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New applications of metal catalysis in natural product synthesis

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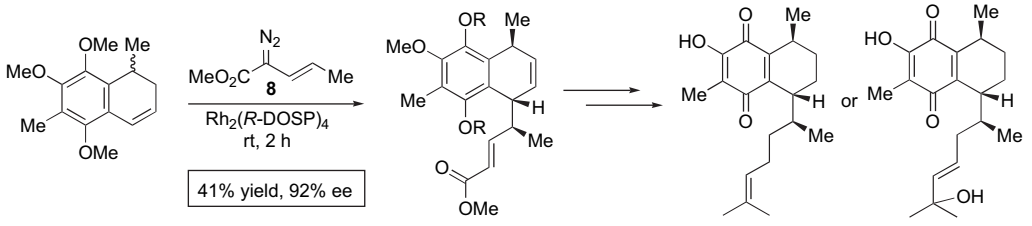
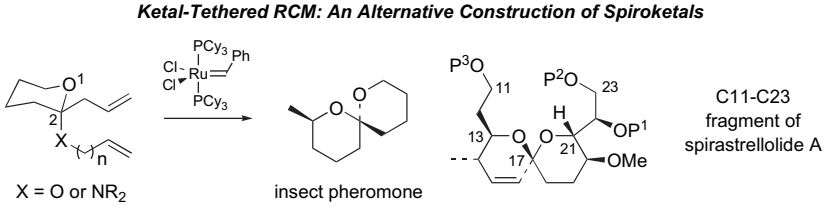
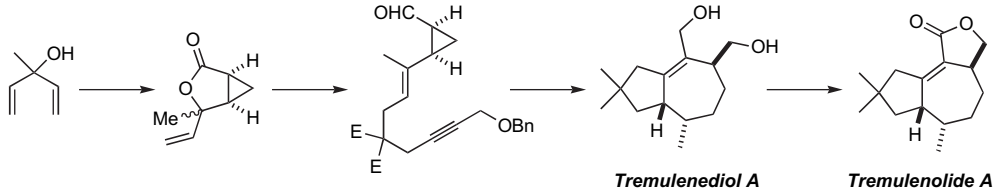
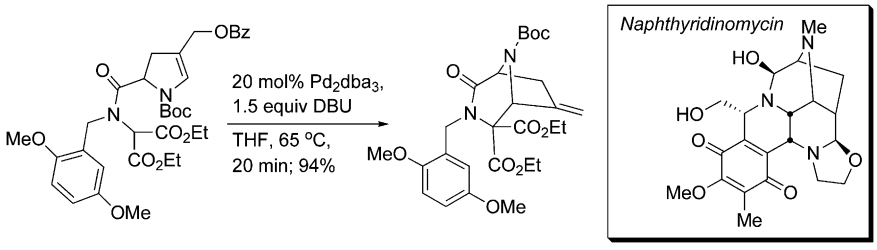
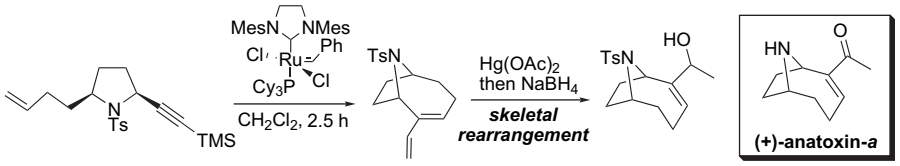
Contents

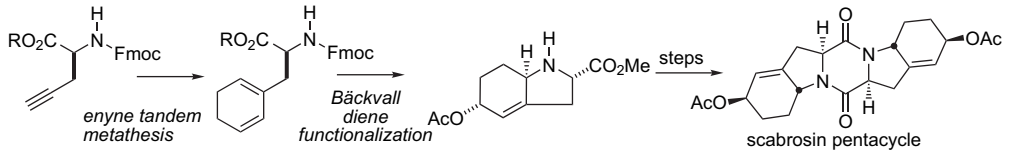


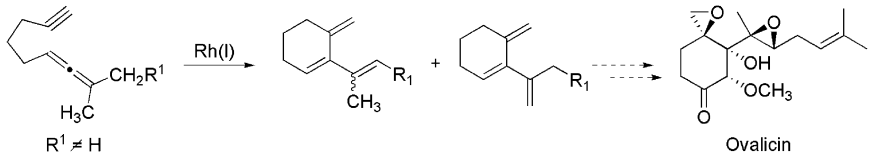


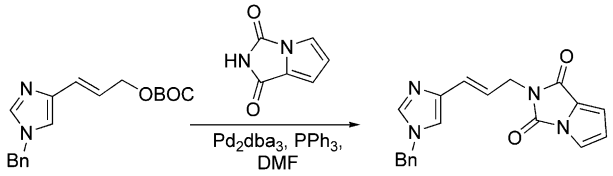


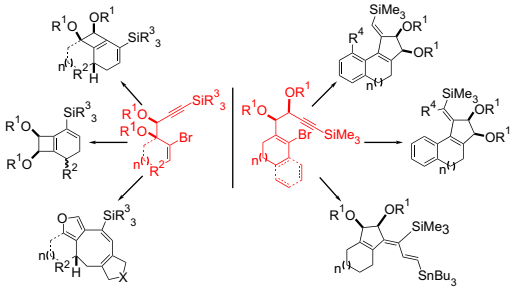


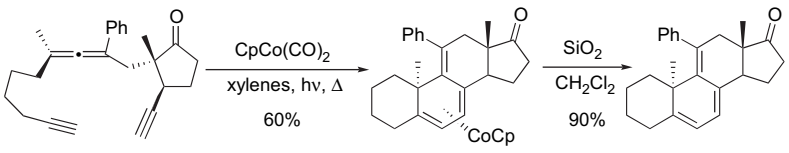


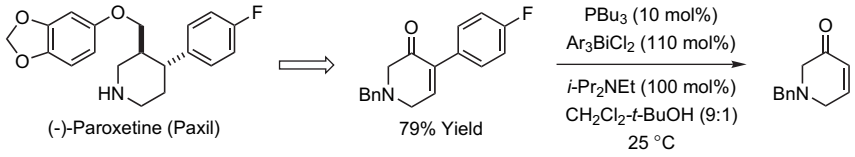












Exposure of dihydropyridinone **1** to the arylbismuth(V) reagent (p-F-Ph)$_3$BiCl$_2$ in the presence of substoichiometric quantities of tributylphosphine results in aryl transfer to the transiently generated (β-phosphonio)enolate, ultimately providing the α-arylated enone **2**. This transformation, which represents a regiochemical complement to the Mizoroki–Heck arylation, is used strategically in concise formal and enantioselective total syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL).

OTHER CONTENT

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COVER

The cover graphic illustrates a projected synthesis of ovalicin which takes place through the cross-conjugated triene intermediate generated in excellent yield using a rhodium(I)-catalyzed allenic Alder-ene reaction discovered in our group.

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112. Applications of catalysis in academia and industry, Michael J. Krische, Ed. *Tetrahedron* **2005**, *61*, 6155–6472.
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114. Multicomponent reactions, Ilan Marek, Ed. *Tetrahedron* **2005**, *61*, 11299–11520.
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116. Organocatalysis in organic synthesis, Pavel Kočovský and Anderi V. Malkov, Eds. *Tetrahedron* **2006**, *62*, 243–502.
117. Supramolecular chemistry of fullerenes, Nazario Martín and Jean-François Nierengarten, Eds. *Tetrahedron* **2006**, *62*, 1905–2132.
118. Chemistry of electron-deficient ynamines and ynamides, Richard P. Hsung, Ed. *Tetrahedron* **2006**, *62*, 3771–3938.
119. Microwave assisted organic synthesis, Nicholas E. Leadbeater, Ed. *Tetrahedron* **2006**, *62*, 4623–4732.
120. Nature-inspired approaches to chemical synthesis, Erik J. Sorensen and Emmanuel A. Theodorakis, Eds. *Tetrahedron* **2006**, *62*, 5159–5354.
121. The chemistry of radical ions, Paul E. Floreancig, Ed. *Tetrahedron* **2006**, *62*, 6447–6594.
122. Recent advances in oxidation chemistry, Dan Yang, Ed. *Tetrahedron* **2006**, *62*, 6595–6718.
123. Stereoselective and catalyzed halogenation reactions, Thomas Lectka, Ed. *Tetrahedron* **2006**, *62*, 7141–7204.
124. Recent advances in organonickel chemistry, Timothy F. Jamison, Ed. *Tetrahedron* **2006**, *62*, 7493–7610.
125. New applications of metal catalysis in natural product synthesis, Kay M. Brummond, Ed. *Tetrahedron* **2006**, *62*, 10467–10602.

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Preface

New applications of metal catalysis in natural product synthesis

Metal catalysis has dramatically altered the way we design syntheses and assemble natural products. Moreover, metal catalysis provides entry to molecular structures and functionalities that were previously inaccessible or difficult to obtain using more classical approaches. The contributors to this symposium have provided a snapshot of recently discovered methods involving metal catalysis and the application to natural product synthesis. Importantly, the scope of each of these methods has been extended by the pursuit of natural product synthesis.

For example, Diver and Mori have given us a new way to think about assembling functionalized dienes. Substituted cyclohexadienes are obtained via a ruthenium catalyzed tandem metathesis reaction between a diene and an alkyne. This protocol is used by Diver to access the cyclohexenyl subunits of pentacyclic core of scabrosin. In addition, Mori has validated the synthetic usefulness of an intramolecular ruthenium catalyzed enyne metathesis reaction, which affords an azabicyclo[4.2.1]nonene ring system possessing an appropriately placed diene particularly well-suited for the enantioselective synthesis of anatoxin A.

Hsung has shown that the ruthenium catalyzed metathesis conditions are mild enough to afford spiroketals stereoselectively via the reaction of a diene possessing a ketal tethering unit. This strategy for preparing sprioketals has been successfully applied to the synthesis of an insect pheromone and a key fragment of spirastrellolide.

The wide-ranging utility of palladium catalyzed allylic alkylation reactions has been reaffirmed by Wipf and Lovely in their efficient synthetic approaches to the alkaloid cores of naphthyridinomycin and iroidins, respectively. Martin and Davies used chiral rhodium(II) catalysis to install the requisite absolute stereochemistry in their respective targets and both showcase the power of tandem transition-metal catalyzed reactions. Martin has prepared tremulenolide A and tremulenediol A using an enantioselective rhodium(II) catalyzed cyclopropanation reaction followed by a tandem rhodium(I) catalyzed allylic alkylation and carbocyclization reaction. Davies has successfully applied a C–H activation/Cope rearrangement strategy to the first synthesis of (+)-elisabethadione.

Malacria and our group have shown that a selective reaction of one double bond of an allene gives unprecedented substructures. In Malacria's case an allenediyne provides the steroidal carbocyclic core in one-step via an intramolecular Co(I) mediated [2+2+2] cycloaddition reaction. A carbocyclization reaction of an allenyne has been accomplished in our group, leading to a carbocyclic skeleton that will be used as a framework in the projected synthesis of ovalicin.

Suffert has extended the scope of the 4-*exo-dig* cyclocarbopalladation/Stille cross coupling reaction by adding on an 8π electrocyclization reaction. This extraordinary cascade of reactions lead to carbocyclic cores present in a number of biologically important terpenes. Finally, a complement to palladium catalyzed alpha arylation of ketones has been provided by the Krische laboratory where they have shown that enones can be regioselectively alpha arylated via the conjugate addition of tributylphosphine and trapping the resulting enolate with an aryl bismuth reagent. Using this method an enantioselective synthesis of paroxetine was accomplished.

As the guest editor of this Symposium-in-Print, I would like to thank all authors and referees who contributed to this issue. I am especially grateful to Thomas Dunn who has designed the cover graphic to correlate the natural products in this issue with the transition metals used to access them. In addition, a special thanks goes to Jamie McCabe for her help with the organization and submission of the finalized proofs.

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Application of the combined C–H activation/Cope rearrangement as a key step in the total syntheses of the assigned structure of (+)-elisabethadione and a (+)-*p*-benzoquinone natural product

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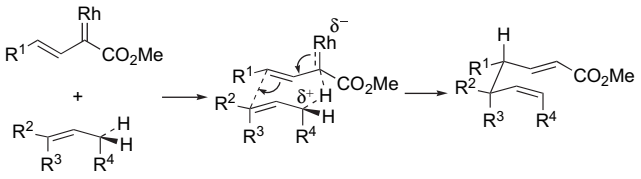
Abstract—The enantioselective total syntheses of the assigned structure of (+)-elisabethadione (**3**) and the (+)-*p*-benzoquinone natural product **4** is described. The stereocontrolled formation of the three key stereocenters in the natural products is achieved in a single step through the combined C–H activation/Cope rearrangement, a C–H functionalization process catalyzed by the dirhodium tetraprolinate, Rh_2(*R*-DOSP)$_4$ (DOSP=(*N*-dodecylbenzenesulfonyl)prolinate).

1. Introduction

Natural product synthesis is the classic proving ground for evaluating new synthetic methods. The successful implementation of a new method in a complex synthesis will require the process to be compatible with a range of functional groups and will demonstrate the viability of the new method compared to the established strategies of organic synthesis. The use of new metal-catalyzed processes in natural product synthesis is especially attractive because it opens up the possibility for the development of unusual organometallic transformations. If chiral catalysts are used, new enantioselective strategies for synthesis could be designed. Thus, the opportunity exists for considering revolutionary retrosynthetic disconnections that would not have been realistic using more conventional chemistry. In this paper, we describe a new C–H functionalization process that has the potential of broad utility for the synthesis of a family of marine diterpenes isolated from gorgonian corals.[1–6]

For the last few years, our group has been exploring the possibility of developing practical methods for enantioselective intermolecular C–H activation by means of metal carbenoid-induced C–H insertion.[7] If sufficient selectivity can be engineered into the chemistry, then the methodology could be extremely attractive because it would avoid many of the functional group manipulations that are often required in a natural product total synthesis. The intermolecular metal carbenoid-induced C–H insertion has been shown to be complimentary to some of the classic strategic reactions in synthesis, such as the aldol reaction,[8] the Mannich reaction,[9] the Michael addition,[10] the Claisen condensation[11] and the Claisen rearrangement.[12] In this paper, we describe the application to natural product total synthesis of a variant of the direct C–H activation, which we have described as the 'combined C–H activation/Cope rearrangement' (Scheme 1).[13] As the name suggests, the process begins as a C–H activation but before this is completed, a Cope rearrangement occurs to form a 1,5-diene.[13b] The reaction is highly diastereoselective (>98% de), which is typical for a Cope rearrangement, and when an appropriate chiral catalyst is used the reaction can also be highly enantioselective (>97% ee).[2g,4c,13]



Scheme 1. General scheme of the combined C–H activation/Cope rearrangement.

In order to demonstrate the synthetic potential of this chemistry, we have explored its application in total synthesis.[2g,4c] Diterpenes isolated from **Pseudopterogorgia elisabethae** were chosen as targets because they have broad range of biological activity and are of intense current interest.[1] This

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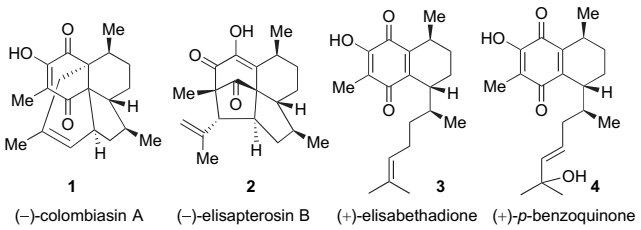
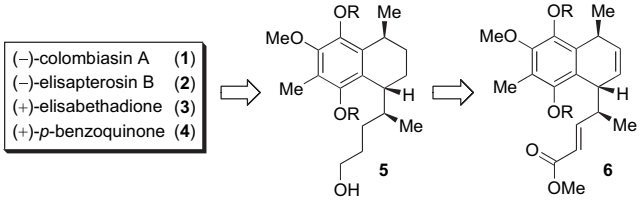


Figure 1. Structures of natural products **1**–**4**.

class of diterpenes exhibits a diverse range of structures, from bicyclic to polycyclic systems as illustrated in the representative examples shown in Figure 1.[2,3,14,15] These targets were considered especially attractive for the application of new methodology because even though a number of total syntheses of these compounds have been reported,[1] controlling the three stereocenters common to this class of diterpenes has been challenging.[2–6] The three stereocenters lack neighboring functional groups and this has been the main cause for the difficulty in developing a direct stereoselective synthesis. Therefore, a C–H activation strategy would be an intriguing approach to solve the stereochemical problem.

The ideal strategy to these synthetic targets not only would efficiently generate the three common stereogenic centers of these natural products, but also would introduce a side chain with appropriate functionality for rapid conversion to the natural products. A generally applicable precursor to the representative targets **1**–**4** would be the alcohol **5** (Scheme 2). This could be easily prepared from the



Scheme 2. Retrosynthetic analysis of natural products **1**–**4**.

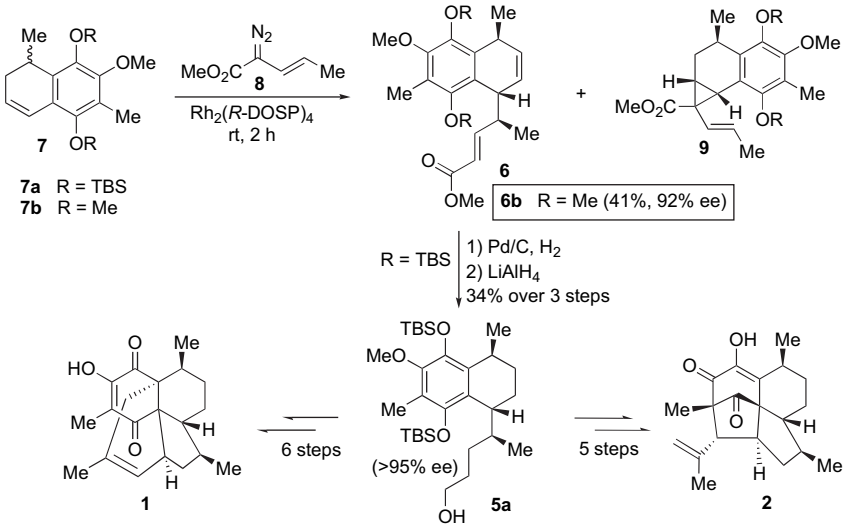
1,5-diene **6**, a product of the combined C–H activation/Cope rearrangement between a dihydronaphthalene and a vinylcarbenoid. We have recently described the application of this strategy to the synthesis of (–)-colombiasin A (**1**) and (–)-elisapterosin B (**2**).[2g] In this paper, we describe the extension of this chemistry to the total synthesis of the assigned structure of (+)-elisabethadione (**3**)[14] and the (+)-*p*-benzoquinone natural product **4**.[15] Both of these compounds display potent anti-inflammatory activity but neither has been previously synthesized.

The initial steps in the synthesis of **3** and **4** follow the same strategy that was used in the synthesis of (–)-colombiasin A (**1**) and (–)-elisapterosin B (**2**).[2g] The crucial step is the combined C–H activation/Cope rearrangement between the dihydronaphthalene **7** and the vinyldiazoacetate **8** (Scheme 3). An exceptional chiral catalyst for this transformation is Rh_2(*R*-DOSP)$_4$. When the reaction is catalyzed by Rh_2(*R*-DOSP)$_4$, one enantiomer of the dihydronaphthalene undergoes a C–H activation/Cope rearrangement to form **6** while the other enantiomer of **7** undergoes cyclopropanation to form **9**. Thus, in this process, the three crucial stereocenters common to these natural products are formed with excellent control of both relative and absolute configuration. The reaction has been equally effective in the reaction with the siloxy derivative **7a** and the methoxy derivative **7b**.[2g] The siloxy derivative **6a** has been effectively converted to (–)-colombiasin A (**1**) and (–)-elisapterosin B (**2**) in a very direct manner (eight and seven steps, respectively).[2g] In this paper, we demonstrate that the methoxy derivative **6b** is ideally functionalized for further manipulation and can be readily utilized for the synthesis of **3** and **4**.

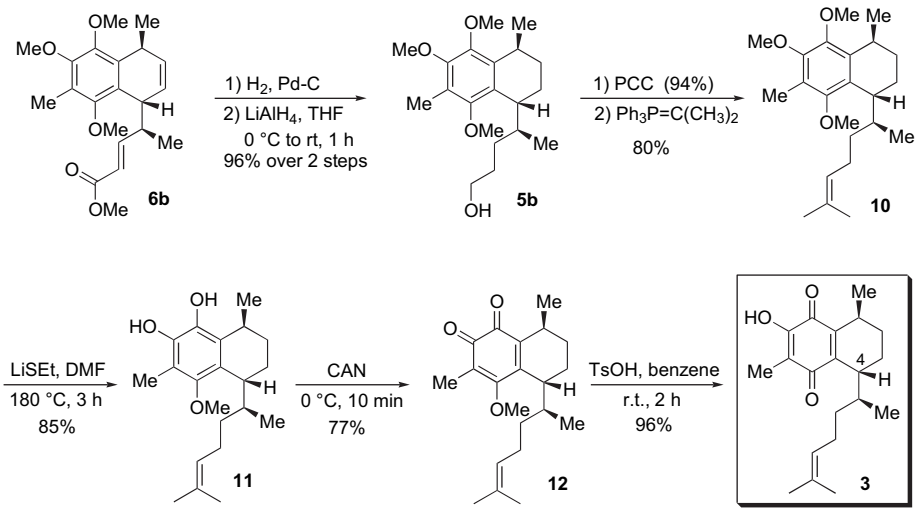
2. Results and discussion

2.1. Total synthesis of the assigned structure of (+)-elisabethadione

(+)-Elisabethadione (**3**) was isolated from the marine organism *P. elisabetha*, collected from the Florida Keys by Kerr



Scheme 3. Key step: combined C–H activation/Cope rearrangement.



Scheme 4. Total synthesis of the assigned structure of (+)-elisabethadione.

and co-workers.[14] Its gross structure was assigned on the basis of detailed NMR analysis, but its stereochemistry was assumed by analogy to other members of this class of biogenetically related natural products.[16] Anti-inflammatory assays indicate that elisabethadione is more potent than the related and commercially used natural products, the pseudopterosins.[17]

Our synthesis of the assigned structure of elisabethadione (**3**) began with the previously described combined C–H activation/Cope rearrangement of the dihydronaphthalene **7b** with the vinyldiazoacetate **8** (Scheme 3).[2g] The Rh_2(*R*-DOSP)$_4$ catalyzed reaction of **7b** and **8** gave a 1:1 mixture of the C–H functionalization product **6b** (41% yield, 92% ee, enantiomeric excess was determined from the alcohol **5b**) and the cyclopropane **9b** (43% yield) as single diastereomers. In this key step, the correct configuration of the three stereocenters in **3** was generated.

The C–H functionalization product **6b** is well suited for further elaboration to **3** (Scheme 4). The 1,5-diene in **6b** was hydrogenated and then the ester group was reduced to the alcohol **5b** in 96% yield over two steps. Oxidation of **5b** with PCC followed by a Wittig reaction on the resultant aldehyde furnished the alkene **10**. Having installed the side chain, the next operation was the oxidation of the aromatic ring to the quinone. Several initial attempts for the demethylation (BBr_3) and the oxidative demethylation [PhI(OAc)$_2$;[18] AgO/HNO_3[19,2b,c]] of **10** failed. Fortunately, heating the compound **10** with lithium ethanethiolate in DMF at 180 °C for 3 h resulted in the formation of the bisphenol **11** in 85% yield (Scheme 4).[20] Oxidation of **11** with cerium ammonium nitrate followed by demethylation and bond reorganization of the resultant red *ortho*-quinone **12** under acidic conditions gave **3**, the assigned structure of elisabethadione, in 96% yield as a yellow oil.

Contrary to our expectations, the reported ^{1}H and ^{13}C NMR data for the natural product (+)-elisabethadione, while similar, were different from our synthetic compound **3** (Fig. 2). The NMR, IR, and HRMS data indicated that the synthetic material had the same number of protons, carbons, and molecular weight as the natural material. The specific rotation of the synthetic material (+278, *c* 0.58, $CHCl_3$) was quite different from that of the natural product (+93). On the basis of this data, either the assigned structure of the natural material or our synthetic material is incorrect. Another possibility could be the errors in the reported data for the natural material. Unfortunately, it was not possible to evaluate this possibility because neither an authentic sample nor the original NMR spectra of the natural product were available.[21]

The most convincing method to determine whether the synthetic material had the assigned structure would be X-ray crystallographic analysis. Unfortunately, we were unable to prepare a crystal suitable for X-ray analysis. The NOE

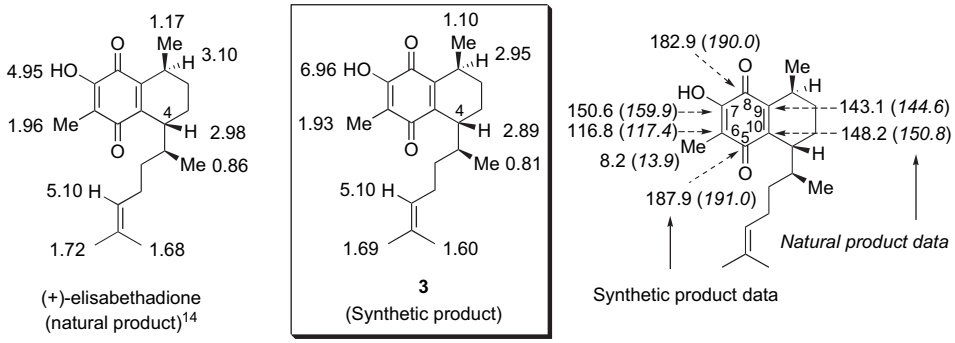
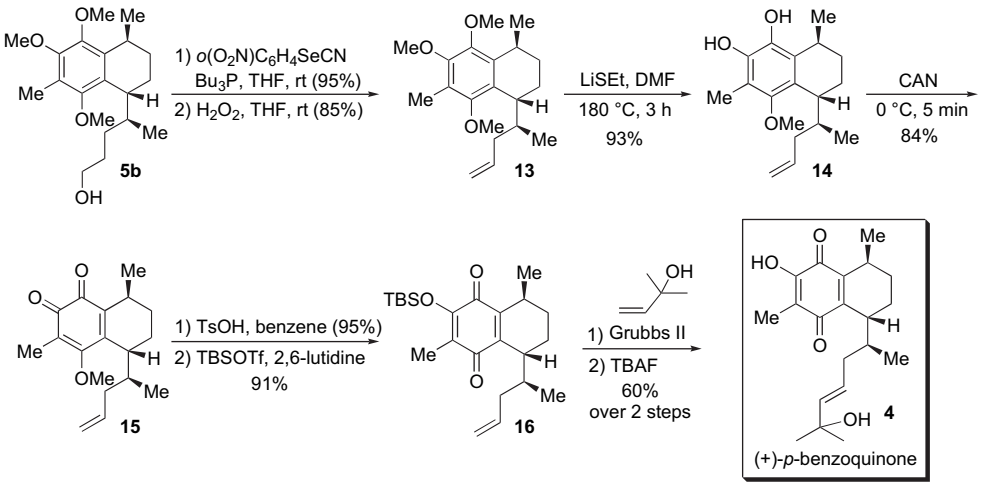


Figure 2. ^{1}H and ^{13}C NMR data of the natural and synthetic (+)-elisabethadione.



Scheme 5. Total synthesis of (+)-*p*-benzoquinone **4**.

studies also proved inconclusive. Therefore, a re-analysis of the synthetic scheme to **3** was made to determine if at any stage, an unexpected diastereomer could conceivably be formed. Five steps in Scheme 4 were identified to have the potential for the introduction of the wrong stereochemistry. The first was the combined C–H activation/Cope rearrangement to form **6b**. This was unlikely to be a problem because the enantio-divergent step to form **6b** has been reliable with a range of substrates.[2g,4c] This included the generation of the siloxy derivative **6a**, which has been successfully converted to (−)-colombiasin A (**1**) and (−)-elisapterosin B (**2**).[2g] The unsaturated ester in **6b** has a potentially epimerizable center at the γ-position, and so isomerization might have occurred under the hydrogenation conditions. The harsh conditions of the demethylation of **10** to **11** (LiSEt, 180 °C) could have caused an isomerization to occur although no obvious pathway is apparent. Finally, the formation of the *ortho*-quinone **12** and its conversion to the *para*-quinone **3** could have caused isomerization because the quinones **12** and **13** do have potentially epimerizable centers. None of these potential epimerization steps, however, is likely because there does not appear to be a driving force for a complete isomerization, especially as the tetrahydronaphthalene is already trans disubstituted.

2.2. Total synthesis of the (+)-*p*-benzoquinone 4

In order to confirm the proposed configuration of the synthetic material as **3**, the total synthesis of a second related natural product, the (+)-*p*-benzoquinone **4**, was conducted using all of the potentially epimerizable steps that has been used in the synthesis of **3**. The general outline of the synthesis is shown in Scheme 5. The synthesis started from the primary alcohol **5b**, the same intermediate used in the synthesis of compound **3**. The terminal alkene **13** was generated by the application of Grieco's selenoxide introduction/elimination procedure.[22] Then performing a similar sequence as used in the synthesis of **3**, **13** was converted to the quinone **16**. Selective demethylation of **13** to form the bisphenol **14**, followed by oxidation with cerium ammonium nitrate gave the *ortho*-quinone **15** in 84% yield. The subsequent isomerization of the *ortho*-quinone **15** gave the *para*-quinone, which was then protected by a TBS group to form **16** in 91% yield. Completion of the synthesis proceeded in a straightforward fashion. Installation of the allylic alcohol by a cross-metathesis reaction catalyzed by the Grubbs' second-generation ruthenium catalyst, using Jacobsen's strategy,[2f] followed by deprotection of the siloxy group afforded the natural product **4** in 60% yield over two steps. The spectral data of synthetic and natural (+)-*p*-benzoquinone **4** were identical (Fig. 3).[15] Furthermore, there was an excellent agreement in the ^{1}H and ^{13}C NMR data for the bicyclic portion of the synthetic material of **3**, the synthetic material of **4**, and the natural material of **4**. Assuming that the natural product **4** is correctly assigned, these results imply that the assigned structure of (+)-elisabethadione is incorrect or the reported spectral data for elisabethadione contain errors.

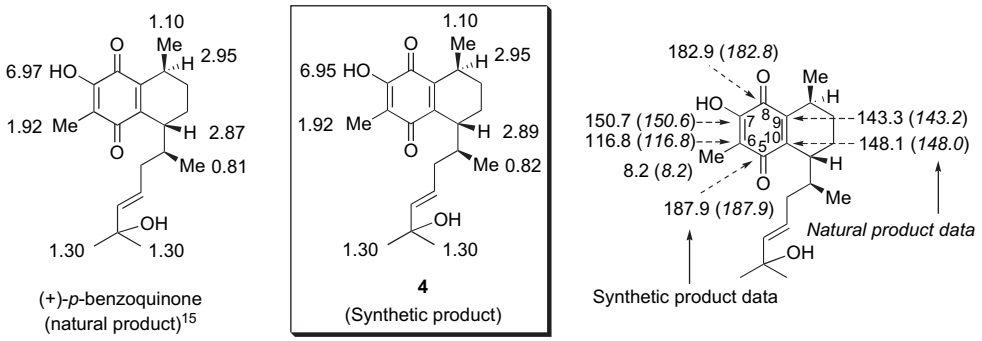


Figure 3. ^{1}H and ^{13}C NMR data of the natural and synthetic (+)-*p*-benzoquinone.

3. Conclusion

In summary, we have developed the first total syntheses of the assigned structure of (+)-elisabethadione (**3**) and the (+)-*p*-benzoquinone natural product **4**. The synthesis featured a Rh_2(*R*-DOSP)$_4$ catalyzed combined C–H activation/Cope rearrangement for the formation of the three key stereocenters in a single step.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in an oven-dried glassware with magnetic stirring. Low temperature (−78 °C) was maintained using dry ice/acetone. Hexanes, THF, DCM, CH_3CN, and Et_2O were purified by passage through a bed of activated alumina. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230–400 mesh). ^{1}H NMR spectra were measured at 300, 400, or 500 MHz spectrometers and are reported in parts per million using TMS as an internal standard (TMS at 0.00 ppm). Data were reported as (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad; coupling constant(s) in hertz; integration). ^{13}C NMR spectra were recorded at 75 or 125 MHz spectrometer and reported in parts per million using solvent as an internal standard ($CDCl_3$ at 77.0 ppm).

4.1.1. (*S*,2*E*)-Methyl 4-((1*S*,4*R*)-1,4-dihydro-5,7,8-trimethoxy-1,6-dimethylnaphthalen-4-yl)pent-2-enoate (6b). A solution of methyl vinyldiazoacetate **8** (3.40 g, 24.2 mmol, 3.0 equiv) in dry degassed 2,2-dimethylbutane (20 mL) was added by syringe pump over a 1 h period at room temperature to a solution of dihydronaphthalene **7b** (2.00 g, 8.1 mmol) and Rh_2(*R*-DOSP)$_4$ (306 mg, 0.16 mmol, 0.02 equiv) in dry degassed 2,2-dimethylbutane (30 mL). Once the addition had finished the brown solution was stirred at room temperature for an additional 30 min. The solvent was removed under vacuum to give a brown gum. Purification by column chromatography on silica gel (eluting with 7–10% ether/pentane) gave the *title compound* **6b** (1.19 g, 41%) along with cyclopropane **9b** (1.27 g, 43%). R_f 0.36 (7:1 pentane/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, J=16.0, 6.0 Hz, 1H), 5.85 (dd, J=16.0, 2.0 Hz, 1H), 5.84 (m, 1H), 5.49 (ddd, J=10.0, 4.0, 2.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.71 (m, 1H), 3.45 (m, 1H), 3.12 (m, 1H), 2.19 (s, 3H), 1.27 (d, J=7.0 Hz, 3H), 0.55 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 154.3, 152.2, 150.4, 147.4, 133.0, 132.9, 124.9, 123.3, 121.2, 119.7, 60.7, 60.3, 60.0, 51.4, 40.6, 39.3, 30.4, 23.9, 12.0, 9.3; IR (neat) 2953, 1723, 1651, 1462, 1318, 1079, 1015 cm^{-1}; HRMS *m*/*z* (EI) calcd for $C_{21}H_{28}O_5Na$, required: 383.1829; found: 383.1837.

4.1.2. (*S*)-4-((1*S*,4*R*)-1,2,3,4-Tetrahydro-5,7,8-trimethoxy-1,6-dimethylnaphthalen-4-yl)pentan-1-ol (5b). To a solution of ester **6b** (944 mg, 2.62 mmol) in ethanol (50 mL) was added 5% palladium on carbon (ca. 50 mg). The suspension was placed on a Parr Hydrogenator at 45 psi for 3 h. The reaction mixture was filtered through a pad of Celite™ on silica gel. The filtrate was concentrated in vacuo to give a clear gum, which was used without further purification for the next step. The crude product was dissolved in dry tetrahydrofuran (60 mL) and cooled to 0 °C. Lithium aluminum hydride (5.24 mL, 1.0 M in THF, 5.24 mmol, 2.0 equiv) was added and the mixture was stirred at room temperature for 1 h. Water (20 mL) was added drop-wise followed by ether (40 mL). The organic layer was separated, and the aqueous layer was extracted with ether (20×4 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent 20–33% ether/pentane) to give the *title compound* as a clear gum (847 mg, 94% over two steps, 92% ee). The enantiomeric excess of **5b** was determined by HPLC (Daicel Chiralcel OD-H, hexanes/*i*-PrOH=99:1, flow rate=0.7 mL/min) t_R=21.3 min (major), t_R=23.3 min (minor). $[\alpha]_D^{25}$ 6.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.61 (m, 2H), 3.16 (m, 1H), 2.85 (m, 1H), 2.17 (s, 3H), 1.92–2.03 (m, 2H), 1.75–1.79 (m, 2H), 1.66 (m, 1H), 1.58 (m, 1H), 1.45 (m, 1H), 1.35 (m, 2H), 1.14 (d, J=7.0 Hz, 3H), 0.75 (d, J=7.0 Hz, 3H), OH signal was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 149.5, 147.1, 134.8, 128.6, 122.2, 63.3, 60.5, 60.2, 59.9, 37.4, 35.4, 31.2, 30.6, 27.0, 26.4, 23.2, 18.5, 18.1, 9.4; IR (neat) 2932, 1403, 1071, 731 cm^{-1}; HRMS *m*/*z* (EI) calcd for $C_{20}H_{32}O_4Na$ [M]$^+$, required: 359.2193; found: 359.2197.

4.1.3. (*S*)-4-((1*S*,4*R*)-1,2,3,4-Tetrahydro-5,7,8-trimethoxy-1,6-dimethylnaphthalen-4-yl)pentanal. To a solution of **5b** (210 mg, 0.62 mmol) in dry DCM (20 mL), pyridinium chlorochromate (202 mg, 0.94 mmol, 1.5 equiv) was added in one portion at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h and then diluted with ether (100 mL). The crude reaction mixture was filtered through a plug of Celite on silica gel. The filtrate was concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (eluting with 13% ether/pentane) gave the *title compound* as a clear gum (194 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.16 (m, 1H), 2.83 (m, 1H), 2.32–2.50 (m, 2H), 2.17 (s, 3H), 1.90–2.01 (m, 2H), 1.78 (m, 2H), 1.56–1.69 (m, 2H), 1.48 (m, 1H), 1.40 (d, J=7.0 Hz, 3H), 0.78 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 152.9, 149.7, 147.1, 134.7, 127.9, 122.3, 60.5, 60.1, 59.9, 42.4, 37.5, 35.6, 27.4, 27.0, 26.4, 23.2, 18.8, 18.1, 9.4; IR (neat) 2933, 1724 (C=O), 1457, 1403, 1072 cm^{-1}; HRMS *m*/*z* (EI) calcd for $C_{20}H_{30}O_4Na$ [M]$^+$, required: 357.2036, found: 357.2033.

4.1.4. (1*R*,4*S*)-1,2,3,4-Tetrahydro-5,6,8-trimethoxy-4,7-dimethyl-1-((*S*)-6-methylhept-5-en-2-yl)naphthalene (10). *n*-BuLi (*n*-hexane solution, 0.54 mL, 0.87 mmol, 2.90 equiv) was added drop-wise to a solution of isopropyltriphenylphosphonium iodide (389 mg, 0.90 mmol, 3.0 equiv) in dry THF (15 mL) at 0 °C under argon. The mixture was stirred for 1 h at the same temperature. A solution of aldehyde **17** (100 mg, 0.29 mmol) in dry THF (20 mL) was charged into the solution at 0 °C, and the resulting solution was stirred for an additional 30 min at the same temperature. The reaction was allowed to warm to room temperature for 30 min, and then refluxed under argon for

another 2 h. After cooling down, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 2% ether/pentane) gave the *title compound* (86 mg, 80%). $[\alpha]_D^{25}$ 6.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (t, *J*=7.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.15 (m, 1H), 2.88 (m, 1H), 2.18 (s, 3H), 1.91–2.07 (m, 4H), 1.79 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.45 (m, 1H), 1.22–1.38 (m, 2H), 1.14 (d, *J*=7.5 Hz, 3H), 0.72 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 149.5, 147.0, 134.9, 130.8, 128.7, 125.3, 122.2, 60.5, 60.1, 59.9, 37.5, 35.74, 35.71, 27.0, 26.7, 26.4, 25.7, 23.2, 18.6, 18.3, 17.6, 9.5; IR (neat) 2930, 1458, 1404, 1074, 1030 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{23}H_{36}O_3Na$ $[M]^+$, required: 383.2557, found: 383.2562.

4.1.5. (5*R*,8*S*)-5,6,7,8-Tetrahydro-4-methoxy-3,8-dimethyl-5-((*S*)-6-methylhept-5-en-2-yl)naphthalene-1,2-diol (11). To a solution of ethanethiol (2.07 g, 33.31 mmol) in dry hexanes (15 mL) at 0 °C under argon was added *n*-butyllithium (5.20 mL, 8.33 mmol, 1.6 M in hexanes). The mixture was stirred at room temperature for 30 min. Then the mixture was concentrated in vacuo to give a white powder. The white powder and **10** (100 mg, 0.23 mmol) were dissolved in dry DMF (15 mL) at room temperature and the mixture was heated to reflux (180 °C oil bath) for 3 h. The reaction mixture was allowed to cool down to room temperature, acidified with 5% hydrochloric acid, and extracted with Et_2O (2×50 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 13% ether/pentane) gave the *title compound* (76 mg, 85%) as a yellow oil. $[\alpha]_D^{25}$ 13.0 (*c* 0.94, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (t, *J*=7.0 Hz, 1H), 4.92 (s, 1H), 4.78 (s, 1H), 3.63 (s, 3H), 3.05 (m, 1H), 2.86 (m, 1H), 2.18 (s, 3H), 2.00 (m, 4H), 1.80 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.50 (m, 1H), 1.30 (m, 2H), 1.18 (d, *J*=7.0 Hz, 3H), 0.74 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 140.1, 136.9, 130.8, 127.3, 125.3, 124.7, 114.9, 60.5, 37.6, 35.7, 35.5, 26.7, 26.5 (2C), 25.7, 21.6, 18.8, 18.2, 17.6, 9.2; IR (neat) 3419, 2957, 2927, 1450, 1292, 1093, 1008 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{21}H_{32}O_3$ $[M]^+$, required: 332.2346; found: 332.2346.

4.1.6. (5*R*,8*S*)-5,6,7,8-Tetrahydro-4-methoxy-3,8-dimethyl-5-((*S*)-6-methylhept-5-en-2-yl)naphthalene-1,2-dione (12). To a solution of diol **11** (76 mg, 0.228 mmol) in CH_3CN (8 mL), a solution of cerium ammonium nitrate (376 mg, 0.686 mmol, 3.0 equiv) in distilled water (8 mL) was added by syringe at 0 °C. The resulting red solution was stirred at 0 °C for 10 min. The reaction mixture was quenched with water (10 mL) and extracted with Et_2O (2×40 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 20% ether/pentane) gave the *title compound* (58 mg, 77%) as an orange red oil. $[\alpha]_D^{25}$ 271.0 (*c* 0.0317, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (br t, *J*=7.0 Hz, 1H), 3.92 (s, 3H), 2.89 (m, 1H), 2.65 (m, 1H), 2.06–1.98 (m, 2H), 1.98 (s, 3H), 1.93–1.88 (m, 1H), 1.86–1.73 (m, 2H), 1.70 (s, 3H), 1.67 (m, 1H), 1.62 (s, 3H), 1.44–1.34 (m, 3H), 1.08 (d, *J*=7.0 Hz, 3H), 0.85 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 179.4, 167.7, 150.6, 140.2, 131.5, 124.3, 119.6, 61.2, 37.1, 36.4, 35.6, 26.2, 26.1, 25.8, 25.7, 21.3, 18.5, 17.7, 17.5, 9.7; IR (neat) 2924, 1732, 1673, 1657, 1454, 1376, 1234 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{21}H_{30}O_3Na$ $[M]^+$, required: 353.2078, found: 353.2097.

4.1.7. Elisabethadione (3). To a solution of *ortho*-quinone **12** (20 mg, 0.06 mmol) in benzene (5 mL) at room temperature under argon was added 4-methylbenzenesulfonic acid monohydrate (23.0 mg, 0.12 mmol, 2.0 equiv). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 2–7% ether/pentane) gave the *title compound* (18 mg, 96%) as a yellow oil. $[\alpha]_D^{25}$ 278.0 (*c* 0.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, OH, 1H), 5.10 (br t, *J*=7.0 Hz, 1H), 2.95 (m, 1H), 2.89 (m, 1H), 2.10–1.94 (m, 2H), 1.93 (s, 3H), 1.88–1.74 (m, 3H), 1.69 (s, 3H), 1.63 (m, 1H), 1.60 (s, 3H), 1.49–1.43 (m, 1H), 1.35–1.21 (m, 2H), 1.10 (d, *J*=7.0 Hz, 3H), 0.81 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.9, 182.9, 150.6, 148.2, 143.1, 131.3, 124.5, 116.8, 36.9, 36.0, 35.7, 26.3, 26.1, 26.0, 25.7, 20.8, 18.1, 17.7, 17.6, 8.2; IR (neat) 3675, 2970, 2920, 1738, 1714, 1406, 1242, 1067 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{20}H_{28}O_3$ $[M]^+$, required: 316.2033; found: 316.2026. ^1H NMR (500 MHz, benzene) δ 6.73 (s, OH, 1H), 5.25 (m, 1H), 2.93 (m, 1H), 2.83 (m, 1H), 2.20–1.95 (m, 3H), 1.92 (s, 3H), 1.68 (s, 3H), 1.57 (s, 3H), 1.55 (m, 2H), 1.42–1.26 (m, 3H), 1.51 (m, 1H), 0.97 (d, *J*=7.0 Hz, 3H), 0.71 (d, *J*=7.0 Hz, 3H).

4.1.8. (1*R*,4*S*)-1,2,3,4-Tetrahydro-5,6,8-trimethoxy-4,7-dimethyl-1-((*S*)-pent-4-en-2-yl)naphthalene (13).[22] To a stirring solution of **5b** (95 mg, 0.28 mmol) and *o*-nitrophenyl selenocyanate (192 mg, 0.85 mmol) in dry THF (7 mL) under argon at room temperature was added tri-*n*-butylphosphine (212 μL, 0.85 mmol). After stirring for 3 h, the reaction mixture was quenched with ethanol (4 mL) and concentrated. The crude product was used directly for the next step. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J*=8.0 Hz, 1H), 7.52 (m, 2H), 7.30 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H), 3.16 (m, 1H), 2.98–2.83 (m, 3H), 2.17 (s, 3H), 2.10–1.65 (m, 6H), 1.54–1.40 (m, 3H), 1.14 (d, *J*=6.8 Hz, 3H), 0.76 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 149.6, 147.1, 146.9, 134.8, 134.1, 133.4, 129.2, 128.2, 126.4, 125.1, 122.2, 60.5, 60.2, 59.9, 37.3, 35.8, 35.5, 27.0, 26.6, 26.5 (2C), 23.2, 18.7, 18.4, 9.4; IR (neat) 2931, 1513, 1330, 1071, 729 cm^{-1}; HRMS *m/z* (EI) calculated for $C_{26}H_{35}NO_5Se$ $[M]^+$, required: 521.1675; found: 521.1675.

To a solution of the above crude product in THF (7 mL) was slowly added 30% aqueous hydrogen peroxide (0.35 mL) at 0 °C. Stirring was continued for 1 day at room temperature. Water was added and extracted with ether (twice). The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluting with 2–5% ether/pentane) to give **13** (80 mg, 90% yield) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.02–4.95

(m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.16 (m, 1H), 2.86 (m, 1H), 2.17 (s, 3H), 2.10–1.92 (m, 4H), 1.80–1.75 (m, 2H), 1.49–1.45 (m, 1H), 1.14 (d, J=7.0 Hz, 3H), 0.76 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 149.5, 147.0, 138.9, 134.8, 128.5, 122.2, 114.9, 60.5, 60.1, 59.9, 40.0, 37.8, 35.2, 27.0, 26.5, 23.2, 18.6, 18.1, 9.4; IR (neat) 2956, 1458, 1404, 1072 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{20}H_{30}O_3$ $[M]^+$, required: 318.2189; found: 318.2200.

4.1.9. (5*R*,8*S*)-5,6,7,8-Tetrahydro-4-methoxy-3,8-dimethyl-5-((*S*)-pent-4-en-2-yl)naphthalene-1,2-diol (14). To a solution of alcohol ethanethiol (0.47 g, 7.54 mmol) in dry hexanes (10 mL) at 0 °C under argon was added *n*-butyllithium (2.36 mL, 3.77 mmol, 1.6 M in hexanes). The mixture was stirred at room temperature for 30 min. Then the mixture was concentrated in vacuo to give white powder. The white powder and **13** (60 mg, 0.18 mmol) were dissolved in dry DMF (10 mL) at room temperature and the mixture was heated to reflux (180 °C oil bath) for 3 h. The red-brown reaction mixture was allowed to cool down to room temperature, acidified with 5% hydrochloric acid, and extracted with Et_2O (2×50 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 7–13% ether/pentane) gave the *title compound* (50 mg, 93%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.02–4.95 (m, 2H), 3.61 (s, 3H), 3.07 (m, 1H), 2.84 (m, 1H), 2.17 (s, 3H), 2.08–1.90 (m, 4H), 1.85–1.72 (m, 2H), 1.51–1.46 (m, 1H), 1.18 (d, J=7.0 Hz, 3H), 0.77 (d, J=7.0 Hz, 3H), OH signals were not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 140.2, 139.0, 137.1, 127.3, 124.6, 115.0, 114.9, 60.5, 39.9, 37.8, 35.0, 26.7, 26.2, 21.6, 18.7, 18.0, 9.2; IR (neat) 3437, 2932, 1451, 1294, 1097, 1006, 907 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{18}H_{26}O_3$ $[M+1]^+$, required: 291.1955, found: 291.1949.

4.1.10. (5*R*,8*S*)-5,6,7,8-Tetrahydro-4-methoxy-3,8-dimethyl-5-((*S*)-6-methylhept-5-en-2-yl)naphthalene-1,2-dione (15). A solution of diol **14** (50 mg, 0.17 mmol) in CH_3CN (5 mL) was cooled to 0 °C. A solution of cerium ammonium nitrate (254 mg, 0.46 mmol, 2.7 equiv) in distilled water (4 mL) was added by syringe. The reaction mixture was stirred at 0 °C for 5 min. The red reaction mixture was quenched with water (10 mL) and extracted with Et_2O (2×40 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting 13% ether/pentane) gave the *title compound* (41 mg, 84%) as an orange red oil. ^{1}H NMR (500 MHz, benzene-d_6) δ 5.68 (m, 1H), 5.02–4.98 (m, 2H), 3.03 (s, 3H), 2.91 (m, 1H), 2.41 (m, 1H), 2.02–1.81 (m, 3H), 1.69 (s, 3H), 1.57–1.48 (m, 1H), 1.44–1.33 (m, 2H), 1.12 (m, 1H), 1.08 (d, J=7.0 Hz, 3H), 0.65 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 180.9, 179.5, 166.4, 149.2, 140.5, 138.0, 121.0, 116.0, 60.2, 40.2, 36.8, 36.4, 26.6, 26.1, 21.4, 18.4, 17.4, 9.5; IR (neat) 2959, 1657, 1643, 1578, 1322, 1232, 983 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{18}H_{24}O_3Na$ $[M]^+$, required: 311.1618; found: 311.1614.

4.1.11. (5*S*,8*R*)-5,6,7,8-Tetrahydro-3-hydroxy-2,5-dimethyl-8-((*S*)-pent-4-en-2-yl)naphthalene-1,4-dione. To a solution of *ortho*-quinone **15** (41 mg, 0.14 mmol) in benzene (8 mL) at room temperature under argon was added 4-methylbenzenesulfonic acid monohydrate (54 mg, 0.28 mmol, 2.0 equiv). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 2–5% ether/pentane) gave the *title compound* (37 mg, 95%) as yellow oil. $[\alpha]_D^{25}$ 312 (*c* 0.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, OH, 1H), 5.80 (m, 1H), 5.04–4.98 (m, 2H), 2.95 (m, 1H), 2.89 (m, 1H), 2.09–1.89 (m, 3H), 1.93 (s, 3H), 1.88–1.74 (m, 2H), 1.65–1.57 (m, 1H), 1.51–1.45 (m, 1H), 1.10 (d, J=7.0 Hz, 3H), 0.83 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 182.9, 150.6, 148.1, 143.3, 137.8, 116.9, 115.9, 40.3, 37.0, 35.2, 26.2, 26.0, 20.8, 18.0, 17.6, 8.2; IR (neat) 3383, 2961, 1636, 1340, 1235, 912 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{17}H_{22}O_3$ $[M]^+$, required: 274.1563; found: 274.1564.

4.1.12. Dione (16). To a solution of the above *para*-quinone (22 mg, 0.076 mmol) in DCM (3 mL) at 0 °C under argon were added 2,6-lutidine (25 mg, 0.229 mmol, 3.0 equiv) and TBSOTf (24 mg, 0.092 mmol, 1.2 equiv) successively. The mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$ (4 mL) and extracted with Et_2O (2×30 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with pure pentane to 1% ether/pentane) gave the *title compound* (26 mg, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.04–4.97 (m, 2H), 2.94 (m, 1H), 2.84 (m, 1H), 2.09–1.90 (m, 3H), 1.93 (s, 3H), 1.87–1.79 (m, 1H), 1.77–1.71 (m, 1H), 1.63–1.58 (m, 1H), 1.48–1.43 (m, 1H), 1.05 (d, J=7.0 Hz, 3H), 0.97 (s, 9H), 0.82 (d, J=7.0 Hz, 3H), 0.30 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 183.2, 152.3, 145.5, 144.7, 138.0, 124.4, 115.8, 40.3, 36.7, 34.9, 26.2, 26.1, 25.8 (3C), 20.9, 19.0, 18.0, 17.5, 9.0, −3.9, −4.0; IR (neat) 2956, 1658, 1234, 1165, 836 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{23}H_{36}O_3Si$ $[M+1]^+$, required: 389.2506; found: 389.2506.

4.1.13. (+)-*p*-Benzoquinone (4). To a solution of terminal olefin **16** (15 mg, 0.038 mmol) in DCM (2 mL) were added 2-methyl-3-buten-2-ol (20 μL, 0.193 mmol, 5.00 equiv) and Grubbs' second-generation catalyst (3.3 mg, 0.0038 mmol, 0.10 equiv). The red reaction mixture was refluxed for 12 h then directly filtered through a pipette column, eluting with 13% ether/pentane to give a yellow oil.

To a solution of the above crude product in THF (4 mL) at 0 °C under argon was added TBAF (38 μL, 0.038 mmol, 1.0 M solution in THF, 1.0 equiv). The yellow solution turned out to purple immediately. After 1 min, the reaction mixture was quenched with saturated H_2O (4 mL) and extracted with Et_2O (2×30 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 13–25% ether/pentane) gave the *title compound* **4** (7.7 mg, 60% over two steps) as a yellow oil. $[\alpha]_D^{25}$ 270 (*c* 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, OH, 1H), 5.62 (m, 2H), 2.95 (br q, J=7.0 Hz, 1H), 2.89 (br t, J=4.5 Hz, 1H), 2.04–1.91 (m, 2H), 1.92 (s, 3H), 1.91–1.79

(m, 2H), 1.78–1.73 (m, 1H), 1.65–1.57 (m, 1H), 1.50–1.45 (m, 1H), 1.30 (s, 6H), 1.10 (d, J=7.0 Hz, 3H), 0.82 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 182.9, 150.7, 148.1, 143.3, 139.6, 126.2, 116.8, 70.6, 38.5, 37.4, 35.3, 29.8, 29.7, 26.2, 26.0, 20.8, 18.2, 17.6, 8.2; HRMS m/z (EI) calcd for $C_{20}H_{28}O_4$ $[M]^+$, required: 332.1982; found: 332.1982.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.086.

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A ketal-tethered RCM strategy toward the synthesis of spiroketal related natural products

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Abstract—An unconventional approach to construct spiroketals and spiroaminals via ring-closing metathesis [RCM] of cyclic ketals and aminals, respectively, is described here. This method possesses a good generality with no loss of stereochemical integrity at the spirocenter under the standard RCM conditions. This approach has been applied to the synthesis of an insect pheromone to demonstrate its synthetic potential, and also to the synthesis of the C11-*epi*-C22-C23 fragment in spirastrellolide A. Both are proof-of-concept applications to feature a ketal-tethered RCM as an alternative strategy for construction of spiroketals.

1. Introduction

Ring-closing metathesis [RCM] represents an important strategy in natural product synthesis.[1,2] It has come to our attention that despite being well known entities, acetals or ketals have not been extensively utilized as tethers, whether 'temporary' or 'permanent', in RCMs. A survey of the literature reveals that most RCM reactions involving acetal or ketal functionalities can be divided into four types with overlaps in concept. As shown in Figure 1, type **a** [see **1**] is the most common with both olefins connected through the ketal carbon C2. However, in these cases, the ketal is used primarily as a carbonyl-protecting group and not as a tether,[1,2] and likewise, the ketal in type **b** [see **2**], another common scenario, is to primarily protect diols. Types **c** [**3**] and **d** [**4**] would best represent an acetal or ketal serving as a tether in RCM, but they are much less common. Some elegant examples of type **c** would be those reported by Burke,[3] and Grubbs and Scholl[4] in constructing bridged ketals via RCM, and by Rutjes[5] in syntheses of pyrans and piperidines via either acetal- or aminal-tethered RCMs.

It was surprising to find that there were even fewer examples of type **d** [**4**] ketal-tethered RCM besides van Boom's precedent-setting work employing more robust carbohydrate-based cyclic ketals[6] and Harrity's beautiful RO-RCM study that led to syntheses of spiroketals.[7] Type **d** ketal-tethered RCM using **4**, or in fact reactions in general, would represent a conceptually different synthesis of spiroketals or spiroaminals **5**, although spiroketals have been conventionally constructed through conventional internal ketalizations of

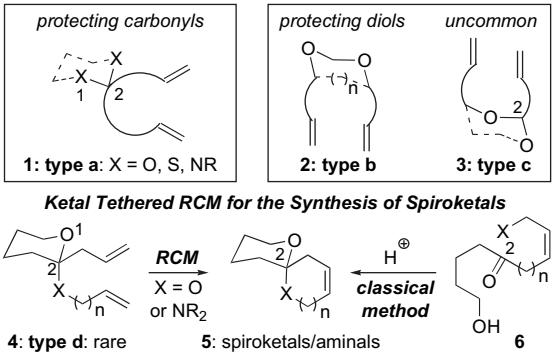

Figure 1.

ketones [**6**→**5** in Fig. 1] under acidic conditions or variations of that principle concept.[8]

Given the significance of spiroketals in natural products, we explored the type **d** RCM as part of an ongoing program in developing ketal-tethered synthetic strategies toward natural product syntheses.[9–12] Specifically, we became interested in spirastrellolide A, a novel spiroketal-rich macrolide from marine sponge *Spirastrellolide coccinea* reported by Roberge et. al.,[13a] and recently, its structure was revised as shown in Figure 2.[13b] In addition to its ability to cause untimely mitotic arrest in cells, spirastrellolide A was shown to exhibit potent inhibitory activity against protein phosphatase 2A [IC_{50}=1 nM] with an excellent selectivity for PP2A over PP1 [ratio of IC_{50} values=1:50].[13,14] The C11-C23 fragment in spirastrellolide A became an ideal proof-of-concept application to feature a ketal-tethered RCM as an alternative strategy for construction of spiroketals. We report

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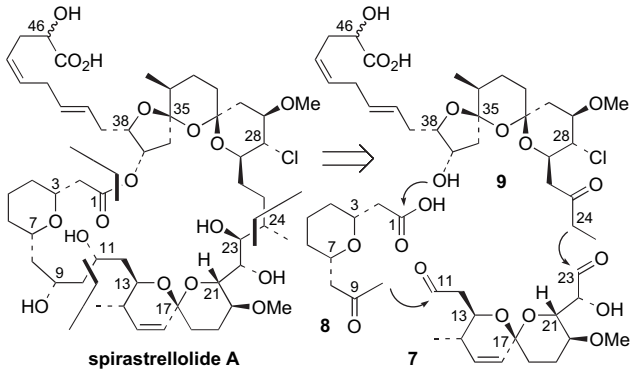


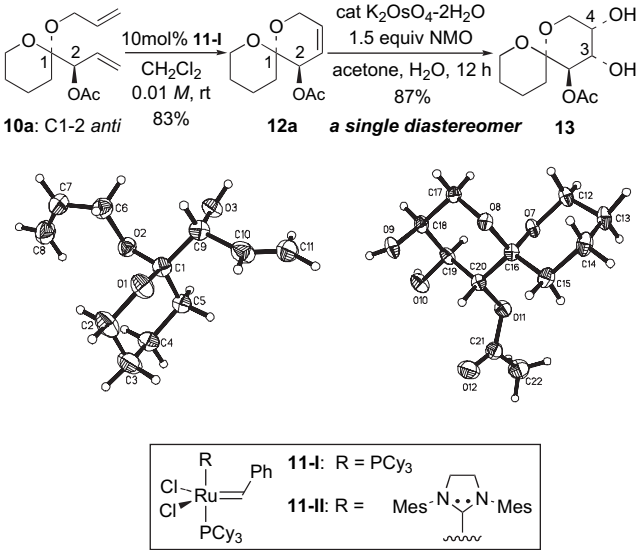
Figure 2.

here details of ketal- and aminal-tethered RCM in the synthesis of spiroketals and spiroaminals, respectively, in addition to the synthesis of the C11-*epi*-C22-C23 fragment of spirastrellolide A.

2. Results and discussions

2.1. Feasibility: RCM of 1,2-*anti*- and 1,2-*syn*-ketals

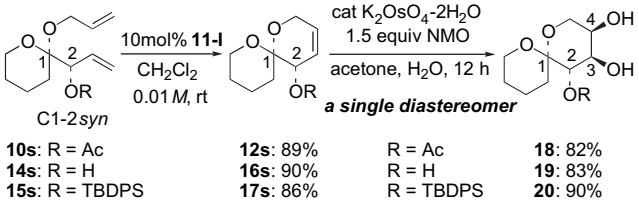
To demonstrate the feasibility of this concept, we first employed cyclic 1,2-*anti*-ketal **10a**, which was readily prepared from dihydropyran.[9] The notation '**a**' represents the *anti* [or trans] relative stereochemical relationship between the C1-*O*-allyl and C2-OAc groups. The relative stereochemistry of **10a** was unambiguously assigned using its X-ray structural analysis [Scheme 1] because we were interested in the stereointegrity of the C1 spirocenter under RCM conditions. The subsequent RCM of **10a** was carried out at rt employing the Grubbs' generation-I Ru-catalyst[1,2] [**11-I**] in CH_2Cl_2 and led to the desired C1,2-*anti* spiroketal **12a** in 83% yield, although generation-II Ru-catalyst [**11-II**][15–18] could also be employed with comparable efficiency.



Scheme 1.

We could quickly demonstrate that it was feasible to functionalize the C3-4 olefin in a highly stereoselective manner. Dihydroxylation of **12a** using K_2OsO_4 and NMO led to diol **13** in 87% yield as a single diastereomer [Scheme 1]. The relative stereochemistry of diol **13** was assigned also using X-ray structural analysis. This study suggests the possibility of building up stereochemical complexity of the spiroketal ring system using **12a** as a chiral template. It is also noteworthy that the assignment of **13** implies there was no erosion of stereochemical integrity at the C1 spirocenter during the RCM.

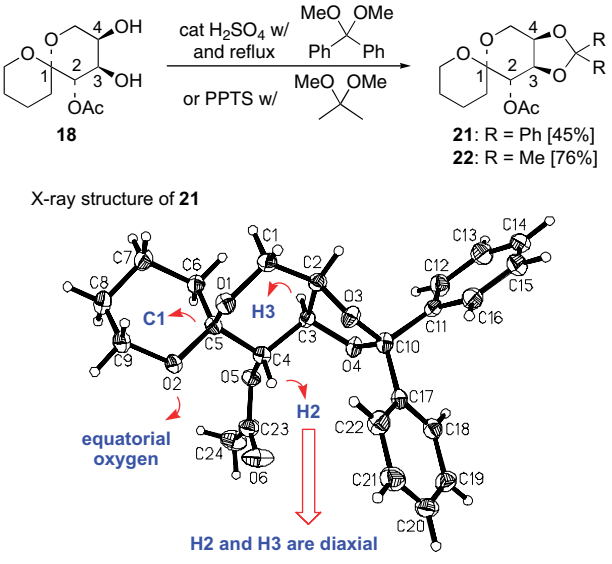
Subsequently, when we used cyclic 1,2-*syn*-ketals such as **10s**, **14s**, and **15s**, we were able to also establish the feasibility of their respective RCM without encountering any unexpected problems to afford C1,2-*syn* spiroketals **12s**, **16s**, and **17s**, respectively, in high yields [Scheme 2]. Likewise, the ensuing dihydroxylations of these *syn* spiroketals were also highly diastereoselective, leading to diols **18**–**20**, respectively, in good yields. However, this was where we observed an interesting case of equatorial or kinetic spiroketal.



Scheme 2.

2.2. A solid-state kinetic *syn* spiroketal

To confirm the relative stereochemistry of these dihydroxylated C1,2-*syn* spiroketals, and that there was no erosion of stereochemical integrity at the C1 spirocenter during the RCM, diphenyl methylidene and *iso*-propylidene acetals, **21** and **22**, respectively, were prepared from **18** using standard protection conditions [Scheme 3]. Acetal **21** was found to be quite crystalline, and an X-ray structure was obtained as shown in Scheme 3.



Scheme 3.

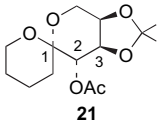
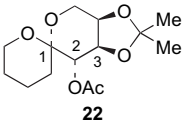
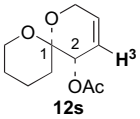
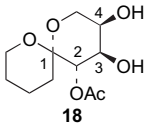
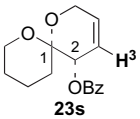
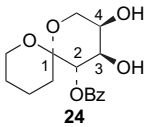
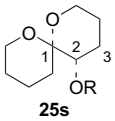
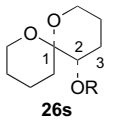
The X-ray structure of acetal **21** revealed that the oxygen atom O2 [the X-ray designation] is equatorial to the pyran ring bearing the acetal motif, whereas the oxygen atom O1 is still axial with respect to the original pyran ring. This effectively establishes acetal **21** as an equatorial spiroketal or one of those rare kinetic spiroketals.[8,19] At least, it represents one that is trapped in the solid state. We recognized that if ketal **21** is also a kinetic spiroketal in solution then coupling constants of H2 and H3 [see arrow indications in Scheme 3] should be large, as they should be for diaxial. This led us to reexamine a range of C1,2-*syn* spiroketal derivatives obtained from cyclic 1,2-*syn*-ketals.

As shown in Table 1, unfortunately, among all C1,2-*syn* spiroketals, only **22** containing the *iso*-propylidene acetal motif gave a *J* value of 5.0 Hz in $CDCl_3$ for protons H2 and H3. This value indicates that protons H2 and H3 in **22** definitely do not exist as diaxial—at least not predominately—in solution. However, it does suggest that **22** could still exist as a conformational mixture in solution that would contain the kinetic spiroketal [Fig. 3]. The *J* value for H2 and H3 in acetal **21** is even lower, thereby implying that the kinetic spiroketal observed in the X-ray structure is solely a solid-state phenomenon.

With the remaining coupling constants being equally small for *syn* spiroketals **18**, **24**, **25s**, and **26s**, it indicates that they too most likely adopt an anomerically favored conformation in which H2 and H3 are also not diaxial. In the case of **12s** and **23s**, the coupling constants are also around 5–5.5 Hz, but this is likely due to H3 being a vinyl proton, and the dihedral angle of H2–H3 in these cases does not really reflect that of axial or equatorial.

Finally, we could further confirm that these C1,2-*syn* spiroketals derived from cyclic 1,2-*syn*-ketals do not likely exist as kinetic spiroketals in solution, as they do not possess less stability than those of C-1,2-*anti* spiroketals. As shown in Scheme 4, under a range of different acidic conditions, pure **27a** or **27s** could be equilibrated to a mixture of **27a** and **27s** with a ratio of 1:1.

Table 1. Proton coupling constants for H2–H3

	$J_{2\text{-}3}$		$J_{2\text{-}3}$
 **21**	d, 3.5 Hz	 **22**	d, 5.0 Hz
 **12s**	d, 5.5 Hz	 **18**	d, 3.0 Hz
 **23s**	d, 5.0 Hz	 **24**	d, 3.0 Hz
 **25s**	t, 3.0 Hz R = *p*-Br-PhCO	 **26s**	t, 3.0 Hz R = *p*-O_2N-PhCO

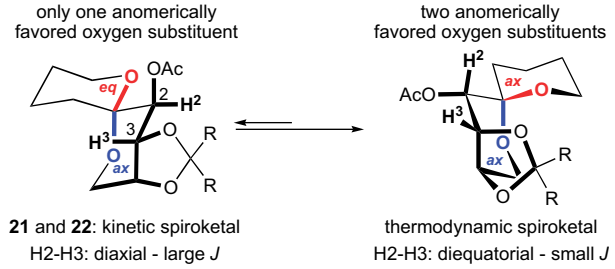
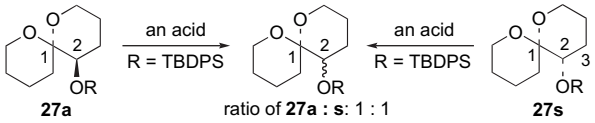


Figure 3.



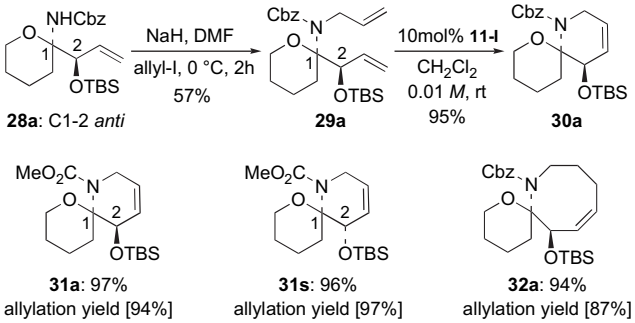
Conditions:
a) 1.1 equiv of PPTS, MeOH, rt to reflux. **b)** 1.1 equiv of *p*-TsOH, CH_2Cl_2, rt to reflux. **c)** TMSCl in MeOH, rt. **d)** TFA, benzene, rt.

Scheme 4.

2.3. Synthesis of spiroaminals

Very much unlike spiroketals, spiroaminals are far from being a prevalent structural motif among natural products.[20] Thus, it is not clear for future applications of constructing spiroaminals through a ketal-tethered RCM strategy. However, we demonstrated that it could be accomplished with comparable efficiency.

As shown in Scheme 5, the RCM precursor **29a** could be attained via allylation of the anomeric amide nitrogen atom in 1,2-*anti* cyclic aminal **28a**. RCM of **29a** employing 10 mol % **11-I** led to *anti* spiroaminal **30a** in 83% yield. Finally, both C1,2-*anti* spiroaminal **31a** and C1,2-*syn* spiroaminal **31s** could be attained through RCM of their respective cyclic *anti* and *syn* aminal precursors in a stereospecific manner. We also demonstrated here an example of eight-membered ring spiroaminal **32a**.

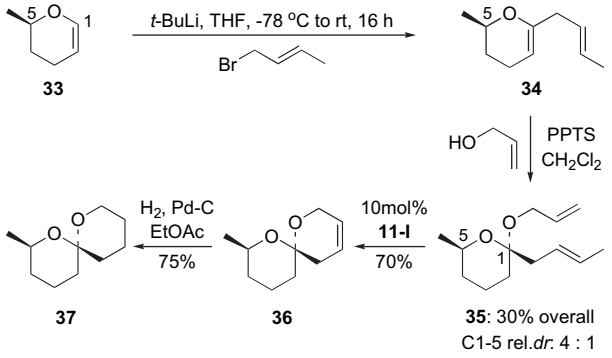


Scheme 5.

2.4. Applications in natural product synthesis

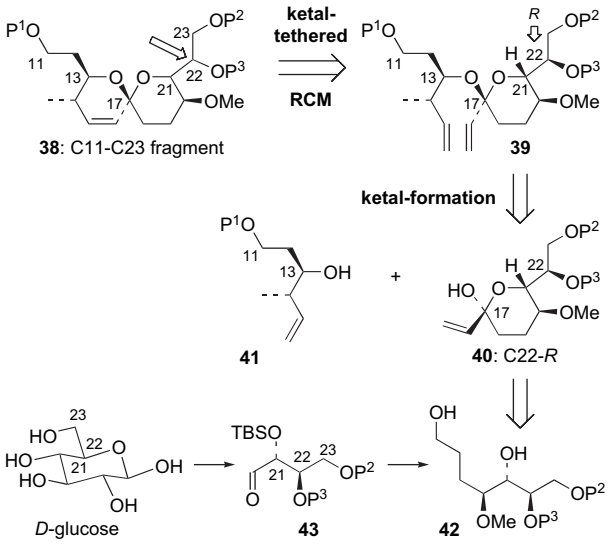
2.4.1. Synthesis of a simple insect pheromone. The ketal-tethered RCM method can be quickly applicable to a short total synthesis of an insect pheromone.[21] As shown in Scheme 6, cyclic ketal **35** could be prepared from dihydropyran **33** in 30% overall yield via addition of its 2-lithiated intermediate to crotyl bromide[22] followed by the ketal

formation using allyl alcohol and PPTS. There is a modest diastereoselective induction from the C5 methyl group with an isomeric ratio being 4:1 in favor of the addition of allyl alcohol to the oxocarbenium intermediate from the anomerically favored axial trajectory.[23–25] The ensuing RCM using the Grubbs' generation-I Ru-catalyst **11-I** led to spiroketal **36** in 70% yield, and subsequent hydrogenation provided the bee pheromone **37**.[21,26]



Scheme 6.

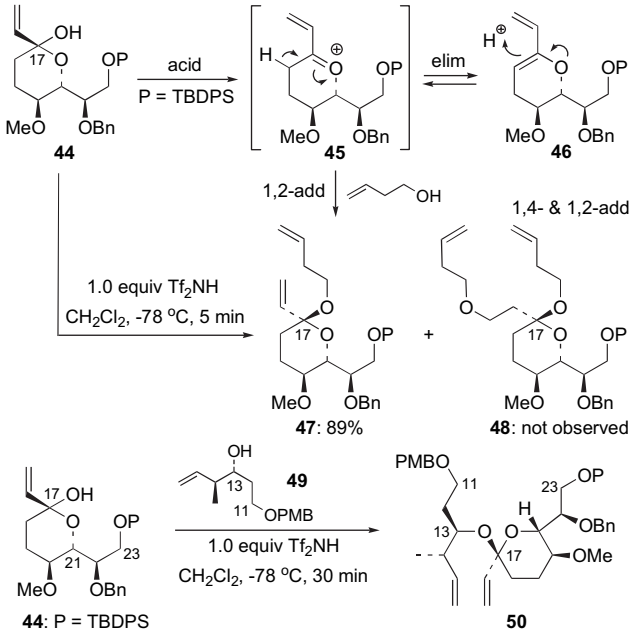
2.4.2. The C11-C23 fragment of spirastrellolide A. A more complex application would involve spirastrellolide A[27,28] and specifically the synthesis of the C11-C23 fragment. Retrosynthetically, the synthesis of the C11-C23 fragment [**38**] would feature the ketal-tethered RCM strategy employing cyclic ketal **39** [Scheme 7]. The relative stereochemistry at C22 [see the arrow] was not unassigned at the time we began our efforts,[13a] and we continued our efforts to focus on establishing the feasibility of the ketal-tethered RCM approach even after we had the knowledge that we had elected the wrong one epimerically.[13b]



Scheme 7.

Cyclic ketal **39** can be envisioned from an acid promoted ketal formation from lactol **40** and the known alcohol **41**.[29] Lactol **40** can be prepared from aldehyde **43** in which the stereocenters at C21 and C22-*R* could be borrowed from D-glucose.[30] These early stages of preparative chemistry have been communicated,[11] and thus, we will focus here on the key RCM chemistry.

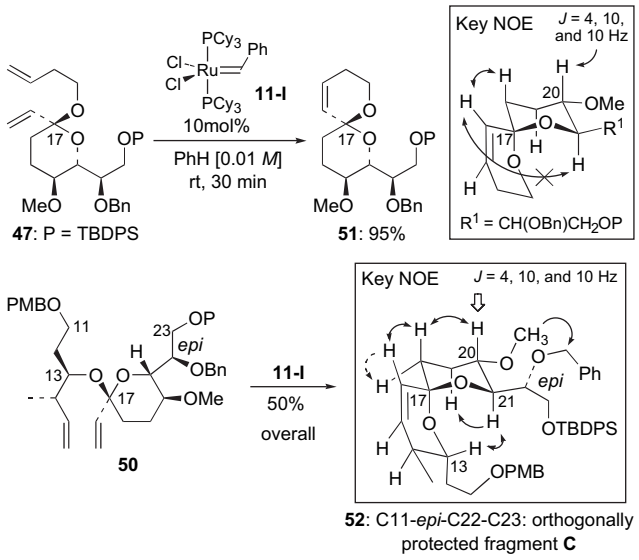
Despite having protocols that are known for the ketal formation using simple pyranyl systems[8–11,22,25] and also those reported by van Boom for more robust carbohydrate-based systems,[6a,b] the cyclic ketal formation using lactol **44** with an anomeric vinyl group at C17 proved to be difficult. The major problem involved is the competing pathways between the elimination of oxacarbenium ion **45** to give diene **46**, which surprisingly in our hand represents a dead end, and 1,2-addition of 3-buten-1-ol gave the desired ketal **47** [as shown in Scheme 8]. In addition, we faced 1,4- and 1,2-additions, which was another dead end in ketal **48**.



Scheme 8.

A range of acids as well as solvents and temperatures were screened,[11] and fortuitously, while most frequently used Lewis acids and Brønsted acids in anomeric substitution[22] led to the over addition product **48**, Tf_2NH[31] [entry 5] proved to be an excellent Brønsted acid at −78 °C, leading to **47** as the sole product in 89% yield as a single diastereomer with the oxo-butenyl group at C17 being axial. Consequently, by using the known chiral alcohol **49**,[29] cyclic ketal **50** was obtained from **44** also as a single isomer under the same Tf_2NH conditions. On occasions, we still found diene **46** presumably because alcohol **49** is more sterically demanding than the model system.

The ensuing RCM of **47** gave spiroketal **51** in 95% yield using Grubbs' generation-I Ru-catalyst **11-I**[1] [Scheme 9]. Selected NOE experiments of **51** revealed that the C17 spirocenter possesses the desired relative stereochemistry. A successful RCM employing **50** was achieved to give spiroketal **52** in 50% overall yield.



Scheme 9.

It is noteworthy that comprehensive NOE experiments in $CDCl_3$ and C_6D_6 confirmed the key relative stereochemistry in spiroketal **52** [see the box in Scheme 9; the dashed arrow implies relatively a weaker NOE]. Despite being *epi* at the C22 stereocenter relative to the natural product, most proton chemical shifts in C_6D_6 [i.e., protons from C13 to C21] along with their respective couplings constants are quite similar to those reported for the methyl ester of spirastrellolide A.[13] More importantly, the key NOE enhancements observed for **52** closely matched those reported for the same region in spirastrellolide A.[13]

3. Conclusion

We have described here a ketal- and aminal-tethered RCM strategy that conceptually represents a very different or an unconventional approach toward the synthesis of spiroketals and spiroaminals. The ketal-tethered strategy was applied successfully to the synthesis of simple insect pheromone and the C11-*epi*-C22-C23 fragment of spirastrellolide A.

4. Experimental

4.1. General

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separation was performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VXR-300, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and vanillin or $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses were performed at University of Minnesota, Department of Chemistry, Mass Spectrometry Laboratory. X-ray analyses were performed at University of Minnesota, Department of Chemistry, X-ray facility. All spectral data obtained for new compounds are reported here.

4.2. Spiroketal syntheses

4.2.1. General procedure for the preparation of the cyclic ketal RCM precursor. To a mixture of acetic acid 1-(5,6-dihydro-4*H*-pyran-2-yl)-allyl ester [1.35 g, 7.45 mmol] and allyl alcohol [1.30 g, 22.3 mmol, 3 equiv] in anhyd CH_2Cl_2 [100 mL] at rt was added pyridinium *p*-toluene sulfonate [187.0 mg, 0.074 mmol, 10 mol %]. The reaction mixture was stirred at rt for 12 h. The solvent was removed in vacuo and the crude product was purified using silica gel flash column chromatography [gradient eluent: 5–10% EtOAc in hexanes] to afford cyclic ketals **10a** and **10s** [combined mass and yield: 1.29 g, 72%] with a 1.6:1 diastereomeric ratio. Isomers **10a** and **10s** can be cleanly separated via a second and more careful flash column chromatography.

4.2.2. Cyclic ketal 10a. R_f=0.50 [20% EtOAc in hexanes]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42–1.56 (m, 4H), 1.67–1.81 (m, 2H), 2.05 (s, 3H), 3.54–3.63 (m, 2H), 3.92 (dq, *J*=1.5, 1.5, 5.5, 13.5 Hz, 1H), 4.01 (dddd, *J*=1.5, 1.5, 5.5, 13.5 Hz, 1H), 5.07 (dq, *J*=1.5, 10 Hz, 1H), 5.15 (dt, *J*=1.5, 9.0 Hz, 1H), 5.17 (m, 1H), 5.26 (dq, *J*=1.5, 17.5 Hz, 1H), 5.41 (dt, *J*=1.5, 5.0 Hz, 1H), 5.82–5.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 20.9, 24.9, 28.3, 61.0, 61.6, 73.4, 98.5, 115.7, 116.5, 133.2, 134.8, 169.5; IR (Neat) cm^{-1} 3091w, 2945s, 2875m, 1748s, 1371m, 1238s; mass spectrum (APCI): *m/e* (% relative intensity) 183 (24) [M−*O*-allyl]$^+$, 123 (100).

4.2.3. Cyclic ketal 10s. R_f=0.43 [20% EtOAc in hexanes]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46–1.70 (m, 5H), 1.73–1.84 (m, 1H), 2.10 (s, 3H), 3.61 (dddd, *J*=3.0, 11.0, 11.0, 11.0 Hz, 1H), 3.65–3.68 (m, 1H), 4.00 (dddd, *J*=1.5, 1.5, 5.0, 13.0 Hz, 1H), 4.17 (dddd, *J*=1.5, 1.5, 5.0, 13.0 Hz, 1H), 5.14 (dq, *J*=1.5, 10.5 Hz, 1H), 5.22 (dq, *J*=1.5, 10.5 Hz, 1H), 5.25 (dq, *J*=1.5, 17.5 Hz, 1H), 5.32 (dq, *J*=1.5, 17.5 Hz, 1H), 5.47 (dt, *J*=1.5, 5.0 Hz, 1H), 5.86 (ddd, *J*=5.5, 10.5, 17.0 Hz, 1H), 5.91 (dddd, *J*=5.5, 5.5, 15.5, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 21.2, 24.8, 28.0, 61.2, 62.0, 74.5, 98.7, 115.9, 117.6, 131.9, 134.8, 169.8; IR (Neat) cm^{-1} 2944s, 2873m, 1748s, 1371m, 1236s; mass spectrum (APCI): *m/e* (% relative intensity) 183 (24) [M−*O*-allyl]$^+$, 123 (100).

4.2.4. General procedure for the ring-closing metathesis of cyclic ketal 10s. To a solution of Grubbs' generation-I Ru-catalyst [16.4 mg, 0.02 mmol, 10 mol %] in anhyd benzene [30 mL] at rt was added a solution of **10s** [48.0 mg, 0.20 mmol] in benzene [10 mL] via syringe. The resulting reaction mixture was stirred at rt for 0.5 h before it was concentrated in vacuo and purified using silica gel flash column chromatography [isocratic eluent: 15% EtOAc in hexanes] to give **12s** [38.0 mg, 89%] as colorless oil.

4.2.5. Spiroketal 12a. Yield: 83%; R_f=0.31 [30% EtOAc in hexanes]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48–1.67 (m, 5H),

1.80–1.85 (m, 1H), 2.11 (s, 3H), 3.71 (ddd, J=2.0, 11.0, 11.0 Hz, 1H), 3.77–3.80 (m, 1H), 4.03 (dq, J=2.5, 16.5 Hz, 1H), 4.09–4.14 (m, 1H), 5.17–5.19 (m, 1H), 5.48 (dq, J=1.5, 10.0 Hz, 1H), 5.87 (dq, J=2.0, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 21.2, 24.7, 30.9, 60.2, 62.4, 70.4, 94.1, 121.9, 128.1, 170.8; IR (Neat) cm^{-1} 2941m, 2883w, 1735s, 1371m, 1240s; mass spectrum (APCI): *m/e* (% relative intensity) 153 (100) $[M-OAc]^+$, 135 (24), 125 (8); ESIHRMS *m/e* calcd for $C_{11}H_{16}NNaO_4$: 235.0946, found: 235.0942.

4.2.6. Spiroketal 12s. Yield: 89%; R_f=0.40 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35–1.41 (m, 1H), 1.48–1.64 (m, 3H), 1.77–1.87 (m, 2H), 2.04 (s, 3H), 3.66 (ddd, J=3.0, 11.0, 11.0 Hz, 1H), 3.72–3.76 (m, 1H), 4.15 (d, J=2.0 Hz, 2H), 4.86 (d, J=5.5 Hz, 1H), 5.78–5.82 (m, 1H), 6.04 (dt, J=2.5, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 21.0, 24.8, 30.3, 60.1, 62.8, 67.7, 95.4, 120.5, 130.8, 170.2; IR (Neat) cm^{-1} 2942s, 2851m, 1743s, 1371m, 1240s; mass spectrum (APCI): *m/e* (% relative intensity) 153 (100) $[M-OAc]^+$, 135 (22), 125 (8); ESIHRMS *m/e* calcd for $C_{11}H_{16}O_4Na$: 235.0946, found: 235.0946.

4.2.7. Synthesis of diol 13. To a solution of **12a** [39.0 mg, 0.18 mmol] in acetone/water [9:1, 10 mL] was added *N*-methyl morpholine *N*-oxide [32.5 mg, 0.27 mmol, 1.5 equiv] and cat $K_2OsO_4\cdot 2H_2O$ [~5.0 mg] at rt. The reaction mixture was stirred at rt for 12 h and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography [isocratic eluent: EtOAc] to afford diol **13** [35.0 mg, 87%] as a crystalline solid. R_f=0.42 [EtOAc]; mp 150–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.60 (m, 5H), 1.60–1.85 (m, 1H), 2.19 (s, 3H), 2.92 (br s, 2H), 3.64 (ddd, J=2.5, 12.0, 12.0 Hz, 2H), 3.77 (s, 2H), 3.94–3.99 (m, 2H), 4.93 (d, J=10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 21.2, 24.5, 30.2, 61.4, 62.4, 68.9, 69.9, 74.5, 97.6, 172.2; IR (Neat) cm^{-1} 3456s, 2942s, 2874m, 1734s, 1223s; mass spectrum (APCI): *m/e* (% relative intensity) 247 (13) $(M+H)^+$, 211 (19), 187 (66), 169 (72), 157 (24), 151 (100), 139 (93), 127 (65); ESIHRMS *m/e* calcd for $C_{11}H_{18}O_6Na$: 269.1001, found: 269.0999.

4.2.8. Cyclic ketal 14s. Yield: 90%; R_f=0.46 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45–1.80 (m, 6H), 2.42 (br s, OH), 3.66–3.71 (m, 2H), 4.01–4.02 (m, 1H), 4.12–4.13 (m, 1H), 4.24–4.25 (m, 1H), 5.14–5.16 (m, 2H), 5.37 (ddd, J=1.5, 17.5, 19.0 Hz, 2H), 5.82–6.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 24.9, 26.9, 61.1, 62.2, 73.0, 99.8, 115.9, 116.6, 134.2, 134.9; IR (Neat) cm^{-1} 3487s, 2945s, 2873s; mass spectrum (APCI): *m/e* (% relative intensity) 152 (30), 141 (100).

4.2.9. Cyclic ketal 15s. Yield: 70%; R_f=0.52 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.40–1.60 (m, 4H), 1.73–1.87 (m, 1H), 2.01 (ddd, J=4.5, 13.0, 13.0 Hz, 1H), 3.48–3.54 (m, 2H), 3.65 (dddd, J=1.5, 1.5, 3.0, 12.5 Hz, 1H), 3.90 (dddd, J=1.5, 1.5, 3.5, 13.0 Hz, 1H), 4.24 (d, J=6.5 Hz, 1H), 5.01–5.05 (m, 3H), 5.16–5.21 (m, 1H), 5.76–5.86 (m, 2H), 7.31–7.40 (m, 6H), 7.66–7.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.6, 24.9, 26.8, 27.3, 60.4, 61.5, 76.0, 100.1, 115.6, 116.9, 127.0, 127.2, 129.3, 134.1, 134.4, 135.2, 135.9, 136.2, 136.4; IR (Neat) cm^{-1} 2942s, 2858s, 1428m; mass spectrum (ESI): *m/e* 459.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{27}H_{36}O_3SiNa$: 459.2331, found: 459.2338.

4.2.10. Spiroketal 16s. Yield: 90%; R_f=0.22 [30% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49–1.65 (m, 3H), 1.66–1.72 (m, 1H), 1.72–1.85 (m, 1H), 2.00–2.04 (m, 1H), 2.12–2.18 (m, 1H), 3.55 (d, J=8.0 Hz, 1H), 3.69 (ddd, J=3.0, 6.5, 6.5 Hz, 1H), 3.75–3.79 (m, 1H), 4.13 (ddd, J=1.5, 17.0, 17.0 Hz, 2H), 5.90–5.95 (m, 1H), ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.2, 24.8, 30.2, 60.1, 62.9, 66.8, 96.9, 124.5, 128.0; IR (Neat) cm^{-1} 3438s, 2940s, 2869m, 1083s; mass spectrum (ESI): *m/e* 431.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_9H_{14}O_3Na$: 193.0841, found: 193.0839.

4.2.11. Spiroketal 17s. Yield: 86%; R_f=0.46 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.55–1.63 (m, 3H), 1.70–1.77 (m, 1H), 1.91 (dddd, J=3.5, 3.5, 8.0, 25.5 Hz, 1H), 2.24–2.30 (m, 1H), 3.73 (dd, J=2.5, 9.0 Hz, 2H), 3.85 (d, J=5.0 Hz, 1H), 4.13–4.15 (m, 2H), 5.38 (dddd, J=2.5, 2.5, 5.0, 5.0 Hz, 1H), 5.72 (dt, J=2.5, 10.0 Hz, 1H), 7.38–7.45 (m, 6H), 7.76–7.79 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.7, 19.6, 25.2, 27.0, 31.0, 60.4, 62.8, 68.7, 97.3, 124.5, 127.3, 127.8, 128.1, 129.4, 129.8, 133.8, 134.5, 135.8, 136.1; IR (Neat) cm^{-1} 2934s, 2857m, 1428m, 1094s; mass spectrum (ESI): *m/e* 431.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{25}H_{32}O_3SiNa$: 431.2018, found: 431.2019.

4.2.12. Diol 18. Yield: 82%; R_f=0.57 [EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (ddd, J=4.5, 13.0, 13.0 Hz, 1H), 1.42–1.75 (m, 5H), 2.05 (s, 3H), 2.62 (d, J=10.5 Hz, OH), 3.47 (t, J=11.5 Hz, 1H), 3.64–3.68 (m, 3H), 3.74–3.80 (m, 2H), 4.92 (d, J=3.0 Hz, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 17.5, 20.7, 24.4, 30.2, 59.0, 61.2, 63.4, 69.0, 71.7, 96.9, 169.4; IR (Neat) cm^{-1} 3454s, 2945s, 2888m, 1739s; mass spectrum (ESI): *m/e* 269.2 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{11}H_{18}O_6Na$: 269.1001, found: 269.0997.

4.2.13. Diol 19. Yield: 83%; R_f=0.37 [4% MeOH in EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47–1.67 (m, 4H), 1.69–1.79 (m, 1H), 1.86–1.89 (m, 1H), 2.94 (br s, 3H), 3.53 (dd, J=10.0, 11.5 Hz, 1H), 3.66–3.77 (m, 3H), 3.86–3.90 (m, 1H), 3.92–4.00 (m, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 17.7, 24.7, 29.5, 59.8, 61.4, 63.5, 71.5, 72.0, 98.3; IR (Neat) cm^{-1} 3423s, 2943m; mass spectrum (ESI): *m/e* 227.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_9H_{16}O_5Na$: 227.0895, found: 227.0886.

4.2.14. Diol 20. Yield: 90%; R_f=0.30 [50% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (ddd, J=5.0, 13.5, 13.5 Hz, 1H), 1.08 (s, 9H), 1.39–1.46 (m, 3H), 1.64–1.73 (m, 1H), 1.89 (dt, J=3.0, 13.5 Hz, 1H), 2.31 (d, J=5.0 Hz, 1H), 3.40 (t, J=11.0 Hz, 1H), 3.57–3.60 (m, 1H), 3.62–3.67 (m, 1H), 3.71–3.78 (m, 4H), 4.10 (br s, 1H), 7.37–7.45 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 17.8, 19.5, 24.5, 27.1, 31.2, 59.2, 61.0, 63.0, 71.2, 73.4, 98.5, 127.7, 127.8, 129.9, 130.0, 132.8, 133.1, 135.9, 136.0; IR (Neat) cm^{-1} 3459s, 2944s, 2859m, 1428m, 1114s; mass spectrum (ESI): *m/e* 465.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{25}H_{34}O_5SiNa$: 465.2073, found: 465.2078.

4.2.15. Acetal 21. To a solution of the respective diol [30.0 mg, 0.12 mmol] in dichloromethane [10 mL] was added benzophenone dimethyl ketal [56.0 mg, 0.25 mmol] and catalytic amount of concd sulfuric acid. It was refluxed for 24 h, washed by water, dried, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography [isocratic eluent: 10% EtOAc in hexanes] to afford acetal **21** [25.0 mg, 45%]. R_f=0.37 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48–1.54 (m, 2H), 1.58–1.64 (m, 3H), 1.71–1.78 (m, 1H), 2.08 (s, 3H), 3.62 (ddd, J=2.5, 12.0, 12.0 Hz, 1H), 3.69–3.73 (m, 2H), 3.77 (dd, J=6.5, 11.5 Hz, 1H), 4.02 (dd, J=3.5, 6.5 Hz, 1H), 4.44 (ddd, J=7.0, 9.5, 13.5 Hz, 1H), 5.31 (d, J=3.5 Hz, 1H), 7.26–7.36 (m, 6H), 7.49–7.54 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.1, 20.9, 24.5, 29.7, 59.4, 61.1, 69.6, 70.9, 74.6, 95.8, 110.1, 126.3, 126.4, 127.9, 128.1, 128.2, 142.1, 142.5, 169.3; IR (Neat) cm^{-1} 2927m, 2855w, 1753s, 1230s; mass spectrum (ESI): *m/e* 433.3 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{24}H_{26}O_6Na$: 433.1627, found: 433.1634.

4.2.16. Acetal 22. Yield: 76%; R_f=0.25 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.52 (s, 3H), 1.41–1.76 (m, 6H), 2.12 (s, 3H), 3.70–3.74 (m, 2H), 3.77–3.81 (m, 2H), 4.07 (t, J=5.0 Hz, 1H), 4.33 (dd, J=7.0, 13.5 Hz, 1H), 5.10 (d, J=5.0 Hz, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.0, 21.0, 24.6, 26.1, 27.9, 28.7, 59.8, 61.3, 70.0, 72.0, 74.6, 96.5, 110.1, 169.5; IR (Neat) cm^{-1} 2944s, 2884w, 1754s, 1232s; mass spectrum (ESI): *m/e* 309.4 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{14}H_{22}O_6Na$: 309.1314, found: 309.1315.

4.2.17. Spiroketal 23s. Yield: 90%; R_f=0.32 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47–1.66 (m, 4H), 1.81–1.91 (m, 1H), 1.98–2.01 (m, 1H), 3.73 (ddd, J=2.5, 11.0, 11.0 Hz, 1H), 3.80–3.83 (m, 1H), 4.24 (t, J=1.5 Hz, 1H), 5.13 (d, J=5.0 Hz, 1H), 5.94–5.98 (m, 1H), 6.11 (dt, J=2.5, 10.5 Hz, 1H), 7.41–7.44 (m, 2H), 7.54–7.55 (m, 1H), 8.05–8.07 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 24.9, 30.6, 60.2, 62.8, 68.3, 95.7, 120.5, 128.3, 129.7, 130.0, 131.1, 133.1, 165.8; IR (Neat) cm^{-1} 2943m, 2850w, 1717s, 1271s; mass spectrum (ESI): *m/e* 297.2 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{16}H_{18}O_4Na$: 297.1103, found: 297.1101.

4.2.18. Diol 24. Yield: 90%; R_f=0.30 [50% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47–1.81 (m, 6H), 2.58 (br s, OH), 3.59 (t, J=11.0 Hz, 1H), 3.75–3.81 (m, 3H), 3.86–3.97 (m, 1H), 3.99–4.10 (m, 2H), 5.24 (d, J=3.0 Hz, 1H), 7.44–7.47 (m, 2H), 7.58–7.59 (m, 1H), 8.04–8.06 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 24.5, 30.4, 59.1, 61.3, 63.6, 69.1, 72.0, 97.2, 128.5, 128.6, 129.1, 129.7, 129.8, 133.5, 164.9; IR (Neat) cm^{-1} 3462s, 2942s, 2879m, 1728s; mass spectrum (ESI): *m/e* 331.2 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{16}H_{20}O_6Na$: 331.1158, found: 331.1164.

4.2.19. Benzoyl ester 25s. To a solution of the respective alcohol [28.0 mg, 0.16 mmol] in dichloromethane was added 4-bromobenzoyl chloride [63.0 mg, 0.29 mmol], triethylamine [0.10 mL, 0.72 mmol], and catalytic amount of DMAP. The reaction mixture was stirred at rt for 2 h and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography [isocratic eluent: 5% EtOAc in hexanes] to give the benzoyl ester **25s** [53.0 mg, 91%]. R_f=0.40 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31–1.42 (m, 2H), 1.51–1.61 (m, 3H), 1.69–1.85 (m, 3H), 1.92–1.96 (m, 2H), 2.13–2.19 (m, 2H), 3.66–3.83 (m, 4H), 4.92 (t, J=3.0 Hz, 1H), 7.58–7.60 (m, 1H), 7.96–7.97 (m, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.0, 19.9, 23.7, 24.9, 31.5, 60.0, 60.5, 71.8, 94.9, 128.1, 129.2, 131.2, 131.7, 165.0; IR (Neat) cm^{-1} 2945s, 2874m, 1722s, 1590m, 1272s; mass spectrum (ESI): *m/e* 377.1 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{16}H_{19}BrO_4Na$: 377.0364, found: 377.0360.

4.2.20. Benzoyl ester 26s. Yield: 80%; R_f=0.40 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (ddd, J=2.5, 12.5, 12.5 Hz, 1H), 1.43 (dd, J=2.0, 13.5 Hz, 1H), 1.52–1.67 (m, 3H), 1.73–1.87 (m, 3H), 1.94 (dddd, J=4.5, 4.5, 9.0, 26.5 Hz, 1H) 2.16–2.23 (m, 1H), 3.67–3.84 (m, 4H), 4.95 (t, J=3.0 Hz, 1H), 8.25–8.30 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 17.9, 19.8, 23.7, 24.8, 31.5, 59.9, 60.5, 72.6, 94.7, 123.5, 130.8, 135.6, 140.4, 150.5, 163.8; IR (Neat) cm^{-1} 2947s, 2875m, 1726s, 1530s, 1276s; mass spectrum (ESI): *m/e* 344.1 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{16}H_{19}NO_6Na$: 344.1110, found: 344.1116.

4.2.21. Hydrogenated spiroketal 27s. To a solution of **17s** [50.0 mg, 0.12 mmol] in EtOAc [3 mL] at rt was added 10 mg of 10% Pd/C. This heterogeneous mixture was stirred under 1 atm of H_2 for 12 h and filtered through Celite to give the hydrogenated product **27s** [43.0 mg, 90%]. R_f=0.34 [5% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.11–1.17 (m, 2H), 1.40–1.58 (m, 4H), 1.73–1.77 (m, 2H), 2.00–2.07 (m, 2H), 3.52–3.55 (m, 2H), 3.62–3.67 (m, 3H), 7.33–7.42 (m, 6H), 7.68–7.71 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.3, 19.6, 25.1, 26.1, 27.2, 31.9, 60.2, 60.4, 71.5, 96.6, 127.4, 127.5, 129.5, 129.6, 133.8, 134.4, 136.0, 136.1; IR (Neat) cm^{-1} 2957s, 2934s, 285m, 1111s; mass spectrum (ESI): *m/e* 433.3 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{25}H_{34}O_3SiNa$: 433.2175, found: 433.2175.

4.2.22. Hydrogenated spiroketal 27a. Yield: 83%; R_f=0.35 [5% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.40–1.78 (m, 8H), 1.90 (dddd, J=5.5, 12.0, 12.0, 12.0 Hz, 1H), 2.03 (ddd, J=4.5, 13.0, 13.0 Hz, 1H), 3.37–3.45 (m, 2H), 3.54 (ddd, J=4.0, 5.0, 15.0 Hz, 1H), 3.67 (ddd, J=1.5, 10.5, 12.5 Hz, 1H), 3.76–3.83 (m, 1H), 7.33–7.42 (m, 6H), 7.69–7.75 (m, 4H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 18.4, 19.4, 25.1, 25.5, 27.1, 27.5, 30.6, 59.1, 60.6, 74.6, 97.1, 127.4, 127.5, 129.5, 129.6, 133.9, 134.3, 136.0, 136.1; IR (Neat) cm^{-1} 2957s, 2934s, 2857m; mass spectrum (ESI): *m/e* 433.5 (M+Na)$^+$; ESIHRMS *m/e* calcd for $C_{25}H_{34}O_3SiNa$: 433.2175, found: 433.2173.

4.3. Spiroaminal syntheses

4.3.1. Aminal 28a. Yield: 70%; R_f=0.37 [15% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 1.46–1.70 (m, 5H), 1.85–2.0 (m, 1H), 3.69 (ddd, J=3.0, 12.0, 19.5 Hz, 1H), 3.69–3.74 (m, 1H), 4.61 (d, J=5.0 Hz, 2H), 5.04 (dd, J=15, 27 Hz, 1H), 5.12 (d, J=12 Hz, 1H), 5.18 (ddd, J=1.5, 2.0, 11.0 Hz, 1H),

5.29 (ddd, J=1.5, 2.0, 17.5 Hz, 1H), 5.96 (ddd, J=5.5, 11.0, 17.5 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.0, −4.3, 18.3, 18.9, 25.2, 26.1, 27.4, 61.6, 66.5, 75.9, 87.0, 116.6, 128.3, 128.4, 128.6, 136.7, 137.2, 154.1; IR (thin film) cm^{-1} 3441br m, 3055m, 2954s, 2858s, 1734s, 1503s, 1264s, 1099s, 739s; mass spectrum (ESI): *m/e* (% relative intensity) 444.2 (9) (M+K$^+$), 428.3 (100) (M+Na$^+$), 255.2 (3); HRMS calcd for $C_{22}H_{35}NNaO_4Si^+$ [M+Na]$^+$: 428.2233, found: 428.2240.

4.3.2. General procedure for the allylation of cyclic aminals. To a flame dried 5-mL RB-Flask under nitrogen were added NaH (9.0 mg, 0.211 mmol) and DMF (1 mL) at rt. To this stirring suspension was added a solution of cyclic aminal **28a** (57.0 mg, 0.141 mmol) in DMF (1 mL) at rt. The reaction mixture was stirred for additional 10 min. Allyl iodide (43.0 μL, 0.211 mmol) was then added to the reaction mixture at 0 °C, and the mixture was stirred for 2–3 h at this temperature until TLC analysis indicated the complete consumption of the starting material. The mixture was quenched with satd aq NH_4Cl and extracted with Et_2O (3×5 mL). The combined organic layers were washed with satd aq NaCl (2 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified using silica gel flash column chromatography [gradient eluent; 15:1–4:1 EtOAc in hexanes] to give the allylated cyclic aminal **29a** [33.0 mg, 57%] as colorless oil.

4.3.3. Aminal RCM precursor 29a. Yield: 57%; R_f=0.43 [10% EtOAc in hexanes], ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 1.45–1.71 (m, 5H), 3.02 (d, J=10.2 Hz, 1H), 3.52–3.70 (m, 2H), 3.89–4.04 (m, 2H), 4.24 (d, J=6.6 Hz, 1H), 5.05 (ddt, J=1.5, 1.5, 10.5 Hz, 1H), 5.09 (ddt, J=1.5, 1.5, 16.8 Hz, 1H), 5.09 (s, 2H), 5.16 (ddd, J=1.2, 1.8, 10.5 Hz, 1H), 5.19 (ddd, J=1.2, 1.8, 17.1 Hz, 1H), 5.91 (ddd, J=6.6, 10.5, 17.1 Hz, 1H), 5.95 (ddt, J=5.4, 10.8, 16.8 Hz, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.0, 18.3, 19.4, 25.4, 26.1, 38.9, 46.6, 63.1, 67.0, 78.5, 92.5, 105.7, 115.5, 117.2, 128.0, 128.3, 128.5, 136.9, 137.6, 137.7, 155.8; IR (thin film) cm^{-1} 2955s, 2859s, 1714s, 1462s, 1272s, 1091s, 989.9s, 838s; mass spectrum (ESI): *m/e* (% relative intensity) 482.3 (8) (M+K$^+$), 468.3 (100) (M+Na$^+$), 446.3 (8) (M+H$^+$), 418.2 (1), 314.2 (1), 255.2 (5); ESIHRMS *m/e* calcd for $C_{25}H_{39}NNaO_4Si$: 468.2546, found: 468.2544.

4.3.4. General procedure for the ring-closing metathesis of cyclic aminals. Please see Section 4.2.4.

4.3.5. Spiroaminal 30a. Yield: 95%; R_f=0.33 [10% EtOAc in hexanes], ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.12 (s, 3H), 0.94 (s, 9H), 1.44–1.73 (m, 4H), 2.08 (dt, J=2.1, 7.8 Hz, 1H), 3.78 (d, J=7.8 Hz, 1H), 3.50 (ddd, J=1.2, 1.5, 6.6 Hz, 1H), 3.55 (ddd, J=1.2, 2.7, 10.8 Hz, 1H), 3.83 (ddd, J=1.2, 2.1, 6.6 Hz, 1H), 4.24 (ddd, J=1.2, 1.2, 2.4 Hz, 1H), 4.43 (ddd, J=1.2, 1.5, 10.8 Hz, 1H), 5.09 (d, J=7.5 Hz, 1H), 5.14 (d, J=7.5 Hz, 1H), 5.48 (dd, J=1.2, 6.0 Hz, 1H), 5.72 (dddd, J=1.2, 1.2, 2.4, 6.0 Hz, 1H), 7.32–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −3.9, 18.4, 19.8, 25.5, 26.2, 29.3, 43.3, 58.1, 63.0, 67.3, 71.2, 88.3, 125.9, 127.5, 128.1, 128.3, 128.7, 136.6, 154.9; IR (thin film) cm^{-1} 2953s, 2857s, 1715s, 1471s, 1399s, 1337s, 1227s, 1163s, 1026s; mass spectrum (ESI): *m/e* (% relative intensity) 456.3 (6) (M+K$^+$), 440.3 (100) (M+Na$^+$), 418.3 (11) (M+H$^+$), 268.2 (30), 195.1 (3); ESIHRMS *m/e* calcd for $C_{23}H_{35}NNaO_4Si$: 440.2233, found: 468.2239.

4.3.6. Spiroaminal 31a. *RCM precursor.* Yield: 94%; R_f=0.37 [10% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.89 (s, 9H), 1.45–1.70 (m, 5H), 2.90–3.10 (m, 1H), 3.50–3.70 (m, 2H), 3.64 (s, 3H), 3.79 (dddd, J=1.2, 1.5, 5.1, 16.2 Hz, 1H), 3.95 (dddd, J=1.2, 1.8, 6.3, 16.2 Hz, 1H), 4.22 (d, J=6.3 Hz, 1H), 5.06 (ddt, J=1.5, 1.5, 10.2 Hz, 1H), 5.11 (ddt, J=1.5, 1.5, 17.4 Hz, 1H), 5.19 (ddd, J=1.2, 1.8, 10.2 Hz, 1H), 5.22 (ddd, J=1.2, 1.8, 17.4 Hz, 1H), 5.90 (ddd, J=6.3, 10.5, 17.4 Hz, 1H), 5.97 (ddt, J=5.4, 10.2, 17.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.1, 18.2, 19.3, 25.3, 25.9, 28.7, 46.3, 52.0, 62.8, 78.3, 92.3, 115.3, 117.0, 137.5, 137.7; IR (thin film) cm^{-1} 2987s, 2857s, 1757s, 1671s, 1415s, 1333w, 1265s, 1032m, 950m, 837s; mass spectrum (EI): *m/e* (% relative intensity) 369 (1) (M$^+$), 312 (10), 255 (3), 198 (100), 115 (10).

Compound **31a**. Yield: 97%; R_f=0.29 [10% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 1.45–1.76 (m, 4H), 2.08 (dt, J=3.9, 13.0 Hz, 1H), 2.47 (d, J=13.0 Hz, 1H), 3.43–3.54 (m, 1H), 3.51 (dddd, J=1.8, 1.8, 3.6, 18.0 Hz, 1H), 3.69 (s, 3H), 3.78–3.88 (m, 1H), 4.22 (ddd, J=1.8, 3.3, 3.9 Hz, 1H), 4.36 (dddd, J=1.8, 1.8, 3.6, 18.0 Hz, 1H), 5.46 (dddd, J=1.8, 1.8, 2.7, 10.5 Hz, 1H), 5.71 (dddd, J=2.1, 2.1, 4.2, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.1, 18.3, 19.6, 25.4, 26.0, 29.2, 42.1, 52.5, 62.9, 71.1, 86.1, 125.8, 127.9; IR (thin film) cm^{-1} 2987s, 2857s, 1757s, 1415s, 1333w, 1265s, 1100s, 1032m, 837s; mass spectrum (GC–MS): *m/e* (% relative intensity) 341 (1) (M$^+$), 284 (30), 210 (7), 184 (60), 127 (100), 59 (10); ESIHRMS *m/e* calcd for $C_{17}H_{31}NNaO_4Si$: 364.1915, found: 364.1911.

4.3.7. Spiroaminal 31s. *RCM precursor.* Yield: 97%; R_f=0.40 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.43–1.69 (m, 4H), 1.85 (dt, J=4.0, 13.0 Hz, 1H), 2.81 (d, J=13.0 Hz, 1H), 3.50 (dt, J=2.5, 12.5 Hz, 1H), 3.63–3.70 (m, 1H), 3.65 (s, 3H), 3.92 (dd, J=6.0, 16.0 Hz, 1H), 4.02 (dd, J=6.0, 16.0 Hz, 1H), 4.20 (d, J=6.0 Hz, 1H), 5.08 (ddd, J=1.5, 2.0, 10.5 Hz, 1H), 5.14 (ddt, J=1.5, 1.5, 17.0 Hz, 1H), 5.15 (ddt, J=1.5, 1.5, 11.0 Hz, 1H), 5.26 (ddd, J=1.5, 2.0, 17.0 Hz, 1H), 5.82 (ddd, J=6.0, 10.5, 17.0 Hz, 1H), 5.94 (ddd, J=5.0, 11.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.3, 18.5, 19.4, 25.3, 26.1, 26.2, 46.0, 52.2, 62.8, 77.0, 92.7, 115.9, 116.9, 136.8, 137.3; IR (thin film) cm^{-1} 2987s, 2857s, 1757s, 1671s, 1415s, 1333w, 1265s, 1032m, 950m, 837s; mass spectrum (EI): *m/e* (% relative intensity) 369 (1) (M$^+$), 312 (10), 255 (3), 198 (100), 115 (10).

Compound **31s**. Yield: 96%; R_f=0.31 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.41 (dt, J=5.5, 10.3 Hz, 1H), 1.48–1.55 (m, 1H), 1.60–1.78 (m, 3H), 3.28 (d, J=13.0 Hz, 1H), 3.50 (dddd, J=2.0, 2.0, 4.0, 18.5 Hz, 1H), 3.51 (dd, J=2.0, 11.0 Hz, 1H), 3.66 (s, 3H), 3.72 (dd, J=1.5, 5.0 Hz, 1H),

3.78 (dd, J=2.0, 11.0 Hz, 1H), 4.55 (dd, J=3.0, 18.5 Hz, 1H), 5.67 (dddd, J=2.5, 2.5, 5.0, 10.0 Hz, 1H), 5.82 (dddd, J=2.0, 2.0, 4.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −3.6, 18.10, 20.0, 25.4, 25.8, 32.8, 43.1, 52.5, 63.5, 71.7, 88.4, 125.2, 127.9; IR (thin film) cm^{-1} 2987s, 2857s, 1757s, 1415s, 1333w, 1265s, 1100s, 1032m, 837s; mass spectrum (EI): *m/e* (% relative intensity) 341 (1) (M^+), 284 (30), 210 (7), 184 (60), 127 (100), 59 (10); ESIHRMS *m/e* calcd for $C_{17}H_{31}NNaO_4Si$: 364.1915, found: 364.1911.

4.3.8. Spiroaminal 32a. *RCM precursor.* Yield: 87%; R_f=0.45 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.44–1.95 (m, 7H), 1.98 (q, J=6.6 Hz, 2H), 2.93 (d, J=6.0 Hz, 1H), 3.17–3.35 (m, 2H), 3.54 (dt, J=3.6, 11.1 Hz, 1H), 3.72 (dt, J=1.2, 2.4 Hz, 1H), 4.26 (d, J=6.6 Hz, 1H), 4.92 (ddt, J=1.4, 1.9, 10.5 Hz, 1H), 4.97 (ddt, J=1.4, 1.9, 17.1 Hz, 1H), 5.09 (s, 2H), 5.15 (ddd, J=1.2, 1.8, 10.5 Hz, 1H), 5.20 (ddd, J=1.2, 1.8, 17.1 Hz, 1H), 5.74 (ddt, J=6.6, 10.5, 17.1 Hz, 1H), 5.90 (ddd, J=6.6, 10.5, 17.1 Hz, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.0, 18.4, 19.4, 25.3, 26.1, 29.0, 29.4, 32.1, 43.8, 62.7, 66.9, 78.6, 92.3, 114.8, 117.1, 128.1, 128.3, 128.6, 136.5, 137.0, 137.8, 138.4, 155.9; IR (thin film) cm^{-1} 2952s, 2858s, 1715s, 1446s, 1394s, 1247s, 1090s, 995s, 839s; mass spectrum (ESI): *m/e* (% relative intensity) 512.3 (8) ($M+K^+$), 496.3 (100) ($M+Na^+$), 474.3 (5) (M), 365.1 (5), 255.2 (7); ESIHRMS *m/e* calcd for $C_{27}H_{43}NNaO_4Si^+$: 496.2854, found: 496.2855.

Compound **32a**: Yield: 94%; R_f=0.44 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.25–1.40 (m, 2H), 1.44 (d, J=7.5 Hz, 1H), 1.55–1.75 (m, 2H), 1.81–1.85 (m, 1H), 1.92–1.93 (m, 1H), 2.06 (dt, J=2.1, 8.1 Hz, 1H), 2.14–2.25 (m, 1H), 2.90–3.10 (m, 1H), 3.20–3.40 (m, 2H), 3.40 (dd, J=3.6, 5.4 Hz, 1H), 3.75 (dd, J=3.0, 6.9 Hz, 1H), 4.47 (s, 1H), 5.14 (d, J=7.5 Hz, 1H), 5.17 (d, J=7.5 Hz, 1H), 5.49–5.56 (m, 2H), 7.31–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.7, 18.2, 18.7, 23.7, 25.0, 25.6, 25.8, 28.1, 38.8, 52.5, 63.0, 66.7, 73.0, 94.2, 126.8, 128.0, 128.1, 128.4, 135.3, 136.4, 155.8; IR (thin film) cm^{-1} 2956s, 2859s, 1707s, 1471s, 1408s, 1338s, 1301s, 1279s, 1179s, 1026s; mass spectrum (ESI): *m/e* (% relative intensity) 484.4 (7) ($M+K^+$), 468.4 (100) ($M+Na^+$), 446.4 (24) ($M+H^+$), 314.6 (14); ESIHRMS *m/e* calcd for $C_{25}H_{39}NNaO_4Si$: 468.2541, found: 468.2539.

4.4. Insect hormone synthesis

4.4.1. Synthesis of cyclic ketal 35. To a solution of dihydropyran [460.0 mg, 4.68 mmol] in anhyd THF [10 mL] at −78 °C was added 3.0 mL of *t*-BuLi [1.7 M in pentane, 5.15 mmol]. It was stirred at 0 °C for 45 min before being cooled back down to −78 °C. A solution of HMPA [0.95 mL, 5.5 mmol] in THF [4 mL] was added to the mixture followed by the dropwise addition of a solution of crotyl bromide [371.0 mg, 2.75 mmol] in THF [3 mL]. The mixture was allowed to warm to rt and stirred for an additional 16 h. After the standard quenching, solvent was reduced in vacuo and the residue was filtered through a small bed of silica gel column chromatography [isocratic eluent: 2% EtOAc in hexanes] to give the desired crotylated product [416.0 mg, 58% yield] as light yellow oil.

To a solution of the above crotylated product [235.0 mg, 1.5 mmol] and allyl alcohol [200.0 mg, 3.5 mmol] in anhyd CH_2Cl_2 [15 mL] was added pyridinium *p*-toluene sulfonate [40.0 mg, 0.010 mmol] at −78 °C. The reaction mixture was stirred for 2 h at −78 °C before it was concentrated in vacuo and purified by silica gel flash column chromatography [isocratic eluent: 5% EtOAc in hexanes] to give **35** [150.0 mg, 46%, *dr*=4:1] as colorless oil. *Major isomer*: R_f=0.31 [5% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, J=6.0 Hz, 3H), 1.16–1.38 (m, 2H), 1.52–1.62 (m, 2H), 1.66 (dd, J=1.0, 6.0 Hz, 3H), 1.72–1.86 (m, 2H), 2.14–2.18 (m, 1H), 2.43–2.47 (m, 1H), 3.67–3.74 (m, 1H), 3.89–3.98 (m, 1H), 3.99–4.04 (m, 1H) 5.13 (dq, J=1.5, 10.0 Hz, 1H), 5.32 (dq, J=1.5, 17.0 Hz, 1H), 5.35–5.45 (m, 1H), 5.47–5.53 (m, 1H), 5.85–6.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 18.9, 21.8, 32.5, 32.6, 41.0, 60.6, 66.5, 99.4, 115.6, 125.5, 128.2, 135.4; mass spectrum (LC–MS) for $C_{13}H_{22}O_2$: *m/e* (% relative intensity) 153 (100) [M−*O*-allyl]$^+$.

4.4.2. Spiroketal 36. To a solution of Grubbs' generation-I Ru-catalyst [35.0 mg, 0.042 mmol, 10 mol %] in anhyd benzene [30 mL] at rt was added a solution of the major isomer of **35** [90.0 mg, 0.42 mmol] in anhyd benzene [10 mL] via syringe. The reaction mixture was stirred for 1 h before it was concentrated and purified by silica gel flash column chromatography [isocratic eluent: 5% EtOAc in hexanes] to give **36** [46.0 mg, 70%] as colorless oil. R_f=0.38 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J=5.5 Hz, 3H), 1.17–1.25 (m, 1H), 1.46 (ddd, J=4.5, 14.0, 14.0 Hz, 1H), 1.57–1.62 (m, 2H), 1.67–1.71 (m, 1H), 1.85–1.95 (m, 1H), 2.03–2.08 (m, 1H), 2.17–2.23 (m, 1H), 3.80–3.86 (m, 1H), 4.00–4.04 (m, 1H), 4.09–4.15 (m, 1H), 5.67–5.71 (m, 1H), 5.73–5.77 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 21.9, 32.5, 34.3, 35.9, 59.7, 66.5, 95.0, 121.6, 124.8; mass spectrum (LC–MS) for $C_{10}H_{16}O_2$: *m/e* (% relative intensity) 169 (20) ($M+H)^+$, 151 (100).

4.4.3. Synthesis of 37. To a solution of spiroketal **36** [30.0 mg, 0.17 mmol] in EtOAc [5 mL] at rt was added 10.0 mg of 10% Pd/C. This heterogeneous mixture was stirred under 1 atm of H_2 for 3 h and filtered through Celite to give the hydrogenated product **37** [24.0 mg, 75%] as colorless liquid. R_f=0.44 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J=6.0 Hz, 3H), 1.24–1.66 (m, 10H), 1.78–1.93 (m, 2H), 3.55–3.58 (m, 1H), 3.62–3.67 (m, 1H), 3.70–3.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 18.9, 21.8, 25.4, 32.6, 35.0, 35.8, 60.2, 65.1, 95.6; mass spectrum (LC–MS) for $C_{10}H_{18}O_2$: *m/e* (% relative intensity) 171 (100) ($M+H)^+$, 153 (30), 135 (17). The synthetic compound spectroscopically [^{1}H and ^{13}C NMR] matched with those reported from the isolation work.[21,26]

4.5. The C11-C23 of spirastrellolide A

4.5.1. Diol 42. Yield: 78%; R_f=0.3 [50% EtOAc in hexanes]; $[\alpha]_D^{23}$ −22.5 [*c* 3.97, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.093 (s, 6H), 0.092 (s, 9H), 1.51–1.69 (m, 4H), 2.64 (br,

2H), 3.36 (s, 3H), 3.38 (m, 1H), 3.53 (m, 1H), 3.57 (t, J=6.0 Hz, 1H), 3.86 (dd J=5.0, 6.0 Hz, 1H), 3.93 (dd, J=4.5, 6.5 Hz, 1H), 3.98 (dd, J=3.5, 11.0 Hz, 1H), 4.56 (d, J=11.5 Hz, 1H), 4.75 (d, J=11.5 Hz, 1H), 7.29 (m, 1H), 7.34 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.4, −5.4, 18.3, 25.0, 25.9, 28.6, 57.2, 62.8, 63.8, 70.9, 72.3, 79.0, 81.4, 127.7, 128.0, 128.4, 138.4; IR (film) cm^{-1} 3420br s, 3071w, 2930s, 2858s, 1671m, 1255m, 1085s; mass spectrum (APCI): *m/e* 399.2 $(M+H)^+$; ESIHRMS *m/e* calcd for $C_{21}H_{38}O_5SiNa$: 421.2381, found: 421.2384.

4.5.2. Lactol 44. To a solution of the respective lactone precursor [223.0 mg, 0.43 mmol] in Et_2O [3 mL] was added vinyl magnesium bromide [0.45 mL, 1 M] dropwise at −78 °C. The solution was stirred at −78 °C for 1 h and quenched with satd aq NH_4Cl [5 mL] at −78 °C. The organic phase was separated and the aqueous fraction was extracted with Et_2O [3×5 mL]. The combined organic phases were washed with satd aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel [gradient eluent: 22–35% EtOAc in hexanes] to lactol **44** in 73% yield [92.7 mg] as pale yellow oil based on the starting material recovered [99.1 mg]. *Lactone*: R_f=0.32 [50% EtOAc in hexanes]; $[\alpha]_D^{23}$ 5.00 [*c* 5.115, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.92 (m, 2H), 2.38 (ddd, J=5.0, 5.0, 17.0 Hz, 1H), 2.61 (ddd, J=7.0, 10.5, 17.5 Hz, 1H), 3.29 (s, 3H), 3.74 (dd, J=4.0, 8.0 Hz, 1H), 3.80 (m, 2H), 4.51 (d, J=11.0 Hz, 1H), 4.61 (d, J=11.0 Hz, 1H), 4.64 (dd, J=3.5, 2.5 Hz, 1H), 7.25 (m, 2H), 7.31 (m, 3H), 7.39 (m, 4H), 7.41 (m, 2H), 7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 22.2, 25.9, 26.6, 55.8, 50.2, 62.4, 71.3, 73.4, 60.0, 81.2, 127.7, 127.8, 128.3, 129.8, 132.8, 132.9, 135.5, 137.7, 171.1; IR (film) cm^{-1} 3070w, 2931s, 2858s, 1742s, 1428m, 1113s; mass spectrum (APCI): *m/e* 519.2 $(M+H)^+$; ESIHRMS *m/e* calcd for $C_{31}H_{38}NaO_5Si$: 541.2381, found: 541.2382. Compound **44**: R_f=0.32 [50% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.85 (m, 1H), 1.91 (m, 1H), 2.60 (ddd, J=6.5, 9.0, 17.0 Hz, 1H), 2.71 (br, 1H), 2.73 (dddd, J=6.0, 9.0, 17.0, 17.0 Hz, 1H), 3.28 (s, 3H), 3.38 (ddd, J=4.5, 4.5, 8.5 Hz, 1H), 3.94 (ddd, J=0.5, 5.0, 11.0 Hz, 1H), 3.61 (ddd, J=3.5, 3.5, 7.5 Hz, 1H), 4.01 (ddd, J=1.0, 3.5, 11.5 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.72 (d, J=11.5 Hz, 1H), 5.80 (dd, J=1.0, 10.5 Hz, 1H), 6.22 (d, J=17.5 Hz, 1H), 6.35 (dd, J=10.5, 17.5 Hz, 1H), 7.27–7.45 (m, 11H), 7.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 22.7, 26.9, 57.1, 64.2, 70.9, 72.3, 76.9, 79.0, 80.2, 96.5, 127.6, 127.7, 127.8, 127.9, 128.4, 129.8, 129.8, 133.0, 133.2, 135.6, 135.7, 135.7, 136.6, 138.4; IR (film) cm^{-1} 3459br s, 3069m, 2932s, 2859s, 1681m, 1428m, 1113s; mass spectrum (APCI): *m/e* 529.3 $(M-H_2O+H)^+$; ESIHRMS *m/e* calcd for $C_{33}H_{42}O_5SiNa$: 569.2694, found: 569.2697.

4.5.3. Cyclic ketal 47. To a solution of **44** [5.00 mg, 0.0094 mmol] in CH_2Cl_2 [0.1 mL] were added MS 4 Å [10 mg] and 3-butene-1-ol [6.77 mg, 0.094 mmol] followed by Tf_2NH [2.64 mg, 0.0094 mmol] at −78 °C. The solution was stirred at −78 °C for 5 min before quenching with Et_3N [0.10 mL] at −78 °C. The mixture was warmed to rt and filtered through Celite. After evaporation of the solvent under reduced pressure, the resulting crude residue was purified by flash column chromatography on silica gel [gradient eluent: 2–10% EtOAc in hexanes] to provide cyclic ketal **47** in 89% yield [5.00 mg]. R_f=0.80 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ 28.9 [*c* 0.36, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.45 (ddd, J=4.0, 14.0, 14.0 Hz, 1H), 1.74 (ddd, J=4.0, 14.0, 24.0 Hz, 1H), 1.88 (ddd, J=4.0, 4.0, 14.0 Hz, 1H), 1.95 (dddd, J=4.0, 4.0, 8.0, 8.0 Hz, 1H), 3.23 (s, 3H), 3.25 (ddd, J=5.0, 10.5, 10.5 Hz, 1H), 3.37 (ddd, J=7.0, 7.0, 9.5 Hz, 1H), 3.40 (ddd, J=7.0, 7.0, 9.5 Hz, 1H), 3.76 (d, J=9.5 Hz, 1H), 3.92 (m, 3H), 4.73 (d, J=11.5 Hz, 1H), 4.79 (d, J=11.5 Hz, 1H), 5.00 (dd, J=1.0, 10.5 Hz, 1H), 5.17 (dd, J=1.5, 11.0 Hz, 1H), 5.31 (dd, J=2.0, 17.5 Hz, 1H), 5.70 (dd, J=11.0, 17.5 Hz, 1H), 5.78 (ddt, J=10.5, 17.5, 7.0 Hz, 1H), 7.27–7.41 (m, 11H), 7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 24.1, 26.9, 34.0, 34.3, 56.0, 60.5, 64.5, 73.1, 73.6, 74.7, 80.9, 97.3, 116.2, 116.3, 127.2, 127.6, 127.6, 127.6, 127.9, 128.2, 129.5, 133.6, 133.8, 135.6, 135.7, 135.7, 138.8, 139.3; IR (film) cm^{-1} 3071w, 2929s, 2857s, 1456m, 1104s; mass spectrum (ESI): *m/e* 623.3 $(M+Na)^+$.

4.5.4. Diene 46. R_f=0.80 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ −5.87 [*c* 0.92, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.17 (t, J=3.9 Hz, 2H), 3.40 (s, 3H), 3.74 (ddd, J=3.0, 5.1, 10.2 Hz, 1H), 3.79 (ddd, J=7.5, 7.5, 7.5 Hz, 1H), 3.93 (dd, J=5.4, 11.4 Hz, 1H), 4.01 (dd, J=3.3, 11.4 Hz, 1H), 4.35 (dd, J=14.5, 6.9 Hz, 1H), 4.56 (d, J=11.8 Hz, 1H), 4.71 (dd, J=3.9, 3.9 Hz, 1H), 4.84 (d, J=11.8 Hz, 1H), 4.97 (d, J=10.8 Hz, 1H), 5.40 (d, J=17.1 Hz, 1H), 6.01 (dd, J=10.8, 17.1 Hz, 1H), 7.43 (m, 11H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 24.0, 26.7, 56.4, 63.4, 71.6, 72.5, 73.9, 78.0, 99.4, 112.5, 127.5, 127.6, 127.8, 128.2, 129.5, 131.6, 133.3, 135.6, 138.3, 148.9; IR (film) cm^{-1} 3070m, 2931s, 2858s, 1428m, 1112s; mass spectrum (APCI): *m/e* (% relative intensity) 529.2 $(M+H)^+$; ESIHRMS *m/e* calcd for $C_{33}H_{41}O_4Si$: 529.2769, found: 529.2780.

4.5.5. Cyclic ketal 48. R_f=0.80 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ 46.1 [*c* 0.33, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.48 (ddd, J=4.0, 13.0, 13.0 Hz, 1H), 1.65 (dddd, J=4.0, 13.0, 13.0, 13.0 Hz, 1H), 1.81 (m, 2H), 1.95 (m, 2H), 2.29 (ddd, J=6.0, 6.0, 6.0 Hz, 1H), 3.15 (ddd, J=4.5, 10.5, 10.5 Hz, 1H), 3.21 (s, 3H), 3.39 (m, 5H), 3.49 (dd, J=7.0, 14.0 Hz, 1H), 3.68 (d, J=9.5 Hz, 1H), 3.92 (m, 3H), 4.74 (s, 2H), 5.00 (d, J=10.5 Hz, 1H), 5.02 (dd, J=1.0, 11.0 Hz, 1H), 5.06 (d, J=18.0 Hz, 1H), 5.07 (dd, J=1.5, 17.5 Hz, 1H), 5.79 (ddt, J=10.0, 17.0, 7.0 Hz, 1H), 7.27–7.41 (m, 11H), 7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 23.9, 26.9, 32.3, 34.2, 34.4, 36.1, 56.0, 59.2, 64.4, 66.7, 70.2, 73.1, 73.7, 74.8, 80.7, 98.0, 116.3, 116.4, 127.2, 127.6, 127.6, 127.6, 129.2, 129.5, 133.6, 133.8, 135.3, 135.5, 135.6, 135.6, 135.7, 139.2; IR (film) cm^{-1} 3071m, 2931s, 2858s, 1428m, 1105s; mass spectrum (ESI): *m/e* 695.6 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{41}H_{56}O_6SiNa$: 695.3738, found: 695.3760.

4.5.6. Cyclic ketal 50. To a solution of **44** [40.0 mg, 0.075 mmol] in CH_2Cl_2 [0.8 mL] were added MS 4 Å [40 mg], alcohol **49** [187.0 mg, 0.75 mmol], and Tf_2NH [10.5 mg, 0.038 mmol] at −78 °C. The solution was stirred at −78 °C for 15 min before quenching with Et_3N [1 mL] at −78 °C. The mixture was warmed to rt and filtered through

Celite™. After evaporating the solvent under reduced pressure, the resulting crude residue was purified by flash column chromatography on silica gel [gradient eluent: 2–10% EtOAc in hexanes] to provide cyclic ketal **50** and diene **46** as an inseparable mixture in 2:1 ratio. R_f=0.80 [25% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J=6.9 Hz, 3H), 1.06 (s, 9H), 1.54 (ddd, J=9.0, 12.0, 12.0 Hz, 1H), 1.71 (m, 2H), 1.85 (m, 1H), 1.94 (m, 1H), 2.01 (m, 1H), 2.36 (ddd, J=3.0, 7.2, 7.2 Hz, 1H), 3.21 (s, 3H), 3.31 (ddd, J=3.6, 12.0, 12.0 Hz, 1H), 3.39 (m, 1H), 3.73 (m, 1H), 3.78 (s, 3H), 3.78 (m, 1H), 3.85 (m, 1H), 3.88–3.97 (m, 3H), 4.22 (d, J=11.4 Hz, 1H), 4.34 (d, J=11.4 Hz, 1H), 4.71 (d, J=11.7 Hz, 1H), 4.79 (d, J=11.7 Hz, 1H), 4.94–4.99 (m, 2H), 5.16 (dd, J=2.1, 10.8 Hz, 1H), 5.36 (dd, J=1.8, 17.1 Hz, 1H), 5.75 (dd, J=9.6, 17.4 Hz, 1H) 5.80 (m, 1H), 6.82 (d, J=8.7 Hz, 1H), 7.19 (d, J=8.7 Hz, 1H), 7.34 (m, 11H), 7.70 (m, 4H).

4.5.7. Spiroketal 51. To the solution of Grubbs' generation-I Ru-catalyst [0.60 mg, 0.00072 mmol] in benzene [1.5 mL] was added slowly the solution of cyclic ketal **47** (4.30 mg, 0.0072 mmol] in benzene [0.5 mL] at rt. The solution was stirred at rt for 30 min and benzene was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel [gradient eluent: 5–10% EtOAc in hexanes] to provide the spiroketal **51** in 95% yield [3.90 mg] as colorless oil. R_f=0.75 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ 0.44 [c 0.45, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.56 (ddd, J=4.0, 13.0, 13.0 Hz, 1H), 1.75 (m, 2H), 1.86 (ddd, J=4.0, 4.0, 18.0 Hz, 1H), 1.99 (ddd, J=4.0, 4.0, 8.5 Hz, 1H), 2.29 (dddd, J=3.0, 6.0, 12.0, 21.5 Hz, 1H), 3.21 (s, 3H), 3.28 (ddd, J=5.0, 10.0, 10.0 Hz, 1H), 3.72 (dd, J=6.5, 12.0 Hz, 1H), 3.92 (m, 5H), 4.73 (d, J=12.0 Hz, 1H), 4.77 (d, J=12.0 Hz, 1H), 5.55 (dd, J=1.0, 10.5 Hz, 1H), 5.92 (dd, J=5.0, 10.5 Hz, 1H), 7.27–7.41 (m, 11H), 7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 24.0, 24.7, 29.7, 33.6, 56.0, 57.8, 64.6, 73.0, 73.1, 74.7, 81.4, 93.0, 127.1, 127.5, 127.6, 127.6, 127.9, 128.1, 129.5, 129.5, 129.9, 133.8, 133.9, 135.7, 137.5, 139.5; IR (film) cm^{-1} 3070m, 2961s, 2857s, 1428m, 1261m, 1102s; mass spectrum (ESI): *m/e* 595.3 $(M+Na)^+$; ESIHRMS *m/e* calcd for $C_{35}H_{44}NaO_5Si$: 595.2850, found: 595.2852.

4.5.8. Spiroketal 52. To the solution of Grubbs' generation-I Ru-catalyst [1.60 mg, 0.0020 mmol] in benzene [3 mL] was added the solution of the mixture of cyclic ketal **50** and diene **46** obtained above in benzene [1.0 mL] at rt. The solution was stirred at rt for 30 min and benzene was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel [gradient eluent: 5–15% EtOAc in hexanes] to provide the desired spiroketal **52** in 50% overall yield [20.8 mg] from **44** as colorless oil in addition to recovered diene **46** [10.0 mg]. R_f=0.65 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ 11.4 [c 0.63, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J=7.0 Hz, 3H), 1.04 (s, 9H), 1.56 (ddd, J=4.0, 13.0, 13.0 Hz, 1H), 1.72 (m, 3H), 1.97 (m, 2H), 2.06 (ddd, J=2.0, 7.0, 7.0 Hz, 1H), 3.20 (s, 3H), 3.25 (ddd, J=4.0, 9.5, 9.5 Hz, 1H), 3.47 (ddd, J=6.5, 8.5, 8.5 Hz, 1H), 3.53 (ddd, J=2.5, 9.5, 9.5 Hz, 1H), 3.70 (m, 1H), 3.78 (s, 3H), 3.85 (m, 1H), 3.92 (m, 2H), 4.29 (d, J=12.0 Hz, 1H), 4.32 (d, J=12.0 Hz, 1H), 4.75 (s, 2H), 5.49 (dd, J=2.5, 10.5 Hz, 1H), 5.64 (dd, J=1.5, 10.0 Hz, 1H), 6.84 (d, J=9.0 Hz, 2H), 7.21 (ddd, J=9.0 Hz, 2H), 7.26–7.38 (m, 11H), 7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 19.2, 23.9, 26.9, 33.1, 33.7, 34.4, 55.3, 56.0, 65.0, 67.5, 71.1, 72.7, 73.1, 73.8, 74.7, 81.3, 93.4, 113.7, 127.1, 127.5, 127.6, 127.6, 128.1, 128.6, 129.3, 129.5, 129.5, 130.7, 133.7, 133.9, 134.4, 135.7, 135.8, 139.6, 159.1; IR (film) cm^{-1} 3070m, 2958s, 2930s, 2858s, 1513m, 1249m, 1103s; mass spectrum (APCI): *m/e* (% relative intensity) 751.2 $(M+H)^+$; ESIHRMS *m/e* calcd for $C_{46}H_{58}NaO_7Si$: 773.3844, found: 773.3840.

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Enantioselective syntheses of tremulenediol A and tremulenolide A

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Abstract—A concise entry to the skeleton of the tremulane sesquiterpenes is described that culminated in the first enantioselective syntheses of tremulenediol A and tremulenolide A. The approach features a series of efficient transition metal-catalyzed reactions commencing with an enantioselective rhodium(II)-catalyzed intramolecular cyclopropanation followed by a regioselective allylic alkylation and a diastereoselective rhodium(I)-catalyzed [5+2] cycloaddition.

1. Introduction

The tremulanes constitute a novel class of sesquiterpene natural metabolites that is characterized by an unusual carboskeletal array **1** isomeric to the lactarane skeleton (**2**).[1] Tremulenolide A (**3**) and tremulenediol A (**4**) are two representative tremulanes that were isolated in 1993 from the fungal pathogen *Phellinus tremulae* during the course of a project to develop tactics to control fungal decay and staining in trembling or quaking aspen (*Populus tremuloides*).[1] Aspen represents 11% of the entire Canadian timber resource and 54% of the net merchantable hardwood timber. *P. tremulae*, the most serious wood rotting pathogen of aspen in Canada, greatly reduces the potential economic value of this timber reserve (Fig. 1).

Although the commercial advantages associated with the potential biological activity of these two natural products are of considerable interest in itself, the structural features of the skeletal core of **3** and **4** present an even greater stimulus to their selection as synthetic targets. For example, in 1998 Davies and Doan reported the syntheses of racemic **3** and **4** in overall yields of 0.8 and 0.9%, respectively.[2] His strategy featured the cyclopropanation of an appropriately functionalized diene with the requisite vinylcarbenoid followed by a Cope rearrangement of the intermediate divinylcyclopropane generated in situ to assemble the seven-membered ring of the hydroazulene core with a high level of relative stereoselectivity.[3,4] However, efforts to apply this plan to an efficient enantioselective synthesis using a chiral dirhodium(II) catalyst were unsuccessful.

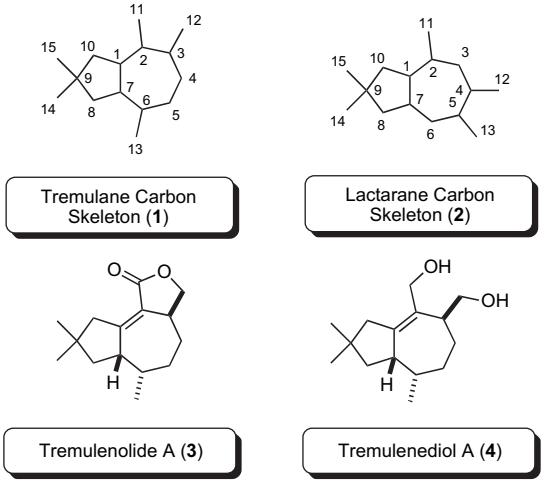

Figure 1.

We have long been interested in developing methods for the enantioselective synthesis of biologically relevant natural products. In this context, the 2,3,6,9-substitution pattern on the bicyclo[5.3.0]decane skeleton and the relative configurations of the three stereogenic centers on the seven-membered ring captured our attention as being well suited for application of synthetic methodology that was being contemporaneously developed by our group.

The initial stimulus for our general approach to the tremulane skeleton **5**, which is outlined in Scheme 1, was a report by Wender that vinylcyclopropanes with tethered alkyne functional groups could undergo diastereoselective intramolecular rhodium(I)-catalyzed [5+2] cycloadditions to give hydroazulenes.[5] Based upon this account, we reasoned that an intermediate such as **6** might be accessible by allylic

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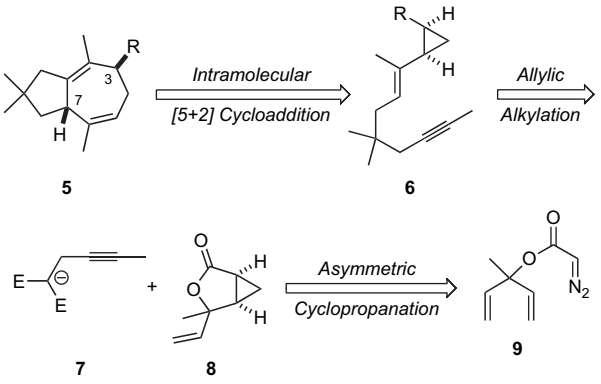
alkylation of the vinylcyclopropyl lactone **8** that would in turn arise from an intramolecular cyclopropanation of the divinyl diazoacetate **9**. We had previously demonstrated that vinylcyclopropanes related to **8** underwent several kinds of regioselective allylic alkylations via a S_N2'-like manifold.[6] Because the stereochemistry at C(3) and C(7) of **5** is established in the cyclopropanation step, it occurred to us that **8** should be accessible via an enantioselective cyclopropanation using the chiral carboxamide dirhodium(II)-catalysts we had developed in collaboration with Doyle.[7] Our recent total synthesis of ambruticin establishes a benchmark for the application of this method to the construction of complex natural products.[8,9] This methodology has also been used for the synthesis of conformationally constrained peptide analogs to study protein–ligand interactions.[10]



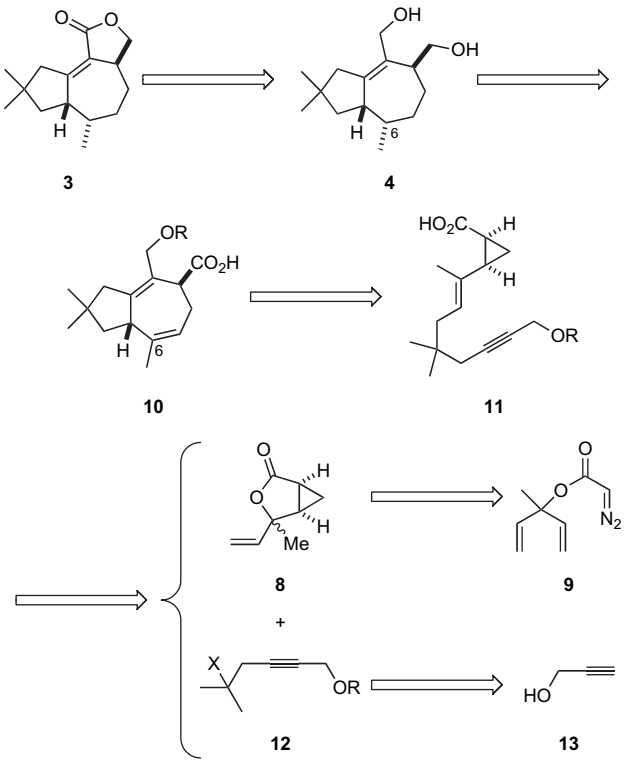
Scheme 1.

Having thus formulated our overall strategy, we set to the task of synthesizing tremulenolide A (**3**) and tremulenediol A (**4**). These efforts recently culminated in the first enantioselective entry to this class of sesquiterpene natural products.[11] We were also intrigued by the possibility of conducting one or more of the transition metal-catalyzed transformations in one pot to streamline the overall operation, and this hypothesis led to the development of some novel tandem reactions.[12] We now report some details of these investigations.

2. Results and discussion

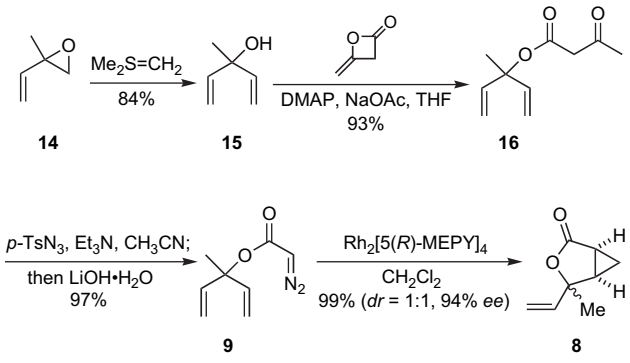
2.1. First generation strategy

Our first generation approach toward the tremulane sesquiterpenes is illustrated in Scheme 2. We envisioned that tremulenolide A (**3**) would arise from an allylic oxidation of the diol moiety in tremulenolide A (**4**), which would be readily accessible via refunctionalization of **10**. The selective hydrogenation of the trisubstituted $\Delta^{5,6}$-double bond in **10** was anticipated to proceed preferentially from the less hindered face. The hydroazulene **10** would then in turn be derived from enyne **11** via a diastereoselective rhodium(I)-catalyzed intramolecular [5+2] cycloaddition. An organocopper mediated S_N2' ring opening of lactone **8** with alkyl halide **12** would lead to the vinylcyclopropane **11**, which comprises all the carbon atoms present in **3** and **4**. As noted previously, **8** would be prepared from the enantioselective, intramolecular rhodium(II)-catalyzed cyclopropanation of diazoester **9**, whereas propargyl alcohol (**13**) was viewed as a suitable precursor of **12**.



Scheme 2.

The opening move in the synthesis was the enantioselective construction of cyclopropyl lactone **8** via a straightforward four-step sequence of reactions beginning with commercially available 2-methyl-2-vinyl oxirane (**14**) (Scheme 3). Thus, treatment of oxirane **14** with the sulfur ylide of trimethylsulfonium iodide followed by spontaneous β-elimination of dimethylsulfide provided the known divinyl carbinol **15** in 84% yield.[13] Subsequent acylation of **15** with diketene in the presence of 4-dimethylaminopyridine (DMAP) and sodium acetate provided acetoacetate **16** in 93% yield. A one-pot diazo transfer reaction of **16** with *p*-toluenesulfonyl azide (*p*-TsN_3) and Et_3N, followed by hydrolytic cleavage of the ketone functionality with $LiOH\cdot H_2O$ provided diazoester **9** in 97% overall yield. The use of the Corey–Myers diazoesterification protocol to prepare **9** directly from **15** was also explored,[14] but the sterically hindered tertiary alcohol proved resistant to acylation under these conditions.

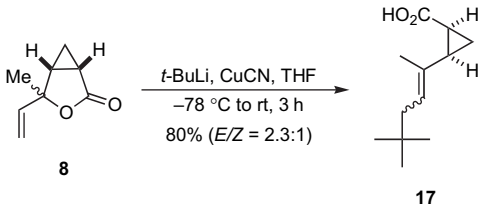


Scheme 3.

When diazoester **9** was exposed to 0.1 mol % of Rh_2[5(*R*)-MEPY]$_4$, intramolecular cyclopropanation proceeded

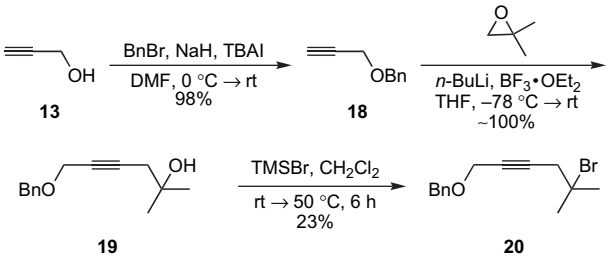
smoothly to yield the desired cyclopropyl lactone **8** as a mixture (1:1) of products epimeric at C(4) in 99% yield and 94% ee for each diastereomer.[7] The enantioselectivity of the cyclopropanation reaction was determined by treating the diastereomeric mixture of cyclopropyl lactones **8** with 1 equiv of phenyllithium to yield the corresponding diastereomeric ketones. Subsequent analytical chiral HPLC analysis of each ketoalcohol showed that the cyclopropanation of diazoester **9** proceeded in 94% ee and that a diastereomeric mixture of cyclopropyl lactones obtained in the cyclization is inconsequential because the epimeric center was slated for destruction in the next step of the synthesis. The optimized sequence provided the requisite cyclopropyl lactone **8** in 71% overall yield from **14**.

In order to examine the underlying feasibility of the proposed organocuprate-mediated S_N2' ring opening reaction, cyclopropyl lactone **8** was treated with the tertiary organocuprate reagent derived from *t*-BuLi and CuCN (Scheme 4).[15] Gratifyingly, the desired vinylcyclopropane **17** was obtained in 80% yield as a mixture (2.3:1) of *E*/*Z*-olefinic isomers. Thus, our strategy for preparing a vinylcyclopropane related to **11** appeared soundly based.



Scheme 4.

Buoyed with confidence that the more complex organocuprate reagent derived from alkyne **12** would behave similarly, we turned our attention toward the task of synthesizing the homopropargylic tertiary bromide **20** (Scheme 5). Toward this end, the alcohol **19** was first prepared in high overall yield by a simple two-step sequence of reactions. Propargyl alcohol (**13**) was first treated with BnBr and NaH in the presence of TBAI to yield **18** in 98% yield. The benzyl protecting group was selected in anticipation that it could be removed concomitantly with the catalytic hydrogenation that would reduce the $\Delta^{5,6}$-olefin later in the synthesis (vide supra). The homopropargyl alcohol **18** was converted into the alcohol **19** in nearly quantitative yield by sequential deprotonation with *n*-BuLi and reaction of the resultant acetylide anion with isobutylene oxide in the presence of $BF_3 \cdot OEt_2$. Unfortunately, conversion of alcohol **19** into the corresponding bromide **20** proved troublesome. After considerable experimentation, the conversion was effected using TMSBr in CH_2Cl_2,[16] but the reaction was inefficient, proceeding in a mere 23% yield.



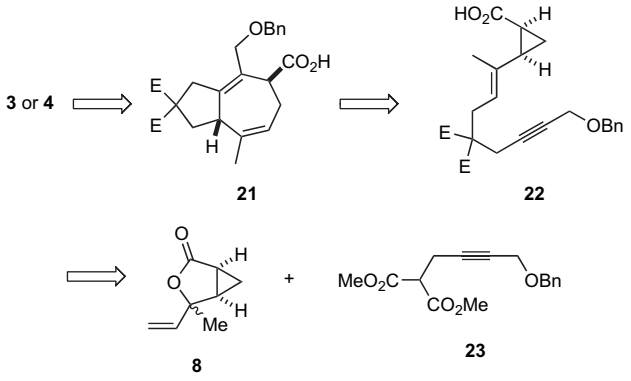
Scheme 5.

A number of conditions were screened, including, but not limited to, PBr_3, PBr_3 and pyridine, and TMSCl and LiBr; none of these procedures gave any better results. The instability of **20** no doubt contributed to the problem.

With limited quantities of bromide **20** in hand, we turned our attention toward coupling the derived organocuprate with cyclopropyl lactone **8**. However, perhaps not surprisingly, metallation of the tertiary homopropargylic halide **20** proved exceedingly difficult. Several attempts to effect metal–halogen exchange to give the derived organolithium or Grignard reagent were universally unsuccessful. It thus became apparent that introducing the *gem*-dimethyl moiety directly at an early stage would not be feasible, and a change in tactics was indicated.

2.2. Second generation approach: some initial studies

The difficulties that had been encountered in generating an unstabilized tertiary carbanion led us to consider a more traditional means of effecting the allylic alkylation of the cyclopropyl lactone **8** to provide a vinyl cyclopropane that would participate in the proposed [5+2] cycloaddition. We thus formulated the modified plan as summarized in Scheme 6 in which a conventional transition metal-catalyzed allylic alkylation of **8** served as a pivotal step. Indeed, we had previously shown that such lactones underwent highly regioselective, Pd(0)-catalyzed alkylations with stabilized carbanions to give the expected products in high yields.[6] The slight drawback of this approach relative to the original plan was the necessity of reducing the malonate moiety in an intermediate derived from **21** into a *gem*-dimethyl group. Nevertheless, the strategy was still concise and merited examination.

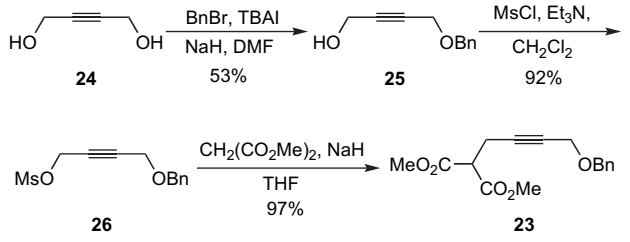


Scheme 6.

Because the cyclopropanation and the [5+2] cycloaddition steps in our synthetic plan were both rhodium catalyzed, we were intrigued by the notion that the allylic alkylation step might also be rhodium catalyzed. Hence, Evans' use of a modified Wilkinson's catalyst to promote allylic alkylations captured our attention.[17,18] We were of course cognizant of the fact that such reactions typically proceeded to give products in which the nucleophile attacked the *more* substituted terminus of the allylic moiety, irrespective of the structure of the starting material. Such a regiochemical outcome was *opposite* to that which was required for the problem at hand. Nevertheless, if $RhCl(PPh_3)_3/P(OMe)_3$ or another rhodium catalyst were capable of catalyzing the allylic alkylation of cyclopropyl lactone **8** to give **22**, the possibility of inducing

the subsequent intramolecular [5+2] cycloaddition in situ was too attractive to ignore. Such a tandem rhodium(I)-catalyzed allylic alkylation and [5+2] cycloaddition sequence would represent a novel and rapid entry to hydroazulenes in general and the tremulane bicyclic core in particular.

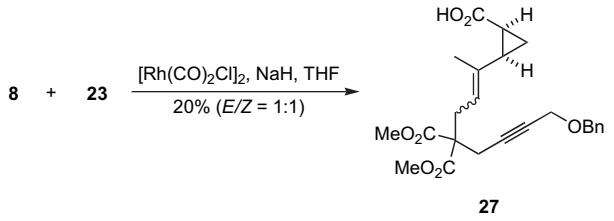
The malonate **23** was prepared in good overall yield from commercially available 2-butyn-1,4-diol (**24**) by a relatively straightforward sequence of reactions, although the monoprotection of **24** was somewhat problematic (Scheme 7). Initial experiments to monobenzylate **24** relied upon a report that showed symmetrical diols could be selectively monobenzylated with Ag_2O and benzyl bromide.[19] When diol **24** was treated with Ag_2O and BnBr, **25** was obtained, albeit in 51% yield. Given the modest yield and high cost of a silver-mediated monoalkylation procedure, more conventional benzylation methods were explored. In a preliminary experiment, the diol **24** was treated with BnBr and NaH, but **25** was obtained in only 17% yield. Changing the solvent from THF to DMF led to a slight increase in the yield to 24%. Finally, it was found that reaction of diol **24** with benzyl bromide, NaH, and tetrabutylammonium iodide (TBAI) in DMF, provided **25** in 53% yield. Subsequent treatment of propargyl alcohol **25** with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 provided the known mesylate **26** in 92% yield.[20] Treatment of mesylate **26** with sodiodimethyl malonate gave **23** in 97% yield. This three-step sequence enabled the production of multigram quantities of **23** in an overall yield of 48%.



Scheme 7.

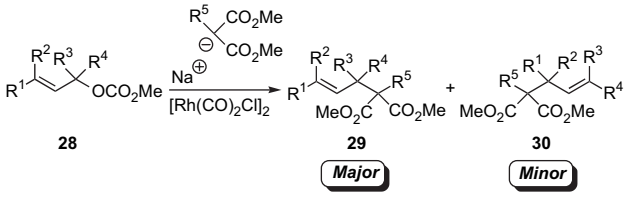
The stage was thus set to explore the transition metal-catalyzed allylic alkylation of **8** with the anion derived from **23**. Because of our penchant to develop novel rhodium-catalyzed domino reactions, we ignored the ample literature precedent that strongly suggested such a reaction involving **8** would proceed with the *incorrect* regiochemistry. In initial experiments we found that treating the cyclopropyl lactone **8** with the sodium enolate of malonate **23** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$ gave no isolable alkylation product, even after extended reaction times and elevated temperatures. Because the dimeric rhodium(I) catalyst $[Rh(CO)_2Cl]_2$ was known to catalyze the intramolecular [5+2] cycloadditions,[21] we queried if perchance it might also catalyze allylic alkylations. In the event, reaction of **8** with the sodium salt of **23** in the presence of $[Rh(CO)_2Cl]_2$ afforded an *E*/*Z*-mixture (1:1) of **27** as the only isolable product, albeit in only about 20% (unoptimized) yield (Scheme 8).

Not only did we thus discover that $[Rh(CO)_2Cl]_2$ could catalyze allylic alkylations, but we also found that the regiochemistry of such reactions was opposite to that expected. This unexpected yet felicitous result led us to develop $[Rh(CO)_2Cl]_2$ as a novel catalyst for promoting allylic



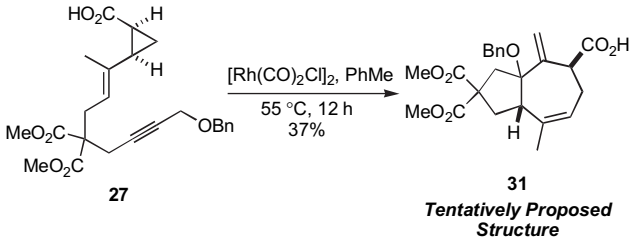
Scheme 8.

alkylations.[22] In exploring the scope of these processes, we showed that the reactions proceeded with good to excellent regioselectivity for a variety of allylic carbonates. The preferred product was generally the one in which the nucleophile became attached to the carbon bearing the carbonate leaving group, irrespective of the structure of the starting carbonate (Scheme 9). *The structure of the starting material generally maps directly on the product, an unusual phenomenon in transition metal-catalyzed allylic alkylations. Ignoring the considerable body of literature on the regiochemistry of Rh-catalyzed allylic alkylations thus paid considerable dividends.*



Scheme 9.

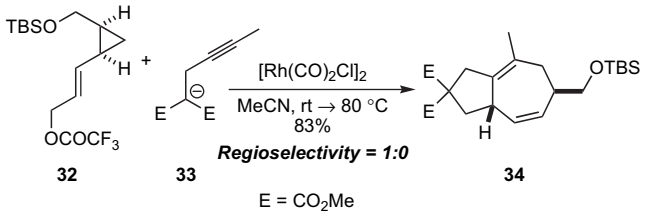
Encouraged by the formation of cyclopropyl enyne **27** from the $[Rh(CO)_2Cl]_2$-catalyzed reaction of **8** and the sodium salt of **23**, the feasibility of conducting a domino allylic alkylation/[5+2] cycloaddition sequence was examined. However, these exploratory experiments were unsuccessful, and none of the desired cycloadduct was obtained. It should be noted that there are no examples in the literature of rhodium-catalyzed [5+2] cycloadditions of *cis*-cyclopropyl enyne carboxylates like **27**.[5] In order to assess whether such compounds were suitable substrates for these carbocyclizations, a number of experiments were conducted in which the catalyst, additive, solvent, and temperature were varied to see whether **27** would cyclize as expected. In one of the experiment, a solution of **27** containing $[Rh(CO)_2Cl]_2$ in toluene was heated to 55 °C for 12 h to give a compound that has not been unequivocally identified, but the NMR spectral data are consistent with the tentatively assigned structure **31** (Scheme 10).



Scheme 10.

Although we were unsuccessful in developing a domino $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation and [5+2] cycloaddition route to **3** and **4**, we were able to apply such reactions

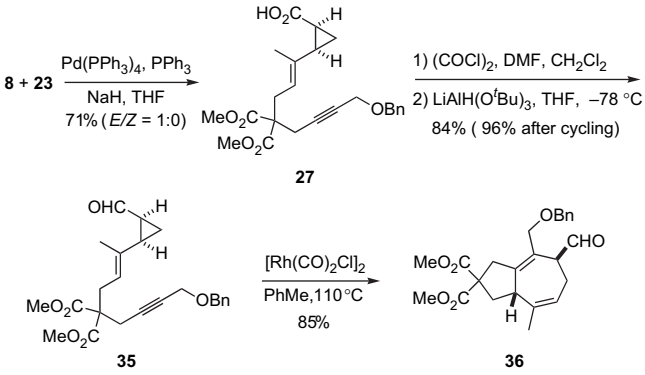
to simpler, yet closely related, substrates.[12] For example, reaction of **32** with the malonate anion **33** in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %) led to the cycloadduct **34** in excellent overall yield (Scheme 11). The regio- and diastereoselectivity in this domino process was the same as that observed by Wender.[21]



Scheme 11.

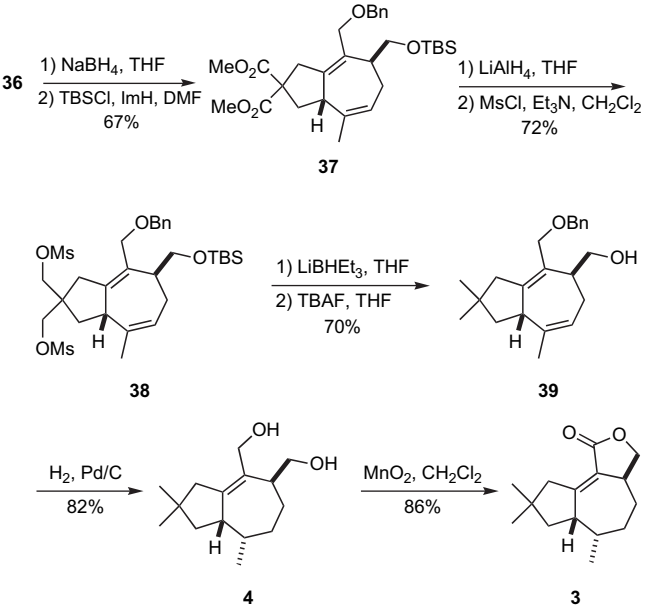
2.3. Second generation approach: successful endgame

Given the poor efficiency with which $[Rh(CO)_2Cl]_2$ catalyzed the allylic alkylation of cyclopropyl lactone **8** with malonate **23**, we decided to examine the use of the more traditional Pd(0) catalysts. After brief experimentation to optimize conditions, we found that the reaction of **8** with the sodium enolate of **22** in the presence of 10 mol % $Pd(PPh_3)_4$ and additional PPh_3 (70 mol %) provided enyne **27** in 71% yield (Scheme 12). The next stage of the sequence involved a [5+2] cycloaddition in which cleavage of the more substituted cyclopropane bond was needed to construct the requisite bicyclo[5.3.0]decane. Based upon results reported by Wender,[21] we reasoned that such cleavage would require that the carboxylic acid moiety in **27** be first reduced to the corresponding aldehyde. Thus, treatment of **27** with oxalyl chloride and DMF followed by reduction of the crude acid chloride with $LiAlH(O^tBu)_3$ provided aldehyde **35** in 84% yield.[23] The primary alcohol resulting from over-reduction was also obtained in 12% yield, but subsequent oxidation with Dess–Martin periodinane proceeded quantitatively to provide **35** in 96% overall yield. Heating **35** in the presence of $[Rh(CO)_2Cl]_2$ proceeded with high regioselectivity to furnish the desired cycloadduct **36** in 85% yield. The structure of **36** was assigned based upon analysis of the HMQC and HMBC NMR data, together with comparisons to Wender's reported spectral data for similar compounds.[21]



Scheme 12.

With cycloadduct **36** in hand, completion of the syntheses of **3** and **4** required a series of refunctionalizations. Thus, reduction of the aldehyde group in **36** with $NaBH_4$ followed by protection of the intermediate primary hydroxyl as its TBS–ether provided **37** in 67% overall yield (Scheme 13). It was now necessary to reduce the diester moiety to install the requisite *gem*-dimethyl moiety. Although treatment of **37** with DIBALH in toluene did reduce the methyl esters to generate the expected 1,3-diol, some silyl deprotection also occurred. However, reduction of **37** with $LiAlH_4$ gave the desired 1,3-diol in 91% yield. Subsequent treatment with methanesulfonyl chloride (MsCl) and Et_3N provided bismesylate **38** in 79% yield.



Scheme 13.

Initial attempts to reduce the bismesylate functionality in **38** to provide the *gem*-dimethyl moiety were performed utilizing $LiAlH_4$. Unfortunately, the reaction was somewhat recalcitrant and failed to proceed to completion. Partially reduced monomesylate was recovered, even after extended reaction times (>24 h). Ultimately, **38** was cleanly reduced using $LiBHEt_3$ to give the desired *gem*-dimethyl intermediate that was treated with TBAF in THF to deliver **39** in 70% overall yield for the two steps. When **39** was subjected to heterogeneous catalytic hydrogenation in the presence of base-washed palladium on carbon under H_2 (1 atm), stereo- and chemoselective reduction of the trisubstituted olefin ensued with concomitant removal of the benzyl protecting group to provide tremulenediol A (**4**) in 82% yield as the only isolable product. The spectral data (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR and IR) and optical rotation for synthetic **4** were consistent with those reported in the literature.[1] Subsequent treatment of **4** with MnO_2 provided tremulenolide A (**3**), which also exhibited spectral characteristics (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR) and optical rotation consistent with those reported in the literature.[1]

3. Conclusions

In summary, concise, enantioselective syntheses of tremulenediol A (**4**) and tremulenolide A (**3**), two representative sesquiterpene metabolites of the tremulane class, have been achieved. The synthetic route is highlighted by a chiral

rhodium(II)-catalyzed cyclopropanation to establish the requisite absolute stereochemistry. A transition metal-catalyzed allylic alkylation is then utilized to assemble the complete carbon ensemble present in the natural products and set the stage for a diastereoselective rhodium(I)-catalyzed [5+2] intramolecular cycloaddition. These studies led to the discovery and development of a novel $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction that generally proceeds with a unique regioselective outcome for structurally different substrates. This allylic alkylation has been coupled in tandem with a number of different $[Rh(CO)_2Cl]_2$-catalyzed carbocyclizations, including [5+2] cycloadditions, to enable rapid access to complex cyclic carboskeletal frameworks. The trio of transition metal-catalyzed operations described herein results in a convergent and highly efficient enantioselective entry to **3** and **4** as evidenced by their synthesis in 6% (16 steps) and 5.2% (17 steps) overall yields, respectively. Other applications of these and other sequential and domino transition metal-catalyzed reactions are in progress and will be reported in due course.

4. Experimental

4.1. General

Solvents and reagents were reagent-grade and used without purification unless otherwise noted. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and diisopropylamine were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. All reactions were done in flame-dried glassware under nitrogen unless otherwise indicated. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at either 500, 400 or 300 MHz as solutions in $CDCl_3$. ^{13}C NMR were obtained at either 125, 100 or 75 MHz as solutions in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ), and referenced from tetramethylsilane. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex; and br, broad. Infrared (IR) spectra were obtained using a Perkin–Elmer FTIR 1600 spectrophotometer using sodium chloride plates as indicated, and reported as wave numbers. Low-resolution chemical ionization mass spectra were obtained with a Finnigan TSQ-70 instrument. High-resolution measurements were made with a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica gel plates. The plates were visualized with UV light, ninhydrin, phosphomolybdic acid, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's procedure[24] using ICN Silitech 32-63 D 60A silica gel.

4.1.1. 3-Methylpenta-1,4-dien-3-yl acetoacetate (16). A solution of freshly distilled diketene (1.048 g, 12.5 mmol) in THF (2 mL) was added dropwise to a stirred mixture of *N*,*N*-dimethylaminopyridine (DMAP) (152 mg, 1.25 mmol), sodium acetate (102 mg, 1.25 mmol), and **15**[13] (610 mg, 6.23 mmol) in THF (18 mL) at −10 °C. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath and stirred for 5.5 h. Satd aq NaCl (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2×20 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by Kugelrohr distillation (55–57 °C, 0.1 mmHg) to yield 1.052 g (93%) of **16** as a colorless oil: ^{1}H NMR (300 MHz) δ 6.08 (dd, J=17.4, 10.8 Hz, 2H), 5.20 (m, 4H), 3.38 (s, 2H), 2.23 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (65 MHz) δ 200.7, 165.6, 139.7, 114.7, 83.3, 51.0, 30.1, 23.9; IR ($CHCl_3$) 2987, 1744, 1720, 1642, 1410, 1361, 1318, 1269, 1149, 997, 932 cm^{-1}; mass spectrum (CI) *m*/*z* 183.1028 [$C_{10}H_{15}O_3$ (M+1) requires 183.1021], 165, 161, 159, 139, 135, 121, 103 (base).

4.1.2. 3-Methylpenta-1,4-dien-3-yl diazoacetate (9). A solution of *p*-toluenesulfonyl azide (826 mg, 4.28 mmol) (synthesized from *p*-toluenesulfonyl chloride and sodium azide) in CH_3CN (6 mL) was added to a stirred solution of **16** (648 mg, 3.57 mmol) and Et_3N (0.75 mL, 5.35 mmol) in CH_3CN (30 mL) at room temperature. The reaction mixture was stirred for 4 h, whereupon a solution of $LiOH\cdot H_2O$ (449 mg, 10.7 mmol) in H_2O (3.5 mL) was added, and the reaction mixture was stirred for an additional 4 h. The mixture was diluted with water (30 mL) and extracted with Et_2O (3×30 mL). The combined organic fractions were washed with satd aq NaCl (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (10:1) to give 573 mg (97%) of **9** as a yellow oil: ^{1}H NMR (300 MHz) δ 6.08 (dd, J=17.5, 10.7 Hz, 2H), 5.23 (d, J=17.5 Hz, 2H), 5.18 (d, J=10.7 Hz, 2H), 4.69 (br s, 1H), 1.65 (s, 3H); ^{13}C NMR (65 MHz) δ 171.0, 140.2, 131.8, 114.1, 82.6, 20.8; IR ($CHCl_3$) 3033, 2985, 2109, 1694, 1371, 1248, 1186, 1092, 992, 924, 740 cm^{-1}; mass spectrum (CI) *m*/*z* 167.0821 [$C_8H_{11}N_2O_2$ (M+1) requires 167.0821], 166 (base), 143, 142.

4.1.3. [1*S*-(1β,5α)]-4-Methyl-4-vinyl-3-oxabicyclo[3.1.0]-hexan-2-one (8). A solution of **9** (23 mg, 0.137 mmol) in CH_2Cl_2 (7 mL) was added to a refluxing solution of $Rh_2[5(R)\text{-MEPY}]_4$ (13 mg, 13.7 μmol) in CH_2Cl_2 (114 mL) over 17 h using a syringe pump. The resulting mixture was heated under reflux for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and a crude ^{1}H NMR spectra indicated a mixture (1:1) of *endo* and *exo* isomers. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 19 mg (99%) of **8** as a clear, colorless oil (combined mass of both isomers isolated). *Isomer A*: ^{1}H NMR (300 MHz) δ 5.98 (dd, J=17.2, 10.7 Hz, 1H), 5.37 (d, J=17.2 Hz, 1H), 5.18 (d, J=10.7 Hz, 1H), 2.16–2.04 (m, 2H), 1.44 (s, 3H), 1.17 (ddd, J=8.8, 7.6, 5.0 Hz, 1H), 1.00 (dt, J=5.0, 3.2 Hz, 1H); ^{13}C NMR (65 MHz) δ 174.3, 133.0, 119.0, 66.7, 31.6, 29.8, 28.3, 21.5; IR ($CHCl_3$) 2987, 1769, 1453, 1413, 1313, 1248, 1196, 1044, 959, 838 cm^{-1}; mass spectrum (CI) *m*/*z* 139.0764 [$C_8H_{11}O_2$ (M+1) requires 139.0759], 139 (base). *Isomer B*: ^{1}H NMR (300 MHz) δ 5.85 (dd, J=17.3, 10.9 Hz, 1H), 5.27 (dd, J=17.3, 1.0 Hz, 1H), 5.15 (dd, J=10.9, 1.0 Hz, 1H), 2.21–2.04 (m, 2H), 1.55 (s, 3H), 1.14 (ddd, J=8.8, 7.6, 4.9 Hz, 1H), 0.88 (dt, J=4.9, 3.4 Hz, 1H).

4.1.4. 2-((1*R*,2S)-2-(Hydroxydiphenylmethyl)cyclopropyl)but-3-en-2-ol. A 1.0 M solution of PhLi in THF (0.58 mL, 0.58 mmol) was added to a stirred solution of **8** (20 mg, 0.14 mmol) in THF (1.5 mL) at 0 °C, the cooling bath was removed, and the mixture was stirred for 1.5 h. It was then cooled to 0 °C, and satd aq $NaHCO_3$ (2 mL) was added. The layers were separated, and the aqueous phase was extracted with Et_2O (3×2 mL). The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 38 mg (92%) of the target ketone as a mixture (1:1) of diastereomers as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.69–7.66 (comp, 2H), 7.42–7.39 (comp, 2H), 7.38–7.31 (comp, 2H), 7.28–7.23 (comp, 3H), 7.17 (app tt, J=7.5, 1.5 Hz, 1H), 6.02 (dd, J=17.5, 11.0 Hz, 1H), 5.19 (dd, J=17.5, 1.0 Hz, 1H), 5.02 (dd, J=11.0, 1.0 Hz, 1H), 1.98 (ddd, J=16.5, 9.0, 7.0 Hz, 1H), 1.23 (ddd, J=12.5, 7.5, 5.0 Hz, 1H), 1.11 (ddd, J=16.5, 9.0, 7.5 Hz, 1H), 0.95 (s, 3H), 0.80 (ddd, J=14.0, 9.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 149.3, 149.0, 145.5, 127.8, 127.8, 126.8, 126.7, 126.6, 126.2, 111.3, 75.2, 72.0, 30.8, 28.7, 28.4, 3.11; IR (CH_2Cl_2) 3585, 3366, 3003, 1598, 1491, 1448, 1185, 1062, 924 cm^{-1}; mass spectrum (CI) *m/z* 239.1499 [$C_{20}H_{21}O_2$ (M+1) requires 239.1541], 277 (base), 259, 199, 193; HPLC (Chiralcel AD column, hexanes/isopropanol 98:2, flow=0.5 mL/min, t_R=60.8, 62.7, 73.1, 78.1 min).

4.1.5. (2*S*,3*S*)-(2-(1,4,4-Trimethylpent-1-enyl)cyclopropanecarboxylic acid (17). A 1.40 M solution of *t*-BuLi in pentane (0.31 mL, 0.43 mmol) was added to a solution of CuCN (20 mg, 0.22 mmol) in degassed THF (1 mL) at −78 °C, and the resulting slurry was allowed to warm slowly to 0 °C with stirring (app 10 min). This yellow solution was then transferred via cannula to a solution of **8** (20 mg, 0.14 mmol) in degassed THF (0.5 mL) at 0 °C, the solution was allowed to warm to room temperature by removal of the cooling bath and stirred for 4 h. The mixture was then cooled to 0 °C and satd aq NH_4Cl/NH_4OH (9:1, 2 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL), the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 22 mg (80%) of **17** as a mixture (2.3:1) of *trans* and *cis* isomers as a clear, colorless oil: *trans isomer*: ^{1}H NMR (400 MHz) δ 5.43–5.40 (m, 1H), 2.06–1.79 (m, 4H), 1.62 (d, J= 0.7 Hz, 3H), 1.43 (app dt, J=7.8, 5.2 Hz, 1H), 1.11 (ddd, J=12.4, 7.6, 4.8 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR (100 MHz) δ 177.9, 130.1, 126.0, 41.8, 31.7, 30.7, 29.2, 19.6, 17.1, 12.0; IR ($CHCl_3$) 3689, 3022, 1602, 1226 cm^{-1}; mass spectrum (CI) *m/z* 197.1543 [$C_{12}H_{21}O_2$ (M+1) requires 197.1542], 393, 197 (base), 179, 151, 141, 125.

4.1.6. 6-Benzyloxy-2-methyl-4-hexyn-2-ol (19). A 1.9 M solution of *n*-BuLi in hexanes (1.1 mL, 2.0 mmol) was added to a stirred solution of protected propargyl alcohol **18** (292 mg, 2.0 mmol) in THF (2.5 mL) at −78 °C, and the resulting yellow solution was stirred for 1 h. To a solution of isobutylene oxide (72.1 mg, 0.089 mL, 1 mmol) in THF (2.5 mL), freshly distilled $BF_3\cdot OEt_2$ (283 mg, 0.25 mL, 2 mmol) was added and the reaction mixture was stirred for 7 h at −78 °C. The solution was allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 40 min. Satd aq $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×5 mL), and the combined organic fractions were washed with satd aq NaCl (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 218 mg (~100%) of **19** as a clear, yellow oil: ^{1}H NMR (400 MHz) δ 7.34–7.25 (m, 5H), 4.58 (s, 2H), 4.18 (t, J=2.0 Hz, 2H), 2.42 (t, J=2.0 Hz, 2H), 2.29 (br s, 1H), 1.31 (s, 6H); ^{13}C NMR (100 MHz) δ 137.2, 128.2, 127.8, 127.6, 83.5, 78.7, 71.4, 69.9, 57.5, 34.4, 28.7; IR (Neat) 3416, 3031, 2973, 2930, 2858, 2282, 2220, 1496, 1454 cm^{-1}; mass spectrum (CI) *m/z* 219.1374 [$C_{14}H_{19}O_2$ (M+1) requires 219.1385], 237, 219, 183, 171 (base), 161, 143.

4.1.7. 6-Benzyloxy-2-bromo-2-methyl-4-hexyne (20). Trimethylsilyl bromide (0.12 mL, 0.916 mmol) was added to a solution of **19** (50 mg, 0.229 mmol) in CH_2Cl_2 (3 mL) at room temperature, and the reaction mixture was stirred for 4 h. The mixture was warmed to 50 °C (bath temperature), stirred for an additional 2 h, and allowed to cool to room temperature by removal of the cooling bath. The reaction mixture was diluted with satd aq $NaHCO_3$ (3 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3×12 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (20:1) to give 15 mg (23%) of **20** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.38–7.26 (m, 5H), 4.61 (s, 2H), 4.19 (t, J=2.0 Hz, 2H), 2.86 (t, J=2.0 Hz, 2H), 1.85 (s, 6H); ^{13}C NMR (100 MHz) δ 137.2, 128.3, 128.0, 127.7, 83.1, 78.9, 71.3, 62.4, 57.4, 38.3, 33.6; IR ($CDCl_3$) 2969, 2926, 2859, 2259, 1721, 1453, 1371, 1264, 1107, 1070, 707 cm^{-1}; mass spectrum (CI) *m/z* 279.0378 [$C_{14}H_{16}O_1Br$ (M−1) requires 279.0384], 281, 279, 265, 263, 201, 183, 171 (base).

4.1.8. 4-Benzyloxy-2-butyn-1-ol (25). NaH (2.326 g of a 60% mineral oil suspension, 58.0 mmol) was added portion wise to a solution of 2-butyn-1,4-diol (**24**) (10.0 g, 116.3 mmol) in DMF (250 mL) at 0 °C. The resulting mixture was stirred for 30 min, whereupon TBAI (2.148 g, 5.8 mmol) and benzyl bromide (6.9 mL, 58.0 mmol) were added and the reaction mixture allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 2 h. H_2O (200 mL) and 10% HCl (200 mL) were added, and the layers separated. The aqueous phase was extracted with Et_2O (3×200 mL), and the combined organic fractions were dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5.460 g (53%) of **25** as a clear, yellow oil. ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 4.57 (s, 2H), 4.30 (t, J=1.8 Hz, 2H), 4.19 (t, J=1.8 Hz, 2H), 1.82 (br s, 1H); ^{13}C NMR (65 MHz) δ 137.1, 128.4, 128.0, 127.8, 84.7, 81.6, 71.7, 57.3, 51.0; mass spectrum (CI) *m/z* 176 (base), 154, 146.

4.1.9. 2-(4-Benzyloxy-2-butynyl)malonic acid dimethyl ester (23). Dimethyl malonate (2.58 mL, 22.6 mmol) was added to a suspension of NaH (542 mg of a 60% mineral

oil suspension, 13.5 mmol) in THF (15 mL) at 0 °C, and the mixture was stirred for 25 min. A solution of **26** (1.147 g, 4.51 mmol) in THF (5 mL) was then added via syringe, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 2.5 h. The mixture was cooled to 0 °C, H_2O (20 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×20 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 1.269 g (97%) of **23** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.33–7.25 (comp, 5H), 4.53 (s, 2H), 4.10 (t, J=2.1 Hz, 2H), 3.74 (s, 6H), 3.60 (t, J=7.6 Hz, 1H), 2.84 (dt, J=7.5, 2.1 Hz, 2H); ^{13}C NMR (65 MHz) δ 168.3, 137.3, 128.3, 128.0, 127.7, 82.4, 79.4, 71.1, 57.2, 52.7, 23.9; IR (Neat) 3031, 2954, 2853, 1738, 1454, 1345, 1071 cm^{-1}; mass spectrum (CI) m/z 291.1232 [$C_{16}H_{19}O_5$ (M+1) requires 291.1230], 261, 183.

4.1.10. 2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,3*S*)-(2-carboxycyclopropyl)but-2-enyl]malonic acid dimethyl ester (27). $Pd(PPh_3)_4$ (81 mg, 73 μmol) and PPh_3 (190 mg, 0.725 mmol) were added sequentially to a solution of **8** (100 mg, 0.725 mmol) in degassed THF (4 mL) at room temperature, and the resulting solution was stirred for 20 min. In a separate flask, **23** (462 mg, 1.59 mmol) was added to a slurry of NaH (58 mg of a 60% mineral oil suspension, 1.45 mmol) in degassed THF (4 mL) at room temperature. After stirring for 20 min at room temperature, the resulting homogeneous solution was transferred via cannula to the flask containing the catalyst and substrate. The mixture was heated under reflux for 4 h. The resulting dark brown solution was allowed to cool to room temperature by removal of the oil bath and then cooled to 0 °C. Aq 1 M $NaHSO_4$ (8 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with satd aq NaCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1–1:1) to give 220 mg (71%) of **27** as a clear, yellow oil: ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 5.13 (t, J=7.4, 1.5 Hz, 1H), 4.57 (s, 2H), 4.07 (t, J=1.0 Hz, 6H), 3.68 (s, 3H), 3.66 (s, 3H), 2.83 (br s, 2H, C9-H), 2.81 (br s, 2H, C7-H), 1.95 (br q, J=16.2, 8.1 Hz, 1H), 1.81 (m, 1H), 1.70 (s, 3H), 1.36 (m, 1H), 1.10 (m, 1H); ^{13}C NMR (125 MHz) δ 175.9, 170.5, 137.5, 128.4, 128.2, 127.8, 127.8, 121.1, 82.0, 78.8, 71.2, 57.1, 52.7, 30.7, 29.7, 22.8, 19.6, 17.3, 17.3; IR ($CDCl_3$) 2952, 2259, 1735, 1698, 1436, 1291, 1211, 1070 cm^{-1}; mass spectrum (CI) m/z 429.1907 [$C_{16}H_{19}O_5$ (M+1) requires 429.1913], 399, 321, 279.

4.1.11. 2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,4*S*)-(2-formylcyclopropyl)but-2-enyl]malonic acid dimethyl ester (35). Oxalyl chloride (50 μL, 0.485 mmol) was added dropwise to a solution of **27** (104 mg, 0.242 mmol) and DMF (five drops) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath and then stirred for 3 h. The mixture was concentrated under reduced pressure, and the crude acid chloride was dissolved in THF (2 mL). The solution was cooled to −78 °C, and a slurry of $LiAlH(O^tBu)_3$ (124 mg, 0.485 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. Aq 1 M HCl (2 mL) was added, and the mixture allowed to warm to room temperature by removal of the cooling bath, and then the layers were separated. The aqueous phase was extracted with EtOAc (3×2 mL), and the combined organic fractions were then dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 84 mg (84%) of **35** as a clear, colorless oil: ^{1}H NMR (300 MHz) δ 8.74 (d, J=6.9 Hz, 1H), 7.36–7.28 (comp, 5H), 5.31 (t, J=7.8 Hz, 1H), 4.55 (s, 2H), 4.13 (t, J=2.1 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 2.91–2.83 (comp, 4H), 2.11 (app dt, J=15.9, 8.1 Hz, 1H), 1.86 (app ddt, J=12.0, 7.8, 4.8 Hz, 1H), 1.72 (s, 3H), 1.59 (app dt, J=7.2, 5.1 Hz, 1H), 1.33 (app dt, J=7.8, 5.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 201.7, 170.3, 137.5, 134.9, 128.1, 127.8, 121.1, 81.3, 79.3, 71.2, 57.3, 56.9, 52.8, 30.6, 30.2, 28.3, 23.2, 17.8, 11.8; IR ($CDCl_3$) 2953, 2853, 2256, 1736, 1697, 1437, 1292, 1208, 1069 cm^{-1}; mass spectrum (CI) m/z 413.1959 [$C_{24}H_{29}O_6$ (M+1) requires 413.1964], 413 (base), 305, 245.

4.1.12. (3a*S*,7*S*)-8-Benzyloxymethyl-7-formyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester (36). $[Rh(CO)_2Cl]_2$ (2 mg, 4.8 μmol) was dissolved in degassed toluene (2 mL), and a solution of **35** (20 mg, 0.048 mmol) in degassed toluene (5 mL) was added. The resulting mixture was heated for 30 min at 110 °C (bath temperature). The mixture was allowed to cool to room temperature by removal of the oil bath, and then filtered through a short plug of neutral alumina. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 17 mg (85%) of **36** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 9.59 (s, 1H), 7.36–7.27 (comp, 5H), 5.51–5.49 (m, 1H), 4.51 (d, J=11.6 Hz, 1H), 4.46 (d, J=11.8 Hz, 1H), 4.01 (app dt, J=12.1, 1.2 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.37 (br s, 1H), 3.23 (dd, J=17.3, 2.0 Hz, 1H), 3.20 (t, J=6.0 Hz, 1H), 2.89 (dd, J=16.7, 1.4 Hz, 1H), 2.73 (ddd, J=12.4, 7.4, 2.0 Hz, 1H), 2.68–2.59 (m, 1H), 2.35–2.29 (m, 1H), 2.07 (t, J=12.7 Hz, 1H), 1.68 (d, J=0.6 Hz, 1H); ^{13}C NMR (125 MHz) δ 200.4, 171.7, 171.4, 142.5, 138.2, 134.3, 128.4, 127.7, 127.6, 122.8, 71.9, 71.2, 57.3, 52.9, 52.8, 51.7, 44.5, 39.3, 39.3, 26.4, 24.2; IR ($CDCl_3$) 3022, 2954, 1732, 1698, 1436, 1374, 1291, 1211, 1071 cm^{-1}; mass spectrum (CI) m/z 413.1956 [$C_{24}H_{29}O_6$ (M+1)], 413, 305 (base), 273, 245.

4.1.13. [2*S*,3*S*]-8-Benzyloxymethyl-7-hydroxymethyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester. $NaBH_4$ (2 mg, 0.029 mmol) was added in one portion to a solution of **36** (6 mg, 0.014 mmol) in THF (1 mL) at 0 °C, and the mixture was stirred for 1 h 15 min. Satd aq NH_4Cl (1 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3×1 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5 mg (83%) of the primary alcohol as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 5.50–5.48 (m, 1H), 4.53 (s, 2H), 4.03 (d, J=10.0 Hz, 1H), 3.79 (d, J=10.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.69 (dd, J=13.9, 5.2 Hz, 1H), 3.64 (dd, J=10.6, 6.0 Hz, 1H), 3.60–3.55 (m, 1H), 3.17 (br d,

J=16.7 Hz, 1H), 2.95–2.92 (m, 1H), 2.75 (ddd, J=12.4, 7.4, 2.0 Hz, 1H), 2.42–2.35 (m, 2H), 2.28–2.20 (comp, 2H), 2.04 (t, J=12.6 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (125 MHz) δ 171.9, 171.7, 141.8, 137.9, 135.2, 130.7, 128.4, 127.8, 127.7, 123.2, 72.7, 72.2, 64.1, 57.0, 52.9, 52.8, 45.2, 42.9, 39.4, 39.2, 29.0, 23.8; IR ($CHCl_3$) 3468, 3015, 2954, 1731, 1436, 1273, 1201, 1060 cm^{-1}; mass spectrum (CI) m/z 415.2124 [$C_{25}H_{31}O_6$ (M+1) requires 415.2121], 415, 307 (base), 207, 247.

4.1.14. (3a*S*,4*Z*,7*S*,8*E*)-Dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-[(*t*-butyldimethylsiloxy)methyl]-4-methylazulene-2,2(1*H*)-dicarboxylate (37). TBSCl (24 mg, 0.16 mmol) was added in one portion to a solution of imidazole (11 mg, 0.16 mmol) and the alcohol from the preceding experiment (32 mg, 78.0 μmol) in DMF (2 mL) at room temperature, and the reaction mixture was stirred for 4 h. Satd aq NaCl (1 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×1 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to provide 33 mg (81%) of **37** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.32–7.31 (comp, 5H), 5.42–5.41 (m, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.42 (d, J=12.0 Hz, 1H), 3.96 (d, J=10.0 Hz, 1H), 3.95 (d, J=10.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.64 (app t, J=9.5 Hz, 1H), 3.59 (dd, J=9.5, 5.5 Hz, 1H), 3.37–3.36 (m, 1H), 3.10 (d, J=17.0 Hz, 1H), 2.96 (dd, J=17.5, 2.5 Hz, 1H), 2.54 (m, 1H), 2.35–2.31 (m, 1H), 2.27–2.23 (m, 1H), 1.96 (app t, J=13.0 Hz, 1H), 1.70 (d, J=1.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz) δ 171.9, 171.9, 138.8, 138.4, 133.2, 131.9, 128.3, 127.6, 127.4, 123.4, 72.4, 71.8, 62.6, 57.4, 56.7, 52.7, 46.5, 41.7, 39.1, 25.8, 25.6, 17.9, −3.7; mass spectrum (CI) m/z 529.2957 [$C_{30}H_{45}O_6Si$ (M+1) requires 529.2985], 529, 421, 289 (base), 275.

4.1.15. (3a*S*,4*Z*,7*S*,8*E*)-Dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-[(*t*-butyldimethylsiloxy)methyl]-4-methylazulene-2,2(1*H*)-diol. $LiAlH_4$ (21 mg, 0.55 mmol) was added to a stirred solution of diester **20** (145 mg, 0.27 mmol) in THF (3 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 4 h. The mixture was then cooled to 0 °C, and satd aq potassium sodium tartrate (3 mL) was added, and the mixture was stirred for 30 min at room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5×5 mL). The combined organic fractions were washed with satd aq NaCl (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 120 mg (91%) of diol as an opaque, colorless oil: ^{1}H NMR (500 MHz) δ 7.34–7.28 (comp, 5H), 5.42–5.40 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 3.97 (d, J=10.4 Hz, 1H), 3.95 (d, J=10.4 Hz, 1H), 3.71 (d, J=9.2 Hz, 1H), 3.65 (d, J=9.2 Hz, 1H), 3.74–3.57 (comp, 4H), 3.43–3.38 (m, 1H), 2.55–2.52 (m, 1H), 2.41–2.16 (comp, 6H), 1.71 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz) δ 141.8, 138.5, 134.8, 131.5, 128.3, 127.8, 127.6, 122.7, 72.8, 72.1, 71.1, 67.4, 62.9, 45.7, 45.3, 44.5, 42.4, 42.2, 37.6, 37.5, 35.9, 18.3, −5.4, −5.4; mass spectrum (CI) m/z 473.3063 [$C_{28}H_{45}O_4Si$ (M+1) requires 473.3087], 473, 365, 233, 215 (base).

4.1.16. ((3a*S*,4*Z*,7*S*,8*E*)-8-(Benzyloxymethyl)-7-((*tert*-butyldimethylsilyloxy)methyl)-2-methanesulfonyloxymethyl-4-methyl-1,2,3,3a,6,7-hexahydroazulen-2-yl)-methyl methanesulfonate (38). Methanesulfonyl chloride (291 mg, 0.20 mL, 2.50 mmol) was added dropwise to a stirred solution of the diol from the preceding experiment (120 mg, 0.25 mmol) and Et_3N (257 mg, 0.35 mL, 2.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the resultant mixture was stirred for 3 h. Satd aq $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×5 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 137 mg (79%) of **38** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.37–7.28 (comp, 5H), 5.48–5.44 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.21–4.06 (comp, 2H), 4.16 (d, J=9.6 Hz, 1H), 4.08 (d, J=9.6 Hz, 1H), 3.92 (br s, 1H), 3.70–3.62 (comp, 2H), 3.51–3.44 (m, 1H), 3.03 (s, 3H), 3.03 (s, 3H), 2.54–2.53 (m, 1H), 2.42–2.25 (comp, 3H), 2.17 (dd, J=13.2, 8.0 Hz, 1H), 1.70 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz) δ 138.8, 138.2, 133.9, 133.1, 128.2, 127.6, 127.5, 123.4, 72.5, 72.3, 72.3, 72.1, 69.1, 62.7, 42.8, 37.2, 37.1, 36.6, 36.6, 31.4, 25.8, 24.3, 18.1, −5.1, −5.2; IR ($CDCl_3$) 3100, 3031, 2929, 2856, 2260, 1730, 1469, 1362, 1255, 1178, 1094, 978, 850, 778, 527; mass spectrum (CI) m/z 629.2627 [$C_{30}H_{49}O_8SiS_2$ (M+1) requires 629.2638], 629, 557, 555 (base).

4.1.17. [(3a*E*,5*S*,7*Z*,8a*S*)-4-(Benzyloxymethyl)-2,2,8-trimethyl-1,2,3,5,6,8a-hexahydroazulen-5-yl]methanol (39). A 1.0 M solution of $LiBHEt_3$ (0.71 mL, 0.71 mmol) in THF was added to a solution of **38** (56 mg, 0.08 mmol) in THF (2 mL) at room temperature, and the mixture was stirred for 8 h. The reaction mixture was then cooled to 0 °C, 1 M HCl (2 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5×5 mL). The combined organic fractions were washed with satd aq NaCl (mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was then dissolved in THF (1.7 mL), and a solution of TBAF (85 mg, 0.27 mmol) in THF (0.3 mL) was added at room temperature. The reaction was stirred for 3 h and then satd aq NaCl (5 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (5×5 mL), the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 20 mg (70%) of **39** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.38–7.27 (comp, 5H), 5.49–5.44 (m, 1H), 4.52 (s, 1H), 4.01 (d, J=9.6 Hz, 1H), 3.75–3.68 (comp, 3H), 2.51 (app t, J=6.0 Hz, 1H), 2.47–2.78 (comp, 2H), 2.25 (dd, J=16.0, 2.0 Hz, 1H), 2.20–2.18 (m, 1H), 2.13 (d, J=16.0 Hz, 1H), 1.76 (ddd, J=11.6, 7.6, 2.0 Hz, 1H), 1.68 (s, 3H), 1.51 (app t, J=12.0 Hz, 1H), 1.07 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz) δ 147.2, 138.1, 137.2, 129.2, 128.4, 127.8, 127.7, 122.5, 72.7, 72.5, 64.3, 47.0, 46.0, 44.8, 43.3, 35.4, 29.4, 29.3, 26.8, 23.9; IR ($CDCl_3$) 2955, 2247, 1602, 1454, 1365, 1307, 1058; mass spectrum (CI) m/z 325.2171 [$C_{22}H_{29}O_2$ (M+1) requires 325.2168], 327, 323, 295, 247, 219 (base).

4.1.18. Tremulenediol A (4). Palladium on carbon (10 wt %, 1 mg) was added to a solution of **39** (5 mg, 15.3 μmol) in MeOH (0.1 mL) at room temperature. The atmosphere in the flask was then replaced with H_2 (1 atm) and the mixture was stirred under an atmosphere of H_2 (balloon) for 3 d. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 3 mg (82%) of **4** as a clear, colorless oil; $[\alpha]_D^{25}$ +40.0 (*c* 0.24, MeOH) [lit.[1] $[\alpha]_D$ +41.7 (*c* 0.24, MeOH)]. Spectra were consistent with literature data:[1] ^{1}H NMR (500 MHz) δ 4.25 (d, J=11.0 Hz, 1H), 4.02 (app t, J=9.5 Hz, 1H), 3.84 (dt, J=11.0, 1.5 Hz, 1H), 3.62 (dd, J=9.5, 5.0 Hz, 1H), 3.10 (br t, J=8.5 Hz, 1H), 2.57–2.54 (m, 1H), 2.29 (dd, J=15.5, 2.5 Hz, 1H), 1.93 (br d, J=15.0 Hz, 1H), 1.84–1.81 (m, 1H), 1.80 (br d, J=11.5 Hz, 1H), 1.79–1.74 (m, 1H), 1.61 (dd, J=12.5, 3.0 Hz, 1H), 1.59–1.58 (m, 1H), 1.54–1.51 (m, 1H), 1.38 (br d, J=12.0 Hz, 1H), 1.07 (s, 3H), 0.87 (s, 3H), 0.82 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 145.8, 132.4, 65.8, 63.3, 48.0, 46.0, 45.5, 45.4, 37.0, 32.6, 31.6, 28.5, 26.9, 22.5, 11.6.

4.1.19. Tremulenolide A (3). MnO_2 (3.0 mg, 33.0 μmol) was added to a solution of **4** (4.0 mg, 16.0 μmol) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred for 24 h, filtered through a short plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 3.4 mg (86%) of **3** as a clear, colorless oil; $[\alpha]_D^{25}$ +99.6 (*c* 0.24, MeOH) [lit.[1] $[\alpha]_D$ +110.7 (*c* 0.14, MeOH)]. Spectra results were consistent with literature data:[1] ^{1}H NMR (500 MHz) δ 4.35 (app t, J=8.5 Hz, 1H), 3.63 (dd, J=10.5, 8.0 Hz, 1H), 3.23–3.20 (m, 1H), 3.12–3.07 (m, 1H), 2.88 (dd, J=19.0, 3.0 Hz, 1H), 2.47 (ddd, J=19.0, 4.5, 3.0 Hz, 1H), 2.17–2.11 (m, 1H), 2.08–2.02 (m, 1H), 1.86–1.80 (m, 1H), 1.78–1.71 (m, 1H), 1.50 (d, J=10.0 Hz, 1H), 1.50–1.43 (comp, 2H), 1.13 (s, 3H), 0.99 (s, 3H), 0.95 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 172.2, 161.7, 121.0, 70.8, 48.4, 45.5, 44.9, 41.0, 37.3, 32.9, 32.7, 29.1, 28.2, 27.4, 17.8.

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π-Allyl palladium approach toward the diazabicyclo[3.2.1]octane core of the naphthyridinomycin alkaloids

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Abstract—A novel and efficient protocol for the synthesis of the 3,8-diazabicyclo[3.2.1]octane system found in the naphthyridinomycin, dnacin, and tetrazomine families of alkaloids is described. The key transformation involves an intramolecular palladium-catalyzed allylic alkylation. The cyclization proceeds smoothly under mild conditions (20 mol % Pd_2dba_3, 1.5 equiv DBU, 65 °C, THF, 20 min) to afford 3,8-diazabicyclo[3.2.1]octanes in excellent yields (94–98%).

1. Introduction

Over the past three decades, antitumor antibiotics belonging to the tetrahydroisoquinoline alkaloid family have been extensively investigated.[1] These natural products which include saframycin, naphthyridinomycin/bioxalomycin, and quinocarcin/tetrazomine exhibit a wide range of biological activities, such as antitumor, antifungal, antimicrobial activities, and others.[1–5] Dnacins A_1 (**1**) and B_1 (**2**) are new members of the naphthyridinomycin/bioxalomycin class, isolated from *Actinosynnema pretiosum* C-14482 in 1980,[2] although their structures were not determined until 1994.[3] Interestingly, dnacin B_1 (**2**) is structurally equivalent to naphthyridinomycin (**3**) with the exception of the amino group at C_{11} and the hydrogen atom at C_{12}.[3] Akin to naphthyridinomycin, dnacin B_1 inhibits DNA synthesis as evidenced by its ability to prevent the incorporation of ^{3}H-thymidine into DNA, and it has been shown to cleave DNA by the formation of superoxide.[4] Both dnacins A_1 and B_1 have been recognized as novel inhibitors of Cdc25 phosphatase,[5] thereby broadening their potential for use as chemotherapeutics. Inspired by the wide range of biological activities and the structural complexity of these alkaloids, several total syntheses and a number of partial synthesis efforts have been documented.[6] Nonetheless, more practical and efficient routes to these natural products that would allow an improved stereocontrol in the assembly of the core structure need to be developed.

As a general strategy toward the synthesis of naphthyridinomycins, we envisioned two distinct approaches for the construction of the 3,8-diazabicyclo[3.2.1]octane core structures **5** and **6**, which are embedded in all targets shown in Figure 1: the palladium-catalyzed intramolecular Heck cyclization of vinyl phosphate **7** (Fig. 2, route A) and the palladium-catalyzed intramolecular allylic alkylation of malonate **8** (Fig. 2, route B). By employing the intramolecular processes, the configuration at the stereogenic C_1 (*) in bicycles **5** and **6** should derive from the attachment of the

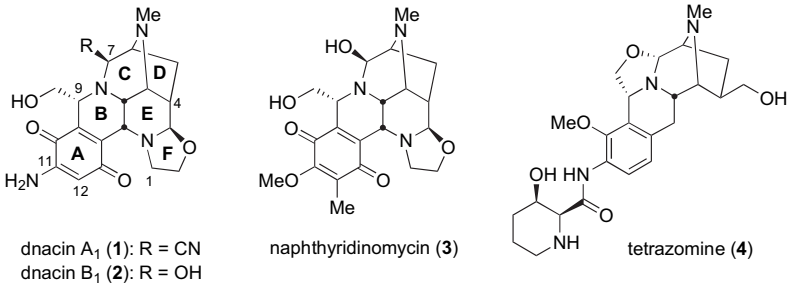

Figure 1. Selected examples of natural products containing the 3,8-diazabicyclo[3.2.1]octane core (C,D-ring system).

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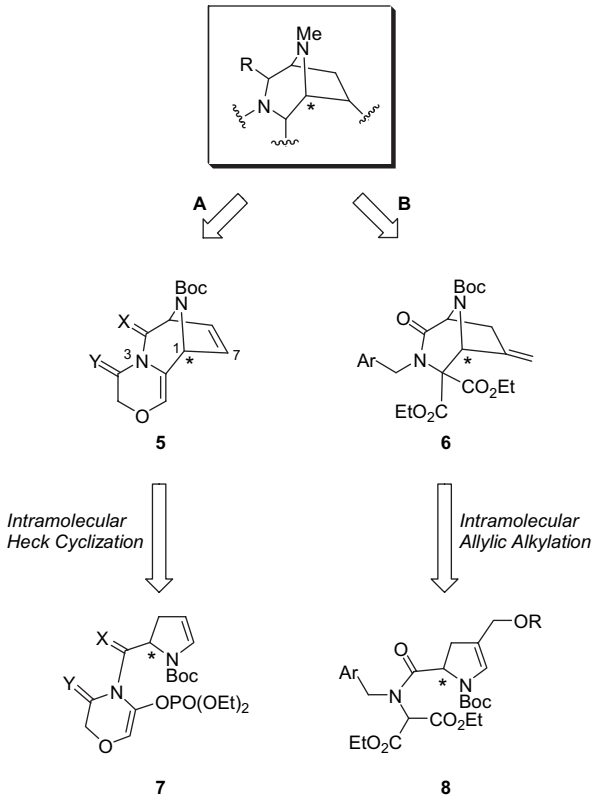
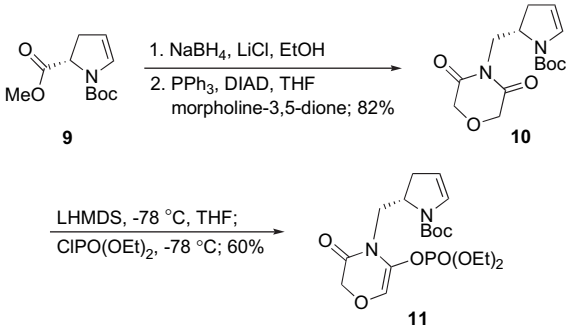


Figure 2. Retrosynthetic analysis of dnacins and related compounds.

tether in precursors **7** and **8**. Furthermore, both **5** and **6** provide adequate functionalization for the introduction of the remaining substituents in dnacins and related naphthyridinomycins. In this report, we describe our pursuit of these new synthetic routes toward the 3,8-diazabicyclo[3.2.1]-octane ring system.

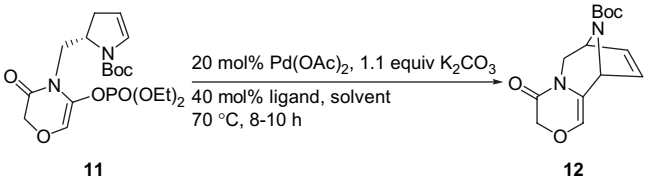
2. Results and discussion

Our initial strategy for the synthesis of 3,8-diazabicyclo[3.2.1]octanes relied upon the intramolecular Heck cyclization (Fig. 2, route A). Although a large number of Heck reactions have been applied to natural product syntheses,[7] only a handful of examples have been documented for the construction of bridged bicyclic ring systems.[8] As outlined in Scheme 1, starting from the known ester **9** derived from (*S*)-pyroglutamic acid,[9] vinyl phosphate **11** was prepared in three steps. The vinyl phosphate was chosen to explore the key Heck cyclization because vinyl phosphates[10a–e] were found to be more reactive than the corresponding triflates.[10f] Hence, reduction of **9** with $NaBH_4$/LiCl, followed by Mitsunobu reaction with morpholine-3,5-dione, afforded **10** in 82% yield (two steps). The desired Heck precursor **11** was subsequently obtained in 60% yield by treatment of **10** with LHMDS (−78 °C, THF) followed by slow addition of diethyl chlorophosphate (Scheme 1). With the desired precursor in hand, the key intramolecular Heck cyclization was explored under several different reaction conditions (Table 1). With $Pd(OAc)_2$ and dppf as a ligand (70 °C, THF), cyclization failed completely (entry 1). After several attempts, we found that bidentate ligands and K_2CO_3 as a base were most effective. Several bidentate ligands and reaction parameters were screened, and dppp as a ligand in DME or THF (Table 1, entries 5–7) provided the desired product **12** in modest yields (45–53%). A similar result was obtained when the cyclization of **11** was carried out under microwave heating at 100 °C for 30 min (54%, entry 8).[11]



Scheme 1.

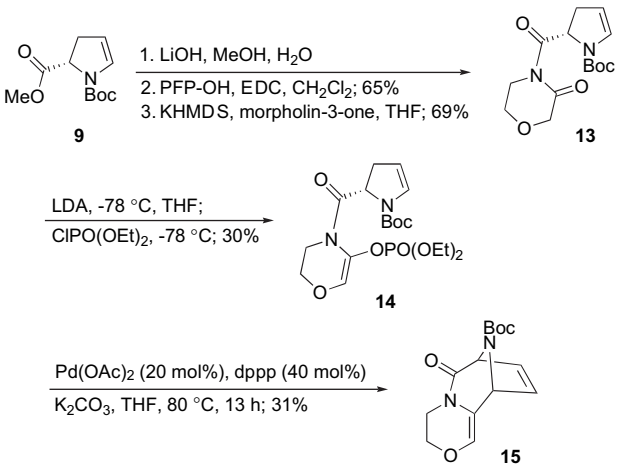
Table 1. Optimization of Heck cyclization of vinyl phosphate **11**



Entry	Ligand	Solvent	Product **12** (%)	Starting material **11** (%)
1	dppf	THF	—	—
2	BINAP	THF	12	—
3	dppe	THF	13	25
4	dppb	DME	36	22
5	dppp	THF	41	7
6	dppp	DME	45	21
7[a]	dppp	DME	53	<5
8[a,b]	dppp	DME	54	—

[a] $Pd(OAc)_2$ (40 mol %) and dppp (80 mol %) were used.
[b] Reaction mixture was heated in the microwave at 100 °C for 30 min.

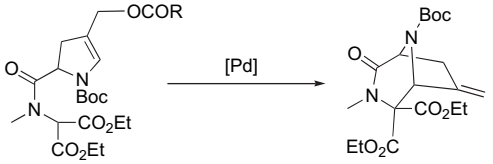
To further explore the scope of the Heck cyclization for the construction of the 3,8-diazabicyclo[3.2.1]octane unit, we extended this chemistry to a vinyl phosphate substrate bearing a carbonyl group adjacent to a bridgehead carbon (Scheme 2). Hydrolysis of **9** followed by EDC-promoted esterification with pentafluorophenol (PFP-OH) afforded the activated ester, which was transformed into amide **13** upon treatment with morpholin-3-one and KHMDS (45%, three steps). The Heck precursor **14** was then obtained by treating **13** with LDA (−78 °C, THF) followed by trapping of the enolate anion with diethyl chlorophosphate. Whereas the Heck cyclization of **11** led to the desired 3,8-diazabicyclo[3.2.1]octane **12** in modest yields, cyclization of derivative **14** was sluggish and provided the cyclized product **15** in low yield (31%) under optimized conditions (20 mol % $Pd(OAc)_2$, 40 mol % dppp, 1.1 equiv K_2CO_3 in DME, Scheme 2). Presumably, the poor reactivity of **14** can be attributed to the increased ring strain during the cyclization due to incorporation of an sp^2-hybridized carbon in the tether. In all cases, the Heck cyclization required high catalyst loadings (up to 40 mol % of Pd) and long reaction times for complete conversion.



Scheme 2.

Due to these limitations in route A, an alternative strategy was considered in order to improve the synthesis of the 3,8-diazabicyclo[3.2.1]octane system, and we turned our attention to the intramolecular allylic alkylation methodology (Fig. 2, route B). Although inter- and intramolecular allylic alkylations have been used extensively in complex natural product synthesis,[7h,12] the application of this chemistry to the preparation of bridged carbo- and heterocyclic ring systems is less frequent.[13] For our initial investigations, the key precursors **22a–c** were synthesized from the known aldehyde **16** in eight steps (Scheme 3).[14] Aldehyde **16** underwent *N*-Boc protection, $NaBH_4$ reduction, *O*-TBS protection, and ester hydrolysis to afford acid **19** in 39% overall yield. Subsequently, acid **19** was coupled with sarcosine ethyl ester to afford amide **20** using DCC and HOBt (54%). Treatment of **20** with LHMDS, followed by addition of ethyl chloroformate (−78 °C, THF) furnished the malonate **21** in excellent yield (95%). Several allylic substrates were prepared to examine the palladium-catalyzed allylic alkylation. Desilylation of **21** with TBAF followed by O-acylations provided the allylic substrates **22a–c**. Initially, the allylic carbonate **22a** was examined due to the high reactivity of these derivatives toward allylic alkylation.[15] However, the carbonate was found to be very unstable and decomposed during reaction workup. Therefore, a more stable allylic benzoate **22b** was prepared and subjected to allylic alkylation conditions. Treatment of **22b** with $Pd(OAc)_2$ and dppe in the presence of base such as NaH or DBU in THF gave the cycloadduct **23** in 67 and 71% yields, respectively (Table 2, entries 1 and 2). Encouraged by these results, we then screened different allylic substrates and catalysts. Under the same conditions, the pivaloate **22c** afforded **23** in higher yields (entries 3

Table 2. Optimization of allylic alkylations of malonates **22b** and **22c**

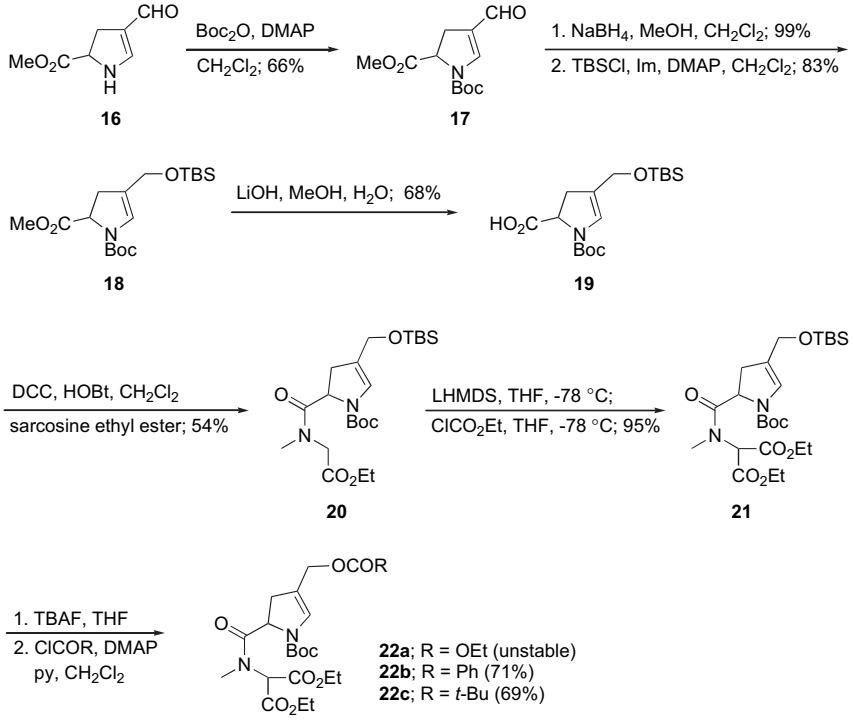


22b; R = Ph
22c; R = *t*-Bu

23

Entry	R	Catalyst	Base	Time (h)	Yield (%)[a]
1	Ph	$Pd(OAc)_2$/dppe	NaH	1	67
2	Ph	$Pd(OAc)_2$/dppe	DBU	4	71
3	*t*-Bu	$Pd(OAc)_2$/dppe	NaH	1	80
4	*t*-Bu	$Pd(OAc)_2$/dppe	DBU	4	83
5	*t*-Bu	$Pd(PPh_3)_4$	DBU	4	95
6	*t*-Bu	Pd_2dba_3	DBU	2	98

[a] Standard conditions: 10% palladium catalyst, 20% ligand, 1.5 equiv base, THF (0.02–0.05 M) at 65 °C.

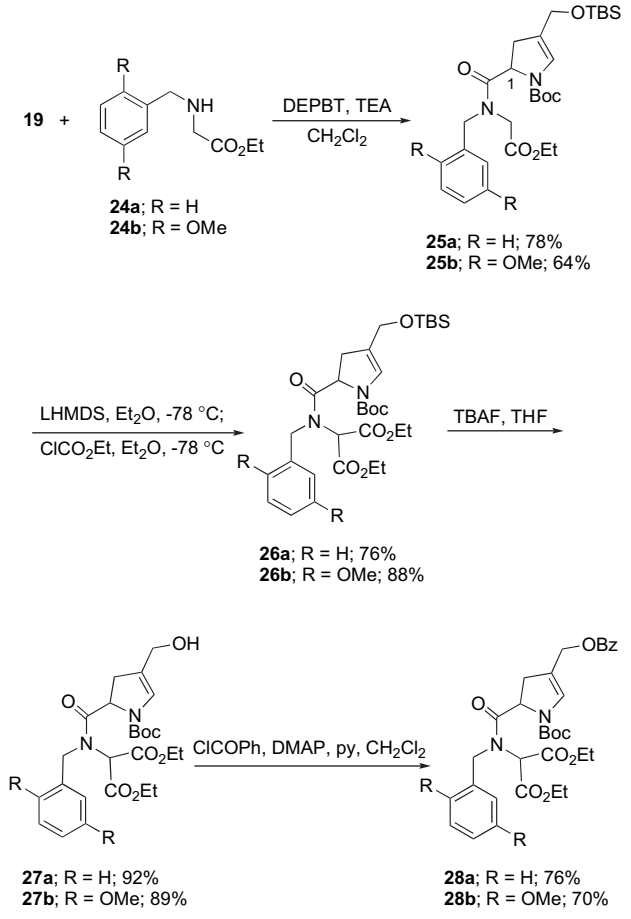


22a; R = OEt (unstable)
22b; R = Ph (71%)
22c; R = *t*-Bu (69%)

Scheme 3.

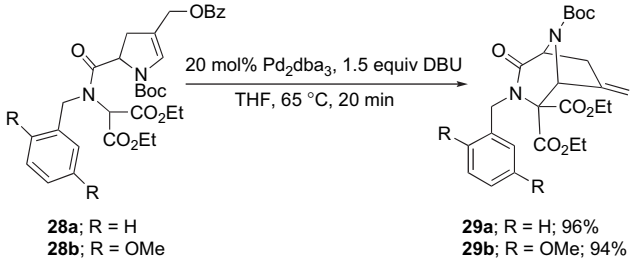
and 4). Furthermore, cycloadducts were formed in excellent yields by employing $Pd(PPh_3)_4$ and Pd_2dba_3 (entries 5 and 6).

To test the efficacy of this new methodology for the preparation of the 3,8-diazabicyclo[3.2.1]octane core structure in our natural product targets, we introduced the aromatic dnacin A-ring into the malonate moiety (Scheme 4). DEPBT-promoted[16] coupling of **19** and *N*-benzylglycine ethyl ester (**24a**) gave amide **25a** in good yield (78%). In a similar manner, amide **25b** was prepared from the coupling of **19** and *N*-(2,5-dimethoxy)benzylglycine ethyl ester **24b**, which is readily available from 2,5-dimethoxybenzylamine and ethyl bromoacetate.[17] At this stage, the A- and D-rings of the target molecule are present in the cyclization precursor (Scheme 4). Treatment of **25a** and **25b** with LHMDS followed by ethyl chloroformate provided malonates **26a** and **26b** (76 and 88%, respectively). It is noteworthy that excess amounts of LHMDS and ethyl chloroformate (6 equiv each) were necessary in order to drive the reaction to completion. An undesired acylation at C_1 of the pyrrolidine was not observed in either case, presumably due to steric hindrance around this position. Desilylations of **26a** and **26b** provided alcohols **27a** and **27b** in excellent yields of 92 and 89%, respectively.



Scheme 4.

The allylic pivaloate derivative of **27** was first chosen as a substrate due to its high reactivity toward Pd-catalyzed allylic alkylation. However, this pivaloate proved to be too unstable and decomposed during isolation. Alternatively, the allylic benzoates **28a** and **28b** were prepared using standard conditions (ClCOPh, DMAP, pyridine). The benzoates were significantly more stable than the pivaloates and could be purified by silica gel chromatography immediately after workup. However, extended storage must be avoided for intermediates **25**–**28** due to concomitant decomposition. With the key precursors in hand, the palladium-catalyzed allylic alkylations of **28a** and **28b** were studied (Scheme 5). To our delight, intramolecular allylic alkylations of **28a** and **28b** proceeded smoothly in the presence of 20 mol % of Pd_2dba_3 and 1.5 equiv of DBU in THF at 65 °C for 20 min to afford adducts **29a** and **29b** in excellent yields (96 and 94%, respectively).



Scheme 5.

3. Conclusion

We have developed two alternative approaches for the construction of the 3,8-diazabicyclo[3.2.1]octane ring system. Whereas the initial intramolecular Heck cyclization approach suffered from poor yields, the palladium-catalyzed intramolecular allylic alkylation provided an expedient route to these bridged heterocycles. To the best of our knowledge, this is the first time that a Pd-based route was used for the synthesis of the diazabicyclo[3.2.1]octane ring system. In addition, the functionalization of the 3,8-diazabicyclo-[3.2.1]octane core obtained from the intramolecular allylic alkylation protocol provides access to properly functionalized A,C,D-rings for the synthesis of dnacins and related naphthyridinomycin alkaloids. Since the Pd-coupling strategy is highly convergent and the two precursor segments are readily available in enantiomerically pure form, this strategy should lend itself to an asymmetric synthesis of the target molecules. Further improvements of this methodology and its application to natural product synthesis are currently in progress and will be reported in due course.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of argon and glassware was flame dried under vacuum or dried in an oven at 150 °C prior to use. DME, THF, and Et_2O were dried by distillation over Na/Benzophenone; Et_3N and CH_2Cl_2 were dried by distillation over CaH_2, and KHMDS and LDA were prepared prior to use. Unless stated otherwise, solvents or reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates (particle size 0.040–0.055 mm, 230–400 mesh) and

visualization was accomplished with a 254 nm UV light and/or by staining with $KMnO_4$ reagent (1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10% NaOH in 200 mL water). NMR spectra were recorded in $CDCl_3$ (298 K) at either 300.1 MHz (^1H) or 75.5 MHz (^{13}C) using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are reported in parts per million (ppm) with the residual solvent peak used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet, br d=broad doublet, br t=broad triplet, app.=apparent), coupling constants, and integration. Melting points were obtained using a heating rate of 2 °C min^{-1} on a MelTemp melting point apparatus with digital temperature reading and were reported uncorrected. Microwave heating was performed in an Emrys Optimizer single mode microwave reactor (Biotage) using 5 mL Emrys process vials.

4.1.1. 2-(3,5-Dioxomorpholin-4-ylmethyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (10). To a mixture of $NaBH_4$ (499 mg, 13.2 mmol) and LiCl (560 mg, 13.2 mmol) in EtOH (18 mL) was added a solution of 2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**9**)[9] (1 g, 4.4 mmol) in THF (18 mL) at 0 °C. The reaction mixture was stirred at rt for 10 h, quenched with water (30 mL), and extracted with Et_2O (100 mL×2). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to afford crude alcohol (861 mg).

To a solution of this alcohol (804 mg, 4.04 mmol), morpholine-3,5-dione (464 mg, 4.04 mmol), and PPh_3 (1.06 g, 4.04 mmol) in THF (20 mL) was added diazadiisopropyl dicarbonate (801 μL, 4.04 mmol) over 30 min (syringe pump) at rt. After 1 h, the solvent was removed in vacuo and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 6:4) to afford **10** (980 mg, 82%) as a pale yellow oily (6.3:1) mixture of rotamers: IR (neat) 2977, 1742, 1692, 1390, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.38 (br s, 1H), 4.96 (br s, 1H), 4.66 (br t, J=10.0 Hz, 1H), 4.41–4.19 (m, 6H), 3.49 (dd, J=12.1, 2.1 Hz, 1H), 2.87 (dd, J=16.4, 10.1 Hz, 1H), 2.14 (br d, J=16.4 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.7 (two peaks), 152.4, 129.4, 106.4, 80.2, 67.7 (two peaks), 53.8, 42.1, 33.6, 28.3; EIMS *m/z* (intensity) 297 ($[M+H]^+$, 5), 296 (M^+, 40), 223 (27), 68 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1369.

4.1.2. 2-[5-(Diethoxyphosphoryloxy)-3-oxo-2,3-dihydro[1,4]oxazin-4-ylmethyl]-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (11). To a solution of **10** (300 mg, 1.01 mmol) in THF (11 mL) was added LHMDS (1.22 mL, 1.22 mmol) at −78 °C. After 20 min, the reaction mixture was allowed to warm to −30 °C and stirred at this temperature for 30 min. The mixture was cooled to −78 °C and a solution of diethyl chlorophosphate (176 μL, 1.22 mmol) in THF (3 mL) was added. After warming to 0 °C, the reaction mixture was quenched with 5% aqueous NH_4OH (4 mL), extracted with Et_2O (15 mL×3), washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3, 1% NEt_3) to afford **11** (260 mg, 60%) as a pale yellow oily mixture of rotamers: IR (neat) 2980, 1704, 1619, 1402, 1360, 1278, 1226, 1183, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55, 6.40 (2br s, 1H), 6.50 (d, J=2.9 Hz, 1H), 5.01, 4.93 (2br s, 1H), 4.54 (br s, 1H), 4.42–4.17 (m, 6H), 3.89, 3.85 (2d, J=7.2 Hz, 1H), 3.85–3.65 (m, 1H), 2.78 (dd, J=16.3, 10.1 Hz, 1H), 2.26 (br d, J=15.8 Hz, 1H), 1.47 (s, 9H), 1.38 (tt, J=7.1, 1.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 164.5, 134.1, 134.0, 129.5, 120.1 (2C), 106.1, 80.2, 68.0, 67.7, 65.4 (2C), 65.3, 64.4, 54.9, 42.2, 32.7, 28.3, 16.1, 16.0; EIMS *m/z* (intensity) 432 (M^+, 6), 265 (31), 178 (91), 68 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{29}N_2O_8P$ 432.1662, found 432.1647.

4.1.3. 6-Oxo-4-oxa-7,12-diazatricyclo[7.2.1.$0^{2,7}$]dodeca-2,10-diene-12-carboxylic acid *tert*-butyl ester (12). *Table 1, entry 7*: $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), dppp (16 mg, 0.04 mmol), and K_2CO_3 (15 mg, 0.11 mmol) were added to a solution of **11** (21 mg, 0.05 mmol) in DME (490 μL). This mixture was deoxygenated using freeze thaw cycles under vacuum and the reaction mixture was heated to 70 °C for 8 h. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1) to afford **12** (7.3 mg, 53%) as a colorless oily (2.4:1) mixture of rotamers: IR (neat) 2977, 1693, 1673, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.21–6.15 (m, 2H), 6.12 (s, 1H), 4.84–4.64 (m, 2H), 4.39 (d, J=14.5 Hz, 1H), 4.22 (d, J=14.5 Hz, 1H), 3.65 (d, J=12.8 Hz, 1H), 3.43 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.1, 152.3, 133.8, 131.9, 125.8, 116.7, 80.7, 67.6, 56.1, 55.2, 40.7, 40.1, 28.2; EIMS *m/z* (intensity) 278 (M^+, 20), 222 (34), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1265.

Table 1, entry 8: $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), dppp (19 mg, 0.046 mmol), and K_2CO_3 (16 mg, 0.108 mmol) were added to a solution of **11** (21 mg, 0.049 mmol) in DME (390 μL). The reaction mixture was stirred for 5 min and heated in the microwave for 30 min (hold time) at 100 °C. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1) to afford **12** (8.8 mg, 54%) as a colorless oil.

4.1.4. *tert*-Butyl 2-(3-oxomorpholine-4-carbonyl)-2,3-dihydropyrrole-1-carboxylate (13). To a solution of 2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**9**)[9] (6.5 g, 28.6 mmol) in MeOH (153 mL) was added LiOH (2.4 g, 57.2 mmol) followed by H_2O (39 mL) at 0 °C and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated, and partitioned between water (80 mL) and Et_2O (50 mL×2). The aqueous layer was acidified to pH 2–4 with 3 N HCl and extracted with Et_2O (100 mL×3 and 50 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude acid. To a solution of the crude acid in CH_2Cl_2 (143 mL) was added pentafluorophenol (5.26 g, 28.6 mmol) followed by EDC (5.48 g, 28.6 mmol) at rt. Reaction mixture was stirred for 4.5 h, quenched with H_2O (100 mL), and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the residue was purified

by chromatography on SiO_2 (hexanes/EtOAc, 9:1) to afford the activated ester (10.89 g, 65%) as a colorless oily (6.3:1) mixture of rotamers: IR (neat) 3120, 2982, 2936, 1800, 1716, 1522, 1458, 1398 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79, 6.67 (2s, 1H), 5.20–5.00 (m, 2H), 3.46–3.26 (m, 1H), 3.10–2.92 (m, 1H), 1.58, 1.56 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.8, 167.5, 151.2, 151.0, 142.9 (2C), 142.8, 142.7, 141.4, 139.5 (2C), 139.4, 137.9, 136.2, 130.1, 104.7, 81.8, 81.6, 57.8, 57.6, 35.8, 34.4, 28.2, 28.0; EIMS *m/z* (intensity) 379 (M^+, 20), 324 (60), 279 (75), 278 (65), 112 (62), 57 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{14}F_5NO_4$ 379.0843, found 379.0845.

A solution of morpholine-3-one (288 mg, 2.84 mmol) in THF (15 mL) was treated with KHMDS (5.7 mL, 2.84 mmol, 0.5 M in THF) dropwise at −78 °C and stirred for 1 h at this temperature. A solution of activated ester (863 mg, 2.28 mmol) in THF (10 mL) was then added and stirred for additional 0.5 h. Reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL), diluted with CH_2Cl_2 (10 mL) at −78 °C, and warmed to rt. Reaction mixture was extracted with CH_2Cl_2 (100 mL×2). The combined extracts were dried ($MgSO_3$), filtered, concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **13** (464 mg, 69%) as a colorless foamy (1.7:1) mixture of rotamers: IR (neat) 2976, 2869, 1704, 1623, 1461, 1401, 1310, 1285, 1250, 1203, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71, 6.57 (2 m, 1H), 5.63–5.50 (m, 1H), 4.93–4.87 (m, 1H), 4.38–4.22 (m, 2H), 4.02–3.73 (m, 4H), 3.33–3.20 (m, 1H), 2.62–2.48 (m, 1H), 1.49, 1.41 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.6, 173.2, 169.2, 169.1, 151.3, 151.2, 130.3, 104.7, 104.6, 80.8, 80.4, 68.7 (2C), 63.9, 63.8, 61.4, 61.2, 43.7, 43.6, 35.8, 34.8, 28.3, 28.2; EIMS *m/z* (intensity) 297 ($[M+H]^+$, 7), 296 (M^+, 27), 222 (34), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1368.

4.1.5. *tert*-Butyl 2-(5-(diethoxyphosphoryloxy)-3,4-dihydro-2*H*-1,4-oxazine-4-carbonyl)-2,3-dihydropyrrole-1-carboxylate (14). A solution of **13** (213 mg, 0.78 mmol) in THF (8 mL) was treated with freshly prepared LDA (1.6 mL, 1.01 mmol, 0.65 M in THF) at −78 °C. The resulting mixture was slowly warmed up to −40 °C over 1 h, quenched with 5% aqueous NH_4OH solution (5 mL), and extracted with Et_2O (20 mL×3). The combined organic layers were washed with brine, dried ($MgSO_3$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1, 1% NEt_3) to afford **14** (100 mg, 30%) as a colorless foamy (1.4:1) mixture of rotamers: IR (neat) 2978, 2933, 1702, 1392, 1327, 1275, 1196, 1167, 1116, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71–6.70, 6.55–6.53 (2m, 1H), 6.47 (dd, *J*=8.8, 3.5 Hz, 1H), 5.04–4.98 (m, 1H), 4.95–4.87 (m, 1H), 4.31–4.07 (m, 6H), 4.01–3.86 (m, 1H), 3.37–3.30 (m, 1H), 3.23–3.03 (m, 1H), 2.71–2.63 (m, 1H), 1.46, 1.42 (2s, 9H), 1.37 (t, *J*=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 171.2, 170.9, 151.2, 151.0, 130.3, 130.1, 126.1, 126.0, 125.1, 125.0, 124.9 (2C), 104.7, 80.3, 65.9, 65.8, 64.9, 64.8 (2C), 58.2, 57.8, 39.9, 39.5, 36.3, 34.8, 28.2, 28.1, 16.1, 16.0, 15.9; EIMS *m/z* (intensity) 433 ($[M+H]^+$, 12), 432 (M^+, 50), 359 (30), 239 (100), 155 (69); HRMS (EI) *m/z* calcd for $C_{18}H_{29}N_2O_8P$ 432.1662, found 432.1656.

4.1.6. 8-Oxo-4-oxa-7,12-diazatricyclo[7.2.1.0^{00}]dodeca-2,10-diene-12-carboxlic acid *tert*-butyl ester (15). $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), dppp (11.4 mg, 0.028 mmol), and K_2CO_3 (19.2 mg, 0.139 mmol) were added to a solution of **14** (30 mg, 0.069 mmol) in THF (360 μL). This mixture was deoxygenated using freeze thaw cycles under vacuum and heated to 80 °C for 13 h. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) to afford **15** (6 mg, 31%) as a colorless oil: IR (neat) 3400, 2978, 2935, 2975, 1705, 1459, 1379, 1311, 1284, 1165, 1111, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.35 (dd, *J*=5.6, 2.4 Hz, 1H), 6.25 (dd, *J*=5.6, 2.4 Hz, 1H), 5.98 (s, 1H), 4.88 (br s, 1H), 4.81 (d, *J*=2.1 Hz, 1H), 4.11–3.96 (m, 2H), 3.90–3.86 (m, 1H), 3.56–3.50 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.3, 153.6, 132.2, 131.0, 124.5, 114.1, 81.5, 64.8, 64.3, 58.4, 38.9, 28.3; EIMS *m/z* (intensity) 279 ($[M+H]^+$, 5), 278 (M^+, 33), 222 (45), 150 (34), 93 (46), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1270.

4.1.7. 4-Formyl-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (17). To a solution of 4-formyl-2,3-dihydropyrrole-2-dicarboxylic acid 2-methyl ester **16**[14] (1.04 g, 6.70 mmol) in CH_2Cl_2 (30 mL) was added DMAP (82 mg, 0.67 mmol) and Boc_2O (1.61 g, 7.37 mmol). The reaction mixture was stirred at rt for 10 h and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **17** (1.13 g, 66%) as a pale yellow oily (1:1) mixture of rotamers: IR (neat) 3094, 2981, 2951, 1753, 1727, 1662, 1609, 1415 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.63, 7.46 (2s, 1H), 4.79 (2dd, *J*=12.2, 4.6 Hz, 1H), 3.78 (s, 3H), 3.20 (app. t, *J*=15.1 Hz, 1H), 2.88 (2br dd, *J*=15.1, 4.6 Hz, 1H), 1.53, 1.47 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 185.0, 170.6, 170.4, 150.0, 146.8, 146.5, 122.3, 122.1, 83.3, 83.0, 59.7, 59.1, 52.4, 31.2, 30.1, 27.8, 27.6, 27.3; EIMS *m/z* (intensity) 255 (M^+, 25), 155 (40), 96 (40), 57 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{17}NO_5$ 255.1107, found 255.1118.

4.1.8. 4-Hydroxymethyl-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester. A solution of aldehyde **17** (95 mg, 0.370 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C, treated with solid $NaBH_4$ (30 mg, 0.740 mmol) and then methanol (700 μL) dropwise. The reaction mixture was warmed to 0 °C over a 2 h period, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) to afford the corresponding alcohol (95 mg, 99%) as a clear oily (1:1) mixture of rotamers: IR (neat) 3434, 2977, 2866, 1754, 1704, 1479, 1419 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63, 6.51 (2br s, 1H), 4.72, 4.64 (2dd, *J*=11.9, 5.2 Hz, 1H), 4.18 (app. s, 2H), 3.77 (s, 3H), 3.11 (app. q, *J*=14.9 Hz, 1H), 2.69 (dt, *J*=16.8, 4.9 Hz, 1H), 1.49, 1.43 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.2, 172.0, 151.2, 126.0, 125.8, 119.6, 119.4, 80.8, 58.7, 58.5, 58.1, 52.2, 52.0, 35.4, 34.3, 28.0, 27.9; EIMS *m/z* (intensity) 258 ($[M+H]^+$, 11), 257 (M^+, 75), 198

(50), 157 (62), 53 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{19}NO_5$ 257.1263, found 257.1275.

4.1.9. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (18). To a solution of the above alcohol (1.54 g, 5.99 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (3.30 mL, 24.0 mmol) and DMAP (1.5 mg, 1.2 mmol) followed by a solution of TBSCl (1.08 g, 7.18 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 10 h, diluted with CH_2Cl_2 (30 mL), and washed with brine. The organic layer was dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2) to afford **18** (1.84 g, 83%) as a pale yellow oily (1:1) mixture of rotamers: IR (neat) 2954, 2931, 2858, 2887, 1758, 1712, 1419, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55, 6.42 (2s, 1H), 4.70, 4.63 (2dd, J=11.9, 5.1 Hz, 1H), 4.18 (app. s, 2H), 3.76 (s, 3H), 3.15–3.00 (m, 1H), 2.60 (dt, J=18.5, 4.8 Hz, 1H), 1.48, 1.43 (2s, 9H), 0.9, 0.89 (2s, 9H), 0.07, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.7, 151.1, 151.0, 125.4, 125.1, 119.2 (two peaks), 80.5, 80.3, 59.3, 58.6, 58.0, 52.0, 51.8, 35.4, 34.3, 28.0, 27.8, 25.6, 18.0, −5.6; EIMS *m/z* (intensity) 371 (M^+, 10), 271 (35), 228 (35), 80 (57), 75 (65), 57 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{33}NO_5Si$ 371.2128, found 371.2136.

4.1.10. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester (19). To a solution of ester **18** (570 mg, 1.53 mmol) in methanol (8 mL) was added LiOH (78 mg, 1.84 mmol) at 0 °C, followed by H_2O (1.5 mL). The solution was warmed to rt, stirred for 10 h, concentrated, redissolved in H_2O (10 mL), acidified to pH 2–4 with 1 N HCl, and extracted with Et_2O (10 mL×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 3:1) to afford **19** (350 mg, 68%) as a clear oily mixture of rotamers: IR (neat) 2955, 2931, 2858, 1712, 1421, 1392, 1368, 1251, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56, 6.36 (2s, 1H), 4.76, 4.65 (2dd, J=11.3, 5.4 Hz, 1H), 4.20 (app. s, 2H), 3.19–2.58 (m, 2H), 1.50, 1.44 (2s, 9H), 0.91, 0.90 (2s, 9H), 0.08, 0.07 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.7, 175.5, 152.1, 151.3, 125.3, 125.0, 120.3, 119.5, 81.5, 81.1, 59.5, 58.5, 58.2, 35.5, 34.0, 28.1, 28.0, 25.7, 25.5, 18.2, −3.9, −5.6; EIMS *m/z* (intensity) 357 (M^+, 10), 312 (10), 255 (15), 180 (15), 82 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{31}NO_5Si$ 357.1972, found 357.1964.

4.1.11. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2-(ethoxycarbonylmethylmethylcarbamoyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (20). To a solution of ester **18** (1 g, 3.01 mmol) in MeOH (15 mL) was added LiOH (190 mg, 4.52 mmol) followed by H_2O (3 mL) at 0 °C. The reaction mixture was stirred at rt for 10 h, concentrated, and partitioned between water (15 mL) and Et_2O (15 mL). The aqueous layer was acidified to pH 2–4 with 3 N HCl (~1.7 mL) and extracted with Et_2O (30 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude acid (804 mg). To a solution of this acid (804 mg, 3.01 mmol), sarcosine ethyl ester hydrochloride (461 mg, 3.01 mmol) and HOBt (4.05 mg, 3.01 mmol) in CH_2Cl_2 (10 mL) was added a solution of DCC (743 mg, 3.6 mmol) in CH_2Cl_2 (5 mL) at −10 °C. After 20 min, NEt_3 (1.25 mL, 9.09 mmol) was added. The reaction mixture was warmed to rt and stirred for 12 h, diluted with EtOAc (40 mL), and filtered. The solid was washed with EtOAc (5 mL). The combined filtrates were concentrated and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **20** (734 mg, 54%) as a colorless glassy mixture of rotamers: IR (neat) 2955, 2930, 2857, 1749, 1705, 1669, 1423, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60, 6.48 (2s, 1H), 5.02, 4.94 (2dd, J=11.9, 5.3 Hz, 1H), 4.84–4.66 (m, 1H), 4.29–4.11 (m, 4H), 4.01, 3.53 (2d, J=17.3 Hz, 1H), 3.19–3.01 (m, 4H), 2.62–2.53 (m, 1H), 1.47, 1.43 (2s, 9H), 1.33–1.25 (m, 3H), 0.90, 0.89 (2s, 9H), 0.07, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.4, 171.0, 168.9, 168.7, 151.2, 126.1, 126.0, 125.7, 119.5, 118.8, 118.6, 80.3, 61.3, 60.8, 59.6, 57.0, 56.2, 51.3, 49.6, 49.5, 35.8, 35.7, 35.4, 35.2, 34.9, 34.0, 28.1, 27.9, 25.7, 18.1, 13.9, −5.5; EIMS *m/z* (intensity) 456 (M^+, 25), 356 (45), 299 (35), 80 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{40}N_2O_6Si$ 456.2656, found 456.2652.

4.1.12. 2-{[1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-methylamino}malonic acid diethyl ester (21). A solution of **20** (200 mg, 0.438 mmol) in THF (4 mL) was added to a solution of LHMDS (1.05 mL, 1.05 mmol, 1 M in THF) in THF (2 mL) at −78 °C. After 10 min, ethyl chloroformate (101 μL, 1.05 mmol) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature and then quenched with a saturated aqueous NH_4Cl solution (5 mL) at this temperature. The mixture was warmed to rt and partitioned between water (10 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **21** (221 mg, 95%) as a colorless glassy mixture of rotamers: IR (neat) 2980, 2962, 2934, 2851, 1740, 1703, 1670, 1487, 1421, 1367 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60, 6.47 (2br s, 1H), 5.98, 5.91 (2s, 1H), 5.03, 4.96 (2d, J=11.9, 5.2 Hz, 1H), 4.34–4.10 (m, 6H), 3.23–3.04 (m, 4H), 2.58–2.48 (m, 1H), 1.47, 1.41 (2s, 9H), 1.36–1.24 (m, 3H), 0.89, 0.88 (2s, 9H), 0.06, 0.05 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.5, 166.2, 166.2, 166.1, 165.9, 151.1, 151.1, 126.2, 125.9, 118.6, 80.4, 80.3, 61.8, 61.8, 60.2, 60.0, 59.5, 56.9, 56.4, 35.0, 34.1, 32.9, 32.7, 32.1, 31.2, 28.1, 27.8, 25.6, 18.1, 18.0, 13.8, −5.5; EIMS *m/z* (intensity) 528 (M^+, 7), 428 (45), 212 (66), 154 (83), 80 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{44}N_2O_8Si$ 528.2867, found 528.2866.

4.1.13. 2-{[1-*tert*-Benzoyloxymethyl-l-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl]methylamino}malonic acid diethyl ester (22b). To a solution of **21** (221 mg, 0.420 mmol) in THF (5 mL) was added TBAF (840 μL, 0.840 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 10 h, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:8 to 1:9) to afford the alcohol (167 mg, 96%) as a colorless oil.

To a solution of this alcohol (167 mg) in CH_2Cl_2 (4 mL) was added DMAP (10 mg, 0.081 mmol), pyridine (130 μL, 1.61 mmol), and benzoyl chloride (94 μL, 0.81 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for

14 h, and diluted with CH_2Cl_2. The solution was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 6.5:3.5) to afford **22b** (154 mg, 74%) as a colorless glassy mixture of rotamers: IR (neat) 2980, 2937, 1740, 1717, 1676, 1422, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–8.09, 8.03–8.00 (2m, 2H), 7.63–7.53 (m, 1H), 7.50–7.40 (m, 2H), 6.86, 6.72 (2s, 1H), 5.96–5.89 (2s, 1H), 5.08, 5.02 (2d, J=11.9, 5.0 Hz, 1H), 4.94–4.79 (m, 2H), 4.31–4.18 (m, 4H), 3.32–3.02 (m, 4H), 2.68 (dd, J=16.0, 5.0 Hz, 1H), 1.48, 1.42 (2s, 9H), 1.33–1.23 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.4, 166.4, 166.3, 166.2 (2C), 151.2 (2C), 133.5, 133.0, 130.5, 130.1, 130.0, 129.6, 128.4, 128.3, 113.2, 113.1, 81.2, 81.1, 62.1, 62.0, 61.2, 60.5, 57.2, 56.8, 35.8, 34.8, 33.1, 33.0, 28.3, 28.2, 28.0, 14.0; ESIMS m/z (intensity) 542 ([M+H]$^+$, 15), 541 (M$^+$, 60), 451 (45), 437 (100), 319 (60), 297 (85); HRMS (ESI) m/z calcd for $C_{26}H_{34}N_2O_9Na$ 541.2162, found 541.2180.

4.1.14. 2-{[l-*tert*-Butoxycarbonyl-4-(2,2-dimethylpropionyloxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-methylamino}malonic acid diethyl ester (22c). To a solution of **21** (256 mg, 0.484 mmol) in THF (6 mL) was added TBAF (968 μL, 0.968 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 10 h, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:8 to EtOAc) to afford the alcohol (197 mg, 96%) as a colorless oil.

To a solution of this alcohol (197 mg) in CH_2Cl_2 (5 mL) was added DMAP (5.8 mg, 0.048 mmol), pyridine (95 μL 1.9 mmol), and pivaloyl chloride (117 μL, 0.95 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for 14 h, and diluted with CH_2Cl_2. The product portion was washed with a saturated aqueous NH_4Cl solution, dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 7:3) to afford **22c** (170 mg, 72%) as a colorless glassy mixture of rotamers: IR (neat) 2978, 2937, 2974, 1737, 1715, 1675, 1485, 1414 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75, 6.62 (2s, 1H), 5.96, 5.89 (2s, 1H), 5.05, 4.98 (2dd, J=11.9, 4.9 Hz, 1H), 4.67–4.55 (m, 2H), 4.34–4.19 (m, 4H), 3.17, 3.14 (2s, 3H), 3.07 (d, J=15.9 Hz, 1H), 2.58 (dd, J=15.9, 4.7 Hz, 1H), 1.48, 1.45 (2s, 9H), 1.33–1.28 (m, 6H), 1.20, 1.19 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.0, 171.4, 171.2, 166.1, 166.0, 165.9, 165.8, 150.9, 150.8, 129.5, 129.2, 113.4, 113.3, 80.8, 61.9, 60.3, 60.0, 56.9, 56.5, 38.5, 35.4, 34.4, 32.9, 32.7, 28.0, 27.8, 26.9, 13.8; ESIMS m/z (intensity) 522 ([M+H]$^+$, 31), 521 (M$^+$, 100); HRMS (ESI) m/z calcd for $C_{24}H_{38}N_2O_9Na$ 521.2475, found 521.2476.

4.1.15. 8-(3,3-Dimethylbutyryl)-3-methylene-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,2-dicarboxylic acid diethyl ester (23). *Table 2, entry 1*: to a suspension of NaH (4 mg, 0.1 mmol) in THF (1 mL) was added a solution of **22b** (35 mg, 0.068 mmol) in THF (2.4 mL) at 0 °C. After stirring for 15 min at rt, the Pd-catalyst, preformed for 1 h at rt from $Pd(OAc)_2$ (1.5 mg, 6.8×10^{-3} mmol) and dppe (5.4 mg, 1.4×10^{-2} mmol) in THF (1 mL), was added, and the reaction mixture was heated at 65–70 °C for 1 h. After cooling to 0 °C, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1) to afford **23** (18 mg, 67%) as a colorless glassy solid: IR (neat) 2981, 2936, 1749, 1708, 1682, 1478, 1368 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (br s, 1H), 5.15 (br s, 2H), 4.70 (br d, J=5.8 Hz, 1H), 4.38–4.16 (m, 4H), 2.97 (s, 3H), 2.75–2.60 (m, 2H), 1.44 (s, 9H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8, 166.0, 165.3, 152.4, 142.1, 112.3, 81.3, 76.3, 62.9, 62.4, 58.9 (br), 36.8, 34.3, 28.1, 13.9; EIMS m/z (intensity) 396 (M$^+$, 10), 296 (41), 190 (85), 57 (100); HRMS (EI) m/z calcd for $C_{19}H_{28}N_2O_7$ 396.1897, found 396.1895.

Table 2, entry 5: to a solution of **22c** (45 mg, 0.09 mmol) in THF (3 mL) were added DBU (21 μL, 0.14 mmol) and a solution of $Pd(PPh_3)_4$ (10.4 mg, 9.03×10^{-3} mmol) in THF (1.5 mL). The reaction mixture was heated at 65–75 °C for 4 h, cooled to rt, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **23** (34 mg, 95%) as a colorless glassy solid.

Table 2, entry 6: to a solution of **22c** (36 mg, 0.072 mmol) in THF (3 mL) were added DBU (16 μL, 0.108 mmol) and a solution of Pd_2dba_3 (6.6 mg, 7.2×10^{-3} mmol) in THF (1 mL). The reaction mixture was heated at 65–75 °C for 2 h, cooled to rt, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **23** (29 mg, 98%) as a colorless glassy solid.

4.2. General procedure A for the coupling of acid 19 and amines (24a and 24b)

4.2.1. 2-(Benzylethoxycarbonylmethylcarbamoyl)-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (25a). To a solution of acid **19** (123 mg, 0.369 mmol), *N*-benzylglycine ethyl ester hydrochloride (170 mg, 0.738 mmol), and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (170 mg, 0.554 mmol) in CH_2Cl_2 (3.7 mL) was added triethylamine (205 μL, 1.48 mmol) dropwise at 0 °C. The solution was warmed to rt and stirred for 4 h. Saturated aqueous NaCl (5 mL) was added and the mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with 1 N HCl, 5% Na_2CO_3, H_2O, and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:1 to 4:1) to afford **25a** (153 mg, 78%) as a clear oily mixture of rotamers: IR (neat) 2955, 2930, 2857, 1748, 1706, 1674, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.28 (m, 5H), 6.62, 6.47 (2s, 1H), 5.13–4.66 (m, 2H), 4.61–4.29 (m, 2H), 4.24–4.11 (m, 4H), 3.87–3.54 (m, 1H), 3.13–2.90 (m, 1H), 2.66 (dt, J=16.6, 4.8 Hz, 1H), 1.48 (s, 9H), 1.28–1.22 (m, 3H), 0.92–0.89 (m, 9H), 0.11–0.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.5, 168.9, 168.7, 151.3, 151.2, 136.2, 135.6, 128.7, 128.4, 128.3, 127.9 (2C), 127.1, 126.9, 118.7, 118.4, 80.6, 80.2, 59.5, 57.2, 56.6, 51.6, 51.3, 47.1, 47.0, 36.2, 35.9, 35.2, 34.6, 28.1 (2C), 25.7, 18.1, 13.9, −5.54; ESIMS m/z (intensity) 1087 ([2M+Na]$^+$, 15), 555 ([M+Na]$^+$, 100); HRMS (ESI) m/z calcd for $C_{28}H_{44}N_2NaO_6Si$ (M+Na) 555.2866, found 555.2826.

4.2.2. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2-[(2,5-dimethoxybenzyl)ethoxycarbonylmethylcarbamoyl]-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (25b). According to general procedure A, acid **19** (70 mg,

0.210 mmol), *N*-(2,5-dimethoxy)benzylglycine ethyl ester[17] **24b** (59 mg, 0.231 mmol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (69 mg, 0.231 mmol), and triethylamine (60 μL, 0.420 mmol) afforded ester **25b** (80 mg, 64%) as a pale yellow oily (2.2:1) mixture of rotamers: IR (neat) 2955, 2931, 2856, 1748, 1705, 1674, 1502, 1463, 1421, 1391, 1366, 1279, 1250, 1224, 1166, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03 (s, 1H), 6.83–6.75 (m, 2H), 6.59, 6.47 (2br s, 1H), 5.06, 4.94 (2dd, J=11.9, 5.5 Hz, 1H), 4.61–4.44 (m, 3H), 4.30–4.10 (m, 5H), 3.95–3.48 (m, 7H), 3.10–2.86 (m, 1H), 2.73–2.60 (m, 1H), 1.45, 1.43 (2s, 9H), 1.29–1.22 (m, 3H), 0.89, 0.88 (2s, 9H), 0.06, 0.04 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.9, 171.4, 169.0, 168.9, 153.7, 153.5, 151.4 (2C), 151.0, 126.3, 126.2, 124.9, 124.3, 119.7, 119.1, 118.5 (2C), 114.0, 113.7, 111.0, 110.8, 80.5, 80.0, 61.2, 60.7, 59.6, 56.8, 56.4, 55.5, 55.4, 49.2, 48.7, 47.2, 46.9, 36.0, 34.6, 28.1, 28.0, 25.7, 18.1, 13.9, −5.5; ESIMS *m/z* (intensity) 1207 ([2M+Na]$^+$, 85), 615 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{30}H_{48}N_2NaO_8Si$ (M+Na) 615.3078, found 615.3049.

4.3. General procedure B for the C-acylations of esters 25a and 25b with ethyl chloroformate

4.3.1. 2-{Benzyl[1-*tert*-butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]amino}malonic acid diethyl ester (26a). To a solution of ester **25a** (270 mg, 0.507 mmol) in Et_2O (5 mL) was added freshly prepared LHMDS (3.00 mL, 3.04 mmol, 1 M in THF) dropwise at −78 °C. After stirring for 1 h at this temperature, ethyl chloroformate (290 μL, 3.04 mmol) was added dropwise. The reaction mixture was stirred for 7 h at −78 °C and then quenched with saturated aqueous NH_4Cl (5 mL) at this temperature. The mixture was warmed to rt and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:1 to 4:1) to afford **26a** (233 mg, 76%) as a clear oily mixture of rotamers: IR (neat) 2956, 2930, 2857, 1742, 1706, 1462, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.30 (m, 5H), 6.59, 6.43 (2s, 1H), 5.46, 5.40 (2s, 1H), 4.91–4.61 (m, 3H), 4.29–4.00 (m, 5H), 3.91–3.78 (m, 1H), 2.99, 2.81 (2app. t, J=13.9 Hz, 1H), 2.68, 2.57 (2dd, J=15.8, 4.8 Hz, 1H), 1.52, 1.47 (2s, 9H), 1.27, 1.25 (2t, J=7.1 Hz, 3H), 1.15, 1.13 (2t, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.7, 172.4, 166.1, 166.0, 165.9, 165.8, 151.4, 151.1, 136.2, 135.9, 128.5, 127.8, 127.5, 126.8 (2C), 126.5, 126.3, 118.6, 118.3, 81.1, 80.3, 61.9, 61.8, 61.4, 61.2, 59.6, 57.3, 56.7, 50.5, 50.3, 36.1, 34.8, 28.2, 25.8, 18.2, 13.8 (two peaks), 13.6, −5.4; ESIMS *m/z* (intensity) 1232 ([2M+Na]$^+$, 50), 628 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{31}H_{48}N_2NaO_8Si$ (M+Na) 627.3078, found 627.3078.

4.3.2. 2-{[1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-(2,5-dimethoxybenzyl)amino}malonic acid diethyl ester (26b). According to general procedure B, ester **25b** (550 mg, 0.927 mmol), LHMDS (6.5 mL, 6.49 mmol), and ethyl chloroformate (620 μL, 6.49 mmol) afforded **26b** (540 mg, 88%) as a clear foamy mixture of rotamers: IR (neat) 2955, 2932, 2856, 1742, 1705, 1501, 1464, 1421, 1391, 1301, 1281, 1251, 1266, 1223, 1165, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28, 7.10 (2s, 1H), 6.81–6.75 (m, 2H), 6.57, 6.43 (2s, 1H), 5.30, 5.23 (2s, 1H), 4.91–4.56 (m, 3H), 4.23–4.03 (m, 5H), 3.86 (s, 2H), 3.80, 3.79 (2s, 3H), 3.75 (s, 2H), 2.98 (app. t, J=11.9 Hz, 1H), 2.65 (dt, J=18.1, 4.5 Hz, 1H), 1.50, 1.44 (2s, 9H), 1.28–1.10 (m, 6H), 0.89, 0.88 (2br s, 9H), 0.05, 0.04 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.6, 172.3, 165.9, 165.7, 165.6, 165.5, 153.6, 151.3, 150.8, 150.4, 150.3, 126.2, 125.1, 124.6, 118.4, 118.3, 114.7, 114.2, 112.7, 111.9, 110.8, 110.6, 80.9, 80.0, 62.1, 61.7, 59.5, 56.7, 56.5, 55.6, 55.4, 45.8, 36.2, 34.3, 28.1, 28.0, 25.6, 18.0, 13.7, 13.6, 13.4, −5.6 (two peaks); ESIMS *m/z* (intensity) 1351 ([2M+Na]$^+$, 65), 687 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{33}H_{52}N_2NaO_{10}Si$ (M+Na) 687.3289, found 687.3286.

4.4. General procedure C for the TBS-deprotection of malonates 26a and 26b

4.4.1. 2-[Benzyl-(1-*tert*-butoxycarbonyl-4-hydroxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)amino]-malonic acid diethyl ester (27a). Malonate **26a** (100 mg, 0.165 mmol) was dissolved in THF (2 mL), cooled to 0 °C, and treated with TBAF (330 μL, 0.330 mmol, 1.0 M in THF). The solution was warmed to rt, stirred for 10 h, quenched with H_2O, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to afford **27a** (74 mg, 92%) as a clear oily mixture of rotamers: IR (neat) 3468, 2980, 2934, 1741, 1702, 1497, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.31 (m, 5H), 6.68, 6.53 (2s, 1H), 5.38, 5.34 (2s, 1H), 4.95–4.84 (m, 1H), 4.81–4.61 (m, 2H), 4.27–4.04 (m, 5H), 3.93–3.84 (m, 1H), 3.09–2.68 (m, 2H), 1.53, 1.48 (2s, 9H), 1.27, 1.25 (2t, J=7.1 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 172.5, 166.0, 165.9, 165.8, 151.5, 151.2, 136.0, 135.8, 128.6, 127.9, 127.6, 127.3, 126.9, 126.8, 118.6, 118.3, 81.3, 80.6, 62.0, 61.6, 61.5, 59.0 (2C), 57.4, 56.7, 50.5, 36.1, 34.7, 28.3, 28.2, 13.8 (2C), 13.7; ESIMS *m/z* (intensity) 1003 ([2M+Na]$^+$, 65), 985 (100), 513 ([M+Na]$^+$, 40); HRMS (ESI) *m/z* calcd for $C_{25}H_{34}N_2NaO_8$ (M+Na) 513.2213, found 513.2228.

4.4.2. 2-[(1-*tert*-Butoxycarbonyl-4-hydroxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)-amino]malonic acid diethyl ester (27b). According to general procedure C, malonate **26b** (540 mg, 0.810 mmol) and TBAF (1.6 mL, 1.62 mmol) afforded alcohol **27b** (396 mg, 89%) as a clear foamy mixture of rotamers: IR (neat) 3479, 2978, 2837, 1741, 1702, 1501, 1465, 1420, 1391, 1368, 1301, 1282, 1223, 1178, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26, 7.11 (2s, 1H), 6.84–6.76 (m, 2H), 6.67, 6.52 (2s, 1H), 5.21, 5.12 (2s, 1H), 4.93–4.54 (m, 3H), 4.32–4.08 (m, 5H), 3.86 (s, 2H), 3.80 (s, 3H), 3.74 (s, 2H), 3.02 (app. t, J=13.8 Hz, 1H), 2.88–2.74 (m, 1H), 1.50, 1.45 (2s, 9H), 1.28–1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 172.3, 165.5, 165.4, 165.3, 153.5, 151.2, 150.7, 150.4, 150.3, 126.7, 126.5, 124.8, 124.3, 118.6, 114.6, 114.2, 112.8, 112.1, 110.7, 110.6, 80.9, 80.0, 62.1, 61.7, 61.6, 58.4, 56.7, 56.5, 55.4, 55.3, 45.9, 35.9, 34.3, 27.9, 27.8, 13.5, 13.4, 13.3; ESIMS *m/z* (intensity) 1123 ([2M+Na]$^+$, 35), 573 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{27}H_{38}N_2NaO_{10}$ (M+Na) 573.2424, found 573.2433.

4.5. General procedure D for the O-benzylation of alcohols 27a and 27b

4.5.1. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)benzylamino]-malonic acid diethyl ester (28a). A solution of alcohol **27a** (375 mg, 0.765 mmol) and DMAP (9.3 mg, 0.0765 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and treated with pyridine (250 μL, 3.06 mmol) followed by benzoyl chloride (178 μL, 1.53 mmol). The solution was warmed to rt, stirred for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 2:1) to afford **28a** (346 mg, 76%) as a clear oily (6.7:1) mixture of rotamers: IR (neat) 2980, 1713, 1452, 1418, 1368, 1269, 1107, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, J=8.1 Hz, 2H), 7.55 (t, J=7.4 Hz, 1H), 7.45–7.29 (m, 7H), 6.85, 6.69 (2s, 1H), 5.37, 5.35 (2s, 1H), 4.97–4.57 (m, 5H), 4.28–4.00 (m, 3H), 3.90–3.76 (m, 1H), 3.15–2.75 (m, 2H), 1.53, 1.49 (2s, 9H), 1.25, 1.23 (2t, J=7.1 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 172.0, 166.4, 166.1, 165.9, 165.8, 151.4, 151.0, 135.9, 135.7, 132.9, 130.5, 130.1, 130.0, 129.6, 128.7, 128.4, 128.3, 127.9, 127.6, 126.8, 126.7, 113.1, 112.8, 81.6, 81.0, 62.1, 62.0, 61.5, 61.4, 61.2 (two peaks), 57.5, 56.9, 50.5, 50.4, 36.5, 35.2, 28.3, 28.2, 13.9, 13.8, 13.7; ESIMS m/z (intensity) 635 ([M+K]$^+$, 100), 617 ([M+Na]$^+$, 65); HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2NaO_9$ (M+Na) 617.2475, found 617.2448.

4.5.2. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)amino]malonic acid diethyl ester (28b). According to general procedure D, alcohol **27b** (390 mg, 0.707 mmol), DMAP (9 mg, 0.0707 mmol), pyridine (63 μL, 0.778 mmol), and benzoyl chloride (165 μL, 1.41 mmol) afforded **28b** (320 mg, 70%) as a clear foamy (4.8:1) mixture of rotamers: IR (neat) 2979, 1712, 1681, 1501, 1451, 1392, 1368, 1318, 1270, 1223, 1163, 1108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J=7.5 Hz, 2H), 7.56 (t, J=6.8 Hz, 1H), 7.43 (app. t, J=7.5 Hz, 2H), 7.27 (s, 0.5H), 7.12 (s, 0.5H), 6.84 (s, 0.5H), 6.81–6.74 (m, 2H), 6.69 (s, 0.5H), 5.27, 5.14 (2s, 1H), 4.95–4.57 (m, 5H), 4.23–4.01 (m, 3H), 3.85 (s, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 3.08 (app. t, J=13.8 Hz, 1H), 2.86 (dt, J=18.2, 4.7 Hz, 1H), 1.50, 1.47 (2s, 9H), 1.28–1.09 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.8, 166.0, 165.6, 165.4, 165.3, 151.1, 150.4, 150.4, 150.2, 132.6, 130.1, 130.0, 129.7 (2C), 129.6, 129.2, 127.9, 124.7, 124.2, 114.6, 114.2, 112.8, 112.7, 112.6, 112.0, 110.7, 110.6, 81.1, 80.4, 62.2, 61.7, 61.6, 60.8, 56.9, 56.7, 55.4, 55.3, 45.9, 45.8, 36.4, 34.8, 27.9, 27.8, 13.6, 13.5, 13.3; ESIMS m/z (intensity) 1331 ([2M+Na]$^+$, 20), 677 ([M+Na]$^+$, 100); HRMS (ESI) m/z calcd for $C_{34}H_{42}N_2NaO_{11}$ (M+Na) 677.2686, found 677.2662.

4.6. General procedure E for the palladium-catalyzed allylic alkylation of malonates 28a and 28b

4.6.1. 3-Benzyl-7-methylene-4-oxo-3,8-diazabicyclo[3.2.1]-octane-2,2,8-tricarboxylic acid 8-*tert*-butyl ester 2,2-diethyl ester (29a). A suspension of malonate **28a** (50 mg, 0.084 mmol) and Pd_2dba_3 (15 mg, 0.0168 mmol) in degassed THF (4 mL) was cooled to −78 °C and treated with DBU (19 μL, 0.126 mmol). The reaction mixture was warmed to rt and then heated to 65 °C for 20 min. Upon cooling, the mixture was transferred to a short Celite column and washed with CH_2Cl_2 (10 mL). The eluant was concentrated and purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 1:1) to afford **29a** (38 mg, 96%) as a clear oil: IR (neat) 2981, 2935, 1748, 1690, 1392, 1368, 1310, 1254, 1166, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (dd, J=7.2, 7.2 Hz, 2H), 7.15 (t, J=7.2 Hz, 1H), 7.07 (d, J=7.2 Hz, 2H), 5.48 (br s, 1H), 5.24 (br s, 2H), 4.80–4.65 (m, 3H), 4.23–3.86 (m, 4H), 2.78–2.67 (m, 2H), 1.48 (s, 9H), 1.19 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 166.0, 165.7, 152.7, 142.2, 137.8, 128.0, 126.3, 125.8, 112.8, 81.3, 75.8, 62.6, 62.3, 59.1, 49.7, 36.6, 28.2, 13.6, 13.5; ESIMS m/z (intensity) 967 ([2M+Na]$^+$, 100), 495 ([M+Na]$^+$, 75); HRMS (ESI) m/z calcd for $C_{25}H_{32}N_2NaO_7$ (M+Na) 495.2107, found 495.2088.

4.6.2. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)amino]malonic acid diethyl ester (29b). According to general procedure E, malonate **28b** (310 mg, 0.473 mmol), Pd_2dba_3 (87 mg, 0.0946 mmol), and DBU (107 μL, 0.709 mmol) afforded **29b** (273 mg, 94%) as a clear foam: IR (neat) 2981, 2939, 1747, 1689, 1499, 1466, 1433, 1391, 1368, 1309, 1277, 1254, 1219, 1164, 1111, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67–6.57 (m, 2H), 6.37 (d, J=2.7 Hz, 1H), 5.44 (br s, 1H), 5.22 (app. d, J=12.4 Hz, 2H), 4.78 (br d, J=5.2 Hz, 1H), 4.63, 4.59 (AB q, J=17.6 Hz, 2H), 4.15–3.73 (m, 4H), 3.69 (s, 3H), 3.62 (s, 3H), 2.79–2.62 (m, 2H), 1.48 (s, 9H), 1.11–1.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 169.9, 165.7, 165.3, 153.2, 152.4, 150.1, 142.0, 126.7, 112.7, 111.6, 111.5, 110.6, 81.0, 77.2, 75.6, 62.4, 62.1, 59.0, 55.4, 55.1, 44.9, 36.6, 28.0, 27.9, 13.3 (2C), 13.2; ESIMS m/z (intensity) 1087 ([2M+Na]$^+$, 100), 555 ([M+Na]$^+$, 72); HRMS (ESI) m/z calcd for $C_{27}H_{36}N_2NaO_9$ (M+Na) 555.2319, found 555.2314.

Acknowledgements

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Further studies on enantioselective synthesis of (+)-anatoxin-*a* using enyne metathesis: unexpected inversion of chirality via a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative

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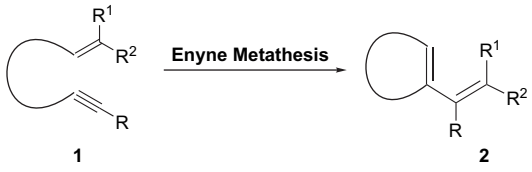
Abstract—The formal total synthesis of (+)-anatoxin-*a* was accomplished using enyne metathesis as a key step. It is very interesting that (+)-anatoxin-*a* was synthesized from (*S*)-pyroglutamic acid via an unusual inversion of chirality, which is rationalized in terms of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative at the stage of oxymercuration of the diene.

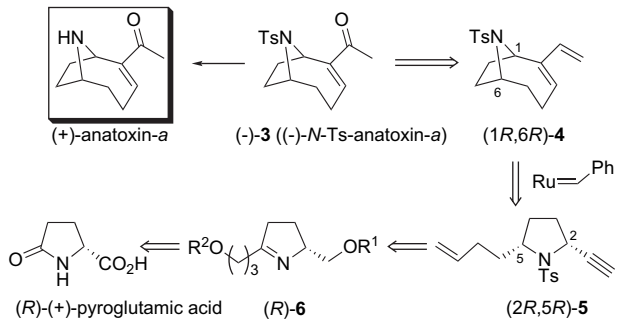
1. Introduction

Metathesis reaction is now one of the most promising strategies for the construction of various functionalized rings contained in natural products and biologically active substances.[1,2] Among the various types of metathesis reaction, enyne metathesis[3] has the following unique and useful properties for organic synthesis: (1) the terminal alkylidene moiety of alkene in the substrate **1** formally migrates on the alkyne carbon to produce the cyclized product **2** containing 1,3-diene, which should serve for further functionalization on the ring (Scheme 1) and (2) enyne metathesis is completely atom economical compared to the corresponding diene metathesis.



Scheme 1.

Recently, we have shown the efficiency of enyne metathesis for the construction of various ring-sized cyclic compounds and the synthesis of natural products and related compounds via ring-closing enyne metathesis and also for the synthesis of 1,3-diene derivatives from alkyne and ethylene via intermolecular enyne metathesis.[4] In that context, we had interest in the synthesis of anatoxin-*a*, which has a strained azabicyclo[4.2.1]nonene skeleton, via ring-closing enyne metathesis.[5] Anatoxin-*a*, which was isolated from the blue-green freshwater algae *Anabaena flos-aquae*, is one of the most powerful agonists of the nicotinic acetylcholine receptor[6] and has an azabicyclo[4.2.1]nonene skeleton bearing α,β-unsaturated ketone. Because of the unique structure and biological activity of anatoxin-*a*, many groups have synthesized anatoxin-*a* by various interesting methods.[7] The structure of anatoxin-*a* prompted us to attempt its synthesis using enyne metathesis as a key step. Our retrosynthetic analysis is shown in Scheme 2.



Scheme 2. Retrosynthetic analysis of (+)-anatoxin-*a*.

The synthesis of (+)-anatoxin-*a* from (−)-*N*-Ts-anatoxin-*a* ((−)-**3**) has been reported in the literature,[8] and (−)-**3** would be synthesized from (1*R*,6*R*)-**4** through oxidation of the 1,3-diene moiety. The compound (1*R*,6*R*)-**4** having a strained azabicyclo[4.2.1]nonene ring system would be constructed by metathesis of enyne (2*R*,5*R*)-**5** in the cis-substituents on the pyrrolidine ring. In the synthesis of

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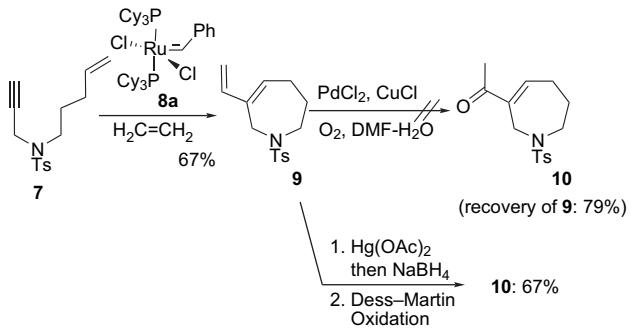
(2*R*,5*R*)-**5**, a *p*-toluenesulfonyl group as a protecting group on nitrogen was chosen because it was expected that ^{1}H and ^{13}C NMR spectral data in the case of an amide protecting group would be complicated because of the existence of rotation isomers of the amide carbonyl group. To synthesize the substrate (2*R*,5*R*)-**5** for enyne metathesis, hydrogenation of imine (*R*)-**6** should be suitable, and the compound (*R*)-**6** could be derived from (*R*)-(+)-pyroglutamic acid. We describe herein the synthesis of (+)-anatoxin-*a* using enyne metathesis as a key step.[9–11] Furthermore, during the course of our investigation, we encountered an unexpected inversion of chirality by a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative, which is also described.

2. Model study for conversion of 1,3-diene to α,β-unsaturated ketone

In the above-mentioned retrosynthetic analysis (Scheme 2), conversion of the 1,3-diene moiety in the cyclized product **4** is a very important process. Thus, the oxidation condition of the diene moiety was examined. As a model compound, azepine derivative **9** having a diene moiety was used (Scheme 3). We have already reported that metathesis of enyne having a terminal alkene and alkyne proceeded smoothly under ethylene gas using first-generation ruthenium–carbene complex **8a**[12] and that compound **9** was obtained from **7** in good yield.[4e]

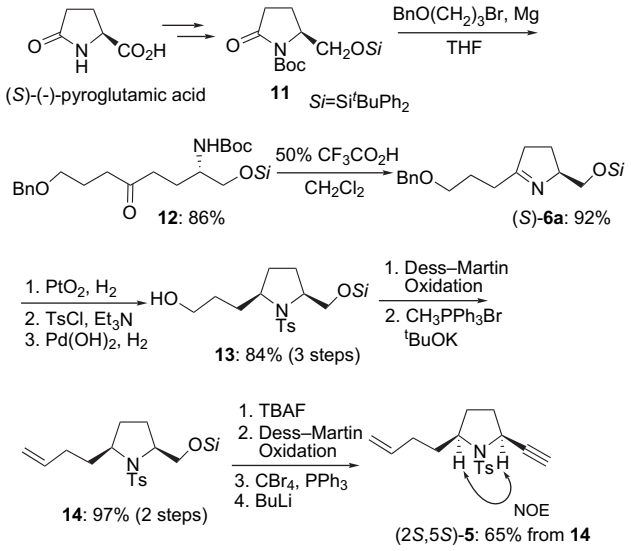


Scheme 3. Conversion of diene into α,β-unsaturated ketone.

First, oxidation of **9** with $PdCl_2$ and CuCl in aqueous DMF was carried out under oxygen.[13] However, the reaction mixture changed to yellow color and the starting material was recovered in 79% yield after 24 h, presumably indicating that the diene moiety in **9** strongly coordinated to the palladium complex and the oxidation of 1,3-diene moiety did not proceed. Next, oxymercuration of **9** followed by treatment with $NaBH_4$ was carried out and then the resultant alcohol was subjected to Dess–Martin oxidation[14] to give desired **10** in 67% yield from **9**.

3. Synthesis of anatoxin-*a* from (*S*)-(−)-pyroglutamic acid

Having achieved the conversion of diene **9** into α,β-unsaturated ketone **10**, we next investigated the synthesis of anatoxin-*a* as an optically active form. Initially, we chose (*S*)-(−)-pyroglutamic acid as the starting material because this material is readily available and is inexpensive compared to its enantiomer, (*R*)-(+)-pyroglutamic acid. In this case, (2*S*,5*S*)-**5** would be synthesized as the substrate for enyne metathesis, which should lead to the synthesis of (−)-anatoxin-*a*, the antipode of the naturally occurring form. The synthesis of (2*S*,5*S*)-**5** was carried out as shown in Scheme 4.

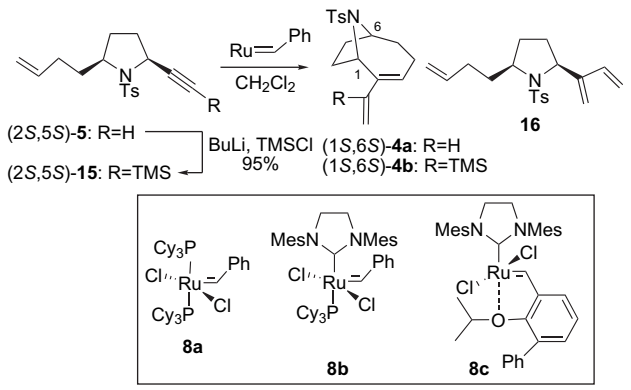


Scheme 4. Synthesis of a substrate.

Conversion of (−)-pyroglutamic acid into **11** by a known method[15] followed by treatment of **11** with Grignard reagent smoothly proceeded with opening of the pyrrolidine ring to give ketone **12**.[16] Deprotection of the *tert*-butoxycarbonyl group with CF_3CO_2H gave cyclized imine (*S*)-**6a**.[16] Hydrogenation of (*S*)-**6a** using PtO_2 followed by protection of nitrogen with the tosyl group and then deprotection of the benzyl group gave pyrrolidine derivative **13**. Dess–Martin oxidation followed by Wittig reaction afforded alkene **14**, which was converted into enyne (2*S*,5*S*)-**5** by the usual method. The stereochemistry of the substituents on (2*S*,5*S*)-**5** was confirmed by an NOE experiment to be cis. Next, the construction of a 9-azabicyclo[4.2.1]nonene structure using enyne metathesis was investigated, and the results are summarized in Table 1.

We have already reported that the use of ethylene gas is effective for enyne metathesis of the substrate having a terminal alkyne.[4e,17] Thus, enyne metathesis of **5** was initially carried out using 5 mol % of **8a** in CH_2Cl_2 under ethylene gas, but the expected product **4a** was obtained in only 15% yield along with the starting material **5** and diene **16** in 25% and 13% yields, respectively (run 1). The diene **16** would be produced via an intermolecular metathesis reaction between the alkyne moiety in **5** and ethylene.[4c,4f,4m,4p,4t,18] Next, the second-generation Ru–carbene complex **8b**[19] was used and the reaction was carried out in CH_2Cl_2 upon heating under ethylene gas (run 2). However, the desired compound **4a** was obtained in only 7% yield along with **16** in 61% yield. When the reaction of **5** using **8c**[20] was carried out in CH_2Cl_2 at room temperature under ethylene gas, the yield of the desired product was slightly improved to 28%. However, no other identified product was obtained in this reaction (run 3). Next, we tried enyne metathesis of **15**, which was easily synthesized from **5** by protection of the terminal

Table 1. Enyne metathesis of (2*S*,5*S*)-**5** and (2*S*,5*S*)-**15**

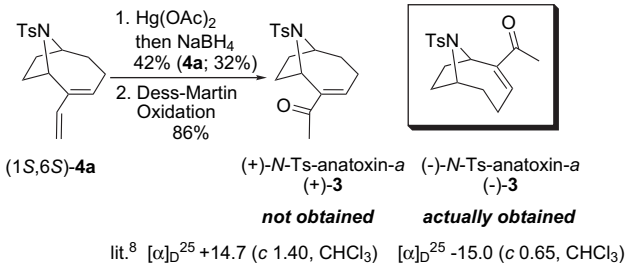


Run[a]	Substrate	Ru catalyst[b]	Temp	Time (h)	Product (%)		SM recov. (%)
					4	**16**	
1	(2*S*,5*S*)-**5**	**8a**	rt	24.5	15	13	25
2		**8b**	Reflux	2	7	61	—
3		**8c**	rt	4	28	—	—
4	(2*S*,5*S*)-**15**	**8b**	Reflux	3.5	27	—	65
5		**8c**	rt	3.5	27	—	—
6		**8b**	Reflux	2.5	85	—	—

[a] Reactions for runs 1–3 were carried out under an atmosphere of ethylene, and reactions for runs 4–6 were carried out under an atmosphere of Ar.
[b] Run 1: 5 mol % of Ru–carbene complex was used; runs 2–5: 10 mol % of Ru–carbene complex was used; run 6: 20 mol % of Ru–carbene complex was used.

alkyne moiety with the silyl group.[4p] When enyne metathesis of **15** was carried out in CH_2Cl_2 using 10 mol % of **8b** under argon upon heating, the desilylated product **4a** instead of the expected product **4b** was obtained in 27% yield along with the starting material **15** in 65% yield (run 4). The reaction of **15** using Ru–carbene complex **8c** in CH_2Cl_2 at room temperature also gave the desilylated product **4a** in 27% yield, in which case, however, the starting material was completely consumed (run 5). Thus, enyne metathesis of **15** was carried out in CH_2Cl_2 using 20 mol % of **8b** under argon upon heating (run 6). As a result, the reaction was completed in 2.5 h and the cyclized product **4a** was obtained in 85% yield. In these reactions, desilylation occurred during the metathesis reaction,[21] although the reason is not clear.

Next, we investigated the final stage for the synthesis of anatoxin-*a* from the enyne metathesis product (1*S*,6*S*)-**4a** (Scheme 5).

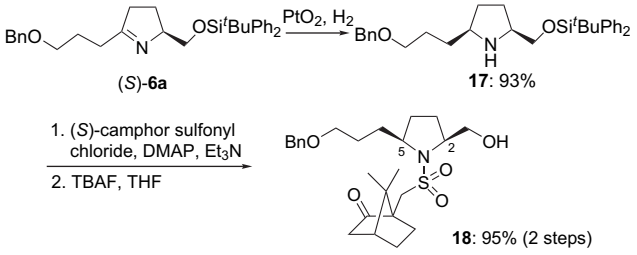


Scheme 5. Synthesis of *N*-tosylanatoxin-*a*.

Oxymercuration of (1*S*,6*S*)-**4a** followed by treatment with $NaBH_4$ afforded alcohol in 42% yield, and the starting material **4a** was recovered in 32% yield.[22] Dess–Martin oxidation of the alcohol afforded *N*-tosylanatoxin-*a*, whose spectral data unambiguously agreed with those reported in the literature.[8] However, we were surprised that *the* $[\alpha]_D$ *value of our synthetic N-tosylanatoxin-a showed a sign opposite to that of (+)-N-tosylanatoxin-a in the literature, although the absolute value was in agreement with that in the literature. This means that (−)-N-tosylanatoxin-a was synthesized from (S)-(−)-pyroglutamic acid along with an unexpected inversion of chirality during the synthesis.* Since conversion of (−)-*N*-tosylanatoxin-*a* to (+)-anatoxin-*a* had been already reported,[8] the formal total synthesis of (+)-anatoxin-*a* was achieved.[23]

4. Consideration of the inversion of chirality during the synthesis

We succeeded in the formal total synthesis of (+)-anatoxin-*a* from (*S*)-(−)-pyroglutamic acid using enyne metathesis as a key step. However, there remained the important question of when the inversion of chirality takes place during the synthesis. In order to answer this question, we first tried to confirm the absolute configuration of an intermediate before the metathesis reaction (Scheme 6). Hydrogenation of (*S*)-**6a**, which was derived from (*S*)-(−)-pyroglutamic acid as shown in Scheme 4, gave pyrrolidine derivative **17** in good yield. The compound **17** was successfully converted to the corresponding (*S*)-camphor sulfonamide **18**, which was easily crystallized.



Scheme 6. Confirmation of the absolute configuration of **6a**.

The absolute configuration of **18** was unequivocally determined by X-ray analysis as shown in Figure 1,[24] which means that the compound **17** maintained the chirality derived from (*S*)-(−)-pyroglutamic acid.

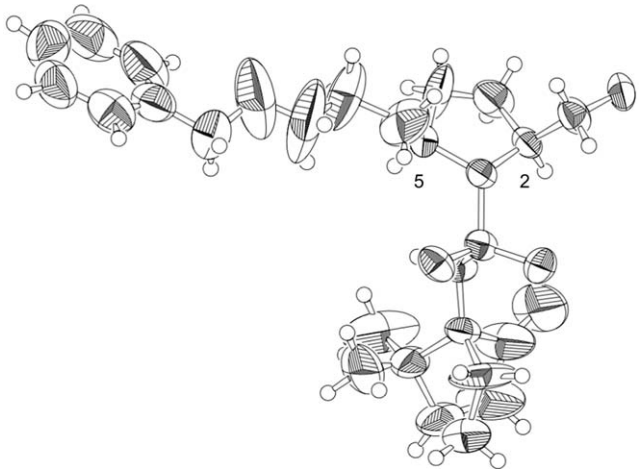
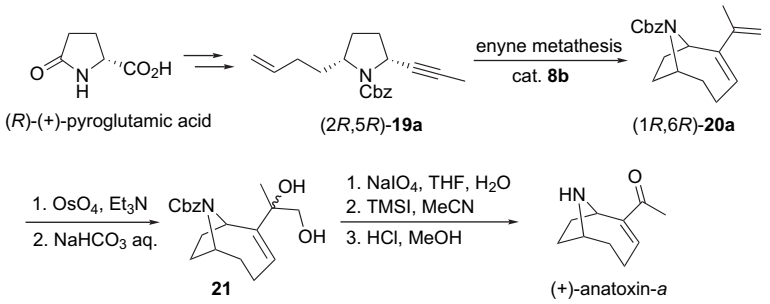


Figure 1. X-ray structure of compound **18**.

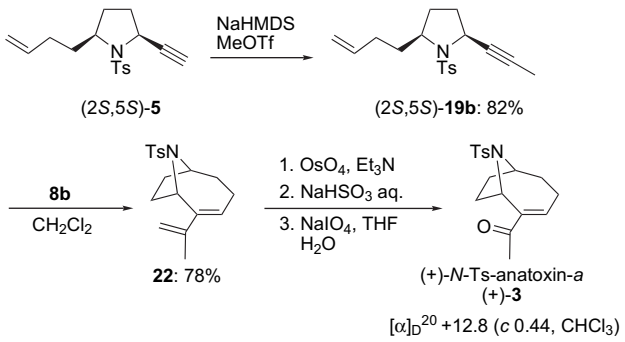


Scheme 7. Martin's total synthesis of (+)-anatoxin-*a*.

Since it is unlikely that the inversion of chirality with respect to both chiral centers at C2 and C5 positions takes place during the conversion of **17** to the metathesis substrate **5** (cf. Scheme 4), we presume that the compound **5** also maintains the chirality derived from (*S*)-(−)-pyroglutamic acid and that the inversion of chirality takes place at a later stage.

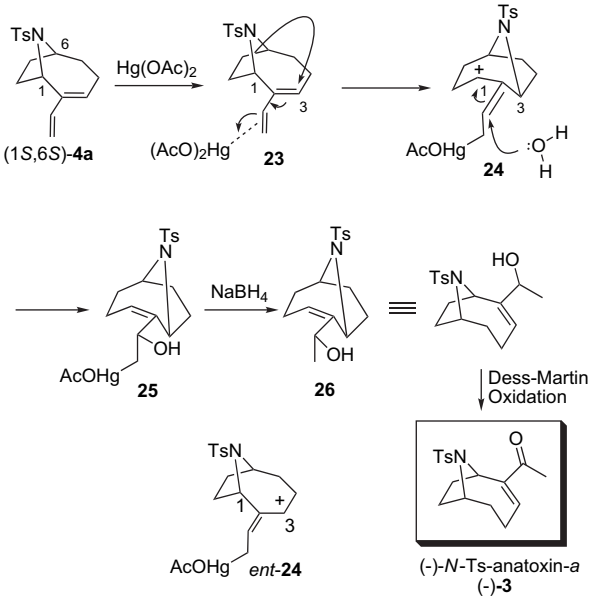
The total synthesis of (+)-anatoxin-*a* via enyne metathesis was reported by Martin at almost the same time as our report.[10] In Martin's synthesis, (1*R*,6*R*)-**20a** was constructed by enyne metathesis of (2*R*,5*R*)-**19a**, which was derived from (*R*)-(+)-pyroglutamic acid. Conversion of (1*R*,6*R*)-**20a** to (+)-anatoxin-*a* was achieved with the maintenance of chirality through osmylation of the alkene followed by cleavage of the corresponding diol (Scheme 7).

Martin's synthesis is very similar to our synthesis, although the substrate of enyne metathesis as well as the procedure for conversion of the diene moiety to α,β-unsaturated ketone is different. Thus, we investigated the conversion of (2*S*,5*S*)-**5** to *N*-Ts-anatoxin-*a* (**3**) according to Martin's procedure (Scheme 8).



Scheme 8. Conversion of (2*S*,5*S*)-**5** to *N*-Ts-anatoxin-*a* according to Martin's procedure.

As a result, (+)-*N*-Ts-anatoxin-*a* was obtained without the inversion of chirality originating from the substrate. This result strongly suggests that enyne metathesis proceeds with the maintenance of chirality regardless of the substrate and that the inversion of chirality in our synthesis takes place at the stage of conversion of the diene moiety to α,β-unsaturated ketone using oxymercuration reaction. One plausible mechanism for the inversion of chirality during the oxymercuration reaction is shown in Scheme 9.



Scheme 9. Plausible mechanism for inversion of chirality.

The diene moiety in (1*S*,6*S*)-**4a** would coordinate to $Hg(OAc)_2$ complex to produce olefin–Hg complex **23**. Migration of the nitrogen atom from the C1-position to the C3-position along with cleavage of the N–C1 bond would take place in the complex **23** to give **24**. Spontaneous nucleophilic attack of H_2O on the allyl cation moiety in **24** would take place to give **25**, which was converted to the alcohol **26** by reduction with $NaBH_4$. It is noteworthy that the alcohol **26** has a (1*R*,6*R*)-configuration, which could be converted to (−)-*N*-Ts-anatoxin-*a* by Dess–Martin oxidation. If *ent*-**24** was produced along with **24** from the olefin–Hg complex **23**, or if **24** was in equilibrium with *ent*-**24**, racemization should occur in both cases to give **26** as a racemic mixture. The fact that (1*R*,6*R*)-**26** was obtained from (1*S*,6*S*)-**4a** with a high optical purity strongly suggests that the migration of the nitrogen atom from the C1-position to the C3-position in **23** took place in a stereospecific manner without the formation of *ent*-**24** and also that equilibrium between **24** and *ent*-**24** may not exist.

5. Conclusion

In summary, we have accomplished the formal total synthesis of (+)-anatoxin-*a* using enyne metathesis as a key step.

The remarkable features of our synthesis are as follows: (1) a highly strained azabicyclo[4.2.1]nonene skeleton was constructed by ring-closing enyne metathesis of a pyrrolidine derivative and (2) the synthesis of (+)-anatoxin-*a* was achieved from (*S*)-pyroglutamic acid via an unusual inversion of chirality, which is rationalized in terms of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative at the stage of oxymercuration of the diene.

6. Experimental

6.1. General

All manipulations were carried out under an atmosphere of argon unless otherwise mentioned. Ethylene gas was purified by passage through the aqueous CuCl solution (2.0 g of CuCl in 180 mL of saturated NH_4Cl aqueous solution) and concentrated H_2SO_4 and then KOH tubes. Ruthenium complexes **8a** and **8b** were purchased from Strem Chemicals, Inc. Ruthenium complex **8c** was prepared according to the literature procedure.[19] All other solvents and reagents were purified when necessary using standard procedure.

6.1.1. 3-Acetyl-2,5,6,7-tetrahydro-1-*p*-toluenesulfonyl-1*H*-azepine (10). To a solution of **9** (20 mg, 74 mmol) in H_2O/THF (1/1, 0.9 mL) was added $Hg(OAc)_2$ (36 mg, 112 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added MeOH (0.9 mL), 3 M NaOH aq (0.5 mL), and $NaBH_4$ (19 mg, 0.50 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1) to give the alcohol (15 mg, 71%) as a colorless oil. IR (neat) ν 3482, 2925, 2853 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 5.79 (dd, J=5.5, 5.7 Hz, 1H), 4.29 (dd, J=12.9, 12.9 Hz, 1H), 3.91 (d, J=16.4 Hz, 1H), 3.76 (d, J=16.4 Hz, 1H), 3.51 (dd, J=12.7, 12.7 Hz, 1H), 3.33 (dd, J=11.7, 12.7 Hz, 1H), 2.42 (s, 3H), 2.23 (m, 2H), 1.94 (br, 1H), 1.81 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 142.1 (C), 136.1 (C), 129.5 (CH×2), 127.7 (CH×2), 127.0 (CH), 71.9 (CH), 50.4 (CH_2), 45.2 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 21.9 (CH_3), 21.5 (CH_3); LRMS (EI) m/z 295 (M^+), 277, 250, 224, 184, 155, 122, 91; HRMS (EI) calcd for $C_{15}H_{21}NSO_3$ (M^+) 295.1244, found 295.1242.

To a solution of the alcohol (11 mg, 0.037 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (47 mg, 0.11 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give **10** (10 mg, 95%) as a colorless oil. IR (neat) ν 3204, 2925, 1665, 1340, 1228, 1159, 1093 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 6.95 (dd, J=5.5, 5.9 Hz, 1H), 4.12 (s, 2H), 3.44 (t, J=6.3 Hz, 2H), 2.47 (dt, J=5.5, 5.9 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.84–1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (C), 144.8 (CH), 142.9 (C), 140.9 (C), 136.1 (C), 129.4 (CH×2), 127.0 (CH×2), 49.5 (CH_2), 43.9 (CH_2), 27.1 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 21.8 (CH_3); LRMS (EI) m/z 293 (M^+), 155, 138, 109, 96; HRMS (EI) calcd for $C_{15}H_{19}O_3NS$ (M^+) 293.1083, found 293.1085.

6.1.2. (2*S*)-8-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)-2-(*tert*-butyloxycarbonyl)-amino-octan-5-one (12). A solution of 1-benzyloxy-3-bromo-propane (1.90 g, 8.3 mmol) in THF (7 mL) was added dropwise to a suspension of Mg (229 mg, 9.94 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 30 min. To a THF solution of the Grignard reagent was added a solution of **11**[15] (2.25 g, 4.5 mmol) in THF (16 mL) at 0 °C, and the mixture was stirred at room temperature for 1.7 h. The reaction mixture was quenched by adding satd NH_4Cl aq at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **12** (2.77 g, 86%) as a colorless oil. IR (neat) ν 3364, 1714, 739, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.62–7.65 (m, 4H), 7.29–7.43 (m, 11H), 4.64 (d, J=8.9 Hz, 1H), 4.47 (s, 2H), 3.55–3.64 (m, 3H), 3.44–3.49 (m, 2H), 2.40–2.52 (m, 4H), 1.86–1.92 (m, 2H), 1.76–1.83 (m, 2H), 1.43 (s, 9H), 1.07 (s, 9H); LRMS (EI) m/z 603 (M^++1), 546, 306, 278, 91; HRMS (EI) calcd for $C_{36}H_{50}O_5NSi$ (M^++H) 604.3459, found 604.3450. $[\alpha]_D^{21}$ −13.0 (c 1.03, $CHCl_3$).

6.1.3. (*S*)-5-(3-(Benzyloxy)propyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydro-2*H*-pyrrole ((*S*)-6a). To a solution of **12** (51 mg, 0.08 mmol) in CH_2Cl_2 (0.2 mL) was added trifluoroacetic acid (0.2 mL), and the mixture was stirred at room temperature for 2.5 h. To the mixture was added 3 M NaOH aq, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give (*S*)-**6a** (38 mg, 92%) as a colorless oil. IR (neat) ν 1646, 1112, 737, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.22–7.69 (m, 15H), 4.47 (s, 2H), 4.15 (m, 1H), 3.87 (dd, J=3.5, 10.0 Hz, 1H), 3.73 (dd, J=5.1, 10.0 Hz, 1H), 3.52 (t, J=6.2 Hz, 2H), 2.40–2.64 (m, 4H), 1.79–1.97 (m, 4H), 1.03 (s, 9H); LRMS (EI) m/z 485 (M^+), 394, 336, 278; HRMS (EI) calcd for $C_{31}H_{39}O_2NSi$ (M^+) 604.3459, found 604.3450. $[\alpha]_D^{22}$ +41.5 (c 1.01, $CHCl_3$).

6.1.4. 3-((2*S*,5*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-1-*p*-toluenesulfonylpyrrolidin-5-yl)-propan-1-ol (13). A solution of (*S*)-**6a** (118 mg, 0.24 mmol) and PtO_2 (6 mg, 0.02 mmol) in EtOH (1 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt only) to give the corresponding pyrrolidine (i.e., the compound **17** in Scheme 6) (109 mg, 92%) as a colorless oil. IR (neat) ν 3346, 1472, 739, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.26–7.67 (m, 15H), 4.50 (s, 2H), 3.71 (dd, J=4.6, 10.0 Hz, 1H), 3.61 (dd, J=4.9, 10.0 Hz, 1H), 3.49 (t, J=5.4 Hz, 2H), 3.07–3.12 (m, 2H), 2.93 (br, 1H), 1.32–1.95 (m, 8H), 1.06

(s, 9H); LRMS (EI) *m/z* 603 (M^+), 546, 306, 278, 91; HRMS (EI) calcd for $C_{31}H_{42}O_2NSi$ (M^+-1) 488.2985, found 488.3009. $[\alpha]_D^{23}$ +2.0 (*c* 1.00, $CHCl_3$).

To a solution of the pyrrolidine (2.25 g, 4.5 mmol) in CH_2Cl_2 (9 mL) were added Et_3N (2.0 mL, 15 mmol), *p*-toluenesulfonyl chloride (940 mg, 4.9 mmol), and DMAP (16 mg, 0.13 mmol), and the mixture was stirred at room temperature for 14 h. To the mixture was added 10% HCl aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the tosylamide (2.76 g, 96%) as a colorless oil. IR (neat) ν 2931, 2857, 2360, 1738, 1598, 1347, 1162, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.68 (m, 4H), 7.58 (d, *J*=7.9 Hz, 2H), 7.22–7.44 (m, 13H), 4.47 (s, 2H), 3.94 (d, *J*=5.9 Hz, 1H), 3.39–3.62 (m, 5H), 2.41 (s, 3H), 1.82–1.91 (m, 2H), 1.42–1.65 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8 (C), 138.3 (C), 135.3 (CH×2), 134.4 (C), 133.2 (C), 133.0 (C), 129.4 (CH×4), 129.2 (CH×4), 127.9 (CH×2), 127.4 (CH×2), 127.2 (CH×2), 127.1 (CH×3), 72.5 (CH_2), 69.9 (CH_2), 66.3 (CH_2), 61.8 (CH), 61.5 (CH), 60.0 (CH_2), 33.0 (CH_2), 29.3 (CH_2), 26.7 (CH_3), 26.2 (CH_2), 21.2 (CH_3×2), 19.0 (C), 14.0 (CH_3); LRMS (EI) *m/z* 584 (M^+-t-Bu), 486, 372, 280, 155, 91; HRMS (EI) calcd for $C_{34}H_{38}O_4NSSi$ (M^+-t-Bu) 584.2296, found 584.2291. $[\alpha]_D^{27}$ −15.3 (*c* 0.96, $CHCl_3$).

A solution of the tosylamide (238 mg, 0.37 mmol) and $Pd(OH)_2/C$ (20 wt %, 55 mg, 0.08 mmol) in EtOH (4 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 62 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt only) to give **13** (195 mg, 95%) as a colorless oil. IR (neat) ν 3420, 2931, 2858, 1345, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.68 (m, 4H), 7.60 (d, *J*=8.4 Hz, 2H), 7.37–7.47 (m, 6H), 7.27 (d, *J*=8.4 Hz, 2H), 3.94 (d, *J*=5.9 Hz, 1H), 3.59–3.64 (m, 6H), 2.42 (s, 3H), 1.80–1.93 (m, 2H), 1.37–1.63 (m, 7H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (C), 135.2 (CH×4), 135.1 (CH×4), 134.1 (C), 133.0 (C), 132.9 (C), 129.3 (CH), 129.2 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 66.4 (CH_2), 62.3 (CH_2), 61.9 (CH), 61.6 (CH), 32.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 26.9 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 19.2 (C); LRMS (EI) *m/z* 550 (M^+-1), 494, 416, 338, 320, 155, 91; HRMS (EI) calcd for $C_{31}H_{40}O_4NSSi$ (M^+-1) 584.2296, found 584.2291. $[\alpha]_D^{27}$ −26.6 (*c* 1.42, $CHCl_3$).

6.1.5. (2*S*,5*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(but-3-enyl)-1-*p*-toluenesulfonylpyrrolidine (14). To a solution of **13** (385 mg, 0.7 mmol) in CH_2Cl_2 (7 mL) was added Dess–Martin periodinane (442 mg, 1.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the aldehyde (380 mg, 99%) as a colorless oil. IR (neat) ν 2931, 2858, 1732, 1346, 1161; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.66–7.69 (m, 4H), 7.57 (d, *J*=8.4 Hz, 2H), 7.38–7.47 (m, 6H), 7.27 (d, *J*=8.4 Hz, 2H), 3.94 (dd, *J*=3.8, 10.0 Hz, 1H), 3.56–3.71 (m, 3H), 2.72–2.78 (m, 1H), 2.45–2.51 (m, 1H), 2.42 (s, 3H), 1.92–1.98 (m, 1H), 1.76–1.85 (m, 2H), 1.60–1.64 (m, 1H), 1.40–1.43 (m, 1H), 1.19–1.31 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7 (C), 143.2 (C), 135.4 (CH×2), 134.1 (C), 133.2 (C), 133.1 (C), 129.5 (CH×4), 129.4 (CH×4), 127.5 (CH×2), 127.4 (CH×2), 66.6 (CH_2), 62.4 (CH), 60.7 (CH), 40.4 (CH_2), 30.2 (CH_2), 28.2 (CH_2), 27.1 (CH_2, CH_3), 21.7 (CH_3×3), 19.5 (C); LRMS (EI) *m/z* (M^+-t-Bu) 492, 414, 336, 280, 259, 155, 91; HRMS (EI) calcd for $C_{27}H_{30}O_4NSSi$ (M^+-t-Bu) 492.1654, found 492.1665. $[\alpha]_D^{27}$ −40.2 (*c* 0.97, $CHCl_3$).

To a solution of $Ph_3P^+CH_3Br^-$ (3.83 g, 10.7 mmol) in THF (27 mL) was added ^{t}BuOK (1.09 g, 9.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 min. To the solution was added a solution of the aldehyde (2.68 g, 4.9 mmol) in CH_2Cl_2 (22 mL) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at 0 °C for 14 h. To the mixture was added satd NH_4Cl aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **14** (2.61 g, 98%) as a colorless oil. IR (neat) ν 3070, 2958, 2930, 2857, 1736, 1639, 1598, 1348, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=7.0 Hz, 4H), 7.60 (d, *J*=8.4 Hz, 2H), 7.38–7.46 (m, 6H), 7.26 (d, *J*=8.4 Hz, 2H), 5.78 (ddt, *J*=6.3, 10.2, 17.2 Hz, 1H), 5.00 (dd, *J*=0.9, 17.2 Hz, 1H), 4.94 (dd, *J*=0.9, 10.2 Hz, 1H), 3.94 (dd, *J*=2.4, 5.9 Hz, 1H), 3.49–3.67 (m, 3H), 2.42 (s, 3H), 1.87–2.08 (m, 4H), 1.18–1.51 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (C), 137.7 (CH), 135.3 (CH×2), 134.5 (C), 133.3 (C), 133.1 (C), 129.4 (CH×2), 129.3 (CH×4), 127.5 (CH×4), 127.3 (CH×2), 114.5 (CH_2), 66.5 (CH_3), 62.0 (CH), 61.5 (CH), 35.8 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 21.7 (CH_3×3), 19.4 (C); LRMS (EI) *m/z* 546 (M^+), 490, 414, 334, 292, 278, 252, 199, 155, 91; HRMS (EI) calcd for $C_{32}H_{41}O_3NSSi$ (M^+) 547.2569, found 547.2576. $[\alpha]_D^{23}$ −25.2 (*c* 1.07, $CHCl_3$).

6.1.6. (2*S*,5*S*)-5-(But-3-enyl)-2-ethynyl-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-5). To a solution of **14** (112 mg, 4.5 mmol) in THF (2 mL) was added TBAF (1.0 M THF solution, 0.3 mL, 0.3 mmol), and the mixture was stirred at room temperature for 1.5 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give the alcohol (62 mg, 98%) as a colorless oil. IR (neat) ν 3510, 2954, 2874, 1736, 1640, 1598, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 5.84 (ddt, *J*=6.8, 10.3, 17.0 Hz, 1H), 5.06 (dd, *J*=1.8, 17.0 Hz, 1H), 4.99 (dd, *J*=1.8, 10.3 Hz, 1H), 3.60–3.71 (m, 4H), 2.86 (br, 1H), 2.44 (s, 3H), 2.10–2.16 (m, 2H), 1.91–1.98 (m, 1H), 1.49–1.70 (m, 4H), 1.34–1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4 (C), 137.5 (CH), 133.9 (C), 129.5 (CH×2), 127.3 (CH×2), 114.7 (CH_2), 66.0 (CH_3), 63.0 (CH), 62.1 (CH), 35.7 (CH_2), 30.5

(CH_2), 29.4 (CH_2), 27.3 (CH_2), 21.7 (CH_2); LRMS (EI) *m/z* 309 (M^+), 278, 254, 224, 155, 122, 91; HRMS (EI) calcd for $C_{16}H_{23}O_3NS$ (M^+) 303.1396, found 309.1398. $[\alpha]_D^{21}$ +51.1 (*c* 1.33, $CHCl_3$).

To a solution of the alcohol (1.42 g, 4.6 mmol) in CH_2Cl_2 (46 mL) was added Dess–Martin periodinane (2.34 g, 5.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the aldehyde (1.20 g, 86%) as a colorless oil. IR (neat) ν 2924, 1734, 1639, 1598, 1348, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J*=1.9 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 2H), 7.34 (d, *J*=8.2 Hz, 2H), 5.83 (ddt, *J*=6.2, 10.2, 16.8 Hz, 1H), 5.06 (dd, *J*=1.7, 16.8 Hz, 1H), 5.01 (dd, *J*=1.7, 10.2 Hz, 1H), 3.87 (dd, *J*=1.9, 7.9 Hz, 1H), 3.67–3.71 (m, 1H), 2.44 (s, 3H), 1.97–2.17 (m, 4H), 1.69–1.75 (m, 1H), 1.52–1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7 (C), 143.9 (C), 137.3 (C), 129.7 (CH×3), 127.5 (CH×2), 115.1 (CH_2), 67.8 (CH), 61.4 (CH), 35.4 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 25.7 (CH_2), 21.8 (CH_3); LRMS (EI) *m/z* 307 (M^+), 278, 252, 224, 155, 91; HRMS (EI) calcd for $C_{16}H_{21}O_3NS$ (M^+) 307.1242, found 307.1242. $[\alpha]_D^{22}$ −50.6 (*c* 1.22, $CHCl_3$).

To a solution of CBr_4 (5.16 g, 16 mmol) in CH_2Cl_2 (19 mL) were added PPh_3 (8.16 g, 31 mmol) and a solution of the aldehyde (1.20 g, 3.9 mmol) in CH_2Cl_2 (59 mL) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. To the mixture was added H_2O, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the corresponding dibromide (1.74 g, 96%) as a colorless oil. IR (neat) ν 2924, 1734, 1640, 1598, 1348, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 6.46 (d, *J*=7.9 Hz, 1H), 5.84 (ddt, *J*=6.7, 10.3, 17.0 Hz, 1H), 5.06 (dd, *J*=1.8, 17.0 Hz, 1H), 5.01 (dd, *J*=1.8, 10.3 Hz, 1H), 4.13 (dt, *J*=7.8, 7.8 Hz, 1H), 3.73–3.76 (m, 1H), 2.44 (s, 3H), 2.09–2.15 (m, 2H), 1.90–1.97 (m, 2H), 1.50–1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4 (C), 139.9 (CH), 137.4 (CH), 134.2 (C), 129.5 (CH×2), 127.5 (CH×2), 114.8 (CH_2), 89.3 (C), 62.9 (CH), 61.4 (CH), 35.8 (CH_2), 30.6 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 21.7 (CH_3); LRMS (EI) *m/z* 463 (M^+), 408, 384, 308, 278, 252, 155, 91; HRMS (EI) calcd for $C_{17}H_{21}O_2NSBr_2$ (M^+) 460.9680, found 460.9659. $[\alpha]_D^{22}$ −76.6 (*c* 1.03, $CHCl_3$).

To a solution of the dibromide (129 mg, 0.3 mmol) in THF (3 mL) was added BuLi (1.55 M hexane solution, 0.6 mL, 0.9 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*S*,5*S*)-**5** (68 mg, 80%) as a viscous oil. IR (neat) ν 3250, 2928, 1641, 1598, 1348, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.80 (ddt, *J*=6.5, 10.0, 17.0 Hz, 1H), 5.03 (dd, *J*=1.8, 17.0 Hz, 1H), 4.97 (dd, *J*=1.8, 10.0 Hz, 1H), 4.41–4.47 (m, 1H), 3.73–3.76 (m, 1H), 2.34 (s, 3H), 2.12 (d, *J*=2.4 Hz, 1H), 2.00–2.14 (m, 3H), 1.89–1.96 (m, 1H), 1.60–1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 137.6 (CH), 135.4 (C), 129.4 (CH×2), 127.2 (CH×2), 114.7 (CH_2), 83.5 (CH), 71.5 (C), 61.1 (CH), 51.4 (CH), 35.5 (CH_2), 32.8 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 21.7 (CH_3); LRMS (EI) *m/z* 303 (M^+), 274, 262, 248, 222, 155, 148, 91, 77, 65; HRMS (EI) calcd for $C_{17}H_{21}O_2NS$ (M^+) 303.1284, found 303.1293. $[\alpha]_D^{26}$ −41.9 (*c* 0.82, $CHCl_3$).

6.1.7. (2*S*,5*S*)-5-(But-3-enyl)-2-(2-(trimethylsilyl)-ethynyl)-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-15). To a solution of (2*S*,5*S*)-**5** (36 mg, 0.12 mmol) in THF (1 mL) was added BuLi (2.6 M hexane solution, 0.07 mL, 0.18 mmol) at −78 °C, and the mixture was stirred at the same temperature for 45 min. To the solution was added trimethylsilyl chloride (0.05 mL, 0.35 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added H_2O, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5:1) to give (2*S*,5*S*)-**15** (42 mg, 95%) as a viscous oil. IR (neat) ν 2923, 1642, 1599, 1344, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.6 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 2H), 5.77 (ddt, *J*=6.5, 11.1, 17.2 Hz, 1H), 4.97 (dd, *J*=11.1, 17.2 Hz, 2H), 4.55 (dd, *J*=2.3, 7.3 Hz, 1H), 3.79–3.86 (m, 1H), 2.42 (s, 3H), 2.04–2.10 (m, 2H), 1.58–1.99 (m, 6H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 137.8 (CH), 136.5 (C), 129.3 (CH×2), 127.2 (CH×2), 114.5 (CH_2), 105.2 (C), 88.0 (C), 60.9 (CH), 52.1 (CH), 35.1 (CH_2), 33.2 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 21.7 (CH_3), 0.1 (CH_3×3); LRMS (EI) *m/z* 375 (M^+), 360, 320, 220, 155, 91; HRMS (EI) calcd for $C_{20}H_{29}O_2NSSi$ (M^+) 375.1681, found 375.1688.

6.1.8. Typical procedure for enyne metathesis of (2*S*,5*S*)-15 using Ru–carbene complex 8b (Table 1, run 6). A solution of (2*S*,5*S*)-**15** (13 mg, 0.034 mmol) and Ru–carbene complex **8b** (6 mg, 0.007 mmol) in degassed CH_2Cl_2 (0.7 mL) was heated under reflux for 2.5 h. Upon cooling to room temperature, an excess amount of ethyl vinyl ether was added to the mixture in order to stop the metathesis reaction, and the mixture was stirred at room temperature for 1 h. After the mixture was concentrated, the residue was purified by column chromatography on silica gel (hexane/AcOEt=8:1) to give (1*S*,6*S*)-**4a** (9 mg, 85%) as a viscous oil.

IR (neat) ν 2925, 2852, 1732, 1633, 1598, 1337, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H), 6.21 (dd, *J*=10.9, 17.7 Hz, 1H), 5.67 (dd, *J*=5.8, 6.2 Hz, 1H), 5.14 (d, *J*=17.7 Hz, 1H), 4.98 (d, *J*=10.9 Hz, 1H), 4.90 (d, *J*=8.1 Hz, 1H), 4.41–4.44 (m, 1H), 2.42 (s, 3H), 2.16–2.29 (m, 2H), 2.00–2.08 (m, 2H), 1.72–1.85 (m, 2H), 1.56–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 142.8 (C), 138.1 (CH), 137.5 (C), 131.9 (CH), 129.4 (CH×2), 126.8 (CH×2), 111.0 (CH_2), 58.7 (CH), 57.6 (CH), 34.2 (CH_2), 31.8 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 21.7 (CH_3); LRMS (EI) *m/z* 303 (M^+), 155, 148, 121, 91; HRMS (EI) calcd for

$C_{17}H_{21}O_2NS$ (M^+) 303.1294, found 303.1293. $[\alpha]_D^{22}$ −5.2 (*c* 1.03, $CHCl_3$).

6.1.9. Spectral data of (2*S*,5*S*)-5-(but-3-enyl)-2-(1,3-butadien-2-yl)-1-*p*-toluenesulfonylpyrrolidine (16). IR (neat) ν 2924, 2849, 1725, 1638, 1600, 1346, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.1 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 6.34 (dd, *J*=11.1, 17.8 Hz, 1H), 5.85 (ddt, *J*=6.3, 12.3, 16.6 Hz, 1H), 5.46 (s, 1H), 4.98–5.19 (m, 5H), 4.42–4.47 (m, 1H), 3.59–3.68 (m, 1H), 2.41 (s, 3H), 1.94 (m, 4H), 1.53 (m, 4H); LRMS (EI) *m*/*z* 331 (M^+), 276, 248, 176, 155, 91; HRMS (EI) calcd for $C_{19}H_{25}O_2NS$ (M^+) 331.1602, found 331.1606. $[\alpha]_D^{20}$ −16.9 (*c* 0.15, $CHCl_3$).

6.1.10. Synthesis of (−)-*N*-Ts-anatoxin-*a* ((−)-3) from (1*S*,6*S*)-4a. To a solution of $Hg(OAc)_2$ (12 mg, 38 mmol) in H_2O (0.4 mL) was added a solution of (1*S*,6*S*)-**4a** (6 mg, 19 mmol) in THF (0.4 mL) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. To the mixture was added MeOH (0.8 mL), 3 M NaOH aq (0.8 mL), and $NaBH_4$ (5 mg, 0.13 mmol) at 0 °C, and the mixture was stirred at room temperature for 37 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5:1) to give the alcohol (3 mg, 42%) as a colorless oil along with the starting (1*S*,6*S*)-**4a** (2 mg, 32%). IR (neat) ν 3511, 2966, 2928, 1735, 1598, 1338, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 5.62 (dd, *J*=5.7, 5.8 Hz, 1H), 4.53 (d, *J*=9.2 Hz, 1H), 4.44–4.45 (m, 1H), 4.30 (q, *J*=6.4 Hz, 1H), 2.42 (s, 3H), 2.25–2.31 (m, 1H), 1.86–1.95 (m, 3H), 1.49–1.75 (m, 4H), 1.35 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (C), 142.9 (C), 137.2 (C), 130.8 (C×2), 129.5 (CH×2), 126.9 (CH×2), 124.4 (CH), 72.2 (CH), 60.1 (CH), 57.6 (CH), 33.1 (CH_2×2), 28.9 (CH_2), 23.4 (CH_2), 22.1 (CH_3), 21.7 (CH_3); LRMS (EI) *m*/*z* 321 (M^+), 303, 166, 155, 91; HRMS (EI) calcd for $C_{17}H_{23}O_3NS$ (M^+) 321.1406, found 321.1398. $[\alpha]_D^{23}$ −39.0 (*c* 0.73, $CHCl_3$).

To a solution of the alcohol (7 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) was added Dess–Martin periodinane (20 mg, 0.05 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give (−)-*N*-Ts-anatoxin-*a* ((−)-**3**) (6 mg, 86%) as a colorless solid, whose spectral data were identical with those previously reported.[8] $[\alpha]_D^{25}$ −15.0 (*c* 0.65, $CHCl_3$).

6.1.11. (2*S*,5*R*)-5-(3-Benzyloxypropyl)-2-(hydroxymethyl)-1-((1*S*)-10-camphorsulfonyl)-pyrrolidine (18). To a solution of **17** (323 mg, 0.66 mmol), which is an intermediate for the synthesis of **13** from (*S*)-**6a** (see, Section 6.1.4), in CH_3CN (3 mL) were added Et_3N (0.2 mL, 1.6 mmol), (1*S*)-10-camphorsulfonyl chloride (327 mg, 2.0 mmol), and DMAP (162 mg, 1.3 mmol), and the mixture was stirred at room temperature for 24 h. To the mixture was added 10% HCl aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the camphorsulfonamide (432 mg, 93%) as a colorless oil. IR (neat) ν 2957, 2859, 1745, 1345, 1150 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.63–7.68 (m, 4H), 7.23–7.43 (m, 6H), 4.45 (s, 2H), 3.82–3.73 (m, 1H), 3.58 (dd, *J*=7.3, 9.2 Hz, 1H), 3.41 (ddd, *J*=6.6, 9.2, 15.8 Hz, 2H), 3.23 (d, *J*=14.4 Hz, 1H), 2.61 (d, *J*=14.4 Hz, 1H), 2.48–2.59 (m, 1H), 2.37 (dt, *J*=4.0, 18.5 Hz, 1H), 1.79–2.10 (m, 7H), 1.26–1.69 (m, 6H), 1.13 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0 (C), 138.3 (C), 135.3 (CH×4), 133.1 (C), 133.0 (C), 129.4 (CH×4), 128.1 (CH×2), 127.5 (CH×2), 127.4 (CH×2), 127.2 (CH), 72.8 (CH_2), 70.1 (CH_2), 66.3 (CH_2), 62.0 (CH), 61.7 (CH), 58.3 (C), 47.7 (C), 44.3 (CH_2), 43.0 (CH), 42.7 (CH_2), 33.4 (CH_2), 30.3 (CH_2), 27.3 (CH_2), 27.0 (CH_2, CH_3×3), 26.6 (CH_2), 25.5 (CH_2), 20.0 (CH_3×2), 19.4 (C); LRMS (EI) *m*/*z* 701 (M^+), 686, 644, 432, 218, 91; HRMS (EI) calcd for $C_{41}H_{55}O_5NSSi$ (M^+) 701.3556, found 701.3570. $[\alpha]_D^{20}$ +6.1 (*c* 1.34, $CHCl_3$).

To a solution of the camphorsulfonamide (432 mg, 0.62 mmol) in THF (7 mL) was added TBAF (1.0 M THF solution, 1.0 mL, 1 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give **18** (271 mg, 95%) as a colorless solid, which was recrystallized from ether to give a colorless plate (mp 107–109 °C) for X-ray analysis.[24]

IR (neat) ν 3482, 2956, 2882, 1744, 1340, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.36 (m, 5H), 4.49 (s, 2H), 3.84–3.91 (m, 1H), 3.77–3.83 (m, 2H), 3.55–3.69 (m, 2H), 3.49 (dd, *J*=6.1, 6.5 Hz, 2H), 3.29 (d, *J*=4.2 Hz, 1H), 2.84 (d, *J*=4.2 Hz, 1H), 2.50–2.56 (m, 1H), 2.35–2.41 (m, 1H), 1.51–2.11 (m, 14H), 1.15 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9 (C), 138.2 (C), 128.1 (CH×2), 127.4 (CH×2), 127.3 (CH), 72.9 (CH_2), 70.0 (CH_2), 66.2 (CH_2), 63.1 (CH), 62.2 (CH), 58.3 (C), 47.8 (C), 44.0 (CH_2), 43.0 (CH), 42.6 (CH_2), 33.3 (CH_2), 30.2 (CH_2), 27.5 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 20.3 (CH_3), 20.0 (CH_3); LRMS (EI) *m*/*z* 464 (M^+), 446, 432, 248, 218, 91; HRMS (EI) calcd for $C_{25}H_{37}O_5NS$ (M^+) 463.2404, found 463.2392. $[\alpha]_D^{20}$ +34.1 (*c* 0.73, $CHCl_3$).

6.1.12. (2*S*,5*S*)-5-(But-3-enyl)-2-(prop-1-ynyl)-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-19b). To a solution of (2*S*,5*S*)-**5** (101 mg, 0.33 mmol) in THF (1.6 mL) was added NaHMDS (1.0 M THF solution, 1.0 mL, 1 mmol) at −78 °C, and the mixture was stirred at the same temperature for 5 min. To the mixture was added methyl trifluoromethanesulfonate (0.2 mL, 1.7 mmol) at −78 °C, the mixture was stirred at the same temperature for 2 h. To the mixture was added satd $NaHCO_3$ aq, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*S*,5*S*)-**19b** (87 mg, 82%)

as a colorless oil. IR (neat) ν 2925, 2852, 1732, 1633, 1598, 1337, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 5.82 (ddt, J=6.2, 10.3, 16.4 Hz, 1H), 5.03 (d, J=16.4 Hz, 1H), 4.97 (d, J=10.3 Hz, 1H), 4.41 (m, 1H), 3.66–3.77 (m, 1H), 2.41 (s, 3H), 2.00–2.12 (m, 3H), 1.55–1.94 (m, 1H). $[\alpha]_D^{21}$ −61.4 (c 0.94, $CHCl_3$).

6.1.13. (1*S*,6*S*)-2-(2-Propen-2-yl)-9-*p*-toluenesulfonyl-9-azabicyclo[4.2.1]nona-2ene (22). A solution of (2*S*,5*S*)-**19b** (87 mg, 0.3 mmol) and Ru–carbene complex **8c** (23 mg, 0.03 mmol) in degassed CH_2Cl_2 (3 mL) was stirred at room temperature for 29 h. To the mixture was added DMSO (0.1 mL), and the mixture was stirred at room temperature for 23 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **22** (68 mg, 78%) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 7.72 (d, J=8.3 Hz, 2H), 7.27 (d, J=8.3 Hz, 2H), 5.77 (dd, J=5.9, 6.6 Hz, 1H), 4.93–5.04 (m, 3H), 4.39–4.40 (m, 1H), 2.44–2.53 (m, 1H), 2.41 (s, 3H), 2.14–2.27 (m, 1H), 2.00–2.10 (m, 1H), 1.88 (s, 3H), 1.52–1.83 (m, 5H); LRMS m/z 317 (M^+), 302, 261, 162, 155, 91; HRMS calcd for $C_{18}H_{23}O_2NS$ (M^+) 317.1452, found 317.1449. $[\alpha]_D^{21}$ −12.4 (c 1.03, $CHCl_3$).

6.1.14. (+)-*N*-Ts-anatoxin-*a* ((+)-3). To a solution of OsO_4 (47 mg, 0.15 mmol) in THF (2 mL) was added Et_3N (0.04 mL, 0.3 mmol), and the mixture was stirred at room temperature for 5 min. To the mixture was added a solution of **22** (47 mg, 0.15 mmol) in THF (1.2 mL) at −78 °C, the mixture was stirred at room temperature for 64 h. To the mixture was added satd $NaHSO_3$ aq (2.6 mL), and the mixture was heated under reflux for 2.5 h. The mixture was extracted with AcOEt, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the diol (31 mg, 59%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 5.69 (dd, J=7.0, 7.0 Hz, 1H), 4.73 (d, J=9.4 Hz, 1H), 4.43 (dd, J=3.5, 3.8 Hz, 1H), 3.72 (d, J=11.1 Hz, 1H), 3.58 (d, J=11.1 Hz, 1H), 2.75 (br, 1H), 2.55 (br, 1H), 2.42 (s, 3H), 2.23–2.39 (m, 2H), 1.91–2.05 (m, 2H), 1.49–1.79 (m, 4H), 1.36 (s, 3H). $[\alpha]_D^{21}$ −62.8 (c 1.23, $CHCl_3$).

To a solution of the diol (31 mg, 0.09 mmol) in H_2O/THF (1/1, 1.7 mL) was added $NaIO_4$ (58 mg, 0.27 mmol), and the mixture was stirred at room temperature for 1.5 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give *N*-Ts-anatoxin-*a* **3** (24 mg, 85%) as a colorless solid, whose spectral data were identical to those previously obtained. And the $[\alpha]_D$ value of the synthetic *N*-Ts-anatoxin-*a* ($[\alpha]_D^{20}$ +12.8 (c 0.44, $CHCl_3$)) was identical to that previously reported.[7e]

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22. The optical purity of the recovered **4a** was completely same to that of the starting material **4a** of the oxymercuration reaction.
23. In our preliminary communication,[9] the structure of the synthetic (+)-*N*-Ts-anatoxin-*a* was incorrectly drawn as that of the antipode (i.e., (−)-*N*-Ts-anatoxin-*a*) because of the confusion arising from the unexpected inversion of chirality.
24. Crystallographic data for the structure of **18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 295170. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Studies directed toward the synthesis of the scabrosins: validation of a tandem enyne metathesis approach

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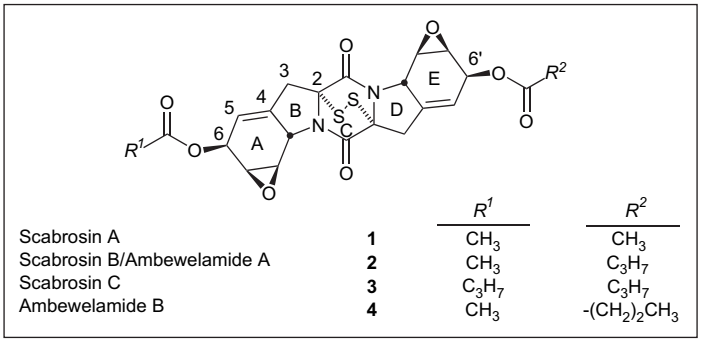
Abstract—A synthetic approach to the scabrosin family of antibiotics using a ruthenium carbene-catalyzed tandem metathesis and a Pd(II)-catalyzed cyclization is described. The chiral propargyl amino acid is furnished through enantioselective phase-transfer propargylation. The synthesis of the cyclohexadiene ring system is achieved through ring synthesis using tandem enyne metathesis, previously developed in our lab. The complementary methods of methylene-free and 1,5-hexadiene-alkyne metatheses are compared. The indoline heterocycles are formed using a two-step chloroacetoxylation (Bäckvall reaction) with subsequent nucleophilic attack by an amide nucleophile. The indoline subunits were joined and cyclized to furnish the core diketopiperazine ring. The stereochemical assignment of intermediates is also discussed.

1. Introduction

The scabrosins are a group of epidithiadiketopiperazines (edtdkp) symmetrically flanked by two highly functionalized cyclohexene rings (Scheme 1). Scabrosins **1–3** and ambewelamides **2** and **4** share the same core pentacarbocyclic framework with the symmetrical disposition of epoxide functionality. Scabrosin A was isolated from a lichen *Xanthoparmelia scabrosa* isolated on a coastal cliff face in New South Wales, Australia; it features acetyl groups at the flanks and is symmetrical. The same pentacyclic carbocycle was isolated in 1998 by Williams et al. from a lichen *Usnea* sp. found on a rotting tree in Ambewela, Sri Lanka; these molecules, the ambewelamides, bear different acyl



Scheme 1. Scabrosin/ambewelamide group of epidithiadiketopiperazines.

Keywords: Enyne metathesis; Tandem metathesis; 1,3-Cyclohexadienes; Scabrosin; Epidithiadiketopiperazine; Grubbs' catalyst; Hoveyda catalyst; Bäckvall reaction.
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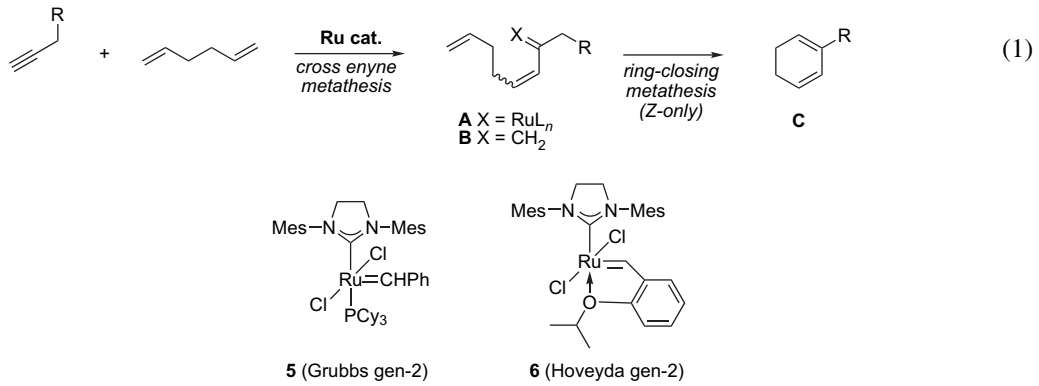
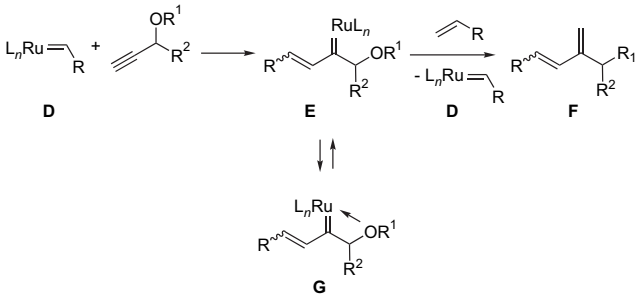


Scheme 2. Cyclohexadiene synthesis by tandem enyne metathesis.

substitution at the C6 and C6′ positions.[1] The best known relative of ambewelamides is gliotoxin. Additional fungal metabolites belonging to the edtdkp family have been isolated including aranotin,[2–4] epicorazine,[5] the rostratins,[6] and others. The central diketopiperazine ring is bridged by a disulfide. This latter functionality spanning the diketopiperazine core (the C-ring) gives this family of natural products their root name: epidithiadiketopiperazines. Of the natural products in Scheme 1, only gliotoxin has been synthesized despite an enormous amount of synthetic activity directed toward the delicate introduction of the disulfide moiety. Kishi and Fukuyama's synthesis of gliotoxin stands as a landmark achievement.[7,8] In this report, we detail our synthetic approach to the scabrosins relying on metal-catalyzed transformation. In particular, ring building of the A and E cyclohexene rings was accomplished through a Grubbs' ruthenium carbene-catalyzed tandem enyne metathesis, developed in our labs (Eq. 1) and the nitrogen heterocycle formed by Pd(II)-catalyzed Bäckvall reaction. The conjunction of the cyclohexadiene ring synthesis with the Pd(II) chemistry for 1,4-difunctionalization validates our approach and offers a powerful sequence of metal catalysis for synthesis (Scheme 2).

The ambewelamide/scabrosins have potential as anticancer agents. In general, the epidithiadiketopiperazine class of fungal natural products display a range of biological activities. For instance, aranotin inhibits viral RNA polymerase[9,10] and gliotoxin is a reverse transcriptase inhibitor.[11–13] However, the scabrosin/ambewelamide group displays unique cytotoxicity and therefore has potential as anticancer agents. This chemical biology is unique due to its dense functionality, the presence of the epidisulfide and because of the flanking epoxides. These factors combined are thought to give scabrosins their unique and potent anticancer activity.[1] Recent studies suggest that the epoxides may not be a major determinant in the unusual cytotoxicity observed for these agents.[14] Ambewelamide A is one of the best studied in the scabrosin family, with an acetyl and butanoyl group at the flanks. Ambewelamide A is toxic to cancer cell lines with an IC_{50} of 8.6 ng/mL (15 nM) for cytotoxicity against the murine P388 leukemia cell line.[1] Waring et al. have also shown potent cytotoxicity against the MCF7 human breast cancer cell line with an IC_{50} of 1 nM.[15] Moreover, tritiated thymidine incorporation was inhibited with an IC_{50} of 0.5 μM in the P815 mastocytomia cell line (gliotoxin gives IC_{50} of 2.9 μM in the same assay). Scabrosin A gives an IC_{50} of 0.56 μM in the same assay, showing identical inhibition profile as found for ambewelamide.[14,15] Because of their identical core structure and similar biological profiles, the ambewelamide/scabrosin family will be hereafter called scabrosins.

Metathesis has become a powerful method for carbon–carbon bond construction in synthesis.[16–18] Enyne metathesis is an adaptation of the parent reaction that provides conjugated dienes as products. In particular, the cross, or intermolecular, enyne metathesis[19] offers a simple coupling of unsaturated reactants to furnish diene products in a single catalytic operation. The power of metathetic processes in synthesis is amplified when metathesis reactions are used in tandem. Our group developed the tandem diene–alkyne metathesis as a cyclohexadiene ring synthesis as illustrated above (Eq. 1). This methodology is attractive because it generates a useful 2-substituted-1,3-cyclohexadiene from simple alkynes and diene starting materials. There are few methods for 1,3-cyclohexadiene synthesis and none that offer a direct, catalytic synthesis achieved on mixing of acyclic reactants. However, this tandem process, triggered by intermolecular enyne metathesis, is not stereoselective. The reaction between ruthenium carbene **D** and alkyne produces *E*- and *Z*-vinyl carbene isomers **E** (Scheme 3). The lack of *Z*-selectivity in intermolecular metathesis is a general problem in alkene metathesis research. Intermolecular enyne metatheses can be more difficult than the intramolecular ring-closing metathesis. The difficulty of the intermolecular or 'cross' enyne metathesis is thought to arise due to the slow catalyst turnover step **E** to **F**. The kinetics are known for only a limited number of cross metatheses and the rate-determining step can change depending on reactants and catalyst employed.[20]



Scheme 3. The vinyl carbene intermediate in enyne metathesis.

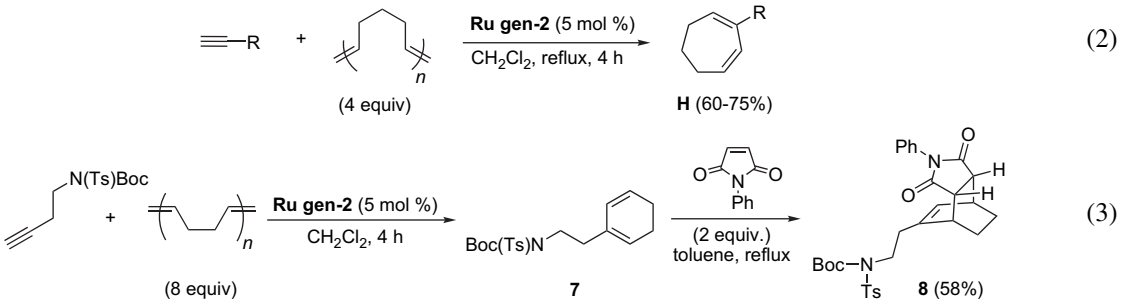
Reaction conditions must be appropriate to kinetically drive the reaction forward to nullify functional group coordination (such as **G**) or chelative decomposition pathways. Functional group chelation to the vinyl carbene intermediate and catalyst decomposition occur by largely unstudied and unknown pathways. Chelates have been suggested in order to account for reduced efficiency in certain enyne metatheses. Though plausible (see carbene **6**), there is no experimental or kinetic evidence of their formation, and further studies are needed to elucidate their relevance to catalytic efficiency. For a typical intermolecular enyne metathesis, excess alkene is used to drive the reaction. High alkene concentration may also help propel catalysis forward relative to unwanted interactions by functional groups (chelative traps are leading to metal carbene decomposition).

Tandem enyne metathesis has evolved as a useful procedure for ring synthesis. Our synthetic goal has been focused on cyclohexadiene synthesis. The one-step cyclohexadiene synthesis was achieved in our original report.[21] However, this study also identified weaknesses. In particular, the lack of stereoselection in the cross metathesis step of the tandem process presented a difficult challenge. We developed a workable solution to this problem using methylene-free conditions (Scheme 4). These conditions proved effective for cycloheptadiene (Eq. 2) and cyclohexadiene synthesis (Eq. 3). The cycloheptadiene ring synthesis engendered a net two-carbon ring expansion of cyclopentene by alkyne insertion, giving **H**. This overall process is actually the result of a threefold metathesis: ring-opening metathesis, cross metathesis, and ring-closing metathesis. The cyclohexadiene synthesis was accomplished from strain-free polybutadiene to form **7**, which was subsequently trapped in a thermal Diels–Alder reaction with *N*-phenyl maleimide to provide **8** in good yield.

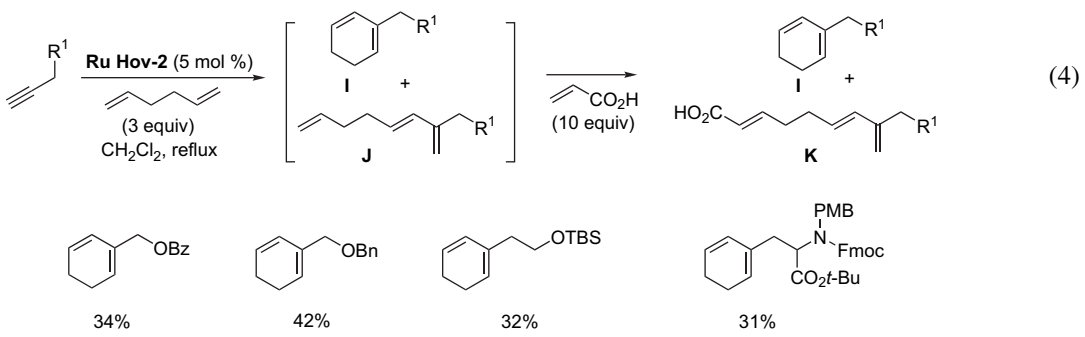
The methylene-free conditions provide higher yields of cyclohexadienes but the reactions are generally slower than the metatheses of 1,5-hexadiene and alkynes.

For alkynes with certain functional groups, the tandem cross metathesis using 1,5-hexadiene provides a complementary ring synthesis to that of the methylene-free metathesis conditions. The cross 1,5-hexadiene-alkyne metatheses are faster in comparison, usually being done in minutes. We have proposed that the 1,5-hexadiene-alkyne metatheses[21] proceed quickly due to a fast vinyl carbene turnover step, due to better binding of a 1-alkene and the high alkene concentration used. These conditions are attractive for ring synthesis where functional group interactions might pose a problem or where low catalyst loadings are desired. In contrast, the conditions of methylene-free metathesis were designed to be slow, and in our original study,[23] we speculated that this might reduce functional group tolerance. Going into the synthesis of the scabrosins, we wanted to have two alternative procedures in hand to tackle potential difficulties in the metathesis step.

The fast cross metathesis with 1,5-hexadiene improves functional group scope but this comes with reduced yield. The yield is compromised by the triene by-product arising from nonstereoselective cross metathesis (Eq. 4). Moreover, the triene by-product **J** is difficult to separate from the desired cyclohexadiene **I**. We developed a simple procedure to separate the undesired triene from cyclohexadiene **I**. This 'one-pot' clean-up procedure transforms the triene **J** into a polar, separable by-product **K** by alkene cross metathesis (Scheme 5). The procedure can be executed with a variety of alkenes in the second step of this sequential one-pot transformation. To increase the polarity of the triene, we typically



Scheme 4. Methylene-free ring synthesis from polyalkenes.[22,23]



Scheme 5. Tandem enyne metathesis and subsequent alkene cross metathesis.[25]

used acrylic acid. The procedure was designed with alkene cross selectivity in mind, using the Grubbs model for alkene reactivity.[24]

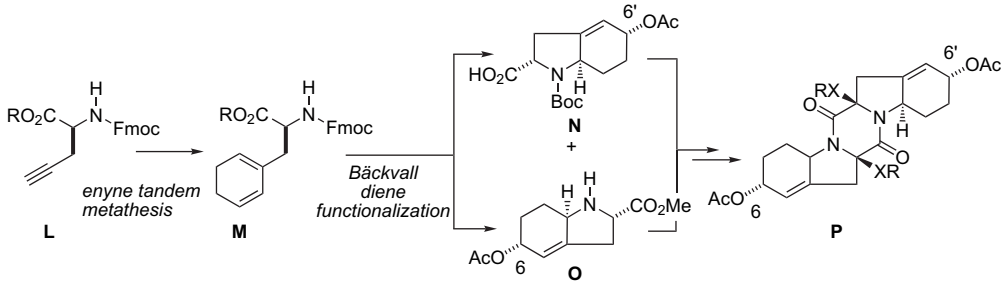
The procedure is remarkably efficient, including a cross enyne metathesis, a ring-closing metathesis, and a cross alkene metathesis, all under the same reaction conditions. In the best cases, a single charge of catalyst was needed. The theoretical yield of cyclohexadienes in these tandem transformations is 50% (based on nonstereoselective cross metathesis), and isolated yields are in the range of 35–45%. Though this is not an ideal solution to the problem of cyclohexadiene ring synthesis by tandem metathesis, the clean-up procedure is attractive due to its simplicity and practicality. The clean-up procedure can be used in cases where functional groups interfere with the efficiency of stereoselective, methylene-free enyne metathesis.

2. Synthesis

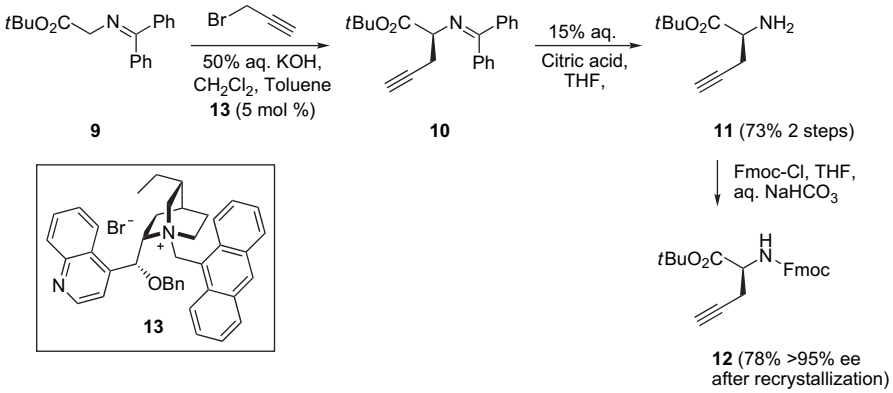
Our approach to the ambewelamides is shown in Scheme 6. Scabrosin is a symmetrical molecule, but we wanted to develop a synthetic scheme that was applicable to the unsymmmetrical ambewelamides (e.g., **2**, **4**). In these cases, two different halves with differing acyl groups on the flanking A and E rings would be synthesized and then joined. The two metal-catalyzed reactions appear early in the synthesis to make the indoline halves **N** and **O**. For this study, we have chosen the desepoxycongener of scabrosin **P** as the synthetic target in this study. First, the ring synthesis by tandem enyne metathesis will be used to generate the cyclohexadiene in **M**. The next metal-catalyzed reaction is the Pd(II)-promoted Bäckvall reaction, which will be used to effect the 1,4-*N*,*O*-difunctionalization of the 1,3-cyclohexadiene ring (Scheme 6). To make unsymmetrical ambewelamides, there are two possibilities. The cognate carboxylic acid could be used in separate Bäckvall reactions to give different acyl groups at C6 and C6′ on the two indolines. Alternatively, the product of Bäckvall cyclization can be manipulated at the C6/C6′ positions to install the desired acyl groups. Our synthesis employs the latter approach. The Bäckvall product **M** will be transformed to **N** and **O** in two separate reactions. Indolines **N** and **O** are differentially protected and ready for peptide coupling and cyclization to produce the pentacycle **P**.

The first goal in the synthesis was the development of a reliable synthetic route that would deliver significant quantities of the metathesis precursor, chiral alkyne **12**. After considering a number of possible methods for the synthesis of propargylated amino acids, we decided to use the phase-transfer-catalyzed alkylation approach (Scheme 7). The phase-transfer-catalyzed alkylation of glycine imine ester **9** has been well studied by the groups of O'Donnell,[26,27] Maruoka,[28,29] Lygo,[30] and others.[31–33] We were attracted to this approach because it is both operationally simple and amenable to scale-up. We elected to use *O*-benzylated cinchona catalyst **13**[30] due to the simplicity of the procedure, the ready availability of phase-transfer catalyst **13** and the low cost of starting materials.

High chemical and optical yields of chiral propargyl amino acid **12** were obtained. Alkylation of **9** using a slight variation on the published conditions[30] gave a good yield of the propargylated glycine imine **10**. Though **10** could be purified and analyzed at this stage (e.g., for enantiomeric excess), it proved sensitive to hydrolysis. The imine was



Scheme 6. Synthetic plan.



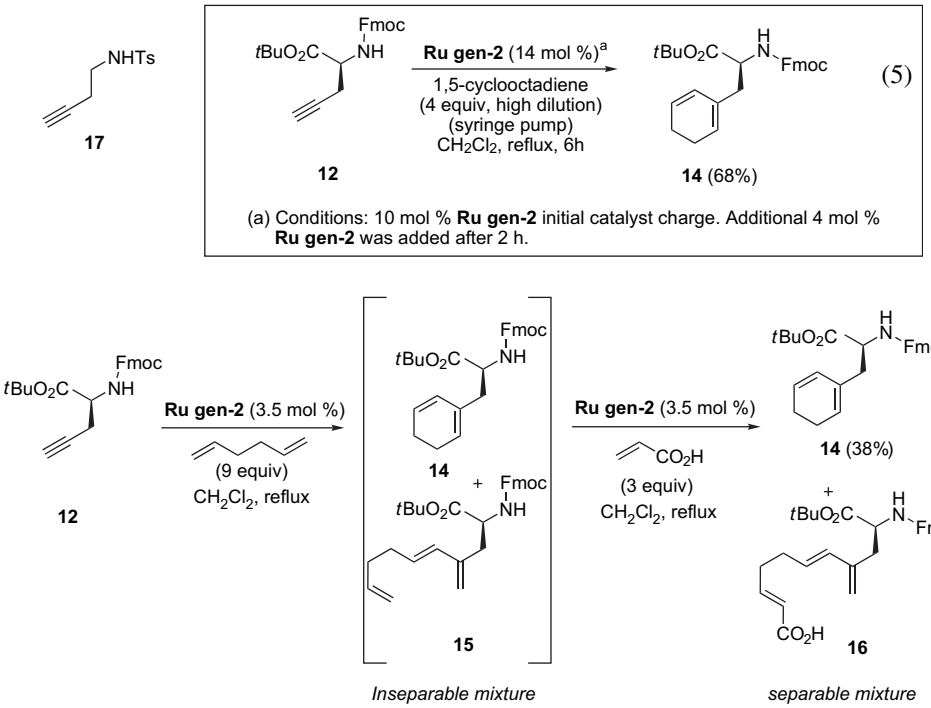
Scheme 7. Synthesis of propargylated amino acid **12**.

isolated after the asymmetric propargylation, and the crude material taken through to hydrolysis with aqueous citric acid in THF. In this way, amine **11** was obtained in 73% isolated yield over the two steps. For stereochemical assignment, imine **10** was analyzed directly. The only absolute configuration data available on chiral propargyl amino acid derivatives comes from alkyne **10**. The optical rotation of **10** was determined on an analytically pure sample (column chromatography), which established the absolute configuration as *S*, based on the literature precedence[29–31,34] for the identical compound. The amine was then protected with (9-fluorenylmethyl)chloroformate under Schotten–Baumann conditions to give **12**.[27] At this point, the enantiopurity of the material was established by HPLC using a chiral stationary phase. The material derived directly from **10** had 89% ee, assigned as the *S*-configuration on the basis of the absolute configuration correlation of imine **10** above. With a single recrystallization, the enantiomeric excess was improved to greater that 95% ee, with a chemical yield of 78% (after a single recrystallization). The sequence outlined in Scheme 7 proved amenable to scale-up and delivered up to 40 g batches of **12**.

The next challenge was the synthesis of cyclohexadiene **14**. The successive alkene metathesis 'clean-up' procedure offered an expedient solution to cyclohexadiene synthesis for the scabrosin synthesis. When **12** was treated with 5 equiv of 1,5-hexadiene and **Ru gen-2**, a 1:1.2 mixture of diene **14** and triene **15** was produced (Scheme 8). The clean-up procedure was then applied. Without isolation or solvent exchange, the mixture of **14** and **15** was directly treated with a second portion of **Ru gen-2** and acrylic acid. Continued reflux in dichloromethane solvent effected the alkene cross metathesis, which occurred with high chemoselectivity on the terminal alkene of **15**. The new mixture of **14** and alkene cross metathesis product **16** could be separated. Separation was readily achieved through extractive work-up using a basic aqueous wash followed by column chromatography, which yielded **14** in 38% overall yield. Initially we ran the two metathesis reactions with 5 mol % each of Grubbs' second-generation carbene catalyst. However, on scale-up this was optimized to a lower loading of 3.5 mol % each, or 7% overall. Lowering the catalyst loading further was unsuccessful: for example, the first cross metathesis stalled at 3 mol % catalyst loading.

Kulkarni and Diver have recently developed the methylene-free metathesis conditions, which deliver good yields of 1,3-cyclohexadienes.[23] Our group is interested in catalytically efficient tandem processes and we typically do not screen reaction conditions employing catalyst loadings above 5 mol % Grubbs carbene complex. In this instance, we were interested in comparatively evaluating the methylene-free method with the clean-up procedure above, which gave modest yields. When alkyne **17** was treated with the second-generation Grubbs carbene complex and polybutadiene, only trace conversion to the cyclohexadiene was detected at high (20 mol %) carbene catalyst loadings.[25] Some conversion was obtained by treating the reaction mixture with successive portions of catalyst, but the loading was too high for practical use in the early stages of total synthesis.

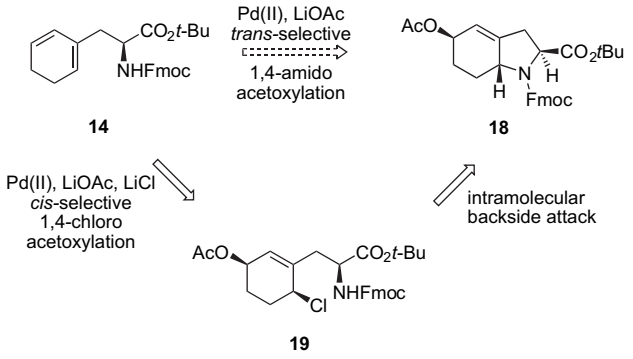
Cyclohexadiene **14** can be accessed by methylene-free enyne metathesis using 1,5-COD as the alkene. In these runs, higher catalyst loadings (10–20 mol %) were required in small-scale reactions.[35] The high catalyst loadings are needed because the free N–H is considered problematic for cross enyne metathesis.[36] Full conversion of alkyne **12** was achieved with 4 equiv COD at 14 mol % total loading of **Ru gen-2** complex (Eq. 5).[37] The cyclodiene was obtained in 68% isolated yield after treatment of the crude reaction with DMSO (the Georg protocol).[38] Typically the reaction requires the addition of a fresh portion of



Scheme 8. Clean-up procedure applied to synthesis of **14**.

catalyst. Currently, the best results are obtained with an initial charge of 10 mol % **Ru gen-2** followed by addition of additional 4 mol % halfway through the 4 h syringe pump addition. We do not fully understand the nature of catalyst decomposition. Further experiments to optimize the reaction conditions are underway.[39]

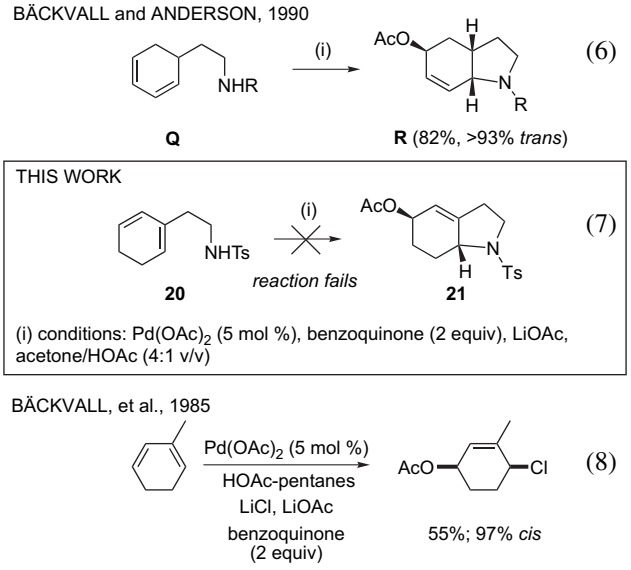
With cyclohexadiene **14** accessible by two different approaches, we proceeded to investigate cyclization to the indoline. Ideally, direct transformation of **14** into indoline **18** would be desired through use of the Bäckvall reaction[40–43] (top path, Scheme 9). Ultimately, we found that an indirect two-step sequence via **19** was necessary to obtain desired indoline **18**.



Scheme 9. Direct and indirect paths to indoline **18**.

Bäckvall's original paper describing the cyclization showed that the amidoacetoxylation[42] proceeds efficiently using diene **Q** (Eq. 6). Our earlier efforts to effect an analogous cyclization on the constitutional isomer **20** failed. The tethered amine must have enough flexibility to attack the η^4-diene–Pd(II) complex; in diene **20** there is too much ring strain for the out-of-plane deformation needed for C–N bond formation to produce **21**. To overcome this difficulty, we imagined that a two-step sequence could be used. Bäckvall has also described Pd(II)-catalysis of a stereoselective *syn*-chloroacetoxylation[44–46] (Eq. 8). Interestingly, the reaction is completely regioselective. Since the direct amidoacetoxylation in Eq. 7 failed, we examined the two-step approach described in Scheme 9 above. The *syn*-selective chloroacetoxylation would be followed by a base-catalyzed intramolecular displacement by an amide nucleophile. This process results in the desired, net 1,4-trans amidoacetoxylation (lower pathway in Scheme 9).

The synthesis of the indoline relied on the Bäckvall chloroacetoxylation–cyclization two-step sequence. Exposing **14** to *syn*-1,4-chloroacetoxyation (LiCl and LiOAc in THF–acetic acid) to Pd(II) under the oxidative conditions (2 equiv benzoquinone) yielded functionalized alkene product **19** and a diastereomer **22**. The diastereomers arise from nondiscriminant complexation to the Pd(II). The α-chiral center is too remote to have any effect on facial selectivity. As a result, both diastereomers were produced in equal yields. During purification of **19** and **22**, phenylalanine **29** was isolated in 17% yield. It is presumed that this oxidation product arises directly from the 1,3-cyclohexadiene **14**. Several observations support this rationalization. Under the extended reaction time, the ratio of the 1,4-acetoxychlorination products **19** and **22** and the oxidation product **29** did not vary significantly. Diene **14** could be undergoing air oxidation or could be undergoing activation by Pd(II) with a β-hydride elimination competing with nucleophilic attack (Scheme 10).



Scheme 10. Cyclization to indoline based on Bäckvall reactions (Eqs. 6 and 8 from Bäckvall[42,44]).

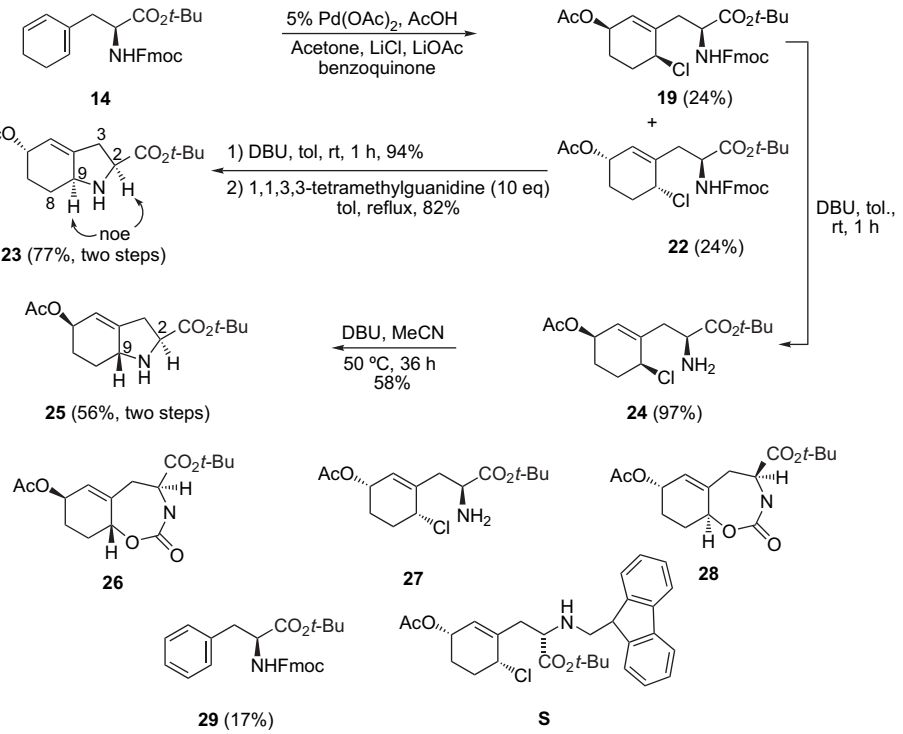
Deprotection of the fluorenylmethyloxycarbonyl (Fmoc) group was accomplished over two discrete treatments with base. Initial experiments using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in acetonitrile on the mixture of diastereomers **19/22** gave Fmoc deprotection with the formation of up to 30% of **26** and **28**. The formation of cyclic carbamates was surprising. This is unusual, seldom observed probably because most carbamic acids formed in situ during Fmoc deprotection do not have a cyclization path. During the deprotection of **19/22** with DBU in acetonitrile, the intermediate carbamic acids gave cyclization by substitution reaction on the allylic chloride providing the cyclic carbamates **26** and **28**. Other solvents such as tetrahydrofuran, dichloromethane, dichloroethane, and benzene all result in the formation of **26** and **28** in decreasing amounts, respectively. Each diastereomer **19/22** gave cleaner deprotection in toluene without the formation of the cyclic carbamates. Treatment of **19** or **22** with DBU in toluene at room temperature afforded the corresponding primary amino acids in 97% and 94% yields, respectively. The addition of DBU too quickly similarly produced trace amounts of **26** and **28** in toluene. Last, when the primary amine was cyclized in the same pot as the Fmoc deprotection, there were several products formed including a nonpolar adduct **S** between the primary amine and fulvene. The fulvene is formed as a by-product of Fmoc protecting group removal. For instance it is known that the primary amines can add into the fulvene to form the adduct.[8] To optimize the yield of cyclization, it proved necessary to remove the nonpolar fulvene before the allylic chloride **27** was subjected to the more forcing conditions required for the cyclization.

The cyclization of **19** and **22** had to be conducted under different conditions. Treatment of **22** with 10 equiv of 1,1,3,3-tetramethylguanidine in refluxing toluene for 15 h

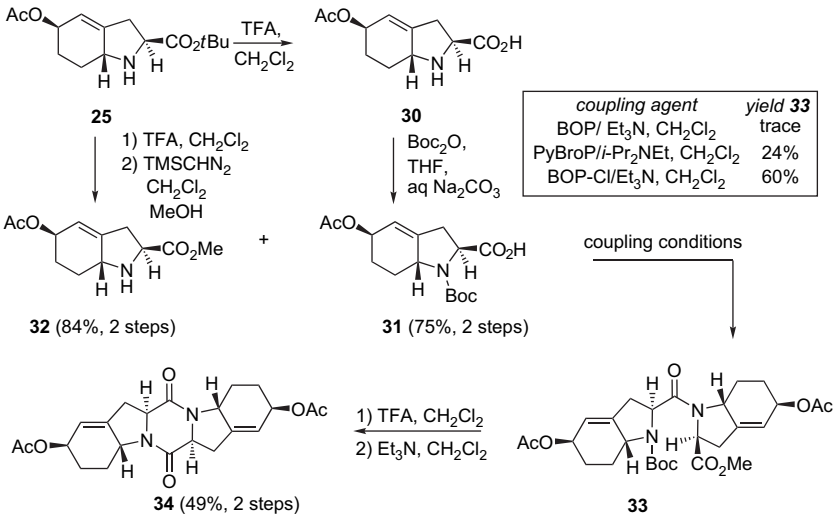
yielded 82% of **23**. In contrast, the 2,5-*trans*-pyrrolidine substructure found in indoline **25** (2,9-*anti*-configuration based on scabrosin numbering) makes it more strained than **23**. As a result, indoline **25** was found to be much harder to synthesize. Treatment of **24** with 1,1,3,3-tetramethylguanidine under identical conditions resulted in trace conversion to indoline **25**. After screening several bases, DBU in acetonitrile at 50 °C for 36 h yielded the desired indoline **25** in 58% isolated yield. Access to both diastereomers of the indolines proved advantageous for the assignment of relative stereochemistry. The stereochemistry of **23** was established directly by NOE experiments. Irradiation of the resonance at δ 3.41 (C9 proton) gave an NOE of the resonances at δ 3.73 (C2 proton, scabrosin numbering) and δ 1.70. Irradiation of the proton at δ 3.73 ppm showed enhancement in the resonances at δ 3.41 (C9 proton) and δ 2.85 (C3 proton). This was expected for a 2,5-*cis*-disubstituted pyrrolidine,[47] and led to the assignment of the indoline relative stereochemistry shown for **23** (Scheme 11). For diastereomer **25**, the analogous NOE between δ 3.77 (C2 proton) and δ 3.64 (C9 proton) of **25** was not observed, suggestive of trans-orientation. The two observations taken together lead to an assignment of the 2,5-*trans*-pyrrolidine substructure in **25**. Ultimately this conclusion was corroborated by crystal structure of the pentacycle (vide supra).

Completion of the synthesis of the pentacyclic core of scabrosin is summarized in Scheme 12. Indoline **25** was divided into two portions and manipulated separately for eventual union to form the diketopiperazine ring. The *tert*-butyl ester was deprotected with trifluoroacetic acid, then esterified with trimethylsilyldiazomethane in 1:1 v/v CH_2Cl_2–methanol to produce methyl ester **32** in 84% yield. This amino ester has a free amine in the proline ring ready for peptide bond coupling. A second portion of amino acid **25** was deprotected and converted (di-*tert*-butyl dicarbonate in aqueous sodium carbonate) to Boc-protected carboxylic acid **31** in 75% yield. Indoline half **31** features the carboxylic acid to be activated in the peptide coupling step. Next, the two pieces were joined through conventional peptide coupling. Conventional peptide coupling agents used for difficult couplings gave poor results. Both BOP reagent and PyBroP were attempted but gave low conversion to dipeptide **33**. The hindered nature of the secondary amine in **32** hampered the efficiency of coupling. Activation of the carboxylic acid **31** with bis(oxazolidinyl)-phosphoryl chloride (BOP-Cl)[48,49] gave an improved yield, providing amide **33**, isolated in 60% yield. Amide **33** appeared as a mixture of amide and carbamate rotamers in the NMR. The final cyclization required intramolecular aminolysis of the methyl ester and was accomplished by deprotection of the *N*-Boc group with TFA in CH_2Cl_2. The excess TFA was then removed and the secondary ammonium salt neutralized with triethylamine, refluxed in CH_2Cl_2 overnight to furnish the pentacycle **34** in 49% yield.

The structure of **34** was confirmed by single crystal X-ray structure (Fig. 1). The pentacyclic diketopiperazine **34** was crystallized from ethyl acetate and hexanes to provide white colorless crystals, mp 259–261 °C. Importantly, the structure determination corroborated the diastereomeric assignment of the indolines based on observed NOE's (Scheme 11 describing the Bäckvall chloroacetoxylation–cyclization sequence). Since the molecule **34** does not contain any heavy atoms and since it crystallized in a centrosymmetric space group, the structure determination was not used to corroborate absolute configuration. The structure determination of **34** illustrates relative configuration. Furthermore, the crystal structure showed disorder in the ester moieties, with the



Scheme 11. Synthesis of diastereomeric indolines **23** and **25**.



Scheme 12. Completion of scabrosin pentacycle synthesis.

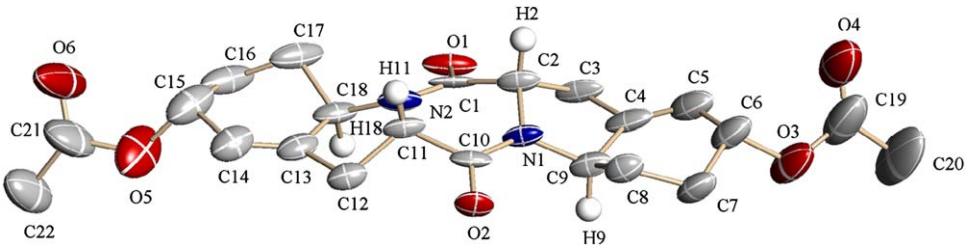


Figure 1. ORTEP drawing of pentacycle **34**. The major conformer (63%) found in the unit cell is shown. Thermal ellipsoids are drawn at the 50% probability level. The numbering on the right half is the same as scabrosin numbering. The crystallographic numbering C10–C18 corresponds to C1′–C9′ (scabrosin numbering).

major (63% population) isomer shown. Both structures have the same relative stereochemistry. A further discussion is provided in Section 3.

In conclusion, we have achieved a stereocontrolled synthesis of the scabrosin pentacycle using tandem diene–alkyne metathesis conjoined with the Pd(II)-promoted chloroacetoxylation–base-catalyzed cyclization. The combination of the two metal-catalyzed reactions demonstrates the value and versatility of the metathesis chemistry when linked with 1,4-difunctionalization. The cyclohexadiene ring synthesis can be achieved under either 1,5-hexadiene-alkyne cross metathesis or under methylene-free conditions using cyclooctadiene as the alkene. The Bäckvall 1,4-*N*,*O*-difunctionalization chemistry of the 1,3-cyclohexadiene results in the formation of the indoline ring system. The synthetic approach is amenable to the synthesis of unsymmetrical epidithiadiketopiperazines of this family of natural products. Further studies directed toward the stereospecific sulfurization of the diketopiperazine ring are in progress.

3. Experimental

3.1. General information

Reactions were conducted under argon atmosphere unless otherwise noted. Solvents were dried and degassed under argon by a solvent purification system and drawn immediately prior to use. Dichloromethane, tetrahydrofuran, and ether were dried by passage through alumina and toluene was dried and deoxygenated using columns of alumina and Q5. Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidine]dichloro(phenylmethylene)(tricyclohexylphosphine) (Grubbs' second-generation catalyst) was obtained from Materia, Inc. (Pasadena, CA) or purchased from Aldrich Chemical Co. 1,5-Hexadiene was purified by distillation from sodium metal. All other chemicals were purchased from Aldrich Chemical Co. and used as received. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz and ^{13}C NMR spectra at either 75 or 125 MHz in the indicated solvent. ^{1}H NMR spectra were referenced on the TMS signal for $CDCl_3$. The ^{13}C NMR spectra were referenced at 77 ppm for $CDCl_3$. Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column (4.6 mm×250 mm, 5 μm particle size) using UV detection. Proton and carbon NMR data can be found in Supplementary data file.

3.1.1. 2-(Benzhydrylidene-amino)-pent-4-ynoic acid *tert*-butyl ester (10). In a 5 L Erlenmeyer flask equipped with magnetic stirbar, *tert*-butyl *N*-(diphenylmethylene)glycinate **9** (53 g, 0.18 mol) was dissolved in toluene (1.3 L) and CH_2Cl_2 (0.54 L). The solution was treated sequentially with catalyst **13** (5.9 g, 9.0 mmol), propargyl bromide (80% in toluene, 24 mL, 0.22 mol), and 50% aqueous potassium hydroxide (0.36 L, 3.2 mol). The mixture was stirred vigorously for 14 h at room temperature, the phases were separated and the aqueous layer was extracted with Et_2O

(2×300 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo (rotary evaporator). The residue was then passed though a short plug of silica gel, eluted with 20% ethyl acetate–hexanes, and concentrated to give crude imine **10** (57 g, 95%), which was used directly in the subsequent hydrolysis step.

An analytical sample of **10** was obtained in a separate small-scale reaction, conducted analogous to the procedure above on 10 mmol scale. After the usual work-up, the residue was further purified by flash column chromatography on silica gel (gradient elution with 1:30 ethyl acetate–hexane to 1:9 ethyl acetate–hexane) to give **10** (2.38 g, 71%) as a green oil: R_f=0.39 (1:9 ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.45–7.25 (m, 8H), 4.19–4.15 (m, 1H), 2.83–2.71 (m, 2H), 1.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 169.6, 139.7, 136.3, 130.4, 129.0, 128.7, 128.4, 128.3, 128.1, 81.6, 81.3, 70.1, 64.8, 28.1, 23.4; FTIR (thin film, cm^{-1}) 3297, 2978, 1732, 1624, 1446, 1368, 1285, 1152, 696; high-resolution MS (ESI$^+$) calcd for $C_{22}H_{24}O_2N_1$ (M^++H): 334.1802, found: 334.1809; $[\alpha]_D^{25}$ −96.8 (*c* 1.0, $CHCl_3$). The negative sign of optical rotation established the *S*-configuration in agreement with the literature assignment.[31,34]

3.1.2. 2-Amino-pent-4-ynoic acid *tert*-butyl ester (11). A 2 L rb flask equipped with magnetic stirbar and rubber septum was charged with imine **10** (57 g, 0.17 mol) and 650 mL THF. To the stirred solution was added 15% aqueous citric acid (350 mL) and stirring was continued for 12 h. The mixture was diluted with 1 M HCl (200 mL), extracted with Et_2O (3×350 mL), and the combined organics were subsequently washed with water (2×300 mL). The combined aqueous layers were basified to pH 11 by the addition of K_2CO_3. The aqueous layer was then extracted with ethyl acetate (3×400 mL) and all of the organic layers were then combined, dried (Na_2SO_4), filtered, and concentrated in vacuo (rotary evaporator). The residue was purified by flash column chromatography on silica gel (elution with 3:1 ethyl acetate–hexanes) to give **11** (22.3 g, 77%) as a clear oil: R_f=0.32 (3:1 ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (dd, *J*=9.0, 9.0 Hz, 1H), 2.61–2.58 (m, 2H), 2.06–2.05 (m, 1H), 1.67 (br s, 1H), 1.48 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 81.6, 79.8, 71.0, 53.6, 28.0, 25.0; FTIR (thin film, cm^{-1}) 2979, 2362, 1730, 1394, 1368, 1251, 1221, 1153; high-resolution MS (ESI$^+$) calcd for $C_9H_{15}O_2N_1Na$ (M^++Na): 192.0995, found: 192.0994; $[\alpha]_D^{25}$ −23.8 (*c* 1.0, $CHCl_3$).

3.1.3. (2*S*)-*tert*-Butyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-pent-4-ynoate (12). A 2 L rb flask containing magnetic stirbar and rubber septum was charged with amine **11** (22.3 g, 0.132 mol) in THF (500 mL) to which 9-(fluorenylmethoxycarbonyl)chloride (38.0 g, 0.145 mol) was added. A solution of 10% aqueous Na_2CO_3 (500 mL) was added and the mixture was stirred for 16 h. After this time, the mixture was diluted with ethyl acetate (400 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×400 mL) and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo (rotary evaporator). The residue was subsequently purified by flash column chromatography on silica gel (gradient elution with 1:20 ethyl acetate–hexanes to 1:5 ethyl acetate–hexanes) to afford a white solid, which was recrystallized (ethyl acetate–hexanes) to give **12** as white needles (39.2 g, 76%): mp 68–70 °C; R_f=0.53 (1:3 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.64 (d, *J*=7.5 Hz, 2H), 7.4 (dd, *J*=7.5, 7.5 Hz, 2H), 7.34 (dd, *J*=8.0, 7.5 Hz, 2H), 5.5 (d, *J*=8.0 Hz, 1H), 4.48–4.38 (m, 3H), 4.27 (dd, *J*=7.0 Hz, 1H), 2.81–2.78 (m, 2H), 2.09 (br s, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 155.6, 143.9, 143.8, 141.3, 127.7, 127.1, 125.2, 120, 82.8, 78.6, 71.6, 67.2, 52.6, 47.1, 28.0, 23.0; FTIR (thin film, cm^{-1}) 3298, 2977, 1721, 1507, 1450, 1349, 1223, 1156; high-resolution MS (EI$^+$) calcd for $C_{24}H_{25}O_4N$ (M^+): 391.1778, found: 391.1776; enantiomeric excess determination by HPLC (0.6 mL/min, gradient elution 15% 2-propanol–hexane to 40% 2-propanol–hexane over 40 min, t_R=15.1, 1.6% (*R*), 26.0, 98.4% (*S*) min) indicated 97% ee of the *S*-enantiomer; $[\alpha]_D^{25}$ +31.6 (*c* 1.0, $CHCl_3$).

3.1.4. (2*S*)-*tert*-Butyl 3-cyclohexa-1,5-dienyl-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-propionate (14).

3.1.4.1. Method A: 1,5-cyclooctadiene. A 50 mL air-free Schlenk tube was charged with dichloromethane (5 mL) and 1,5-cycloctadiene (188 μL, 1.5 mmol). Argon was bubbled through this solution for 10 min. **Ru gen-2** (21.2 mg, 0.025 mmol, 10 mol %) was then added to the room temperature solution and subsequently placed into a 55 °C oil bath. To this solution was added **12** (100 mg, 0.256 mmol) in 2 mL dichloromethane over 4 h via gas-tight syringe (addition rate 0.5 mL/h).[50] After 2 h of addition, an additional 4 mol % of **Ru gen-2** (8.7 mg, 0.010 mmol, 4 mol %) was added to the reaction. After 2 h, the addition was complete and the flask was heated for another 6 h. The reaction was allowed to cool to room temperature, concentrated in vacuo (rotary evaporator) diluted with 5 mL of dichloromethane and 182 μL of dimethyl sulfoxide (2.56 mmol, 1000 mol %), and stirred for 12 h. The solution was then concentrated in vacuo (rotary evaporator) and the residue purified by column chromatography on silica gel, eluting with 1:7 ethyl acetate–hexanes to obtain 75 mg of **14** (68%) as a pale yellow oil: R_f=0.27 (1:5 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.5 Hz, 2H), 7.60 (m, 2H), 7.40 (t, *J*=7.0 Hz, 2H), 7.31 (t, *J*=7.5 Hz, 2H), 5.83 (m, 2H), 5.55 (s, 1H), 5.27 (d, *J*=8.0 Hz, 1H), 4.41 (m, 1H), 4.34 (m, 2H), 4.23 (m, 1H), 2.48 (m, 2H), 2.10 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 155.5, 143.9, 141.3, 130.9, 127.7, 127.3, 127.0, 126.6, 125.2, 124.4, 120.0, 82.1, 66.1, 53.6, 47.2, 38.5, 28.0, 22.3, 22.1; FTIR (thin film, cm^{-1}) 3326, 2933, 1718, 1507, 1450, 1367, 1224, 1155, 1050; high-resolution ESI molecular ion calcd for $C_{28}H_{31}O_4N$+Na 468.2145, found: 468.2152; $[\alpha]_D^{25}$ +10.0 (*c* 1.6, $CHCl_3$).

3.1.4.2. Method B: preparative scale using 1,5-hexadiene. Into a 250 mL rb flask equipped with a condenser, magnetic stirbar, and rubber septum was added alkyne **12** (15.6 g, 40 mmol) and 1,5-hexadiene (24 mL, 200 mmol), dissolved in CH_2Cl_2 (80 mL). The Grubbs' catalyst **Ru gen-2** (1.2 g, 1.4 mmol, 3.5 mol %) was added and the solution was then brought immediately to reflux by immersion in a 50 °C oil bath. Heating was maintained for 5 h, the mixture was subsequently cooled and concentrated to a volume of 10 mL (rotary evaporator). The residue was passed though

a short plug of silica gel (eluting with 20% ethyl acetate–hexanes) and concentrated. The crude mixture was then dissolved in CH_2Cl_2 (80 mL) and acrylic acid (11.0 mL, 160 mmol) was then added. The Grubbs' catalyst **Ru gen-2** (1.2 g, 1.4 mmol, 3.5 mol %) was then added and the solution was then brought immediately to reflux by immersion in a 50 °C oil bath. Heating was maintained for 12 h, the mixture was subsequently cooled to room temperature, diluted with CH_2Cl_2 (200 mL), and washed with saturated aqueous $NaHCO_3$ (2×250 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent removed in vacuo (rotary evaporator). Purification was accomplished by flash column chromatography on silica gel (elution with 1:5 ethyl acetate–hexanes) afforded **14** (6.8 g, 38%), as a brown oil. Spectral data matched that reported for **14** above (using COD), though 17–20% butadiene was present by proton NMR. This by-product proved difficult to remove, so the diene was carried through to the next step.

3.1.5. Preparation of 19, 22, and 29. To a stirred solution of $Pd(OAc)_2$ (149 mg, 0.664 mmol), LiCl (111 mg, 2.6 mmol), LiOAc–$2H_2O$ (667 mg, 6.64 mmol), and benzoquinone (2.87 g, 26.6 mmol) in glacial acetic acid (3.9 mL) and acetone (37 mL) was added two solutions via syringe pump over 12 h. Solution 1 was cyclohexadiene **14** (5.9 g, 13.2 mmol) in acetone (5.7 mL). Solution 2 was LiCl (1.0 g, 23.9 mmol) in glacial acetic acid (5.7 mL). After 15 h, the reaction was concentrated in vacuo (rotary evaporator), diluted with ethyl acetate (300 mL), transferred to a separatory funnel, and washed with 1 M $NaOH_{(aq)}$ (3×200 mL). The aqueous layers were then combined and back-extracted with ethyl acetate (3×100 mL), the organic layers were then combined, dried ($MgSO_4$), concentrated in vacuo (rotary evaporator) to give a viscous black sludge. The black residue was dissolved in a minimal amount of chloroform and passed through a short column of silica gel (3.7 cm×12 cm) eluted with 1:10 ethyl acetate–hexanes ramping up to 1:5 ethyl acetate–hexanes to remove palladium and other polar by-products (this operation removes most of **29** from **19** and **22**). The desired fractions (containing **29** R_f=0.27 in 1:5 ethyl acetate–hexanes) were collected and concentrated into a viscous yellow oil. This oil was further purified by column chromatography on silica gel (3.7 cm×30 cm), eluting with 1:10 ethyl acetate–hexanes ramping polarity to 1:6 ethyl acetate–hexanes giving 1.7 g of **19** (24%), 1.7 g of **22** (24%), and 1.0 g of **29** (17%), each obtained as viscous pale yellow oils. If **19** and **22** are dissolved in a minimal amount of ether (at rt) and diluted with five volumes of pentane and concentrated, a pale yellow solid is obtained in quantitative yield. The pale yellow product is clean enough to be taken on to the next reaction. If another column is performed it is possible to obtain **19** and **22** as a clear oil or white powder as described above. The **19**, **22**, and **29** are stable at room temperature in a vial in regular lab light for months.

Compound **19**: mp=51–54 °C. R_f=0.11 (1:5 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=7.5 Hz, 2H), 7.60 (d, J=7.0 Hz, 2H), 7.40 (t, J=7.5 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 5.63 (s, 1H), 5.34 (d, J=8.0 Hz, 1H), 5.30 (m, 1H), 4.52 (s, 1H), 4.38 (m, 3H), 4.23 (t, J=7.0 Hz, 1H), 2.76 (dd, J=14.5, 5.5 Hz, 1H), 2.49 (dd, J=14.5, 8.0 Hz, 1H), 2.19 (m, 1H), 2.01 (m, 6H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.5, 155.5 (143.8, 143.7, rotamers), 141.8, 137.2, 129.2, 127.7, 127.0, 125.0, 120.0, 82.7, 69.1, 67.0, 55.8, 53.0, 47.1, 37.7, 30.2, 28.0, 23.2, 21.1; FTIR (thin film, cm^{-1}) 3339, 2977, 1733, 1520, 1450, 1369, 1237, 1154, 1033; high-resolution ESI molecular ion calcd for $C_{30}H_{34}O_4ClN$+Na 562.1967, found: 562.1982; $[\alpha]_D^{25}$ −4.4 (*c* 2.00, $CHCl_3$).

Compound **22**: mp=52–54 °C. R_f=0.15 (1:5 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=12.0 Hz, 1H), 7.58 (d, J=11.5 Hz, 1H), 7.40 (t, J=12.0 Hz, 1H), 7.32 (t, J=12.0 Hz, 1H), 5.61 (s, 1H), 5.29 (d, J=13.0 Hz, 1H), 5.20 (m, 1H), 4.66 (s, 1H), 4.31 (m, 4H), 2.94 (m, 1H), 2.10 (m, 6H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.4, 155.9, 143.8, 141.3, 137.4, 129.1, 127.7, 127.0, 125.0, 120.0, 82.7, 69.1, 67.1, 55.7, 52.3, 47.1, 38.4, 30.1, 28.0, 23.3, 21.1; FTIR (thin film, cm^{-1}) 3338, 2978, 1734, 1525, 1450, 1369, 1240, 1156; high-resolution ESI molecular ion calcd for $C_{30}H_{34}O_4ClN$+Na 562.1967, found: 562.1978; $[\alpha]_D^{25}$ +18.5 (*c* 2.00, $CHCl_3$).

Compound **29**: R_f=0.27 (1:5 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=7.5 Hz, 2H), 7.57 (t, J=7.0 Hz, 2H), 7.40 (t, J=7.5 Hz, 2H), 7.28 (m, 5H), 7.15 (d, J=7.0 Hz, 2H), 5.28 (d, J=7.5 Hz, 1H), 4.55 (m, 1H), 4.44 (dd, J=11.0, 7.5 Hz, 1H), 4.32 (dd, J=11.0, 7.5 Hz, 1H), 4.21 (t, J=7.0 Hz, 1H), 3.10 (d, J=5.5 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.4, 143.7, 141.1, 136.0, 129.3, 128.2, 127.5, (126.8, 127.7 rotomers), 124.9, 119.8, 82.0, 66.7, 55.0, 47.0, 38.2, 27.8; FTIR (thin film, cm^{-1}) 3334, 2979, 1723, 1511, 1368, 1253; high-resolution ESI molecular ion calcd for $C_{28}H_{29}O_4N$+Na 466.1989, found: 466.1988; $[\alpha]_D^{25}$ +19.6 (*c* 2.00, $CHCl_3$).

3.1.6. Preparation of 24. A 100 mL Schlenk tube was charged with **19** (780 mg, 1.44 mmol) and 74 mL of toluene. To this stirring solution was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (208 μL, 1.44 mmol) over 2 min, then stirred for 1 h. The color changed from yellow to a pink/red on addition of DBU. The reaction was concentrated in vacuo (rotary evaporator) to a volume of ∼1 mL and purified by column chromatography on silica gel, eluting with 1:1 ethyl acetate–hexane ramping polarity to 100% ethyl acetate (once the fulvene has been eluted, the solvent polarity is increased from 1:1 to 4:1 ethyl acetate–hexane and then to 100% ethyl acetate after **24** starts to elute), to yield 436 mg of **24** (96%) as a pale yellow oil: R_f=0.17 (4:1 ethyl acetate–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (s, 1H), 5.82 (t, J=7.0 Hz, 1H), 4.57 (t, J=3.5 Hz, 1H), 3.5 (t, J=7.0 Hz, 1H), 2.45 (m, 2H), 2.04 (m, 7H), 1.81 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 170.7, 138.4, 128.4, 81.5, 69.2, 56.5, 54.0, 40.2, 30.3, 28.0, 23.2, 21.2; FTIR (thin film, cm^{-1}) 2919, 2850, 1734, 1369, 1241, 1154, 1026; high-resolution ESI molecular ion calcd for $C_{15}H_{24}O_4NCl$+H 318.1467, found: 318.1456; $[\alpha]_D^{25}$ −16.4 (*c* 3.70, $CHCl_3$).

3.1.7. Preparation of 27. A 100 mL Schlenk tube was charged with **22** (511 mg, 0.927 mmol) and 46 mL of toluene. To this stirring solution was added dropwise 1,8-diazabicyclo (5.4.0) undec-7-ene (130 μL, 0.927 mmol) over 2 min and then stirred for 1 h. The color changed from yellow to a pink/red on addition of DBU. The reaction was

concentrated in vacuo (rotary evaporator) to a volume of ~1 mL and purified by column chromatography on silica gel, eluting with 1:1 ethyl acetate–hexanes ramping polarity to 100% to ethyl acetate (once the fulvene been eluted, the solvent polarity is changed from 1:1 to 4:1 ethyl acetate–hexanes and then to straight ethyl acetate after **27** starts to elute), to yield 286 mg of **27** (94%) as a pale yellow oil: R_f=0.10 (4:1 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.34 (t, J=7.5 Hz, 1H), 4.56 (t, J=3.5 Hz, 1H), 3.53 (dd, J=9.5, 4.5 Hz, 1H), 2.76 (dd, J=14.5, 4.5 Hz, 1H), 2.20 (m, 2H), 2.03 (m, 6H), 1.54 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 170.6, 138.2, 128.3, 81.4, 69.2, 56.0, 53.0, 39.4, 30.3, 28.0, 23.3, 21.2; FTIR (thin film, cm^{-1}) 3380, 2977, 1733, 1369, 1243, 1157, 1027; high-resolution ESI molecular ion calcd for $C_{15}H_{24}O_4NCl$+H 318.1467, found: 318.1466; $[\alpha]_D^{25}$ +18.0 (c 2.00, $CHCl_3$).

3.1.8. Preparation of 26 and 28. Substituting toluene for acetonitrile in the procedure above will result in the formation of 20–30% **26** and **28** as a clear oil (R_f=0.30, R_f=0.32, respectively, 4:1 ethyl acetate–hexanes). The use of tetrahydrofuran, dichloromethane, dichloroethane or benzene all resulted in the formation of **26** and **28** in decreasing amounts, respectively. The addition of DBU too quickly will also produce trace amounts of **26** and **28** in toluene. Work-up is the same as for **24** and **27**.

Compound **28**: R_f=0.32 (4:1 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 2H), 5.26 (d, J=4.0 Hz, 1H), 4.72 (t, J=4.0 Hz, 1H), 4.08 (ddd, J=12.5, 8.5, 4.5 Hz, 1H), 2.78 (m, 2H), 2.1 (m, 5H), 1.73 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 168.9, 157.7, 136.5, 127.3, 83.4, 73.6, 66.7, 53.6, 37.8, 27.9, 25.8, 24.1, 21.1; FTIR (thin film, cm^{-1}) 3314, 2967, 1728, 1376, 1244, 1155, 1014; high-resolution ESI molecular ion calcd for $C_{16}H_{23}O_6N$+Na 348.1418, found: 348.1414; $[\alpha]_D^{25}$ −118.0 (c 0.50, $CHCl_3$).

3.1.9. Preparation of 25. To a 100 mL rb flask was added **24** (252 mg, 0.795 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (112 μL, 0.795 mmol) and 40 mL of acetonitrile. This solution was heated to 50 °C for 36 h. After 36 h, the reaction was concentrated in vacuo (rotary evaporator) and purified by column chromatography on silica gel, eluting with 1:1 ramping polarity to 3:1 ethyl acetate–hexane, to yield 130 mg of **25** (58%) as a pale yellow oil: R_f=0.28 (4:1 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (s, 1H), 5.43 (m, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 2.84 (m, 1H), 2.63 (m, 1H), 2.16 (m, 2H), 2.03 (s, 1H), 1.77 (s, 1H), 1.47 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.9, 146.4, 118.0, 81.5, 71.1, 58.1, 56.3, 30.1, 28.0, 27.1, 21.3; FTIR (thin film, cm^{-1}) 3343, 2935, 1731, 1370, 1242, 1156; high-resolution ESI molecular ion calcd for $C_{15}H_{23}O_4N$+H 282.1700, found: 282.1704; $[\alpha]_D^{25}$ +79.3 (c 1.20, $CHCl_3$).

3.1.10. Preparation of 23. To a 50 mL rb flask was added **27** (149 mg, 0.47 mmol), 1,1,3,3-tetramethylguanidine (112 μL, 0.795 mmol) and 24 mL of toluene. This solution was gently refluxed for 15 h. After this time, the reaction was filtered, concentrated in vacuo (rotary evaporator), and purified by column chromatography on silica gel, eluting with 1:1 ethyl acetate–hexane ramping polarity to 3:1 ethyl acetate–hexane, to yield 110 mg of **23** (82%) as a pale yellow oil: R_f=0.22 (4:1 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (m, 2H), 3.73 (dd, J=6.5, 2.5 Hz, 1H), 3.41 (d, J=8.0 Hz, 1H), 2.85 (ddd, J=17.0, 9.5, 2.0 Hz, 1H), 2.43 (ddd, J=17.0, 6.0, 2.0 Hz, 1H), 2.24 (m, 2H), 2.10 (s, 3H), 1.7 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 170.8, 146.5, 117.4, 81.4, 71.1, 58.6, 58.3, 35.4, 28.9, 27.9, 27.4, 21.2; FTIR (thin film, cm^{-1}) 2977, 2939, 2867, 1733, 1369, 1244, 1155, 1020; high-resolution ESI molecular ion calcd for $C_{15}H_{23}O_4N$+H 282.1700, found: 282.1706; $[\alpha]_D^{25}$ −118.2 (c 1.43, $CHCl_3$).

3.1.11. 5-Acetoxy-2,3,5,6,7,7a-hexahydro-1*H*-indole-2-carboxylic acid methyl ester (32). Into a 10 mL rb flask containing magnetic stirbar and rubber septum was placed indoline **25** (30 mg, 0.11 mmol) dissolved in CH_2Cl_2 (1.25 mL) at room temperature. To the stirred solution was added trifluoroacetic acid (1.25 mL), stirred at ambient temperature for 12 h then concentrated in vacuo and placed under high vacuum for 2 h. The residue was dissolved in 1:1 v/v CH_2Cl_2–MeOH (1 mL of each) and (trimethylsily)-diazomethane (2.0 M in Et_2O, 205 μL) was added dropwise by microliter syringe until gas evolution ceased and the solution remained yellow. The mixture was stirred for 8 h, concentrated in vacuo (rotary evaporator) and the residue was subsequently purified by flash column chromatography on silica gel (gradient elution with 3:1 ethyl acetate–hexane to 100% ethyl acetate) to provide **32** (14 mg, 84%), as a brown oil: R_f=0.15 (3:1 ethyl acetate–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (s, 1H), 5.43–5.42 (m, 1H), 3.91 (dd, J=9.0, 5.0 Hz, 1H), 3.74 (s, 3H), 3.64–3.62 (m, 1H), 2.84 (ddd, J=16.5, 9.0, 1.5 Hz, 1H), 2.70 (ddd, J=16.5, 4.5, 2.0 Hz, 1H), 2.49 (br s, 1H), 2.23–2.13 (m, 2H), 2.05 (s, 3H), 1.56–1.48 (m, 1H), 1.39–1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 171.0, 146.0, 118.1, 71.0, 57.4, 56.4, 52.3, 33.9, 29.9, 27.1, 21.4; FTIR (thin film, cm^{-1}) 2950, 1734, 1441, 1373, 1243, 1138; high-resolution MS (ESI$^+$) calcd for $C_{12}H_{18}O_4N_1$ (M^++H): 240.1230, found: 240.1235; $[\alpha]_D^{25}$ +43.6 (c 0.5, $CHCl_3$).

3.1.12. 5-Acetoxy-2,3,5,6,7,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester (31). Into a 10 mL rb flask containing magnetic stirbar and rubber septum was placed indoline **25** (45 mg, 0.16 mmol) dissolved in CH_2Cl_2 (2 mL) at room temperature. To the stirred solution was added trifluoroacetic acid (2 mL), stirred at ambient temperature for 8 h, then concentrated in vacuo (rotary evaporator) and placed under high vacuum for 2 h. The residue was then dissolved in a mixture of THF (4 mL) and 10% aqueous Na_2CO_3 (4 mL). To the stirred solution was added di-*tert*-butyl dicarbonate (Boc_2O, 42 mg, 0.19 mmol), the mixture was stirred at ambient temperature for 11 h, acidified to pH 3 with 1 M aq HCl and then extracted with ethyl acetate (3×15 mL). The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was subsequently purified by flash column chromatography on silica gel (gradient elution with 5% MeOH–CH_2Cl_2 to 10% MeOH–CH_2Cl_2) to afford **31** (50 mg, 96%) as a yellow gum: R_f=0.18 (5% MeOH–CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (s, 1H), 5.41–5.34 (m, 1H), 4.28–4.18 (m, 2H), 2.87–2.81 (m, 1H), 2.65–2.49 (m, 1H), 2.09–2.22

(m, 1H), 2.04 (s, 3H), 1.48–1.22 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 171.1, 154.9, 153.8, 142.8, 142.3, 120.3, 120.2, 81.1, 81.0, 70.4, 70.2, 67.7, 67.5, 58.6, 58.4, 57.1, 56.7, 34.3, 33.8, 29.7, 29.5, 29.0, 28.4, 28.3, 28.2, 26.9, 26.7, 23.8, 21.3; FTIR (thin film, cm^{-1}) 2978, 1733, 1698, 1478, 1418, 1368, 1243, 1145; high-resolution MS (ESI$^+$) calcd for $C_{16}H_{23}O_6NNa$ (M^++Na): 348.1418, found: 348.1418; $[\alpha]_D^{25}$ −23.2 (*c* 1.0, $CHCl_3$).

3.1.13. Amide 33. Into a 10 mL rb flask containing magnetic stirbar and rubber septum was placed acid **31** (18 mg, 0.55 mmol) and amino ester **32** (13 mg, 0.055 mmol), dissolved in CH_2Cl_2 (1 mL). To this solution was added successively BOP-Cl (21 mg 0.083 mmol) then Et_3N (11 mg, 0.11 mmol). The mixture was then stirred at room temperature for 18 h, water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was subsequently purified by flash column chromatography on silica gel (gradient elution with 1:2 ethyl acetate–hexanes to 2:1 ethyl acetate–hexanes) to provide **33** (18 mg, 60%) as a yellow gum: R_f=0.47 (3:1 ethyl acetate–hexanes); The NMR spectra showed a mixture of amide and carbamate rotamers that did not coalesce on heating in the NMR probe. The compound was therefore partially characterized and taken on to the cyclization step. High-resolution MS (ESI$^+$) calcd for $C_{28}H_{38}O_9N_2Na$ (M^++Na): 569.2470, found: 569.2462.

3.1.14. Acetic acid 9-acetoxy-6,13-dioxo-2,4,4a,6a,7,9,10,11,11a,13,13a,14-dodecahydro-3*H*,6*H*-pyrazino [1,2-*a*;4,5-*a*′] diindol-2-yl ester (34). Into a 10 mL rb flask containing magnetic stirbar and rubber septum was placed dipeptide **33** (9.0 mg, 0.017 mmol), dissolved in CH_2Cl_2 (300 μL), and stirred at room temperature. TFA (60 μL, 0.81 mmol) was then added dropwise over 2 min, the mixture stirred at ambient temperature for 1.5 h, the solution was concentrated in vacuo (rotary evaporator) and placed under high vacuum for 1 h. The residue was dissolved in CH_2Cl_2 (1 mL) to which Et_3N (11.5 μL, 0.083 mmol) was added. The mixture was stirred at ambient temperature for 24 h, concentrated in vacuo (rotary evaporator) and the residue was then purified by flash chromatography (gradient elution with 1:1 ethyl acetate–hexane to 3:1 ethyl acetate–hexane) to afford diketopiperazine **34** (3.3 mg, 49%) as a white solid: mp 259–261 °C; R_f=0.22 (3:1 ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.43 (m, 1H), 4.40–4.24 (m, 2H), 2.86–2.80 (m, 3H), 2.30–2.25 (m, 1H), 2.07 (s, 3H), 1.67–1.60 (m, 1H), 1.56 (s, 3H), 1.41–1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 166.1, 141.5, 121.6, 70.0, 59.5, 57.4, 33.9, 28.4, 27.0, 21.3; FTIR (thin film, cm^{-1}) 2925, 1738, 1649, 1439, 1249, 915; high-resolution MS (ESI$^+$) calcd for $C_{22}H_{26}O_6N_2Na$ (M^++Na): 437.1683, found: 437.1672; $[\alpha]_D^{25}$ −73.6 (*c* 0.5, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2006.05.089.

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50. The Schlenk flask is fitted with a rubber septum on the sidearm. This septum accommodates the argon line and the needle from the syringe pump.

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The allenic Alder-ene reaction: constitutional group selectivity and its application to the synthesis of ovalicin

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Abstract—The scope of the novel allenic Alder-ene reaction using Rh(I) and Ir(I) catalysts has been extended to differentially substituted 1,1,3-trisubstituted allenes. This allenyl substitution pattern can give three possible cross-conjugated triene products. The selectivity of this transformation can be controlled by varying reaction temperature, solvent, and catalyst. Progress toward the synthesis of ovalicin using this triene forming protocol is described.

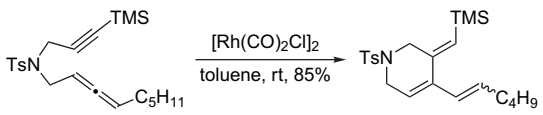
1. Introduction

Transition metal-catalyzed carbon–carbon bond formation is an efficient method to rapidly increase molecular complexity via skeletal reorganization and/or cycloaddition processes.[1] The mild conditions, functional group compatibility, and high regio- and stereoselectivities of these transition metal-catalyzed reactions are just a few reasons for their prominence in natural product synthesis. Transition metal-catalyzed cycloisomerizations such as the formal Alder-ene reaction utilize functionalized enynes or allenynes to access a unique array of cyclic structures.[2] For example, Trost[3] has worked extensively on the intramolecular Alder-ene reaction of 1,6-enynes using palladium or ruthenium to obtain 1,3- or 1,4-dienes, respectively. Ruthenium gives exclusively the 1,4-diene regioisomer while palladium gives regioisomeric ratios dependent on the substrate structure. Trost has also used ruthenium to effect an intermolecular Alder-ene allene–ene coupling to give diene substrates.[4] Buchwald[5] and Takacs[6] formed 1,4-dienes from enynes selectivity using either titanium or iron catalysts, respectively.

Intramolecular Alder-ene reactions of allene–ynes are not as widely studied and only a few examples are known. Both Malacria[7] and Livinghouse[8] used cobalt to effect an intramolecular allenic Alder-ene reaction. Malacria used this cycloisomerization reaction in a synthesis of steroidal analogs,[9] while the triene was obtained as a by-product in 33% yield by Livinghouse. Sato[10] demonstrated an allenic Alder-ene reaction using stoichiometric amounts of titanium.

Recently, rhodium has stepped into the limelight and proven itself as a useful and powerful transition metal catalyst for the Alder-ene reaction.[11] In 2000, Zhang demonstrated the first Rh(I)-catalyzed Alder-ene reaction with 1,6-enynes, yielding 1,4-dienes.[12] Rhodium was beneficial over ruthenium, cobalt, or iron because reactions could be performed at room temperature and the ligands on the catalyst could be easily tuned to accommodate steric or electronic factors in the substrates.[13]

We have previously reported the reaction of Rh(I) with allenynes to produce cross-conjugated trienes. One example is shown in Scheme 1, where allenyne **1** affords an 85% yield of triene **2**.[14] This formal allenic Alder-ene reaction is unique from others because the reaction conditions are used to direct which double bond of the allene reacts. For example, Malacria[7] and Sato[10] reported the same reactivity pattern using cobalt and titanium, respectively; however, π-bond selectivity was obtained using substrate control (sterics and ring strain).[15] Rhodium, unlike other transition metals, was found to give selective cyclization with the distal double bond of the allene regardless of the substitution pattern on the allene or tether length.[16]



1 **2**
[E : Z] = 5 : 1

Scheme 1. Rh(I)-catalyzed allenic Alder-ene reaction.

Cross-conjugated trienes are seldom found in the literature, which may be attributed to a lack of general procedures for

Keywords: Allenes; Alder-ene; Catalysis; Iridium; Rhodium; Trienes.
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the formation of these highly unsaturated systems.[17] Brummond et al. have shown that the formal Alder-ene reaction gives high yields of trienes with moderate *E*/*Z* selectivity for a variety of substrates and that rhodium biscarbonyl chloride dimer is a general catalyst. The *E*/*Z* selectivity was increased by changing the neutral Rh(I) catalyst to a cationic Rh(I) or Ir(I) catalyst; altering selectivity from 5:1 to 13:1 or 99:1, respectively.[14]

The high yields and mild conditions of the Rh(I)-catalyzed allenic Alder-ene reaction motivated us to examine its value in natural product synthesis. The application of this carbocyclization process to the ovalicin/fumagillol class of sesquiterpenoids was the most exciting, due in part to the potentially rapid access to the entire carbocyclic skeleton and the interesting biological activity associated with these compounds (Fig. 1).

Fumagillin (**5**), ovalicin (**4**), and analogs of these compounds have been shown to inhibit angiogenesis in vivo.[18] Angiogenesis is essential for tumor growth and by suppressing this process the tumor does not grow beyond a few cubic millimeters, nor does it metastasize.[19] Fumagillol (**3**) and the analog TNP-470 (**6**) have been found to have an inhibitory effect on the growth and metastasis of various cancers including breast, colon, gastric, renal, ovarian, and prostate.[20] It is known that endothelial cells play a necessary role in angiogenesis, and both ovalicin and TNP-470 were found to inhibit endothelial cell proliferation. However, the mechanism of action for this inhibition is still unclear. Clardy[21] illustrated that fumagillin, ovalicin, and TNP-470 covalently bind to a cobalt-containing enzyme called methionine amino peptidase (MetAP-2), but do not bind to the closely related MetAP-1. It is significant that this binding is selective since inhibition of both MetAP-1 and MetAP-2 is lethal.[22] Methionine amino peptidase-2 removes methionine residues from the N-termini of proteins in a critical co-translational processing event and there is a strong correlation between inhibition of endothelial cell proliferation and inhibition of MetAP-2.[23] However, the significance of the binding is still under great debate since recently it was reported that MetAP-2 function is independent of endothelial cell production.[24] Despite the enigmatic mechanisms of action for these natural products, they are still under investigation in the biological and clinical sector and are synthetically popular targets.[25]

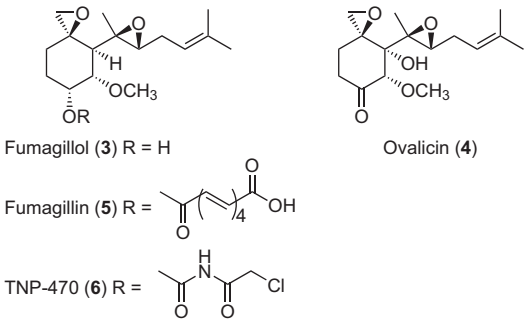


Figure 1. Structure of fumagillol, fumagillin, TNP-470, and ovalicin.

Corey was the first to synthesize (±)-ovalicin in 1985 in 12 steps. After the novel formation of an epoxy ketone, he stereoselectively added the lithiated diene to give the desired carbocyclic skeleton (Fig. 2).[26] Subsequently, Corey published an asymmetric synthesis of ovalicin by preparing the epoxy ketone via an asymmetric dihydroxylation reaction.[27] Bath[28] and Barco[29] gain access to (−)-ovalicin by manipulating naturally occurring optically pure building blocks L-quebrachitol and (−)-quinic acid, respectively. The most recent syntheses of (−)-ovalicin were reported by Takahashi who starts with a simple sugar, D-mannose, while also featuring ring closing metathesis and Hayashi whose approach is similar to that of Corey.[30]

Our retrosynthetic analysis of ovalicin (**4**) is outlined in Scheme 2. Conversion of **7** to ovalicin will be accomplished by a stereoselective hydroxyl directed epoxidation of the double bond, and conversion of the primary hydroxyl group into the terminally trisubstituted double bond via an oxidation and homologation sequence similar to the strategy used by Taber in his synthesis of fumagillin.[31] The highly functionalized cyclohexanone **7**, in turn, can be prepared via a series of selective oxidations carried out on triene **8**.

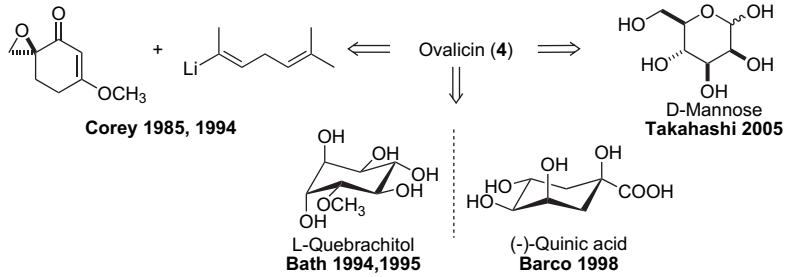
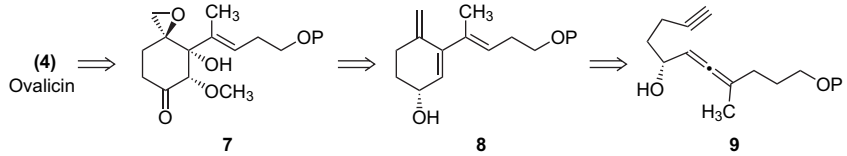
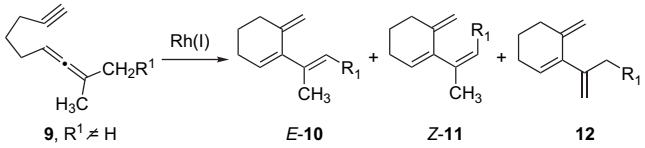


Figure 2. Previous synthetic strategies.



Scheme 2. Retrosynthetic analysis of ovalicin (**7**).

We plan to use the secondary hydroxyl group to direct the regio- and stereoselectivities of the oxidation reactions. The successful conversion of allene **9** to the desired triene **8** will require a regio- and stereoselective β-hydride elimination step. For example, when 1,1,3-trisubstituted allene **9** is used, β-hydride elimination can occur to give *E*-**10**, *Z*-**11**, and the constitutional isomer **12** (Scheme 3). Selective transformations of this type have not been previously addressed in our group[32] and to the best of our knowledge, little is known about the selectivity of these elimination reactions.

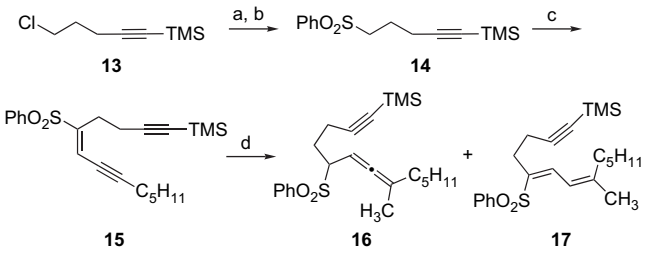


Scheme 3. Rh(I)-catalyzed Alder-ene reaction.

Trost observed competing β-hydride eliminations in a Pd-catalyzed cycloisomerization of 1,6-enynes; however, these cases were different because the elimination reactions gave either 1,3-diene or 1,4-diene products. Trost was able to alter the product distribution by changing the functional groups on the substrates.[33] Bäckvall's[34] Pd-catalyzed carbocyclization of ene–allenes gave constitutional isomers resulting from β-hydride elimination of differentially substituted allenes, which produced 1,4-dienes in a 1:1 ratio. Altering the functional groups on the starting material gave complete constitutional group selectivity. Because so little is known about the selectivity of this reaction, we initiated our synthesis of ovalicin by first examining the selectivity of the key Alder-ene reaction on a readily available precursor. Moreover, since we have previously demonstrated that *E*/*Z* isomeric ratios can be significantly increased by altering the catalyst,[13] we planned on first taking advantage of reagent control and then if necessary substrate control.

2. Results and discussion

With an eye toward the synthesis of ovalicin, model sulfonyl allenyne **16** was prepared to explore the constitutional group selectivity of the β-hydride elimination in the Alder-ene reaction. Reaction of commercially available 5-chloro-1-(trimethylsilyl)-1-pentyne (**13**) with NaI/acetone gave 5-iodo-1-(trimethylsilyl)-1-pentyne in a 99% yield (Scheme 4).



Scheme 4. Preparation of allenyne **16**. Reagents and conditions: (a) NaI, acetone, reflux, 99%; (b) benzenesulfinic acid sodium salt, DMF, 50 °C, 76%; (c) 2-octynal, *n*-BuLi, THF, −78 °C, quench Ac_2O; DBU, THF, 0 °C, 60% (three steps); (d) CuI, MeLi, TMSOTf, ether, −30 °C, 67% [**16**:**17**=7:1].

Treatment of the resulting iodide with benzenesulfinic acid sodium salt formed sulfone **14** in 2 h in 76% yield.[35] Addition of α-sulfonyl anion to 2-octynal followed by quenching with acetic anhydride gave the crude acetate as a 1:1 mixture of diastereomers. This diastereomeric mixture was reacted with DBU to give enyne *E*-**15** selectively in 60% yield in three steps. Then a conjugate 1,6-addition of lithium dimethylcuprate to enyne **15** gave a mixture of allene **16** and diene **17** in 67% yield.[36] Unfortunately, compounds **16** and **17** were only separable via HPLC; therefore, they were taken on as a mixture to the next step. Treatment of sulfonyl allene **16** and diene **17** with 5 mol% of $[Rh(CO)_2Cl]_2$ gave trienes *E*-**18**, *Z*-**18**, **19**, and unreacted **17** in a 90% yield as a 3:5:1 ratio of trienes, respectively. This is a rare example of the *Z*-isomer **18** predominating in any transition metal-catalyzed Alder-ene reaction (entry 1, Table 1).[37]

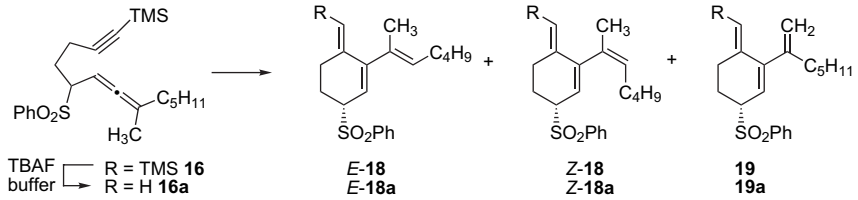
This seemingly anomalous result can be understood by considering the metallocycle intermediates **I** and **II** (Fig. 3). In order for β-hydride elimination to occur the dihedral angle of the Rh–C–C–H_a arrangement must be almost syn periplanar. Two competing conformations are depicted in **I** and **II**, leading to the *E*-**18** and *Z*-**18** isomers, respectively. Conformation **I** reveals an eclipsing interaction between the methyl and butyl groups as well as possible steric interference between the butyl group and the ligands on the rhodium. Conformation **II** alleviates these steric and eclipsing interactions but possesses $A^{1,3}$ strain. Thus, it is postulated that the *Z*-isomer is formed preferentially via the selective reaction of conformation **II**. Interestingly, removal of the TMS moiety from the terminus of the alkyne caused a reversal in the *E*/*Z* selectivity (compare entries 2 and 12, Table 1).

Triene *E*-**18** is the desired isomer for the synthesis of ovalicin; therefore, a systematic study to obtain *E*-**18** selectively was initiated and the results are summarized in Table 1. Reaction of allenyne **16** with $[Rh(CO)_2Cl]_2$ gave *Z*-**18** as the major product at 50 °C and room temperature (entries 1 and 2, Table 1). Because cationic Rh(I) or Ir(I) catalysts give *E*-isomers preferentially,[13] allene **16** was subjected to $[Rh(COD)Cl]_2$/$AgBF_4$. This afforded *E*-**18** in preference to *Z*-**18**, but significant quantities of the constitutional isomer **19** were also formed (*E*-**18**:**19**=1:1) (entry 3, Table 1). Exposure of **16** to the cationic iridium conditions ($[Ir(COD)Cl]_2$/$AgBF_4$) gave a 9:1:5 ratio of trienes *E*-**18**:*Z*-**18**:**19**, respectively (entry 4, Table 1). The use of cationic Rh(I) and Ir(I) catalysts reversed the *E*/*Z* selectivity (1:2 to 9:1), as expected, yet decreased the constitutional group selectivity (8:1 to 2:1) (entries 1–4, Table 1). We do not have an explanation for these results at this time.

Next, a series of reactions were performed on allene **16** using $[Ir(COD)Cl]_2$/$AgBF_4$ as the catalyst (entries 4–7, Table 1) and varying only the temperature. These experiments revealed an increase in selectivity at lower reaction temperature. At −30 °C a 6:1 *E*/*Z* isomeric ratio and a 7:1 constitutional isomeric ratio were obtained (entry 7, Table 1). This produced a 3:1 ratio (*E*-**18** to *Z*-**18**+**19**) and confirms that the regio- and stereoselectivity can be governed by the reaction conditions.

The Alder-ene reactions summarized in Table 1 illustrate that one constitutional isomer (*E*/*Z*-**18**) is preferred over the other (**19**). The selectivity between the constitutional

Table 1. Results of rhodium-catalyzed Alder-ene reaction with sulfonyl allenynes **16** and **16a**[a]



Entry	Substrate	Catalyst[b]	Solvent	*t* (°C)	*E*-**18**:*Z*-**18**:**19**	**18**:**19**	*E*-**18**:*Z*-**18**	Yield (%)
1	**16**	A	Toluene	50	3:5:1	8:1	3:5	73[d]
2	**16**	A	Toluene	rt	2:4:1	6:1	1:2	93
3	**16**	B	DCE	rt	1:0:1	1:1	1:0	97
4[c]	**16**	C	DCE	rt	9:1:5	2:1	9:1	44[d]
5	**16**	C	DCE	0	4:1:1	5:1	4:1	80
6	**16**	C	DCE	−10	5:1:2	3:1	5:1	
7	**16**	C	DCE	−30	6:1:1	7:1	6:1	80
8[c]	**16**	D	Acetone/DCE	rt	4:1:2	3:1	4:1	85
9	**16**	D	Acetone/DCE	−30	4:1:1	5:1	4:1	80
10	**16**	D	Toluene	−40	NR			
11	**16**	D	Toluene	−60	NR			
12	**16a**	A	Toluene	rt	2:1:1	3:1	2:1	87

[a] For reaction conditions see Section 4. Product ratios were determined by integration of olefin peaks in the ^{1}H NMR.
[b] A: 3–5 mol % $[Rh(CO)_2Cl]_2$; B: 5 mol % $[Rh(COD)Cl]_2$, 10 mol % $AgBF_4$; C: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $AgBF_4$; D: 5 mol % $[Ir(COD)Cl]_2$, 10 mol % $In(OTf)_3$.
[c] Desilylated trienes *E*/*Z*-**18a** and **19a** were obtained.
[d] Nonpolar impurity was seen during reaction.

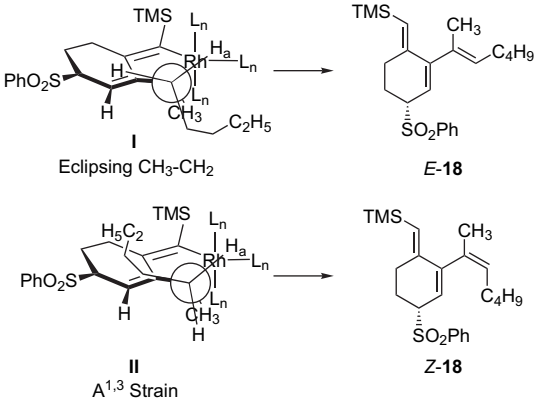


Figure 3. Explanation of *E*/*Z* selectivity.

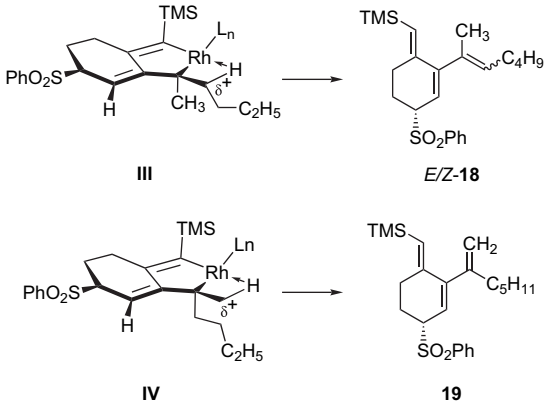
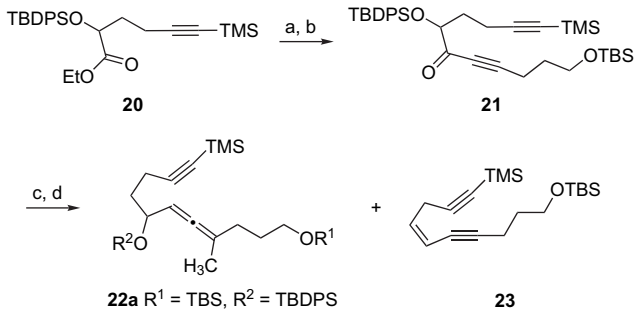


Figure 4. Explanation of constitutional group selectivity.

isomers is rationalized by the ability of either group (methylene (**18**) or methyl (**19**)) to stabilize the partial positive charge developing in the β-hydride elimination step of the reaction. Consequently, the β-hydride elimination is more favorable from the methylene group in **III** rather than the methyl group in **IV**; ultimately favoring elimination from intermediate **III** to give *E*/*Z*-**18**, predominately (Fig. 4).

These studies suggested that we could not obtain the desired selectivity by only altering the reaction conditions, and needed some assistance from the substrate. With this in mind we turned our focus on the preparation of allenyne **22**, which is particularly advantageous due to the changes that can be made to R^1 and R^2, in addition to being a well-suited substrate for the synthesis of ovalicin/fumagillol. Allene **22** is obtained by the addition of 4-magnesium-bromo-1-(trimethylsilyl)-1-butyne to ethyl glyoxylate followed by protection of the newly formed α-hydroxy group to give silyl ether **20** in a 65% combined yield (Scheme 5).[38] Ester **20** was transformed into the Weinreb amide in an 80% yield with MeNHOMe·HCl and *i*-PrMgCl. Addition of the lithium anion of silyl protected 4-pentyn-1-ol[39] to the Weinreb amide gave alkynyl ketone **21**.[40] Exposure of ketone **21** to the Luche reduction conditions gave the desired propargylic alcohol in a 58% yield (over two steps) as a single diastereomer by ^{1}H NMR. The propargylic alcohol was converted to a mesylate with Et_3N and MsCl. After workup the crude mesylate was subjected to lithium dimethylcuprate at −78 °C forming allenyne **22a** and enyne **23** in 80% yield in a 23:1 ratio, respectively.[41] Treatment of allenyne **22a** with $[Rh(CO)_2Cl]_2$ gave an 83% yield of trienes *E*-**24a**, *Z*-**24a**, and **25a** in a 13:5:2 ratio, respectively (entry 1, Table 2).[42] These *E*/*Z* ratios were similar to those observed previously, but are interesting considering that the *E*/*Z* ratios were reversed for the sulfone system (*E*/*Z*-**18**) (entries 1 and 2, Table 1). It is possible that this reversal is due to the differing electronic natures of the sulfone group of **16** and the disilyl ether groups of **22**. This is evidenced by the difference in the reaction rates for **16** and **22** (30 min vs 24 h at rt, respectively). Hence, the slower reaction revealed an increase in the amount of the thermodynamic product, *E*-**24a**.



Scheme 5. Preparation of allenyne **22**. Reagents and conditions: (a) MeNHOMe·HCl, *i*-PrMgCl, THF, 0 °C, 80%; (b) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, −78 to 0 °C; (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, −20 to 0 °C, 58% (two steps); (d) MsCl, TEA, CH_2Cl_2, 0 °C; CuI, MeLi, THF, −78 °C, 80% [**22a**:**23**=23:1].

Allenyne **22a** was subjected to the optimized reaction conditions worked out for sulfone **16** $[Ir(COD)Cl]_2/AgBF_4$, which led to complete decomposition of the starting material (entry 4). Switching the additive from $AgBF_4$ to $In(OTf)_3$ in DCE gave good selectivity but only a trace amount of product formation and mostly starting material were observed by ^1H NMR. The insolubility of indium triflate in DCE is a likely reason for the reaction inhibition; however, changing from DCE to acetone, a solvent that indium triflate is soluble in, resulted in complete decomposition of the starting material.

Since the cationic iridium conditions were not applicable to this system, only moderate variations in rhodium-catalyzed reaction conditions could be made. Changing the solvent in the reaction conditions from toluene to DCE showed a rate enhancement, (12 h at 55 °C to 30 min at rt) and a reversal in *E*/*Z* selectivity (7:3 to 4:6; see entries 10 vs 11 and 13 vs 14). More polar solvents are known to increase the reaction rates in Pd-catalyzed Alder-ene reactions[43] and Rh-catalyzed cycloadditions[44] due to their ability to stabilize charge separation. Also, changing the solvent from toluene to DCE gave isomeric ratios closer to that seen for the sulfone system (3:5:1 vs 4:5:1; compare entry 1, Table 1 to entry 11, Table 2). Altering the temperature had no effect on the *E*/*Z* selectivity or constitutional selectivity when toluene was used as the solvent (compare entries 1 vs 2, 5 vs 6, and 9 vs 10, Table 2); however, decreasing the reaction temperature when using DCE as the solvent further increased the amount of kinetic product shifting the *E*/*Z* ratio from 1:1 to 1:4 (entry 15 vs 16, Table 2).

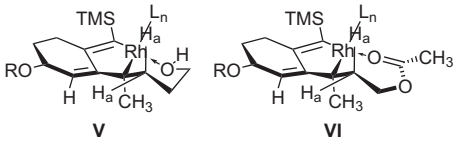
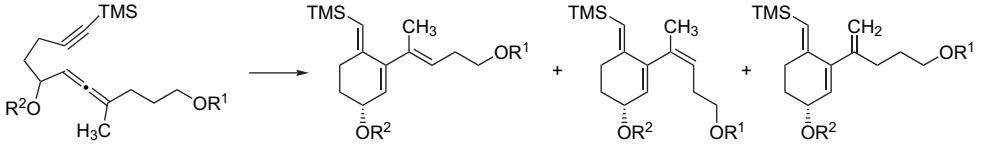


Figure 5. Explanation of changes in constitutional group selectivity.

Further attempts were made to increase the formation of the desired *E*-**24** by modifying R^1 of **22**. Changing R^1 from silyl ether to ester functionality revealed a slight decrease in constitutional group selectivity (9:1 to 4:1) and *E*/*Z* selectivity (7:3 to 6:4; compare entries 1 and 5). The free hydroxyl group had a similar, yet more enhanced effect decreasing the constitutional group selectivity from approximately 9:1 to 3:1 ratio, and it did not effect on the *E*/*Z* selectivity (compare entries 3 vs 8 and 11 vs 15). This increase in the amount of isomer **25** is believed to result from coordination of the free hydroxyl **V** and ester group **VI** to the rhodium metallocycle (Fig. 5). Syn periplanar alignment of the Rh–C–C–H_a

Table 2. Results of rhodium-catalyzed Alder-ene reaction with sulfonyl allenynes **22a–f**[a]



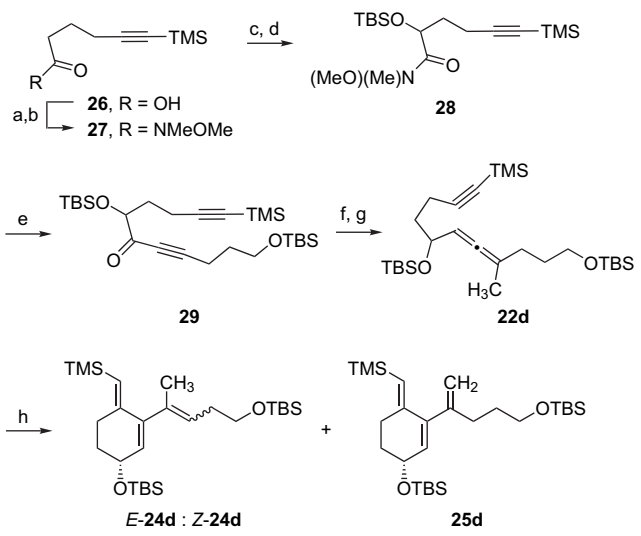
Entry	Substrate	R^1	R^2	Catalyst[b]	Solvent	*t* (°C)	*E*-**24**:*Z*-**24**:**25**	**24**:**25**	*E*-**24**:*Z*-**24**	Yield (%)
1	**22a**	TBS	TBDPS	A	Toluene	55	13:5:2	18:2	7:3	83
2	**22a**			A[c]	Toluene-d_8	rt	11:6:3	17:3	6:4	
3	**22a**			A	DCE	rt	9:8:3	17:3	5:5	55
4[d]	**22a**			B	DCE	rt	13:0:7	13:7	10:0	NA
5	**22b**	Ac	TBDPS	A	Toluene	55	10:6:4	16:4	6:4	87
6	**22b**			A	Toluene	rt	11:6:3	17:3	6:4	85
7	**22b**			C	DCE	rt	12:3:5	15:5	8:2	67[e]
8	**22c**	H	TBDPS	A	DCE	rt	5:7:8	12:8	4:6	50
9	**22d**	TBS	TBS	A	Toluene	80	12:6:2	18:2	7:3	**85**
10	**22d**			A	Toluene	55	12:5:3	17:3	7:3	95
11[f]	**22d**			A	DCE	55	8:10:2	18:2	4:6	
12[d]	**22d**			B	DCE	55				NA
13[f]	**22e**	Ac	TBS	A	Toluene	rt	11:6:3	17:3	6:4	
14	**22e**			A	DCE	rt	8:9:3	17:3	5:5	60
15	**22f**	H	TBS	A	DCE	rt	7:8:5	15:5	5:5	66
16	**22f**			A	DCE	0	3:10:7	13:7	2:8	60

[a] For reaction conditions see Section 4. Product ratios were determined by integration of olefin peaks in the ^1H NMR.
[b] A: 5–10 mol % $[Rh(CO)_2Cl]_2$; B: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $In(OTf)_3$; C: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $AgBF_4$.
[c] Catalyst (1 equiv) was used; no yield was calculated.
[d] Starting materials were recovered and experiments were irreproducible.
[e] Yield includes a mixture of inseparable by-products.
[f] Large amount of product was obtained; exact yield was not calculated.

during the β-hydride elimination step is conformationally hindered by this coordination, leading to an increase in the formation of triene **25**.[45]

Allenynes **22b** and **22c** were subjected to the iridium conditions ($[Ir(COD)Cl]_2/AgBF_4$) in hopes that they would tolerate these conditions better than the bis-silylated allenyne **22a**. Trienes *E*/*Z*-**24b** and **25b** were obtained in a 67% yield; however, the yield included a mixture of inseparable by-products and the reaction was irreproducible (entry 7, Table 2). Subjection of allenyne **22c** to $[Ir(COD)Cl]_2/AgBF_4$ led to complete decomposition of the starting material.

After finding the best isomeric ratios with the bis-silylated allenyne systems (**22a** and **22d**) we decided to separate our desired *E*-**24** isomer and turned our attention to the functionalization of the triene systems toward the synthesis of ovalicin. Diverging from the initial route, esterification of carboxylic acid **19** with MeI and $KHCO_3$ gave a 76% yield of ester **26** (Scheme 6). Reaction of **26** with MeNHOMe·HCl and *i*-PrMgCl generates amide **27** in a 91% yield. Subjection of amide **27** to 1.5 equiv of sodium hexamethyldisilazide and 1.5 equiv of 2-(phenylsulfonyl)-3-phenyloxaziridine gave a 86% yield of the α-hydroxy amide. The α-hydroxyl group was protected as a *tert*-butyldimethylsilyl ether using Et_3N and TBSOTf to give amide **28**, which in turn was subjected to the lithium anion of *tert*-butyldimethyl(pent-4-ynyloxy)-silane to give a 77% yield of alkynone **29**.



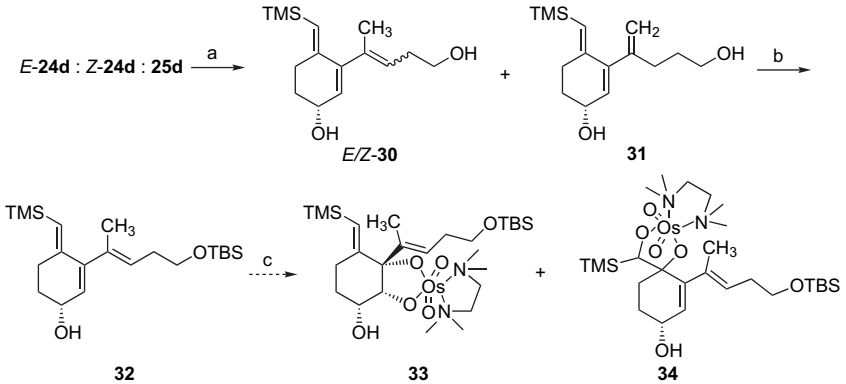
Scheme 6. Alternative preparation of trienes *E*/*Z*-**24** and **25**. Reagents and conditions: (a) $KHCO_3$, MeI, DMF, 76%; (b) MeNHOMe·HCl, *i*-PrMgCl, THF, 0 °C, 91%; (c) NaHMDS, PhNOCHPh, THF, 86%; (d)TEA, TBSOTf, CH_2Cl_2, 94%; (e) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, −78 to 0 °C, 77%; (f) $CeCl_3·7H_2O$, $NaBH_4$, −20 to 0 °C, 88%; (g) MsCl, TEA, CH_2Cl_2, 0 °C; CuI, MeLi, THF, −30 °C, 86% [**22d**:**23**=7:1]; (h) $[Rh(CO)_2Cl]_2$, toluene, 80 °C, 95% [*E*-**24d**:*Z*-**24d**:**25d**=6:3:1].

Ketone **29** was reduced using Luche conditions to yield a propargylic alcohol in a 7:1 diastereomeric ratio. The diastereomers were not separated but taken on to the next step. The propargylic alcohol was converted to its mesylate using Et_3N and MsCl, then after workup the crude mesylate was subjected to lithium dimethylcuprate. Allenyne **22d** was obtained in an 86% yield as a 7:1 diastereomeric ratio as seen by ^1H NMR. Treatment of allenyne **22d** with $[Rh(CO)_2Cl]_2$ and heating to 80 °C gave trienes *E*-**24d**/*Z*-**24d**/**25d** in a 6:3:1 ratio, respectively, and in 95% yield.[46]

Separation of these trienes required removal of both of the silyl ether protecting groups (Scheme 7).[47] Buffering this deprotection reaction was essential, since decomposition of the trienes occurred in the absence of NH_4Cl. After 12 h at 50 °C, complete bis-desilylation was observed, giving trienes *E*/*Z*-**30** and **31** in 92% yield. The trienes were separated using silica gel chromatography; eluting with isopropanol/pentanes. The primary hydroxyl group on *E*-**30** was selectively protected using Et_3N and TBDMSCl giving a 75% yield of triene **32**. Next, a selective dihydroxylation of the endocyclic double bond of **32** was tested via a hydroxyl directed dihydroxylation protocol developed by Donohoe.[48] When triene **32** was subjected to TMEDA and 1 equiv of OsO_4 in CH_2Cl_2 at −78 °C, osmylation to occured forming the stable osmate esters **33** and a by-product **34** in a 6:1 ratio. Unfortunately, a small discrepancy in the ^1H NMR prevents us from knowing conclusively whether we formed our desired product **33**. Future work entails complete determination of the dihydroxylation product followed by further steps to complete the synthesis of ovalicin (**7**).

3. Conclusion

In summary, Rh(I)-catalyzed allenic Alder-ene reaction of **16** and **22a–f** leads to the formation of trienes *E*/*Z*-**18**,



Scheme 7. Attempted dihydroxylation of triene *E*-**30**. Reagents and conditions: (a) TBAF, NH_4Cl, THF, 50 °C, 92%; (b) TBDMSCl, TEA, CH_2Cl_2, 75%; (c) TMEDA, OsO_4, CH_2Cl_2, −78 °C, 90%, (**33**:**34**=6:1).

E/*Z*-**24a–f**, **19**, and **25** in good yields and moderate regioselectivities (Tables 1 and 2). The regioselectivities of the Alder-ene reaction are found to be dependent on a number of factors: temperature, solvent, catalyst (cationic vs neutral), and the ability of the substrate to coordinate with the catalyst. Furthermore, the products from the allenic Alder-ene reaction are useful substrates for further functionalization; and in turn will be a synthetically useful intermediate for the synthesis of ovalicin (**4**).

4. Experimental

4.1. General

All reactions were performed using syringe–septum cap techniques under a nitrogen atmosphere and glassware was flame dried prior to use. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (DCM) were purified with alumina using the Sol-Tek ST-002 solvent purification system. Toluene, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and triethylamine (Et_3N) were freshly distilled from CaH_2 prior to use. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was distilled from phosphorus pentoxide (P_2O_5) and stored in a septum sealed flask in the freezer. Copper iodide (CuI) was purified by following the procedure in Ref. 49.

Purification of the products by flash chromatography was performed using silica gel (32–63 μm particle size, 60 Å pore size) purchased from SAI. TLC analyses were performed on EM Science Silica Gel 60 F_{254} plates (250 μm thickness). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm×10 mm) or Varian Pursuit C8 column (5 μm packing, 250 mm×10 mm).

Melting points were determined using a Laboratory Devices Mel-Temp II apparatus. All ^1H and ^{13}C spectra were obtained on either Bruker Avance 300 MHz or Bruker Avance DRX 500 MHz instrument, and chemical shifts (δ) were reported relative to residual peak $CHCl_3$ or toluene. All NMR spectra were obtained at room temperature unless otherwise specified and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constant(s), number of protons. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high-resolution mass spectrometer. ES low-resolution mass spectrometry was performed on an HPMSD 1100 LC/MS and high-resolution was performed on ESI Biosystem time of flight mass spectrometer.

4.2. Preparation of compounds 14–32

4.2.1. 1-Phenylsulfonyl-5-(trimethylsilyl)-4-pentyne (14). To a solution of 5-chloro-1-(trimethylsilyl)-1-pentyne (4.47 mL, 22.9 mmol) in 8 mL of acetone was added NaI (5.15 g, 34.4 mmol). The mixture was brought to reflux and the progress of the reaction was monitored by ^1H NMR spectroscopy. After 24 h the mixture was quenched by addition of water and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexanes to afford the iodide (6.06 g, 99%) as a colorless liquid. To a solution of 5-iodo-1-(trimethylsilyl)-1-pentyne (11.3 g, 42.3 mmol) in 50 mL of DMF was added anhydrous benzenesulfinic acid sodium salt (8.34 g, 50.7 mmol). The mixture was warmed to 50 °C and after 1.5 h complete consumption of starting material was observed by TLC. The mixture was poured into an Et_2O/water mixture. The aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford sulfone **14** (9.08 g, 76%) as a white solid. R_f 0.2 (20% EtOAc/hexanes); mp=33 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.78–1.87 (m, 2H), 2.26 (t, J=6.8 Hz, 2H), 3.15–3.20 (m, 2H), 7.48–7.64 (m, 3H), 7.82–7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.18 (3C), 18.4, 21.7, 54.8, 86.3, 104.2, 127.7 (2C), 129.1 (2C), 133.5, 138.9; IR (neat) 2958, 2175, 1447, 1307 cm^{-1}; MS (GC/MS) *m*/*e* (relative intensity) 280 ($[M-CH_3]^+$, 0.4), 265 (50), 135 (100), 77 (51), 73 (63); HRMS calcd for $C_{13}H_{17}O_2SiS$: 265.0719 $[M-CH_3]^+$; found: 265.0721 $[M-CH_3]^+$.

4.2.2. (5-Benzenesulfonyltridec-5-ene-1,7-diynyl)trimethylsilane (15). To a solution of sulfone **14** (1.00 g, 3.57 mmol) in 15 mL of THF at −78 °C was added *n*-butyllithium (2.70 mL of a 1.6 M hexanes solution, 4.28 mmol) dropwise over 10 min. After 1 h at −78 °C, a solution of 2-octynal (0.53 g, 4.28 mmol) in 3 mL of THF was added via cannula and the mixture was kept at −78 °C for 1 h and then allowed to warm to 10 °C at which time complete consumption of starting material was observed by TLC. The mixture was then cooled to −78 °C and acetic anhydride (1.47 g, 14.4 mmol) was added. The mixture was quenched at ambient temperature with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography eluting with 10% EtOAc/hexanes. The mixture of diastereomers was collected (1.40 g, 3.14 mmol) and azeotroped in vacuo with benzene (3×), diluted with 8 mL of THF, and cooled to 0 °C. DBU (0.52 g, 3.45 mmol) was added to the solution and after 30 min a 10% HCl/ether solution was added to the reaction. The aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford enyne **15** (738 mg, 60% over two steps) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 0.92 (t, J=7.0 Hz, 3H), 1.28–1.45 (m, 4H), 1.59 (qn, J=7.1 Hz, 2H), 2.35–2.47 (m, 4H), 2.59–2.65 (m, 2H), 6.84 (t, J=2.2 Hz, 1H), 7.52–7.67 (m, 3H), 7.87–7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 13.8, 19.0, 19.8, 22.0, 27.8, 28.0, 30.9, 75.0, 85.2, 105.0, 106.7, 122.3, 128.0 (2C), 129.2 (2C), 133.5, 139.1, 148.5; IR (neat) 2958, 2932, 2860, 2213, 2177, 1446 cm^{-1}; MS

(GC/MS) *m/e* (relative intensity) 386 ([M]$^+$, 2), 371 (3), 135 (45), 73 (100); HRMS calcd for $C_{22}H_{30}O_2SiS$: 386.1736; found: 386. 1739.

4.2.3. (5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-yne)-trimethylsilane (16). To a suspension of CuI (1.51 g, 7.94 mmol) in 40 mL of ether at −30 °C was added MeLi (12.4 mL of a 1.3 M diethyl ether solution, 15.8 mmol) dropwise. The mixture was allowed to warm to 0 °C over a 30 min period and it changed from cloudy yellow to a clear solution. The flask was cooled to −50 °C and a solution of enyne **15** (1.53 g, 3.97 mmol) and TMSOTf (0.77 mL, 3.97 mmol) in 20 mL of ether was added dropwise with a cannula. The mixture was kept at −50 to −30 °C for 3 h and then was warmed to −15 °C and kept at that temperature for 7 h before $NH_4Cl_{(aq)}$ and ether were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The Celite was rinsed with ether to assure complete filtration of products. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc/hexanes to afford 1.08 g of a mixture of allene **16** and diene **17** in a 7:1 ratio (by ^{1}H NMR) for a 67% yield. The mixture was taken on to the next step. However, pure allene **16** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=3 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.88 (t, J=6.3 Hz, 3H), 1.19–1.35 (m, 4H), 1.30 (d, J=2.3 Hz, 3H), 1.75–1.90 (m, 4H), 2.18–2.52 (m, 4H), 3.68 (ddd, J=2.8, 8.5, 11.1 Hz, 1H), 4.88–4.97 (m, 1H), 7.53–7.70 (m, 3H), 7.87–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.5 (3C), 14.4, 17.8, 18.2, 22.8, 26.5, 27.3, 31.9, 33.9, 66.1, 84.0, 86.7, 103.2, 105.3, 129.2 (2C), 129.7 (2C), 133.8, 138.4, 206.0; IR (neat) 2957, 2858, 2175, 1950, 1447, 1307 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 402 ([M]$^+$, 0.6), 387 (0.6), 277 (12), 125 (12), 73 (100); HRMS calcd for $C_{23}H_{34}O_2Si_1S_1$: 402.2049; found: 402.2047. Only crude ^{1}H NMR spectra were obtained for diene **17** after desilylation. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=6.7 Hz, 3H), 1.27–1.51 (m, 6H), 1.94 (m, 4H), 2.28–2.37 (m, 4H), 2.52–2.57 (m, 2H), 6.07 (d, J=11.8 Hz, 1H), 7.52–7.66 (m, 4H), 7.86–7.90 (m, 2H).

4.2.4. (5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-yne) (16a). To a solution of allenyne **16** (0.11 g, 0.26 mmol) in 1.3 mL of THF at 0 °C was added a mixture of TBAF (0.26 mL of a 1 M THF solution, 0.26 mmol) and 0.02 mL of pH 7.38 phosphate buffer solution dropwise via syringe. After 1 h the reaction was quenched at room temperature with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with EtOAc (3×). The combined organic layers were washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford 81 mg of allenyne **16a** in 94% yield as a colorless oil (3:1, allene **16a**/diene **17a**). ^{1}H NMR (300 MHz, $CDCl_3$) allene **16a**: δ 0.87 (t, J=7.2 Hz, 3H), 1.12–1.29 (m, 7H), 1.76–1.90 (m, 4H), 1.07 (t, J=2.4 Hz, 1H), 2.18–2.48 (m, 4H), 3.69 (ddd, J=2.9, 8.6, 11.0 Hz, 1H), 4.90–4.96 (m, 1H), 7.53–7.67 (m, 3H), 7.88–7.91 (m, 2H); diene **17a**: δ 0.93 (t, J=6.7 Hz, 3H), 1.27–1.51 (m, 6H), 1.94 (m, 3H), 2.28–2.37 (m, 4H), 2.52–2.57 (m, 2H), 6.07 (d, J=11.8 Hz, 1H), 7.52–7.66 (m, 4H), 7.86–7.90 (m, 2H).

4.3. General procedure for allenic Alder-ene reaction (Table 1)

4.3.1. [4-Benzenesulfonyl-2-(1-methylhept-1*E*-enyl)-cyclohex-2-enylidenemethyl]trimethylsilane (*E*-18), [4-methylene-3-(1-methylhept-1*Z*-enyl)-cyclohex-2-enesulfonylbenzene]trimethylsilane (*Z*-18), and [4-methylene-3-(1-methyleneheptyl)-cyclohex-2-enesulfonylbenzene]-trimethylsilane (19). *Method A*: (entries 1, 2, and 12) to a flame dried test tube was added a mixture of allene **16** and diene **17**, which was then azeotroped under vacuum with benzene and charged with N_2 (3×). Toluene (0.2 M) was added and the test tube was evacuated under vacuum and charged with N_2 three times. Then, 5 mol % $[Rh(CO)_2Cl]_2$ was added at ambient temperature and the system was evacuated and charged with N_2 once more. The reaction was monitored by GC and quenched by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford trienes *E*-**18**, *Z*-**18**, and **19** and recovered **17** or *E*-**18a**, *Z*-**18a**, and **19a**. The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer. Attempted separation of the isomers by chromatography was unsuccessful.

Method B: (entries 3–11) to a flame dried test tube was added a mixture of allene **16** and diene **17**, which was azeotroped under vacuum with benzene (3×). Dichloroethane (0.2 M) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, 10 mol % $[Ir(COD)Cl]_2$ or $[Rh(COD)Cl]_2$ was added followed by 20 mol % $AgBF_4$ (0.05 M dichloroethane solution) or $In(OTf)_3$ (0.05 M acetone solution) and the system was evacuated and charged with N_2 once more. The mixture was monitored by GC and quenched by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford a mixture of trienes *E*-**18**, *Z*-**18**, and **19**, and recovered **17** or *E*-**18a**, *Z*-**18a**, and **19a** depending on conditions (see Table 1). The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer; however, pure trienes *E*-**18a**, *Z*-**18a**, and **19a** were obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=3 mL/min [*E*-**18a** and **19a**], Varian Pursuit C8, 5 μm, 23 °C, H_2O/MeCN=25%, flow rate=5 mL/min [*Z*-**18a**]). ^{1}H NMR (300 MHz, $CDCl_3$) *E*-**18a**: δ 0.93 (t, J=7.0 Hz, 3H), 1.30–1.44 (m, 4H), 1.70 (s, 3H), 1.85–1.98 (m, 1H), 2.00–2.31 (m, 4H), 2.32–2.45 (m, 1H), 3.86–3.98 (m, 1H), 4.89 (s, 1H), 4.92 (s, 1H), 5.27 (t, J=7.2 Hz, 1H), 5.67 (d, J=2.7 Hz, 1H), 7.50–7.70 (m, 3H), 7.85–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 16.9, 22.6, 23.8, 27.9, 29.5, 31.8, 63.2, 114.3, 116.2, 129.1 (2C), 129.5 (2C), 130.6, 134.0, 134.5, 137.3, 140.0, 150.2; ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-**18a**: δ 0.80–0.90 (m, 3H), 1.18–1.28 (m, 6H), 1.74 (s, 3H), 1.90–2.05 (m, 1H), 2.05–2.20 (m, 1H), 2.21–2.35 (m, 1H), 2.40–2.53 (m, 1H), 3.90–3.98 (m, 1H), 4.88 (s, 1H), 4.94 (s, 1H), 5.30–5.38 (m, 1H), 5.56–5.60 (m, 1H), 7.52–7.69 (m, 3H), 7.86–7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.3, 23.3, 24.3, 28.9, 29.7, 32.0, 63.0, 113.4, 117.1, 128.9, 129.0 (2C), 129.2 (2C),

133.7, 133.9, 137.5, 138.8, 146.5; IR (neat) 2956, 2927, 1447, 1306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) constitutional isomer **19a**: δ 0.89 (t, J=6.6 Hz, 3H), 1.00–1.42 (m, 6H), 1.88–2.30 (m, 5H), 2.38–2.49 (m, 1H), 3.88–3.96 (m, 1H), 4.80 (d, J=2.2 Hz, 1H), 4.90–4.99 (m, 3H), 5.67 (d, J=2.8 Hz, 1H), 7.52–7.69 (m, 3H), 7.86–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 22.6, 23.6, 27.9, 29.3, 31.5, 36.1, 63.0, 114.3, 114.5, 117.0, 129.1 (2C), 129.4 (2C), 133.9, 137.2, 139.8, 147.6, 148.9.

4.3.2. 11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (21). To a solution of ester **20** (1.20 g, 2.57 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.38 g, 3.86 mmol) and the flask was cooled to 0 °C. Then *i*-PrMgCl (2.60 mL of a 2.0 M THF solution, 5.15 mmol) was added dropwise and after addition was finished complete consumption of starting material was observed by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10–15% EtOAc/hexanes to afford amide (1.01 g, 80%) as a colorless oil. R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.10 (s, 9H), 1.91–1.98 (m, 2H), 2.36 (dt, J=6.6, 17.1 Hz, 1H), 2.49 (dt, J=7.8, 17.1 Hz, 1H), 2.90 (s, 3H), 3.11 (s, 3H), 4.66 (t, J=5.8 Hz, 1H), 7.33–7.45 (m, 6H), 7.68–7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3C), 15.9, 19.5, 27.0 (3C), 32.2, 33.7, 60.7, 68.9, 84.8, 106.7, 127.3 (2C), 127.5 (2C), 129.5, 129.6, 133.5 (2C), 133.6 (2C), 136.0, 136.2, 173.1; IR (neat) 2959, 2933, 2857, 2174, 1681 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 466 ($[M-CH_3]^+$, 7), 424 (100): HRMS calcd for $C_{26}H_{36}N_1O_3Si_2$: 466.2234 $[M-CH_3]^+$; found: 466.2244 $[M-CH_3]^+$. To a solution of *tert*-butyldimethyl(pent-4-ynyloxy)silane (0.82 g, 4.15 mmol) in 14 mL of THF at −78 °C was added *n*-butyllithium (1.74 mL of a 2.5 M hexane solution, 4.36 mmol) dropwise. The flask was kept at −78 °C for 10 min and then placed in a bath at −20 °C for 20 min. It was then cooled to −78 °C and added to a solution of 2-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.00 g, 2.08 mmol) in 5 mL of THF at −78 °C via cannula. The mixture was then allowed to slowly warm over 2 h to 0 °C at which time complete consumption of starting material was observed by TLC. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford ketone **21** and *tert*-butyldimethyl(pent-4-ynyloxy)silane. The mixture was not separated at this point but pure ketone **21** was obtained for spectroscopic purposes. R_f 0.7 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.13 (s, 9H), 0.90 (s, 9H), 1.12 (s, 9H), 1.66–1.75 (m, 2H), 1.85–2.06 (m, 2H), 2.21–2.41 (m, 4H), 3.65 (t, J=6.5 Hz, 2H), 4.30 (t, J=5.6 Hz, 1H), 7.33–7.47 (m, 6H), 7.64–7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4 (2C), 0.1 (3C), 15.3, 15.7, 18.3, 19.5, 25.9 (3C), 27.0 (3C), 30.7, 33.7, 61.3, 78.2, 79.4, 85.2, 97.7, 106.1, 127.6 (2C), 127.7 (2C), 129.8, 129.9, 133.1 (2C), 133.3 (2C), 135.8, 136.0, 188.3; IR (neat) 2956, 2857, 2211, 2176, 1675 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 603 ($[M-CH_3]^+$, 1.6), 516 (60), 197 (60), 135 (100); HRMS calcd for $C_{35}H_{51}O_3Si_3$: 603.3146 $[M-CH_3]^+$; found: 603.3120 $[M-CH_3]^+$.

4.3.3. 11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-8-methyl-1-trimethylsilylundeca-6,7-dien-1-yne (22a). Ketone **21** and *tert*-butyldimethyl(pent-4-ynyloxy)silane (≈2.1 mmol) were diluted with $CeCl_3\cdot 7H_2O$ (6.83 mL of a 0.4 M methanol solution, 2.73 mmol), cooled to −20 °C, and $NaBH_4$ (0.10 g, 2.73 mmol) was added in one portion. The mixture was allowed to warm to 0 °C and after 30 min complete consumption of starting material was observed by TLC. The reaction was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 3–10% EtOAc/hexanes to afford the alcohol (772 mg, 58%) over two steps. R_f 0.6 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.10 (s, 9H), 1.65–1.91 (m, 3H), 2.12–2.32 (m, 5H), 3.66 (t, J=6.1 Hz, 2H), 3.88 (q, J=5.3 Hz, 1H), 4.30 (m, 1H), 7.37–7.49 (m, 6H), 7.72 (t, J=6.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3 (2C), 0.1 (3C), 15.2, 15.8, 18.3, 19.5, 25.9 (3C), 27.1 (3C), 31.6, 31.9, 61.6, 65.3, 75.5, 79.0, 84.7, 86.2, 106.5, 127.6 (2C), 127.7 (2C), 129.8 (2C), 133.4 (2C), 133.6 (2C), 135.87 (2C); IR (neat) 3451, 2956, 2858, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 620 ($[M]^+$, 0.3), 563 (10), 199 (97), 135 (100); HRMS calcd for $C_{32}H_{47}O_3Si_3$: 563.2833 $[M-C(CH_3)_3]^+$; found: 563.2830 $[M-C(CH_3)_3]^+$. To a solution of 11-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilyl-1-undeca-1,7-diyn-6-ol (0.33 g, 0.51 mmol) in 1.7 mL of CH_2Cl_2 was added Et_3N (96.0 μL, 0.69 mmol) and the solution was cooled to 0 °C. Then MsCl (48.0 μL, 0.62 mmol) was added and after 30 min at 0 °C the reaction mixture was diluted with pentanes. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite and the resulting solution was washed with $NaHCO_{3(aq)}$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a suspension of CuI (0.12 g, 0.62 mmol) in 2 mL of THF at −30 °C was added MeLi (0.64 mL of a 1.6 M diethyl ether solution, 1.03 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C over a 30 min period while it changed from a cloudy yellow to clear solution. It was cooled to −78 °C and a solution of the mesylate in 1.7 mL of THF was added dropwise with a cannula. The reaction mixture was kept at that temperature for 1 h before $NH_4Cl_{(aq)}$ and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc/hexanes to afford allene **22a** (256 mg, 80%) as a colorless oil (23:1, allene **22a**/enyne **23**, ratio based upon integration of peaks in the ^1H NMR). R_f 0.8 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.12 (s, 9H), 0.98 (s, 9H), 1.06 (s, 9H), 1.42–1.52 (m, 2H), 1.60 (d,

J=2.8 Hz, 3H), 1.65–1.90 (m, 4H), 2.25–2.34 (m, 2H), 3.51 (t, J=6.4 Hz, 2H), 4.27–4.38 (m, 1H), 4.95–5.02 (m, 1H), 7.33–7.45 (m, 6H), 7.67–7.71 (m, 4H); IR (neat) 2956, 2858, 2175, 1966 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 618 ([M]$^+$, 5), 561 (100), 199 (94); HRMS calcd for $C_{37}H_{58}O_2Si_3$: 618.3745; found: 618.3751.

4.4. Procedures for data in Table 2

For entries 1–3, 5–11, and 13–16 general procedure for allenic Alder-ene reaction using method A was followed. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

For entries 4 and 12 general procedure for allenic Alder-ene reaction using method B was followed. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

4.4.1. 4-[3-(*tert*-Butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3*E*-en-1-ol (*E*-24c), 4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3*Z*-en-1-ol (*Z*-24c), and 4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-4-en-1-ol (25c). To a flame dried test tube was added allene **22c** (0.01 g, 0.02 mmol), which was azeotroped under vacuum with benzene (3×). Dichloroethane (0.3 mL) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, $[Ir(COD)Cl]_2$ (2.00 mg, 2.00 μmol) was added followed by $AgBF_4$ (85.0 μL of a 0.05 M dichloroethane solution, 4.00 μmol) and the system was evacuated and charged with N_2 once more. The solution was quenched after 1.75 h by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford 9 mg of a mixture of products. This mixture of products was diluted with 1.6 mL of wet MeOH and one drop of water. Then the solution was cooled to 0 °C and K_2CO_3 (0.02 g, 0.11 mmol) was added. It was then allowed to warm to ambient temperature and after 2 h a complete consumption of the starting material was seen by TLC. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford 5 mg of trienes *E*-**24c**, *Z*-**24c**, and **25c** in 60% yield. Pure trienes could be obtained when a larger scale reaction was performed. The minor isomer was separated with silica gel chromatography and the other two isomers were separated on HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=4 mL/min). R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) major isomer *E*-**24c**: δ 0.10 (s, 9H), 1.07 (s, 9H), 1.71 (s, 3H), 1.74–1.83 (m, 2H), 2.15–2.24 (m, 1H), 2.35 (q, J=6.8 Hz, 2H), 2.54–2.62 (m, 1H), 3.67 (dd, J=6.3, 11.9 Hz, 2H), 4.32–4.37 (m, 1H), 5.23 (dt, J=1.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.50 (d, J=3.2 Hz, 1H), 7.35–7.47 (m, 6H), 7.68–7.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) (one extra peak); IR (neat) 3374, 2957, 2929, 2856, 1472, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 4), 199 (94), 73 (100): HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2903; minor isomer at 343 K with unknown TBDPS impurity from prior reaction. * Designates product *Z*-**24c** where peaks were resolved. ^{1}H NMR (300 MHz, toluene-d_8): δ 0.12* (s, 9H), 1.04* (s, 18H), 1.16* (s, 9H), 1.77* (s, 3H), 1.82–1.90 (m, 4H), 2.00–2.12 (m, 2H), 2.16–2.30 (m, 2H), 2.65–2.75* (m, 1H), 3.32–3.40* (m, 2H), 4.50* (dt, J=3.3, 9.5 Hz, 1H), 5.23–5.32* (m, 1H), 5.61* (s, 1H), 5.65* (d, J=3.4 Hz, 1H), 7.16–7.21 (m, 20H), 7.60–7.68* (m, 6H), 7.72–7.79* (m, 4H); IR (neat) 3383, 2957, 2857, 1427 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 55), 199 (85), 73 (100); HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2899; ^{1}H NMR (300 MHz, $CDCl_3$) constitutional isomer **25c**: δ 0.10 (s, 9H), 1.07 (s, 9H), 1.56–1.64 (m, 3H), 1.75–1.85 (m, 2H), 2.16–2.26 (m, 3H), 2.55–2.64 (m, 1H), 3.60 (dd, J=11.6, 6.3 Hz, 2H), 4.34 (m, 1H), 4.82 (d, J=2.3 Hz, 1H), 4.96 (m, 1H), 5.41 (s, 1H), 5.51 (d, J=3.3 Hz, 1H), 7.34–7.47 (m, 6H), 7.68–7.71 (m, 4H); IR (neat) 3373, 2926, 2855, 1463, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 18), 199 (100), 73 (89); HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2882.

4.4.2. 6-Trimethylsilylhex-5-ynoic acid methoxy methyl amide (27). To a solution of acid **26** (0.60 g, 3.26 mmol) in 2 mL of DMF were added $KHCO_3$ (0.82 g, 8.15 mmol) and MeI (1.16 g, 8.15 mmol). The mixture changed from clear to yellow to orange/brown color and was left at ambient temperature. After 24 h complete consumption of the starting material was seen by TLC and the mixture was poured into EtOAc/water solution. The aqueous layer was separated and extracted with EtOAc (3×). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford the ester (499 mg, 76%) as a yellow oil. R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.85 (qn, J=7.2 Hz, 2H), 2.30 (t, J=6.9 Hz, 2H), 2.45 (t, J=7.4 Hz, 2H), 3.69 (s, 3H). To a solution of 6-trimethylsilylhex-5-ynoic acid methyl ester (0.50 g, 2.52 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.37 g, 3.78 mmol) and the flask was cooled to −25 °C. Then *i*-PrMgCl (3.78 mL of a 2.0 M THF solution, 7.56 mmol) was added dropwise and after addition was finished complete consumption of starting material was observed by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% EtOAc/hexanes to afford amide **27** (520 mg, 91%) as a colorless oil. R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.77–1.86 (m, 2H), 2.29 (t, J=6.8 Hz, 2H), 2.54 (t, J=7.4 Hz, 2H), 3.16 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 19.3, 23.2, 30.4, 32.1, 61.1, 85.1, 106.5, 173.8; IR (neat) 3483, 2959, 2901, 2174, 1667 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 227 ([M]$^+$, 10), 212 (18), 167 (65), 73 (100); HRMS calcd for $C_{11}H_{21}N_1O_2Si_1$: 227.1342; found: 227.1341.

4.4.3. 2-(*tert*-Butyldimethylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (28). To a flame dried round bottom flask was added 20 mL of THF and the flask was cooled to −78 °C. NaHMDS (8.58 mL of a 1 M THF solution, 8.58 mmol) was first added and then a solution of amide **27** (1.30 g, 5.72 mmol) in 40 mL of THF was

added. The solution was left at −78 °C for 30 min and then a solution of $PhSO_2NOCHPh$ (2.24 g, 8.58 mmol) in 30 mL of THF was added via cannula. After 30 min complete consumption of the starting material was seen by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$ and allowed to warm to ambient temperature. The stir bar was removed and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solids were diluted with 3:1 hexane/chloroform solution and filtered via gravity filtration. After removal of solvent, the residue was purified by silica gel chromatography eluting with 20% EtOAc/hexanes to afford α-hydroxy amide (1.20 g, 86%). R_f 0.2 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 1.57–1.70 (m, 1H), 1.89–2.06 (m, 1H), 2.37–2.54 (m, 2H), 3.25 (s, 3H), 3.24 (br d, J=4.9 Hz, 1H), 3.72 (s, 3H), 4.49 (t, J=6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3C), 16.0, 32.4, 33.7, 61.4, 67.3, 84.8, 106.2, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 228 ($[M-CH_3]^+$, 40), 155 (30), 73 (100), 61 (91); HRMS calcd for $C_{10}H_{18}N_1O_3Si_1$: 228.1056 $[M-CH_3]^+$; found: 228.1052 $[M-CH_3]^+$. To a solution of 2-hydroxy-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.20 g, 4.93 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added Et_3N (1.37 mL, 9.86 mmol) and then TBSOTf (1.70 mL, 7.40 mmol). After 20 min at 0 °C a complete loss of the starting material was seen by TLC. The solution was quenched with $NH_4Cl_{(aq)}$ and Et_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford **28** (1.65 g, 94%) as a colorless oil. R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.14 (s, 9H), 0.91 (s, 9H), 1.72–1.91 (m, 2H), 2.28–2.51 (m, 2H), 3.19 (s, 3H), 3.72 (s, 3H), 4.72–4.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, −4.7, 0.1 (3C), 16.0, 18.3, 25.8 (3C), 32.7, 33.1, 61.4, 68.0, 85.2, 106.3, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 342 ($[M-CH_3]^+$, 0.1), 300 (80), 73 (100); HRMS calcd for $C_{13}H_{26}NO_3Si_2$: 300.1451 $[M-C(CH_3)_3]^+$; found: 300.1445 $[M-C(CH_3)_3]^+$.

4.4.4. 5,11-Bis-(*tert*-butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (29). To a solution of *tert*-butyldimethyl(pent-4-ynyloxy)silane (1.30 g, 6.51 mmol) in 18 mL of THF at −78 °C was added *n*-butyllithium (4.07 mL of a 1.6 M hexane solution, 6.51 mmol) dropwise. The flask was left at −78 °C for 10 min and then placed in a −20 °C bath for 20 min and then cooled to −78 °C and added to a solution of amide **28** (1.55 g, 4.34 mmol) in 9 mL of THF at −78 °C via cannula. The mixture was then allowed to slowly warm over 2 h to −10 °C and the temperature was kept at −10 °C for 30 min at which time complete consumption of starting material was observed by TLC. The solution was quenched with $NH_4Cl_{(aq)}$, the stir bar was removed, and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1–5% EtOAc/hexanes to afford ketone **29** (1.66 mg, 77%). R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 0.91 (s, 9H), 1.70–1.86 (m, 3H), 1.87–2.01 (m, 1H), 2.34 (t, J=6.6 Hz, 2H), 2.47 (t, J=7.1 Hz, 2H), 3.67 (t, J=5.8 Hz, 2H), 4.24 (dd, J=3.8, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4 (2C), −5.2, −4.6, 0.1 (3C), 15.7, 15.8, 18.2 (2C), 25.8 (3C), 25.9 (3C), 30.8, 33.3, 61.2, 77.5, 79.3, 85.7, 97.5, 105.9, 189.3; IR (neat) 2956, 2930, 2858, 2211, 2176, 1676 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 479 ($[M-CH_3]^+$, 2), 269 (58), 73 (100); HRMS calcd for $C_{25}H_{47}O_3Si_3$: 479.2833 $[M-CH_3]^+$; found: 479.2844 $[M-CH_3]^+$.

4.4.5. 5,11-Bis-(*tert*-butyldimethylsilyloxy)-8-methyl-1-trimethylsilylundeca-6,7-dien-1-yne (22d). The ketone **29** (0.44, 0.89 mmol) was diluted with a solution of $CeCl_3\cdot 7H_2O$ (2.89 mL of a 0.4 M solution in methanol, 1.16 mmol), cooled to −20 °C, and $NaBH_4$ (0.04 g, 1.16 mmol) was added in one portion. The mixture was allowed to warm to 0 °C and after 30 min complete consumption of the starting material was observed by TLC. The solution was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford alcohol (388 mg, 88%) as a 7:1 diastereomeric ratio (based upon integration of peaks in the ^{1}H NMR). * Designates major diastereomer where peaks were resolved. R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.12 (s, 15H), 0.87 (s, 9H), 0.90 (s, 9H), 1.63–1.91 (m, 4H), 2.23–2.32 (m, 4H), 2.38 (d, J=6.7 Hz, 1H), 3.65 (t, J=6.0 Hz, 2H), 3.81–3.91 (m, 1H), 4.15–4.22* (m, 1H), 4.32–4.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ −5.4 (2C), −4.50, −4.47, 0.0 (3C), 15.2, 15.9, 18.1, 18.2, 25.9 (6C), 31.6, 32.2, 61.6, 65.3, 74.2, 79.5, 85.1, 85.7, 106.6; IR (neat) 3456, 2956, 2857, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 496 ($[M]^+$, 0.2), 307 (4), 73 (100); HRMS calcd for $C_{22}H_{43}O_3Si_3$: 439.2520 $[M-C(CH_3)_3]^+$; found: 439.2526 $[M-C(CH_3)_3]^+$. To a solution of 5,11-bis-(*tert*-butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-ol (0.39 g, 0.78 mmol) in 2.6 mL of CH_2Cl_2 was added Et_3N (140 μL, 1.0 mmol) and the solution was cooled to 0 °C. Then MsCl (73 μL, 0.94 mmol) was added and after 30 min at 0 °C the mixture was diluted with pentanes. The mixture was then filtered through a sintered glass funnel of medium porosity packed with Celite and the resulting solution was washed with $NaHCO_{3(aq)}$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a suspension of CuI (0.18 g, 0.94 mmol) in 3.1 mL of THF at −30 °C was added MeLi (977 μL of a 1.6 M diethyl ether solution, 1.56 mmol) dropwise. The mixture was allowed to warm to 0 °C over a 30 min period while it changed from a cloudy yellow to clear solution. It was then cooled to −78 °C and a solution of mesylate in 2.6 mL of THF was added dropwise with a cannula. The mixture was kept at that temperature for 45 min before $NH_4Cl_{(aq)}$ and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue.

The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 1% EtOAc/hexanes to afford allene **22d** (330 mg, 86%) as a 7:1 allene **22d**/Ene-yne **23** ratio (based upon integration of peaks in the ^{1}H NMR). Pure allene **22d** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=1%, flow rate=3 mL/min). R_f 0.8 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.15 (s, 9H), 1.59–1.82 (m, 7H), 1.90–2.10 (m, 2H), 2.29 (t, J=7.3 Hz, 2H), 3.63 (t, J=6.4 Hz, 2H), 4.16–4.26 (m, 1H), 4.95–5.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3 (2C), −4.9, −4.3, 0.1 (3C), 16.1, 18.2, 18.3, 19.3, 25.9 (3C), 26.0 (3C), 30.2, 31.0, 37.4, 62.8, 70.5, 84.5, 94.7, 100.9, 107.3, 199.7; IR (neat) 2956, 2857, 2176, 1965 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 494 ([M]$^+$, 1.2), 479 (1.5), 269 (45), 73 (100); HRMS calcd for $C_{27}H_{54}O_2Si_3$: 494.432; found: 494.3442.

4.4.6. 7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl acetate (22e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.14 (s, 9H), 0.89 (s, 9H), 1.60–1.81 (m, 7H), 1.95–2.05 (m, 5H), 2.25–2.31 (m, 2H), 4.08 (t, J=6.6 Hz, 2H), 4.22 (q, J=6.2 Hz, 1H), 4.98–5.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.9, −4.4, 0.1 (3C), 16.1, 18.1, 18.2, 20.9, 25.8 (3C), 26.7, 30.1, 37.4, 64.0, 70.2, 84.6, 95.2, 100.2, 107.2, 171.1, 199.7; IR (neat) 2956, 2929, 2174, 1744 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 422 ([M]$^+$, 38), 365 (45), 269 (60), 73 (100); HRMS calcd for $C_{23}H_{42}O_3Si_2$: 422.2673; found: 422.2664.

4.4.7. 7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl-1-ol (22f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 1.62–1.78 (m, 7H), 1.95–2.08 (m, 2H), 2.20–2.31 (m, 2H), 3.64 (t, J=6.4 Hz, 2H), 4.22 (q, J=6.3 Hz, 1H), 4.95–5.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.0, −4.4, 0.1 (3C), 16.0, 18.1, 19.1, 25.8 (3C), 30.2, 30.4, 37.3, 62.3, 70.2, 84.6, 94.8, 100.7, 107.2, 199.7; IR (neat) 3347, 2955, 2929, 2175, 1250 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ([M]$^+$, 30), 323 (20), 269 (60), 75 (100); HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2558.

4.4.8. 3-(*tert*-Butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylbut-1*E*-enyl]-6-trimethylsilylmethylenecyclohexene (*E*-24d), 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methyl-but-1*Z*-enyl]-6-trimethylsilylmethylenecyclohexene (*Z*-24d), and 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylenebutyl]-6-trimethylsilylmethylenecyclohexene (25d). To a flame dried test tube was added allene **22d** (1.66 g, 3.36 mmol), which was azeotroped under vacuum with benzene (3×). Toluene (17 mL) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, $[Rh(CO)_2Cl]_2$ (0.04 g, 0.09 mmol) was added at ambient temperature and the system was evacuated and charged with N_2 once more. The mixture was heated to 80 °C and followed by GC analysis. The mixture was quenched after 1 h by running through a silica gel plug eluting with 5% EtOAc/hexanes to afford 1.57 g of trienes *E*-**24d**, *Z*-**24d**, and **25d** in 6:2:1 ratio, respectively, and a 95% crude yield.

4.4.9. 3-(4-Hydroxy-1-methylbut-1*E*-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*E*-30), 3-(4-hydroxy-1-methylbut-1*Z*-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*Z*-30), and 3-(4-hydroxy-1-methylenebutyl)-4-trimethylsilylmethylenecyclohex-2-enol (31). To a solution of trienes *E*-**24d**, *Z*-**24d**, and **25d** (0.16 g, 0.32 mmol) in 8 mL of THF was added $NH_4Cl_{(s)}$ (0.1 g, 1.86 mmol) and then TBAF (1.3 mL of a 1 M THF solution, 1.3 mmol). The mixture was heated to 50 °C and after 12 h was quenched by addition of water. The stir bar was removed and the organic layer was evaporated under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to afford trienes *E*-**30**, *Z*-**30**, and **31** (78 mg, 92%). R_f 0.1 (30% EtOAc/hexanes); R_f 0.42, 0.6, 0.45 (*E*-**30**, *Z*-**30**, **31**) (10% isopropanol/pentanes); ^{1}H NMR (300 MHz, $CDCl_3$) *E*-**30**: δ 0.11 (s, 9H), 1.58–1.70 (m, 1H), 1.72 (d, J=0.5 Hz, 3H), 2.00 (ddd, J=4.2, 8.1, 16.5 Hz, 1H), 2.10 (br s, 1H), 2.25–2.40 (m, 3H), 2.55 (ddd, J=3.7, 7.8, 14.6 Hz, 1H), 3.66 (t, J=6.6 Hz, 2H), 4.27–4.35 (m, 1H), 5.31 (dt, J=1.3, 7.2 Hz, 1H), 5.37 (s, 1H), 5.63 (d, J=3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 17.2, 28.1, 31.6, 32.8, 62.1, 66.2, 124.7, 127.0, 128.4, 138.5, 147.5, 149.3; IR (neat) 3319, 2952, 1578, 1437 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ([M]$^+$, 1), 192 (34), 145 (100); HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1693; ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-**30**: δ 0.12 (s, 9H), 1.60–1.75 (m, 1H), 1.81 (s, 3H), 2.00–2.19 (m, 3H), 2.29–2.41 (m, 1H), 2.62 (ddd, J=3.7, 6.8, 14.6 Hz, 1H), 3.51–3.63 (m, 2H), 4.31–4.38 (m, 1H), 5.36 (dt, J=1.0, 6.4 Hz, 1H), 5.44 (s, 1H), 5.60 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 24.9, 27.9, 29.7, 32.7, 62.5, 66.3, 123.6, 126.0, 129.7, 138.5, 143.3, 148.5; IR (neat) 3318, 2953, 1577, 1434 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ([M]$^+$, 1.4), 248 (8.4), 73 (100); HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1698; ^{1}H NMR (300 MHz, $CDCl_3$) constitutional isomer **31**: δ 0.13 (s, 9H), 1.59–1.76 (m, 3H), 2.03 (ddd, J=4.3, 8.1, 16.8 Hz, 1H), 2.23 (t, J=7.6 Hz, 2H), 2.36 (dddd, J=1.3, 3.7, 9.8, 14.7 Hz, 1H), 2.57 (ddd, J=3.8, 7.9, 14.6 Hz, 1H), 3.63 (t, J=6.6 Hz, 2H), 4.32–4.37 (m, 1H), 4.89 (d, J=2.2 Hz, 1H), 5.02 (dt, J=1.3, 2.2 Hz, 1H), 5.49 (s, 1H), 5.67 (d, J=3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 27.9, 31.2, 32.3, 32.8, 62.4, 66.2, 114.3, 127.5, 129.2, 144.9, 148.8, 149.1; IR (neat) 3332, 2949, 1577, 1435 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 248 ([M−H_2O]$^+$, 8), 73 (100); HRMS calcd for $C_{15}H_{24}OSi$: 248.1596 [M−H_2O]$^+$; found: 248.1588 [M−H_2O]$^+$.

4.4.10. 3-[4-(*tert*-Butyldimethylsilyloxy)-1-methylbut-1-enyl]-4-trimethylsilyl methylenecyclohex-2-enol (32). To a solution of triene *E*-**30** (0.07 g, 0.26 mmol) in 1.3 mL of CH_2Cl_2 were added Et_3N (150 μL, 1.10 mmol) and TBDMSCl (0.08 g, 0.29 mmol) at 0 °C. The solution was then warmed to ambient temperature and left overnight.

The mixture was quenched by addition of water, and the aqueous layer was separated and washed with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford **32** (74 mg, 75%). R_f 0.6 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.62–1.70 (m, 1H), 1.73 (s, 3H), 1.93–2.05 (m, 1H), 2.28–2.38 (m, 3H), 2.55 (ddd, J=3.6, 7.9, 14.5 Hz, 1H), 3.65 (t, J=7.0 Hz, 2H), 4.24–4.28 (m, 1H), 5.31 (t, J=7.2 Hz, 1H) 5.41 (s, 1H), 5.62 (d, J=3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2 (2C), 0.1 (3C), 17.2, 18.3, 26.0 (3C), 28.0, 32.0, 32.9, 62.8, 66.3, 125.4, 127.1, 128.0, 137.2, 147.9, 149.3; IR (neat) 3334, 2954, 2858, 1578 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ([M]$^+$, 3), 145 (40), 73 (100); HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2567.

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Palladium-catalyzed substitution reactions of 4-allylimidazole derivatives

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Abstract—In the context of synthetic studies toward the oroidin family of pyrrole–imidazole alkaloids, we required an efficient method for conducting substitution reactions of allylic alcohols derived from urocanic acid. While in some cases this could be accomplished quite readily by classical nucleophilic substitution, it was complicated by allylic transposition in others. Application of Pd-catalyzed π–allyl chemistry provided a convenient solution, giving substitution without allylic transposition. Herein we describe the scope of this reaction in imidazole-containing substrates, and the elaboration of one adduct into a homologated histidine derivative, and into a cyclic homohistidine derivative.

1. Introduction

Marine sponges have proven to be remarkable sources of natural products displaying complex and diverse architectures, coupled with important biological activities.[1] Among these is a small family of pyrrole–imidazole natural products, collectively known as the oroidin alkaloids.[2] This family of marine alkaloids, which are thought to be biogenetically derived from oroidin and congeners (**1**–**3**, Fig. 1), presents numerous challenges to organic synthesis due to their often complex architecture and the presence of sensitive functional groups. Among the more complex members of this family of pyrrole–imidazole natural products are the dimeric palau'amine (**4**),[3,4] axinellamine A (**5**),[5,6] and massadine (**6**, Fig. 1),[7] which contain various types of ring fusions, and each possesses a densely functionalized cyclopentane ring. Inspired by these molecules, our lab has been engaged in developing approaches to these targets, and has reported on a Diels–Alder-rearrangement strategy (Fig. 2) involving vinylimidazoles as a means to access the spiro-fused ring system characteristic of **4**–**6**.[8,9]

In the course of implementing this strategy, it was found that the more electron-rich substrates participated in the oxidative rearrangement chemistry more efficiently (**10**→**11**, Fig. 2);[8d] however, the preparation of such substrates was often plagued by difficulties. For example, the DMAS-protected phthalimide **13** could be obtained readily from the corresponding alcohol **12** through either Mitsunobu chemistry or via the in situ preparation of the allyl chloride and reaction with potassium phthalimide (Scheme 1).[8c,10] Whereas, in contrast, the Bn-protected phthalimide **15** derivative could only be obtained in relatively low yield via either pathway (Gabriel route is shown in Scheme 1). The attenuated yield was due to competitive substitution providing the transposed product.[11] The MOM-protected phthalimide **17** can be obtained via the Gabriel pathway in moderate yields, but similar problems with allylic transposition occur during the preparation of *N*-alkoxyphthalimide **18**, where **19** forms in substantial amounts. Access to **18** was required for the

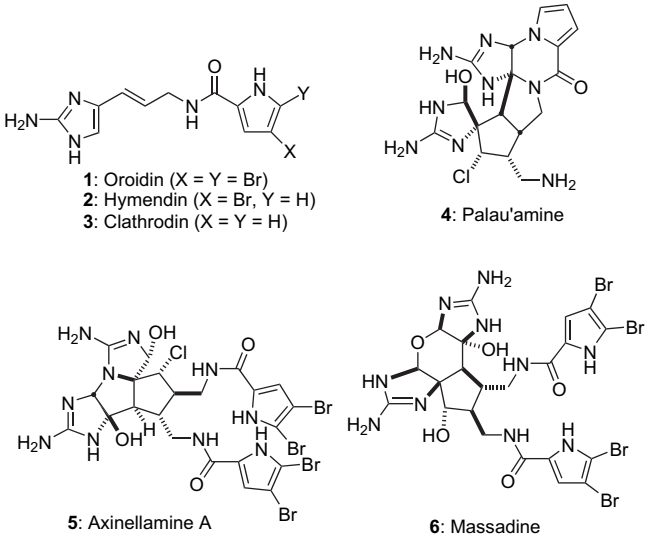

Figure 1. Oroidin and some dimeric congeners.

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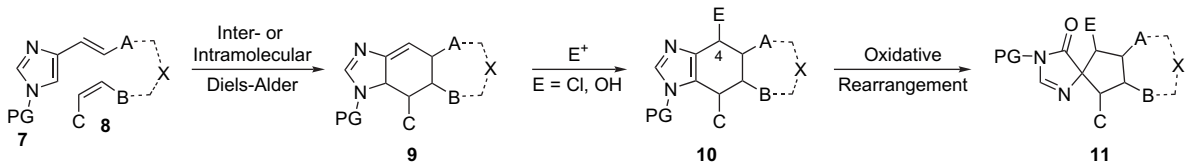
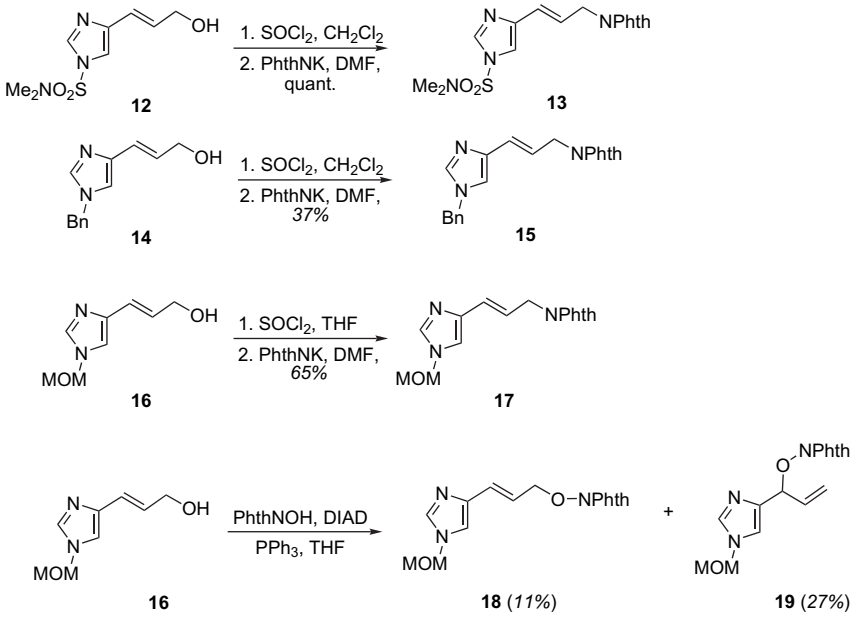


Figure 2. Synthetic strategy toward spiro-fused imidazolylcyclopentane.



Scheme 1.

preparation of some N–O-linked systems for evaluation in intramolecular Diels–Alder reactions.[12] When these results are viewed as a whole, there appears to be a correlation between the electron density of the imidazole moiety and the proportion of allylic transposition, that is the more electron rich the imidazole, the more transposition tends to be observed. We assume that these reactions proceed via SN2/SN2′ pathways but with the development of significant positive charge.[13] Interpretation of these results suggests that the contribution of the resonance form **21** with the positive charge proximal to the imidazole to the overall structure dictates which pathway is followed (Fig. 2). In the case of more electron-rich imidazoles (Bn, MOM) this contribution is more important, and so the SN2′ pathway becomes more competitive, whereas with the more electron poor (dimethylaminosulfonyl = DMAS) this is less important and so SN2 is favored (Fig. 3).

The preparation of the phthalimide derivatives (**13**, **15**, **17**) was driven by our need to access the corresponding amines, while this could be satisfied by using an alternative pathway,

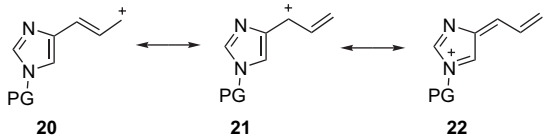
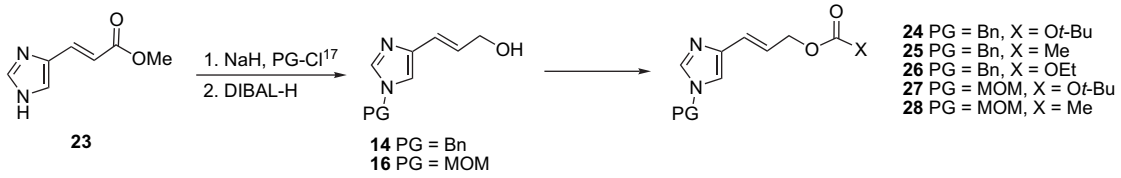


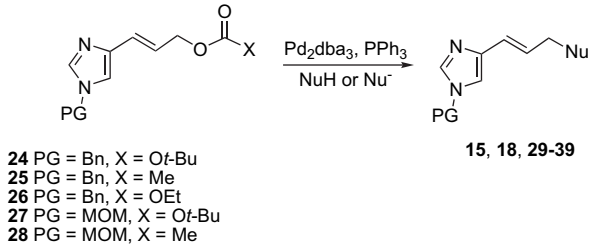
Figure 3. Resonance stabilization of imidazolyl-derived allylic carbocation.

i.e., reductive amination with the corresponding α,β-unsaturated aldehyde.[14] Access to **18** and related congeners however, could not be solved in this way. Furthermore, as our studies progressed, it became increasingly apparent that a solution to the preparation of the more electron-rich Bn- and MOM-protected derivatives had to be found. As indicated above, substrates with these protecting groups engaged in the rearrangement chemistry with greater facility. At this point we became intrigued as to the possibility of using π-allyl chemistry catalyzed by Pd(0).[15] A literature search indicated that no examples involving imidazole substituted allyl systems had been reported,[16] therefore we sought to investigate the viability of this chemistry as it would not only provide a convenient approach to **18**, but may allow access to a variety of other derivatives. The results of this investigation are described below.

The allylic alcohols **14** and **16** are readily available from urocanic acid via the methyl ester (**23**) and chemoselective protection.[17] Acetylation with acetic anhydride, acetyl chloride, ethyl chloroformate or $(BOC)_2O$ occurred uneventfully (Scheme 2), setting the stage for the key substitution reaction. Our initial experiment was conducted with **24** and *N*-hydroxysuccinimide as a nucleophile, using Pd_2dba_3 (3 mol %) and PPh_3 (7 mol %), and we were delighted to discover that the reaction proceeded to provide the terminal substitution product in 86% (Table 1, entry 1) as the sole isolated product. Analysis of the ^1H NMR spectrum of the crude reaction mixture provided evidence that no



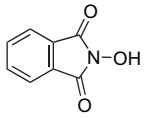
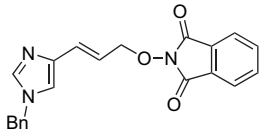
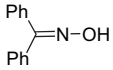
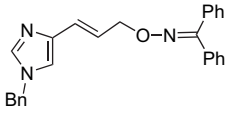
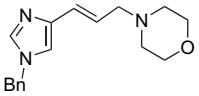
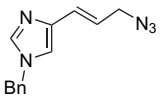
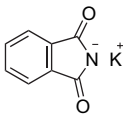
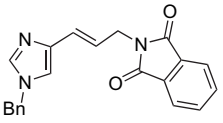
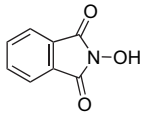
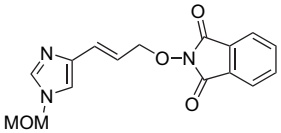
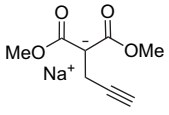
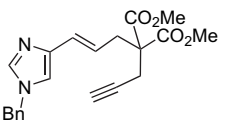
Scheme 2.



Scheme 3.

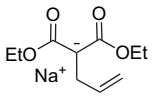
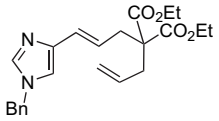
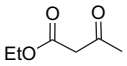
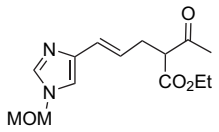
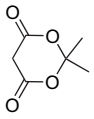
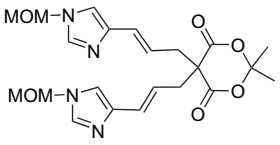
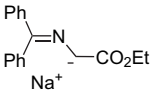
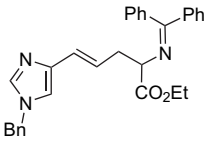
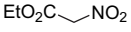
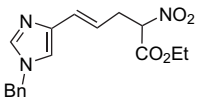
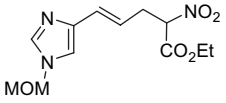
SN2′-susbstitution had occurred. Given the success of this initial reaction, several other nucleophiles were examined, including both heteroatom (Table 1, entries 1–6) and carbon-based (Table 1, entries 7–13). As can be seen from the examples depicted in Table 1, a variety of nucleophiles engage successfully in this reaction. Particularly gratifying was the expedient and selective synthesis of the phthalimide **15** (Table 1, entry 5) and alkoxyphthalimide **18** (Table 1, entry 6). Essentially the same conditions can be employed (3–7 mol % Pd_2dba_3), although some changes in solvent

Table 1. Products and yields from allylic substitution reactions

Entry	Substrate	Nucleophile	Conditions[a]	Product	Yield/%
1	**24**		MeCN, 28 h	 **29**	86
2	**25**		K_2CO_3, CH_2Cl_2, 14 h	 **30**	98
3	**24**		CH_2Cl_2, 16 h	 **31**	83
4	**24**	NaN_3	MeCN, H_2O, 16 h	 **32**	79
5	**26**		DMF, 100 °C, 14 h	 **15**	90
6	**27**		MeCN, 28 h	 **18**	77
7	**24**		THF, 17 h	 **33**	74

(*continued*)

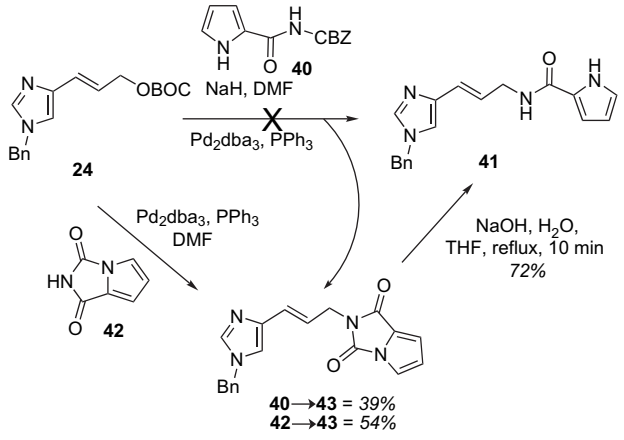
Table 1. (*continued*)

Entry	Substrate	Nucleophile	Conditions[a]	Product	Yield/%
8	**24**		THF, 17 h	 **34**	69
9	**28**		CH_2Cl_2, K_2CO_3, 16 h	 **35**	74
10	**28**		CH_2Cl_2, K_2CO_3, 14 h	 **36**	76
11	**24**		THF, 60 °C, 36 h	 **37**	69
12	**25**		CH_2Cl_2, reflux, 12 h[18]	 **38**	73
13	**28**		CH_2Cl_2, reflux, 12 h	 **39**	62

[a] All reactions were conducted at room temperature unless otherwise noted.

are required to accommodate solubility of some systems, and in some cases heat is required. Of the 13 examples illustrated in Table 1, no evidence of the SN2′ pathway was observed on analysis of the ^{1}H NMR spectra of the crude reaction mixtures (Scheme 3).

Part of the attraction of the successful realization of this chemistry was the possibility of utilizing new types of nucleophiles that might expedite the synthesis of the oroidin alkaloids.[2] In particular, we wanted to examine pyrrole-substituted imides (e.g., **40** in Scheme 4)[19] as a means to incorporate this moiety more directly into targets. Typically, this group is incorporated through acylation of the corresponding amine, which frequently arises through elaboration of an alcohol,[20] and so this strategy would significantly reduce the number of synthetic manipulations. Pyrroles react efficiently with isocyanates to provide the corresponding 2-acyl pyrrole, thus when pyrrole was treated with benzyloxy isocyanate, the corresponding 2-CBZ-imide was obtained. When **40** (after deprotonation with NaH) was used in the Pd-catalyzed substitution chemistry (Scheme 4), it was found that substitution had occurred, but the adduct possessed only one benzyl moiety. Our initial suspicion was that simple reductive debenzylation of the CBZ moiety occurred



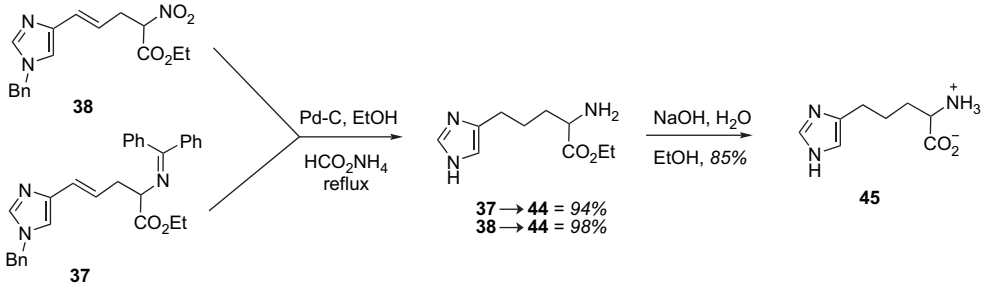
Scheme 4.

after the alkylation through the action of adventitious Pd/H species, providing **41**. However, it quickly became apparent that this analysis was erroneous, as the ^{13}C NMR spectrum revealed the presence of two carbonyl absorptions. It has been shown that imides related to **40** can undergo an intramolecular cyclization reaction between the pyrrole nitrogen and the β-carbonyl to generate a cyclic imide under thermal activation.[19] Based on the two carbonyl absorptions observed in the ^{13}C NMR spectrum, and on mass spectral data, it was thought that the product was in fact **43**. To test this hypothesis, the cyclic imide **42** was prepared according to the method of Papadopoulos and then subjected to the substitution chemistry.[19] Gratifyingly, not only did the imide engage in the substitution reaction, but provided the same adduct as **40**, in 54% yield (Scheme 4). It was found that the pyrrole carboximide in **43** could be revealed simply on treatment with aqueous NaOH, providing **41** in 72% yield, which can be envisioned as a precursor to clathrodin (**3**, Fig. 1).

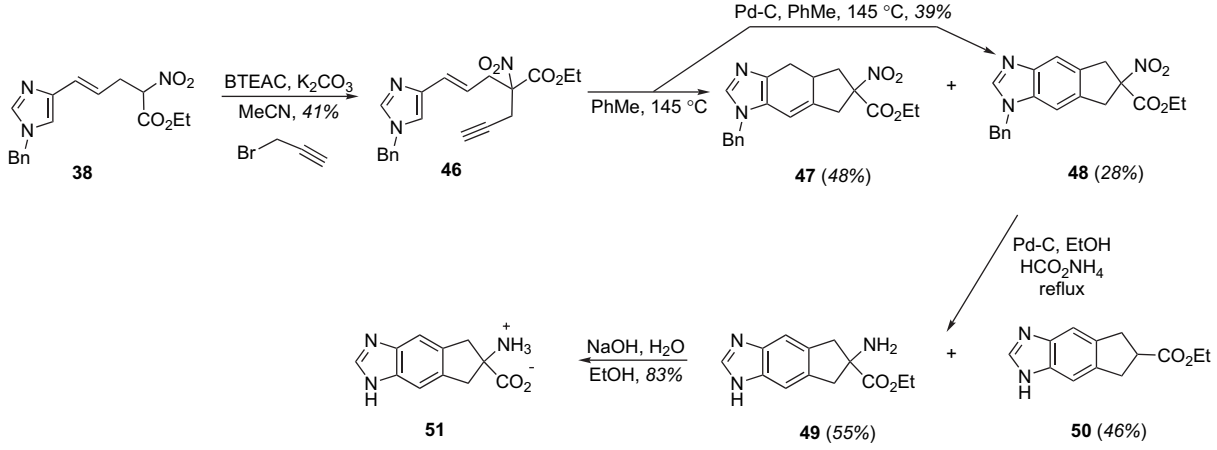
Several active methylene components have been employed in this chemistry with equal facility, including allyl and propargyl malonate systems (Table 1, entries 7 and 8). It was envisioned that these latter derivatives would provide substrates for investigation in the intramolecular Diels–Alder reaction.[21] Meldrum's acid also participates nicely in this substitution chemistry, providing the bis adduct in good yield (Table 1, entry 10). Several glycine synthons were employed in the reaction and found to successfully engage in substitution (Table 1, entries 11–13), potentially providing precursors for the preparation of homologous histidine analogs. Subjection of either **37** or **38** to transfer hydrogenation conditions led to the reduction of the nitro and alkene moieties and cleavage of the benzyl protecting group, providing **44** in excellent yield (Scheme 5).[22,23] Subsequent ester hydrolysis and purification by the ion-exchange chromatography provided the homohistidine analog **45** (Scheme 5).[24]

Additionally, it was found that **38** can serve as a building block for further elaboration, for example, the acidic C–H can be substituted under phase transfer conditions, providing enyne **46** in moderate yield (Scheme 6). This undergoes a Diels–Alder reaction providing the expected cycloadduct **47** in 48% yield, along with the aromatized congener **48** (28%). Treatment of **46** with Pd/C in toluene at 145 °C furnishes the aromatic adduct **48** as the only product in 39% yield. Alternatively the aromatic adduct can be obtained directly from the cycloaddition when it is conducted in the presence of Pd/C (Scheme 6). Subjection of **48** to transfer hydrogenation leads to debenzylation and reduction of the nitro moiety, affording **49**. In addition to the desired compound, and a comparable quantity of the deaminated product **50** was obtained. Ester hydrolysis and purification by ion-exchange chromatography led to the isolation of the constrained homohistidine derivative (Scheme 6).

In summary, we have developed an efficient method for allylic substitution of imidazole derivatives that proceeds without allylic rearrangement. These reactions are tolerant of a variety of nucleophiles, including heteroatom and active methylene compounds. Among the heteroatom nucleophiles, we demonstrate the utility of a pyrrole carboximide (**42**) as a new and more direct means to introduce this moiety



Scheme 5.



Scheme 6.

into the oroidin alkaloids.[25] Two of the adducts were converted to homohistidine adducts, including a novel cyclic derivative. We are currently evaluating other nucleophiles in this chemistry and the utility of asymmetric variants, we will report on these efforts in due course.

2. Experimental

2.1. General

All chemicals were purchased from commercial vendors and were used as received unless stated otherwise. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware. Solvents were dried using a Pure-Solv 400 solvent purification system (Innovative Technologies Inc.), except for DMF, which was dried over CaH_2 and then distilled. ^{1}H NMR spectra were acquired at 300 or 500 MHz in $CDCl_3$, unless indicated otherwise, using residual $CHCl_3$ as a reference. ^{13}C NMR spectra were obtained at 75 or 125 MHz in $CDCl_3$, unless otherwise indicated, using solvent as an internal standard. Low-resolution mass spectra were obtained in-house by electron impact (MS-EI), high-resolution mass spectra were obtained at the University of Florida by electrospray ionization (HRMS-ESI).

2.1.1. (1*E*)-1-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propen-1-ol (16). NaH (60% oil dispersion, 2.10 g, 52.5 mmol) was added portionwise to a cold (0 °C) solution of methyl 3-(1*H*-imidazol-4-yl)acrylate (7.75 g, 50.0 mmol) in dry DMF (100 mL) under N_2 protection. The mixture was allowed to warm to room temperature and stirred for 1.5 h, then cooled to 0 °C again and neat MOMCl (3.99 mL, 52.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The DMF was removed in vacuo. The remaining solid was partitioned between water (50 mL) and EtOAc (300 mL), the organic phase was dried (Na_2SO_4) and concentrated to give an off-white solid. ^{1}H NMR analysis indicated that this material was a 10:3 mixture of the 4- and 5-regioisomers. Separation can be accomplished by column chromatography (EtOAc → EtOAc/MeOH 7:1). However, this mixture was transferred to a sealed tube, acetonitrile (20 mL) and MOMCl (0.10 mL, 1.20 mmol) were added. The mixture was heated at 120 °C for 24 h, the 5-isomer was completely converted to 4-isomer. Concentration gave the desired 4-isomer (8.50 g, 91%) as an off-white solid; mp 85–86 °C. IR (KBr, cm^{-1}): 1703, 1641. ^{1}H NMR (500 MHz): δ=3.28 (s, 3H), 3.76 (s, 3H), 5.21 (s, 2H), 6.57 (d, J=15.6 Hz, 1H), 7.20 (s, 1H), 7.54 (d, J=15.6 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (125 MHz): δ=51.7, 56.5, 78.0, 116.6, 121.1, 136.0, 138.8, 139.1, 168.0; MS-EI (*m*/*z*): 196.1 (M$^+$, 100%), 165.1 (M$^+$−31, 37%). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.17; H, 5.97; N, 14.03.

To a solution of the ester (4.00 g, 20.0 mmol) in CH_2Cl_2 (170 mL) under N_2 was added dropwise DIBAL-H (1 M in hexanes, 3 equiv 60.0 mL, 60.0 mmol) at −78 °C over 100 min, the mixture was allowed to slowly warm up to room temperature (about 80 min) and then cooled to 0 °C. Methanol (10 mL) was added slowly, and then water (70 mL) and NaOH (1 N, 30 mL). The mixture was filtered through Celite and washed with CH_2Cl_2. The organic layer of the filtrate was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to chromatography (EtOAc/methanol 6/1) to afford **16** (2.40 g, 72%) as a light yellow liquid. IR ($CHCl_3$, cm^{-1}): 3237; ^{1}H NMR: δ=3.23 (s, 3H), 4.24 (s, 2H), 5.14 (s, 2H), 6.47–6.48 (m, 2H), 6.92 (s, 1H), 7.51 (s, 1H); ^{13}C NMR: δ=56.2, 63.1, 77.8, 116.3, 121.9, 128.7, 137.7, 140.9; MS-EI (*m*/*z*): 167.9 (M$^+$, 50%), 138.9 (M$^+$−29, 100%).

2.1.2. (1*E*)-1-Benzyl-4-[3-(*N*-phthaloyl)-1-propenyl]imidazole (15). Compound **14** (220 mg, 1.03 mmol) was dissolved in dry THF (30 mL). The mixture was cooled to 0 °C and thionyl chloride (155 mg) was added slowly. The mixture was allowed to warm up to room temperature and stirred for another 2 h. The solution was concentrated in vacuo. The residue was dissolved in DMF (3 mL) and potassium phthalimide (4.7 g, 26 mmol) was added. The mixture was stirred 50 h at rt, and then partitioned between EtOAc (100 mL) and water (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (EtOAc/hexane 3:1 → EtOAc/MeOH 6:1) gave 130 mg of **15** (37%) as an off-white solid; mp 177–178 °C. IR (KBr, cm^{-1}): 1758, 1700; ^{1}H NMR (500 MHz): δ=4.39 (d, J=6.4 Hz, 2H), 5.03 (s, 2H), 6.34 (dt, J=15.6, 6.4 Hz, 1H), 6.49 (d, J=15.6 Hz, 1H), 6.79 (s, 1H), 7.10–7.12 (m, 2H), 7.29–7.34 (m, 3H), 7.44 (s, 1H), 7.68–7.69 (m, 2H), 7.80–7.82 (m, 2H); ^{13}C NMR (125 MHz): δ=39.6, 50.9, 117.4, 121.2, 123.3, 125.4, 127.3, 128.4, 129.1, 132.3, 133.9, 136.0, 137.3, 140.0, 168.0; MS-EI (*m*/*z*): 343.5 (M$^+$, 40%), 252.2 (M$^+$−91, 100%). Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.54; H, 5.22; N, 11.86.

2.1.3. (1*E*)-1-Methoxymethyl-4-[3-(*N*-phthaloyl)-1-propenyl]imidazole (17). Allylic alcohol **16** (1.76 g, 10.5 mmol) was dissolved in dry THF (30 mL). The mixture was cooled to 0 °C and thionyl chloride (0.77 mL, 10.5 mmol) was added slowly. The mixture was allowed to warm up to room temperature and stirred for another 2 h. The solution was concentrated in vacuo. The residue was dissolved in 50 mL of DMF and potassium phthalimide (4.70 g, 25.4 mmol) was added. The mixture was stirred 15 h at rt, and then partitioned between EtOAc (100 mL) and water (20 mL). The organic phase was dried with Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography gave 1.65 g (53%) of **16** as an off-white solid; mp 149–150 °C. IR (KBr, cm^{-1}): 1768, 1701; ^{1}H NMR (500 MHz): δ=3.23 (s, 3H), 4.42 (d, J=6.4 Hz, 2H), 5.15 (s, 2H), 6.39 (dd, J=15.7, 6.4 Hz, 1H), 6.52 (d, J=15.7 Hz, 1H), 6.94 (s, 1H), 7.50 (s, 1H), 7.68–7.71 (m, 2H), 7.81–7.84 (m, 2H); ^{13}C NMR (125 MHz): δ=39.5, 56.2, 77.8, 116.8, 121.9, 123.3, 125.1, 132.3, 134.0, 137.8, 140.4, 168.0; MS-EI (*m*/*z*): 297.2 (M$^+$, 65%), 252.2 (M$^+$−45, 100%), 225.2 (M$^+$−72, 100%). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.62; H, 4.92; N, 14.01.

2.1.4. 2-[(2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (18) and 2-[1-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (19). Diisopropyl azodicarboxylate (337 mg,

1.67 mmol) was added neat to a premixed solution of alcohol **16** (200 mg, 1.19 mmol), PPh_3 (437 mg, 1.67 mmol), and *N*-hydroxyphthalimide (252 mg, 1.55 mmol) in dry THF (10 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure. The oily residue was purified by chromatography (hexane/EtOAc; 1:4) providing **18** and **19**. Further purification by preparative TLC afforded pure **18** and **19**. Compound **18** (100 mg, 27%); mp: 133–135 °C. IR (neat, cm^{-1}): 1786, 1730; ^1H NMR (500 MHz): δ=3.26 (s, 3H), 4.81 (d, *J*=6.9 Hz, 2H), 5.15 (s, 2H), 6.50 (dt, *J*=15.6, 6.9 Hz, 1H), 6.58 (d, *J*=15.6 Hz, 1H), 7.52 (s, 1H), 7.69 (dd, *J*=5.5, 3.0 Hz, 2H), 7.78 (dd, *J*=5.5, 3.0 Hz, 2H); ^{13}C NMR (125 MHz): δ=56.3, 77.8, 78.6, 117.3, 120.9, 123.5, 129.0, 129.1, 134.4, 137.8, 140.0, 163.8; HRMS-ESI: calcd for $C_{16}H_{16}N_3O_4$ $(M+H)^+$ 314.1135, found 314.1129. Compound **19** (40 mg; 11%); mp: 92–94 °C. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): δ=3.56 (s, 3H), 5.49 (ABq, *J*=10.8 Hz, 2H), 5.67 (d, *J*=10.8 Hz, 1H), 5.74 (d, *J*=17.1 Hz, 1H), 6.06 (d, *J*=8.4 Hz, 1H), 6.66 (ddd, *J*=18.9, 10.5, 8.7 Hz, 1H), 7.54 (d, *J*=0.9 Hz, 1H), 7.84 (d, *J*=1.2 Hz, 1H), 7.98–8.01 (m, 2H), 8.05–8.08 (m, 2H); ^{13}C NMR (75 MHz): δ=56.3, 77.9, 84.5, 118.7, 121.8, 123.5, 128.9, 133.7, 134.3, 137.5, 139.2, 163.8; HRMS-ESI: calcd for $C_{16}H_{16}N_3O_4$ $(M+H)^+$ 314.1135, found 314.1133.

2.1.5. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl *tert*-butyl carbonate (24). The allyl alcohol **14** (2.00 g, 9.33 mmol), di-*tert*-butyl dicarbonate (2.50 g, 11.2 mmol), tetra-*n*-butylammonium hydrogen sulfate (158 mg, 0.47 mmol), and 30% w/w aqueous NaOH (4 mL) were mixed together in CH_2Cl_2 (25 mL) at 0 °C and stirred at rt for 6–8 h. The reaction mixture was diluted with water (10 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (EtOAc/hexane; 65:35), affording **26** (2.00 g, 68%) as a pale yellow solid; mp: 73–75 °C. IR (neat, cm^{-1}): 2979, 1738; ^1H NMR (300 MHz): δ=1.47 (s, 3H), 4.67 (d, *J*=6.3 Hz, 2H), 5.05 (s, 2H), 5.06 (s, 2H), 6.37 (dt, *J*=15.6 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.83 (d, *J*=1.2 Hz, 1H), 7.14 (m, 2H), 7.31–7.37 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (75 MHz): δ=27.8, 50.9, 67.5, 82.0, 117.6, 121.3, 126.2, 127.3, 128.4, 129.1, 135.9, 137.8, 140.0, 153.5; HRMS-ESI: calcd for $C_{18}H_{23}N_2O_3$ $(M+H)^+$ 315.1703, found 315.1699.

2.1.6. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl acetate (25). Acetyl chloride (0.37 mL, 5.3 mmol) was added dropwise to a mixture of **14** (750 mg, 3.50 mmol) and K_2CO_3 (966 mg, 7.00 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred at room temperature for 8 h, after which water (3 mL) was added and the organic solution was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (hexane/EtOAc; 4:1) to furnish the pure acetate **25** (440 mg, 73%) as a thick colorless oil. IR (neat, cm^{-1}): 1733; ^1H NMR (300 MHz): δ=2.06 (s, 3H), 4.65 (d, *J*=6.0 Hz, 2H), 5.03 (s, 2H), 6.34 (dt, *J*=15.9, 6.0 Hz, 1H), 6.48 (d, *J*=15.9 Hz, 1H), 6.82 (s, 1H), 7.11–7.13 (m, 2H), 7.29–7.33 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=21.1, 50.9, 65.1, 117.6, 121.6, 125.9, 127.3, 128.4, 129.1, 135.9, 137.8, 139.8, 171.0; HRMS-ESI: calcd for $C_{15}H_{17}N_2O_2$ $(M+H)^+$ 257.1285, found 257.1280.

2.1.7. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl ethyl carbonate (26). Ethyl chloroformate (0.81 mL, 8.4 mmol) was added dropwise to a solution of **14** (1.5 g, 7.0 mmol) and triethylamine (1.95 mL, 14.0 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. After stirring the reaction mixture at rt for 6 h, water (3 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (hexane/EtOAc; 65:35) to furnish the carbonate **26** (1.56 g, 78%) as a thick colorless oil. IR (neat, cm^{-1}): 2926, 1742; ^1H NMR (300 MHz): δ=1.28 (t, *J*=7.2 Hz, 3H), 4.17 (q, *J*=7.2 Hz, 2H), 4.73 (dd, *J*=6.3, 0.9 Hz, 2H), 5.05 (s, 2H), 6.40 (dt, *J*=15.6, 6.3 Hz, 1H), 6.53 (d, *J*=15.6 Hz, 1H), 6.83 (d, *J*=0.9 Hz, 1H), 7.14 (m, 2H), 7.33 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=14.3, 50.9, 64.0, 68.3, 117.8, 120.9, 126.5, 127.3, 128.4, 129.1, 135.9, 137.8, 139.9, 155.1; HRMS-ESI: calcd for $C_{16}H_{19}N_2O_3$ $(M+H)^+$ 287.1396, found 287.1385.

2.1.8. *tert*-Butyl (2*E*)-3-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-propenyl carbonate (27). A mixture **16** (500 mg, 2.98 mmol), di-*tert*-butyl dicarbonate (844 mg, 3.87 mmol), tetra-*n*-butylammonium hydrogen sulfate (50 mg, 0.15 mmol), and 2 mL of 30% w/w aqueous NaOH were mixed together CH_2Cl_2 (25 mL) at 0 °C and stirred at rt for 6–8 h. Water (10 mL) was added to the reaction mixture and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography on a silica gel column (hexane/EtOAc; 30:70), affording the product as a thick oil (495 mg, 62%). IR (neat, cm^{-1}): 2980, 2936, 1738, 1498; ^1H NMR (300 MHz): δ=1.47 (s, 9H), 3.25 (s, 3H), 4.68 (d, *J*=6.0 Hz, 2H), 5.17 (s, 2H), 6.41 (dt, *J*=15.9, 6.0 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.97 (s, 1H), 7.52 (s, 1H); ^{13}C NMR (75 MHz): δ=27.8, 56.2, 67.4, 77.8, 82.1, 117.0, 122.0, 125.8, 137.8, 140.2, 153.4; HRMS-ESI: calcd for $C_{13}H_{21}N_2O_4$ $(M+H)^+$ 269.1496, found 269.1492.

2.1.9. (2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenyl acetate (28). Acetic anhydride (1.01 mL, 10.7 mmol) was added dropwise to a solution of **16** (1.2 g, 7.14 mmol), pyridine (1.13 g, 14.3 mmol), and DMAP (50 mg) in dry CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred at room temperature for 6 h, after which water (3 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish the pure acetate **28** (950 mg, 64%) as a thick colorless oil. IR (neat, cm^{-1}): 2935, 1735; ^1H NMR (300 MHz): δ=2.06 (s, 3H), 3.07 (s, 3H), 4.67 (d, *J*=6.0 Hz, 2H), 5.17 (s, 2H), 6.39 (dt, *J*=15.9, 6.0 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.97 (s, 1H), 7.52 (s, 1H); ^{13}C NMR (75 MHz): δ=21.1, 56.2, 65.0, 116.9, 122.2, 125.6, 137.8, 140.3, 170.9; HRMS-ESI: calcd for $C_{10}H_{15}N_2O_3$ $(M+H)^+$ 211.1077, found 211.1074.

2.1.10. 2-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (29). To a degassed reaction mixture containing allylic carbonate **24** (150 mg, 0.47 mmol), PPh_3 (8 mg, 0.032 mmol), and *N*-hydroxyphthalimide (65 mg, 0.40 mmol) in 5 mL of CH_3CN was added $Pd_2(dba)_3$ (15 mg, 0.016 mmol) and stirred at rt for 28 h. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish **29** (123 mg, 86%) as a pale yellow solid; mp: 121–123 °C. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): 4.81 (d, J=6.3 Hz, 2H), 5.06 (s, 2H), 6.47 (dt, J=15.9, 6.6 Hz, 1H), 6.58 (d, J=15.9 Hz, 1H), 6.90 (s, 1H), 7.15 (m, 2H), 7.34–7.38 (m, 3H), 7.46–7.51 (m, 2H), 7.69–7.72 (dd, J=3.0, 5.1 Hz, 2H), 7.79 (dd, J=5.4, 3.0 Hz, 2H); ^{13}C NMR (75 MHz): δ=51.1, 78.7, 117.9, 120.4, 123.5, 127.5, 128.5, 128.6, 129.0, 129.1, 129.3, 134.4, 135.6, 137.6, 139.5, 163.8; HRMS-ESI: calcd for $C_{21}H_{18}N_3O_3$ $(M+H)^+$ 360.1343, found 360.1335.

2.1.11. *O*-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl]benzophenone oxime (30). To the degassed reaction mixture containing allylic acetate **25** (100 mg, 0.39 mmol), PPh_3 (13 mg, 0.048 mmol), K_2CO_3 (54 mg, 0.39 mmol), and benzophenone oxime (64 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (0.021 g, 0.023 mmol) followed by stirring at rt for 14 h. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (hexane/EtOAc; 21:3) to furnish **30** as a thick oil (0.096 g, 98%). IR (neat): cm^{-1}=1660, 1494, 1444; ^1H NMR (300 MHz): δ=5.07 (d, J=4.8 Hz, 2H), 5.31 (s, 2H), 6.75 (m, 2H), 7.08 (d, J=1.2 Hz, 1H), 7.39–7.42 (m, 2H), 7.51–7.65 (m, 10H), 7.72–7.75 (m, 4H); ^{13}C NMR (75 MHz): δ=51.2, 75.2, 117.5, 124.5, 124.9, 127.6, 128.3, 128.4, 128.4, 128.6, 129.0, 129.3, 129.4, 129.7, 133.7, 136.1, 137.0, 137.9, 140.8, 156.9; HRMS-ESI: calcd for $C_{26}H_{24}N_3O$ $(M+H)^+$ 394.1914, found 394.1905.

2.1.12. 4-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl]morpholine (31). To the degassed reaction mixture containing allylic carbonate **24** (200 mg, 0.64 mmol), PPh_3 (13 mg, 0.05 mmol), and morpholine (0.056 mL, 0.65 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (MeOH/EtOAc; 7:13) to furnish **31** (150 mg, 83%) as thick oil. IR (neat, cm^{-1}): 2856, 2806, 1538, 1495; ^1H NMR (300 MHz): δ=2.47 (dd, J=4.5 Hz, 4H), 3.09 (d, J=6.9 Hz, 2H), 3.69 (dd, J=3.6 Hz, 4H), 5.04 (s, 2H), 6.28 (dt, J=15.3, 7.2 Hz, 1H), 6.39 (d, J=15.3 Hz, 1H), 6.81 (s, 1H), 7.14 (m, 2H), 7.29–7.36 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (75 MHz): δ=50.9, 53.6, 61.3, 67.1, 116.6, 124.3, 125.3, 127.3 (2C), 128.4, 129.1 (2C), 136.0, 137.6, 140.6; HRMS-ESI: calcd for $C_{17}H_{22}N_3O$ $(M+H)^+$ 284.1757, found 284.1751.

2.1.13. (2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl azide (32). To the degassed reaction mixture containing **24** (200 mg, 0.64 mmol), PPh_3 (13 mg, 0.05 mmol), and NaN_3 (50 mg, 0.76 mmol) in 4:1 CH_3CN/H_2O (5 mL) was added $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using hexane/ethyl acetate 3:7 to furnish **32** (120 mg, 79%) as a thick oil. IR (neat, cm^{-1}): 3109, 2112, 1661; ^1H NMR (500 MHz): δ=3.88 (d, J=6.4 Hz, 2H), 5.07 (s, 2H), 6.35 (dt, J=15.6, 6.4 Hz, 1H), 6.49 (d, J=15.6 Hz, 1H), 7.15 (m, 2H), 7.32–7.37 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (125 MHz): δ=51.0, 53.0, 117.7, 120.8, 126.2, 127.4, 128.4, 129.1, 135.9, 137.8, 139.8. HRMS-ESI: calcd for $C_{13}H_{14}N_5$ $(M+H)^+$ 240.1244, found 240.1239.

2.1.14. (1*E*)-1-Benzyl-4-[3-(*N*-phthaloyl)-1-propenyl]-imidazole (15). To the degassed reaction mixture containing **26** (100 mg, 0.35 mmol), PPh_3 (11 mg, 0.041 mmol), and potassium phthalimide (78 mg, 0.42 mmol) in DMF (5 mL) was added $Pd_2(dba)_3$ (20 mg, 0.020 mmol) and stirred at 100 °C for 14 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 3:17) to furnish **15** (108 mg, 90%) as a colorless solid.

2.1.15. 2-[(2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (18). To the degassed reaction mixture containing **27** (145 mg, 0.54 mmol), PPh_3 (17 mg, 0.064 mmol), and *N*-hydroxyphthalimide (132 mg, 0.81 mmol) in acetonitrile (10 mL) was added $Pd_2(dba)_3$ (29 mg, 0.032 mmol) and stirred at room temperature for 38 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 1:4) to furnish **18** (130 mg, 77%) as a colorless solid.

2.1.16. Dimethyl 2-[(2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl]-2-(2-propynyl)malonate (33). To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (10 mg, 0.038 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (18 mg, 0.019 mmol). After stirring at rt for 5 min, freshly generated sodium salt generated from dimethyl propargyl malonate [(132 mg, 0.67 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (26 mg, 1.08 mmol) and then stirred at room temperature for 30 min] was added and stirred at room temperature for 17 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:13) to furnish **33** (130 mg, 74%) as a thick colorless oil. IR (neat, cm^{-1}): 3289, 2935, 1735; ^1H NMR (300 MHz): δ=2.11 (t, J=2.7 Hz, 1H), 2.93 (d, J=2.4 Hz, 2H), 3.03 (d, J=8.1 Hz, 2H), 3.83 (s, 6H), 5.14 (s, 2H), 6.15 (dt, J=15.3, 8.1 Hz, 1H), 6.50 (d, J=15.3 Hz, 1H), 6.87 (s, 1H), 7.27–7.36 (m, 2H), 7.43–7.46 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (75 MHz): δ=22.8, 35.8, 51.0, 53.0, 57.3, 71.6, 79.2, 116.8, 121.2, 126.7, 127.5, 128.5, 129.2, 136.1, 137.6, 140.7, 170.3; HRMS-ESI: calcd for $C_{21}H_{23}N_2O_4$ $(M+H)^+$ 367.1638, found 367.1652.

2.1.17. Diethyl 2-(2-propenyl)-2-[(2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl]malonate (34). To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (10 mg, 0.038 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (19 mg, 0.019 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt generated

from diethyl allylmalonate [(130 mg, 0.65 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (23 mg, 0.95 mmol and stirred at room temperature for 30 min] was added and stirred at room temperature for 17 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:13) to furnish **34** (125 mg, 66%) yield as thick colorless oil. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): δ=1.20 (t, J=6.9 Hz, 6H), 2.65 (d, J=7.2 Hz, 2H), 2.73 (d, J=7.5 Hz, 2H), 4.13 (q, J=6.9 Hz, 4H), 5.01–5.08 (m, 4H), 5.68 (m, 1H), 6.07 (dt, J=15.6, 7.5 Hz, 1H), 6.27 (d, J=15.6 Hz, 1H), 6.73 (s, 1H), 7.12 (m, 2H), 7.29–7.35 (m, 3H), 7.42 (s, 1H); ^{13}C NMR (75 MHz): δ=14.2, 35.9, 36.7, 50.9, 57.7, 61.2, 116.3, 119.1, 122.0, 126.0, 127.3, 128.3, 129.0, 132.6, 136.1, 137.5, 140.7, 170.8; HRMS-ESI: calcd for $C_{23}H_{29}N_2O_4$ $(M+H)^+$ 397.2122, found 397.2112.

2.1.18. Ethyl (4*E*)-2-acetyl-5-(1-methoxymethyl-1*H*-imidazol-4-yl)pent-4-enoate (35). To the degassed reaction mixture containing **28** (150 mg, 0.714 mmol), PPh_3 (15 mg, 0.057 mmol), K_2CO_3 (197 mg, 1.43 mmol), and ethyl acetoacetate (115 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (26 mg, 0.026 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and residue obtained was purified by column chromatography (hexane/EtOAc; 3:17) to furnish **35** (148 mg, 74%) as a thick colorless oil. IR (neat, cm^{-1}): 1733, 1714; ^1H NMR (300 MHz): δ=1.24 (t, J=6.9 Hz, 6H), 2.24 (s, 3H), 2.71 (t, J=6.6 Hz, 2H), 3.25 (s, 3H), 3.58 (t, J=7.2 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 5.15 (s, 2H), 6.22 (dt, J=15.3, 6.6 Hz, 1H), 6.34 (d, J=15.3 Hz, 1H), 6.88 (s, 1H), 7.50 (s, 1H); ^{13}C NMR (75 MHz): δ=14.1, 29.4, 31.4, 56.2, 59.5, 61.5, 77.8, 115.9, 124.1, 124.8, 137.6, 140.9, 169.3, 202.7; HRMS-ESI: calcd for $C_{14}H_{21}N_2O_4$ $(M+H)^+$ 281.1496, found 281.1492.

2.1.19. 5,5-Bis-[(1*E*)-3-(1-methoxymethyl-1*H*-imidazol-4-yl)-1-propenyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (36). To the degassed reaction mixture containing **28** (150 mg, 0.71 mmol), PPh_3 (15 mg, 0.057 mmol), K_2CO_3 (197 mg, 1.43 mmol), and Meldrum's acid (124 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (26 mg, 0.026 mmol) and stirred at room temperature for 14 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (MeOH/EtOAc; 1:9) to furnish **36** (120 mg, 76%) as a pale orange solid; mp: 134–136 °C. IR (neat, cm^{-1}): 2936, 1736; ^1H NMR (300 MHz): δ=1.55 (s, 6H), 2.88 (d, J=7.5 Hz, 4H), 3.23 (s, 6H), 5.14 (s, 4H), 6.22 (dt, J=15.6, 7.5 Hz, 2H), 6.37 (d, J=15.6 Hz, 2H), 6.88 (s, 2H), 7.46 (s, 2H); ^{13}C NMR (75 MHz): δ=29.2, 42.1, 56.2, 56.5, 77.7, 106.1, 116.7, 120.9, 127.17, 137.8, 140.4, 168.7; HRMS-ESI: calcd for $C_{22}H_{29}N_4O_6$ $(M+H)^+$ 445.2082, found 445.2073.

2.1.20. Ethyl (4*E*)-2-(benzhydrylideneamino)-5-(1-benzyl-1*H*-imidazol-4-yl)pent-4-enoate (37). To the degassed reaction mixture containing **24** (500 mg, 1.59 mmol), PPh_3 (50 mg, 0.19 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (87 mg, 0.09 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt prepared from *N*-(diphenylmethylene)glycine ethyl ester [(0.680 g, 2.5 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (96 mg, 2.40 mmol) and stirred at room temperature for 15 min] was added and stirred at 60 °C for 36 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:15) to furnish **37** (508 mg, 84%) as a thick colorless oil. IR (neat, cm^{-1}): 1733, 1621; ^1H NMR (300 MHz): δ=1.22 (t, J=7.5 Hz, 3H), 2.65–2.84 (m, 2H), 4.15 (m, 3H), 4.99 (s, 2H), 6.11 (dt, J=15.9, 6.9 Hz, 1H), 6.24–6.29 (d, J=15.9 Hz, 1H), 6.70 (d, J=1.2 Hz, 1H), 7.09–7.16 (m, 4H), 7.25–7.36 (m, 5H), 7.37–7.41 (m, 4H), 7.61–7.64 (m, 2H); ^{13}C NMR (75 MHz): δ=14.3, 37.3, 50.8, 60.9, 65.8, 116.1, 124.3, 124.7, 127.3, 128.01, 128.07, 128.3, 128.5, 128.6, 128.9, 129.0, 130.3, 136.2, 136.5, 137.4, 139.7, 141.1, 170.6, 171.9; HRMS-ESI: calcd for $C_{30}H_{30}N_3O_2$ $(M+H)^+$ 464.2317, found 464.2333.

2.1.21. Ethyl (4*E*)-5-(1-benzyl-1*H*-imidazol-4-yl)-2-nitropent-4-enoate (38). To the degassed reaction mixture containing **25** (1.00 g, 3.91 mmol), PPh_3 (122 mg, 0.47 mmol), and ethyl nitroacetate (623 mg, 4.68 mmol) in CH_2Cl_2 (10 mL), was added $Pd_2(dba)_3$ (214 mg, 0.23 mmol) and stirred at reflux for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 3:17) to furnish **38** (0.94 g, 73%) as a thick colorless oil. IR (neat, cm^{-1}): 1747, 1559; ^1H NMR (300 MHz): δ=1.25 (t, J=7.2 Hz, 3H), 3.04 (m, 2H), 4.25 (q, J=7.2 Hz, 2H), 5.00 (s, 2H), 5.15 (dd, J=9.3, 6.0 Hz, 1H), 6.16 (dt, J=15.6, 6.9 Hz, 1H), 6.36 (d, J=15.6 Hz, 1H) 6.75 (s, 1H), 7.11 (m, 2H), 7.29 (m, 3H), 7.43 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 33.7, 50.9, 63.1, 87.8, 117.3, 119.4, 126.9, 127.4, 128.4, 129.1 (2C), 135.9, 137.7, 139.8, 164.2; HRMS-ESI: calcd for $C_{17}H_{20}N_3O_4$ $(M+H)^+$ 330.1448, found 330.1439.

2.1.22. Ethyl (4*E*)-5-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-nitropent-4-enoate (39). To the degassed reaction mixture containing **28** (152 mg, 0.72 mmol), PPh_3 (15 mg, 0.057 mmol), and ethyl nitroacetate (115 mg, 0.86 mmol) in CH_2Cl_2 (10 mL), was added $Pd_2(dba)_3$ (26 mg, 0.029 mmol) and stirred at reflux for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish **39** (125 mg, 62%) as a thick colorless oil. IR (neat, cm^{-1}): 2933, 1747, 1560; ^1H NMR (300 MHz): δ=1.27 (t, J=7.2 Hz, 3H), 3.02–3.10 (m, 2H), 3.23 (s, 3H), 4.27 (q, J=7.2 Hz, 2H), 5.14 (s, 2H), 5.18 (dd, J=6.0, 9.3 Hz, 1H), 6.21 (dt, J=15.3, 6.6 Hz, 1H), 6.39 (d, J=15.3 Hz, 1H), 6.90 (s, 1H), 7.49 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 33.7, 56.2, 63.1, 77.8, 87.7, 116.7, 120.2, 126.6, 137.8, 140.2, 164.1; HRMS-ESI: calcd for $C_{12}H_{18}N_3O_5$ $(M+H)^+$ 284.1241, found 284.1237.

2.1.23. Benzyl (1*H*-pyrrole-2-carbonyl)carbamate (40). Benzyloxycarbonyl isocyanate (22.2 g, 0.125 mol) in

toluene (50 mL) was added dropwise to a stirred solution of pyrrole (8.38 g, 0.125 mol) in toluene (50 mL), over the course of 1 h. The reaction mixture was kept under nitrogen and its temperature was held at 30–40 °C by intermittent cooling. After completion of the addition, the solution was stirred at room temperature for a further 22 h, then it was filtered and the gray precipitate was washed with five 25-mL portions of ether. The precipitate was dissolved in dichloromethane and passed through a bed of silica gel to remove the colored impurities. The product (26.8 g, 88%) obtained after concentration was sufficiently pure enough for further use. Mp: 154–156 °C. IR (neat, cm^{-1}): 3274, 1751, 1664, 1508, 1408; ^1H NMR (500 MHz, CD_3OD): δ=5.21 (s, 2H), 6.19 (dd, J=3.7, 2.8 Hz, 1H), 7.02–7.04 (m, H), 7.31–7.37 (m, 3H), 7.42 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ=66.8, 109.5, 113.8, 124.5, 128.0, 128.1, 128.2, 135.9, 152.2, 159.4; HRMS-ESI: calcd for $C_{13}H_{12}N_2O_3Na$ $(M+Na)^+$ 267.0740, found 267.0737.

2.1.24. 2-[(1*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-1-propenyl]pyrrolo[1,2-*c*]imidazole-1,3-dione (43). From **40**: To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (15 mg, 0.057 mmol) in dry DMF (2 mL), was added $Pd_2(dba)_3$ (26 mg, 0.029 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt prepared from **40** [(142 mg, 0.58 mmol) in dry DMF (5 mL) at 0 °C was added 60% NaH (22 mg, 0.95 mmol and stirred for 30 min at room temperature) and stirred at 100 °C for 22 h. The DMF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 3:7) to furnish **43** (62 mg, 39%) as a colorless solid.

From **42**: To the degassed reaction mixture containing **24** (200 mg, 0.64 mmol), PPh_3 (20 mg, 0.076 mmol), and imide **42** (108 mg, 0.82 mmol) in DMF (4 mL) was added $Pd_2(dba)_3$ (35 mg, 0.038 mmol) and stirred at 70 °C for 32 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 3:7) to furnish **43** (115 mg, 54%) as colorless solid; mp: 105–107 °C. IR (neat, cm^{-1}): 3129, 1790, 1726; ^1H NMR (300 MHz): δ=4.31 (d, J=6.4 Hz, 2H), 5.06 (s, 2H), 6.44 (dt, J=15.6, 6.4 Hz, 1H), 6.43 (t, J=3.2 Hz, 1H), 6.77 (d, J=15.6 Hz, 1H), 6.83 (s, 1H), 7.15 (m, 2H), 7.24 (d, J=2.7 Hz, 1H), 7.32–7.37 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=40.7, 51.3, 113.8, 117.6, 117.9, 119.3, 120.8, 126.3, 127.6, 128.7, 129.4, 136.2, 138.1, 140.1, 149.5, 158.6; HRMS-ESI: calcd for $C_{19}H_{17}N_4O_2$ $(M+H)^+$ 333.1346, found 333.1336.

2.1.25. *N*-[(*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)prop-1-enyl] 1*H*-pyrrole-2-carboxamide (41). To **43** (50 mg, 0.15 mmol) in THF (3 mL) was added 10% aqueous sodium hydroxide (0.2 mL) and heated at 70 °C for about 15 min. The reaction mixture was cooled and diluted with CH_2Cl_2. The organic solution was washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (MeOH/EtOAc; 5:95) to furnish the pure **41** (33 mg, 72%) as a colorless solid; mp: 137–139 °C. IR (neat, cm^{-1}): 3229, 1625, 1560, 1522; ^1H NMR (500 MHz, CD_3OD): δ=3.92 (dd, J=1.4, 6.0 Hz, 2H), 5.02 (s, 2H), 6.03 (dd, J=4.2, 2.8 Hz, 1H), 6.11 (dt, J=15.6, 6.0 Hz, 1H), 6.28 (d, J=15.6 Hz, 1H), 6.67 (dd, J=3.7, 1.4 Hz, 1H), 6.77 (dd, J=2.4, 1.4 Hz, 1H), 6.92 (s, 1H), 7.11 (d, J=7.3 Hz, 2H), 7.16–7.24 (m, 4H), 7.53 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ=40.8, 50.5, 109.0, 110.6, 117.3, 121.7, 122.7, 124.5, 125.7, 127.5, 128.1, 128.8, 137.0, 137.8, 139.8, 162.5; HRMS-ESI: calcd for $C_{18}H_{18}N_4O$ $(M+H)^+$ 307.1553, found 307.1547.

2.1.26. Ethyl 5-(1*H*-imidazol-4(5)-yl)-2-aminopentanoate (44). From **37**: To a stirred solution of the diphenylamine Schiff's base **37** (140 mg, 0.30 mmol) in dry ethanol, was added 10% Pd/C (100 mg), followed by anhydrous ammonium formate (285 mg, 4.53 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 14 h under nitrogen. The reaction mixture was filtered over Celite and the filter cake was washed repeatedly with hot ethanol. The filtrate was evaporated under reduced pressure followed by purification of the residue by chromatography on silica gel (MeOH/EtOAc; 1:4) furnished **44** (60 mg, 94%) as viscous oil.

From **38**: To a stirred solution of the nitroester **38** (300 mg, 0.91 mmol) in dry ethanol (5 mL), was added 10% Pd/C (120 mg), followed by anhydrous ammonium formate (0.6 g, 9.5 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 3 h under argon. After cooling to room temperature, the reaction mixture was filtered through Celite and the filter cake was washed repeatedly with hot ethanol. The filtrate was evaporated under reduced pressure to give the pure amino ester **44** in quantitative yield (192 mg). IR (neat, cm^{-1}): 2937, 1731; ^1H NMR (300 MHz): δ=1.23 (t, J=7.2 Hz, 3H), 1.55–1.9 (m, 4H), 2.61 (m, 2H), 3.43 (m, 1H), 4.13 (q, J=7.2 Hz, 2H), 6.73 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (75 MHz): δ=14.2, 25.4, 26.3, 34.2, 54.2, 61.0, 117.1, 134.5, 136.5, 175.8. HRMS-ESI: calcd for $C_{10}H_{18}N_3O_2$ $(M+H)^+$ 212.1394, found 212.1390.

2.1.27. 5-(1*H*-Imidazol-4(5)-yl)-2-aminopentanoic acid (45). The amino ester **44** (50 mg, 0.24 mmol) was treated with NaOH (18 mg, 0.45 mmol) in 3:2 ethanol/water (5 mL) and was allowed to stir at room temperature. The solvent was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 mL). The aqueous layer was rendered acidic with concd HCl solution and loaded on to a prewashed (resin was washed with 100 mL of methanol followed by 100 mL of water) Dowex 50x2, 200 (H^+ form) ion-exchange resin. The column was eluted first with distilled water (100 mL) until the pH was neutral and then with 100 mL of 15% ammonia solution. The eluate was concentrated under reduced pressure to furnish the colorless crystals of the amino acid **45** (85% yield, 37 mg). ^1H NMR (300 MHz, D_2O): δ=1.75 (m, 2H), 1.83 (m, 2H), 2.60 (t, J=6.6 Hz, 2H), 3.66 (t, J=5.1 Hz, 1H), 6.83 (s, 1H), 7.64 (s, 1H).

2.1.28. Ethyl 5-[(4*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)]-2-nitro-2-(2-propynyl)pent-4-enoate acid (46). Propargyl bromide (80 wt % toluene solution, stabilized by MgO,

0.451 mL, 4.01 mmol) was added to a mixture containing the nitroacetate **38** (1.1 g, 3.3 mmol), K_2CO_3 (600 mg, 4.35 mmol), and benzyl triethylammonium chloride (75 mg, 0.33 mmol) in dry CH_3CN (10 mL) and stirred at room temperature overnight. After removing the acetonitrile at rt, the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography using (hexane/EtOAc, 2:3) to furnish pure **46** as thick oil in 41% (500 mg) yield. IR (neat, cm^{-1}): 3293, 1750, 1555; ^1H NMR (300 MHz): δ=1.27 (t, J=7.2 Hz, 3H), 2.11 (t, J=2.7 Hz, 1H), 3.07–3.26 (m, 4H), 4.27 (q, J=7.2 Hz, 2H), 5.00 (s, 2H), 6.05 (dt, J=15.6, 7.8 Hz, 1H), 6.42 (d, J=15.6 Hz, 1H), 6.79 (s, 1H), 7.15 (m, 2H), 7.34–7.36 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 24.4, 36.7, 51.0, 63.3, 73.3, 76.0, 93.5, 117.3, 117.8, 127.4, 128.2, 128.5, 129.1, 135.8, 137.7, 140.0, 165.1; HRMS-ESI: calcd for $C_{20}H_{22}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1588.

2.1.29. Ethyl 1-benzyl-6-nitro-1,4,4a,5,6,7-hexahydroindeno[5,6-*d*]imidazole-6-carboxylate (47). The substrate **46** (115 mg, 0.31 mmol) was dissolved in toluene (20 mL) in a resealable pressure tube. The solution was degassed by bubbling N_2 through the mixture for a few minutes and then the tube was sealed and heated at 145 °C for 48 h. Finally, the solvent was removed by rotary evaporation, followed by purification of the residue by chromatography (hexane/EtOAc; 16:3) furnished the cycloadducts **47** (55 mg, 48%, viscous oil) and **48** (32 mg, 28%, viscous oil). IR (neat, cm^{-1}):=1747, 1552; ^1H NMR (300 MHz): δ=1.277, 1.271 (t, J=7.2 Hz, 3H), 2.26 (m, 1H), 2.46–2.64 (m, 1H), 2.86–3.34 (m, 4H), 3.52–3.59 (m, 1H), 4.26, 4.27 (q, J=7.2 Hz, 2H), 5.02 (ABq, J=15.7 Hz, 2H), 6.02 (d, J=2.1 Hz, 1H), 7.09 (m, 2H), 7.31–7.36 (m, 4H); ^{13}C NMR (75 MHz): δ=13.9, 28.6, 29.1, 39.7, 40.0, 40.3, 40.4, 40.7, 41.7, 48.8, 63.3, 97.3, 98.7, 108.8, 109.0, 126.8, 127.6, 128.2, 129.1, 135.8, 135.9, 136.1, 137.1, 137.4, 137.6, 166.6, 166.8 (mixture of diastereomers); HRMS-ESI: calcd for $C_{20}H_{22}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1588.

2.1.30. Ethyl 1-benzyl-6-nitro-1,5,6,7-tetrahydroindeno[5,6-*d*]imidazole-6-carboxylate (48). The substrate **46** (130 mg, 0.35 mmol) was dissolved in toluene (30 mL) in a resealable pressure tube. The solution was bubbled with N_2 for a few minutes and 10% Pd/C (0.270 g) was added. The tube was sealed and heated at 145 °C for 48 h. Finally, the solvent was removed by rotary evaporation followed by purification of the residue by chromatography (hexane/EtOAc; 4:1) furnished the cycloadduct **48** as thick oil in yield (50 mg, 39%). IR (neat, cm^{-1}): 2924, 1747, 1553; ^1H NMR (300 MHz): δ=1.29 (t, J=7.3 Hz, 3H), 3.87 (dd, J=17.1, 2.7 Hz, 2H), 4.03 (d, J=17.4 Hz, 1H), 4.13 (d, J=17.4 Hz, 1H), 5.00 (s, 2H), 4.31 (q, J=7.3 Hz, 2H), 7.10 (s, 1H), 7.21 (m, 2H), 7.33 (m, 3H), 7.64 (s, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 41.7, 42.0, 49.0, 63.3, 99.4, 106.0, 116.0, 127.0, 128.4, 129.2, 132.2, 133.1, 135.3, 166.7; HRMS-ESI: calcd for $C_{20}H_{20}N_3O_4$ $(M+H)^+$ 366.1448, found 366.1439.

2.1.31. Ethyl 6-amino-1,5,6,7-tetrahydro-indeno[5,6-*d*]imidazole-6-carboxylate (49). To a stirred solution of the nitroester **48** (60 mg, 0.164 mmol) in dry ethanol, was added 10% Pd/C (30 mg), followed by anhydrous ammonium formate (0.103 g, 1.64 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 18 h under argon. The reaction mixture was filtered through Celite and was repeatedly washed with hot ethanol. The filtrate was concentrated by rotary evaporation followed by purification of the residue by chromatography (hexane/EtOAc; 1:19) provided the pure amino ester **49** (22 mg, 55%) as a colorless oil. In addition, the deaminated derivative **50** (17 mg, 45%) was isolated as a white solid. IR (neat, cm^{-1}): 2980, 1725; ^1H NMR (500 MHz): δ=1.26 (t, J=7.3 Hz, 3H), 2.90 (d, J=15.8 Hz, 2H), 3.61 (d, J=15.8 Hz, 2H), 4.19 (q, J=7.3 Hz, 2H), 7.34 (s, 2H), 7.66 (m, 1H); ^{13}C NMR (75 MHz): δ=14.3, 45.6, 61.5, 65.8, 111.4, 135.6, 137.4, 140.5, 176.4. HRMS-ESI: calcd for $C_{13}H_{16}N_3O_2$ $(M+H)^+$ 246.1237, found 246.1233.

2.1.32. Ethyl 1,5,6,7-tetrahydro-indeno[5,6-*d*]imidazole-6-carboxylate (50). Mp: 121–123 °C. IR (neat, cm^{-1}): 2956, 1729; ^1H NMR (300 MHz): δ=1.28 (t, J=7.2 Hz, 3H), 3.31 (m, 5H), 4.17 (q, J=7.2 Hz, 2H), 7.44 (s, 2H), 7.99 (s, 1H); ^{13}C NMR (75 MHz): δ=14.3, 36.0, 44.7, 60.7, 110.8, 137.2, 140.3, 175.4; HRMS-ESI: calcd for $C_{13}H_{15}N_2O_2$ $(M+H)^+$ 231.1128, found 231.1123.

2.1.33. 6-Amino-1,5,6,7-tetrahydroindeno[5,6-*d*]imidazole-6-carboxylic acid (49). The amino ester **49** (15 mg, 0.061 mmol) was treated with NaOH (4 mg, 0.12 mmol) in 3:2 methanol/water (5 mL) and was allowed to stir at room temperature for 6 h. The solvent was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 mL). The aqueous layer was rendered acidic with concd HCl solution and loaded on to prewashed (resin was washed with 100 mL of methanol followed by 100 mL of water) Dowex 50x2, 200 (H^+ form) ion-exchange resin. The column was eluted first with distilled water (100 mL) until neutral pH was achieved and then with 15% ammonia solution (100 mL). The eluate was concentrated under reduced pressure to furnish the colorless crystals of amino acid **51** (11 mg, 83%). Mp: >260 °C. IR (neat, cm^{-1}): 3105, 2123, 1579; ^1H NMR (300 MHz, CD_3OD): δ=3.21 (d, J=16.9 Hz, 2H), 3.82 (d, J=16.9 Hz, 2H), 7.47 (s, 2H), 8.08 (s, 1H); HRMS-ESI: calcd for $C_{11}H_{12}N_3O_2$ $(M+H)^+$ 218.0924, found 218.0920.

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References and notes

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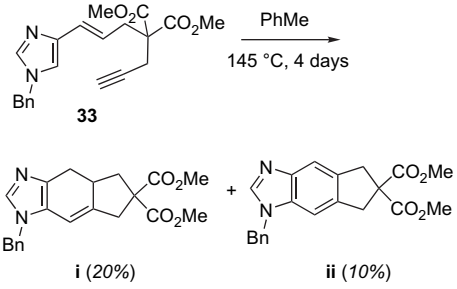

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4-*exo-dig* and 5-*exo-dig* Cyclocarbopalladations: an expeditious solution toward molecular complexity?

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Abstract—The 4-*exo-dig* and 5-*exo-dig* cyclocarbopalladations have been efficiently used to produce molecular complexity in a straightforward manner. Strained 1,2-cyclobutanediols are rapidly obtained under microwave irradiation in high yields. In many cases, the cyclocarbopalladation cascade reaction is associated with a 6 or 8π electrocyclic reaction. During the process of the 5-*exo-dig* cyclocarbopalladation on benzosuberone derivatives, an aromatic C–H activation leads to vinylic substituted aromatics. Polycyclic skeletons of natural products of the family of Ophiobolin and Aleurodiscal can be prepared in few steps from simple starting material.

1. Introduction

The potential of palladium-catalyzed process in organic synthesis has not yet been fully explored. The usefulness of strategies based on palladium cyclization cascades has been demonstrated in the past leading to polycyclic frameworks in regio- and stereoselective manner. One of the most efficient cyclization process that has been used in the literature concerns the intramolecular attack of an organopalladium activated species on a tethered triple bond. Most of the time, an initial 5-*exo-dig*, 6-*exo-dig*, or 7-*exo-dig* cyclocarbopalladation is involved followed by a terminating cross-coupling reaction with CO or various organometallic reagents.[1]

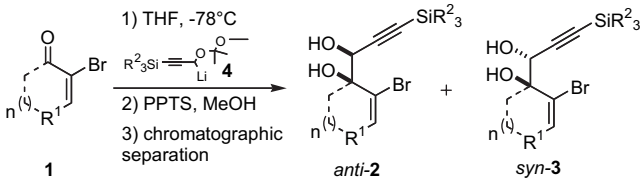
Significant recent studies in our laboratory are directed at the development of cyclocarbopalladation to design and elaborate complex molecules from simple starting material. In this context, we report herein our investigations in the study of cascade reactions involving 4-*exo-dig* and 5-*exo-dig* cyclocarbopalladations.

2. Results and discussion

2.1. An unprecedented 4-*exo-dig* cyclocarbopalladation

Our initial studies focused on a rare 4-*exo-dig* cyclocarbopalladation through a palladium catalysis using a vinyl or alkynylstannane as the terminating trapping species.[2] To the best of our knowledge, before our preliminary work in this field, there was no report on the preparation of related cyclobutanes by this process.

Diols *anti*-**2** and *syn*-**3** were selected as starting materials and prepared in large scale by addition of a properly protected metalated propargylic alcohol **4** onto bromoalkenones **1**, followed by deprotection and chromatographic separation of the two diastereomers *anti*-**2** and *syn*-**3** (Scheme 1).



Scheme 1.

With the diols in hands, we decided to explore the scope and the limitation of the 4-*exo-dig* cyclocarbopalladation. Two possible mechanistic pathways can be envisaged (Scheme 2):

- pathway A: favoring a direct Stille cross-coupling giving compounds of type **5**.
- pathway B: favoring a 4-*exo-dig* cyclocarbopalladation followed by a Stille cross-coupling giving compounds of type **6**.

The 4-*exo-dig* cyclizations are known to be disfavored process according to Baldwin's rules if one considers the organolithium or organomagnesium cyclizations.[3] Of course this

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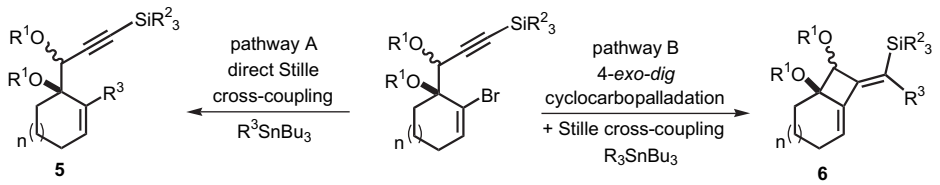


Scheme 2.

type of forbidden reaction can be revisited if in place of a lithium or magnesium intermediate species a transition metal activated route is used. In an effort to favor this process, we examined the effect of several different palladium catalysts, various inorganic and organic bases, and the phosphine ligands.[4] Palladium(II) catalysts such as $PdCl_2(PhCN)_2$, $PdCl_2(CH_3CN)_2$, and $PdCl_2(AsPh_3)_2$ were used, leading only to decomposition of the starting material. The catalytic system $Pd(OAc)_2/PPh_3$ is frequently used in carbopalladative processes. Applying these conditions to our substrates, we observed the exclusive formation of the Stille product **5**. With the same catalyst system, when additives such as Et_4NCl, silver salts,[5] or Et_3N[6] were used only the Stille product **5** was formed and with K_2CO_3 or Na_2CO_3 in benzene, black palladium precipitates rapidly and decomposition of the substrate occurred. When $Pd(PPh_3)_4$ was used, a single product **6** was formed resulting from a 4-*exo-dig* cyclocarbopalladation followed by a Stille cross-coupling. It is remarkable to note that, to this date, the only efficient catalyst for this process is $Pd(PPh_3)_4$. Any other Pd(0) sources gave a trace of the cyclobutane ring system. Different solvents were tested: THF, DMF, NMP, and CH_3CN cause the decomposition of the starting material. Benzene or toluene seems to give the best results for the 4-*exo-dig* cyclocarbopalladation.

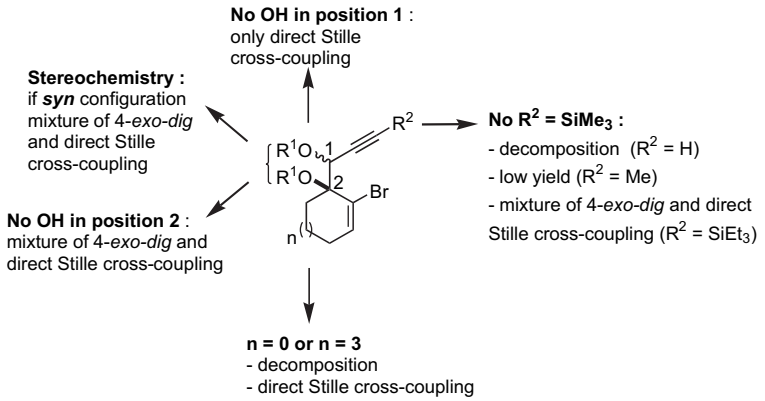
Eventually, this investigation led to the optimized reaction procedure: 10% mol $Pd(PPh_3)_4$ with 1.3 equiv of stannylated reagent in benzene or toluene.

Next, we explored this route to 1,2-cyclobutanediols by examining the influence of the different structural parameters of the substrate in order to favor the cyclocarbopalladation-Stille cross-coupling cascade (Scheme 3).

First the influence of the size of the ring bearing the vinyl bromide function was studied. We noticed that in the case of the five-membered ring the reaction proceeded only via an exclusive direct Stille cross-coupling, and decomposition lowered the yield. This result can be explained by the high ring strain induced by the presence of the cyclobutanediol connected to a smaller ring. Decomposition of the starting material occurred with the eight-membered ring, probably caused by transannular interactions in the cyclooctene. The six- and seven-membered rings led to compounds via a cyclocarbopalladation process followed by a Stille cross-coupling.

The presence of the diol functionality seems to be essential in the competition between the direct Stille cross-coupling and the cyclocarbopalladation-Stille cross-coupling cascades. We next turned our attention to examine the role of each of the hydroxyl groups at positions 1 and 2 (Scheme 3). Applying the same catalyst system described previously, it appeared that the propargylic hydroxyl group (position 1) controls the feasibility of the 4-*exo-dig* cyclocarbopalladation. Indeed, without this hydroxyl group in the propargylic position, the direct Stille cross-coupling was the only observed pathway. A mixture of the Stille product **5** and the cyclobutanediol **6** was isolated when the hydroxyl in the homopropargylic position (position 2) was removed. Therefore, to favor the exclusive 4-*exo-dig* cyclocarbopalladation, the presence of these two oxygen atoms is necessary.

Moreover, the stereochemistry of the diol is also important by directing the triple bond more or less into close proximity of the vinyl bromide. Thus, the experiments on the *syn*-propargylic diol **3** showed a versatile reactivity: a mixture of Stille product **5** and cyclobutanediol derivatives **6** was obtained unlike the reaction with the *anti* diol **2**, which gave only cyclobutanediol derivatives. As a consequence, the *anti* diol **2** was selected as a starting material, in all cases, for the rest of the studies.



Scheme 3.

To complete the studies on the different parameters related to the starting material, the substitution of the triple bond was varied. With the unprotected triple bond decomposition occurred, and even Sonogashira coupling was not observed. With a terminal methyl group, the substrate underwent a 4-*exo-dig* cyclocarbopalladation in moderate yields compared to the triple bond substituted by the trimethylsilyl group. In addition changing the terminal silyl group from trimethylsilyl to triethylsilyl group did not improve the reaction. The trimethylsilyl group turned out to be the most appropriate for protection of the triple bond, which may be due to an electronics effect.

In summary, the two oxygens in the γ-bromopropargylic diols in an *anti* configuration turned out to be essential for the reaction and the trimethylsilyl group is the most appropriate substituent on the triple bond for high reaction efficiency.

2.2. 4-*exo-dig* Cyclocarbopalladation followed by Stille cross-coupling

The previous study of different parameters of the reaction (catalyst, solvent, and temperature) and the starting materials allowed optimization of the conditions to favor the cyclocarbopalladation process.

Thus, different diols (cyclic **7**, **8**, and acyclic **9**) were treated according to the conditions described above in the presence of alkynes (entries 1, 4, and 6), heteroaromatics (entry 2), vinyl (entry 3), and allyltributylstannanes (Table 1, entry 5). Two methods of activation of the reaction were used: activation by heating the reaction mixture at 85 °C (method A) or by using microwave irradiation as a source of molecular activation for the catalytic process (method B).

In each case, the only product isolated resulted from a 4-*exo-dig* cyclocarbopalladation coupling following by a Stille termination coupling and not from a direct Stille cross-coupling reaction in keeping with the previous study. In majority of the cases, the isolated compounds are stable and were purified by chromatography on silica gel without any precaution.

The bicyclic and tricyclic cyclobutanediols **10**–**19** were obtained in moderate to good yields (12–84%) from cyclic diols **7** and **8**, and highly substituted cyclobutanedienynes **20**–**36** were prepared in high yields (46–86%) with acyclic diols **9**.[7] In the presence of stannylated aromatic heterocycles derived from thiophene and furan, it is possible to access the new heteroaromatic substrates (**12**, **13**, **18**, **26**, and **27**, entry 2).

2.3. The 6π electrocyclization process

In several examples, depending on the stannylated reagents, the original reaction of cyclocarbopalladation followed by Stille cross-coupling reaction is terminated by a 6π electrocyclization process.

Thermal conditions and microwave irradiation were also used with protected (**8**–**38**), unprotected (**7**, **9**, **37**), cyclic (**7**, **8**), and acyclic (**9**, **37**, **38**) diols (Table 2).

This process gave tricyclic or tetracyclic structures **39**–**45** bearing a strained cyclobutene ring fused to the two other rings and an anti-Bredt double bond is shared by three cycles (entries 1 and 2).

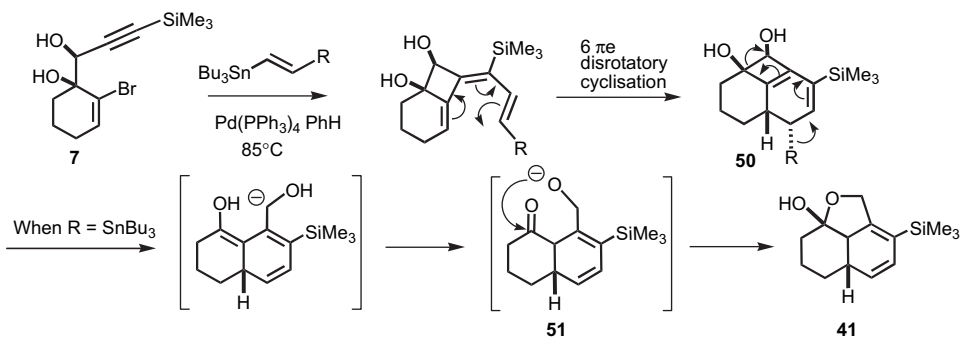
With acyclic diols, bicyclic compounds **46**–**49** were obtained, and the double bond in the bicycle system could be selectively oxidized to give functionalized cyclooctenes.

To explain the formation of compounds **41** and **42**, in the case of use of bis-stannane **B** with unprotected diols **7**, the non-isolated strained tricyclic compounds **50** underwent a subsequent elimination of the three alkyl tin group followed by an opening of the 1,2-cyclobutendiol (Scheme 4, Table 2, entry 1). A final attack of the allylic oxygen on ketone **51** afforded the hemiketals **41**.

It is important to note that the absence of a tributylstannane group in molecule of type **50** completely prevents the opening of the cyclobutenediol through a 4π electron opening electrocyclic reaction. In the same manner, this elimination of the tin is not feasible with the protected diol because of the dioxolane protection that also prevents the opening of the cyclobutenediol. Thus, after the electrocyclization, a dehydrostannation event provides the unusual aromatic tetracyclic dioxolane **45** (Table 2, entry 2).

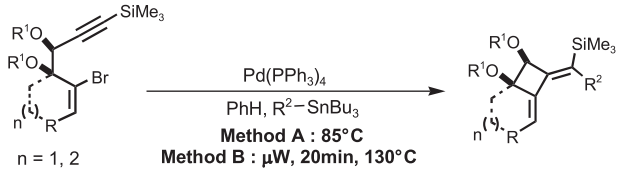
2.4. The 8π electrocyclization process

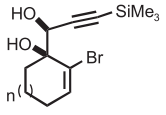
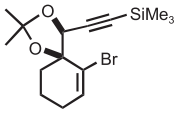
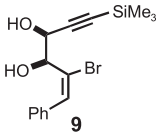
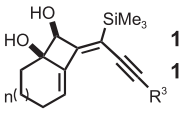
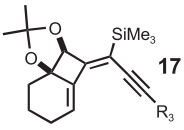
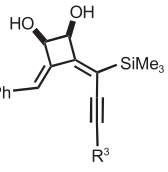
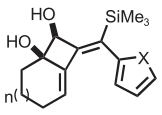
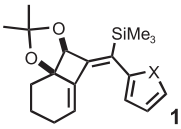
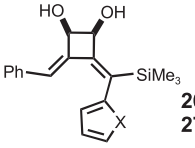
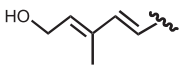
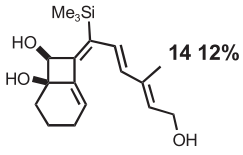
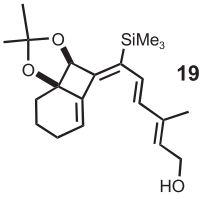
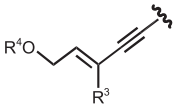
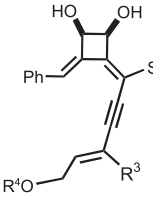
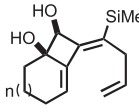
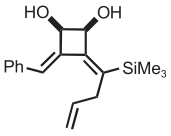
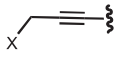
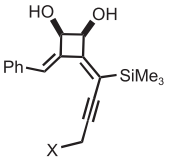
During the studies toward the extension of this new methodology to the synthesis of other polycyclic structures, we decided to examine the feasibility of a conrotatory 8π electrocyclization in the same reaction sequence. This cascade



Scheme 4.

Table 1. Cyclocarbopalladation followed by Stille cross-coupling

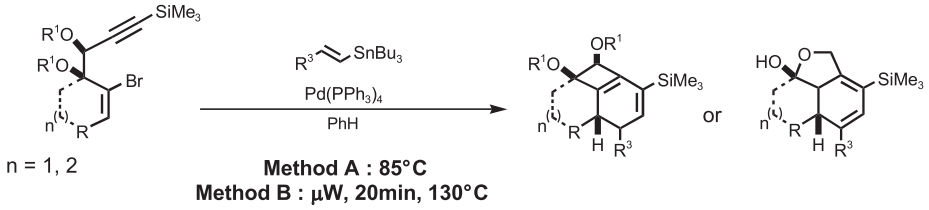


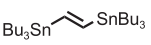
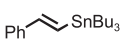
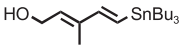
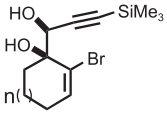
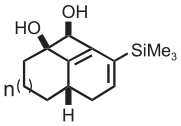
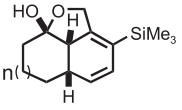
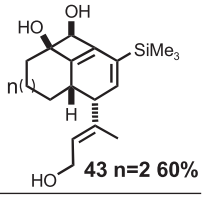
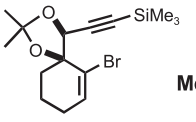
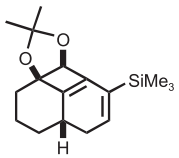
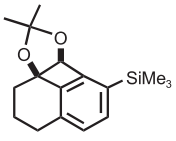
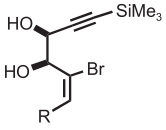
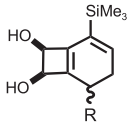
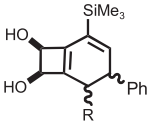
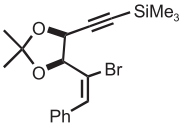
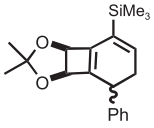
		Starting diol		
		 **7** **Method A**	 **8** **Method A**	 **9** **Method B**
Entries	R^2-SnBu_3	Products and yields		
1		 **10 n=1 R^3=Ph 69%** **11 n=2 R^3=Ph 61%**	 **17 R^3=Ph 53%**	 **20 R^3=Ph 85%** **21 R^3=TMS 80%** **22 R^3=$(CH_2)_2CH_3$ 86%** **23 R^3=$(CH_2)_3CH_3$ 85%** **24 R^3=$(CH_2)_4CH_3$ 80%** **25 R^3=$(CH_2)_7CH_3$ 80%**
2		 **12 n=1 X=O 84%** **13 n=2 X=O 70%**	 **18 X=O 83%**	 **26 X=O 63%** **27 X=S 46%**
3		 **14 12%**	 **19 40%**	
4			 **28 R^3=Me R^4=TMS 77%** **29 R^3=H R^4=TBDMS 75%** **30 R^3=Me R^4=TBDMS 71%**	
5		 **15 n=1 56%** **16 n=2 71%**	 **31 63%**	
6			 **32 X=OMe 84%** **33 X=OBn 72%** **34 X=CH_2OTBDMS 85%** **35 X=OTBDPS 80%** **36 X=N(Me)Ph 79%**	

sequence leads to an eight-membered ring, which is present in over hundred different natural products, many exhibiting exceptional and broad-ranging biological activity. For example, Ophiobolin A[8] have a broad spectrum of biological activity against nematodes, fungi, and bacteria[9] as well as potent antitumor activity.[10] Aleurodiscal[11] is an antifungal antibiotic and one of the most notable examples is the diterpene paclitaxel (taxol) (Scheme 5).

Due to high degree of ring strain, transannular interactions and unfavorable entropic and enthalpic factors, the synthesis of eight-membered ring compounds remains a difficult area.

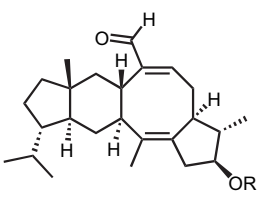
Table 2. Cyclocarbopalladation followed by Stille cross-coupling terminated by a 6π electrocyclization process

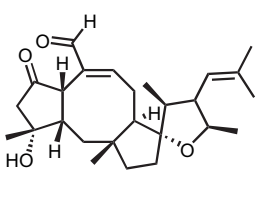


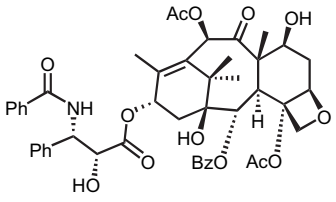
		Stannanes R^3–SnBu$_3$			
					
		A	**B**	**C**	**D**
Entries	Starting diol	Products and yields			
1	 **7**	**Method A**  **39 n=1 35%** **40 n=2 62%**	 **41 n=1 62%** **42 n=2 24%**		 **43 n=2 60%**
2	 **8**	**Method A**  **44 45%**	 **45 21%**		
3	 **37 R=H** **9 R=Ph**	**Method B**  **46 R=H 44%** **47 R=Ph 49%**		 **48 R=Ph 36%**	
4	 **38**	**Method B**  **49 91%**			

To solve this difficulty, several authors have presented, in the recent past, elegant approaches using transition metal catalysis.[12] The most recent approach implied the formation of a bicyclic structure using a rhodium catalyst in a one pot operation.[13] Extensive studies by several research groups[14] have been performed to reach analogues of Ophiobolin A and Aleurodiscal. The total synthesis of Ophiobolin C was completed by Kishi in 1989.[15] However, none of these approaches involved the direct formation of a 5-8-5 tricyclic skeleton.

Four types of diols were used for this study, unprotected (**7**, **9**, and **52**), protected (**38**), cyclic (**7** and **52**), and acyclic (**9** and **38**).[16] The stannanes were prepared by a straightforward method developed by Lautens et al.[17] The reaction cascade is based on three consecutive transformations starting from the

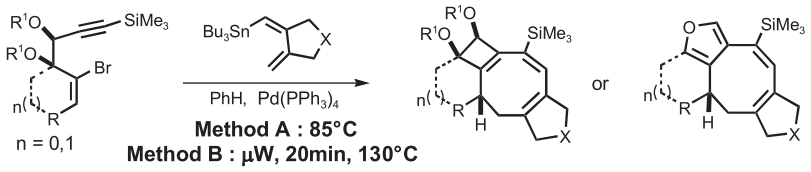

Aleurodiscal

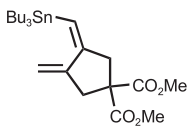
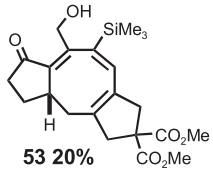
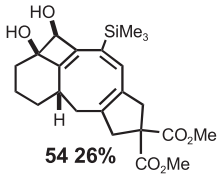
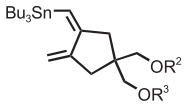
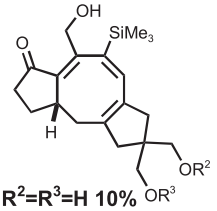
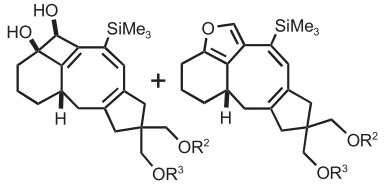
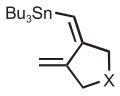
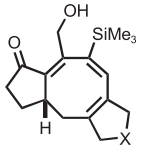
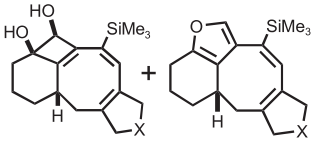
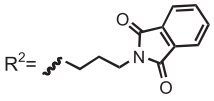
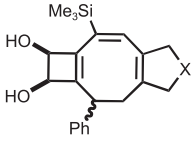
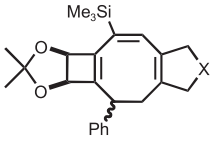

Ophiobolin A


Taxol

Scheme 5.

Table 3. Cyclocarbopalladation followed by a Stille cross-coupling terminating by a 8π electrocyclization process



Entries	Stannanes	Starting diol: 52 (Method A)	7 (Method A)	9 (Method B)	38 (Method B)
1		 53 20%	 54 26%		
2		 55 R^2=R^3=H 10% 56 R^2,R^3=$C(CH_3)_2$ 16%	 57-58 R^2=R^3=H 61% ratio 59:41 59-60 R^2,R^3=$C(CH_3)_2$ 15% ratio 100:0	Decomposition R^2,R^3=$C(CH_3)_2$	Decomposition R^2,R^3=$C(CH_3)_2$
3		 61 X=NTs 16% 62 X=O 24%	 63-64 X=NTs 56% ratio 48:52 65-66 X=O 11% ratio 100:0 67-68 X=CH-CH_2-OH 41% ratio 100:0 69-70 X=NR^2 58% ratio 40:60 	 71 X=NTs 27% 2 dias	 72 X=NTs 62% 2 dias

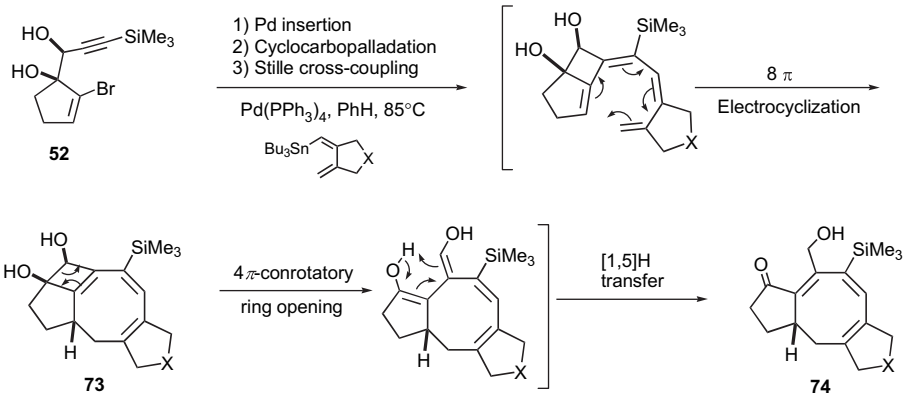
diol: an initial 4-*exo-dig* cyclocarbopalladation followed by a Stille cross-coupling and eventually a concerted conrotatory 8π electrocyclization. The results are summarized in Table 3.

Different types of products were obtained with this cascade depending on the ring size of the starting substrate. The first product type (**53**, **55**, **56**, **61**, and **62**) was generated from cyclopentene diol **52** in a sequence of six steps (Scheme 6). After the palladium insertion, the cyclocarbopalladation, the Stille cross-coupling, and the 8π electrocyclization, the strained cyclobutene **73** underwent a 4π conrotatory ring opening and a [1,5]-hydrogen shift to give the compound of type **74**.

When the cyclohexene diol **7** were used, the reaction to obtain the corresponding cyclobutenediol was limited by the formation of furyl derivatives (**58**, **64**, and **70**), which probably result from a final rearrangement (ring opening, cyclization, and elimination). The yields observed ranging up to 58% were modest to acceptable if one consider the complexity of the new products formed in formally just one step from the readily available diols.

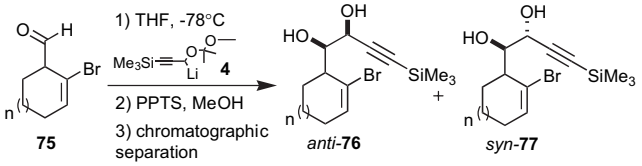
2.5. 5-*exo-dig* Cyclocarbopalladation

Considering the results obtained with the 4-*exo-dig* cyclocarbopalladation, our attention next focused on the use of



Scheme 6.

another type of reaction: the 5-*exo-dig* cyclization, a favored process according to Baldwin's rules,[8] starting from a substrate containing a propargylic diol function and the vinyl bromide included in an aliphatic ring. The starting diols *anti*-**76** and *syn*-**77** were again easily prepared in good yields by addition of the protected metalated propargylic alcohol **4** on bromo-aldehydes **75** followed by deprotection and chromatographic separation of the two *anti*- and *syn*-diastereomers (Scheme 7).[18]



Scheme 7.

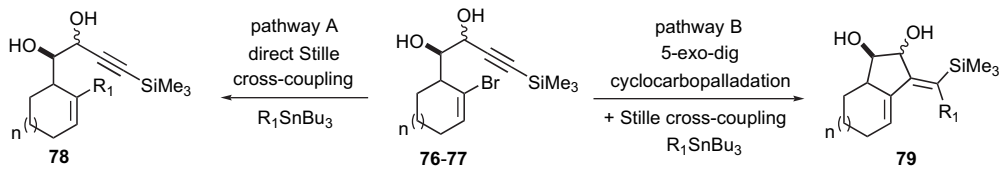
The impact of the stereochemistry of the starting diol and the size of the ring bearing the vinyl bromide function was examined with the same conditions and catalytic system described before for the 4-*exo-dig* cyclocarbopalladation: at 85 °C in benzene in the presence of a catalytic amount of $Pd(PPh_3)_4$ (10 mol %). The *trans*-bis(tributylstannyl)-ethylene was used to explore the competition between the two reactions: a direct Stille reaction (pathway A, compound **78**) or cyclocarbopalladation followed by a Stille termination (pathway B, compound **79**) (Scheme 8).

It turns out that the diols *anti*-**76** and *syn*-**77**, irrespective of cycle size, afforded only the products resulting from a 5-*exo-dig* cyclocarbopalladation, **82** and **83** (Table 4, entries 1 and 2), generally with acceptable to good yields. However, when the diols are protected (entries 3 and 4, **80** and **81**) as a dioxolane, the direct Stille cross-coupling competes significantly. Independent of considerations of the size of the ring, we distinguished the *cis*-dioxolane **80** that proceeded via a cyclocarbopalladation process to obtain compound **84**, from the *trans* dioxolane **81** that led exclusively to the direct Stille cross-coupling product **85**. In the later case, the cyclocarbopalladation did not proceed at all due to the highly strained tricyclic derivatives that should be obtained in theory.

2.6. 5-*exo-dig* Cyclocarbopalladation and CH activation

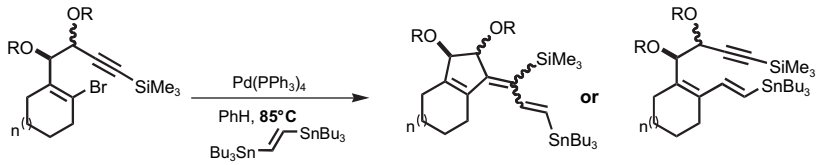
Considering the results obtained from the 5-*exo-dig* cyclocarbopalladation, our attention focused on the use of new, original *anti*-propargylic-1,2-diols **86**, **87**, **88**, **89** derived, respectively, from acetophenone, indole, tetralone, or benzosuberone (Table 5).[19] In the presence of vinylic (entry 1), allylic, or heteroaromatic stannane derivatives (entry 2), 5-*exo-dig* cyclocarbopalladation under classical conditions (85 °C, PhH, 10% mol $Pd(PPh_3)_4$) is efficient and products were isolated ranging up to 70% yields. The use of diol **88** gave the expected products **93** and **94** after the 5-*exo-dig* cyclocarbopalladation and the Stille cross-coupling. The five-membered ring diol **87**, under the same reaction conditions, led to the decomposition of starting materials. However, when acyclic diol **86** and benzosuberone derivative diol **89** are employed under these conditions, none of the expected products were obtained but only the styrene derivatives **90**, **95**–**103** were observed. The formation of these products resulted from a C–H palladative activation. Some recent papers describe a new C–H activation process of nonactivated aromatic derivatives using metal catalysis.[20] In the case of the diol **87**, this C–H activation was not observed probably because of the low flexibility of the ring. Thus, the regioselectivity of the final vinylic stannane partner is totally dependent of the substrate.

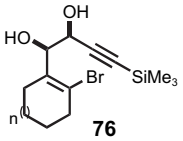
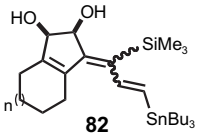
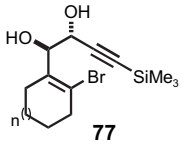
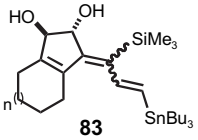
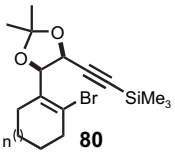
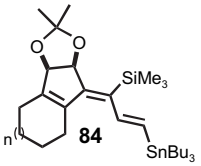
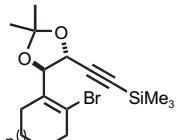
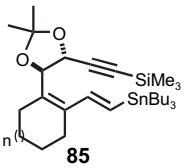
On the other hand, when alkynylstannanes were used, only the Stille cross-coupling product was observed with yields



Scheme 8.

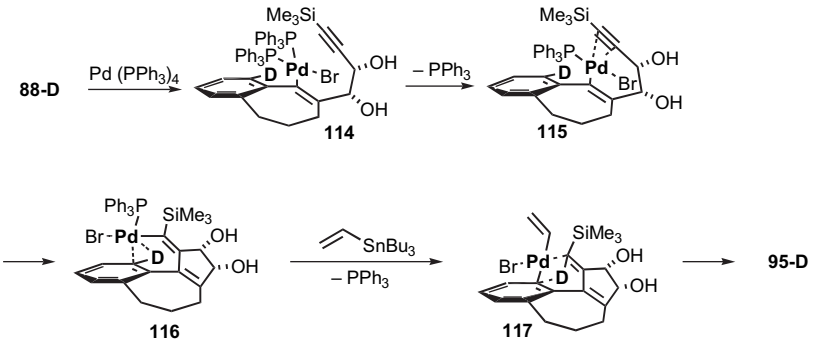
Table 4. Effect of the ring size and the protection of the hydroxyl functions



Entries	Starting diol	Products	*n*	Time (h)	Yield (%)	Ratio (*E*/*Z*)
1	 **76**	 **82**	0	14	75	78/22
			1	27	71	66/34
			2	16	45	100/0
			3	23	27	100/0
2	 **77**	 **83**	0	14	54	70/30
			1	27	52	100/0
			2	16	31	100/0
			3	23	—	100/0
3	 **80**	 **84**	0	17	54	—
			1	18	64	—
			2	14	48	—
4	 **81**	 **85**	0	17	38	—
			1	20	56	—
			2	17	52	—

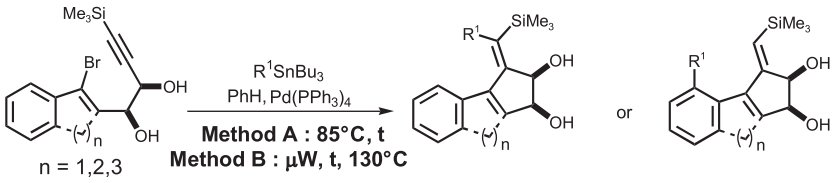
ranging up to 75% after cyclocarbopalladation on the silylated exocyclic double bond (**104**–**113**, Table 5, entry 3).

The mechanism of the C–H activation could be as follows. The sequence is initiated by the insertion of palladium(0) into the vinylic C–Br bond giving **114** by an oxidative addition (Scheme 9). After elimination of the first PPh_3 and cyclocarbopalladation of the triple bond (compound **116**), one can postulate a strong agostic interaction of the palladium atom with the closest aromatic C–H bond as shown in compound **117**. This intermediate is determinant for the C–H activation. Theoretical studies have been performed and corroborated with our postulation.[21] The intimate mechanism of the 1,5-vinyl to aryl palladium shift best corresponds to a proton transfer between the two formally negatively charged carbon atoms of the vinyl and the phenyl groups that are bound to the palladium atom in the transition state. As a consequence, the palladium center retains its +II oxidation state throughout the tandem reaction.[22] Deuterium labeled diol confirms that the H is transferred to the terminal vinyl silane through the coordination sphere of palladium.[24]

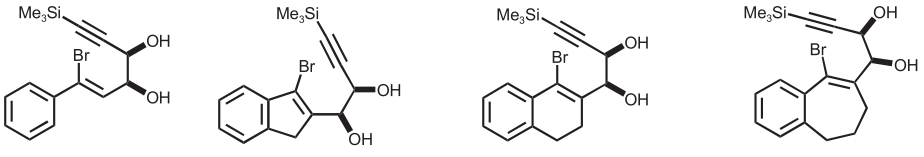


Scheme 9.

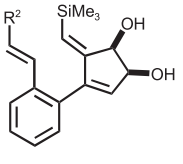
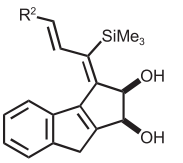
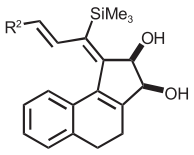
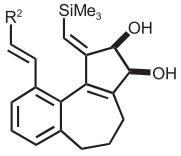
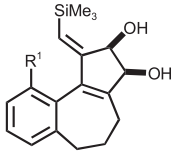
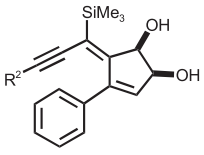
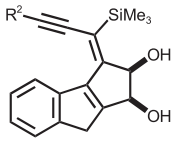
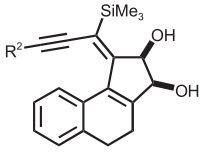
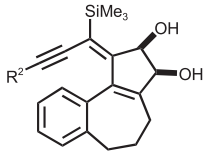
Table 5. Synthesis of Polycycles via palladium CH activation



Starting diol



86 **87** **88** **89**

Entries	R^1SnBu_3	Products
1		 **90 R^2=H, 30 min, 43%, B**  **91 R^2=H, 20 min, 0%, B** **92 R^2=$SnBu_3$, 20 min, 0%, B**  **93 R^2=H, 20 min, 59%, B** **94 R^2=$SnBu_3$, 20 min, 55%, B**  **95 R^2=H, 8h, 70%, A** **96 R^2=$SnBu_3$, 5h, 58%, A** **97 R^2=Ph, 10 min, 45%, B** **98 R^2=$SiMe_3$, 18 min, 70%, B** **99 R^2=(3-hydroxymethyl)phenyl, 18h, 61%, A**
2	R^1—$SnBu_3$	 **100 R^1=pyr, 20h, 53%, A** **101 R^1=thio, 54h, 48%, A** **102 R^1=allyl, 20h, 52%, A** **103 R^1=fur, 30 min, 53%, B**
3	R^2—≡—$SnBu_3$	 **104 R^2=$SiMe_3$, 38 min, 63%, B**  **105 R^2=Ph, 20 min, 0%, B** **106 R^2=$SiMe_3$, 20 min, 0%, B**  **107 R^2=Ph, 20 min, 49%, B** **108 R^2=$SiMe_3$, 20 min, 56%, B**  **109 R^2=Ph, 12h, 58%, A** **110 R^2=$SiMe_3$, 5h, 45%, A** **111 R^2=Pr, 18h, 75%, A** **112 R^2=TBSO$(CH_2)_3$, 8h, 54%, A** **113 R^2=TBSO$(CH_2)_2$, 8h, 48%, A**

3. Conclusion

In conclusion, we have shown that different sequences including a 4-*exo-dig* cyclization can be realized from γ-bromopropargylic diols under palladium catalysis. We first summarized the study of different parameters of the reaction (catalyst, solvent, and temperature) and the starting materials giving the optimal conditions to favor the cyclocarbopalladation process. These conditions were applied to realize different cascades: 4-*exo-dig* cyclocarbopalladation followed by a Stille cross-coupling and a 6π or 8π electrocyclizations.

The same kind of cascades has been realized including a 5-*exo-dig* cyclocarbopalladation and Stille cross-coupling. In some cases, with acetophenone and benzosuberone diols, a C–H palladative activation after the Stille cross-coupling was observed and styrene derivatives were isolated.

We have shown a major advancement in the field of cyclocarbopalladation cascades for the consecutive formation of several new carbon–carbon bonds in a single-step process. These approaches have already allowed impressive and economical constructions of polycyclic compounds with high molecular complexity. Some applications to the synthesis

of analogues of natural compounds are already in progress in the laboratory. These results will be disclosed in the future.

4. Experimental

4.1. General

Reactions were run under an atmosphere of argon in oven-dried glassware using a standard syringe, cannula, and septa apparatus. Et_2O and THF were distilled from sodium benzophenone. Benzene and DMF were distilled from CaH_2, and CH_2Cl_2 was distilled from P_2O_5. EtN_3 and *i*-Pr_2NH were distilled from KOH. Crude products were purified by flash column chromatography on Merck 230–400 mesh silica gel. For some compounds, 5% Et_3N treated silica gel was used to avoid decomposition. Analytical TLC was carried out on Merck (Kieselgel $60F_{254}$) silica gel plates. ^1H NMR spectra were recorded at 200 or 300 MHz using the residual solvent signal as internal reference ($CDCl_3$, 7.26, C_6D_6, 7.16 ppm). Chemical shifts are quoted in parts per million, coupling constants (*J*) are given in hertz. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), ap (apparent), br (broad). ^{13}C NMR spectra were recorded at 50 or 75 MHz at ambient temperature in $CDCl_3$ at 77.0 as internal reference. Multiplicities were determined in some cases by Jmod pulse sequence. Melting points were determined with a glass capillary apparatus and were uncorrected. IR were determined with a Perkin–Elmer 2000 apparatus. Mass spectra were obtained from the *Service de spectrométrie de Masse* of the Chemistry Institute of Strasbourg (France). High-Resolution Mass Spectral Analysis (HRMS) was performed using a Mariner ESI-Tof instrument from Applied Bio-System Perkin–Elmer. *n*-BuLi was titrated using pivaloyl *o*-toluidine following the Suffert method.[23] Microwave irradiations have been performed using BIOTAGE Smith Creator. Stannanes derivatives were prepared according to the literature methods[24] or commercially available.

4.2. Method A: general procedure: 4-*exo-dig* or 5-*exo-dig* cyclocarbopalladation under classical conditions

The reaction was carried out in an oven-dried 25 mL two-necked flask, equipped with a reflux condenser, under argon atmosphere. To a solution of the diol (1 equiv) in dried benzene was added $Pd(PPh_3)_4$ (0.1 equiv) followed by the stannylated reagent (1.3 equiv). The reaction mixture was stirred for 1–17 h in a preheated 85 °C oil bath. The reaction is followed by TLC. Then, the reaction mixture was concentrated in vacuo and immediately purified by flash chromatography.

4.3. Method B: general procedure: 4-*exo-dig* or 5-*exo-dig* cyclocarbopalladation under microwave irradiation (BIOTAGE system initiator)

The reaction was carried out in a special BIOTAGE flask, under argon atmosphere. To a solution of the diol (1 equiv) in dried benzene (2 mL) was added $Pd(PPh_3)_4$ (0.1 equiv) followed by the stannylated reagent (1.3 equiv). The mixture was purged 20 min with argon and heated at 130 °C under microwave irradiation. The reaction was followed by TLC. After the reaction time, the mixture was cooled, diluted with Et_2O (10 mL), treated with active charcoal, filtrated over Celite, and concentrated to dryness. The reaction mixture was purified by flash chromatography (in the majority of the cases two chromatographies are necessary).

4.3.1. Cyclocarbopalladation 4-*exo-dig* following by a Stille cross-coupling. Compounds **10**–**19** are already described in Ref. 2b.

4.3.2. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-(3-phenyl-1-(trimethylsilyl)prop-2-ynylidene)cyclobutane-1,2-diol (20). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (90 mg, 85%) as a yellow solid. R_f: 0.36 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J*=1.5 Hz, Ar*H*), 7.63 (d, 2H, *J*=7.1 Hz, Ar*H*), 7.48 (d, 1H, *J*=1.5 Hz, Ar*H*), 7.45 (d, 1H, *J*=1.5 Hz, Ar*H*), 7.38-7.31 (m, 6H, Ar*H*, Ph-C*H*), 4.99 (t, 1H, *J*=5.6 Hz, HO-C*H*-CH-OH), 4.81 (t, 1H, *J*=6 Hz, HO-CH-C*H*-OH), 3.74 (br s, 1H, OH), 3.61 (br s, 1H, OH), 0.32 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 142.8, 135.8, 131.2, 129.7, 129.5, 128.6, 128.5, 128.3, 128.1, 124.2, 121.0, 103.4, 91.9, 72.4, 71.3, −1.0. HRMS (ESI, positive ion 180 eV) calcd for $(C_{23}H_{24}O_2SiNa)^+$: 383.1441; found: 383.1502. IR (FTIR, film): ν=3400 (br), 2118, 1646, 1485, 1249, 1047, 976, 844, 756 cm^{-1}.

4.3.3. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1,3-bis(trimethylsilyl)prop-2-ynylidene]cyclobutane-1,2-diol (21). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (108 mg, 80%) as a yellow solid. R_f: 0.30 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J*=1.5 Hz, Ar*H*), 7.57 (d, 2H, *J*=6.8 Hz, Ar*H*), 7.35–7.29 (m, 3H, Ar*H*, Ph-C*H*), 4.89 (br t, 1H, HO-C*H*-CH-OH), 4.68 (t, 1H, *J*=6.2 Hz, HO-CH-C*H*-OH), 4.40 (br s, 1H, OH), 4.22 (br s, 1H, OH), 0.24 (s, 9H, $SiMe_3$), 0.22 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 142.6, 135.8, 129.9, 129.5, 128.7, 128.3, 121.3, 109.35, 106.9, 72.3, 71.3, 0.1, −1.0. HRMS (ESI, positive ion 180 eV) calcd for $(C_{20}H_{28}O_2Si_2Na)^+$: 379.1526; found: 379.1519. IR (FTIR, film): ν=3410 (br), 2116, 1639, 1487, 1245, 1045, 975, 842, 752 cm^{-1}.

4.3.4. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1-(trimethylsilyl)-hex-2-ynylidene]cyclobutane-1,2-diol (22). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (83 mg, 86%) as a yellow powder. R_f: 0.30 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar*H*), 7.58 (d, 2H, *J*=7.8 Hz, Ar*H*), 7.35–7.25 (m, 3H, Ar*H*, Ph-C*H*), 4.90 (t, 1H, *J*=5.9 Hz, HO-C*H*-CH-OH), 4.72 (t, 1H, *J*=5.9 Hz, HO-CH-C*H*-OH), 3.89 (br s, 1H, O*H*), 3.69 (br s, 1H, O*H*), 2.50 (t, 2H, *J*=6.8 Hz, CH_2), 1.65 (q, 2H, *J*=7.2 Hz, CH_2), 1.05 (t, 3H, *J*=7.2 Hz, CH_3), 0.23 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 142.8, 136.0, 129.3, 128.6, 128.3, 128.0, 122.6, 105.4, 82.7, 72.2, 71.1, 22.5, 13.7, −1.1. HRMS (ESI, positive ion 180 eV) calcd for $(C_{20}H_{26}O_2SiNa)^+$: 349.1600; found: 349.1595.

4.3.5. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1-(trimethylsilyl)-hept-2-ynylidene]cyclobutane-1,2-diol (23). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (85 mg, 85%) as a yellow powder. R_f: 0.32 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar*H*), 7.58 (d, 2H, *J*=7.8 Hz, Ar*H*), 7.36–7.26 (m, 3H, Ar*H*, Ph-C*H*), 4.92 (t, 1H, *J*=5.3 Hz, HO-C*H*-CH-OH), 4.74 (t, 1H, *J*=6.24 Hz, HO-CH-C*H*-OH), 3.62 (d, 1H, *J*=6.8 Hz, O*H*), 3.44 (d, 1H, *J*=7.5 Hz, O*H*), 2.53 (t, 2H, *J*=6.8 Hz, CH_2), 1.64–1.27 (m, 4H, 2×CH_2), 0.94 (t, 3H, *J*=7.2 Hz, CH_3), 0.24 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 142.7, 136.0, 129.3, 128.6, 128.3, 128.0, 122.7, 105.6, 82.6, 72.1, 71.1, 31.1, 22.1, 20.1, 13.6, −1.1. HRMS (ESI, positive ion 180 eV) calcd for $(C_{21}H_{28}O_2SiNa)^+$: 363.1756; found: 363.1760.

4.3.6. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1-(trimethylsilyl)-oct-2-ynylidene]cyclobutane-1,2-diol (24). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (83 mg, 80%) as a yellow powder. R_f: 0.33 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H, Ar*H*), 7.56 (d, 2H, *J*=6.8 Hz, Ar*H*), 7.33–7.24 (m, 3H, Ar*H*, Ph-C*H*), 4.85 (br d, 1H, *J*=5.2 Hz, HO-C*H*-CH-OH), 4.68 (br m, 1H, HO-CH-C*H*-OH, O*H*), 2.51 (t, 2H, *J*=7.2 Hz, CH_2), 1.68–1.57 (m, 2H, CH_2), 1.46–1.27 (m, 4H, 2×CH_2), 0.94 (t, 3H, *J*=7.2 Hz, CH_3), 0.19 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 142.8, 136.0, 129.3, 128.6, 128.3, 128.0, 122.7, 105.7, 82.6, 72.2, 71.1, 31.2, 28.7, 22.2, 20.4, 13.9, 13.6, −1.1. HRMS (ESI, positive ion 180 eV) calcd for $(C_{22}H_{30}O_2SiNa)^+$: 377.1913; found: 377.1829.

4.3.7. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1-(trimethylsilyl)-undec-2-ynylidene]cyclobutane-1,2-diol (25). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (84 mg, 80%) as a yellow oil. R_f: 0.39 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar*H*), 7.59 (d, 2H, *J*=7.1 Hz, Ar*H*), 7.35–7.25 (m, 3H, Ar*H*, Ph-C*H*), 4.92 (t, 1H, *J*=7.2 Hz, HO-C*H*-CH-OH), 4.73 (t, 1H, *J*=7.2 Hz, HO-CH-C*H*-OH), 3.63 (d, 1H, *J*=6.2 Hz, O*H*), 3.45 (d, 1H, *J*=7.2 Hz, O*H*), 2.52 (t, 2H, *J*=6.9 Hz, CH_2), 1.68–1.58 (m, 2H, CH_2), 1.48–1.27 (m, 10H, 5×CH_2) 0.93 (t, 3H, *J*=7.2 Hz, CH_3), 0.24 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 143.0, 136.0, 129.4, 128.5, 128.2, 127.9, 122.5, 105.6, 82.7, 72.2, 71.2, 31.8, 29.1, 29.0, 22.6, 20.4, 17.3, 14.1, 13.6, −1.1. HRMS (ESI, positive ion 180 eV) calcd for $(C_{25}H_{36}O_2SiNa)^+$: 419.2382; found: 419.2377.

4.3.8. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[2-furyl(trimethylsilyl)methylene]cyclobutane-1,2-diol (26). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with AcOEt/Hept (20/80) afforded the product (61 mg, 63%) as a yellow oil. R_f: 0.40 (AcOEt/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 2H, *J*=7.2 Hz, Ar*H*), 7.44 (s, 1H, Ar*H*), 7.33–7.24 (m, 3H, Ar*H*, Ph-C*H*), 6.48 (br s, 1H, furyl-*H*), 6.46 (t, 1H, *J*=3.2 Hz, furyl-*H*), 6.24 (d, 1H, *J*=3.2 Hz, furyl-*H*), 4.93 (d, 1H, *J*=5.6 Hz, HO-C*H*-CH-OH), 5.82 (d, 1H, *J*=5.6 Hz, HO-CH-C*H*-OH), 3.29 (br s, 2H, O*H*), 0.24 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.9, 141.5, 140.9, 135.9, 130.8, 129.3, 129.2, 128.6, 128.1, 111.3, 107.9, 71.8, 70.5, −0.3. MS (ESI, positive ion 180 eV) calcd for $(C_{19}H_{22}O_3SiNa)^+$: 349.12; found: 349.13.

4.3.9. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[thien-2-yl(trimethylsilyl)methylene]cyclobutane-1,2-diol (27). Preparation by method B on 0.295 mmol scale with a reaction time of 30 min. Purification by flash chromatography eluting with AcOEt/Hept (20/80) afforded the product (47 mg, 46%) as a yellow oil. R_f: 0.31 (AcOEt/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.21 (m, 6H, Ar*H*, Ph-C*H*), 7.05 (dd, 1H, *J*=3.1, 1.5 Hz, thionyl-*H*), 6.66 (d, 1H, *J*=3.1 Hz, thionyl-*H*), 5.98 (d, 1H, *J*=1.5 Hz, thionyl-*H*), 4.95 (d, 1H, *J*=5.3 Hz, HO-C*H*-CH-OH), 4.84 (d, 1H, *J*=6.5 Hz, HO-CH-C*H*-OH), 2.90 (br s, 2H, O*H*), 0.21 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 153.5, 141.0, 140.9, 135.8, 130.2, 129.1, 129.0, 127.9, 127.6, 110.9, 107.5, 71.6, 70.1, −0.2. MS (ESI, positive ion 180 eV) calcd for $(C_{19}H_{22}O_2SSiNa)^+$: 365.10; found: 365.12.

4.3.10. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-{(4*E*)-4-methyl-1-(trimethylsilyl)-6-[(trimethylsilyl)oxy]hex-4-en-2-ynylidene}cyclobutane-1,2-diol (28). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (97 mg, 77%) as a yellow powder. R_f: 0.36 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H, Ph-C*H*), 7.59 (d, 2H, *J*=7.8 Hz, Ar*H*), 7.38–7.19 (m, 3H, Ar*H*), 5.98 (t, 1H, *J*=6.3 Hz, CH_2-C*H*), 4.93 (dd, 1H, *J*=7.8, 6.8 Hz HO-C*H*-CH-OH), 4.77 (dd, 1H, *J*=7.1, 6.8 Hz, HO-C*H*-CH-OH), 4.28 (d, 2H, *J*=6.3 Hz, O-CH_2), 3.35 (d, 1H, *J*=7.1 Hz, O*H*), 3.23 (d, 1H, *J*=7.1 Hz, O*H*), 1.92 (s, 3H, CH_3), 0.27 (s, 9H, O-$SiMe_3$), 0.15 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 142.5, 141.5, 134.8, 129.3, 128.6, 128.1, 121.5, 109.8, 102.0, 92.1, 73.2, 72.6, 65.5, 57.3, 17.7, 0.2, −1.3. MS (ESI, positive ion 180 eV) calcd for $(C_{24}H_{34}O_3SiNa)^+$: 449.19; found: 449.23.

4.3.11. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[(4*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(trimethylsilyl)hex-4-en-2-ynylidene]cyclobutane-1,2-diol (29). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (98 mg, 75%) as a yellow oil. R_f: 0.40 (Et_2O/Hept: 30/70). ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (s, 1H, Ph-C*H*), 7.60 (d, 2H, *J*=6.8 Hz, Ar*H*), 7.35–7.29 (m, 3H, Ar*H*), 6.21 (dt, 1H, *J*=15, 4.4 Hz, O-CH_2-C*H*=CH), 6.06 (d, 1H, *J*=15 Hz, O-CH_2-CH=C*H*), 4.91 (t, 1H, *J*=5.9 Hz, HO-C*H*-CH-OH), 4.72 (t, 1H, *J*=5.9 Hz, HO-CH-C*H*-OH), 4.30 (d, 2H, *J*=4.4 Hz, O-CH_2), 4.05 (br s, 1H, O*H*), 3.88 (br s, 1H, O*H*), 0.94 (s, 9H, O-Si-*t*Butyl), 0.24 (s, 9H, $SiMe_3$), 0.10 (s, 6H, O-$SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 142.7, 141.6, 135.9, 129.4, 128.7, 128.2, 121.5, 109.9, 102.0, 92.1, 72.2, 71.2, 63.2, 25.9, 18.4, −1.1, −5.3. MS (ESI, positive ion 180 eV) calcd for $(C_{23}H_{38}O_3Si_2Na)^+$: 477.23; found: 477.22.

4.3.12. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[(4*E*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-1-(trimethylsilyl)hex-4-en-2-ynylidene]cyclobutane-1,2-diol (30). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (98 mg, 71%) as a yellow powder. R_f: 0.41 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H, Ph-C*H*), 7.58 (d, 2H, J=7.7 Hz, Ar*H*) 7.39–7.20 (m, 3H, Ar*H*), 6.01 (t, 1H, J=6.2 Hz, CH_2-C*H*), 4.98 (dd, 1H, J=7.3, 6.8 Hz, HO-C*H*-CH-OH), 4.77 (dd, 1H, J=7.3, 6.8 Hz, HO-CH-C*H*-OH), 4.19 (d, 2H, J=6.2 Hz, O-CH_2), 3.60 (d, 1H, J=7.3 Hz, O*H*), 3.46 (d, 1H, J=7.3 Hz, O*H*), 1.92 (s, 3H, CH_3), 0.96 (s, 9H, O-Si-*t*Butyl), 0.23 (s, 9H, $SiMe_3$), 0.12 (s, 6H, O-$SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 142.4, 141.2, 137.0, 136.0, 129.2, 128.7, 128.3, 121.5, 119.7, 106.3, 102.0, 89.1, 72.0, 71.1, 60.2, 26.8, 18.3, −1.0, −5.1. MS (ESI, positive ion 180 eV) calcd for $(C_{27}H_{40}O_3Si_2Na)^+$: 491.24; found: 491.20.

4.3.13. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[1-(trimethylsilyl)but-3-enylidene]cyclobutane-1,2-diol (31). Preparation by method B on 0.295 mmol scale with a reaction time of 30 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (60 mg, 63%) as a yellow oil. R_f: 0.30 (Et_2O/Hept: 30/70). ^1H NMR (200 MHz, $CDCl_3$) δ 7.58 (d, 2H, J=7.6 Hz, Ar*H*), 7.38–7.25 (m, 3H, Ar*H*), 6.75 (s, 1H, Ph-C*H*), 5.97–5.78 (m, 1H, CH_2=C*H*), 5.15–5.05 (m, 2H, CH_2=CH), 4.87 (ap t, 1H, J=7.3 Hz, HO-C*H*-CH-OH), 4.73 (ap t, 1H, J=6.8 Hz, HO-C*H*-CH-OH), 3.17 (d, 2H, J=5.6 Hz, CH_2), 2.97 (d, 1H, J=6.6 Hz, O*H*), 2.72 (d, 1H, J=7.3 Hz, O*H*), 0.22 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.9, 142.3, 141.1, 136.2, 135.3, 128.8, 128.6, 127.9, 115.7, 71.5, 70.4, 36.4, −0.6. HRMS (ESI, positive ion 180 eV) calcd for $(C_{18}H_{24}OSiNa)^+$: 323.1438; found: 323.1421.

4.3.14. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[4-methoxy-1-(trimethylsilyl)but-2-ynylidene]cyclobutane-1,2-diol (32). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (86 mg, 84%) as a yellow oil. R_f: 0.39 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar*H*), 7.57 (d, 2H, J=7.5 Hz, Ar*H*), 7.33–7.26 (m, 3H, Ar*H*, Ph-C*H*), 4.87 (d, 1H, J=6.5 Hz, HO-C*H*-CH-OH), 4.68 (d, 1H, J=6.5 Hz, HO-CH-C*H*-OH), 4.40 (s, 2H, CH_2-OMe), 3.43 (s, 3H, O*Me*), 0.21 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 142.1, 135.8, 129.5, 129.3, 128.7, 128.4, 120.5, 98.8, 88.1, 72.0, 71.1, 61.0, 57.6, −1.0. MS (ESI, positive ion 180 eV) calcd for $(C_{19}H_{24}O_3SiNa)^+$: 351.56; found: 351.56.

4.3.15. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[4-benzyloxy-1-(trimethylsilyl)but-2-ynylidene]cyclobutane-1,2-diol (33). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (90 mg, 72%) as a yellow oil. R_f: 0.45 (Et_2O/Hept: 30/70). ^1H NMR (200 MHz, $CDCl_3$) δ 7.56–7.34 (m, 11H, Ar*H*, Ph-C*H*), 5.31 (s, 2H, HO-C*H*-C*H*-OH), 4.53 (s, 2H, Ph-CH_2-O), 4.49 (s, 2H, Ph-CH_2-O-CH_2), 0.39 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 149.0, 142.3, 135.7, 130.9, 129.5, 129.2, 129.1, 128.5, 128.1, 127.3, 120.8, 118.1, 114.1, 99.3, 85.7, 72.0, 71.1, 43.7, 38.7, −1.2. MS (ESI, positive ion 180 eV) calcd for $(C_{25}H_{28}O_3SiNa)^+$: 427.17; found: 427.18.

4.3.16. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[5-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(trimethylsilyl)pent-2-ynylidene]-cyclobutane-1,2-diol (34). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80 → 30/70) afforded the product (111 mg, 85%) as a yellow powder. R_f: 0.29 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H, Ar*H*), 7.57 (d, 2H, J=7.2 Hz, Ar*H*), 7.33–7.26 (m, 3H, Ar*H*, Ph-C*H*), 4.84 (br s, 2H, HO-CH-C*H*-OH, O*H*), 4.66 (br s, 2H, HO-C*H*-CH-OH, O*H*), 3.82 (t, 2H, J=7.6 Hz, O-CH_2), 2.74 (t, 2H, J=7.6 Hz, O-CH_2-CH_2), 0.90 (s, 9H, Si-*t*Butyl), 0.19 (s, 9H, $SiMe_3$), 0.08 (s, 6H, $SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 142.8, 129.5, 128.6, 128.0, 122.0, 101.4, 83.7, 72.2, 71.1, 62.2, 25.8, 24.8, 18.2, −1.1, −5.3. MS (ESI, positive ion 180 eV) calcd for $(C_{25}H_{38}O_3Si_2Na)^+$: 475.22; found: 475.18.

4.3.17. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[4-{[*tert*-butyl(diphenyl)silyl]oxy}-1-(trimethylsilyl)but-2-ynylidene]-cyclobutane-1,2-diol (35). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (101 mg, 80%) as a yellow powder. R_f: 0.33 (Et_2O/Hept: 30/70). ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.30 (m, 16H, Ar*H*, Ph-C*H*), 4.86–4.81 (m, 2H, HO-C*H*-C*H*-OH), 4.62 (s, 2H, O-CH_2), 0.91 (s, 9H, Si-*t*Butyl), 0.31 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 144.5, 138.2, 137.8, 136.7, 136.5, 136.1, 135.6, 135.5, 134.7, 134.6, 133.5, 129.7, 129.6, 129.4, 128.8, 128.5, 128.4, 128.1, 127.6, 127.4, 73.5, 72.9, 63.8, 26.7, 19.2, −0.9. MS (ESI, positive ion 180 eV) calcd for $(C_{34}H_{40}O_3SiNa)^+$: 575.25; found: 575.32.

4.3.18. (1*S*,2*R*,3*Z*,4*Z*)-3-Benzylidene-4-[4-[methyl(phenyl)-amino]-1-(trimethylsilyl)but-2-ynylidene]cyclobutane-1,2-diol (36). Preparation by method B on 0.295 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded the product (94 mg, 79%) as a yellow powder. R_f: 0.18 (Et_2O/Hept: 30/70). ^1H NMR (200 MHz, $CDCl_3$) δ 7.56–7.11 (m, 11H, Ar*H*, Ph-C*H*), 5.11 (d, 1H, J=6.8 Hz, HO-C*H*-CH-OH), 4.86 (d, 1H, J=6.8 Hz, HO-CH-C*H*-OH), 3.89 (s, 2H, N-CH_2), 3.05 (s, 3H, N-CH_3), 0.22 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.6, 148.9, 147.0, 139.5, 138.9, 137.8, 128.7, 128.4, 127.5, 127.3, 127.0, 117.3, 95.1, 88.6, 72.2, 69.8, 51.0, 38.9, −1.3. MS (ESI, positive ion 180 eV) calcd for $(C_{25}H_{29}O_2SiNa)^+$: 403.19; found: 403.22.

4.3.19. The 6π electrocyclization process. Compounds **39**–**45** are already reported in Ref. 2b.

4.3.20. (7*R*,8*S*)-2-(Trimethylsilyl)bicyclo[4.2.0]octa-1(6),2-diene-7,8-diol (46). Preparation by method B on 0.758 mmol scale with a reaction time of 30 min. Purification by flash chromatography eluting with Et_2O/Hept (30/70) afforded the product (65 mg, 44%) as a white solid. R_f: 0.28 (Et_2O/Hept: 30/70). ^1H NMR (200 MHz, $CDCl_3$)

δ 6.06 (t, 1H, J=4.9 Hz, C*H*-CH_2), 4.69 (d, 1H, J=4.4 Hz, HO-C*H*-CH-OH), 4.28 (d, 1H, J=4.4 Hz, HO-CH-C*H*-OH), 2.25–1.98 (m, 6H, 2×CH_2, 2×O*H*), 0.18 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 146.2, 138.4, 132.2, 74.4, 73.6, 24.2, 19.4, −1.5. MS (ESI, positive ion 180 eV) calcd for $(C_{11}H_{18}O_2SiNa)^+$: 233.09; found: 233.13.

4.3.21. (7*R*,8*S*)-5-Phenyl-2-(trimethylsilyl)bicyclo[4.2.0]-octa-1(6),2-diene-7,8-diol (47). Preparation by method B on 0.295 mmol scale with a reaction time of 30 min. Purification by flash chromatography eluting with AcOEt/Hept (20/80) afforded the product (65 mg, 49%) as a white solid. R_f: 0.36 (Et_2O/Hept: 30/70). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.21 (m, 3H, Ar*H*), 7.17–7.12 (m, 2H, Ar*H*, Ph-C*H*), 6.10 (t, 1H, J=4.9 Hz, Ar*H*), 4.85 (d, 1H, J=3 Hz, HO-C*H*-CH-OH), 4.73 (d, 1H, J=3 Hz, HO-CH-C*H*-OH), 3.70 (dd, 1H, J=11, 5 Hz, C*H*-CH_2), 2.94–2.45 (m, 4H, CH_2, 2×O*H*), 0.18 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 147.2, 137.8, 132.1, 128.6, 127.3, 126.6, 73.0, 73.0, 36.2, 35.4, −1.5. HRMS (ESI, positive ion 180 eV) calcd for $(C_{17}H_{22}O_2SiNa)^+$: 309.1287; found: 309.1253. IR (FTIR, film): ν=3410 (br), 2924, 2845, 1652, 1490, 1448, 1250, 1107, 1062, 893, 749 cm^{-1}.

4.3.22. [(3a*S*,7b*R*)-2,2-Dimethyl-7-phenyl-3a,6,7,7b-tetrahydrobenzo[3,4]cyclobuta[1,2-*d*][1,3]dioxol-4-yl](trimethyl)silane (49). Preparation by method B on 0.78 mmol scale with a reaction time of 20 min. Purification by flash chromatography eluting with Et_2O/Hept (5/95→40/60) afforded product (232 mg, 91%) as a white solid. R_f: 0.38 (Et_2O/Hept: 40/60). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, Ar*H*), 6.16 (t, 1H, J=4.4 Hz, =C*H*-CH_2), 5.36 (d, 1H, J=3 Hz, HO-C*H*-CH-OH), 5.26 (d, 1H, J=3 Hz, HO-CH-C*H*-OH), 3.74 (t, 1H, J=12 Hz, C*H*-CH_2), 2.84–2.67 (m, 1H, CH_{2a}), 2.54–2.37 (m, 1H, CH_{2b}), 1.53 (s, 3H), 1.43 (s, 3H), 0.19 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 146.8, 142.7, 138.1, 132.3, 128.6, 127.5, 126.5, 115.2, 81.7, 81.4, 37.4, 33.7, 29.4, 28.9, −1.5. HRMS (ESI, positive ion 180 eV) calcd for $(C_{20}H_{26}O_2SiNa)^+$: 346.1600; found: 346.1595.

4.3.23. The 8π electrocyclization process. Compounds **53–54** and **56–65** are already described in Ref. 16.

4.3.24. (10a*S*)-4,8,8-Tris(hydroxymethyl)-5-(trimethylsilyl)-1,7,8,9,10,10a-hexahydrodicyclopenta[*a,d*][8]annulen-3(2*H*)-one (55). Preparation by method A on 0.265 mmol scale with a reaction time of 9 h. Purification by flash chromatography eluting with Et_2O/Hept (20/80) afforded product (19 mg, 10%) as yellow oil. R_f: 0.13 (AcOEt/Hept: 30/70). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.00 (s, 1H, =C*H*), 4.48 (d, 1H, J=13.3 Hz, CH_{2a}-OH), 4.07 (d, 1H, J=13.3 Hz, CH_{2b}-OH), 3.63 (s, 2H, CH_2-OH), 3.58 (s, 2H, CH_2-OH), 3.40–3.21 (m, 1H, C*H*), 3.01–2.71 (br s, 2H, 2×O*H*), 2.62–1.89 (m, 7H), 0.15 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 156.3, 144.0, 138.8, 136.7, 136.1, 131.6, 69.8, 69.7, 62.3, 45.5, 45.0, 44.6, 40.0, 37.5, 37.0, 26.7, −0.5. HRMS (ESI, positive ion 175 eV) calcd for $(C_{20}H_{36}O_4Si)^+$: 363.1992; found: 363.1999.

4.3.25. (7*R*,12*S*)-2-(Hydroxymethyl)-5-(trimethylsilyl)-1,2,3,8,9,10,10a,11-octahydro-7*H*-6,7-methanobenzo[*a*]-cyclopenta[*d*][8]annulene-7,12-diol (67). Preparation by method B on 0.33 mmol scale with a reaction time of 38 min. Purification by flash chromatography eluting with AcOEt/Hept (5/95→40/60) afforded two diastereoisomers (47 mg, ratio 1/1, 41%) as yellow oils. R_f: 0.30, 0.35 (AcOEt/Hept: 40/60). Diastereoisomer **A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.05 (s, 1H, =C*H*), 4.52 (s, 1H, C*H*-OH), 3.56 (d, 1H, J=6.4 Hz, CH_2-OH), 2.57–2.44 (m, 12H, 4×CH_2, C*H*, 3×O*H*), 2.31–1.64 (m, 6H), 0.21 ($SiMe_3$).^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 144.3, 140.5, 136.7, 135.6, 134.9, 133.1, 79.6, 75.5, 67.10, 41.3, 40.0, 38.6, 36.8, 34.8, 33.4, 26.7, 22.4, −0.29 ($SiMe_3$). HRMS (ESI, positive ion 180 eV) calcd for $(C_{20}H_{30}O_3SiNa)^+$: 369.1862; found: 369.2182. Diastereoisomer **B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.0 (s, 1H, =C*H*), 4.4 (s, 1H, C*H*-OH), 3.5 (d, 1H, J=4.9 Hz, CH_2-OH), 2.8 (br s, 3H, 3×O*H*), 2.7–1.6 (m, 15H), 0.20 ($SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 144.2, 139.6, 136.3, 135.6, 134.8, 133.1, 80.7, 75.9, 67.3, 41.2, 39.8, 38.4, 36.8, 34.9, 33.5, 26.7, 22.4, −0.3. HRMS (ESI, positive ion 180 eV) calcd for $(C_{20}H_{30}O_3SiNa)^+$: 369.1862; found: 369.1934.

Preparation by method B on1.64 mmol scale with a reaction time of 32 min. Purification by flash chromatography eluting with AcOEt/Hept (20/80→80/20) afforded two products: furan derivative **69** (28 mg, 34%) as yellow oil, R_f: 0.30 (AcOEt/Hept: 40/60) and diol derivative **70** (20 mg, 24%) as yellow oil, R_f: 0.05 (AcOEt/Hept: 40/60); 58% as global yield.

4.3.26. 2-{3-[(7*S*,10a*S*,12*S*)-7,12-Dihydroxy-10a-methyl-5-(trimethylsilyl)-1,3,7,8,9,10,10a,11-octahydro-2*H*-6,7-methanobenzo[4,5]cycloocta[1,2-*c*]pyrrol-9(1*H*)-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (69). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H, Ar*H*), 7.73–7.71 (m, 2H, Ar*H*), 5.96 (s, 1H, =C*H*), 4.48 (s, 1H, C*H*-OH), 3.81–3.72 (ap t, 2H, J=7.2 Hz, N-CH_2), 3.64–3.43 (m, 4H), 2.74 (m, 3H), 2.53–2.46 (m, 1H), 2.04–1.83 (m, 10H), 1.63 (m, 1H), 0.21 ($SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 143.4, 139.1, 135.6, 134.3, 133.9, 131.0, 123.2, 79.5, 75.1, 65.8, 64.5, 53.4, 35.9, 34.7, 30.3, 29.7, 29.4, 27.0, 22.3, 21.5, −0.5. MS (ESI, positive ion 180 eV) calcd for $(C_{29}H_{36}N_2O_4SiNa)^+$: 527.23; found: 527.22.

4.3.27. 2-{3-[(11a*S*)-11a-Methyl-6-(trimethylsilyl)-2,3,8,10,11,11a-hexahydro[1]benzofuro[3′,4′:5,6,7]cycloocta[1,2-*c*]pyrrol-9(1*H*)-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (70). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2H, Ar*H*), 7.72–7.68 (m, 2H, Ar*H*), 7.05 (s, 1H, furyl-*H*), 6.05 (s, 1H, =C*H*), 3.81–3.72 (ap t, 4H, J=7.2 Hz, 2×N-CH_2), 3.51–3,43 (m, 2H), 2.83–2.70 (m, 2H), 2.60–2.54 (m, 4H), 2.48–2.38 (m, 1H), 2.21–2.17 (m, 1H), 2.04–1.83 (m, 4H), 1.82 (m, 1H), 0.11 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 149.1, 136.5, 135.6, 135.4, 133.9, 132.1, 125.2, 123.2, 120.7, 65.7, 64.5, 53.4, 36.0, 34.8, 30.3, 29.7, 29.3, 27.0, 23.0, 19.3, −1.2. MS (ESI, positive ion 180 eV) calcd for $(C_{29}H_{34}N_2O_3SiNa)^+$: 509.22; found: 509.22.

4.3.28. (6*R*,7*S*)-2[(4-Methylphenyl)sulfonyl]-5-phenyl-8-(trimethylsilyl)-2,3,4,5,6,7-octahexahydro-1*H*-cyclobuta[5,6]cycloocta[1,2-*c*]pyrrole-6,7-diol (71). Preparation by method B on 0.59 mmol scale with a reaction time of 38 min. Purification by flash chromatography eluting

with AcOEt/Hept (5/95→40/60) afforded two diastereoisomers (36 mg, 1/1, 27%) as yellow oil. R_f: 0.30, 0.35 (AcOEt/Hept: 40/60). ^{1}H NMR (200 MHz, $CDCl_3$). Diastereoisomer **A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=8.1 Hz, Ar*H*), 7.40–7.17 (m, 7H, Ar*H*), 6.00 (s, 1H, =C*H*), 4.53 (d, 1H, J=6.2 Hz, C*H*-OH), 4.47 (d, 1H, J=5.3 Hz, C*H*-OH), 4.15 (s, 2H, CH_2-N), 4.05-4.00 (br s, 2H, 2×O*H*), 3.63–3.50 (br s, 2H, CH_2-N), 2.58 (d, 1H, J=7.2 Hz, CH_a), 2.45 (s, 3H, Ar-CH_3), 2.34 (d, 1H, J=7.2 Hz, CH_b), 1.66 (s, 1H, C*H*-Ar), 0.21 ($SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 147.5, 143.7, 143.4, 142.7, 136.6, 133.1, 129.7, 128.9, 127.8, 127.5, 127.2, 73.0, 71.9, 58.4, 57.1, 44.0, 33.4, 26.8, −0.59. HRMS (ESI, positive ion 180 eV) calcd for $(C_{28}H_{33}NO_4Si_2Na)^+$: 507.19; found: 507.19. Diastereoisomer **B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H, Ar*H*), 7.40–7.23 (m, 7H, Ar*H*), 6.02 (s, 1H, =C*H*), 4.71 (br s, 1H, O*H*), 4.30–4.15 (m, 5H), 4.05–4.00 (d, 2H, J=7.1 Hz), 3.52–3.47 (m, 2H, CH_2-N), 2.43 (s, 3H, Ar-CH_3), 1.62 (s, 1H, C*H*-Ar), 0.26 ($SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.4, 143.4, 142.9, 142.7, 135.6, 133.1, 130.1, 128.8, 127.6, 127.5, 127.2, 73.1, 71.9, 58.4, 57.1, 44.0, 33.4, 26.8, −0.7. MS (ESI, positive ion 180 eV) calcd for $(C_{28}H_{33}NO_4Si_2Na)^+$: 507.19; found: 507.21.

4.3.29. (3a*R*,10b*S*)-2,2-Dimethyl-7-[(4-methylphenyl)sulfonyl]-4-phenyl-10-(trimethylsilyl)-4,5,6,7,10b-hexahydro-3a*H*-[1,3]dioxolo[3′,4′]cycloocta[1′,2′:5,6]cycloocta-[1,2*c*]pyrrole (72). Preparation by method B on 0.264 mmol scale with a reaction time of 30 min. Purification by flash chromatography eluting with AcOEt/Hept (20/80→40/60) afforded two nonseparable diastereoisomers (91 mg, 1/1, 62%) as yellow solid. R_f: 0.33, 0.35 (AcOEt/Hept: 40/60). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, Ar*H*), 7.67–7.20 (m, 5H, Ar*H*), 7.07 (m, 2H, Ar*H*), 6.04 (s, 1H, =C*H*), 5.18 (d, 1H, J=3.4 Hz, C*H*-OH), 4.65 (d, 1H, J=3.4 Hz, C*H*-OH), 4.30–4.06, (m, 4H, 2×CH_2-N), 3.47 (dd, 1H, J=8.7, 3.1 Hz, C*H*-Ar), 2.58–2.49 (m, 2H, CH_2), 2.43 (s, 3H, Ar-CH_3), 1.27 (br s, 6H, 2×CH_3), 0.25 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.1, 143.4, 141.2, 140.1, 132.9, 131.0, 129.8, 129.7, 128.8, 128.4, 128.3, 127.4, 127.0, 114.8, 81.5, 78.2, 58.0, 57.2, 41.2, 32.9, 29.2, 28.3, 21.4, −0.7. MS (ESI, positive ion 180 eV) calcd for $(C_{31}H_{37}NO_4SiNa)^+$: 570.21; found: 570.20.

4.3.30. 5-*exo*-*dig* Cyclocarbopalladation. Compounds **74**–**84** and **85**–**112** are already described in Refs. 18 and 19.

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Diastereoselective approach to 11-aryl steroid skeletons through a cobalt(I)-mediated [2+2+2] cyclization of allenediynes

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Abstract—The cobalt(I)-mediated [2+2+2] cycloaddition reactions of allenediynes of yne-allene-yne type bearing an aryl group on the allene are described. The cyclizations are totally chemo- and regioselective and show low diastereoselectivities. η^4-Complexed tricyclic (6,6,6) compounds were obtained in good yields as mixtures of *endo*/*exo* diastereomers. The cyclization is also compatible with an oxyfunctionality at C3. By designing an allenediyne having a preexisting D ring, we succeeded in building skeletons of 11-aryl steroids in one step and in a totally diastereoselective manner and with simultaneous introduction of an angular methyl group at C10 and an aryl substituent at C11.

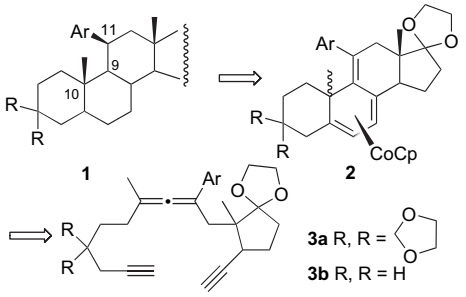
1. Introduction

In the last two decades, the synthesis, biological evaluation, and clinical applications of a new class of antiprogestational steroids, which present an 11β-aryl unit have been studied.[1,2] Due to their relevant pharmacological properties, a large number of synthetic efforts aimed at producing new compounds has been reported.[3] However the synthesis of such steroids is still in need of the development of new synthetic methods.

In the context of our interests in metal-catalyzed or radical cyclizations cascades directed toward the construction of basic skeletons of natural products,[4] we have explored the feasibility of building 11-aryl steroid frameworks by using an intramolecular cobalt(I)-mediated [2+2+2] cycloaddition reaction of allenediynes.

Transition metal-catalyzed cyclizations have already been used in the synthesis of the steroid nucleus.[5,6] As for an example, the cobalt(I) synthesis of racemic oestrone is probably the most spectacular illustration of the potency of such an approach.[7] In addition, intramolecular cyclizations of enediynes that allow the simultaneous formation of either the BCD or ABCD ring systems have been proposed.[8] Although 11-trimethylsilyl-substituted steroid frameworks have been described,[9] only one example of a low yielding access to 11-α-heterosubstituted steroid skeleton has been reported.

Our strategy depicted in Scheme 1 would allow in one step the creation of the ABC ring system and most interestingly, the simultaneous introduction of the substituents at both C11 and C10. Indeed, tetracyclic complex **2** could be reached from the intramolecular [2+2+2] cyclization of allenediyne **3** incorporating a preexisting D ring. Subsequent transformations of **2** might lead to 11β-aryl steroids **1**.



Scheme 1.

In this paper, after having presented the cyclizations of allenediynes of yne-allene-yne type, we will document and discuss the above approach that was achieved in our laboratory.[10]

2. Results and discussion

2.1. Cobalt(I)-mediated cyclizations of allenediynes of yne-allene-yne type

Allenes, which present cumulated C–C bonds are highly appealing candidates for the transition metal-catalyzed

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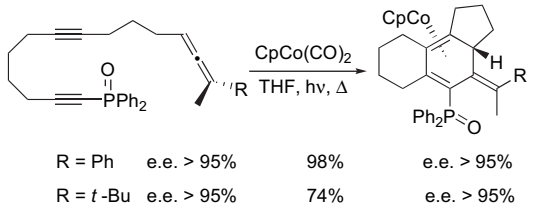
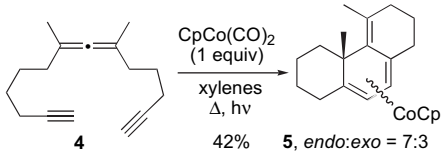
reactions. Over the last years, their reactivity in presence of various catalysts in a large variety of cyclizations and subsequently, their synthetic applications have been extensively investigated.[11,12] Although allenes are good ligands in organometallic complexes, only few examples involving this unsaturated component in [2+2+2] cycloaddition reactions have been reported.[13] Previously, it was discovered in our group that allenes are relevant partners for intramolecular [2+2+2] cocyclizations to alkynes.[14] For instance, upon treatment with $CpCo(CO)_2$, allenediynes of yne-yne-allene type furnished the corresponding cycloadducts in high yields and in a complete chemo-, regio-, and diastereoselective manner.[15] Moreover, with optically active allenes, the process can be performed with a total transfer of chirality (Scheme 2).



Scheme 2.

However, under the same conditions the allenediyne **4** with tetrasubstituted internal allene led chemo- and regioselectively to the corresponding η^4-complexed tricyclic compound **5** as a 7:3 diastereomeric mixture in moderate yield (Scheme 3).

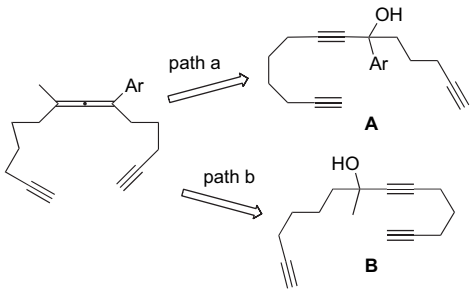


Scheme 3.

Before starting the synthesis of **2**, we initially decided to investigate the behavior of different allenediynes of yne-allene-yne type bearing an aryl group on the allene and to evaluate the influence of such substituent on the course of the cyclization.

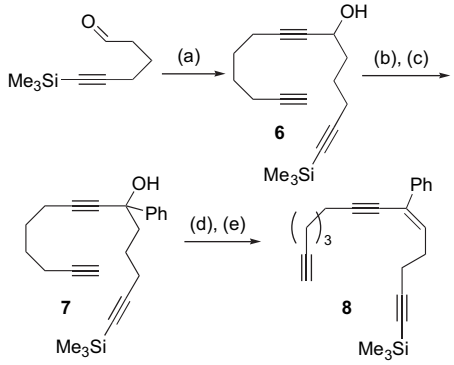
2.1.1. Preparation of the allenediynes. The preparation of allenic compounds has been widely investigated and highly useful methods have been developed for obtaining numerous substituted allenes.[16] In this study, we chose to introduce the allene unit via a copper(I) salt S_N2' displacement of propargylic sulfonate group.[17] Therefore, the allenediynes were prepared following the general sequence: (1) preparation of the requisite triyne and (2) introduction of the allene in the last step. However, it was possible to envision for this last step the addition of either methylcopper or arylcopper reagent onto the mesylates derived from the alcohol of type **A** or **B**, respectively (path a or b) (Scheme 4).

Thus, considering path a the addition of monolithiated octa-1,7 diyne to 6-trimethylsilyl-5-hexynal[18] furnished the corresponding alcohol **6**, which is readily transformed to the



Scheme 4.

tertiary alcohol **7** (Ar=Ph) (Scheme 5). However, its conversion into the corresponding mesylate failed and the enediyne **8** was obtained in 76%. Several attempts to carry out the S_N2' reaction with the corresponding methylether, even in presence of Lewis acid, were unsuccessful, the ether remaining unchanged.



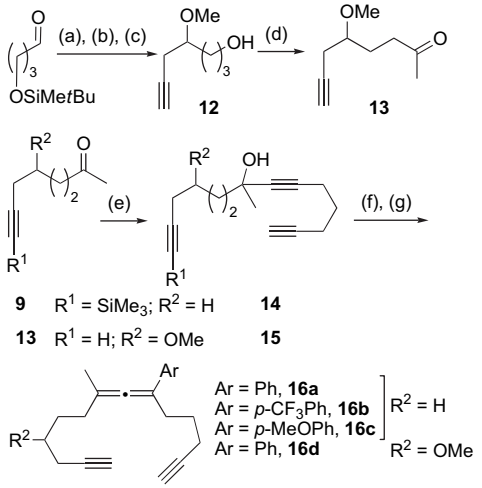
Scheme 5. (a) *n*-BuLi, octa-1,7-diyne, THF, −78 °C, 76%; (b) PCC, Al_2O_3, CH_2Cl_2, rt, 75%; (c) PhLi, THF, −78 °C, 86%; (d) *n*-BuLi, THF, −78 °C, MsCl; and (e) K_2CO_3, MeOH, rt, 76% from **7**.

In contrast, the allenediynes **16a–d** were obtained from the mesylates derived from alcohols **14** and **15** of type **B**, prepared from 8-(trimethylsilyl)-oct-7-yn-2-one[†] **9** or 5-methoxy-oct-7-yn-2-one **13**, which is readily prepared from 4-(*tert*-butyldimethylsilyloxy)-butyraldehyde[19] as described in Scheme 6.

Addition of the lithio derivative of hepta-1,6-diyne with the ketone **9** furnished the corresponding alcohol **14** in 70%. Then, the sequence—mesylation, S_N2' with arylcopper reagent, deprotection of the triple bond—led to the allenediynes **16a–c**. Starting from the ketone **13**, the whole sequence, which was carried out without purifying the intermediates led to **16d** in 36% overall yield.

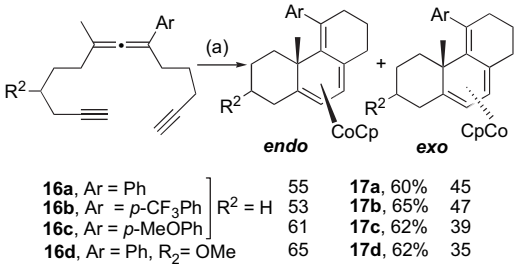
2.1.2. Cobalt(I)-mediated cyclizations of the allenediynes 16a–d. Exposure of **16a–d** to a stoichiometric amount of $CpCo(CO)_2$ in refluxing xylenes under irradiation (300 W visible lamp, 50% of its power) led to the complexed tricyclic compounds **17a–d** in 60–65% yield as a nearly 1:1

[†] 8-(Trimethylsilyl)-oct-7-yn-2-one was prepared by using the same reactions as for the parent compound 7-(trimethylsilyl)-hept-6-yn-2-one, see Ref. 18.



Scheme 6. (a) $HC{\equiv}CCH_2MgBr$, THF, −30 °C, **10**: 85%; (b) NaH, THF, rt, MeI, **11**: quantitative; (c) *n*-Bu_4NF, THF, 0 °C–rt, **12**: 86%; (d) 1. $(COCl)_2$, DMSO, NEt_3, −78 °C to rt, CH_2Cl_2; 2. MeMgBr, THF; 3. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, **13**: 75% from **12**; (e) *n*-BuLi, hepta-1,6-diyne, THF, −78 °C, **14**: 70%; (f) 1. *n*-BuLi, THF, −78 °C, MsCl; 2. ArMgBr/$Me_2S{\cdot}CuBr$/LiBr (1.5 equiv), THF, −50 °C, **16d**: 36% from **13**; and (g) K_2CO_3, MeOH, rt, **16b**: 72%; **16c**: 51%; **16d**: 33%.

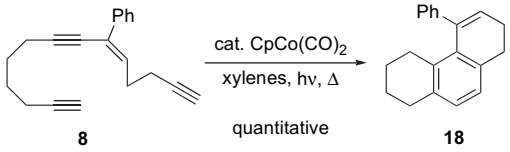
mixture of *endo*/*exo* diastereomers (Scheme 7). The *endo*/*exo* stereochemical assigments and ratios were determined by ^1H NMR on the basis of the chemical shift and integration of Cp-, dienic protons, and the angular CH_3, which is deshielded when located *syn* to cobalt and shielded when located *anti* (δCH_3 *endo*=1.80 ppm; δCH_3 *exo*=1.20 ppm).[14b,20]



Scheme 7. $CpCo(CO)_2$ (1 equiv), xylenes, hν, Δ.

Several features in these cyclizations are noteworthy: (i) they are totally regioselective and lead only to the (6,6,6) tricyclic cycloadducts; (ii) the yields are higher compared to the cyclization of allenediyne **4** due to an increase in the stability of the isolated complexes since they could be purified with non-degassed solvents on silica gel; (iii) the *endo*/*exo* diastereoselectivity is independent of the substitution on the allene; and (iv) the cyclization is compatible with an oxygenated functionality at C3.

Having in hands the diyne-ene-yne **8**, we checked its behavior in presence of a catalytic amount of $CpCo(CO)_2$ under the same conditions as above. The cycloadduct **18** was obtained in quantitative yield showing that the cyclotrimerization of the three alkynes is favored over the [2+2+2] cycloaddition of the enediyne moiety (Scheme 8).

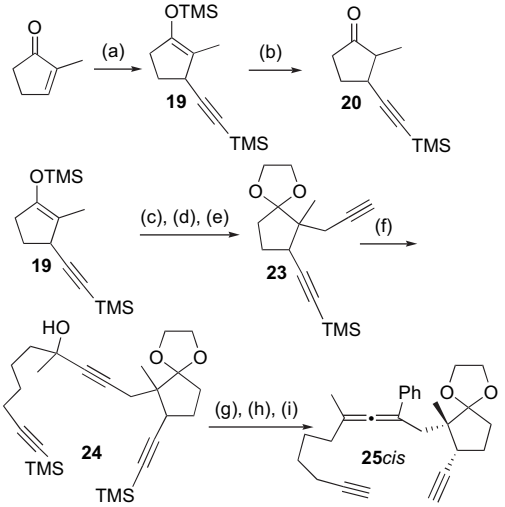


Scheme 8.

2.2. Diastereoselective approach to 11-aryl steroid skeletons

Since an aryl group was compatible with the conditions of the cyclization, we undertook the preparation of **3b** (R=H and Ar=Ph) starting from the commercially available 2-methyl-2-cyclopenten-1-one. Conjugate addition of (trimethylsilyl)ethynyl copper(I) reagent in the presence of iodotrimethylsilane provided the corresponding silyl enol ether **19** in 95% yield.[21] Subsequent acid hydrolysis furnished the ketone **20** in 85% yield.

Different methods at effecting the alkylation of **19** were quite unsuccessful; the use of MeLi or $NaNH_2$ in THF/HMPA resulted in decomposition of the starting material whereas the use of NaH led to a complex mixture of the ketone **20** and mono- and trialkylated adducts albeit in low yields (10–12%). The expected alkylated adduct was obtained from **19** with a slightly modified Nicholas reaction[22] (Scheme 9).



Scheme 9. (a) *n*-BuLi, $Me_3SiC{\equiv}CH$, TMSI, CuI, THF, −78 to −30 °C, **19**: 95%; (b) 1 M HCl, **20**: 85%; (c) $MeOCH_2{-}C{\equiv}CH{\cdot}Co_2(CO)_6$, $Et_2O{\cdot}BF_3$, CH_2Cl_2, rt, **21**: 95%; (d) CAN, acetone, rt, **22**: 78%; (e) 5 mol % PTSA, ethylene glycol (2 equiv), benzene (0.01 M), **23***cis*/*trans*: 95%; (f) *n*-BuLi, −78 °C, THF, $CH_3C(O)(CH_2)_4C{\equiv}CSiMe_3$, **24***cis*: 60%; **24***trans*: 50%; (g) *n*-BuLi; MsCl, THF, −78 °C; (h) $Me_2S{\cdot}CuBr$, PhMgCl, LiBr, THF, −50 °C, 10%; and (i) K_2CO_3, MeOH, rt, **25***cis*: quantitative.

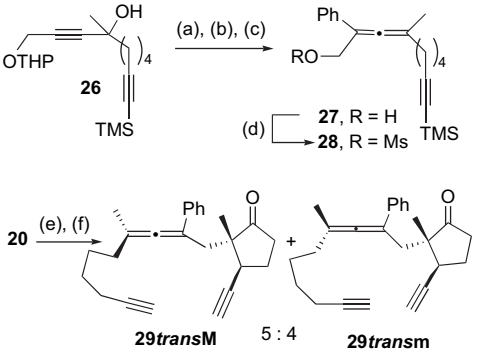
Indeed the following sequence—addition of **19** at rt to a solution of (propargyl)dicobalt hexacarbonyl cation, demetalation,[23] and acetalization[‡] of the corresponding adducts—furnished a 2:1 mixture of the ketals **23***cis*/*trans*. The cis

[‡] The acetalization proceeded in excellent yield only if the following conditions are respected: 10^{-2} M in benzene, 5 mol % PTSA, and 2 equiv of ethylene glycol.

relationship between the ethynyl and the propargyl groups for the major diastereomer was assigned by NOE NMR experiments. Alkylation of the lithium acetylide of **23***cis*/*trans* with 8-trimethylsilyl-oct-7-yn-2-one provided the corresponding alcohols **24***cis*/*trans* in 66% and 50% yields, respectively. Almost all attempts in generating the allenes through the sequence—mesylation of the alcohols followed by a S_N2' with copper(I)reagents—were unsuccessful. Only the addition of phenylcopper(I) reagent on **24***cis* furnished the corresponding allene in 10% yield whereas under the same conditions **24***trans* (or the mesylate) was recovered. Subsequent quantitative deprotection of the triple bonds afforded the allenediyne **25***cis*.

Since the allene formation occurred only for the cis adduct in poor yield, we decided to study another synthetic path to the allene **25**. As alkylation of the ketone **20** with propargyl bromide furnished the corresponding adduct in 60% yield, we checked the feasibility of such an alkylation with the mesylate **28** derived from the alcohol **27**.

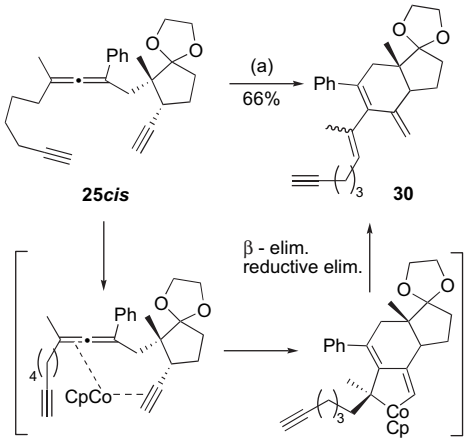
The starting material of this sequence was the alcohol **26**, which was generated from the addition of the lithium derivative of the tetrahydropyranyl propargyl ether with 8-trimethylsilyl-oct-7-yn-2-one (Scheme 10). Smooth formation of the allene and acid hydrolysis of the ether provided the alcohol **27** in 94% overall yield. The addition of the corresponding mesylate **28** to the potassium enolate of **20** afforded, after desilylation of the triple bonds, the allenediyne **29***trans* as a 5:4 mixture of two diastereomers in 50% yield over the three steps (mesylation, alkylation, and desilylation).



Scheme 10. (a) *n*-BuLi, MsCl, THF, −78 °C; (b) $Me_2S{\cdot}CuBr$, PhMgBr, LiBr, −50 °C; (c) cat. PTSA, MeOH, rt, 94% from **26**; (d) Et_3N, cat. 4-DMAP, MsCl, −40 °C, CH_2Cl_2; (e) KHMDS, −15 °C, THF; −50 °C, **28**, THF; and (f) K_2CO_3, MeOH, 50%.

The assigned stereochemistry of the major **29***trans*M, which was obtained pure after flash chromatography and crystallization, was unambiguously established by X-ray analysis.[§] In addition, NMR experiments also showed the trans relationship between the ethynyl group on the five-membered ring and the chain incorporating the allene for the minor **29***trans*m diastereomer. However, we were unable to separate it from the major diastereomer and we got a 41:59 mixture of **29***trans*(M/m).

The cobalt(I)-mediated cyclizations were carried out in the presence of a stoichiometric amount of $CpCo(CO)_2$ in boiling xylenes under irradiation and depending on the stereochemical relationship (cis or trans) between the ethynyl group and the chain incorporationg the allene, we disclosed two different trends. Indeed, the allenediyne **25***cis* afforded the bicyclic yne-trienic compound **30** as a mixture of diastereomers in 66% yield. This cycloadduct could result from a formal Alder ene type reaction between the ethynyl group and the double bond of the allene bearing the methyl group (Scheme 11).



Scheme 11. (a) $CpCo(CO)_2$ (1 equiv), xylenes, hν, Δ.

Such an Alder ene reaction, which had already been observed by our group[24] occurs competitively with the [2+2+2] cyclization when the latter is disfavored for geometrical reasons. In the present case, molecular models show that both of the unsaturations can be easily brought closer together, thus allowing a straightforward complexation of cobalt. After oxidative coupling, β-elimination followed by reductive elimination furnished compound **30**.

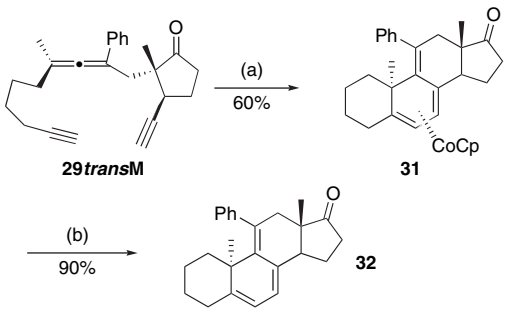
In contrast, the allenediyne **29***trans*M in presence of a stoichiometric amount of the cobalt(I) mediator gave the expected fused tetracyclic complex **31** in 60% yield as a single diastereomer (Scheme 12). On the basis of ^{1}H NMR spectrum, the cis relationship between CpCo and the A/B angular methyl was established (δ=1.75 ppm). The structure of **31** was secured by a single crystal X-ray analysis,[¶] which showed an *endo* stereochemistry between CpCo and the vicinal methyl group and a trans relationship between the two angular methyl groups. The free ligand **32** could be readily obtained in 90% yield upon the treatment of the complex **31** with silica gel. Therefore, the cyclization and decomplexation sequence could also be carried out without purifying the complex to allow the formation of 11-aryl steroid skeleton in 48% overall yield.

Although the minor allenediyne **29***trans*m was not obtained pure, it appears interesting to check if it could exhibit the same reactivity as the major diastereomer. Thus, a mixture of **29***trans*(M/m) (41:59)[‖] was exposed to the usual

[§] Crystal structure of **29***trans* has been deposited at the Cambridge Crystallographic Data Centre with the following deposition number: CCDC 245955; see Ref. 10 supporting information.

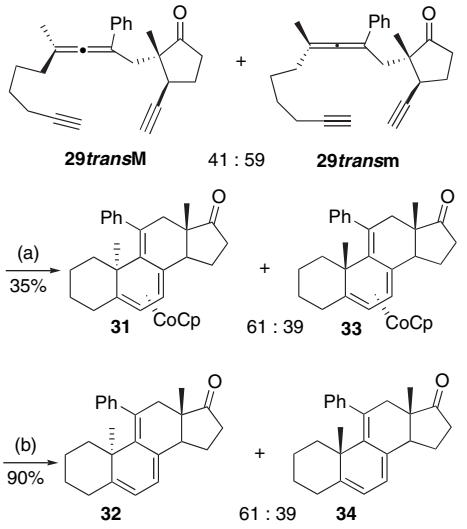
[¶] Crystal structure of **31** has been deposited at the Cambridge Crystallographic Data Centre with the following deposition number: CCDC 245954; see Ref. 10.

[‖] The ratio **29***trans*(M/m) (41:59) was determined by GC and **31:33** (61:39) by ^{1}H NMR on the basis of the integration of Cp-protons.



Scheme 12. (a) $CpCo(CO)_2$ (1 equiv), xylenes, hν, Δ and (b) SiO_2, CH_2Cl_2, rt.

conditions of cyclization and this led to (61:39) mixture of complexes **31** and **33** in 35% yield, which reveals to be the *exo* complex (Scheme 13).

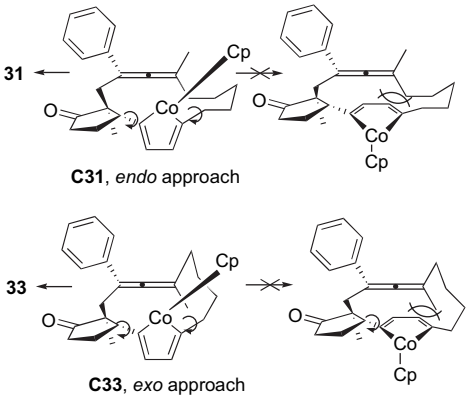


Scheme 13. (a) $CpCo(CO)_2$ (1 equiv), xylenes, hν, Δ and (b) SiO_2, CH_2Cl_2, rt.

The results were unexpected: the yield is inferior to the cyclization of **29***trans*M and the ratio of the cycloadducts is different from the starting material one meaning that **33** could be less stable than **31** or/and the cyclization of **29**m is more difficult than the cyclization of **29**M leading to degradation. Indeed, besides **31** and **33**, intractable materials were formed. In addition, a third compound was isolated, which may potentially result from an unanticipated side reaction of **29***trans*m, but we were unable to unambiguously identify its structure. Based upon similarities of spectral data, it seems to exhibit the steroid framework, which has been modified by several double bond migrations.

Finally, the mixture of **31** and **33** underwent efficient decomplexation with silica gel to furnish the free ligands **32** and **34** in 90%, the ratio 61:39 remaining unchanged.

The total diastereoselectivity observed for the cyclization of both diastereomers **29***trans* could be explained by the most probable mechanism of the [2+2+2], which may involve a cobaltacyclopentadiene.[15] The latter could react with the double bond of the allene bearing the methyl group via an intramolecular [4+2] cycloaddition process, which will deliver the fused tetracyclic complex (Scheme 14). Due to the presence of the five-membered ring, the intermediate cobaltacyclopentadienes **C31** and **C33** are quite rigid. For **C31**, the most favored approach of the polyunsaturated partners in which the non-bonded interactions are minimized is the *endo* approach relatively to the chain, which would lead to the *endo* complex **31**. On the contrary for **C33**, the *exo* approach relatively to the chain would be the favored one.



Scheme 14.

Thus, the diastereoselectivity of the cyclization for such allenediynes appears to be controlled by the stereochemistry of the allene.

3. Conclusion

In summary, we reported that the cobalt(I)-mediated [2+2+2] cyclizations of allenediynes of yne-allene-yne type bearing an aryl group on the allene are totally chemo- and regioselective and show low diastereoselectivities. η^4-Complexed tricyclic (6,6,6) compounds were obtained in good yields as mixtures of *endo*/*exo* diastereomers, which are independent of the substitution of the allene. The cyclization is also compatible with an oxyfunctionality at C3.

Having disclosed that aryl substituted allenes are relevant partners for these cyclizations, we carefully designed an allenediyne having a preexisting D ring. We observed that, depending on the stereochemical relationship (cis or trans) between the ethynyl group on the five-membered ring and the chain incorporating the allene, two different trends occurred in the cobalt(I)-mediated cyclizations. If *trans*-11-aryl steroids have been built in one step and in a totally diastereoselective manner, with simultaneous introduction of an angular methyl group at C10 and an aryl substituent at C11 in 48% overall yield. In contrast, if cis then the allenediyne **25***cis* furnished a bicyclic yne-trienic compound in 66% yield resulting from a formal Alder ene reaction between the ethynyl group and the double bond of the allene bearing the methyl group.

Interestingly we also observed that the diyne-ene-yne **8** furnished in a quantitative yield the corresponding cycloadduct bearing an aryl substituent at C11. This result could open a new synthetic pathway to the steroid nucleus by designing a judiciously functionalized unsaturated precursor.

4. Experimental

4.1. General

Reactions were carried out under argon in flame-dried glassware, with magnetic stirring and degassed anhydrous solvents. All commercially available reagents were used without further purification unless otherwise noted. All solvents were reagent grade and distilled under positive pressure of dry nitrogen before use. THF was distilled from sodium/benzophenone. Xylenes and benzene were distilled from CaH_2. Solid reagents were dried in vacuo (0.5–0.1 mmHg). Thin layer chromatography (TLC) was performed on Merck 60 F_{254} silica gel. Merck Geduran SI 60 Å silica gel (35–70 μm) was used for column chromatography. PE and EE refer to petroleum ether and Et_2O.

Chemical shifts are reported in parts per million referenced to the residual proton resonances of the solvents (δ=7.26 for $CDCl_3$; δ=7.16 for C_6D_6). Coupling constants (J) are given in hertz (Hz). The terms m, s, d, t, q, and quint refer to multiplet, singlet, doublet, triplet, quartet, and quintet; br means that the signal is broad. Coupling constants are expressed in hertz. We use (I), (II), (III), and (IV) to characterize primary, secondary, tertiary, and quaternary carbons.

Elemental analyses were performed by the Service Régional de Microanalyse de l'Université Pierre et Marie Curie—low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were measured by Service de spectrométrie de masse de l'ICSN-CNRS, Gif-sur-Yvette. Infrared spectra (IR) were recorded on a Bruker Tensor 27 spectrometer (ATR diamond spectrometer). Absorbance frequencies are given at maximum of intensity in cm^{-1}.

4.1.1. 6-Phenyl-1-(trimethylsilyl)-tetradeca-1,7,13-triyn-6-ol (7). To a solution of alcohol **6** (1.85 g, 6.74 mmol) in CH_2Cl_2 (65 mL) were successively added neutral alumina (10 g) and pyridinium chlorochromate (PCC, 2 g, 9.44 mmol, 1.4 equiv). The mixture was stirred until completion of the reaction by TLC and then, was filtered on Celite pad. The filtered solution was successively washed with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE/EE=90/10) and furnished the ketone (1.37 g, 75%). IR (neat) 3060, 2970, 2850, 2200, 1630, 1440, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, J=7.1 Hz, 2H), 2.37 (t, J=7.1 Hz, 2H), 2.18 (m, 2H), 2.10 (t, J=7.1 Hz, 2H), 1.85 (t, J=2.5 Hz, 1H), 1.69–1.57 (m, 4H), 1.40 (qt, J=7.1, 7.1 Hz, 2H), −0.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1 (IV), 106.6 (IV), 92.6 (IV), 84.7 (IV), 82.5 (IV), 81.0 (IV), 69.3 (III), 44.7 (II), 27.6 (II), 26.3 (II), 22.9 (II), 19.4 (II), 17.7 (II), 17.4 (II), 0.0 (3C, I). HRMS calcd for $C_{17}H_{24}OSi$ (272.46) (MH^+) 273.160. Found 273.167.

To a cooled (−78 °C) solution of the previously prepared ketone (1.37 g, 5.1 mmol) in Et_2O (20 mL) was added a solution of phenyllithium (1.8 M in THF, 6.72 mmol, 1.2 equiv). The mixture was stirred until completion of the reaction by TLC and diluted with Et_2O, washed with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=85/15) led to the alcohol **7** (1.33 g, 86%). IR (neat) 3450, 3060, 2970, 2850, 2200, 1630, 1440, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.28 (m, 5H), 2.43 (t, J=6.4 Hz, 2H), 2.27 (m, 2H), 2.19 (m, 2H), 1.99 (t, J=2.8 Hz, 1H), 2.10–1.90 (m, 2H), 1.75 (m, 6H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7 (IV), 127.9 (2C, III), 127.5 (III), 126.4 (2C, III), 107.0 (IV), 88.5 (IV), 84.3 (IV), 83.8 (IV), 79.8 (IV), 79.0 (IV), 68.5 (III), 44.0 (II), 27.5 (II), 27.4 (II), 23.9 (II), 19.6 (II), 18.2 (II), 17.8 (II), 0.0 (3C, I).

4.1.2. 1-Trimethylsilyl-6-phenyl-tetradec-5-ene-1,7,13-triyne (8). Step 1. To a cooled (−78 °C) solution of **7** (1.07 g, 3.1 mmol), in THF (20 mL) was added a solution of *n*-BuLi (2.2 M in hexane, 3.1 mmol). After being stirred for 10 min at −78 °C, mesyl chloride (0.24 mL, 3.1 mmol) was added. The mixture was stirred for additional 30 min and neutralized with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was used without further purification in the next step.

Step 2. At rt, to a solution of the previously prepared compound in MeOH (5 mL) was added K_2CO_3 (3.43 g, 24.8 mmol, 8 equiv). The mixture was stirred until TLC indicated the completion of the reaction. Then, the reaction mixture was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=95/5) gave **8** (0.605 g, 76%). IR (neat) 3060, 2970, 2850, 1640, 1440, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 6.42 (t, J=7.4 Hz, 1H), 2.70 (m, 2H), 2.50 (m, 2H), 2.42 (m, 2H), 2.29 (m, 2H), 2.01 (t, J=3.5 Hz, 1H), 1.99 (t, J=3.5 Hz, 1H), 1.77 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (IV), 137.2 (IV), 132.2 (IV), 128.6 (2C, III), 128.3 (III), 127.1 (2C, III), 85.2 (IV), 85.0 (IV), 84.7 (IV), 84.2 (IV), 68.3 (III), 67.9 (III), 32.0 (II), 29.9 (II), 29.5 (II), 24.9 (II), 23.5 (II), 22.5 (II).

4.1.3. 7-(*tert*-Butyldimethylsilyloxy)-hept-1-yn-4-ol (10). At −30 °C, to a solution of 4-(*tert*-butyldimethylsilyloxy)-butyraldehyde (15.46 g, 76.4 mmol) in Et_2O (80 mL) was slowly added a solution of propargylic magnesiumbromide (80 mmol, 1.05 equiv). The resulting solution was warmed up to rt and stirred for 2 h. Then, the mixture was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=80/20) led to **10** (15.8 g, 85%). IR (neat) 3450, 2950, 2200, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.77–3.62 (m, 2H), 3.23 (br s, 1H), 2.39 (dd, J=3.2, 2.8 Hz, 2H), 2.03 (t, J=2.43 Hz, 1H), 1.80–1.78 (m, 2H), 1.69–1.65 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.3 (IV), 70.4 (III), 69.8 (III), 63.4 (II), 33.6 (II), 29.1 (II), 27.2 (II), 25.9 (3C, I), 18.3 (IV), −5.3 (2C, I).

4.1.4. 1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-hept-6-yne (11). At 0 °C, to a suspension of sodium hydride (60% in mineral oil, 1 g, 24 mmol, 1.2 equiv) in THF (60 mL) was added a solution of alcohol **10** (4.85 g, 20 mmol) in

THF (60 mL). After 30 min at rt, iodomethane (6.2 mL, 14.2 g, 100 mmol, 5 equiv) was added. After being stirred for 2 h, the resulting mixture was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (PE/EE=95/5) to furnish the ether **11** (5.12 g, quantitative). IR (neat) 2950, 2200, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 1H), 3.64–3.61 (m, 2H), 3.37 (s, 3H), 2.42–2.38 (m, 2H), 1.98 (t, J=2.48 Hz, 1H), 1.68–1.55 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0 (IV), 79.0 (I), 69.9 (III), 63.1 (II), 57.0 (III), 29.8 (II), 28.5 (II) 26.0 (3C, I), 23.2 (II), 18.4 (IV), −5.2 (2C, I).

4.1.5. 4-Methoxy-hept-6-yn-1-ol (12). At 0 °C, to a solution of **11** (5.12 g, 20 mmol) in THF (100 mL) was added dropwise a 1 M solution in THF of TBAF (20 mL, 20 mmol). The reaction was stirred at rt until TLC indicated the completion of the reaction. Then, it was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/AcOEt=60/40) led to **12** (2.44 g, 86%). IR (neat) 3450, 2970, 2200, 1450, 870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 1H), 3.63–3.60 (m, 2H), 3.35 (s, 3H), 2.42–2.38 (m, 2H), 1.98 (t, J=2.48 Hz, 1H), 1.68–1.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.1 (IV), 79.5 (I), 70.5 (IV), 63.0 (II), 57.0 (III), 30.4 (II), 28.8 (II), 23.3 (II).

4.1.6. 5-Methoxy-oct-7-yn-2-one (13). Step 1. To a cooled solution (−78 °C) of oxalyl chloride (4 mL, 46 mmol, 1.3 equiv) in CH_2Cl_2 (130 mL) was added dropwise a solution of DMSO (6.5 mL, 91 mmol, 2.6 equiv) in CH_2Cl_2 (70 mL). After 5 min, a solution of **12** (5 g, 35 mmol) in CH_2Cl_2 (50 mL) was added dropwise and after being stirred for an additional 15 min, triethylamine (24 mL, 175 mmol, 5 equiv) was added. The mixture was allowed to warm to rt, diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was used without further purification in the next step.

Step 2. At 0 °C, to a solution of the preceding aldehyde in Et_2O (40 mL) was added a solution of methylmagnesium bromide (3 M in Et_2O, 12.8 mL, 1.1 equiv). The mixture was warmed up to rt, stirred until TLC indicated the completion of the reaction. Then, it was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was used without further purification in the next step.

Step 3. The previously prepared alcohol was oxidized following the same procedure as described for step 1. Purification by flash chromatography (PE/EE=90/10) gave the ketone **13** (4.07 g, 75% from **12**). IR (neat) 3300, 2970, 2200, 1650, 1450, 870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 1H), 3.37 (s, 3H), 2.42–2.38 (m, 4H), 2.10 (s, 3H), 1.98 (t, J=2.48 Hz, 1H), 1.80–1.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (IV), 81.1 (IV), 79.5 (I), 70.5 (III), 57.0 (III), 47.3 (I), 31.4 (II), 28.7 (II), 23.3 (II).

4.1.7. 7-Methyl-1-(trimethylsilyl)-tetradeca-1,8,13-triyn-7-ol (14). At −78 °C n-BuLi (2.1 M in hexane, 29.1 mL, 61.1 mmol, 1.2 equiv) was added dropwise to a solution of hepta-1,6-diyne (10 g, 102 mmol, 2 equiv) in THF (300 mL). After being stirred at −78 °C for 30 min, a solution of 8-(trimethylsilyl)-oct-7-yn-2-one **9** (10 g, 50.9 mmol, 1 equiv) in THF (50 mL) was added. The reaction mixture was warmed up at rt, stirred for 2 h and was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=90/10) furnished **14** (10.28 g, 70%). IR (neat) 3400, 3300, 2240, 2180, 1240, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.34–2.25 (m, 4H), 2.23 (m, 2H), 1.96 (t, J=2.6 Hz, 1H), 1.70 (qt, J=7.04 Hz, 2H), 1.68–1.54 (m, 6H), 1.44 (s, 3H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.4, (IV), 84.8 (IV), 84.6 (IV), 82.5 (2C, IV), 68.9 (III), 68.2 (IV), 57.0 (III), 43.4 (II), 30.1 (I), 28.8 (II), 27.6 (II), 24.1 (II), 19.9 (II), 17.7 (II), 17.6 (II), 0.2 (3C, I). Anal. Calcd for $C_{26}H_{32}O_2Si$ (288.50): C, 74.94; H, 9.78. Found: C, 75.08; H, 9.66.

4.2. General procedure for the preparation of allenediynes 16a–c

A THF solution of arylmagnesium chloride or bromide (2.6 mmol, 1.5 equiv) was added dropwise at −50 °C to a suspension of $Me_2S\cdot CuBr$ (0.535 g, 2.6 mmol, 1.5 equiv) and LiBr (0.224 g, 2.6 mmol, 1.5 equiv) in THF (20 mL) and the resulting mixture was stirred at −50 °C for 15 min.

At −78 °C, a 2.1 M solution of n-BuLi in hexane (0.82 mL, 1.73 mmol, 1 equiv) was added dropwise to a solution of the alcohol **14** (0.50 g, 1.73 mmol). After being stirred for 5 min, pure mesyl chloride (0.15 mL, 1.90 mmol, 1.1 equiv) was added. The resulting solution was stirred for 5 min and transferred via a cannula into a solution of the previously prepared copper(I) reagent. After stirring for 30 min at −50 °C, the temperature was allowed to warm up at rt. The reaction mixture was hydrolyzed with a saturated solution of NH_4Cl/NH_4OH (2/1) and partitioned with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the corresponding allenediynes. The crude mixture was used in the next step without any further purification.

K_2CO_3 (1.88 g, 13.6 mmol, 8 equiv) was added to a solution of previously prepared crude compound in MeOH (10 mL) and the resulting mixture was stirred until TLC had indicated the completion of the reaction. The mixture was diluted with Et_2O, washed with a saturated solution of NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (PE/EE=9/1) led to the allenediynes **16a–c**.

4.2.1. (3-Methyl-1-pent-4-ynyl-nona-1,2-dien-8-ynyl)-benzene (16a). 0.344 g, 72%. IR (neat) 2950, 2210, 2180, 1960, 1440, 950 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.37 (m, 2H), 7.25 (m, 1H), 2.61 (t, J=7.3 Hz, 2H), 2.36 (dt, J=4.6, 2.4 Hz, 2H), 2.24 (m, 2H), 2.17 (m, 2H), 2.05 (t, J=2.44 Hz, 1H), 2.01 (t, J=2.5 Hz, 1H), 1.87 (s, 3H), 1.84 (m, 2H), 1.82 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (IV), 138.0 (IV), 128.4 (2C, III), 126.3

(III), 125.9 (2C, III), 103.9 (IV), 103.1 (IV), 84.5 (2C, IV), 68.6 (2C, III), 33.9 (II), 29.3 (II), 28.4 (II), 27.0 (II), 26.8 (II), 19.8 (II), 18.9 (I), 18.2 (II). HRMS calcd for $C_{21}H_{24}$ (276.42) (MH^+) 277.188. Found: 277.187.

4.2.2. 1-(3-Methyl-1-pent-4-ynyl-nona-1,2-dien-8-ynyl)-4-trifluoromethyl-benzene (16b). 0.303 g, 51%. IR (neat) 2950, 2210, 2180, 1960, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8.0 Hz, 2H), 7.50 (d, J=8.0 Hz, 2H), 2.56 (t, J=7.6 Hz, 2H), 2.34–2.30 (m, 2H), 2.22–2.18 (m, 2H), 2.16–2.13 (m, 2H), 2.01 (t, J=1.6 Hz, 1H), 1.96 (t, J=2.4 Hz, 1H), 1.84 (s, 3H), 1.81–1.77 (m, 2H), 1.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1 (IV), 144.2 (q, J=81 Hz, IV), 142.0 (IV), 126.3 (q, J=140 Hz, IV), 127.7 (III), 126.0 (2C, III), 125.2 (III), 103.9 (IV), 103.5 (IV), 84.2 (2C, IV), 68.7 (III), 68.4 (III), 33.7 (II), 29.1 (II), 28.2 (II), 26.9 (II), 26.7 (II), 18.8 (I), 18.3 (II), 18.1 (II).

4.2.3. 1-Methoxy-4-(3-methyl-1-pent-4-ynyl-nona-1,2-dien-8-ynyl)-benzene (16c). 0.175 g, 33%. IR (neat) 2980, 2200, 2180, 1960, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 6.89 (m, 2H), 3.82 (s, 3H), 2.52 (t, J=7.3 Hz, 2H), 2.33–2.29 (m, 2H), 2.22–2.20 (m, 2H), 2.12 (m, 2H), 2.01 (t, J=2.5 Hz, 1H), 1.97 (t, J=2.5 Hz, 1H), 1.82 (s, 3H), 1.80–1.79 (m, 2H), 1.61–1.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (IV), 158.3 (IV), 132.2 (IV), 127.0 (2C, III), 113.8 (2C, III), 103.6 (IV), 102.8 (IV), 84.5 (2C, IV), 68.6 (III), 68.4 (III), 55.3 (I), 33.9 (II), 29.5 (II), 28.3 (II), 27.0 (II), 26.8 (II), 19.1 (I), 18.3 (II), 18.2 (II).

4.2.4. (6-Methoxy-3-methyl-1-pent-4-ynyl-nona-1,2-dien-8-ynyl)-benzene (16d). It was obtained using the same procedure as for the preparation of **14** (the intermediate alcohol was not purified) followed by the sequence described for **16a–c**. 0.303 g, 36% overall yield. IR (neat) 2950, 2210, 2180, 1960, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.33 (m, 2H), 7.25 (m, 1H), 3.72 (m, 1H), 3.35 (s, 3H), 2.61 (t, J=7.4 Hz, 2H), 2.36 (dt, J=4.7, 2.5 Hz, 2H), 2.24 (m, 2H), 2.17 (m, 2H), 2.05 (t, J=2.5 Hz, 1H), 2.01 (t, J=2.5 Hz, 1H), 1.87 (s, 3H), 1.84 (m, 2H), 1.82 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 201.2 (IV), 138.0 (IV), 128.4 (2C, III), 126.3 (III), 125.9 (2C, III), 103.9 (IV), 103.1 (IV), 84.5 (2C, IV), 78.7 (I), 68.6 (2C, III), 57.1 (III), 33.9 (II), 29.3 (II), 28.4 (II), 26.8 (II), 19.8 (II), 18.9 (I), 18.2 (II).

4.3. General procedure for the preparation of the cycloadducts 17a–d

Cyclopentadienyldicarbonylcobalt(I) (1.2 equiv) was added to a boiling solution of allenediyne **16a–d** (1 equiv) in xylenes degassed by three freeze-pump-thaw cycles and was irradiated (light from projector lamp; ELW, 300 W, 50% of its power). The reaction was monitored by TLC and after completion, the reaction mixture was concentrated in vacuo. The crude oil was purified by flash chromatography (the solvents of chromatography were not degassed) either on deactivated alumina with 3% H_2O (PE) or on silica gel neutralized with NEt_3 and dried (PE/EE 95/5) to furnish **17a–d** as an inseparable *endo*/*exo* mixture.

4.3.1. Cycloadduct (17a). 0.180 g, 60% (*endo*/*exo*=55/45).

17a *endo*: ^1H NMR (400 MHz, C_6D_6) δ 7.83 (m, 2H), 7.46 (m, 3H), 5.24 (d, J=3.9 Hz, 1H), 4.37 (s, 5H), 4.36 (d, J=3.9 Hz, 1H), 2.45–2.42 (m, 2H), 2.2–2.05 (m, 2H), 1.96–1.95 (m, 2H), 1.81 (s, 3H), 1.57–1.56 (m, 4H), 1.33–1.31 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6) δ 150.3 (IV), 142.3 (IV), 126.0 (IV), 129–125 (5C, III), 81.7 (5C, III), 76.9 (III), 73.5 (IV), 72.8 (III), 65.2 (IV), 48.2 (IV), 36.9 (II), 36.5 (II), 35.0 (II), 31.8 (II), 27.5 (I), 26.4 (II), 25.0 (II), 24.7 (II).

17a *exo*: ^1H NMR (400 MHz, C_6D_6) δ 7.32–7.23 (m, 5H), 4.91 (d, J=3.9 Hz, 1H), 4.64 (s, 5H), 4.47 (d, J=3.9 Hz, 1H), 2.35–2.22 (m, 2H), 2.2–2.05 (m, 2H), 1.88–1.83 (m, 2H), 1.57–1.56 (m, 4H), 1.55–1.45 (m, 4H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 146.3 (IV), 144.2 (IV), 126.0 (IV), 129–125 (5C, III), 80.9 (5C, III), 78.0 (III), 77.5 (IV), 76.0 (III), 65.3 (IV), 48.2 (IV), 40.9 (II), 37.7 (II), 37.4 (II), 35.6 (II), 30.8 (II), 26.1 (II), 24.3 (I), 22.7 (II). HRMS calcd for $C_{26}H_{29}Co$ (400.44) $(MH)^+$ 401.168. Found: 401.165.

4.3.2. Cycloadduct (17b). 0.268 g, 65% (*endo*/*exo*=53/47).

17b *endo*: ^1H NMR (400 MHz, C_6D_6) δ 7.48 (d, J=8.2 Hz, 2H), 7.13 (d, J=8.2 Hz, 2H), 5.2 (d, J=3.9 Hz, 1H), 4.33 (d, J=3.9 Hz, 1H), 4.26 (s, 5H), 2.35–2.25 (m, 2H), 2.2–2.05 (m, 2H), 1.91–1.85 (m, 2H), 1.67 (s, 3H), 1.57–1.56 (m, 4H), 1.49–1.45 (m, 2H), 1.33–1.31 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ 150.3 (2C, IV), 142.3 (2C, IV), 126.0 (IV), 129–125 (4C, III), 81.6 (5C, III), 77.0 (III), 73.5 (IV), 72.7 (III), 65.2 (IV), 48.2 (IV), 37.1 (II), 36.8 (II), 36.2 (II), 31.5 (II), 27.6 (I), 26.3 (II), 24.4 (II), 24.2 (II).

17b *exo*: ^1H NMR (400 MHz, C_6D_6) δ 7.48 (d, J=8.2 Hz, 2H), 7.13 (d, J=8.2 Hz, 2H), 4.90 (d, J=3.9 Hz, 1H), 4.63 (s, 5H), 4.44 (d, J=3.9 Hz, 1H), 2.35–2.25 (m, 2H), 2.2–2.05 (m, 2H), 1.91–1.85 (m, 2H), 1.57–1.56 (m, 4H), 1.49–1.45 (m, 2H), 1.33–1.31 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 150.3 (2C, IV), 143.0 (2C, IV), 126.0 (IV), 129–125 (4C, III), 81.6 (5C, III), 78.1 (III), 76.0 (III), 73.5 (IV), 65.2 (IV), 48.2 (IV), 40.8 (II), 35.5 (II), 34.8 (II), 30.7 (II), 25.9 (II), 24.2 (I), 22.6 (II), 22.5 (II). IR (neat): 3250, 2950, 2920, 1950, 1630, 1470, 1450, 1350, 850 cm^{-1}. HRMS calcd for $C_{27}H_{28}CoF_3$ (468.44) $(MH)^+$ 469.148. Found: 469.154.

4.3.3. Cycloadduct (17c). 0.152 g, 62% (*endo*/*exo*=61/39).

17c *endo*: ^1H NMR (400 MHz, C_6D_6) δ 7.16 (m, 2H), 6.85 (m, 2H), 5.25 (d, J=3.9 Hz, 1H), 4.38 (s, 5H), 4.37 (d, J=3.9 Hz, 1H), 3.57 (s, 3H), 2.52–2.48 (m, 2H), 2.2–2.05 (m, 2H), 1.99–1.87 (m, 4H), 1.84 (s, 3H), 1.57–1.56 (m, 2H), 1.47–1.36 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6) δ 158.0 (IV), 142.5 (IV), 129.9 (IV), 128.1 (2C, III), 127.2 (IV), 112.1 (2C, III), 81.6 (5C, III), 76.9 (III), 73.3 (IV), 72.7 (III), 64.4 (IV), 54.6 (I), 48.2 (IV), 36.9 (II), 36.6 (II), 35.1 (II), 31.8 (II), 27.5 (I), 26.4 (II), 25.0 (II), 24.6 (II).

16c *exo*: ^1H NMR (400 MHz, C_6D_6) δ 7.75 (m, 2H), 7.09 (m, 2H), 4.93 (d, J=3.9 Hz, 1H), 4.65 (s, 5H), 4.48 (d, J=3.9 Hz, 1H), 3.37 (s, 3H), 2.52–2.48 (m, 2H), 2.2–2.05 (m, 2H), 1.99–1.87 (m, 4H), 1.57–1.56 (m, 2H), 1.47–1.36 (m, 4H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 157.9, 142.3,

129.9, 129.8 (2C), 127.2, 113.4 (2C), 80.9 (5C), 78.0 (III), 76.0 (III), 74.8 (IV), 65.5 (IV), 54.5 (I), 46.7 (IV), 40.9 (II), 37.9 (II), 37.4 (II), 35.6 (II), 30.9 (II), 26.2 (II), 24.2 (I), 22.8 (II). HRMS calcd for $C_{27}H_{31}CoO$ $(MH)^+$ 431.179. Found: 431.177.

4.3.4. Cycloadduct (17d). 0.077 g, 62% (*endo*/*exo*=65/35). This cyclization led to the formation of an inseparable mixture of four diastereomers *endo*/*exo* and it was impossible to fully describe the compounds particularly the ^{13}C NMR spectra were unexploitable. Only the characteristic data in ^1H NMR are given.

17d *endo* (two diastereomers): 7.60 (m, 4H), 7.46 (m, 6H), 5.62 (d, *J*=3.9 Hz, 1H), 5.35 (d, *J*=3.9 Hz, 1H), 4.33 (s, 5H), 4.31 (s, 5H), 4.65 (d, *J*=3.9 Hz, 1H), 4.41 (d, *J*=3.9 Hz, 1H), 3.38 (s, 3H), 3.36 (m, 2H), 3.35 (s, 3H), 2.45–1.3 (m, 24H), 1.54 (s, 3H), 1.45 (s, 3H).

17d *exo* (two diastereomers): 7.60 (m, 4H), 7.46 (m, 6H), 5.02 (d, *J*=3.9 Hz, 1H), 4.99 (d, *J*=3.9 Hz, 1H), 4.76 (s, 5H), 4.67 (s, 5H), 4.66 (d, *J*=3.9 Hz, 1H), 4.5 (d, *J*=3.9 Hz, 1H), 3.32 (m, 2H), 3.30 (s, 3H), 3.28 (s, 3H), 2.45–1.3 (m, 24H), 1.02 (s, 3H), 0.96 (s, 3H).

4.3.5. 5-Phenyl-1,2,3,4,7,8-hexahydro-phenanthrene (18). 0.150 g, quantitative. IR (neat) 3060, 2970, 2850, 1630, 1440, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.28–7.25 (m, 3H), 7.09 (d, *J*=7.6 Hz, 1H), 7.00 (d, *J*=7.6 Hz, 1H), 6.28 (t, *J*=5.1 Hz, 1H), 2.79 (t, *J*=6.6 Hz, 2H), 2.71 (t, *J*=7.1 Hz, 2H), 2.29–2.24 (m, 2H), 2.01 (t, *J*=6.2 Hz, 2H), 1.66 (m, 2H), 1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (IV), 141.2 (IV), 137.2 (IV), 136.6 (IV), 135.0 (IV), 134.8 (IV), 132.2 (III), 128.6 (2C, III), 128.3 (III), 127.1 (2C, III), 126.6 (III), 125.0 (III), 31.0 (II), 30.6 (II), 30.1 (II), 23.9 (II), 23.5 (II), 22.9 (II).

4.3.6. 2-Methyl-2-prop-2-ynyl-3-(trimethylsilylethynyl)-cyclopentanone (22). To a cooled (−78 °C) solution of (propargyl)methyl ether hexacarbonyl dicobalt complex (0.69 g, 1.92 mmol, 1.03 equiv) in CH_2Cl_2 (8 mL) was added $Et_2O{\cdot}BF_3$ (0.5 mL, 1.92 mmol, 1.03 equiv). After warming up at rt, the reaction mixture was stirred for 15 min and silyl enol ether **19**[21] (0.50 g, 1.87 mmol) was added. After being stirred at rt until completion of the reaction (TLC), the reaction mixture was diluted with Et_2O, washed with a saturated solution of NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish the ketones **21**. The crude mixture was used in the next step without any further purification.

To a solution of the previously prepared ketones **21** in acetone (250 mL) was added portionwise CAN (8.2 g, 14.96 mmol, 8 equiv). After being stirred for 5 min at rt, the reaction mixture was diluted with Et_2O (1 L), washed successively with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (PE/EE=95/5) of the residue furnished the ketones **22***cis*/*trans* (0.318 g, cis/trans=2/1, 74% over the two steps).

22*cis*: ^1H NMR (400 MHz, $CDCl_3$) δ 3.28 (dd, *J*=11.2, 6.8 Hz, 1H), 2.49–2.05 (m, 6H), 1.96 (t, *J*=2.4 Hz, 1H), 1.02 (s, 3H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4 (IV), 104.9 (IV), 88.2 (IV), 80.4 (IV), 71.0 (III), 51.3 (IV), 36.7 (III), 36.6 (II), 25.9 (II), 25.2 (II), 18.0 (I), 0.2 (3C, I). EIMS (*m*/*z*, %) 233 (100), 217 (35).

22*trans*: ^1H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, *J*=13.8 Hz, 1H), 2.44–2.00 (m, 6H), 1.97 (t, *J*=2.4 Hz, 1H), 1.14 (s, 3H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4 (IV), 105.0 (IV), 89.2 (IV), 80.5 (IV), 70.5 (III), 51.2 (IV), 39.8 (III), 35.5 (II), 25.7 (II), 23.7 (II), 20.7 (I), 0.0 (3C, I). EIMS (*m*/*z*, %) 233 (100), 217 (35).

4.3.7. Trimethyl-(6-methyl-6-prop-2-ynyl-1,4-dioxa-spiro[4,4]non-7-ylethynyl)-silane (23). A solution of ketone **22***cis*/*trans* (0.313 g, 1.35 mmol), ethylene glycol (0.15 mL, 2.7 mmol, 2 equiv) and PTSA (0.01 g, 0.07 mmol, 0.05 equiv) in benzene (13 mL) was refluxed with a Dean–Stark apparatus for 12 h. After being cooled at rt, the reaction mixture was diluted with Et_2O, washed successively with a 2:1 saturated solution of NH_4Cl/NH_4OH and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Filtration through silica gel (PE/EE=9/1) gave the acetals **23***cis*/*trans* (0.355 g, cis/trans=2/1, 95%).

23*cis*: Mp 62–64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (m, 4H), 2.69 (t, *J*=17.7 Hz, 1H), 2.51–2.26 (m, 2H), 1.98–1.88 (m, 3H), 1.79–1.66 (m, 2H), 1.09 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.0 (IV), 107.2 (IV), 87.8 (IV), 83.2 (IV), 69.0 (III), 65.5 (II), 64.8 (II), 48.9 (IV), 40.2 (III), 33.6 (II), 26.7 (II), 23.0 (II), 19.7 (I), 0.2 (3C, I). Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.51; H, 8.75. Found: C, 69.33; H, 8.95.

23*trans*: ^1H NMR (400 MHz, $CDCl_3$) δ 4.00–3.85 (m, 4H), 2.69 (t, *J*=17.7 Hz, 1H), 2.29 (m, 2H), 1.99–1.87 (m, 3H), 1.79–1.62 (m, 2H), 1.16 (s, 3H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.0 (IV), 107.1 (IV), 87.4 (IV), 82.5 (IV), 69.5 (III), 65.1 (II), 64.6 (II), 48.4 (IV), 39.0 (III), 33.2 (II), 26.0 (II), 23.7 (II), 16.6 (I), 0.2 (3C, I). Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.51; H, 8.75. Found: C, 69.33; H, 8.95.

4.3.8. Methyl-1-[6-methyl-7-(trimethylsilylethynyl)-1,4-dioxa-spiro[4,4]non-6-yl]-10-trimethylsilyl-deca-2,9-diyn-4-ol (24). To a cooled (−78 °C) solution of **23** (0.50 g, 1.81 mmol) in THF (10 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 0.72 mL, 1.81 mmol). After being stirred at −78 °C for 30 min, a solution of 8-(trimethylsilyl)-oct-7-yn-2-one (0.355 g, 1.81 mmol) in THF (5 mL) was added. The temperature was allowed to warm up at rt, the mixture was stirred until TLC had indicated the completion of the reaction. The reaction was diluted with Et_2O, washed with a saturated solution of NH_4Cl, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=85/15) afforded the alcohols **24***cis* and **24***trans*.

24*cis*: 0.564 g, 66%. IR(neat) 3610, 2980, 2950, 2290, 2000, 1470, 1390, 1350 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (m, 4H), 2.70 (t, *J*=17.7 Hz, 1H), 2.45 (m, 2H), 2.30–2.24 (m, 4H), 1.81–1.69 (m, 2H), 1.60–1.59 (m, 6H), 1.44 (s, 3H), 1.08 (s, 3H), 0.13 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.1 (IV), 107.3 (2C, IV), 87.6

(IV), 84.4 (IV), 82.5 (2C, IV), 68.2 (IV), 65.5 (II), 64.8 (II), 49.1 (IV), 43.3 (II), 40.2 (III), 33.7 (II), 30.0 (I), 28.8 (II), 26.7 (II), 24.1 (II), 23.2 (II), 20.3 (II), 19.9 (I), 0.28 (3C, I), 0.22 (3C, I). Anal. Calcd for $C_{27}H_{44}O_3Si_2$: C, 68.59; H, 9.38. Found: C, 68.44; H, 9.57.

24*trans*: 0.43 g, 50%. IR(neat) 3610, 2980, 2950, 2290, 2000, 1470, 1390, 1350 cm^{-1}. ^1H NMR (200 MHz, C_6D_6) δ 3.77–3.50 (m, 2H), 3.46–3.35 (m, 2H), 2.90 (t, J=18.7 Hz, 1H), 2.54 (br s, 2H), 2.11 (t, J=13.7 Hz, 2H), 1.92–1.52 (m, 10H), 1.46 (s, 3H), 1.44 (s, 3H), 0.22 (s, 9H), 0.18 (s, 9H). ^{13}C NMR (50 MHz, C_6D_6) δ 119.0 (IV), 108.9 (2C, IV), 88.5 (IV), 87.1 (IV), 85.6 (IV), 82.4 (IV), 68.9 (IV), 66.0 (II), 65.6 (II), 49.9 (IV), 44.7 (II), 40.6 (III), 34.4 (II), 31.2 (I), 30.2 (II), 26.6 (II), 25.6 (II), 25.4 (II), 21.2 (II), 18.3 (I), 1.3 (6C, I). Anal. Calcd for $C_{27}H_{44}O_3Si_2$: C, 68.59; H, 9.38. Found: C, 68.44; H, 9.57.

4.3.9. 7-Ethynyl-6-methyl-6-(4-methyl-2-phenyl-deca-2,3-diene-9-ynyl)-1,4-dioxa-spiro[4,4]nonane (25*cis*). A 1.5 M THF solution of phenylmagnesium chloride (1.28 mL, 1.92 mmol, 1.5 equiv) was added dropwise at −50 °C to a suspension of $Me_2S\cdot CuBr$ (1.92 mmol, 1.5 equiv) and LiBr (0.167 g, 1.92 mmol, 1.5 equiv) in THF (20 mL) and the resulting mixture was stirred at −50 °C for 15 min.

At −78 °C, a 2.1 M solution of *n*-BuLi in hexane (0.61 mL, 1.28 mmol) was added dropwise to a solution of the alcohol **24***cis* (0.61 g, 1.28 mmol). After being stirred for 5 min, pure mesyl chloride (0.12 mL, 1.53 mmol, 1.2 equiv) was added. The resulting solution was stirred for 5 min and transferred via a cannula into a solution of the previously prepared copper(I) reagent. After stirring for 30 min at −50 °C, the temperature was allowed to warm up at rt. The reaction mixture was hydrolyzed with a saturated solution of NH_4Cl/NH_4OH (2/1) and partitioned with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was used in the next step without any further purification.

K_2CO_3 (1.42 g, 10.24 mmol, 8 equiv) was added to the previously prepared silylated allenediyne in MeOH (10 mL) and the resulting mixture was stirred until TLC had indicated the completion of the reaction. The mixture was diluted with Et_2O, washed with a saturated solution of NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (PE/EE=9/1) to yield allenediyne **25***cis* (two diastereomers, 0.05 g, 10%). IR(neat) 3100, 2970, 2150, 2010, 1470 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.27 (m, 2H), 7.17 (m, 1H), 3.95 (t, J=8.8 Hz, 2H), 3.86 (t, J=8.8 Hz, 2H), 3.14–3.04 (m, 1H), 2.80 (m, 1H), 2.43–2.33 (m, 1H), 2.17–2.12 (m, 6H), 1.94–1.92 (m, 4H), 1.79 (s, 3H), 1.60–1.56 (m, 4H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (**25***cis*, major) 203.2 (IV), 140.2 (IV), 128.0 (2C, III), 126.3 (2C, III), 125.9 (III), 119.1 (IV), 103.2 (IV), 101.8 (IV), 87.2 (IV), 79.0 (IV), 70.3 (III), 68.2 (III), 64.8 (2C, II), 49.7 (IV), 37.8 (III), 33.9 (II), 32.9 (II), 32.4 (II), 28.3 (II), 26.8 (II), 26.6 (II), 20.7 (I), 18.7 (II), 18.3 (I). δ (**25***cis*, minor) 203.2 (IV), 140.2 (IV), 128.0 (2C, III), 126.3 (2C, III), 125.9 (III), 119.1 (IV), 103.2 (IV), 101.7 (IV), 87.2 (IV), 79.0 (IV), 70.5 (III), 68.3 (III), 64.8 (2C, II), 49.7 (IV), 38.0 (III), 33.7 (II), 32.8 (II), 32.2 (II), 28.3 (II), 26.9 (II), 26.5 (II), 20.7 (I), 18.7 (II), 18.3 (I).

4.3.10. 4-Methyl-1-(tetrahydropyran-2-yloxy)-10-trimethylsilyl-deca-2,9-diyn-4-ol (26). To a cooled (−78 °C) solution of 8-trimethylsilyl-oct-7-yn-2-one (1.19 g, 6.04 mmol, 1 equiv) in THF (10 mL) was added at −78 °C the lithium acetylide derived from tetahydropyranyl propargyl ether (0.6 M in THF, 6.04 mmol, 1 equiv). After warming up at rt, the reaction mixture was stirred until TLC indicated the completion, diluted with Et_2O, washed with a saturated solution of NH_4Cl, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (PE/EE=9/1) of the residue furnished the alcohol **26** (1.93 g, 95%). IR(neat) 3400, 2950, 2100, 1250, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, J=3.2 Hz, 1H), 4.24 (d, J=8.4 Hz, 2H), 3.82–3.76 (m, 1H), 3.52–3.47 (m, 1H), 2.20 (t, J=6.4 Hz, 2H), 1.77–1.48 (m, 12H), 1.43 (s, 3H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.4 (IV), 96.6 (III), 89.9 (IV), 84.6 (IV), 79.0 (IV), 67.9 (IV), 61.9 (II), 54.3 (II), 43.0 (II), 30.2 (II), 28.7 (II), 29.7 (I), 25.4 (II), 24.0 (II), 19.8 (II), 18.9 (II), 0.2 (3C, I). Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 68.03; H, 9.67.

4.3.11. 4-Methyl-2-phenyl-10-trimethylsilyl-deca-2,3-dien-9-yn-1-ol (27). To a cooled (−50 °C) THF (50 mL) suspension of $Me_2S\cdot CuBr$ (1.82 g, 8.85 mmol, 1.5 equiv) and LiBr (0.77 g, 8.85 mmol, 1.5 equiv) was added dropwise a solution of phenylmagnesium bromide (2.7 M in Et_2O, 8.85 mmol, 1.5 equiv). The resulting mixture was stirred for 15 min (during this period a yellow precipitate appeared).

At −78 °C, *n*-BuLi (2.4 M in hexane, 2.46 mL, 5.9 mmol, 1 equiv) was added to a solution of alcohol **26** (2 g, 5.9 mmol, 1 equiv) in THF (20 mL) and after 5 min, pure mesyl chloride (0.51 mL, 6.49 mmol, 1.1 mmol) was added. The resulting solution was stirred for 5 min and was added to the previously prepared copper(I) reagent. After being stirred at −50 °C for 30 min, the reaction mixture was allowed to warm to rt. Then, the reaction was hydrolyzed with a 2:1 saturated solution of NH_4Cl/NH_4OH, diluted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was used in the next step without any further purification.

To a solution of the previously prepared crude mixture in MeOH (30 mL) was added PTSA (0.118 g, 0.6 mmol, 0.1 equiv). After being stirred at rt until TLC had indicated the completion of the reaction, the mixture was diluted with Et_2O, washed successively with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE=85/15) afforded **27** (1.73 g, 94% over the two steps). IR(neat) 3400, 2950, 2200, 1640, 1240, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.21 (m, 5H), 4.53 (br s, 2H), 2.25–2.16 (m, 4H), 1.86 (s, 3H), 1.67–1.37 (m, 4H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 (IV), 135.5 (IV), 128.6 (2C, III), 126.8 (III), 126.0 (2C, III) 115.4 (IV), 107.3 (IV), 106.1 (IV), 84.7 (IV), 61.8 (II), 33.7 (II), 28.1 (II), 26.6 (II), 19.7 (II), 19.0 (I), 0.2 (3C, I). Anal. Calcd for $C_{20}H_{28}OSi$: C, 76.86; H, 9.03. Found: C, 76.86; H, 9.21.

4.3.12. 3-Ethynyl-2-methyl-2-(4-methyl-2-phenyl-deca-2,3-dien-9-ynyl)-cyclopentanone (29*trans*). To a cooled (−50 °C) THF (50 mL) solution of KHMDS (1.10 g, 5.54 mmol) was added a solution of ketone **20**[21](1.29 g, 6.65 mmol, 1.2 equiv) in THF (50 mL). After warming up at −15 °C, the reaction mixture was stirred for 45 min. Then, after being cooled to −50 °C a solution of the mesylate (2.16 g, 5.54 mmol, 1 equiv) [generated from alcohol **27**] in THF (10 mL) was added. After stirring for 30 min at −50 °C, the temperature was allowed to warm up at rt. The reaction mixture was hydrolyzed with a saturated solution of NH_4Cl/NH_4OH (2/1) and partitioned with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was used in the next step without any further purification.

To a solution of the crude allenediyne previously prepared in MeOH (20 mL) was added K_2CO_3 (6.15 g, 44.3 mmol, 8 equiv) at rt. The reaction was stirred at rt until TLC had indicated the completion of the reaction. The mixture was diluted with Et_2O, washed successively with a saturated solution of NH_4Cl and brine, dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash chromatography (PE/EE 9/1) furnished a 5:4 mixture of **29*trans*** (0.954 g, 50%).

Successive recrystallization in pentane allowed the isolation of pure major **29*trans*M** (0.300 g). IR(neat) 2970, 2900, 2100, 1675, 1640, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.31–7.28 (m, 2H), 7.21–7.17 (m, 1H), 3.38 (m, 1H), 2.94 (d, J=15.6 Hz, 1H), 2.64 (d, J=15.6 Hz, 1H), 2.41–2.16 (m, 4H), 1.98–1.92 (m, 4H), 1.72 (s, 3H), 1.54 (m, 6H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8 (IV), 203.0 (IV), 138.0 (IV), 128.3 (2C, III), 126.6 (III), 126.3 (2C, III), 103.2 (IV), 100.8 (IV), 84.2 (IV), 83.6 (IV), 68.6 (III), 68.3 (III), 51.3 (IV), 36.3 (II), 34.3 (III), 33.8 (II), 28.2 (II), 26.4 (II), 25.7 (II), 20.7 (I), 18.3 (I), 18.2 (II). HRMS calcd for $C_{25}H_{28}O$ $(MH)^+$ 345.214. Found: 345.222.

29*trans*m: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.31–7.28 (m, 2H), 7.21–7.17 (m, 1H), 3.38 (m, 1H), 2.97 (d, J=15.5 Hz, 1H), 2.63 (d, J=15.6 Hz, 1H), 2.41–2.16 (m, 4H), 1.98–1.92 (m, 4H), 1.79 (s, 3H), 1.54 (m, 6H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8 (IV), 202.9 (IV), 137.9 (IV), 128.2 (2C, III), 126.6 (III), 126.2 (2C, III), 103.4 (IV), 100.6 (IV), 84.2 (IV), 83.6 (IV), 71.5 (III), 68.6 (III), 51.2 (IV), 36.3 (II), 34.4 (III), 33.9 (II), 28.2 (II), 26.6 (II), 25.7 (II), 20.8 (I), 18.3 (2C, II and I), 18.2 (II).

4.3.13. Cycloadduct (30). $CpCo(CO)_2$ (20 μL, 0.16 mmol, 1.2 equiv) was added to a boiling solution of **25*cis*** (0.049 g, 0.13 mmol) in xylenes (10 mL) degassed by three freeze-pump-thaw cycles and was irradiated (light from projector lamp; ELW, 300 W, 50% of its power). The reaction was monitored by TLC and after completion, the reaction mixture was concentrated in vacuo. The crude oil was purified by flash chromatography (the solvents of chromatography were not degassed) either on deactivated alumina with 3% H_2O (PE) or on silica gel neutralized with NEt_3 and dried (PE/EE 95/5) to furnish **30** (0.033 g, 66%) as a mixture of diastereomers. IR(neat) 3300, 2950, 2100, 1640, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 5H), 5.11–4.77 (m, 3H), 3.94–3.88 (m, 4H), 2.6–2.5 (m, 2H), 2.17–1.67 (m, 8H), 1.57 (s, 3H), 1.42–1.32 (m, 4H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (IV), 133.8 (IV), 128.4 (2C, III), 128.0 (IV), 127.9 (IV), 127.6 (2C, III), 127.4 (IV), 126.4 (III), 119.9 (IV), 116.0 (III), 113.7 (II), 84.7 (IV), 68.2 (III), 65.3 (II), 64.4 (II), 49.2 (III), 45.5 (IV), 37.8 (II), 36.1 (II), 34.2 (II), 29.8 (II), 28.2 (II), 27.6 (II), 26.4 (I), 17.8 (I). HRMS Calcd for $C_{27}H_{32}O_2$ (388.54) $(MH)^+$ 389.248. Found: 389.248.

4.3.14. Cycloadduct (31). The procedure is identical as the one described for (**30**). The cyclization was carried out with $CpCo(CO)_2$ (27 μL, 0.19 mmol, 1.2 equiv) and a solution of **29*trans*M** (0.054 g, 0.16 mmol) in degassed xylenes (10 mL). Purification by flash chromatography (PE/EE 9/1) gave **31** (0.045 g, 60%) as a red solid. Mp 68–70 °C. ^1H NMR (400 MHz, C_6D_6) δ 7.26–7.21 (m, 2H), 7.18–7.11 (m, 3H), 5.04 (d, J=4.2 Hz, 1H), 4.59 (s, 5H), 4.46 (d, J=4.2 Hz, 1H), 2.41 (d, J=17.4 Hz, 1H), 2.29–2.22 (m, 1H), 2.15 (d, J=17.4 Hz, 1H), 1.98–1.89 (m, 4H), 1.75 (s, 3H), 1.60–1.15 (m, 8H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 218.0 (IV), 145.9 (IV), 144.8 (IV), 129.6 (IV), 128.2 (2C, III), 127.8 (III), 125.9 (2C, III), 80.8 (5C, III), 77.6 (IV), 75.1 (III), 73.5 (III), 63.7 (IV), 50.0 (III), 48.0 (IV), 47.2 (IV), 46.1 (II), 41.0 (II), 35.8 (II), 35.7 (II), 30.8 (II), 27.7 (I), 22.5 (II), 21.3 (II), 14.7 (I). HRMS Calcd for $C_{30}H_{33}CoO$ (468.52) $(MH)^+$ 469.194. Found: 469.194.

4.3.15. Compound (32). A solution of complex **31** (0.08 g, 0.17 mmol) in CH_2Cl_2 (5 mL) was stirred in presence of silica gel at rt. The reaction was monitored by TLC and after completion, the reaction mixture was filtered and furnished **32** (0.052 g, 90%). IR (neat) 2970, 2900, 2100, 1675, 1640, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 3H), 7.11 (m, 2H), 5.63 (m, 2H), 2.56–2.45 (m, 3H), 2.32–2.23 (m, 3H), 2.09–2.06 (m, 2H), 1.88 (m, 1H), 1.65 (m, 2H), 1.45 (m, 1H), 1.27 (s, 3H), 1.25–1.23 (m, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8 (IV), 147.4 (IV), 146.2 (IV), 140.2 (IV), 134.7(IV), 132.1 (IV), 128.3 (III), 128.2 (III), 127.4 (III), 126.0 (2C, III), 118.1 (III), 116.0 (III), 47.3 (II), 46.8 (III), 46.5 (IV), 43.0 (IV), 39.8 (II), 36.3 (II), 33.1 (II), 27.3 (II), 26.1 (I), 23.2 (II), 21.1 (II), 14.3 (I). HRMS Calcd for $C_{25}H_{28}O$ (344.49) $(MH)^+$ 345.214. Found: 345.221.

4.3.16. Cycloadduct (33). The procedure is the same as the one described for (**31**). The cyclization was carried out with a 41:59 mixture of **29*trans*(M/m)** (0.200 g, 0.59 mmol) and $CpCo(CO)_2$ (100 μL, 0.70 mmol, 1.2 equiv) in degassed xylenes (10 mL). Purification by flash chromatography (PE/EE 9/1) gave a 61:39 mixture of **31** and **33** (0.097 g, 35%). Besides 0.0264 g of unidentified compound was isolated. (**33**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.18–7.11 (m, 3H), 4.98 (d, J=4.2 Hz, 1H), 4.64 (s, 5H), 4.54 (d, J=4.2 Hz, 1H), 2.41 (d, J=17.4 Hz, 1H), 2.29–2.22 (m, 1H), 2.15 (d, J=17.4 Hz, 1H), 1.98–1.89 (m, 4H), 1.60–1.15 (m, 8H), 1.01 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1 (IV), 146.4 (IV), 145.5 (IV), 129.6 (IV), 128.2 (2C, III), 127.8 (III), 125.9 (2C, III), 80.8 (5C, III), 77.6 (IV), 75.1 (III), 73.5 (III), 64.0 (IV), 50.5 (III), 46.9 (IV), 46.3 (IV), 45.5 (II), 39.1 (II),

35.7 (II), 33.1 (II), 30.0 (II), 25.8 (I), 25.6 (II), 21.2 (II), 14.0 (I).

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Enantioselective total and formal syntheses of paroxetine (PAXIL) via phosphine-catalyzed enone α-arylation using arylbismuth(V) reagents: a regiochemical complement to Heck arylation

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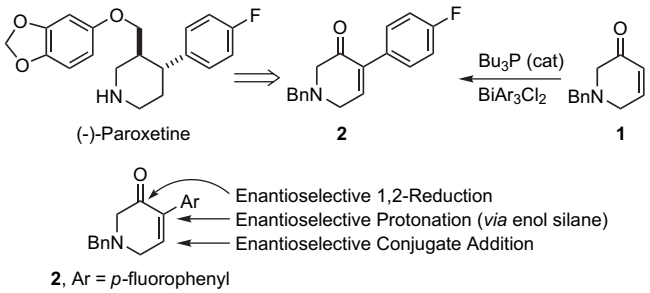
Abstract—Exposure of dihydropyridinone **1** to the arylbismuth(V) reagent $(p\text{-F-Ph})_3BiCl_2$ in the presence of substoichiometric quantities of tributylphosphine (10 mol %) results in aryl transfer to the transiently generated (β-phosphonio)enolate to provide the α-arylated enone **2**. This transformation, which represents a regiochemical complement to the Mizoroki–Heck arylation, is used strategically in concise formal and enantioselective total syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL).

1. Introduction

Nucleophilic or Lewis base catalysis represents a major subset of organocatalytic transformations.[1] As part of an ongoing program in this area, we have developed a family of catalytic transformations that exploit the unique reactivity of enolates derived upon phosphine-conjugate addition to α,β-unsaturated carbonyl compounds.[2–5] These studies encompass a catalytic method for the regiospecific α-arylation of enones and enals, wherein transiently generated (β-phosphonio)enolates or oxaphospholenes are captured by arylbismuth(V) reagents.[5–7] The scope of this process complements corresponding palladium-catalyzed enolate arylations,[8] as strongly basic reagents are not required for enolate generation. Further, the use of enones as enolate precursors enables regiospecific enolate generation. In this account, the synthetic utility of the phosphine-catalyzed enone α-arylation is highlighted through its strategic use in concise formal and enantioselective total syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL).

Paroxetine, a GlaxoSmithKline product marketed as Paxil/Seroxat, is an enantiomerically enriched *trans*-3,4-disubsituted piperidine used for the treatment of depression, obsessive compulsive disorder, and panic disorder.[9] As one of the leading prescription drugs worldwide, paroxetine has received considerable attention from synthetic chemists, evoking a surprisingly diverse array of strategies for its asymmetric synthesis. To date, approaches to the asymmetric synthesis of paroxetine encompass the physical resolution of racemates,[10] enzyme-catalyzed asymmetric transformations,[11] chiral auxiliary-based approaches,[12] asymmetric deprotonation using chiral bases,[13] catalytic enantioselective transformations,[14] as well as the use of naturally occurring chiral starting materials.[15] We envisioned a concise approach to (−)-paroxetine based on phosphine-catalyzed α-arylation of *N*-benzyl dihydropyridinone **1**, which may be prepared from commercially available *N*-benzyl glycine ethyl ester in only three steps.[16] The resulting α-arylated enone **2** represents an attractive synthetic intermediate *en route* to (−)-paroxetine, as closely related α-aryl enones are amenable to a range of relevant catalytic enantioselective transformations. These include asymmetric conjugate addition, asymmetric 1,2-reduction, as well as asymmetric protonation by way of the enol silane (Scheme 1).[17,18]



Scheme 1. Retrosynthesis of (−)-paroxetine via enone α-arylation.

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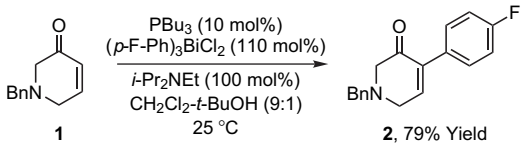
1.1. Formal synthesis of (±)-paroxetine (PAXIL)

Preparation of the arylation substrate, dihydropyridinone **1**, is achieved readily in accordance with the literature procedure.[16] The requisite bismuth reagent $(p\text{-F-Ph})_3BiCl_2$ is prepared by treating *p*-F-PhMgBr with $BiCl_3$ followed by oxidation of the resulting triarylbismuth(III) compound with elemental chlorine.[5,6] Gratifyingly, exposure of dihydropyridinone **1** to $(p\text{-F-Ph})_3BiCl_2$ (110 mol %) in the presence of tributylphosphine (10 mol %) and Hünig's base (100 mol %) at ambient temperature in CH_2Cl_2/^{t}BuOH (9:1) provides the α-arylated dihydropyridinone **2** in 79% isolated yield as a single regioisomer, based on ^{1}H NMR analysis (Scheme 2).



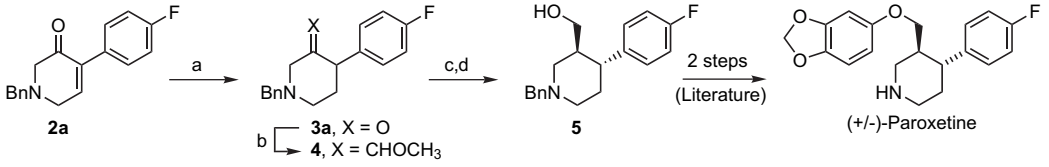
Scheme 2. Catalytic α-arylation of dihydropyridinone **1**.

Subsequent efforts focused on the conversion of aryl enone **2a** to *N*-benzyl aminoalcohol **5**, which has been converted to paroxetine in two steps.[10i,11e,13b,c,15] Conjugate reduction of **2a** using L-Selectride provides the corresponding saturated α-aryl ketone **3a** in 87% yield.[19] Ketone olefination using $Ph_3P{=}CHOMe$[20] affords the enol ether **4** in 65% yield as a single alkene geometrical isomer, as determined by ^{1}H NMR. Acid hydrolysis of enol **4** followed by $NaBH_4$ reduction of the resulting aldehyde provides *N*-benzyl aminoalcohol **5** in 63% yield over the two-step sequence as a single diastereomer, as determined by ^{1}H NMR. Aminoalcohol **5** exhibits spectral properties identical in all respects to previously reported material that has been converted to paroxetine in two steps.[10i,11e,13b,c,15] Hence, the preparation of **5** from dihydropyridinone **1** represents a formal synthesis of (±)-paroxetine (Scheme 3).

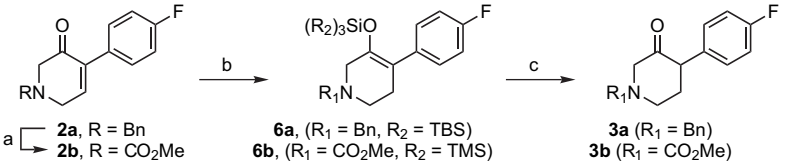
1.2. Enantioselective total synthesis of (−)-paroxetine (PAXIL)

Having completed a formal racemic synthesis of paroxetine, efforts toward an enantioselective total synthesis were made. Here, a potentially effective strategy involves asymmetric protonation[17,18] of enol silanes **6a** or **6b**, which are derived in a single manipulation from enones **2a** and **2b** by way of conjugate reduction with trapping of the resulting enolate in situ using trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride, respectively.[19] However, enol silane **6a** did not react upon exposure to Yamamoto's BINOL/$SnCl_4$ reagent,[17a–c] perhaps due to the presence of the Lewis basic *N*-benzyl amine. Treatment of the carbamoyl-protected enone **6b** to the BINOL/$SnCl_4$ reagent gave the desired α-aryl ketone **3b** in 80% yield, but with very low levels of optical enrichment (10% ee). Yanagisawa's recently reported silver fluoride-catalyzed asymmetric protonation gave a more promising result, providing the α-aryl ketone **3b** in 90% yield and 39% ee (Scheme 4).[17d]

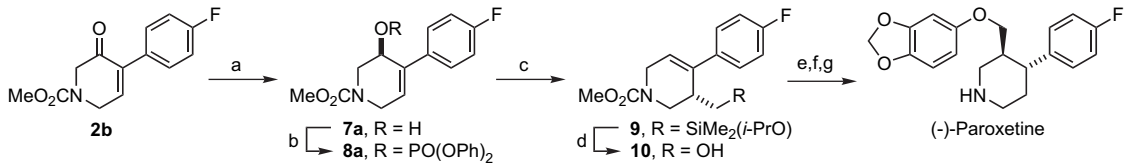
The difficulties encountered in preparing optically enriched aminoketones **3a** or **3b** led us to consider alternative synthetic routes. Accordingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of enones **2a** and **2b** was explored.[21] The *N*-benzyl-protected enone **2a** gave the corresponding allylic alcohol in 35% yield and 70% ee. It was speculated that the presence of the Lewis basic *N*-benzyl amine of **2a** was incompatible with the Lewis acidic oxazaborolidine catalyst, resulting in diminished yields and selectivities. Gratifyingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of the corresponding *N*-carbamoyl-protected enone **2b** provides allylic alcohol **7a** in 95% yield and 96% ee. The allylic alcohol **7a** was converted to the diphenyl phosphate **8a** and was subjected to conditions for *anti*-selective copper-mediated S_N2' allylic substitution[22] using $(i\text{-PrO})Me_2SiCH_2Cl$ as a hydroxymethyl anion equivalent.[23] The silicon containing product of allylic substitution **9** was obtained in 96% yield and was subjected to Tamao oxidation to provide the homo-allylic alcohol **10** in 70% yield. As revealed by chiral stationary phase HPLC analysis, compound **10** is obtained in 92% ee. The high fidelity of chirality transfer supports an *anti*-S_N2' mechanism for allylic substitution and the slight decrease in enantiomeric excess is attributed to competitive S_N2 substitution. Stereoselective substrate-directed catalytic homogeneous hydrogenation of the homo-allylic alcohol **10** was accomplished using Crabtree's conditions[24,25] to provide the corresponding saturated alcohol in 69% yield as a single diastereomer, as determined by ^{1}H NMR analysis.



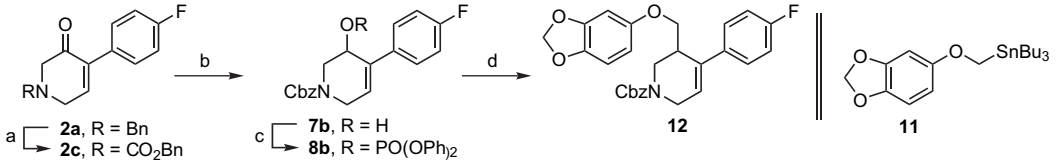
Scheme 3. Conversion of arylation product **2a** to (±)-paroxetine. Conditions: (a) L-Selectride, THF, −78 °C, 87%; (b) Ph_3PCH_2OMeCl, NaHMDS, THF, 0 °C, 65%; (c) 0.1 M H_2SO_4, THF, 50 °C; (d) $NaBH_4$, EtOH, 25 °C, 63% over two steps.



Scheme 4. Attempted asymmetric protonation of enol silanes **6a** and **6b**. Conditions: (a) MeOCOCl, CH_2Cl_2, 25 °C, 86%; (b) Li(s-Bu)$_3$BH, THF, −78 °C, then R_3SiCl, 74% (from **2a** using TBSCl) and 86% (from **2b** using TMSCl); (c) AgF (cat.), *R*-BINAP (cat.), DCM/MeOH (20:1), 90%, 39% ee (refers to the conversion of **6b** to **3b**).



Scheme 5. Enantioselective total synthesis of (−)-paroxetine. Conditions: (a) (*S*)-Me-CBS (cat.), $BH_3 \cdot SMe_2$, CH_2Cl_2, −20 °C, 95%, 96% ee; (b) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 89%; (c) (*i*-PrO)Me_2SiCH_2Cl, Mg, 25 °C, then CuCN, THF, −30 to 0 °C, 96%; (d) KF, H_2O_2, DMF, 25 °C, 70%, 92% ee; (e) $[Ir(COD)(PCy_3)Pyr]PF_6$, CH_2Cl_2, 25 °C, 69%; (f) DIAD, PPh_3, sesamol, THF, 0–50 °C, 76%; (g) KOH, $(HOCH_2)_2$, 100 °C, then HCl, 92%.



Scheme 6. Enantioselective total synthesis of (−)-paroxetine. Conditions: (a) BnOCOCl, CH_2Cl_2, 25 °C, 89%; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_3OH, 25 °C, 76%; (c) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 86%; (d) stannane **11**, *n*-BuLi, THF, −78 °C, then CuBr·DMS, THF, −78 to −10 °C, 27%.

The alcohol was converted to the phenolic ether in 76% yield through its reaction with sesamol under Mitsunobu's conditions.[26] Finally, deprotection of methyl carbamate was achieved under basic conditions[27] and the free amine was treated with anhydrous HCl to provide (−)-paroxetine as the hydrochloride salt in 92% yield. (−)-Paroxetine hydrochloride obtained in this manner exhibits spectral properties identical in all respects to previously reported material (Scheme 5).[10–15]

Finally, it is noteworthy that a more concise approach to (−)-paroxetine is potentially achieved via direct *anti*-selective copper-mediated S_N2' allylic substitution using a sesamol-based phenoxymethyl anion. Stimulated by this prospect, the tributylstannylmethyl ether **11** was prepared from sesamol and tributyl(iodomethyl)stannane.[28] Allylic substitution using the phenoxymethyl anion derived cuprate with allylic phosphate **8b** gave the desired phenolic ether in 27% yield. This low yield is attributed to the instability of the intermediate α-alkoxy organolithium reagent, and the resulting organocuprate, with respect to α-elimination, as suggested by the recovery of sesamol. Hence, this strategy was not implemented in the synthesis of (−)-paroxetine (Scheme 6).

2. Conclusion

In summary, the phosphine-catalyzed α-arylation of enones was used strategically in concise formal and total enantioselective syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL). This methodology complements related Pd-catalyzed enolate arylations in several regards. The use of enones as latent enolates enables regiospecific enolate generation and preservation of the enone moiety in the product facilitates subsequent elaboration of the arylated products. Future studies will focus on the invention of related reagents for aryl transfer under the conditions of nucleophilic catalysis.

3. Experimental

3.1. General

All reactions were performed under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe and degassed with argon prior to use. Flasks were flame-dried and cooled under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium turnings and iodine. Other solvents and chemical reagents obtained from commercial sources were used without further purification, unless otherwise noted. The literature procedures used to prepare dihydropyridinone **1** from *N*-benzyl glycine ethyl ester are described in Ref. 16.

Analytical thin-layer chromatography (TLC) was carried out by using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}, EMD Chemicals). Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer. Samples were prepared as films through evaporation from dichloromethane or chloroform solution on sodium chloride plates. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 by using chemical ionization in the positive ionization mode. Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion. Melting points were determined on a Thomas Hoover Uni-melt apparatus in open capillaries and were uncorrected. Enantiomeric purity was determined by chiral stationary phase HPLC analysis. Optical rotations were measured by using an Atago Polax-2L polarimeter. Concentrations are reported in units of g/100 mL.

Proton NMR (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) spectrometer, a Varian Gemini (400 MHz) spectrometer, and a Inova (500 MHz) spectrometer. Chemical shifts (δ) are expressed as parts per million

relative to trimethylsilane (δ=0.00 ppm), referenced to the residual protic solvent. Coupling constants are reported in hertz. Carbon-13 NMR (^{13}C NMR) spectra were recorded on a Varian Gemini 300 (75 MHz) spectrometer, a Varian Gemini 400 (100 MHz) spectrometer, and a Inova 500 (125 MHz) spectrometer. Chemical shifts (δ) are expressed as parts per million relative to trimethylsilane (δ=0.0 ppm), referenced to the center of the triplet at δ=77.0 ppm for deuteriochloroform and δ=39.5 ppm for deuteriodimethylsulfoxide (DMSO). ^{13}C NMR analyses were run routinely with broadband decoupling.

3.2. Preparation of compounds 2a–12

3.2.1. Aryl enone 2a. To 100 mL flask charged with tris-(4-fluorophenyl)bismuth dichloride (12.3 g, 21.7 mmol, 110 mol %) and **1** (3.7 g, 19.7 mmol, 100 mol %) was added CH_2Cl_2/^{t}BuOH (9:1) (36 mL, 0.5 M), followed by tributylphosphine (0.5 mL, 1.98 mmol, 10 mol %) and diisopropylethylamine (3.4 mL, 19.7 mmol, 100 mol %). The reaction mixture was allowed to stir at room temperature until complete consumption of starting material was observed by TLC (3 h), at which point the reaction mixture was evaporated onto silica gel. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **2a** (4.39 g, 15.6 mmol) in 79% yield as an off white solid. Mp 66.5–68.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 6H), 7.03 (m, 4H), 3.70 (s, 2H), 3.43 (d, J=3.42 Hz, 2H), 3.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 162.5 (d, J=247.5 Hz), 145.2, 137.4, 136.3, 130.8, 130.2 (d, J=8.5 Hz), 129.1, 128.5, 127.6, 114.9 (d, J=21.5 Hz), 61.8, 61.7, 52.6. IR (film): 3063, 3029, 2918, 2803, 2750, 1683, 1601, 1509, 1349, 1223, 1160, 823, 699 cm^{-1}. HRMS: Calcd for $C_{18}H_{17}NOF$ [M+1] 282.12942, found 282.12898.

3.2.2. Aryl enone 2b. Methylchloroformate (2 mL, 24.9 mmol, 200 mol %) was added dropwise to a solution containing **2a** (3.5 g, 12.4 mmol, 100 mol %) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was stirred at this temperature for 18 h, at which point the reaction mixture was evaporated onto silica gel and purified via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give the title compound **2b** (2.64 g, 10.5 mmol) in 86% yield as a white solid. Mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, J=8.6, 5.5 Hz, 2H), 7.05 (t, J=8.6 Hz, 3H), 4.45 (d, J=2.1 Hz, 2H), 4.29 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 162.1 (d, J=247.5 Hz), 155.3, 143.4, 137.2, 130.1 (d, J=3.1 Hz), 130.2 (d, J=7.7 Hz), 115.1 (d, J=21.5 Hz), 53.0, 51.9, 43.6. IR (film): 3053, 2981, 2863, 1723, 1673, 1606, 1463, 1403, 1351, 1236, 1103, 953, 842, 809 cm^{-1}. HRMS: Calcd for $C_{13}H_{13}NO_3F$ [M+1] 250.0879, found 250.0882.

3.2.3. Aryl enone 2c. Benzylchloroformate (1.21 g, 7.1 mmol, 200 mol %) and **2a** (1.0 g, 3.5 mmol, 100 mol %) were reacted according to the procedure described for **2b**. The crude product was purified via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give compound **2c** (1.03 g, 3.16 mmol) in 89% yield as a white solid. Mp 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 5H), 7.31 (dd, J=8.9, 5.5 Hz, 2H), 7.04 (t, J=8.9 Hz, 2H), 5.19 (s, 2H), 4.47 (d, J=3.8 Hz, 2H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 162.7 (d, J=247.5 Hz), 154.7, 143.3, 137.2, 135.8, 130.3 (d, J=7.7 Hz), 128.5, 128.2 (d, J=6.9 Hz), 115.1 (d, J=21.5 Hz), 67.8, 51.9, 43.6. IR (film): 3033, 2956, 2829, 1688, 1601, 1509, 1430, 1350, 1231, 1160, 1100, 814 cm^{-1}. HRMS: Calcd for $C_{19}H_{17}NO_3F$ [M+1] 326.1192, found 326.1195.

3.2.4. Aryl ketone 3a. To a solution containing **2a** (0.71 g, 2.53 mmol, 100 mol %) in dry THF (15 mL) at −78 °C was added L-Selectride (1 M in THF, 2.6 mL, 2.53 mmol, 100 mol %) dropwise. The mixture was stirred at −78 °C for 1 h, at which point aqueous NH_4Cl (10% solution, 20 mL) was added. The reaction mixture was transferred to a separatory funnel and was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives compound **3a** (0.609 g, 2.15 mmol) in 87% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 7.11 (m, 2H), 7.03 (m, 2H), 3.64 (s, 2H), 3.53 (t, J=10.0 Hz, 1H), 3.36 (dd, J=14.1, 1.8 Hz, 1H), 3.06 (dm, J=9.2 Hz, 1H), 2.93 (d, J=13.8 Hz, 1H), 2.58 (m, 1H), 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.2, 162.2 (d, J=246.2 Hz), 136.9, 133.65, 130.2 (d, J=8.4 Hz), 129.0, 128.4, 127.4, 115.3 (d, J=11.5 Hz), 64.4, 62.5, 54.3, 51.9, 32.7. IR (film): 3062, 3029, 2949, 2801, 1722, 1604, 1511, 1454, 1224, 1098, 833, 740, 700 cm^{-1}. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.14507, found 284.14541.

3.2.5. Aryl ketone 3b. A mixture of silver fluoride (2 mg, 0.016 mmol, 10 mol %) and (*R*)-BINAP (5.8 mg, 9.0 μmol, 6 mol %) was dissolved in methanol (0.2 mL) and stirred at room temperature for 10 min in the dark, at which point CH_2Cl_2 (2 mL) was added and the solution was stirred for another 10 min. The solution was cooled to −78 °C and **6b** (50 mg, 0.155 mmol, 100 mol %) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was warmed to −30 °C and stirred at this temperature for 72 h, at which point the mixture was evaporated to dryness. Purification via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives the title compound **3b** (35 mg, 0.014 mmol) in 90% yield as a colorless oil. Chiral HPLC (Daicel Chiralpak OJ-H column, 85:15 hexanes/*i*-PrOH, λ=254 nm, 0.5 mL min^{-1}, t_{major}=67.0 min, t_{minor}=97.7 min, ee=39%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.19 (dd, J=8.6, 5.5 Hz, 2H), 7.10 (t, J=11.1 Hz, 2H), 4.14 (A part of AB pattern, d, J=17.4 Hz, 1H), 4.05 (B part of AB pattern, d, J=17.4 Hz, 1H), 3.85 (m, 2H), 3.63 (s, 3H), 3.56 (m, 2H), 2.21 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 203.9, 160.7 (d, J=243.1 Hz), 154.7, 133.3 (d, J=3.5 Hz), 129.2 (d, J=8.1 Hz), 114.2 (d, J=1.3 Hz), 53.2, 51.9, 41.7, 29.1. IR (film): 2956, 1700, 1602, 1511, 1449, 1404, 1223, 835, 770 cm^{-1}. HRMS: Calcd for $C_{13}H_{15}NO_3F$ [M+1] 252.1036, found 252.1038.

3.2.6. Enol ether 4. To a vigorously stirred suspension of methoxymethyltriphenylphosphonium chloride[20] (500 mg, 1.76 mmol, 100 mol %) in dry THF (18 mL) was added a solution of NaHMDS (2 M in THF, 3.5 mL, 7.06 mmol, 400 mol %) dropwise. The resulting red solution was stirred at this temperature for 2 h, at which point **3a** (500 mg, 1.76 mmol, 100 mol %) in THF (3 mL) was added dropwise

over 10 min. The reaction mixture was allowed to stir at room temperature for 20 h, at which point aqueous NH_4Cl (1 M, 30 mL) was added. The resulting mixture was extracted with diethyl ether (3×15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a yellow oil. Purification of the residue via column chromatography (SiO_2, 9:1 to 4:1 hexane/ethyl acetate) gives the title compound **4** (350 mg, 11.2 mmol) in 65% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.19 (m, 2H), 6.99 (t, J=8.9 Hz, 2H), 5.14 (s, 1H), 3.83 (d, J=12.3 Hz, 1H), 3.70 (A part of AB pattern, J=13.0 Hz, 1H), 3.50 (B part of AB pattern, J=13.0 Hz, 1H), 3.42 (s, 3H), 3.16 (d, J=10.3 Hz, 1H), 2.90 (d, J=11.6 Hz, 1H), 2.60 (d, J=12.3 Hz, 1H), 2.21 (td, J=11.3, 2.7 Hz, 1H), 1.98 (m, 1H), 1.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (d, J=244.4 Hz), 143.2, 137.9, 137.7, 129.8 (d, J=7.6 Hz), 129.4, 128.1, 126.9, 117.5, 114.9 (d, J=21.1 Hz), 63.0, 59.4, 52.8, 51.6, 43.9, 32.7. IR (film): 3029, 2933, 2846, 2798, 1677, 1603, 1509, 1222, 1129, 835, 699 cm^{-1}. HRMS: Calcd for $C_{20}H_{22}NOF$ [M+1] 311.16854, found 311.16756.

3.2.7. Aminoalcohol 5. A solution of the enol ether **4** (50 mg, 0.16 mmol, 100 mol %) in THF (3 mL) was treated with 0.1 M aqueous H_2SO_4 (2.4 mL, 0.24 mmol, 150 mol %). The solution was allowed to reflux for a 12 h period, at which point the heating batch was removed and the reaction was allowed to reach room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to provide the crude aldehyde (34 mg, 0.11 mmol) in 72% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (d, J=1.8 Hz, 1H), 7.34 (m, 5H), 7.28 (m, 2H), 7.02 (t, J=8.5 Hz, 2H), 3.62 (s, 2H), 3.18 (dm, J=11.4 Hz, 1H), 2.99 (dm, J=11.4 Hz, 1H), 2.90 (dm, J=18.4 Hz, 1H), 2.77 (dd, J=9.0, 7.0 Hz, 1H), 2.12 (t, J=11.1 Hz, 2H), 1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.6 (d, J=244.7 Hz), 138.6, 137.8, 129.1, 128.8 (d, J=7.9 Hz), 128.3, 127.2, 115.5 (d, J=21.4 Hz), 63.1, 54.4, 53.5, 53.0, 43.1, 34.1. IR (film): 2938, 2806, 1721, 1603, 1510, 1465, 1224, 1160, 833, 699 cm^{-1}. HRMS: Calcd for $C_{19}H_{21}NOF$ [M+1] 298.1607, found 298.1601.

This crude aldehyde was dissolved in ethanol (2 mL) and treated with $NaBH_4$ (6 mg, 0.16 mmol, 100 mol %), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was treated with 2 N aqueous sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue. Purification of the residue via column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **5** (30 mg, 0.10 mmol) in 63% yield over two steps as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.17 (m, 2H), 6.98 (t, J=8.6 Hz, 2H), 3.60 (A part of AB pattern, J=13.2 Hz, 1H), 3.56 (B part of AB pattern, J=13.2 Hz, 1H), 3.37 (dd, J=11.3, 3.0 Hz, 1H), 3.21 (m, 2H), 2.98 (d, J=11.0 Hz, 1H), 2.33 (m, 1H), 1.98 (m, 3H), 1.79 (m, 3H). IR (film): 3427, 2934, 2848, 2799, 1604, 1510, 1222, 1130, 836, 739, 700 cm^{-1}. HRMS: Calcd for $C_{19}H_{23}NOF$ [M+1] 300.17637, found 300.17487.

3.2.8. Enol silane 6a. To a solution containing **2a** (0.1 g, 0.35 mmol, 100 mol %) in dry THF (2 mL) at −78 °C was added L-Selectride (1 M in THF, 0.36 mL, 0.35 mmol, 100 mol %) dropwise. The mixture was stirred at this temperature for 1 h, at which point TBSCl (59 mg, 0.39 mmol, 110 mol %) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at this temperature for an addition 1 h and then left to warm to room temperature. Removal of the volatiles in vacuo affords an oily residue, which upon purification by column chromatography (SiO_2, 9:1 hexane/ethyl acetate) gives **6a** (104 mg, 2.62 mmol) in 74% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 7H), 6.95 (t, J=8.7 Hz, 2H), 3.63 (s, 2H), 2.99 (s, 2H), 2.63 (t, J=5.6 Hz, 2H), 2.43 (m, 2H), 0.74 (s, 9H), −0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (d, J=243.5 Hz), 140.8, 130.1 (d, J=7.6 Hz), 129.3, 128.3, 114.6 (d, J=21.1 Hz), 62.2, 56.3, 50.1, 29.2, 25.5, 17.9, −4.2. IR (film): 2928, 2856, 1669, 1601, 1509, 1471, 1222, 837, 780 cm^{-1}. HRMS: Calcd for $C_{24}H_{33}NOFSi$ [M+1] 398.2315, found 398.2313.

3.2.9. Enol silane 6b. Aryl enone **2b** (200 mg, 0.80 mmol, 100 mol %), L-Selectride (1 M in THF, 0.8 mL, 0.80 mmol, 100 mol %), and chlorotrimethylsilane (0.12 mL, 0.880 mmol, 110 mol %) were reacted according to the procedure described for **8a**. The crude product was purified via Kugelrohr distillation to give **6b** (230 mg, 0.71 mmol) in 86% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, J=8.2 Hz, 2H), 6.98 (t, J=8.7 Hz, 2H), 3.91 (s, 2H), 3.73 (s, 3H), 3.60 (s, 2H), 2.43 (s, 2H), −0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.2 (d, J=245.0 Hz), 155.8, 140.8, 135.2, 129.8 (d, J=7.6 Hz), 114.5 (d, J=21.4 Hz), 52.6, 46.8, 41.0, 28.5, 0.3. IR (film): 2957, 1707, 1601, 1510, 1448, 1410, 1253, 1226, 1106, 844, 767 cm^{-1}. HRMS: Calcd for $C_{16}H_{23}NO_3FSi$ [M+1] 324.1431, found 324.1437.

3.2.10. Allylic alcohol 7a. To a dry 50 mL flask, a solution of (*S*)-2-methyl-CBS-oxazaborolidine catalyst (1 M in toluene, 0.4 mL, 0.04 mmol, 10 mol %) and a solution of borane dimethyl sulfide complex (2 M in THF, 2 mL, 4.0 mmol, 100 mol %) were added successively at room temperature. The resulting solution was cooled to −20 °C and **2b** (1.0 g, 4.0 mmol, 100 mol %) in dichloromethane (18 mL) was added dropwise over 1 h, the reaction mixture was stirred at this temperature for 1 h. Methanol (15 mL) was added dropwise to the reaction mixture and the reaction mixture was allowed to warm to room temperature. The solution was evaporated to dryness. Purification of the residue via column chromatography (SiO_2, 9:1 to 1:1 hexane/ethyl acetate) gives **7a** (0.96 g, 3.85 mmol) in 95% yield as a white solid. Mp 104–105 °C. $[\alpha]_D^{25}$ +70 (*c* 1.6, CH_2Cl_2). Chiral HPLC (Daicel Chiralpak OJ-H column, 70:30 hexanes/*i*-PrOH, λ=254 nm, 0.5 mL min^{-1}, t_{major}=35.2 min, t_{minor}=39.2 min, ee=96%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.52 (dd, J=8.9, 5.5 Hz, 2H), 7.10 (t, J=12.0 Hz, 2H), 6.08 (t, J=3.5 Hz, 1H), 4.79 (d, J=6.6 Hz, 1H), 4.46 (m, 1H), 4.23 (dd, J=19.0, 2.7 Hz, 1H), 3.86 (dd, J=13.3, 3.8 Hz, 1H), 3.84 (dt, J=17.2, 2.0 Hz, 1H), 3.65 (s, 3H), 3.34 (dd, J=13.3, 3.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=244.1 Hz), 155.1, 136.4, 135.2 (d, J=3.05 Hz), 127.2 (d, J=8.1 Hz), 122.6, 114.2 (d, J=20.8 Hz), 63.0, 51.5, 47.9, 42.9. IR (film): 3412, 2957,

2921, 2851, 1693, 1601, 1511, 1470, 1448, 1411, 1231, 1130, 1062, 818, 767 cm^{-1}. HRMS: Calcd for $C_{18}H_{17}NOF$ [M+1] 250.0879, found 250.0880.

3.2.11. Allylic alcohol 7b. To a solution containing $CeCl_3 \cdot 7H_2O$ (1.09 g, 2.71 mmol, 100 mol %) and **2c** (0.88 g, 2.71 mmol, 100 mol %) in methanol (20 mL) was added $NaBH_4$ (0.10 g, 2.7 mmol, 100 mol %) in small portions over 2 min at room temperature. The mixture was allowed to stir for 5 min, at which point water (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an oily residue. Purification via column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gives **7b** (0.68 g, 2.07 mmol) in 76% yield as a white solid. Mp 106–108 °C. ^1H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.53 (dd, J=8.8, 5.5 Hz, 2H), 7.36 (m, 5H), 7.11 (t, J=8.9 Hz, 2H), 6.09 (t, J=3.5 Hz, 1H), 5.15 (s, 2H), 4.86 (t, J=5.4 Hz, 1H), 4.49 (m, 1H), 4.29 (dd, J=19.1, 3.7 Hz, 1H), 3.92 (dd, J=13.2, 3.7 Hz, 1H), 3.89 (d, J=16.5 Hz, 1H), 3.39 (dd, J=13.2, 3.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=244.1 Hz), 154.5, 136.6, 136.4, 135.2 (d, J=3.05 Hz), 127.8, 127.2 (d, J=7.6 Hz), 127.1, 126.9, 122.6, 114.2 (d, J=21.4 Hz), 71.6, 63.0, 47.9, 43.0. IR (film): 3414, 3033, 2915, 1691, 1510, 1432, 1360, 1229, 1125, 1070, 819, 698 cm^{-1}. HRMS: Calcd for $C_{19}H_{19}NO_3F$ [M+1] 328.1349, found 328.1349.

3.2.12. Allylic alcohol derived from 2a. To a solution of **2a** (0.1 g, 0.355 mmol, 100 mol %) in CH_2Cl_2 (3.5 mL) and isopropyl alcohol (30 μL, 0.355 mmol, 100 mol %) at −20 °C was added dropwise a solution of $BH_3 \cdot SMe_2$ (2 M in THF, 0.45 mL, 0.889 mmol, 250 mol %). The mixture was allowed to stir at −20 °C for 1 h, at which point a solution containing both (*S*)-2-methyl-CBS-oxazaborolidine (2 M in toluene, 36 μL, 0.035 mmol, 10 mol %) and $BH_3 \cdot SMe_2$ (2 M in THF 30 μL) was added in one portion. The reaction mixture was allowed to stir at −20 °C for 30 min. The temperature was increased to −15 °C over 45 min, at which point MeOH (10 mL) was added carefully and the reaction mixture allowed to stir for an additional 15 min. The reaction mixture was placed in heating bath at 50 °C and CH_2Cl_2 and $BH_3 \cdot SMe_2$ were removed via distillation. To the remaining solution was added MeOH (5 mL) and the resulting mixture was allowed to stir at 65 °C for 1 h (to cleave the N–B complex). The heating bath was removed and reaction mixture was allowed to reach ambient temperature. The solvent was removed in vacuo and the resulting residue was purified via column chromatography (SiO_2, 3:2 to 1:1 hexane/ethyl acetate) to provide the allylic alcohol (36 mg, 0.13 mmol) in 35% yield as a white solid. Mp 76–77 °C. Chiral HPLC (Daicel Chiralpak OJ-H column, 98:2 hexanes/*i*-PrOH, λ=254 nm, 1 mL min^{-1}, t_{major}=43.9 min, t_{minor}=31.7 min, ee=70%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J=8.7, 5.5 Hz, 2H), 7.33 (m, 5H), 6.99 (t, J=8.9 Hz, 2H), 6.09 (t, J=3.5 Hz, 1H), 6.02 (dd, J=4.8, 3.4 Hz, 1H), 4.37 (s, 1H), 3.65 (s, 2H), 3.35 (dd, J=17.4, 4.4 Hz, 1H), 3.04 (dd, J=10.6, 2.0 Hz, 1H), 2.84 (d, J=17.4 Hz, 1H), 2.75 (br s, 1H), 2.49 (dd, J=11.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J=246.0 Hz), 137.6, 137.0, 135.2 (d, J=3.1 Hz), 129.0, 128.3, 127.3, 127.1 (d, J=7.7 Hz), 124.5, 115.2 (d, J=21.5 Hz), 66.1, 62.2, 57.7, 53.0. IR (film): 3408, 3061, 3029, 2917, 2804, 1602, 1509, 1454, 1230, 1162, 1054, 822, 699. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.14506, found 284.14320.

3.2.13. Diphenyl phosphate 8a. Chlorodiphenylphosphate (0.9 mL, 4.2 mmol, 150 mol %) was added dropwise to a solution containing **7a** (0.71 g, 2.8 mmol, 100 mol %), pyridine (0.45 mL, 5.6 mmol, 200 mol %), and DMAP (0.51 g, 4.2 mmol, 150 mol %) at room temperature. After stirring for 2 h at this temperature, the reaction mixture was transferred to a separatory funnel, washed with aqueous $CuSO_4$ (2 M, 3×20 mL), dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification via column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) gives **8a** (1.21 g, 2.42 mmol) in 89% yield as a white solid. Mp 99–100 °C. $[\alpha]_D^{23}$ +36 (*c* 3.33, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 4H), 7.18 (m, 6H), 6.94 (t, J=8.4 Hz, 2H), 6.88 (d, J=7.94 Hz, 2H), 6.22 (s, 1H), 5.62 (s, 1H), 4.55 (dd, J=14.6, 2.8 Hz, 2H), 3.91 (d, J=18.2 Hz, 1H), 3.76 (s, 1H), 3.61 (s, 2H), 3.50 (d, J=14.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, J=247.3 Hz), 155.9, 150.4, 150.0, 133.4, 129.0 (d, J=16.0 Hz), 127.8, 127.7, 125.2, 125.1, 119.8, 119.7, 115.4 (d, J=21.4 Hz), 71.7, 52.7, 46.4, 43.5. IR (film): 3063, 3033, 2962, 2840, 1706, 1590, 1512, 1488, 1446, 1410, 1283, 1232, 1190, 1130, 1009, 956, 825, 767 cm^{-1}. HRMS: Calcd for $C_{25}H_{24}NO_7FP$ [M+1] 500.1274, found 500.1278.

3.2.14. Diphenyl phosphate 8b. Chlorodiphenylphosphate (0.5 mL, 2.31 mmol, 150 mol %), **7b** (500 mg, 1.54 mmol, 100 mol %), pyridine (0.25 mL, 3.08 mmol, 200 mol %), and DMAP (0.28 g, 2.3 mmol, 150 mol %) were reacted according to the procedure described for **8a**. The crude product was purified via column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) to give **8b** (0.74 g, 1.323 mmol) in 86% yield as a white solid. Mp 59–61 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 17H), 6.91 (t, J=8.4 Hz, 2H), 6.88 (d, J=7.94 Hz, 2H), 6.20 (s, 1H), 5.62 (s, 1H), 5.2 (s, 1H), 4.60 (dd, J=14.4, 3.0 Hz, 2H), 3.92 (d, J=19.5 Hz, 1H), 3.76 (s, 1H), 3.52 (dd, J=14.1, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, J=247.3 Hz), 155.3, 150.4, 150.0, 136.3, 133.4, 129.0 (d, J=16.0 Hz), 128.4, 127.8, 127.7, 125.2, 125.0, 119.8, 115.4 (d, J=21.4 Hz), 71.7, 67.4, 46.4, 43.6. IR (film): 3065, 2951, 1706, 1590, 1511, 1489, 1429, 1283, 1230, 1190, 1010, 957, 825, 766, 689 cm^{-1}. HRMS: Calcd for $C_{31}H_{28}NO_6FP$ [M+1] 560.163, found 560.1638.

3.2.15. Silane 9. To a slurry of CuCN (0.43 g, 4.81 mmol, 200 mol %) in THF (10 mL) was added a solution of (*i*-PrO)Me_2SiCH_2MgCl (1 M in THF, 4.80 mL, 4.81 mmol, 200 mol %) at −18 °C (ice/NaCl). After stirring at this temperature for 40 min, the reaction mixture was cooled to −50 °C and **8a** (1.20 g, 2.40 mmol, 100 mol %) in THF (10 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C over 40 min, at which point aqueous NH_4Cl (10% solutions, 40 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification of the residue via column chromatography (SiO_2, 3:2 hexane/ethyl acetate) gives **9** (0.84 g, 2.306 mmol) in 96% yield as a colorless oil. $[\alpha]_D^{23}$ +72 (*c* 3.6, CH_2Cl_2). ^1H NMR (300 MHz,

$CDCl_3$): δ 7.29 (m, 2H), 6.99 (t, J=8.7 Hz, 2H), 5.76 (s, 1H), 4.28 (m, 1H), 3.95 (m, 2H), 3.87 (d, J=18.8 Hz, 1H), 3.71 (s, 3H), 3.28 (dd, J=13.2, 3.3 Hz, 1H), 2.87 (s, 1H), 1.12 (2d, J=6.2 Hz, 6H), 0.68 (2d, J=10.8 Hz, 1H), 0.55 (2s, 1H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, J=246.0 Hz), 156.6, 141.6, 135.9, 127.6 (d, J=7.3 Hz), 119.5, 115.1 (d, J=21.1 Hz), 64.9, 52.4, 46.3, 43.8, 32.3, 25.8, 19.5, −0.78. IR (film): 3081, 2956, 2889, 1706, 1601, 1510, 1448, 1412, 1375, 1335, 1250, 1231, 1191, 1118, 1025, 958, 880, 836, 813 cm^{-1}. HRMS: Calcd for $C_{19}H_{27}NO_3FSi$ [M−1] 364.1744, found 364.1745.

3.2.16. Homo-allyl alcohol 10. To a solution of **9** (0.82 g, 2.24 mmol, 100 mol %) in DMF (12 mL) at room temperature were added potassium fluoride (0.52 g, 8.98 mmol, 400 mol %) and 30% aqueous hydrogen peroxide (3 mL, 26.9 mmol, 1200 mol %). The reaction mixture was allowed to stir at room temperature for 18 h, at which point H_2O (60 mL) was added. The resulting mixture was extracted with diethyl ether (3×20 mL), and the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (20 mL) dried ($MgSO_4$), and evaporated to afford a colorless oil. Purification via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives **10** (0.41 g, 1.54 mmol) in 70% yield as a colorless oil. $[\alpha]_D^{23}$ +84 (c 3.06, CH_2Cl_2). Chiral HPLC (Daicel Chiralpak OJ-H column, 90:10 hexanes/i-PrOH, λ=254 nm, 0.4 mL min^{-1}, t_{major}=31.0 min, t_{minor}=45.9 min, ee=92%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.43 (dd, J=8.8, 2.1 Hz, 2H), 7.12 (t, J=8.9 Hz, 2H), 6.00 (t, J=2.4 Hz, 1H), 4.27 (s, 1H), 4.18 (m, 2H), 3.82 (dt, J=19.1, 2.8 Hz, 1H), 3.65 (s, 3H), 3.32 (dt, J=10.6, 3.8 Hz, 1H), 3.18 (m, 2H), 2.83 (dd, J=4.2, 2.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=2.44.1 Hz), 155.3, 135.7 (d, J=3.0 Hz), 135.0, 126.9 (d, J=8.1 Hz), 121.9, 114.4 (d, J=21.4 Hz), 60.3, 51.5, 43.1, 41.5. IR (film): 3426, 3056, 2954, 2876, 1686, 1601, 1510, 1448, 1412, 1375, 1228, 1131, 1091, 1039, 953, 836, 814, 768, 735 cm^{-1}. HRMS: Calcd for $C_{14}H_{17}NO_3F$ [M+1] 266.1192, found 266.1199.

3.2.17. Conversion of 10 to paroxetine hydrochloride. A solution containing **10** (300 mg, 1.13 mmol, 100 mol %) in CH_2Cl_2 (11 mL) was cooled to −78 °C, evacuated and filled with Ar(g). This process was repeated twice. The solution was allowed to warm to room temperature and Crabtree's catalyst (45 mg, 0.056 mmol, 5 mol %) was added as a solid in one portion. The mixture was purged with H_2(g) for 5 min and allowed to stir under 1 atm of hydrogen for 20 h. The reaction mixture was evaporated onto silica gel. Purification via column chromatography (SiO_2, 4:1 to 3:2 hexane/ethyl acetate) gives the saturated alcohol (210 mg, 0.78 mmol) in 69% yield. $[\alpha]_D^{23}$ −40 (c 2.0, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.23 (dd, J=7.9, 6.1 Hz, 2H), 7.06 (t, J=8.9 Hz, 2H), 4.30 (dd, J=13.3, 2.5 Hz, 1H), 4.09 (d, J=5.6 Hz, 1H), 4.07 (d, J=15.7 Hz, 1H), 3.64 (s, 3H), 3.18 (m, 1H), 3.02 (m, 1H), 2.83 (t, J=13.0 Hz, 1H), 2.66 (t, J=11.4 Hz, 1H), 2.53 (td, J=11.6, 3.2 Hz, 1H), 1.72 (m, 2H), 1.57 (qd, J=12.6, 4.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 160.3 (d, J=244.1 Hz), 154.7, 139.8 (d, J=3.0 Hz), 128.5 (d, J=7.6 Hz), 114.3 (d, J=21.4 Hz), 60.8, 51.5, 46.7, 43.6, 43.0, 42.8, 33.2. IR (film): 3435, 3009, 2918, 2853, 1697, 1603, 1510, 1476, 1451, 1413, 1279, 1223, 1159, 1129, 1064, 1014, 832, 767 cm^{-1}. HRMS: Calcd for $C_{14}H_{19}NO_3F$ [M+1] 268.1349, found 268.1350.

The saturated alcohol (100 mg, 0.37 mmol, 100 mol %) was dissolved in THF (3 mL) and PPh_3 (120 mg, 0.45 mmol, 120 mol %) was added. The solution was cooled to 0 °C and DIAD was added dropwise. The solution was allowed to stir at 0 °C for 10 min, at which point sesamol (100 mg, 0.75 mmol, 200 mol %) in THF (1 mL) was added dropwise and the reaction mixture was allowed to stir for another 10 min at 0 °C. The reaction mixture was heated to 50 °C and was allowed to stir at this temperature for 2 h, at which point the reaction mixture was allowed to reach ambient temperature. The reaction mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (5 mL). In order to remove excess sesamol, the organic layer was washed with aqueous NaOH (2 M, 2×10 mL) and the aqueous extracts were back-extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated onto silica gel. Purification via column chromatography (SiO_2, 4:1 hexane/ethyl acetate) gives the phenolic ether (110 mg, 2.84 mmol) in 76% yield as a pale yellow oil. $[\alpha]_D^{23}$ −13 (c 1.5, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.27 (dd, J=8.6, 5.6 Hz, 2H), 7.06 (t, J=8.9 Hz, 2H), 6.9 (d, J=8.5 Hz, 1H), 6.40 (d, J=2.4 Hz, 1H), 6.18 (dd, J=8.3, 2.4 Hz, 1H), 5.89 (s, 2H), 4.31 (dd, J=13.4, 3.0 Hz, 1H), 4.09 (dt, J=13.3, 2.0 Hz, 1H), 3.64 (s, 3H), 3.41 (m, 2H), 2.89 (td, J=12.8, 2.8 Hz, 1H), 2.82 (t, J=11.6 Hz, 1H), 2.70 (td, J=5.8 Hz, 1H), 2.05 (m, 1H), 1.73 (dd, J=13.2, 3.1 Hz, 1H), 1.67 (qd, J=12.1, 4.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): 160.5 (d, J=242.6 Hz), 154.7, 153.6, 147.4, 141.0, 139.7 (d, J=3.0 Hz), 128.6 (d, J=8.1 Hz), 114.5 (d, J=21.4 Hz), 107.3, 105.9, 100.4, 97.6, 69.0, 51.6, 46.4, 43.5, 42.9, 40.6, 32.9. IR (film): 3008, 2916, 1701, 1510, 1488, 1450, 1412, 1276, 1223, 1185, 1132, 1037, 937, 832, 765 cm^{-1}. HRMS: Calcd for $C_{21}H_{23}NO_5F$ [M+1] 388.1560, found 388.1561.

To a reaction vessel charged with the phenolic ether (50 mg, 0.13 mmol, 100 mol %) and KOH (94 mg, 1.68 mmol %, 1300 mol %) were added ethylene glycol (1.5 mL), and water (0.6 mL). The mixture was heated to 100 °C for 20 h and then cooled to room temperature, diluted with water (10 mL), and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with H_2O (2×5 mL), dried ($MgSO_4$), filtered, and evaporated to provide an oily residue. The residue was dissolved in ether (5 mL) and the resulting solution was treated with 4 M HCl in dioxane (5 mL) to give a white solid. The white solid was filtered, washed with ether, and dried to afford (45 mg, 0.12 mmol) paroxetine hydrochloride in 92% yield. Mp 132–134 °C. Lit[10i] 136–138 °C. $[\alpha]_D^{23}$ −85 (c 1.0, CH_3OH). Lit[10i] −86.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J=8.2, 5.5 Hz, 2H), 7.00 (t, J=8.5 Hz, 2H), 6.61 (d, J=8.2 Hz, 1H), 6.32 (d, J=2.73 Hz, 1H), 6.10 (dd, J=8.5, 2.4 Hz, 1H), 5.88 (s, 2H), 3.73 (dd, J=21.5, 14.4 Hz, 2H), 3.60 (d, J=8.2 Hz, 1H), 3.48 (dd, J=9.9, 4.4 Hz, 1H), 3.17 (t, J=10.9 Hz, 1H), 2.04 (m, 1H), 2.90 (t, J=11.3 Hz, 1H), 2.64 (m, 1H), 2.38 (q, J=13.3 Hz, 2H), 2.03 (d, J=6.3 Hz, 1H). IR (film): 3401, 2925, 1605, 1510, 1224, 1185, 1037, 831 cm^{-1}.

3.2.18. Phenolic ether 12. To a stirred solution of **11** (240 mg, 0.54 mmol, 300 mol %) in THF (3 mL) at −78 °C

was added *n*-BuLi (2.5 M in hexanes, 0.18 mL, 0.45 mmol, 250 mol %) dropwise. The reaction mixture was allowed to stir at −78 °C for 1 h, at which point $CuBr \cdot SMe_2$ (110 mg, 0.54 mmol, 300 mol %) in Me_2S (0.5 mL) was added dropwise. The reaction mixture was allowed to stir an additional 30 min at −78 °C, at which point **8b** (100 mg, 0.18 mmol, 100 mol %) in Me_2S (0.5 mL) was added. The reaction mixture was allowed to continue stirring at −78 °C for an additional 1 h period, at which point the reaction mixture was allowed to warm to −10 °C and aqueous NH_4Cl (10% solution, 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification of the residue via column chromatography (SiO_2, 3:2 hexane/ethyl acetate) gives the title compound **12** (22 mg, 0.05 mmol) in 27% yield. ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.45 (dd, J=8.8, 5.5 Hz, 2H), 7.29 (s, 5H), 7.13 (t, J=8.8 Hz, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.41 (d, J=2.4 Hz, 1H), 6.22 (dd, J=8.5, 2.3 Hz, 1H), 6.10 (t, J=3.4 Hz, 1H), 5.89 (s, 2H), 5.08 (AB pattern, J=12.6 Hz, 2H), 4.33 (d, J=13.3 Hz, 2H), 3.90 (d, J=19.2 Hz, 1H), 3.72 (d, J=5.1 Hz, 2H), 3.29 (d, J=3.4 Hz, 2H), 3.20 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): 161.2 (d, J=244.6 Hz), 154.5, 153.5, 147.4, 141.0, 136.5, 135.4, 134.1, 127.7, 127.1, 127.1 (d, J=8.1 Hz), 126.8, 123.2, 114.6 (d, J=21.4 Hz), 107.3, 106.0, 100.4, 97.7, 68.1, 65.8, 43.1, 41.8, 36.9. IR (NaCl): 3033, 2962, 2877, 1701, 1602, 1508, 1465, 1431, 1260, 1224, 1184, 1129, 1037, 814 cm^{-1}. HRMS: Calcd for $C_{27}H_{25}NO_5F$ [M+1] 462.1717, found 462.1711.

Supplementary data

Scanned images of ^{1}H NMR and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.092.

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