usual coupling constants criteria, but a diagnostic based on the chemical shifts of the two olefinic protons located at the macrocyclic double bond was established.



INTRODUCTION

Allenes are a class of compounds with two cumulative carbon−carbon double bonds, which are versatile synthetic intermediates in organic synthesis.[1] In particular, bis(allenols) have recently emerged as useful building blocks.[2] On the other hand, metal-mediated reactions for constructing carbon−carbon bonds through addition of propargyl halides to carbonyl compounds have been the subject of a number of investigations over the past two decades, by virtue of its synthetic usefulness and mechanistic intrigue.[3] The reaction of propargyl bromides with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics,[4] which often results in poor regioselection in the final organic product, because both organometallic species can react with the carbonyl compound. Thus, an important synthetic goal is to tune the regioselectivity toward either acetylenic or allenic products.[5] Although many efforts have been made in these fields for various types of propargyl bromides, the direct preparation of bis(allenols) through one-pot carbonyl bis(allenylation) has not been reported yet.[6] The synthetic advantages of organometallic reactions in aqueous media are due to the fact that many reactive functional groups, such as hydroxy, amine, and carboxylic functions, do not require the protection−deprotection protocol, and many water-soluble compounds do not need to be converted into their derivatives. Besides, the unique reactivity and selectivity of these processes that are not often attained under dry conditions make them profitable in many cases.[7] Because indium has emerged as the metal of choice to mediate a high number of transformations in aqueous media, due to its environmentally benign properties allied with a high degree of chemo-, regio-, and diastereoselectivity,[8] we decided to pursue direct indium-mediated carbonyl bis(allenylation) for the preparation of bis(allenols) and their double gold-catalyzed cyclization to functionalized bis(dihydrofurans). Macrocyclic entities are essential components of various types of bioactive synthetic and natural products.[9] Ring-closing metathesis (RCM) has become a powerful tool for the construction of a variety of cyclic structures, including macrocycles.[10,11] In connection with our current research interest in the area of allenes and metals, we wish to describe herein a simple and versatile approach to produce heterocyclic macrocycles possessing two additional dihydrofurans in their structure. Our approach relies on a sequential bis(allenylation)/bis(oxycyclization) followed by an RCM reaction that allows the construction of macrocycles. The combination of the dihydrofuran moiety with different heterocycles such as β-lactams and sugars allows high levels of skeletal diversity.

RESULTS AND DISCUSSION

First, 1,4-bis(3-bromoprop-1-ynyl)benzene **1** (1.0 mmol) was treated with 2-(allyloxy)benzaldehyde **2a** (2.0 mmol) in the presence of indium in THF/H_2O (1:1), leading to the bis(allenol) **3a** in 51% yield as a single regioisomer but as an inseparable syn/anti mixture (1:1). No signal for methylene protons was detected, indicating that no homopropargylic

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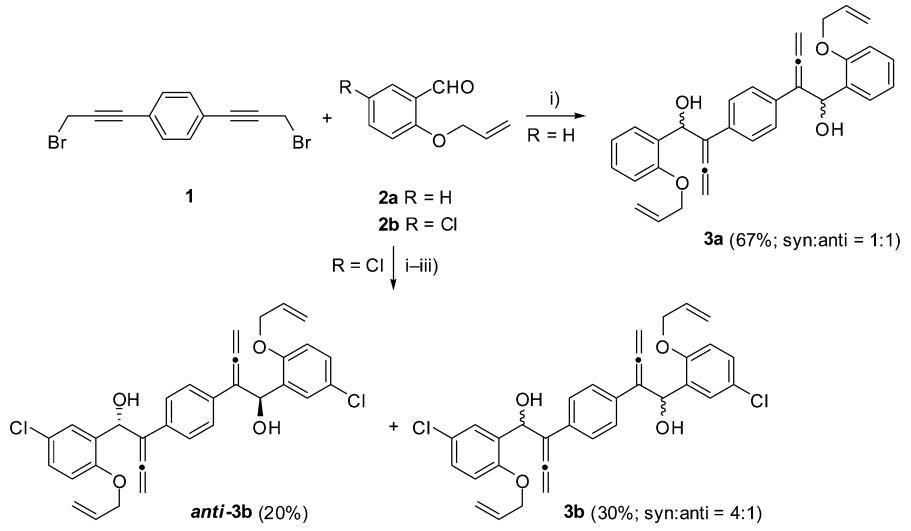
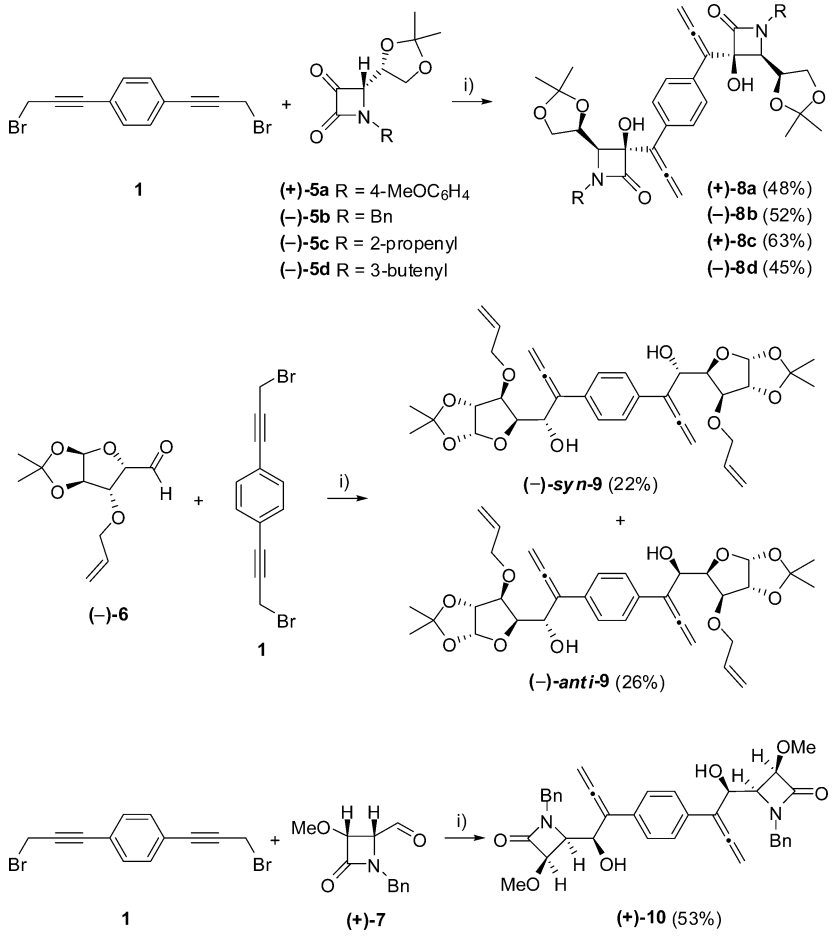
Scheme 1. Indium-Promoted Controlled Bis(allenylation) Reaction of Aromatic Aldehydes[a]



[a]Conditions: (i) In, THF/NH_4Cl (aq. sat.) (1:5), rt; **3a**: 24 h; **3b**: 72 h. (ii) 2-(4-Chlorophenoxy)acetyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; then fractional crystallization. (iii) MeONa, MeOH, 0 °C, 30 min.

Scheme 2. Indium-Promoted Controlled Bis(allenylation) Reaction of Enantiopure Aldehydes[a]



[a]Conditions: (i) In, THF/NH_4Cl (aq. sat.) (1:5), rt; **8a**: 24 h; **8b**: 72 h; **8c**: 24 h; **8d**: 48 h; **9**: 24 h; **10**: 24 h. PMP = 4-$MeOC_6H_4$.

alcohol was observed in this case. Worthy of note, no detectable reaction was observed in anhydrous THF. Several attempts to improve the yield of the bis(allenylation) reaction using dibromide **1** in aqueous media, including addition of additives ($InCl_3$, $HfCl_4$, $BiCl_3$, and AgTfO), were unsuccessful. Fortunatelly, the ionic strength enhancement of the reaction solvent provided by the addition of ammonium chloride resulted in an improved 67% yield for **3a** (Scheme 1). This

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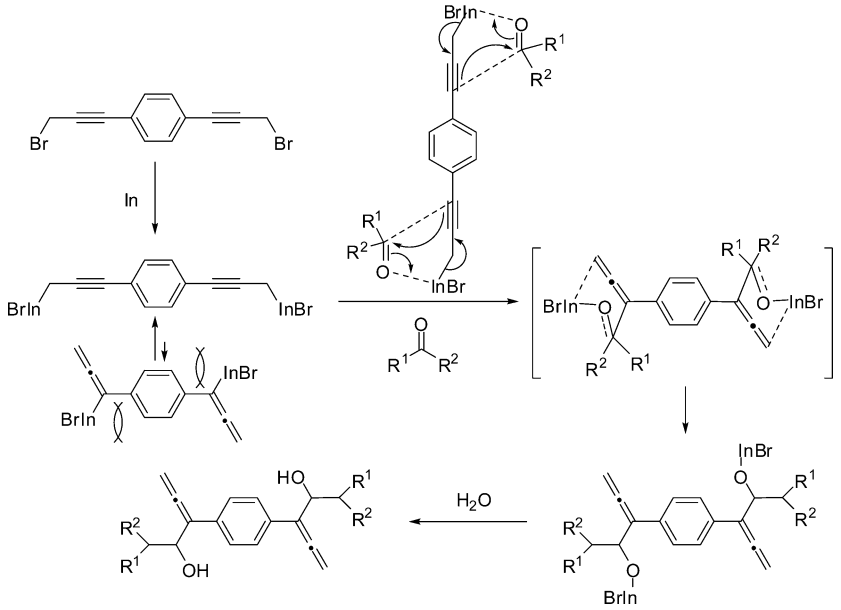
Scheme 3. Possible Pathway for the Indium-Promoted Bis(allenylation) Reaction of Carbonyls



practical preparation encouraged us to investigate the additions of dibromide **1** to various aldehydes and ketones. Consequently, the direct bis(allenylation) reaction of 2-(allyloxy)-5-chlorobenzaldehyde **2b** was conducted in the solvent system THF/NH_4Cl (aq. sat.) (1:5).[12] The result in Scheme 1 shows that the indium-mediated reaction is a good method for the regioselective addition of bis(propargyl bromide) **1** to aromatic aldehyde **2b**, affording adducts **3b** with complete regioselectivity. Despite the poor diastereoselectivity, adduct *anti*-**3b** was obtained as a diastereomerically pure product after fractional crystallization of its bis(4-chlorophenoxy)acetate *anti*-**4**. The simplicity of the proton and carbon NMR spectra of adducts **3** points to their symmetrical nature.

The structure and stereochemistry of adduct *anti*-**3b** was unambiguously assigned through the X-ray structure of its bis(4-chlorophenoxy)acetate **4** (Figure S1, see the Supporting Information).[13]

We were particularly interested in probing the degree of reagent versus substrate regio- and stereocontrol in such reactions with relevant classes of nonracemic aliphatic carbonyl compounds. Thus, we evaluated the feasibility of the indium-mediated Barbier-type carbonyl bis(allenylation) reactions of azetidine-2,3-diones **5a−d**, tetrahydrofuro[3,2-*d*][1,3]dioxole-5-carbaldehyde **6**, and 4-oxoazetidine-2-carbaldehyde **7** in eco-friendly media, studying the diastereochemistry (syn vs anti) and the regiochemistry of the connection (e.g., allenylation vs propargylation). The regioselectivity was totally in favor of the bis(cumulene) moiety. It was found that for α-keto lactams **5** these bis(additions) proceed with full diastereoselectivity (Scheme 2), because the group at C4 was able to control the stereochemistry of the new C3-substituted C3-hydroxy quaternary center in bis(allenes) **8a−d**. Bis(allenol) **9** arising from enantiopure sugar derivative **6** was obtained in fair yield as a mixture of chromatographically separable syn/anti isomers (Scheme 2). The reaction of β-lactam carbaldehyde **7** afforded bis(allenol) **10** as single isomer (Scheme 2).

A plausible mechanism for the bis(allenylation) process is illustrated in Scheme 3. Initially, indium reacts with the bis(halide) to form the bis(allenyl/propargyl organometallic). The two organometallic reagents (allenyl and propargyl metal) could interconvert, but probably, in our case the isomerization of propargylmetal to allenylmetal species is restricted by the steric effect of the aryl substituent in the 1,4-bis(3-bromoprop-1-ynyl)benzene derivative. The addition of the bis(propargylindium) species to the carbonyl compound (aldehyde or ketone), which probably proceeds via a double six-membered cyclic transition state, leads to the corresponding bis(allenol) after protodemetalation.

Since allenes possess a rich chemistry, the resulting enantiopure coupled products are prone to undergo further transformations, making them versatile synthetic tools. Since annonaceous acetogenins are a large family of natural products displaying several biological properties which contains a bis(tetrahydrofuran) core, we decided to test a metal-catalyzed double cyclization in our bis(allenes). To test the reactivity of the bis(allenols), we started the initial investigation on the gold-catalyzed reaction of bis(allene) **3b** under $AuCl_3$ catalysis.[14] Interestingly, it was found that the 2-fold cyclization product **11b** was exclusively formed in 72% yield (Scheme 4). Change in the nature of the gold precatalyst has little effect on the reaction, because replacing $AuCl_3$ by Gagosz' catalyst [(Ph_3P)-$AuNTf_2$] did not show any appreciable difference. Consequently, the much cheaper $AuCl_3$ salt was used in the following reactions. As shown in Schemes 4 and 5, differently functionalized bis(dihydrofurans) **11−13** were smoothly obtained in fair yields.

On the basis of the above gold-catalyzed results and keeping in mind the importance of palladium-catalyzed chemistry for the construction of several heterocycles by selective activation of allenes, we screened the palladium-catalyzed 2-fold cyclization coupling reaction of the challenging bis(allenolic) β-lactam moiety with alkenyl halides. In the event, bis-(dihydrofuryl-β-lactams) **14a,b** and **15** were obtained (Scheme 6).

Macrocycles are essential structural features of biologically relevant compounds, probably because large ring compounds confer both stereochemical and conformational complexity to the parent molecules.[15] Among macrocycles, cyclophanes, which are hydrocarbons consisting of an aromatic unit (typically a benzene ring) and an aliphatic chain that forms a

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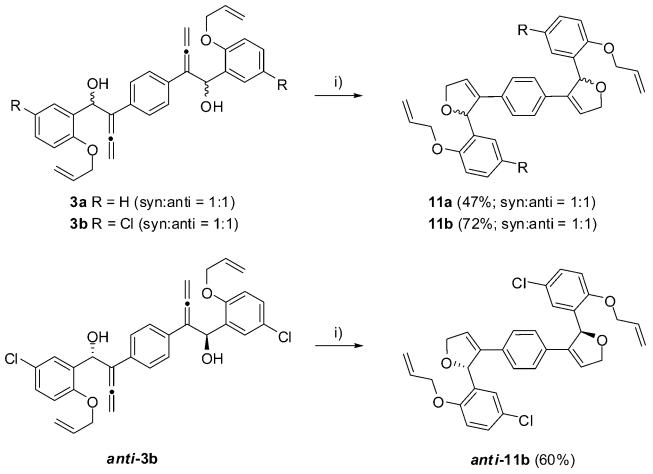
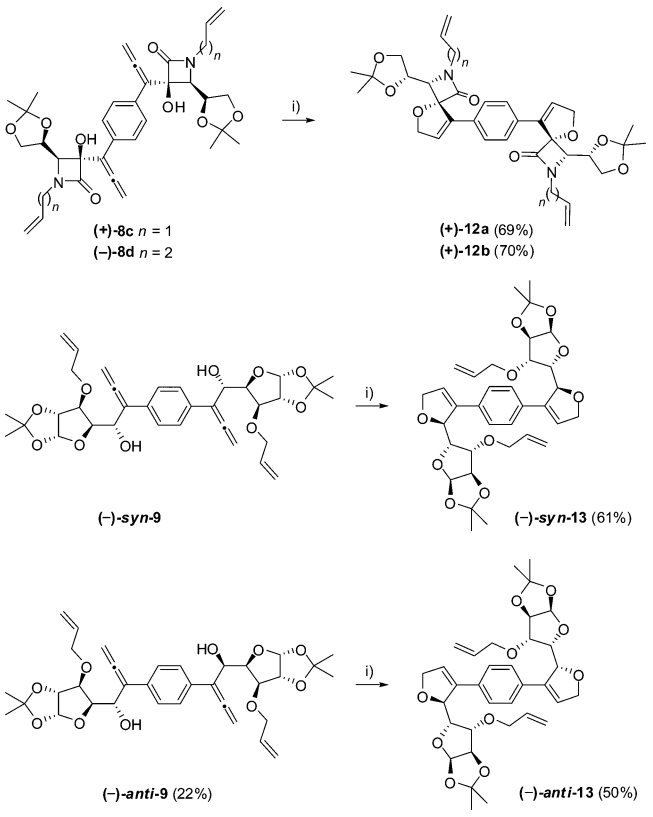
Scheme 4. Gold-Catalyzed Double Cycloetherification Reaction of Racemic Bis(allenols) 3[a]



[a]Conditions: (i) 5 mol % $AuCl_3$, CH_2Cl_2, rt, 2 h.

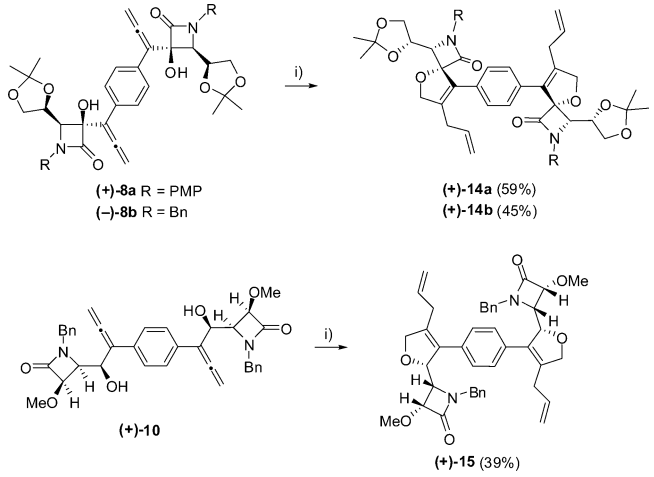
Scheme 5. Gold-Catalyzed Double Cycloetherification Reaction of Enantiopure Bis(allenols) 8c,d and 9[a]



[a]Conditions: (i) 5 mol % $AuCl_3$, CH_2Cl_2, rt; **12a**: 3 h; **12b**: 3 h; *syn*-**13**: 3 h; *anti*-**13**: 4 h.

bridge between two nonadjacent positions of the aromatic ring, have been recognized as catalysts and molecular receptors.[16] Accordingly, we planned a ring closing metathesis (RCM) strategy for obtaining bis(dihydrofuryl) cyclophanes. While the RCM of dienes is well documented, that of polyenes has been much less studied. Furthermore, the RCM studies of polyenes were generally confined to those having a low degree of substitution and functionalization. We initially focused our

Scheme 6. Palladium-Catalyzed Double Cycloetherification–Functionalization Reaction of Enantiopure Bis(allenols) 8a,b and 10[a]



[a]Conditions: (i) 5 mol % $PdCl_2$, allyl bromide, DMF, rt; **14a**: 3 h; **14b**: 4 h; **15**: 24 h.

attention for preparation of macrocycles starting from tetraene precursors **11** through the use of ruthenium-based carbenes. RCM reactions were tested with Grubbs' first generation catalyst **Ru-I**, or Grubbs' second generation catalyst **Ru-II**, or Hoveyda–Grubbs' second generation catalyst **Ru-III** (Figure 1)

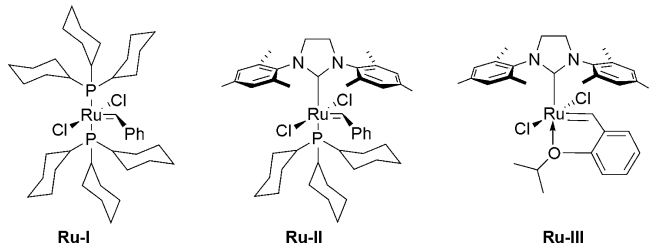


Figure 1. Structures of carbenes **Ru-I**, **Ru-II**, and **Ru-III**.

in dichloromethane under high dilution conditions at reflux temperature under argon atmosphere. To sustain sufficient quantities of catalyst during the reaction progress, the carbene was added in four portions (a total accumulated quantity of 10 mol %) in 1 h intervals. The RCM reaction of **11a** (syn/anti = 1:1) was accomplished first by treatment with a catalytic amount of **Ru-II** catalyst. The desired cyclophane **16a** was isolated as the sole product (inseparable mixture of isomers syn/anti = 1:1) in quantitative yield. Worthy of note, the macrocyclization reaction was totally stereoselective, with the *Z* isomer being exclusively obtained (Scheme 7). Happily, the bis(dihydrofuran) moiety remained untouched. A similar result was obtained for the RCM of **11b** (syn/anti = 1:1). Separating the isomers obtained from salicylaldehyde derivatives was not an easy task. Notably, we successfully isolated compounds *syn*-**16b** and *anti*-**16b** in pure forms by subjecting the mixture of diastereomers to repetitive column chromatography. The stereochemistry of adducts *syn*-**16b** and *anti*-**16b** was unambiguously assigned based on the RCM reaction of isomerically pure *anti*-**11b** which afforded isomerically pure *syn*-**16b** (Scheme 7).

Carbohydrates embedded in large macrocycles are relevant entities because of their specific biological activities[17] and

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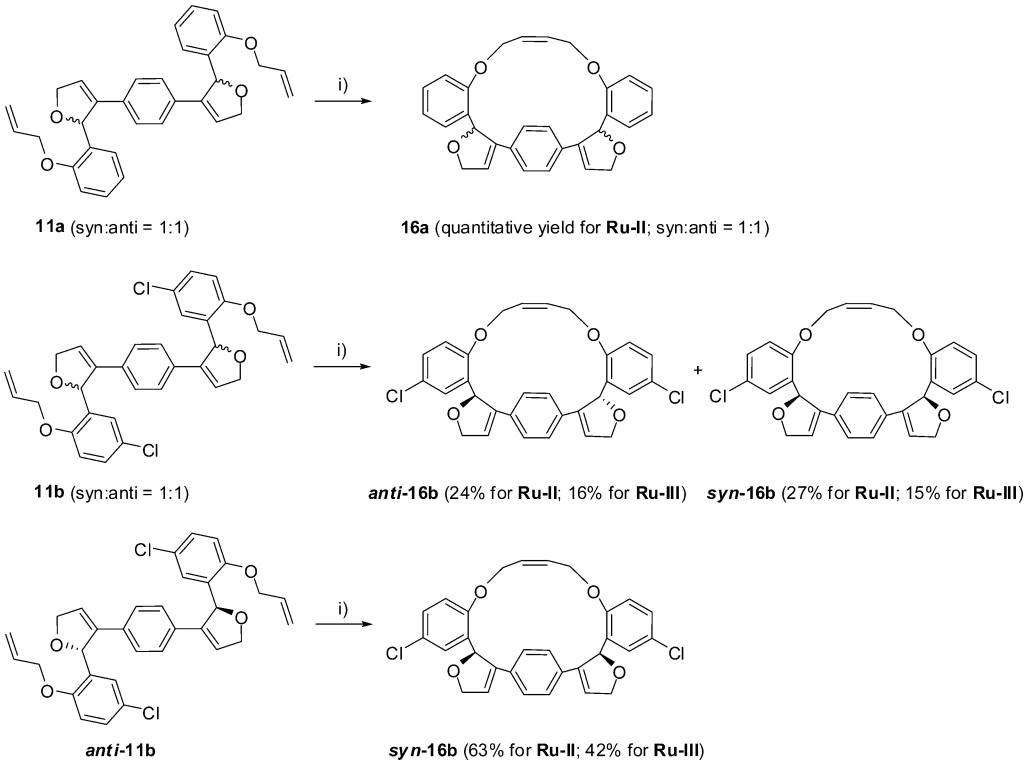
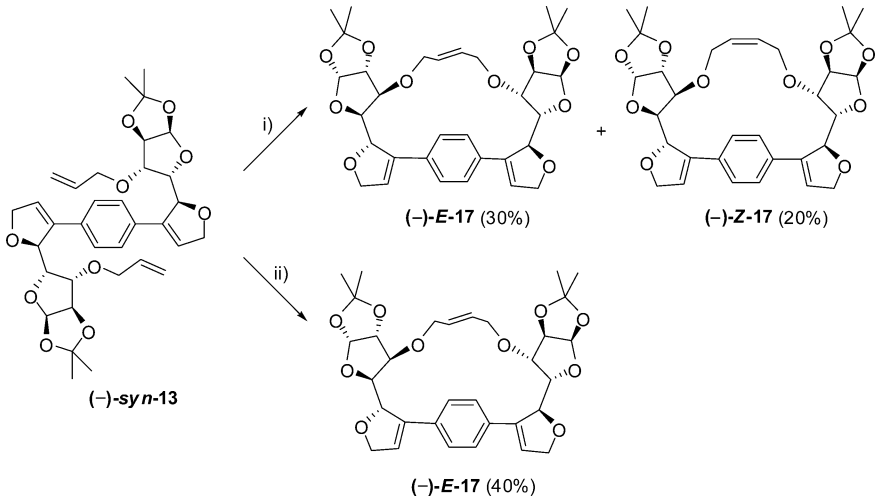
Scheme 7. Ruthenium-Catalyzed RCM Macrocyclization Reaction of Racemic Dienyl Bis(dihydrofurans) 11[a]



[a]Conditions: (i) 10 mol % **Ru-II** or **Ru-III**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

Scheme 8. Ruthenium-Catalyzed RCM Macrocyclization Reaction of Enantiopure Sugar-Based Dienyl Bis(dihydrofuran) *syn*-13[a]



[a]Conditions: (i) 10 mol % **Ru-III**, CH_2Cl_2 (high dilution conditions), reflux, 24 h. (ii) 10 mol % **Ru-II**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

chemical properties,[18] such as their application in bioorganic and supramolecular chemistry. Our synthetic approach to these skeletons make use of sugar-based adducts **13**. We subjected dienes *syn*-**13** and *anti*-**13** to RCM reaction under similar conditions as in the case of salicylaldehyde-derived dienes **11**. An attempted RCM reaction of *anti*-**13** with ruthenium-based carbenes was not successful. To our delight, encouraging results were obtained using the epimeric adduct *syn*-**13**. It is interesting to note that glycocyclophane **17** was obtained as a 3:2 mixture of *E*- and *Z*-isomers using **Ru-III** (Scheme 8). Fortunately, the *E*- and *Z*-isomers were chromatographically separable, which allows the isolation of the thermodynamically less stable *Z*-alkene. Interestingly, the RCM reaction of *syn*-**13** catalyzed by **Ru-II** was totally stereoselective because the sugar-based macrocycle *E*-**17** was isolated as the sole isomer (Scheme 8).

In addition to being the key structural motif in biologically relevant compounds such as antibiotics and enzyme inhibitors,[19] the β-lactam moiety is a versatile building block in organic synthesis.[20] Although the metathesis reaction is known to be a powerful tool for the preparation of macrocycles, in the

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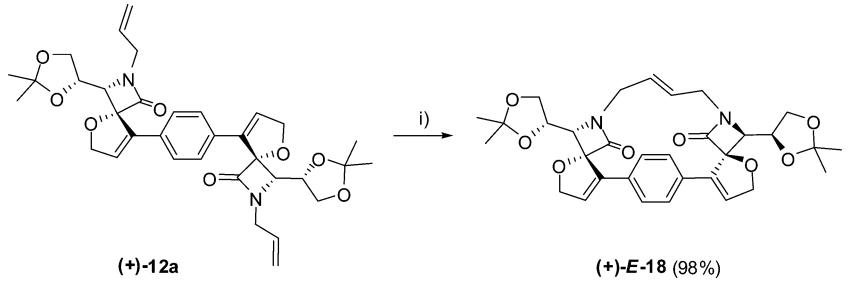
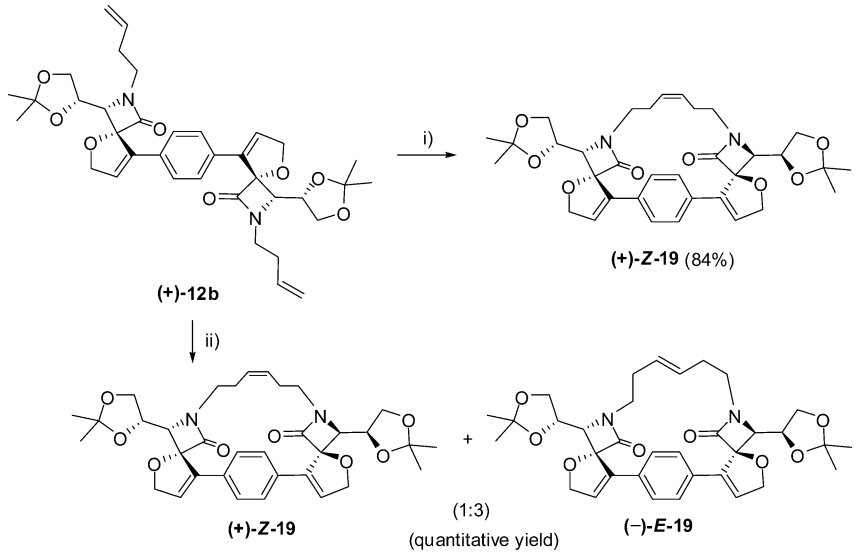
Scheme 9. Ruthenium-Catalyzed RCM Macrocyclization Reaction of Enantiopure β-Lactam-Based Dienyl Bis(dihydrofuran) 12a[a]



[a]Conditions: (i) 10 mol % **Ru-II**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

Scheme 10. Ruthenium-Catalyzed RCM Macrocyclization Reaction of Enantiopure β-Lactam-Based Dienyl Bis(dihydrofuran) 12b[a]



[a]Conditions: (i) 10 mol % **Ru-I**, CH_2Cl_2 (high dilution conditions), reflux, 24 h. (ii) 10 mol % **Ru-II** or **Ru-III**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

field of β-lactam chemistry, only a few syntheses of macrocyclic β-lactams have been reported based on RCM.[21] Initially, dienyl β-lactam **12a** was selected as a model substrate for the RCM. While the reaction of **12a** under **Ru-I** catalysis afforded poor results, the **Ru-II**-catalyzed reaction was extremely clean giving rise to macrocyclic bis(β-lactam) *E*-**18** in almost quantitative yield as a single *E*-isomer (Scheme 9). The structure of the macrocycle compound *E*-**18** was determined by NMR, COSY, and NOESY experiments (300 MHz) and confirmed by the HRESI mass spectra of the molecular ion $C_{32}H_{36}N_2O_8$ $[M]^+$ at *m*/*z* 576.2448.

Having gained stereodefined access to the macrocycle **18** from **12a**, we turned our attention to the conversion of the homologue precursor **12b** to the corresponding macrocyclic derivative. To carry out the macrocyclization reaction, **12b** was subjected to RCM conditions. Nicely, **Ru-I** catalysis led to the formation of the single isomer *Z*-**19** in an excellent 84% yield (Scheme 10). *Z*-Selectivity via RCM reaction is challenging since the majority of catalysts prefer the thermodynamically favored *E*-olefin.[22] The RCM reaction of the diene derivative **12b**, under otherwise identical conditions but catalyzed either by **Ru-II** or **Ru-III**, furnished the desired β-lactam-cyclophane **19** as the sole product (mixture of isomers *E*/*Z* = 3:1; nonseparable by flash chromatography) in quantitative yield (Scheme 10). Fortunately, after fractional crystallization a small amount of adduct *E*-**19** was obtained as an isomerically pure product for X-ray analysis (Figure S2; see the Supporting Information).[23]

Gratifyingly, the scope of the macrocyclization process was extended from *O*- or *N*-tethered dienes to *C*-tethered dienes by using precursors **14** (Scheme 11). The reaction proceeded smoothly with diene **14a** to exclusively afford 12-membered cyclophane *Z*-**20a** in good yield (71%). On the other hand, with the diene **14b** employed, a reaction mixture of cyclophane *Z*-**20b** and nonmacrocyclized adduct **21** was obtained. The pure macrocycle *Z*-**20b** was prepared in low overall yield as a single *Z*-isomer according to NMR spectroscopy. It was also possible to isolate pure isomerized diene **21** by column chromatography.[24] Probably, the obtention of the *Z*-alkenes *Z*-**20a** and *Z*-**20b** as the sole isomers arises from the fact that the small size of the macrocyclic cyclophane makes the formation of the *E*-isomer difficult due to ring strain.

Diene **15** was found to be completely ineffective in carrying out the requisite macrocyclization. Exposure of compound **15** to the ruthenium carbenes under our standard reaction conditions resulted in clean formation of the open-chain

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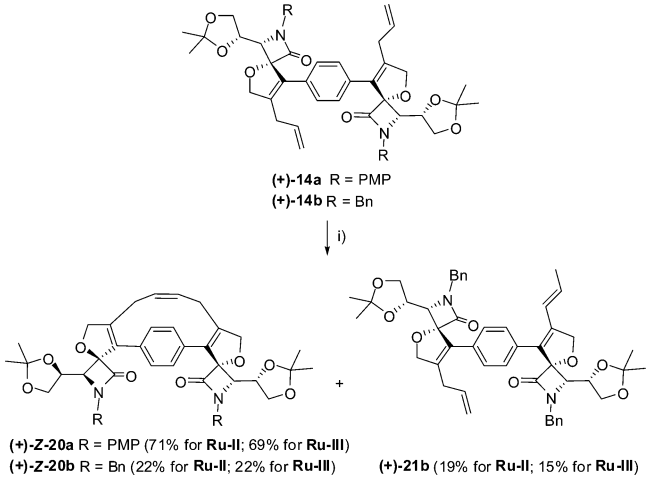
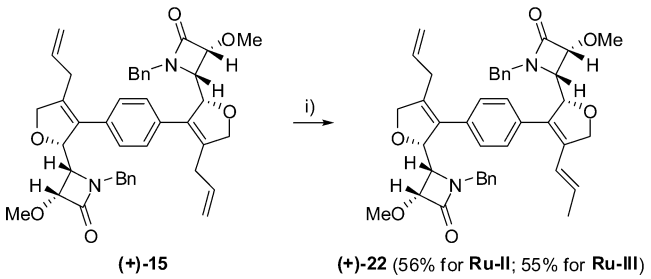
Scheme 11. Ruthenium-Catalyzed RCM Macrocyclization Reaction of Enantiopure β-Lactam-Based Dienyl Bis(dihydrofurans) 14[a]



[a]Conditions: (i) 10 mol % **Ru-II** or **Ru-III**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

monoisomerization adduct **22** (Scheme 12). The sterically more favored (*E*) configuration of the isomerizated double bond was established by ^{1}H NMR spectroscopy (J = 16.0 Hz).

Scheme 12. Ruthenium-Catalyzed Monoisomerization Reaction of Enantiopure β-Lactam-Based Dienyl Bis(dihydrofuran) 15[a]



[a]Conditions: (i) 10 mol % **Ru-II** or **Ru-III**, CH_2Cl_2 (high dilution conditions), reflux, 24 h.

The *E*- versus *Z*-stereochemistry of the metathesis-formed double bonds could not be assigned taking into consideration the usual coupling constants criteria. Fortunately, the chemical shifts of the two olefinic protons located at the macrocyclic double bond were diagnostic of the geometry of these unsaturations. The signals for isomers **16a**, *syn*-**16b**, *anti*-**16b**, *Z*-**17**, *Z*-**19**, *Z*-**20a**, and *Z*-**20b** appeared approximately at 5.5 ppm, which suggests a *Z*-stereochemistry, whereas these chemical shifts for adducts *E*-**17**, *E*-**18**, and *E*-**19** are around 4.5 ppm and indicate an *E*-stereochemistry. These trends in chemical shift may be explained based on the degree of shielding or deshielding. Probably, the double bond of *E*-isomers is located above of the benzene *cone*-shaped *shielding* zone, forcing the signal to appear at higher field (lower chemical shift). This configurational assignment was confirmed by means of the X-ray diffraction analysis of the adduct *E*-**19**.

CONCLUSION

In conclusion, a straightforward metal-mediated method for the synthesis of structurally different bis(dihydrofuryl) cyclophane scaffolds from carbonyl compounds has been developed. The process comprises indium-promoted one-pot carbonyl bis(allenylation) as well as gold- and palladium-catalyzed double cyclization in the resulting bis(allenols), followed by selective ruthenium-catalyzed macrocyclization.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded at 25 °C on a 700 or 300 MHz spectrometer. NMR spectra were recorded in $CDCl_3$ solutions, unless stated otherwise. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were acquired on a QTOF LC−MS spectrometer using the electronic impact (EI) or electrospray modes (ES). Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (c) is expressed in g per 100 mL.

Indium-Promoted Reaction between 1,4-Bis(3-bromoprop-1-ynyl)benzene 1 and Carbonyl Compounds. General Procedure for the Synthesis of Bis(allenols) 3, 8−10. 1,4-Bis(3-bromoprop-1-ynyl)benzene **1** (0.5 mmol) was added to a well stirred suspension of the corresponding aldehyde or ketone (1.0 mmol) and indium powder (6.0 mmol) in THF/NH_4Cl (aq. sat.) (1:5, 12 mL) at 0 °C. The reaction mixture was stirred at room temperature. After disappearance of the starting material (TLC) the mixture was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds. Spectroscopic and analytical data for bis(allenols) **3**, **8−10** follow.

Bis(allenol) 3a. From 117 mg (0.86 mmol) of aldehyde **2a**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, an inseparable syn/anti mixture (1:1) of compound **3a** (137 mg, 67%) as a yellow oil was obtained; ^{1}H NMR (300 MHz, C_6D_6, 25 °C) δ: 7.70 (s, 4H), 7.60 (dd, 2H, J = 8.8, 1.5 Hz), 7.17 (td, 2H, J = 7.0, 1.6 Hz), 6.99 (t, 2H, J = 7.5 Hz), 6.64 (d, 2H, J = 8.2 Hz), 6.30 (br s, 2H), 5.78 (m, 2H), 4.17 (d, 4H, J = 5.0 Hz), 5.26 (d, 2H, J = 17.3 Hz), 5.06 (dt, 2H, J = 10.6, 1.5 Hz), 4.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.1, 156.0, 133.0, 131.6, 130.3, 128.8, 128.1, 126.7, 120.9, 117.5, 112.0, 109.2, 80.8, 80.7, 69.0, 68.3, 68.2; IR ($CHCl_3$) ν = 3340, 1963, 1226; HRMS (ES): calcd for $C_{32}H_{30}O_4$ $[M]^+$: 478.2144; found: 478.2157.

Bis(allenol) 3b. From 300 mg (1.52 mmol) of aldehyde **2b**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, an inseparable syn/anti mixture (1:1) of compound **3b** (144 mg, 35%) as a yellow oil was obtained; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.36 (s, 4H), 7.35 (d, 2H, J = 2.7 Hz), 7.17 (dd, 2H, J = 8.7, 2.6 Hz), 6.79 (d, 2H, J = 8.8 Hz), 6.00 (m, 2H), 6.00 (m, 2H), 5.37 (dt, 2H, J = 17.2, 1.6 Hz), 5.27 (dt, 2H, J = 10.7, 1.3 Hz), 5.17 (qd, 4H, J = 12.4, 2.6 Hz), 4.56 (dd, 4H, J = 5.0, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 207.9 (2C), 154.4 (2C), 132.8, 132.8, 132.6 (2C) 132.2 (2C), 128.4 (2C), 127.8 (2C), 126.7 (4C), 125.8 (C), 117.8 (2C), 113.2 (2C), 108.8 (2C), 81.3 (2C), 81.2 (2C), 69.2 (2C), 67.4 (2C), 67.4 (2C); IR ($CHCl_3$) ν = 3380, 1938, 1243; HRMS (ES): calcd for $C_{32}H_{28}O_4Cl_2$ $[M]^+$: 546.1344; found: 546.1365.

Bis(allenol) (+)-8a. From 100 mg (0.34 mmol) of ketone (+)-**5a**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, compound (+)-**8a** (61 mg, 48%) as a pale brown solid was obtained; mp 128−129 °C; $[\alpha]_D$ = +19.0 (c = 0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (s, 4H), 7.56 (d, 4H, J = 9.0 Hz), 6.82 (d, 4H, J = 9.1 Hz), 5.27 (s, 4H), 4.51 (m, 4H), 4.40 (d, 2H, J = 7.0 Hz), 4.26 (dd, 2H, J = 8.9, 6.7 Hz), 1.46 (s, 6H), 3.78 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 208.1 (2C), 166.2 (2C), 156.7 (2C), 131.9 (2C), 130.7 (2C), 128.5 (4C), 120.2 (4C), 114.0 (4C), 109.8 (2C), 105.7 (2C), 84.2 (2C), 80.9 (2C), 76.5 (2C), 66.8 (2C), 66.6 (2C), 55.4 (2C), 26.4 (2C), 25.2 (2C); IR ($CHCl_3$) ν

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= 3321, 1955, 1740, 1198; HRMS (ES): calcd for $C_{42}H_{44}N_2O_{10}$ $[M]^+$: 736.2996; found: 736.3000.

Bis(allenol) (−)-8b. From 250 mg (0.91 mmol) of ketone (−)-**5b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound (−)-**8b** (333 mg, 52%) as a yellow oil was obtained; $[\alpha]_D$ = −55.1 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.53 (s, 4H), 7.21 (m, 10H), 5.15 (d, 2H, *J* = 12.5 Hz), 5.06 (d, 2H, *J* = 12.5 Hz), 4.91 (d, 2H, *J* = 14.8 Hz), 4.47 (dt, 2H, *J* = 6.7, 5.4 Hz), 4.15 (d, 2H, *J* = 14.8 Hz), 4.14 (dd, 4H, *J* = 8.9, 7.0 Hz), 3.68 (d, 2H, *J* = 6.7 Hz), 3.64 (dd, 2H, *J* = 9.7, 6.7 Hz), 1.37 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 207.5 (2C), 169.9 (2C), 135.2 (2C), 131.9 (2C), 128.6 (4C), 128.5 (4C), 128.4 (4C), 127.6 (2C), 109.9 (2C), 105.2 (2C), 84.9 (2C), 80.5 (2C), 75.8 (2C), 66.6 (2C), 64.4 (2C), 44.8 (2C), 26.4 (2C), 25.0 (2C); IR ($CHCl_3$) *ν* = 3316, 1937, 1732, 1211; HRMS (ES): calcd for $C_{42}H_{44}N_2O_8$ $[M]^+$: 704.3098; found: 704.3096.

Bis(allenol) (+)-8c. From 212 mg (0.94 mmol) of ketone (−)-**5c**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, compound (+)-**8c** (360 mg, 63%) as a yellow oil was obtained; $[\alpha]_D$ = +79.7 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.56 (s, 4H), 5.61 (m, 2H), 5.20 (s, 4H), 5.17 (m, 4H), 4.62 (s, 2H), 4.20 (dd, 2H, *J* = 12.6, 6.8 Hz), 4.18 (m, 4H), 3.83 (d, 2H, *J* = 7.2 Hz), 3.68 (m, 4H), 1.41 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 207.7 (2C), 168.9 (2C), 132.1 (2C), 131.4 (2C), 128.5 (4C), 118.4 (2C), 109.8 (2C), 105.6 (2C), 84.8 (2C), 80.4 (2C), 76.1 (2C), 66.7 (2C), 65.2 (2C), 45.5 (2C), 26.6 (2C), 25.1 (2C); IR ($CHCl_3$) *ν* = 3329, 1943, 1727, 1210; HRMS (ES): calcd for $C_{34}H_{40}N_2O_8$ $[M]^+$: 604.2785; found: 604.2798.

Bis(allenol) (−)-8d. From 1 g (4.35 mmol) of ketone (−)-**5d**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound (−)-**8d** (594 mg, 45%) as a yellow oil was obtained; $[\alpha]_D$ = −14.9 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.56 (s, 4H), 5.70 (ddt, 2H, *J* = 16.9, 10.2, 6.7 Hz), 5.20 (s, 4H), 5.04 (m, 4H), 4.46 (brs, 2H), 4.19 (dd, 2H, *J* = 8.8, 6.8 Hz), 4.42 (dd, 2H, *J* = 13.8, 6.6 Hz), 3.83 (d, 2H, *J* = 7.7 Hz), 3.67 (dd, 2H, *J* = 8.5, 5.9 Hz), 3.59 (m, 2H), 3.24 (dt, 2H, *J* = 13.8, 6.6 Hz), 2.34 (m, 4H), 1.44 (s, 6H), 1.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 207.7 (2C), 168.9 (2C), 134.9 (2C), 132.0 (2C), 128.5 (4C), 117.0 (2C), 109.6 (2C), 105.6 (2C), 84.4 (2C), 80.3 (2C), 76.4 (2C), 66.8 (2C), 65.5 (2C), 40.4 (2C), 31.7 (2C), 26.6 (2C), 25.1 (2C); IR ($CHCl_3$) *ν* = 3308, 1938, 1733, 1067; HRMS (ES): calcd for $C_{36}H_{44}N_2O_8$ $[M]^+$: 632.3098; found: 632.3100.

Reaction of Aldehyde (−)-6. From 500 mg (2.20 mmol) of aldehyde (−)-**6** and chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 182 mg (26%) of the less polar compound (−)-*anti*-**9** and 146 mg (22%) of the more polar compound (−)-*syn*-**9** were obtained.

Bis(allenol) (−)-*syn*-9. Yellow oil; $[\alpha]_D$ = −28.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 1.33 (s, 6H), 1.50 (s, 6H), 2.64 (brs, 2H), 3.74 (ddt, 2H, *J* = 12.5, 6.3, 1.2 Hz), 3.89 (d, 2H, *J* = 3.3 Hz), 3.99 (ddt, 2H, *J* = 12.5, 5.3, 1.3 Hz), 4.41 (dd, 2H, *J* = 8.1, 3.3 Hz), 4.57 (d, 2H, *J* = 3.7 Hz), 4.96 (d, 2H, *J* = 8.1 Hz), 5.13 (m, 4H), 5.22 (dd, 2H, *J* = 12.4, 1.2 Hz), 5.32 (dd, 2H, *J* = 12.4, 0.9 Hz), 5.63 (m, 2H), 5.99 (d, 2H, *J* = 3.7 Hz), 7.47 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 208.4 (2C), 133.6 (2C), 133.3 (2C), 126.8 (4C), 118.1 (2C), 112.0 (2C), 105.3 (2C), 104.9 (2C), 82.9 (2C), 82.6 (2C), 81.3 (2C), 80.6 (2C), 71.1 (2C), 68.3 (2C), 26.9 (2C), 26.4 (2C); IR ($CHCl_3$) *ν* = 3473, 1937, 1073, 1015; HRMS (ES): calcd for $C_{34}H_{42}O_{10}$ $[M]^+$: 610.2778; found: 610.2780.

Bis(allenol) (−)-*anti*-9. Yellow oil; $[\alpha]_D$ = −27.7 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.43 (m, 4H), 6.00 (d, 1H, *J* = 3.6 Hz), 5.99 (d, 1H, *J* = 5.9 Hz), 5.91 (m, 1H, C*H*=CH$_2$), 5.61 (m, 1H), 1.31 (s, 3H), 5.35 (m, 2H), 5.28 (m, 4H), 5.14 (m, 2H), 4.94 (m, 1H), 4.57 (d, 2H, *J* = 3.6 Hz), 4.41 (dd, 1H, *J* = 8.1, 3.2 Hz), 4.33 (dd, 1H, *J* = 5.8, 3.4 Hz), 4.14 (d, 1H, *J* = 3.4 Hz), 4.00 (m, 1H), 3.89 (d, 1H, *J* = 3.3 Hz), 3.73 (m, 1H), 3.28 (brs, 1H), 2.65 (brs, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 208.5, 208.2, 133.6, 133.4, 133.3, 133.1, 126.8 (2C), 126.4 (2C), 118.3, 118.1, 112.0, 111.7, 105.3, 105.0, 104.9, 104.9, 83.1, 82.9, 82.6 (2C), 81.9, 81.3, 80.9, 80.7, 71.1 (2C), 68.4, 68.2, 26.9, 26.8, 26.4, 26.3; IR ($CHCl_3$) *ν* = 3471, 1937, 1073, 1016; HRMS (ES): calcd for $C_{34}H_{42}O_{10}$ $[M]^+$: 610.2778; found: 610.2789.

Bis(allenol) (+)-10. From 140 mg (0.89 mmol) of aldehyde (+)-7, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-**10** (140 mg, 53%) as a yellow oil was obtained; $[\alpha]_D$ = +10.8 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.30 (s, 4H), 7.28 (m, 10H), 5.17 (t, 4H, *J* = 1.9 Hz), 4.90 (brs, 2H), 4.80 (d, 2H, *J* = 15.1 Hz), 4.46 (d, 2H, *J* = 4.8 Hz), 4.32 (d, 2H, *J* = 15.1 Hz), 3.91 (dd, 2H, *J* = 6.0, 5.0 Hz), 3.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 207.6 (2C), 167.9 (2C), 135.8 (2C), 132.9 (2C), 128.7 (4C), 128.1 (4C), 127.6 (2C), 126.9 (4C), 106.6, 83.6, 80.8, 68.9, 60.4, 59.7, 45.5; IR ($CHCl_3$) *ν* = 3364, 1952, 1747; HRMS (ES): calcd for $C_{36}H_{36}N_2O_6$ $[M]^+$: 592.2573; found: 592.2569.

Procedure for the Bis(4-chlorophenoxy)acetylation of the Syn/Anti Mixture (1:1) of Bis(allenol) 3b. Preparation of bis(allenol) *anti*-3b. Triethylamine (2.2 mmol) and 2-(4-chlorophenoxy)acetyl chloride (0.87 mmol) were sequentially added dropwise via syringe to a solution of bis(allenol) *syn*/*anti*-**3b** (402 mg, 0.73 mmol) and DMAP (cat) in dichloromethane (3 mL) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and then was stirred 2 h at room temperature. The crude mixture was diluted with CH_2Cl_2 (8 mL) and washed with saturated aqueous ammonium chloride (3 × 5 mL) and brine (3 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was purified by column chromatography eluting with ethyl acetate/hexanes (1:9) and then by fractional crystallization (ethyl acetate/hexanes) to give 172 mg (27%) of the more polar compound bis(4-chlorophenoxy)acetate *anti*-**4** and 213 mg of the bis(4-chlorophenoxy)acetate *syn*-**4** (4:1 syn/anti mixture).

Bis(4-chlorophenoxy)acetate *anti*-4. Colorless solid; mp 164−166 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.29 (s, 4H), 7.28 (m, 4H), 7.21 (m, 2H), 7.19 (d, 4H, *J* = 8.9 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 6.76 (d, 4H, *J* = 9.0 Hz), 5.95 (ddt, 2H, *J* = 17.3, 10.3, 5.0 Hz), 5.34 (dt, 2H, *J* = 17.2, 1.5 Hz), 5.22 (dq, 2H, *J* = 10.7, 1.3 Hz), 5.16 (d, 4H, *J* = 2.4 Hz), 4.62 (d, 4H, *J* = 1.3 Hz), 4.55 (d, 4H, *J* = 4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 209.2 (2C), 167.6 (2C), 156.3 (2C), 154.2 (2C), 132.5 (4C), 129.4 (4C), 129.3 (2C), 128.2 (2C), 128.0 (2C), 126.7 (2C), 126.6 (4C), 125.7 (2C), 117.6 (2C), 116.0 (4C), 113.3 (2C), 105.9 (2C), 81.3 (2C), 69.3 (2C), 68.0 (2C), 65.5 (2C); IR ($CHCl_3$) *ν* = 3321, 1941, 1762, 1174; HRMS (ES): calcd for $C_{48}H_{38}O_8Cl_4$ $[M]^+$: 882.1321; found: 882.1341.

Procedure for the Transesterification of the Bis(4-chlorophenoxy)acetate *anti*-4. Preparation of Bis(allenol) *anti*-3b. Sodium methoxide (10 mg, 0.19 mmol) was added in portions at 0 °C to a solution of the bis(4-chlorophenoxy)acetate *anti*-**4** (172 mg, 0.19 mmol) in methanol (1.9 mL). The reaction was stirred for 30 min at 0 °C, and then water was added (1 mL). The methanol was removed under reduced pressure, the aqueous residue was extracted with ethyl acetate, and the organic layer was dried ($MgSO_4$). The mixture was concentrated under reduced pressure and was purified by column chromatography eluting with ethyl acetate/hexanes (1:4) to give 82 mg (77%) of analytically pure bis(allenol) *anti*-**3b**.

Bis(allenol) *anti*-3b. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) *δ*: 7.36 (s, 4H), 7.35 (d, 2H, *J* = 2.6 Hz), 7.18 (dd, 2H, *J* = 8.7, 2.6 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 6.00 (m, 4H), 5.37 (dt, 2H, *J* = 17.3, 1.4 Hz), 5.27 (dt, 2H, *J* = 10.5, 1.2 Hz), 5.18 (qd, 4H, *J* = 12.3, 2.6 Hz), 4.56 (dt, 4H, *J* = 5.1, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) *δ*: 208.0 (2C), 154.5 (2C), 132.9, 132.6 (2C) 132.3 (2C), 128.5 (2C), 127.9 (2C), 126.8 (4C), 125.9, 117.8 (2C), 113.3 (2C), 109.0 (2C), 81.2 (2C), 69.4 (2C), 67.5 (2C); IR ($CHCl_3$) *ν* = 3243, 1938, 1241; HRMS (ES): calcd for $C_{32}H_{28}O_4Cl_2$ $[M]^+$: 546.1344; found: 546.1365.

General Procedure for the Gold-Catalyzed Double Cycloetherification Reaction of Bis(allenols) 3, 8, and 9. Preparation of Compounds 11−13. $AuCl_3$ (0.005 mmol) was added to a stirred solution of the corresponding bis(allenol) **3**, **8**, or **9** (0.1 mmol) in dichloromethane (1 mL) under argon. The resulting mixture was stirred at room temperature until complete disappearance (TLC) of the starting material. The reaction was then quenched with brine (0.2 mL), the mixture was extracted with ethyl acetate (3 × 5 mL), and the

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combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes or acetate/dichloromethane mixtures gave analytically pure adducts **11**−**13**.

Dienyl Bis(dihydrofuran) 11a. From 152 mg (0.31 mmol) of bis(allenol) **3a**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound **11a** (83 mg, 47%) as a yellow solid was obtained; mp 154−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.10 (s, 4H), 7.10 (m, 4H), 6.79 (m, 4H), 6.55 (m, 2H), 6.33 (m, 2H), 6.01 (m, 2H), 5.35 (m, 2H), 5.20 (m, 2H), 4.81 (m, 4H), 4.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 156.1 (2C), 140.6 (2C), 140.5 (2C) 133.3 (2C) 132.0 (2C), 131.9 (2C), 129.2 (2C), 129.2 (2C), 129.2 (2C), 129.1 (2C), 128.6 (2C), 128.5 (2C), 126.4 (4C), 126.4 (4C), 122.8 (2C), 122.7 (2C), 121.1 (2C), 117.3 (2C), 117.3 (2C), 112.4 (2C), 112.3 (2C), 80.9 (2C), 80.8 (2C), 75.2 (2C), 69.2 (2C), 69.2 (2C); IR ($CHCl_3$) ν = 1230; HRMS (ES): calcd for $C_{32}H_{30}O_4$ $[M]^+$: 478.2144; found: 478.2143.

Dienyl Bis(dihydrofuran) 11b. From 190 mg (0.35 mmol) of bis(allenol) **3b**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound **11b** (136 mg, 72%) as a colorless oil was obtained; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.19 (s, 4H), 7.13 (m, 4H), 6.80 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.5 Hz), 6.59 (m, 1H), 6.43 (q, 2H, J = 1.9 Hz), 6.40 (q, 2H, J = 1.9 Hz), 6.06 (m, 2H), 5.42 (m, 2H), 5.30 (m, 2H), 4.90 (m, 4H), 4.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.5 (2C), 140.4 (2C), 140.3 (2C), 132.8 (2C), 132.8 (2C), 131.9 (2C), 131.8 (2C), 131.3 (2C), 131.2 (2C), 129.0 (2C), 129.0 (2C), 128.4 (2C), 126.4 (4C), 126.4 (4C), 126.1 (2C), 126.0 (2C), 123.1 (2C), 123.0 (2C), 117.6 (2C), 113.7 (2C), 113.7 (2C), 80.4 (2C), 80.3 (2C), 75.4 (2C), 69.5 (2C), 69.5 (2C); IR ($CHCl_3$) ν = 1247; HRMS (ES): calcd for $C_{32}H_{28}O_4Cl_2$ $[M]^+$: 546.1342; found: 546.1365.

Dienyl Bis(dihydrofuran) *anti*-11b. From 47 mg (0.09 mmol) of bis(allenol) *anti*-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound *anti*-**11b** (28 mg, 60%) as a colorless oil was obtained; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.18 (s, 4H), 7.13 (m, 4H), 6.79 (d, 2H, J = 8.5 Hz), 6.59 (m, 2H), 6.40 (c, 2H, J = 1.8 Hz), 6.05 (m, 2H), 5.41 (dd, 2H, J = 17.3, 1.5 Hz), 5.30 (dd, 2H, J = 10.5, 1.3 Hz), 4.90 (m, 4H), 4.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.6 (2C), 140.5 (2C), 132.9 (2C), 131.9 (2C), 131.4 (2C), 129.0 (2C), 128.5 (2C), 126.5 (4C), 126.1 (2C), 123.2 (2C), 117.7 (2C), 113.7 (2C), 80.5 (2C), 75.4 (2C), 69.6 (2C); IR ($CHCl_3$) ν = 1247; HRMS (ES): calcd for $C_{32}H_{28}O_4Cl_2$ $[M]^+$: 546.1342; found: 546.1365.

Dienyl Bis(dihydrofuran) (+)-12a. From 86 mg (0.14 mmol) of bis(allenol) (+)-**8c**, and after chromatography of the residue using dichloromethane/ethyl acetate (9:1) as eluent, compound (+)-**12a** (60 mg, 69%) as a pale brown solid was obtained; mp 210−212 °C; $[\alpha]_D$ = +31.3 (c = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.33 (s, 4H), 6.29 (t, 2H, J = 1.7 Hz), 5.69 (m, 2H), 5.16 (m, 4H), 4.97 (dd, 2H, J = 14.2, 1.8 Hz), 4.71 (dd, 2H, J = 14.2, 1.7 Hz), 4.42 (m, 2H), 4.22 (dd, 2H, J = 15.0, 5.7 Hz), 4.14 (dd, 2H, J = 8.4, 6.9 Hz), 3.80 (dd, 2H, J = 15.0, 7.2 Hz), 3.51 (d, 2H, J = 8.9 Hz), 3.48 (dd, 2H, J = 8.5, 5.6 Hz), 1.35 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.1 (2C), 137.0 (2C), 131.9 (2C), 130.7 (2C), 127.4 (4C), 127.3 (2C), 119.4 (2C), 109.8 (2C), 99.5 (2C), 76.9 (2C), 76.1 (2C), 66.3 (2C), 65.0 (2C), 44.1 (2C), 26.7 (2C), 24.8 (2C); IR ($CHCl_3$) ν = 1741, 1248; HRMS (ES): calcd for $C_{34}H_{40}N_2O_8$ $[M]^+$: 604.2785; found: 604.2791.

Dienyl Bis(dihydrofuran) (+)-12b. From 130 mg (0.107 mmol) of bis(allenol) (−)-**8d**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-**12b** (90 mg, 70%) as a colorless solid was obtained; mp 234−235 °C; $[\alpha]_D$ = +21.0 (c = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.34 (s, 4H), 6.29 (t, 2H, J = 1.7 Hz), 5.70 (ddt, 2H, J = 16.9, 10.2, 6.7 Hz), 5.00 (m, 4H), 4.96 (dd, 2H, J = 14.1, 1.6 Hz), 4.70 (dd, 2H, J = 14.3, 1.7 Hz), 4.40 (ddd, 2H, J = 8.9, 6.7, 6.0 Hz), 4.15 (dd, 2H, J = 8.4, 6.9 Hz), 3.57 (dt, 2H, J = 13.1, 7.1 Hz), 3.53 (d, 2H, J = 8.8 Hz), 3.47 (dd, 2H, J = 8.5, 5.9 Hz), 3.39 (dt, 2H, J = 13.9, 6.7 Hz), 2.35 (m, 4H), 1.37 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.4 (2C), 136.8 (2C), 134.9 (2C), 131.9 (2C), 127.4 (2C), 127.3 (4C), 117.0 (2C), 109.7 (2C), 99.4 (2C), 76.8 (2C), 76.0 (2C), 66.3 (2C), 65.8 (2C), 40.9 (2C), 31.7 (2C), 26.6 (2C), 24.7 (2C); IR ($CHCl_3$) ν = 1754, 1078; HRMS (ES): calcd for $C_{36}H_{44}N_2O_8$ $[M]^+$: 632.3098; found: 632.3108.

Dienyl Bis(dihydrofuran) (−)-*syn*-13. From 60 mg (0.10 mmol) of bis(allenol) (−)-*syn*-**9**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (−)-*syn*-**13** (33 mg, 61%) as a yellow oil was obtained; $[\alpha]_D$ = −85.7 (c = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.31 (s, 4H), 6.16 (d, 2H, J = 1.7 Hz), 5.92 (m, 2H), 5.89 (d, 2H, J = 4.4 Hz), 5.54 (m, 2H), 5.34 (dd, 2H, J = 17.3, 1.6 Hz), 5.23 (dd, 2H, J = 10.5, 1.4 Hz), 4.85 (m, 4H), 4.65 (dd, 2H, J = 4.2, 1.7 Hz), 4.33 (dd, 2H, J = 5.4, 3.9 Hz), 4.12 (ddt, 2H, J = 13.0, 4.9, 1.5 Hz), 3.80 (dd, 2H, J = 5.5, 1.7 Hz), 3.75 (ddt, 2H, J = 13.0, 5.6, 1.4 Hz), 1.42 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 139.2 (2C), 133.9 (2C), 132.9 (2C), 126.9 (4C), 124.9 (2C), 117.2 (2C), 112.6 (2C), 105.2 (2C), 84.1 (2C), 83.7 (2C), 82.9 (2C), 80.3 (2C), 75.6 (2C), 70.7 (2C), 27.4 (2C), 27.0 (2C); IR ($CHCl_3$) ν = 1070, 1018; HRMS (ES): calcd for $C_{34}H_{42}O_{10}$ $[M]^+$: 610.2778; found: 610.2765.

Dienyl Bis(dihydrofuran) (−)-*anti*-13. From 65 mg (0.11 mmol) of bis(allenol) (−)-*anti*-**9**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (−)-*anti*-**13** (32 mg, 50%) as a yellow oil was obtained; $[\alpha]_D$ = −44.5 (c = 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.45 (d, 2H, J = 8.3 Hz), 7.28 (d, 2H, J = 8.1 Hz), 6.23 (d, 1H, J = 1.4 Hz), 6.13 (d, 1H, J = 1.7 Hz), 5.97 (m, 2H), 5.90 (d, 1H, J = 4.0 Hz), 5.86 (d, 1H, J = 4.3 Hz), 5.54 (m, 2H), 5.35 (m, 2H), 5.23 (m, 2H), 4.80 (m, 4H), 4.63 (dd, 1H), 4.51 (d, 1H, J = 3.8 Hz), 4.32 (t, 1H, J = 4.8 Hz), 4.18 (m, 2H), 4.12 (dd, 1H, J = 8.3, 3.1 Hz), 4.07 (m, 1H), 3.99 (d, 1H, J = 3.0 Hz), 3.75 (m, 1H), 3.74 (dd, 1H, J = 5.3, 1.4 Hz), 1.43 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 141.4, 139.5, 134.4, 134.2, 132.8, 132.6, 127.0 (2C), 126.6 (2C), 124.8, 123.7, 117.5, 117.0, 112.5, 111.3, 105.3, 105.2, 83.8, 83.7, 82.7, 82.4, 82.1, 82.0, 81.4, 80.5, 75.5, 75.1, 71.6, 70.5, 27.3, 27.0, 26.7, 26.1; IR ($CHCl_3$) ν = 1071, 1014; HRMS (ES): calcd for $C_{34}H_{42}O_{10}$ $[M]^+$: 610.2778; found: 610.2801.

General Procedure for the Palladium-Catalyzed Double Cyclization/Cross-Coupling Reaction of Bis(allenols) 8 and 10. Preparation of Compounds 14 and 15. Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding bis(allenol) **8** or **10** (0.10 mmol) and allyl bromide (0.50 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred under an argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being extracted with ethyl acetate (3 × 4 mL). The organic phase was washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **14** and **15**.

Dienyl Bis(dihydrofuran) (+)-14a. From 50 mg (0.07 mmol) of bis(allenol) (+)-**8a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-**14a** (34 mg, 59%) as a pale brown solid was obtained; mp 199−202 °C; $[\alpha]_D$ = +53.6 (c = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.51 (d, 4H, J = 9.1 Hz), 7.16 (s, 4H), 6.81 (d, 4H, J = 9.1 Hz), 5.74 (ddt, 2H, J = 16.6, 10.2, 6.4 Hz), 5.09 (m, 2H), 5.04 (m, 2H), 4.89 (d, 2H, J = 13.4 Hz), 4.72 (d, 2H, J = 13.4 Hz), 4.44 (dt, 2H, J = 8.8, 6.6 Hz), 4.25 (dd, 2H, J = 8.4, 7.2 Hz), 3.77 (s, 6H), 3.71 (d, 2H, J = 8.5 Hz), 3.53 (dd, 2H, J = 8.4, 6.5 Hz), 2.89 (m, 4H), 1.37 (s, 6H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.2 (2C), 156.6 (2C), 138.6 (2C), 133.7 (2C), 131.3 (2C), 130.9 (2C), 130.4 (2C), 129.0 (4C), 119.9 (4C), 117.2, 113.9 (4C), 109.8 (2C), 101.0 (2C), 78.4 (2C), 76.9 (2C), 66.8 (2C), 66.4 (2C), 55.3 (2C), 30.3 (2C), 26.4 (2C), 24.6 (2C); IR ($CHCl_3$) ν = 1739, 1220; HRMS (ES): calcd for $C_{48}H_{52}N_2O_{10}$ $[M]^+$: 816.3622; found: 816.3614.

Dienyl Bis(dihydrofuran) (+)-14b. From 300 mg (0.42 mmol) of bis(allenol) (−)-**8b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound (+)-**14b** (150 mg, 45%) as a colorless solid was obtained; mp 186−187 °C; $[\alpha]_D$ = +86.1 (c = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.12 (m,

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10H), 6.96 (s, 4H), 5.77 (ddt, 2H, J = 16.4, 10.2, 6.2 Hz), 5.13 (m, 2H), 5.07 (m, 2H), 4.86 (d, 2H, J = 13.4 Hz), 4.78 (d, 2H, J = 14.5 Hz), 4.70 (d, 2H, J = 13.3 Hz), 4.45 (dt, 2H, J = 8.9, 6.4 Hz), 4.19 (d, 2H, J = 14.3 Hz), 4.17 (m, 2H), 3.47 (dd, 2H, J = 8.3, 6.1 Hz), 3.24 (d, 2H, J = 8.9 Hz), 2.87 (qd, 4H, J = 15.8, 6.2 Hz), 1.35 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.3 (2C), 138.1 (2C), 135.0 (2C), 134.0 (2C), 130.9 (2C), 130.8 (2C), 128.8 (4C), 128.6 (4C), 128.2 (4C), 127.5 (2C), 117.0, 109.6 (2C), 101.6 (2C), 78.2, 76.9 (2C), 66.3 (2C), 64.5 (2C), 45.2 (2C), 30.2 (2C), 26.4 (2C), 24.5 (2C); IR ($CHCl_3$) ν = 1752, 1208; HRMS (ES): calcd for $C_{48}H_{52}N_2O_8$ $[M]^+$: 784.3724; found: 784.3754.

Dienyl Bis(dihydrofuran) (+)-15. From 190 mg (0.31 mmol) of bis(allenol) (+)-**10**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-**15** (81 mg, 39%) as colorless oil was obtained; $[\alpha]_D$ = +17.3 (c = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.16 (m, 10H), 6.95 (s, 4H), 5.73 (ddt, 2H, J = 17.0, 10.4, 6.6 Hz), 5.42 (d, 2H, J = 2.6 Hz), 5.10 (m, 4H), 4.77 (m, 6H), 4.33 (d, 2H, J = 5.1 Hz), 4.03 (d, 2H, J = 15.3 Hz), 3.65 (dd, 2H, J = 5.1, 2.6 Hz), 3.49 (s, 6H), 2.86 (d, 4H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.5 (2C), 135.9 (2C), 135.2 (2C), 133.8 (2C), 132.8 (2C), 132.2 (2C), 128.5 (4C), 128.1 (4C), 127.7 (4C), 127.4 (2C), 117.2 (2C), 85.3 (2C), 83.3 (2C), 78.6 (2C), 59.6 (2C), 58.0 (2C), 44.7 (2C), 30.5 (2C); IR ($CHCl_3$) ν = 1744, 1217; HRMS (ES): calcd for $C_{42}H_{45}N_2O_6$ $[M + H]^+$: 673.3278; found: 673.3251.

General Procedure for the Ruthenium-Catalyzed RCM Reaction of Dienyl Bis(dihydrofurans) 11−14. Preparation of Cyclophanes 16−20. The appropriate catalyst **Ru-I**, **Ru-II**, or **Ru-III**, (0.01 mmol) was added in portions under argon to a solution protected from the sunlight of the corresponding dienic compound (0.10 mmol) in anhydrous dichloromethane (200 mL), and the mixture was heated at reflux. The reaction was monitored by TLC. After completion, the mixture was concentrated under reduced pressure and was purified by column chromatography eluting with ethyl acetate/hexanes or acetate/dichloromethane mixtures to give analytically pure macrocyclic compounds **16−20**. Spectroscopic and analytical data for some representative pure forms of the above cyclophanes follow.

Cyclophane 16a. From 50 mg (0.104 mmol) of dienyl bis(dihydrofuran) **11a**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, compound **16a** (47 mg, quantiative yield) as a yellow oil was obtained; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.37 (m, 2H), 7.35 (s, 4H), 7.26 (s, 4H), 7.25 (m, 2H), 7.19 (ddd, 2H, J = 8.3, 7.3, 1.8 Hz), 7.06 (ddd, 2H, J = 8.5, 7.4, 1.8 Hz), 6.94 (td, 2H, J = 7.4, 0.7 Hz), 6.83 (td, 2H, J = 7.4, 0.8 Hz), 6.79 (dd, 2H, J = 8.4, 0.8 Hz), 6.66 (m, 2H), 6.66 (d, 2H, J = 7.8 Hz), 6.58 (ddd, 2H, J = 5.6, 3.3, 2.0 Hz), 6.25 (m, 2H, J = 1.9 Hz), 6.22 (q, 2H, J = 1.9 Hz), 5.97 (m, 2H), 5.85 (m, 2H), 5.10 (m, 2H), 4.92 (m, 2H), 4.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.0 (2C), 154.0 (2C), 143.7 (2C), 143.0 (2C) 132.4 (2C), 132.2 (2C), 131.4 (2C), 130.8 (2C), 128.9 (2C), 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.2 (2C), 126.7 (4C), 126.6 (4C), 121.2 (2C), 121.1 (2C), 120.9 (4C), 111.2 (2C), 110.9 (2C), 81.0 (2C), 80.7 (2C), 76.3 (2C), 76.1 (2C), 67.2 (2C), 66.6 (2C); IR ($CHCl_3$) ν = 1681, 1222, 759; HRMS (ES): calcd for $C_{30}H_{26}O_4$ $[M]^+$: 450.1831; found: 450.1811.

Cyclophane *syn*-16b. From 30 mg (0.055 mmol) of dienyl bis(dihydrofuran) *anti*-**11b**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, compound *syn*-**16b** (18 mg, 63%) as a colorless solid was obtained; mp 219−221 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.34 (s, 4H), 7.20 (d, 2H, J = 2.7 Hz), 7.02 (dd, 2H, J = 8.8, 2.7 Hz), 6.60 (m, 1H), 6.57 (d, 2H, J = 8.8 Hz), 6.23 (q, 2H, J = 1.9 Hz), 5.80 (m, 2H), 5.10 (ddd, 2H, J = 13.8, 5.9, 1.7 Hz), 4.94 (ddd, 2H, J = 13.8, 3.4, 2.0 Hz), 4.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 152.6 (2C), 143.1 (2C), 132.6 (2C), 132.2 (2C), 128.7 (2C), 128.4 (2C), 127.9 (2C), 126.6 (4C), 125.8 (2C), 121.6 (2C), 112.0 (2C), 80.6 (2C), 76.4 (2C), 66.8 (2C); IR ($CHCl_3$) ν = 1274; HRMS (ES): calcd for $C_{30}H_{24}O_4Cl_2$ $[M]^+$: 518.1073; found: 518.1052.

Reaction of Dienyl Bis(dihydrofuran) 11b. From 40 mg (0.073 mmol) of dienyl bis(dihydrofuran) **11b** (syn/anti = 1:1), and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent, 9 mg (24%) of the less polar compound *anti*-**16b** and 10 mg (27%) of the more polar compound *syn*-**16b** were obtained.

Cyclophane *anti*-16b. Colorless solid; mp 214−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.29 (d, 2H, J = 2.7 Hz), 7.22 (s, 4H), 7.13 (dd, 2H, J = 8.8, 2.7 Hz), 6.69 (d, 2H, J = 8.8 Hz), 6.51 (ddd, 1H, J = 5.7, 3.5, 2.0 Hz), 6.27 (q, 2H, J = 1.7 Hz), 5.90 (m, 2H), 5.11 (ddd, 2H, J = 13.8, 6.0, 1.7 Hz), 4.90 (ddd, 2H, J = 13.8, 3.5, 2.0 Hz), 4.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 152.7 (2C), 142.4 (2C), 133.2 (2C), 132.1 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 126.6 (4C), 126.1 (2C), 121.9 (2C), 112.5 (2C), 80.5 (2C), 76.2 (2C), 67.4 (2C); IR ($CHCl_3$) ν = 1248; HRMS (ES): calcd for $C_{30}H_{24}O_4Cl_2$ $[M]^+$: 518.1073; found: 518.1052.

Cyclophane (−)-*E*-17. From 73 mg (0.11 mmol) of dienyl bis(dihydrofuran) (−)-*syn*-**13**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (−)-*E*-**17** (26 mg, 40%) as a colorless oil was obtained; $[\alpha]_D$ = −8.6 (c = 3.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.41 (s, 4H), 6.14 (d, 2H, J = 1.3 Hz), 5.91 (d, 2H, J = 3.8 Hz), 5.54 (m, 2H), 4.82 (m, 4H), 4.72 (brs, 2H), 4.52 (d, 2H, J = 3.8 Hz), 4.24 (dd, 2H, J = 6.6, 2.7 Hz), 4.01 (d, 2H, J = 14.1 Hz), 3.81 (d, 2H, J = 14.4 Hz), 3.70 (d, 2H, J = 2.8 Hz), 1.52 (s, 6H), 1.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 141.2 (2C), 133.3 (2C), 127.1 (4C), 126.8 (2C), 125.2 (2C), 111.5 (2C), 103.9 (2C), 83.3, 82.3, 80.2 (2C), 78.7 (2C), 74.0 (2C), 67.0 (2C), 26.7 (2C), 26.2 (2C); IR ($CHCl_3$) ν = 1075, 1020; HRMS (ES): calcd for $C_{32}H_{38}O_{10}$ $[M]^+$: 582.2465; found: 582.2468.

Reaction of Dienyl Bis(dihydrofuran) (−)-*syn*-13. From 80 mg (0.13 mmol) of dienyl bis(dihydrofuran) (−)-*syn*-**13**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 24 mg (30%) of the less polar compound (−)-*E*-**17** and 15 mg (20%) of the more polar compound (−)-*Z*-**17** were obtained.

Cyclophane (−)-*Z*-17. Colorless oil; $[\alpha]_D$ = −38.4 (c = 0.43 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.24 (s, 4H), 6.00 (d, 2H, J = 1.6 Hz), 5.73 (d, 2H, J = 3.7 Hz), 5.53 (m, 2H), 5.23 (brs, 2H), 4.78 (m, 4H), 4.27 (d, 2H, J = 3.7 Hz), 4.18 (dd, 2H, J = 6.0, 2.6 Hz), 1.28 (s, 6H), 3.62 (d, 2H, J = 12.1 Hz), 3.34 (d, 2H, J = 2.5 Hz), 3.07 (d, 2H, J = 14.0 Hz), 1.48 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 141.5 (2C), 133.3 (2C), 127.2 (4C), 126.5 (2C), 123.7 (2C), 111.8 (2C), 104.3 (2C), 83.8 (2C), 82.1 (2C), 82.0 (2C), 81.2 (2C), 74.6 (2C), 67.4 (2C), 26.8 (2C), 26.3 (2C); IR ($CHCl_3$) ν = 1076, 1021; HRMS (ES): calcd for $C_{32}H_{38}O_{10}$ $[M]^+$: 582.2465; found: 582.2489.

Cyclophane (+)-*E*-18. From 20 mg (0.033 mmol) of dienyl bis(dihydrofuran) (−)-**12a**, and after chromatography of the residue using dichloromethane/ethyl acetate (4:1) as eluent, compound (+)-*E*-**18** (19 mg, 98%) as a pale brown solid was obtained; mp 299−300 °C; $[\alpha]_D$ = +73.1 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.32 (s, 4H), 6.05 (t, 2H, J = 1.4 Hz), 5.00 (dd, 2H, J = 13.5, 1.6 Hz), 4.78 (dd, 2H, J = 13.5, 1.4 Hz), 4.38 (m, 2H), 4.30 (m, 2H), 4.18 (m, 2H), 4.15 (dd, 2H, J = 8.5, 6.7 Hz), 3.56 (dd, 2H, J = 8.6, 5.1 Hz), 3.45 (m, 2H), 3.34 (d, 2H, J = 8.6 Hz), 1.34 (s, 6H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.4 (2C), 138.0 (2C), 132.2 (2C), 129.2 (4C), 126.0 (2C), 125.5 (2C), 109.8 (2C), 101.0 (2C), 77.2 (2C), 77.1 (2C), 66.5 (2C), 63.9 (2C), 41.4 (2C), 26.8 (2C), 24.9 (2C); IR ($CHCl_3$) ν = 1743, 1208; HRMS (ES): calcd for $C_{32}H_{36}N_2O_8$ $[M]^+$: 576.2472; found: 576.2448.

Cyclophane (+)-*Z*-19. From 20 mg (0.032 mmol) of dienyl bis(dihydrofuran) (+)-**12b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-*Z*-**19** (16 mg, 84%) as a colorless solid was obtained; mp 157−159 °C; $[\alpha]_D$ = +27.2 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.38 (s, 4H), 6.27 (t, 2H, J = 1.6 Hz), 5.48 (t, 2H, J = 3.9 Hz), 4.96 (dd, 2H, J = 14.2, 1.7 Hz), 4.73 (dd, 2H, J = 14.2, 1.6 Hz), 4.41 (dt, 2H, J = 8.8, 6.2 Hz), 4.18 (dd, 2H, J = 8.5, 6.8 Hz), 3.82 (m, 2H), 3.76 (d, 2H, J = 8.8 Hz), 3.54 (dd, 2H, J = 8.5, 5.9 Hz), 3.24 (m, 2H), 2.08 (m, 4H), 1.43 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.4 (2C), 136.6 (2C), 131.8 (2C), 129.2 (2C), 127.5 (4C), 127.2 (2C), 109.9 (2C), 99.7 (2C), 77.2 (2C), 76.2 (2C), 66.5 (2C), 65.9

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(2C), 40.3 (2C), 26.8 (2C), 26.6 (2C), 25.0 (2C); IR ($CHCl_3$) ν = 1757, 1081; HRMS (ES): calcd for $C_{34}H_{40}N_2O_8$ $[M]^+$: 604.2785; found: 604.2812.

Cyclophane (−)-*E*-19. From 40 mg (0.063 mmol) of dienyl bis(dihydrofuran) (+)-**12b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, 38 mg (quantitative yield) of compound (−)-*E*-**19** (3:1 *E*/*Z* mixture) as a colorless solid were obtained; mp 222−224 °C; $[\alpha]_D$ = −55.4 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C) δ: 7.39 (s, 3H), 7.37 (s, 1H), 6.26 (s, 0.5H), 6.09 (s, 1.5H), 5.47 (t, 0.5H, *J* = 3.8 Hz), 4.96 (d, 1.5H, *J* = 13.8 Hz), 4.93 (d, 0.5H, *J* = 14.1 Hz), 4.74 (m, 1.5H), 4.73 (m, 0.5H), 4.72 (d, 1.5H, *J* = 13.8 Hz), 4.39 (dt, 0.5H, *J* = 8.5, 6.4 Hz), 4.32 (dt, 1.5H, *J* = 8.7, 6.4 Hz), 4.16 (m, 0.5H), 4.16 (dd, 1.5H, *J* = 15.9, 8.8 Hz), 3.80 (m, 1H), 3.78 (m, 1.5H), 3.53 (d, 1.5H, *J* = 8.7 Hz), 3.52 (m, 0.5H), 3.52 (m, 1.5H), 3.23 (m, 0.5H), 3.08 (t, 1.5H, *J* = 11.9 Hz), 2.15 (m, 1H), 1.95 (m, 3H), 1.41 (s, 1.5H), 1.34 (s, 1.5H), 1.31 (s, 4.5H), 1.30 (s, 4.5H); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C) δ: 168.5 (2C-m), 168.0 (2C-M), 137.8 (2C-M), 136.5 (2C-m), 132.7 (2C-M), 131.7 (2C-m), 130.0 (2C-M), 129.2 (2C-m), 128.6 (4C-M), 127.4 (4C-m), 127.3 (2C-M), 127.2 (2C-m), 109.9 (2C-m), 109.8 (2C-M), 100.4 (2C-M), 99.7 (2C-m), 77.5 (2C-M), 77.3 (2C-m), 76.7 (2C-M), 76.2 (2C-m), 67.1 (2C-M), 66.4 (2C-M), 66.4 (2C-m), 65.8 (2C-m), 40.4 (2C-M), 40.3 (2C-m), 33.7 (2C-M), 26.7 (2C-m), 26.7 (2C-M), 26.6 (2C-m), 25.1 (2C-M), 25.0 (2C-m); IR ($CHCl_3$) ν = 1747, 1079; HRMS (ES): calcd for $C_{34}H_{40}N_2O_8$ $[M]^+$: 604.2785; found: 604.2812.

Cyclophane (+)-*Z*-20a. From 30 mg (0.04 mmol) of dienyl bis(dihydrofuran) (+)-**14a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent, compound (+)-*Z*-**20a** (22 mg, 71%) as a pale brown oil was obtained; $[\alpha]_D$ = +37.8 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63 (d, 4H, *J* = 9.0 Hz), 7.40 (s, 4H), 6.93 (d, 4H, *J* = 9.0 Hz), 5.14 (t, 2H, *J* = 7.4 Hz), 5.01 (d, 2H, *J* = 13.3 Hz), 4.80 (d, 2H, *J* = 13.3 Hz), 4.56 (dt, 2H, *J* = 8.5, 6.7 Hz), 4.37 (dd, 2H, *J* = 8.5, 7.5 Hz), 3.90 (s, 6H), 3.81 (d, 2H, *J* = 8.6 Hz), 3.66 (dd, 2H, *J* = 8.5, 6.4 Hz), 2.94 (d, 4H, *J* = 7.3 Hz), 1.78 (s, 6H), 1.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 166.3 (2C), 156.6 (2C), 140.3 (2C), 134.6 (2C), 131.4 (2C), 130.5 (2C), 129.2 (4C), 119.9 (4C), 119.2 (2C), 113.9 (4C), 109.7 (2C), 101.1 (2C), 78.6 (2C), 77.2 (2C), 67.0 (2C), 66.4 (2C), 55.3 (2C), 26.4 (2C), 25.6 (2C), 24.6 (2C); IR ($CHCl_3$) ν = 1753, 1222; HRMS (ES): calcd for $C_{46}H_{48}N_2O_{10}$ $[M]^+$: 788.3309; found: 788.3304.

Reaction of Dienyl Bis(dihydrofuran) (+)-14b. From 52 mg (0.07 mmol) of dienyl bis(dihydrofuran) (+)-**14b**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent, 11 mg (22%) of the less polar compound (+)-*Z*-**20b** and 10 mg (19%) of the more polar compound (+)-**21b** were obtained.

Cyclophane (+)-*Z*-20b. Colorless oil; $[\alpha]_D$ = +45.2 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.07 (m, 5H), 6.98 (s, 4H), 5.02 (t, 2H, *J* = 7.1 Hz), 4.88 (d, 2H, *J* = 13.1 Hz), 4.77 (d, 2H, *J* = 14.5 Hz), 4.65 (d, 2H, *J* = 13.2 Hz), 4.18 (m, 4H), 4.44 (m, 2H), 3.48 (dd, 2H, *J* = 8.2, 6.1 Hz), 3.25 (d, 2H, *J* = 8.9 Hz), 2.80 (d, 4H, *J* = 6.3 Hz), 1.69 (s, 6H), 1.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.5 (2C), 140.1 (2C), 135.1 (2C), 131.0 (2C), 129.4 (2C), 129.0 (4C), 128.7 (4C), 128.2 (4C), 127.4 (2C), 119.4 (2C), 109.6 (2C), 101.7 (2C), 78.4 (2C), 77.2 (2C), 66.3 (2C), 64.6 (2C), 45.2 (2C), 31.5 (2C), 26.4 (2C), 24.6 (2C); IR ($CHCl_3$) ν = 1759, 1210; HRMS (ES): calcd for $C_{46}H_{48}N_2O_8$ $[M]^+$: 756.3411; found: 756.3408.

Isomerized Open-Chain Adduct (+)-21b. Colorless oil; $[\alpha]_D$ = +53.1 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.07 (m, 10H), 7.00 (s, 4H), 6.04 (d, 1H, *J* = 16.1 Hz), 5.75 (m, 1H), 5.69 (dq, 1H, *J* = 16.0, 6.7 Hz), 5.09 (m, 4H), 4.80 (m, 6H, *J* = 13.3 Hz), 4.45 (m, 2H), 4.18 (m, 4H), 3.47 (m, 2H), 3.25 (d, 1H, *J* = 8.8 Hz), 3.23 (d, 1H, *J* = 9.0 Hz), 2.84 (m, 2H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.34 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.3, 168.2, 138.1, 138.0, 135.0, 134.8, 134.0 (2C), 131.9, 131.1, 130.9, 129.9, 129.7, 129.3 (2C), 129.2 (2C), 128.8 (2C), 128.8 (2C), 128.2 (2C), 128.2 (2C), 127.6, 127.5, 122.3, 117.0, 109.6 (2C), 101.6, 101.6, 78.2 (2C), 70.2 (2C), 66.4, 66.3, 64.6, 64.5, 45.2 (2C), 30.3, 26.4 (2C), 24.5 (2C), 18.8; IR ($CHCl_3$) ν = 1760, 1210; HRMS (ES): calcd for $C_{48}H_{52}N_2O_8$ $[M]^+$: 784.3724; found: 784.3761.

Procedure for the Ruthenium-Catalyzed Isomerization Reaction of Dienyl Bis(dihydrofuran) (+)-15. Preparation of Isomerized Open-Chain Adduct (+)-22. The appropriate catalyst **Ru-II** or **Ru-III** (0.01 mmol) was added in portions under argon to a solution protected from the sunlight of the dienic compound (+)-**15** (40 mg, 0.06 mmol) in anhydrous dichloromethane (120 mL), and the mixture was heated at reflux for 24 h. The mixture was concentrated under reduced pressure and was purified by column chromatography eluting with ethyl acetate/hexanes (1:3) to give 23 mg (56%) of analytically pure 1,3-diene (+)-**22**.

Isomerized Open-Chain Adduct (+)-22. Colorless oil; $[\alpha]_D$ = +7.7 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.11 (m, 12H), 6.19 (d, 1H, *J* = 16.3 Hz), 5.68 (m, 1H, *J* = 17.0, 10.4, 6.6 Hz), 5.63 (dq, 1H, *J* = 15.7, 6.9 Hz), 5.43 (brs, 2H), 5.11 (m, 2H), 4.76 (m, 6H), 4.35 (m, 2H), 4.03 (m, 2H), 3.66 (m, 2H), 3.48 (s, 3H), 3.49 (s, 3H), 2.86 (m, 2H), 1.84 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 168.4 (2C), 136.1 (2C), 135.3, 135.3, 133.8, 132.9 (2C), 132.3, 132.2, 131.4, 128.5 (4C), 128.1 (4C), 127.7 (4C), 127.4 (2C), 122.1, 117.1, 85.4, 85.2, 83.4 (2C), 78.6 (2C), 59.6, 59.6, 58.0 (2C), 44.7, 30.5 (2C), 18.9; IR ($CHCl_3$) ν = 1738, 1213; HRMS (ES): calcd for $C_{42}H_{45}N_2O_6$ $[M + H]^+$: 673.3278; found: 673.3249.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

ORTEP drawing of compounds *anti*-**4** and *E*-**19** as well as copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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