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Studies towards the total synthesis of palau'amine. Formation of 4,5-dihydropyrrole-2-carboxylate intermediates by alkene–enamide ring-closing metathesis

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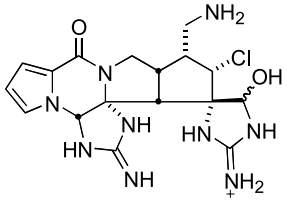
Dedicated to Professor Alois Fürstner on receipt of the 2004 Tetrahedron Chair in Organic Synthesis

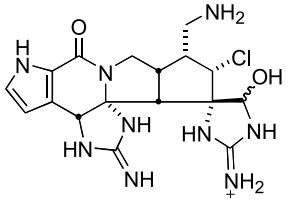
Abstract—A highly functionalized 4,5-dihydropyrrole-2-carboxylate is assembled by alkene–enamide ring-closing metathesis. Subsequent intramolecular azomethine imine dipolar cycloaddition provides a triazacyclopenta[*cd*]pentalene intermediate of potential use in a total synthesis of palau'amine.

1. Introduction

A diverse array of secondary metabolites displaying a broad range of biological activities have been isolated from sponges.[1] A number of these metabolites contain one or more guanidine functional groups embedded in novel polycyclic ring systems.[2] The palau'amines, styloguanidines and konbu'acidin, exemplified by palau'amine (**1**) and styloguanidine (**2**), are some of the most structurally intricate members of this group of marine guanidine alkaloids.[3–5]



palau'amine (**1**)



styloguanidine (**2**)

The diverse biological activities of palau'amine, in particular its substantial immunosupressive activity and apparent low toxicity, make this alkaloid an important target for total synthesis.[3] Much of the structural complexity of palau'amine resides in its 3-azabicyclo[3.3.0]octane ring system, a central fragment that contains six contiguous stereocenters. Five of these stereogenic carbons comprise the cyclopentane ring, which is substituted on the concave α face at every carbon. This density of functionality, combined with the two proximal spiroguanidine fragments, make palau'amine an unusually challenging synthetic target.[6] Published reports from other groups have focused largely on installing the functionality of the cyclopentane ring.[7–10] In contrast, previous work from our laboratories has addressed the issue of relating the configuration of the two spiroguanidine units to that of the central 3-azabicyclo-[3.3.0]octane unit.[11,12] Our approach to this objective has been to employ an intramolecular azomethine imine 1,3-dipolar cycloaddition to construct triazacyclopenta-[*cd*]pentalenes that encode these structural features of palau'amine: **3**→**4**→**5** (Scheme 1).

We recently described the preparation of cycloaddition precursor **6** having a siloxy substituent on the side chain and demonstrated that it, and its siloxy epimer, successfully condensed with thiosemicarbazide to form the desired triazacyclopenta[*cd*]pentalene (azatriquinane) products.[12] However, the Dieckmann cyclization strategy we employed to assemble the 4,5-dihydropyrrole-2-carboxylate moiety of **6** was inefficient, and would not be useful in a total synthesis endeavor directed at palau'amine.

Only a few methods have been described for the synthesis of 4,5-dihydropyrrole-2-carboxylates. Most involve functionalization of proline analogs by either elimination of a heteroatom from the α-[13,14] or β-position[12,15] of a prolinate, or by rearrangement of the double bond of a pyrroline

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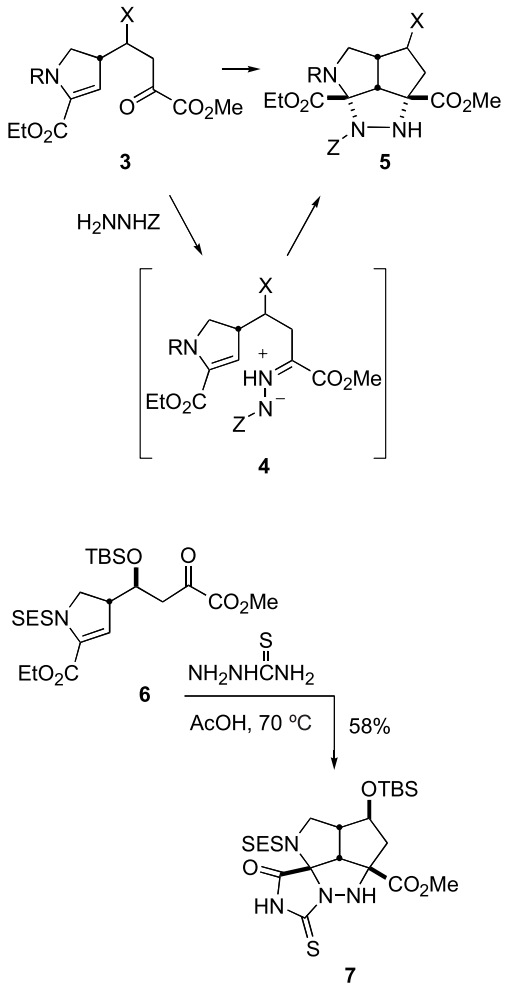


Scheme 1.

precursor.[16,17] Other constructions that have been used to access these heterocycles employ as key steps: oxidative decarboxylations;[18] metalation of enamides;[19] carbonylation of lactam-derived enol triflates[20] or enol phosphates;[21] or intramolecular Mitsunobu alkylations.[22] In this paper, we report the development of a convergent strategy to prepare potential palau'amine precursors that utilizes an alkene–enamide ring-closing metathesis (RCM) to construct the 4,5-dihydropyrrole-2-carboxylate ring system of the cycloaddition substrates.

1.1. Synthesis plan

The retrosynthetic analysis that led to the convergent synthesis sequence described herein is outlined in Scheme 2. We saw the 4,5-dihydropyrrole-2-carboxylate **8** arising by RCM of densely-functionalized diene **9**.[23] The dehydroalanine functionality of diene **9** would be formed from an appropriate amino acid analog, whereas the α-keto ester functionality would be installed by elaboration of an aldehyde precursor. Thus, diene amino ester **9** simplifies to pyrrole acid **10** and unsaturated α-aminoester **11**. Further retrosynthetic simplification of aminoester **11** leads to the simple α-amino ester and homoallylic alcohol precursors **12** and **13**, respectively.

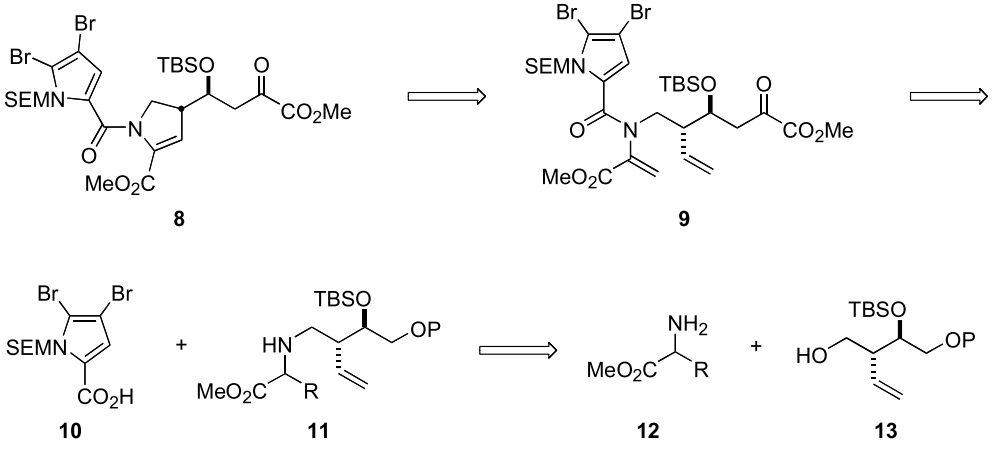
2. Results and discussion

2.1. Model system for the ring-closing metathesis

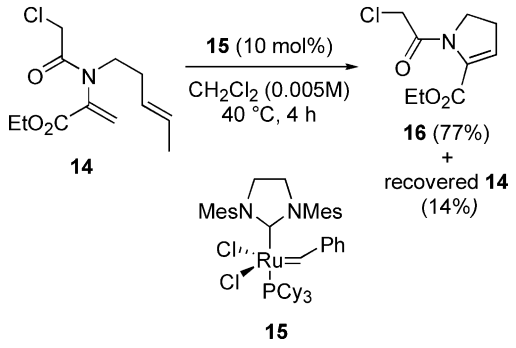
As there were no previous examples of forming 4,5-dihydropyrrole-2-carboxylates by RCM of dehydroalanine precursors,[23–27] we decided to pursue this transformation initially with a simple model substrate. The known diene **14**[28] was chosen for these studies (Scheme 3). We were pleased to observe that addition of 10 mol% of the Grubbs *N*-heterocyclic carbene catalyst **15**[23] to diene **14** at 40 °C led to the formation of the desired 4,5-dihydropyrrole-2-carboxylate **16** in 77% yield after only 4 h. We turned to prepare more elaborate dehydroalanine precursors.

2.2. Synthesis of homoallylic amines 22

The synthesis of the RCM precursors was designed so that enantioenriched intermediates could be prepared from a readily available enantioenriched epoxy alcohol precursor.[29] However, for convenience, our initial survey of this chemistry was carried out in a racemic series. Thus, preparation of homoallylic alcohol **19** began with *m*-CPBA epoxidation[30] of allylic alcohol **17**,[31] followed by copper catalyzed regioselective opening of the epoxy alcohol product with vinylmagnesium bromide to produce 1,3-diol



Scheme 2.



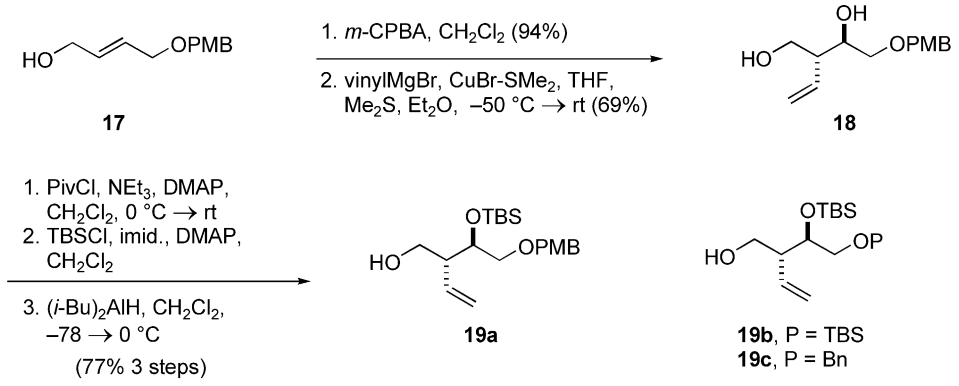
Scheme 3.

18 in 65% overall yield (Scheme 4).[32] Employing CuI or CuI–PBu_3 in the epoxide opening step was less effective because significant quantities of a product resulting from halide opening of the epoxide were produced; the use of CuBr–SMe_2 minimized formation of this halide by-product. The secondary alcohol of diol **18** could be selectively protected to provide homoallylic alcohol **19a** in good yield by a three step sequence that involved sequential masking of the primary alcohol as a pivalate ester, protection of the secondary alcohol, and reductive cleavage of the pivalate.[32c] A similar sequence was employed to prepare congeners **19b**,**c**.

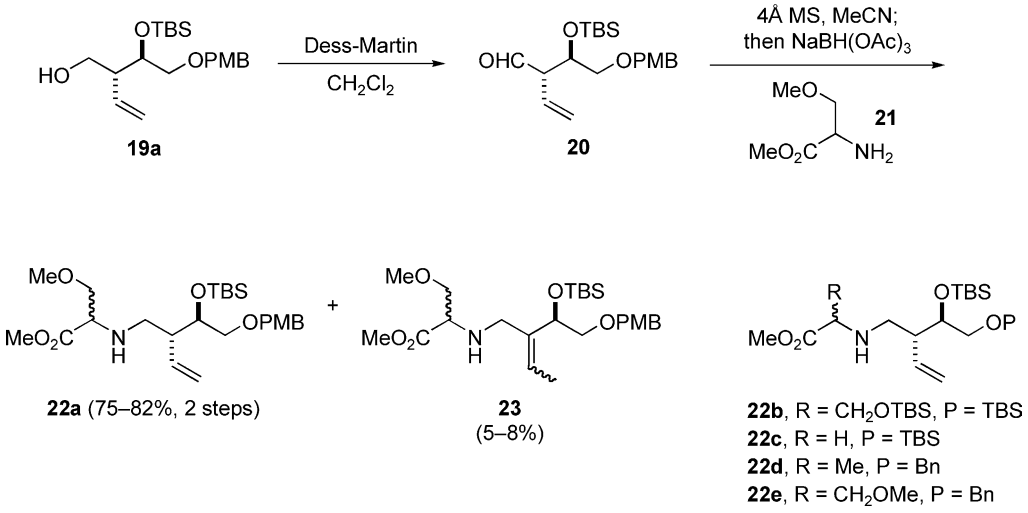
With the homoallylic alcohols in hand, it was necessary to elaborate these intermediates to α-aminoesters. Initial attempts at alkylating serine methyl ester with a triflate derivative of **19b** were unsuccessful, so a reductive amination sequence was developed (Scheme 5). Alcohol **19a** could be oxidized cleanly to the β,γ-unsaturated aldehyde **20** with negligible double bond migration by reaction with the Dess–Martin periodinane.[33] Subsequent reductive amination of this intermediate with serine-derived amino ester **21**[34] and sodium triacetoxyborohydride provided secondary amine **22a** in 70% yield from the alcohol. A small amount of allylic amine **23**, resulting from isomerization of the double bond during the reductive amination step, was also produced. The analogous homoallylic secondary amines **22b–e** were prepared by a similar series of transformations.

2.3. Coupling of the homoallyl amines 22 with pyrrole carboxylic acid 10

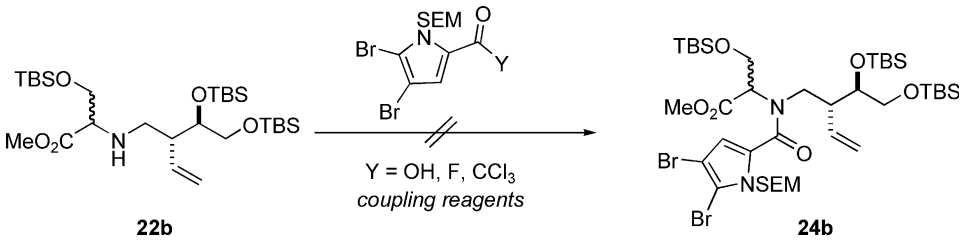
Coupling of the homoallylic amine to the acylpyrrole fragment proved to be quite demanding. Initial attempts to couple the TBS-protected serine analog **22b** with pyrrole acid **10**, mediated by standard coupling reagents (PyBrOP, HATU, or DCC), were unsuccessful (Scheme 6). Related condensations of **22b** with the corresponding pyrrole



Scheme 4.

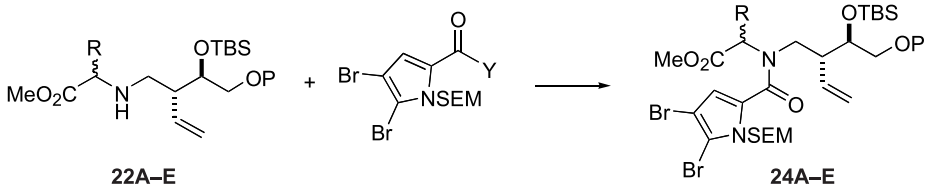


Scheme 5.



Scheme 6.

Table 1.



Amine	R	P	Y	Coupling agent	Amide	Yield (%)
22b	CH_2OTBS	TBS	OH	PyBrOP[a]	**24b**	0
22c	H	TBS	OH	PyBrOP[a]	**24c**	95
22d	Me	Bn	OH	PyBrOP[a]	**24d**	78
22e	CH_2OMe	Bn	OH	PyBrOP[a,b]	**24e**	0
22e	CH_2OMe	Bn	OH	HATU[c]	**24e**	0
22e	CH_2OMe	Bn	OC_6F_5	N/A[d]	**24e**	0
22e	CH_2OMe	Bn	OH	BOPCl[e]	**24e**	87
22a	CH_2OMe	PMB	OH	BOPCl[e]	**24a**	>95

[a] PyBrOP, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt.
[b] PyBrOP, *i*-Pr_2NEt, DMAP, DMF, rt.
[c] HATU, HOAt, *i*-Pr_2NEt, DMF, rt.
[d] *i*-Pr_2NEt, DMAP, CH_2Cl_2 or NaH, THF, rt.
[e] BOPCl, *i*-Pr_2NEt, MeCN, 0 °C to rt.

carboxylic acid fluoride or trichloromethyl ketone failed also.

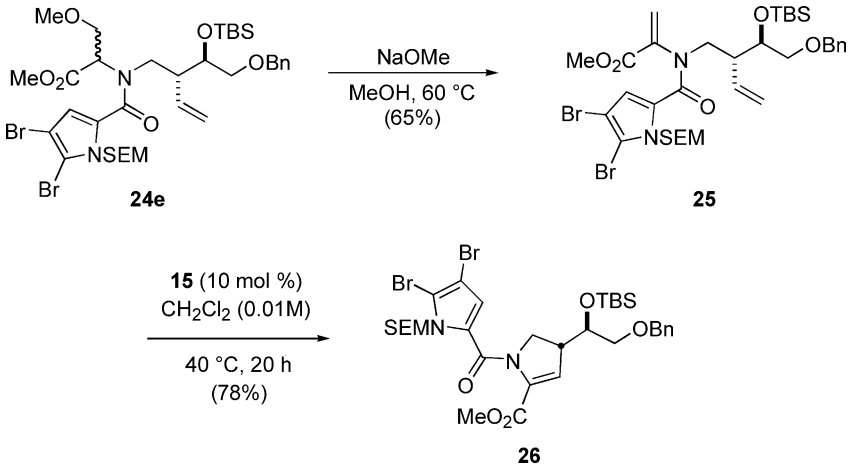
To examine the role of the steric environment around the amino acid substituent in the amide formation, we investigated the coupling of simpler amino acid analogs with the pyrrole acid. As can be seen in Table 1, PyBrOP-mediated coupling of pyrrole acid **10** with glycine derivative **22c** proceeded in high yield.[35] Under the same reaction conditions, alanine derivative **22d** was converted to the amide **24d** in 78% yield. Taken together with the failure of the TBS-protected serine derivative **22b** to couple with pyrrole acid **10**, these experiments indicated that the size of the amino acid side chain had a large effect on the efficiency of the amide coupling. Fortunately, we discovered that the *O*-methyl serine analog **22e** could be coupled to pyrrole acid **10** if BOPCl, rather than PyBrOP, was used as the coupling agent. Using BOPCl, secondary amines **22a** and **22e** were converted to amides **24a** and **24e** in >95 and 87% yields, respectively.‡

‡ After these results were obtained, BOPCl-mediated coupling of the TBS derivative **22b** with acid **10** was attempted; however this reaction proceeded to only 10–15% conversion.

2.4. Ring-closing metathesis and assembly of the potential palau'amine precursor 31

With the acylpyrrole installed, we turned to investigate formation of the dehydroalanine functionality (Scheme 7). Treatment of the methyl ether derivative **24e** with sodium methoxide in methanol resulted in elimination of methanol to give the dehydroamino ester **25** in an unoptimized 65% yield, 89% based on consumed starting material.[36] Exposure of this diene to metathesis catalyst **15** delivered dihydropyrrole **26** in 78% yield, demonstrating that alkene–enamide RCM would be a viable strategy for forming highly functionalized 4,5-dihydropyrrole-2-carboxylates.

In our earlier preparations of substrates for intramolecular azomethine imine cycloadditions, a Horner–Emmons reaction was employed to install the α-ketoester functionality.[12] We hypothesized that the basic conditions employed to generate the dehydroalanine might also facilitate the Horner–Emmons reaction.[37] To pursue this possibility, *p*-methoxybenzyl ether **24a** was cleaved selectively with DDQ to give primary alcohol **27** in high yield (Scheme 8). This intermediate was then oxidized with the Dess–Martin reagent and the aldehyde product was immediately condensed at room temperature with phosphonate **28**[38] in the presence of sodium *tert*-butoxide in a *tert*-butanol-THF solvent mixture. As hoped, these conditions promoted both

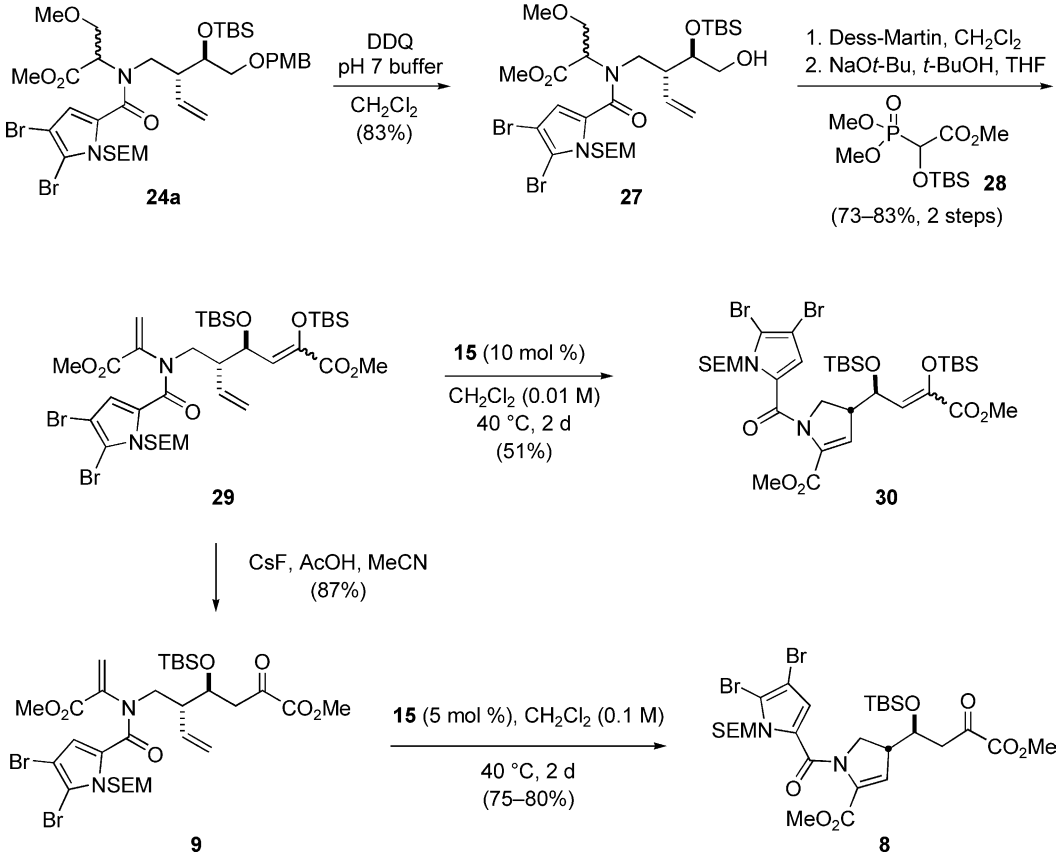


Scheme 7.

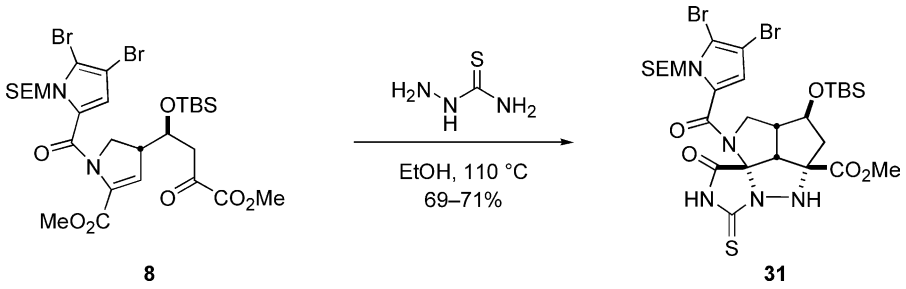
the Horner–Emmons condensation and the β-elimination of methanol to deliver dehydroalanine derivative **29** in 73–83% yield as an inconsequential 2:1 mixture of enoxysilane stereoisomers.

We turned to examine RCM for generating a fully constituted cycloaddition substrate. Cyclization of **29** using the RCM conditions optimized earlier with less intricate substrates provided dihydropyrrole **30** in 51% yield, together with 28% of recovered starting material (Scheme 8). It was significant that the dihydropyrrole product was highly enriched in one enoxysilane stereoisomer, whereas recovered diene **29** was enriched in the other geometric isomer. Obviously, ring formation was occurring more rapidly with one of the two side chain stereoisomers. To avoid this complication, we decided to examine the pivotal RCM step after discharge of the siloxy group. Therefore, siloxy diene **29** was allowed to react with buffered CsF to generate α-keto ester **9**. Cyclization of this intermediate with RCM catalyst **15** at 40 °C for 2 days at substrate concentrations as high as 0.1 M now delivered the desired dihydropyrrole **8** in excellent yield (75–80%).

Although the main focus of this study was to develop a practical route to fully functionalized cycloaddition substrates such as **8**, we briefly examined the condensation of **8**



Scheme 8.



Scheme 9.

with thiosemicarbazide to form triazatriquinane **31**. Using conditions we had employed earlier with less elaborate substrates (AcOH, 70 °C),[12] this conversion was extremely slow, requiring >7 days to go to completion. After a brief survey of reaction conditions, we found that heating an ethanolic solution of dihydropyrrole **8** and thiosemicarbazide in a sealed tube at 110 °C provided triazacyclopenta[*cd*]pentalene **31** in 69–71% yield after only two days (Scheme 9).

3. Conclusion

A RCM is the central step in the practical synthesis of 4,5-dihydropyrrole-2-carboxylate **8**. As this product contains a wealth of diverse functionality—acylpyrrole, bromide, α,β-unsaturated ester, α-keto ester and silyl ether—this RCM reaction superbly highlights the remarkable functional group tolerance of the Grubbs ruthenium metathesis catalysts.[23] Efforts to further elaborate triazacyclopenta-[*cd*]pentalene-containing cycloadducts such as **31** to palau'amine and congeners are underway.

4. Experimental

4.1. General methods

The procedure we employ to purify THF, CH_2Cl_2, Et_2O, DME, and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.; *Organometallics* **1996**, *15*, 1518–1520. Triethylamine, *i*-Pr_2NEt, DMF, and MeCN were purified in a similar manner using modified alumina columns provided by GlassContour. All reactions were conducted using flame-dried glassware under a nitrogen atmosphere unless stated otherwise. Commercial reagents were used as received unless otherwise indicated.

Analytical thin layer chromatography was carried out using 0.25 mm silica plates from Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulphate/molybic acid or basic potassium permanganate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on Bruker 500 FT NMR instruments. NMR spectra were typically recorded in $CDCl_3$ as solvent and were reported as δ values in ppm relative to chloroform. Infrared (IR) spectra were obtained were obtained using a ASI React IR module.

Although certain compounds were isolated as inseparable mixtures of diastereomers, the various resonances are distinct in the ^1H NMR spectra. In these instances, the signal has been reported in the following format: [3.30 (s), 3.25 (s), 3H]. This particular example would represent a methyl ether present in the diastereomeric mixture. In one diastereomer, the methyl group appears as a singlet at δ 3.30, whereas in the other diastereomer it appears at δ 3.25 as a singlet.

4.1.1. 4-(4-Methoxybenzyloxy)-2-vinylbutane-1,3-diol (18). A 3 L three-neck reaction flask equipped with a low temperature thermometer and an addition funnel was charged with freshly prepared CuBr–SMe_2 (7.65 g, 37.2 mmol), 1.7 L of Et_2O, and 335 mL of SMe_2 at room temperature. This clear, colorless solution was cooled to −50 °C, during which time a small amount of a fine white precipitate formed. A solution of freshly prepared vinylmagnesium bromide (370 mL of a 1 M solution in THF, 370 mmol) was added via cannula such that the internal temperature remained below −50 °C, then the slurry was maintained at −50 °C for an additional 1 h. The slurry initially turned a deep brown color upon addition of the Grignard reagent and over the course of the addition changed to a greenish-yellow and then a reddish-brown color. A solution of the (*E*)-2,3-epoxy-4-(4-methoxybenzyloxy)butanol (21.0 g, 93.0 mmol) in 170 mL of Et_2O was added dropwise via an addition funnel such that the internal temperature remained below −50 °C, then the slurry was maintained at −50 °C for an additional 1 h. The slurry was allowed to warm to −30 °C over 2 h then maintained at −30 °C for an additional 2 h. The reaction mixture was cooled to −45 °C and then allowed to warm to 10 °C over an 11 h period to give a purplish solution. Excess Grignard reagent was quenched by the addition of 100 mL of a 2:1 solution of saturated aqueous NH_4Cl-concentrated NH_4OH, then the mixture was poured into an additional 1.5 L of this buffer and was stirred vigorously until all of the solids had dissolved and the aqueous layer was a deep blue. The layers were separated and the organic layer was washed with this ammonia buffer solution (200 mL) and brine (200 mL). This solution was dried (Na_2SO_4) and concentrated to give a yellow oil containing crude **18** and the regioisomeric 1,2-diol.

This yellow oil was diluted with 230 mL of MeOH, 50 mL of THF, and 230 mL of H_2O, and then $NaIO_4$ (19.8 g, 93.0 mmol) was added in one portion. The $NaIO_4$ initially starts to dissolve, but a heavier white precipitate quickly forms. After the suspension was rapidly stirred for 1 h, it was poured into 1 L of EtOAc and washed with saturated

aqueous $NaHCO_3$ (3×100 mL) and brine (100 mL). The combined aqueous layers were back-extracted with EtOAc (3×50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 30% EtOAc–hexanes to 45% EtOAc–hexanes) gave 15.8 g of **18** as a pale yellow oil that was contaminated with approximately 340 mg of the starting epoxide and 460 mg of material from bromide opening of the epoxide. Another 2.11 g of material was isolated that contained an additional 2.1 mmol of diol **18** along with 5.1 mmol of bromide. Total yield of diol **18** was 69%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.28 (m, 2H), 6.88–6.92 (m, 2H), 5.62 (ddd, J=17.3, 10.3, 9.0 Hz, 1H), 5.13–5.19 (m, 2H), 4.48 (AB_q, J_{AB}=11.5 Hz, $\Delta\nu_{AB}$=14.9 Hz, 2H), 3.80–3.90 (m, 2H), 3.82 (s, 3H), 3.66–3.71 (m, 1H), 3.56 (dd, J=9.8, 3.3 Hz, 1H), 3.39 (dd, J=9.8, 7.3 Hz, 1H), 2.80 (br s, 1H), 2.73 (br s, 1H), 2.38–2.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 135.6, 130.0, 129.6, 118.6, 114.1, 73.3, 73.1, 72.8, 65.4, 55.5, 49.1; IR (film) 3391, 3082, 2904, 1614, 1514, 1305, 1244, 1174, 1081 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{20}O_4$ (M): 252.1362, found: 252.1362.

4.1.2. 2,2-Dimethylpropionic acid 2-[1-hydroxy-2-(4-methoxybenzyloxy)-ethyl]but-3-enyl ester. The mixture of diol **18** (15.8 g, 62.7 mmol) contaminated with bromide (460 mg, 1.5 mmol) and epoxide (340 mg, 1.5 mmol) impurities was diluted with 1.3 L of CH_2Cl_2 and NEt_3 (22.6 mL, 161 mmol) and cooled to 0 °C. Pivaloyl chloride (8.34 mL, 67.4 mmol) and DMAP (393 mg, 3.21 mmol) were added and the solution was allowed to warm to room temperature overnight. The yellow solution was poured into saturated aqueous $NaHCO_3$ (400 mL) and the organic layer was washed with $NaHCO_3$ (200 mL) and brine (200 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 8% EtOAc–hexanes to 15% EtOAc–hexanes to 25% EtOAc–hexanes) gave 19.9 g (92%) of a pale yellow oil that consisted of a 9.9:1 mixture of the primary and secondary pivalate esters: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.28 (m, 2H), 6.87–6.91 (m, 2H), 5.62–5.71 (m, 1H), 5.11–5.16 (m, 2H), 4.48 (AB_q, J_{AB}=11.3 Hz, $\Delta\nu_{AB}$=11.7 Hz, 2H), 4.31 (dd, J=11.0, 6.5 Hz, 1H), 4.21 (dd, J=11.0, 4.5 Hz, 1H), 3.82 (s, 3H), 3.74–3.80 (m, 1H), 3.56 (dd, J=9.5, 3.0 Hz, 1H), 3.40 (dd, J=9.5, 7.0 Hz, 1H), 2.57 (d, J=4.5 Hz, 1H), 2.50–2.57 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 159.5, 135.6, 130.1, 129.6, 118.5, 114.1, 73.3, 72.4, 70.2, 64.5, 55.5, 47.1, 39.0, 27.4; IR (film) 3494, 3078, 2975, 2906, 2871, 1725, 1613, 1515, 1285, 1248, 1165 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{28}O_5$ (M): 336.1937, found: 336.1937.

4.1.3. 2,2-Dimethylpropionic acid 2-[1-(*tert*-butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enyl ester. The 9.9:1 mixture of pivalate esters (23.2 g, 69.2 mmol combined) was diluted in 350 mL of CH_2Cl_2. Imidazole (20.7 g, 304 mmol) was added and the mixture was allowed to stir until all of the imidazole had dissolved. Then TBSCl (20.9 g, 138 mmol) was added (a colorless precipitate immediately formed), followed by the addition of DMAP (422 mg, 3.46 mmol). The slurry was allowed to stir overnight, then poured into saturated aqueous $NaHCO_3$ (100 mL) and the organic layer was washed with $NaHCO_3$ (100 mL) and brine (100 mL) then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, hexanes to 5% EtOAc–hexanes) gave 30.5 g (98%) of a pale yellow oil that consisted of a 9.9:1 mixture of regioisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.28 (m, 2H), 6.86–6.90 (m, 2H), 5.69–5.77 (m, 1H), 5.08–5.13 (m, 2H), 4.40–4.46 (m, 2H), 4.22 (dd, J=11.0, 5.0 Hz, 1H), 4.16 (dd, J=11.0, 7.3 Hz, 1H), 3.89 (ddd, J=5.8, 5.8, 4.3 Hz, 1H), 3.82 (s, 3H), 3.49 (dd, J=10.0, 4.5 Hz, 1H), 3.38 (dd, J=10.0, 5.8 Hz, 1H), 2.59–2.67 (m, 1H), 1.19 (s, 9H), 0.88 (s, 9H), 0.053 (s, 3H), 0.050 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 159.3, 136.7, 130.5, 129.5, 117.6, 113.9, 73.2, 72.5, 64.1, 55.4, 47.2, 39.0, 27.4, 26.1, 18.4, −4.0, −4.8; IR (film) 2958, 2931, 2858, 1729, 1613, 1515, 1465, 1362, 1248, 1036 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{43}O_5Si$ $(M+H)^+$: 451.2880, found: 451.2879.

4.1.4. 2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-en-1-ol (19a). A three-neck reaction flask equipped with a mechanical stirrer, a low temperature thermometer, and an addition funnel was charged with the 9.9:1 mixture of TBS ethers (30.5 g, 67.6 mmol combined) and 750 mL of CH_2Cl_2. The solution was cooled to −78 °C and a solution of DIBAL-H (99.0 mL of a 1.5 M solution in toluene, 149 mmol) was added dropwise via addition funnel over 90 min. After the addition was complete, the solution was maintained at −78 °C for 40 min, then allowed to warm to 0 °C. Excess DIBAL-H was quenched by the careful addition of 500 mL of a half-saturated potassium–sodium tartrate solution to give a gelatinous mixture. Then 100 mL of THF were added and the mixture was stirred rapidly for 2 h at room temperature, during which time it gradually turned from a gel to a heterogeneous mixture. The layers were separated and the organic layer was washed with H_2O (2×100 mL) and brine (100 mL). The combined aqueous layers were back extracted with EtOAc (100 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 5% EtOAc–hexanes to 20% EtOAc–hexanes) gave 21.1 g of isomerically pure **19a** (94% based on the amount of primary pivalate ester in the starting mixture) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.27 (m, 2H), 6.86–6.90 (m, 2H), 5.84 (ddd, J=17.0, 10.5, 8.5 Hz, 1H), 5.15–5.20 (m, 2H), 4.44 (AB_q, J_{AB}=11.5 Hz, $\Delta\nu_{AB}$=6.1 Hz, 2H), 3.94 (app q, J=5.5 Hz, 1H), 3.82 (s, 3H), 3.74–3.80 (m, 1H), 3.67–3.73 (m, 1H), 3.52 (dd, J=10.0, 5.5 Hz, 1H), 3.43 (dd, J=10.0, 5.5 Hz, 1H), 2.52–2.57 (m, 1H), 2.44–2.51 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 137.3, 130.2, 129.6, 117.8, 114.0, 74.4, 73.3, 73.0, 63.3, 55.5, 49.1, 26.1, 18.3, −4.1, −4.7; IR (film) 3445, 3074, 2935, 2858, 1614, 1514, 1468, 1251 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{25}O_4Si$ $(M-t\text{Bu})^+$: 309.1522, found: 309.1521.

4.1.5. 2-{2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enylamino}-3-methoxypropionic acid methyl ester (22a). To a solution of alcohol **19a** (10.3 g, 28.1 mmol) in 400 mL of wet CH_2Cl_2 was added Dess–Martin periodinane (17.9 g, 42.1 mmol). A fine white precipitate quickly formed to give a milky suspension. After 30 min, the mixture was diluted with 400 mL of Et_2O and

then 200 mL of a 1:1 solution of saturated aqueous $NaHCO_3$ −10% (w/w) aqueous $Na_2S_2O_3$ was added, and the mixture was allowed to stir until all of the solids had dissolved. The layers were separated and the organic layer was washed with the 1:1 solution (2×100 mL) and brine (100 mL), then dried (Na_2SO_4) and concentrated. The crude aldehyde was passed through a short plug of silica gel (10% EtOAc–hexanes) then concentrated to give a pale yellow oil, which was immediately used in the following reaction.

The crude aldehyde **20** was dissolved in 280 mL of MeCN, then 4 Å molecular sieves (23 g) were added and the mixture was allowed to stir for 5 min. A solution of serine methyl ester **21**[34] (7.48 g, 56.1 mmol) in 10 mL of MeCN was added via syringe. The mixture was allowed to stir for 10 min, then $NaBH(OAc)_3$ (23.8 g, 112.0 mmol) was added in one portion. After stirring for 1 h, 300 mL of a half-saturated potassium–sodium tartrate solution was added, and the mixture was stirred vigorously for an additional 1 h. The mixture was diluted with EtOAc (600 mL), washed with $NaHCO_3$ (2×75 mL) and brine (75 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 15% EtOAc–hexanes to 35% EtOAc–hexanes) gave 11.1 g (82%) of **22a** as a pale yellow oil that was contaminated with small quantities of the isomeric internal olefins **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.27 (m, 2H), 6.85–6.90 (m, 2H), 5.67–5.76 (m, 1H), 5.11–5.19 (m, 2H), 4.38–4.44 (m, 2H), 3.74–3.84 (m, 1H), 3.81 (s, 3H), [3.731 (s), 3.728 (s), 3H], 3.51–3.62 (m, 2H), 3.40–3.49 (m, 2H), 3.31–3.38 (m, 1H), [3.334 (s), 3.331 (s), 3H], [2.88 (dd, J=11.0, 4.0 Hz), 2.72 (dd, J=11.0, 4.0 Hz), 1H], [2.59 (dd, J=9.5, 9.5 Hz), 2.52 (dd, J=11.0, 9.0 Hz), 1H], 2.41–2.50 (m, 1H), 1.79 (br s, 1H), [0.88 (s), 0.87 (s), 9H], [0.041 (s), 0.037 (s), 0.03 (s), 6H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.6, 159.3, 138.4, 130.7, 129.44, 129.43, 129.2, 117.9, 117.7, 113.9, 74.0, 73.9, 73.6, 73.4, 73.3, 73.2, 73.12, 73.11, 62.0, 61.8, 59.4, 59.3, 55.5, 52.1, 52.0, 48.6, 48.4, 47.9, 47.8, 34.5, 26.13, 26.11, 18.4, −3.9, −4.67, −4.69; IR (film) 3346, 2929, 2856, 1740, 1613, 1515, 1472, 1246, 1036 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{44}NO_6Si$ $(M+H)^+$: 482.2938, found: 482.2947.

4.1.6. 2-{{2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enyl}-[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]-amino}-3-methoxypropionic acid methyl ester (24a). To a suspension of pyrrole acid **10** (31.1 g, 79.9 mmol) in 500 mL of MeCN at 0 °C was added BOPCl (23.4 g, 91.8 mmol) and the mixture was stirred at 0 °C for 90 min. Then a solution of amine **22a** (13.4 g, 27.8 mmol) in 50 mL of MeCN was added via syringe (30 mL plus 2×10 mL rinses), followed by the addition of *i*-Pr_2NEt (20.8 mL, 120.0 mmol). The mixture was allowed to warm to room temperature and the solids slowly dissolved. The reaction mixture was stirred overnight, during which time a white precipitate formed. This slurry was diluted with EtOAc (500 mL), washed with saturated aqueous $NaHCO_3$ (2× 200 mL) and brine (200 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 5% EtOAc–hexanes to 10% EtOAc–hexanes) gave 17.4 g (93% recovered) of the acid anhydride together with 23.3 g (99%) of amide **24a** as a pale yellow oil. NMR spectra are complex due to slow rotation on the NMR timescale so only distinct resonances are noted: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.28 (m, 2H), 6.85–6.90 (m, 2H), 6.57 (br s, 1H), 4.38–4.44 (m, 2H), 3.81 (s, 3H), [3.72 (s), 3.71 (s), 3H], 3.51 (app t, J=3.0 Hz, 2H), 3.34 (s, 3H), [2.69–2.77 (m), 2.58–2.66 (m), 1H], [0.87 (s), 0.86 (s), 9H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.5, 159.4, 138.1, 137.8, 129.55, 129.52, 128.1, 128.0, 113.91, 113.89, 99.5, 75.5, 73.6, 73.19, 73.16, 66.6, 66.32, 66.29, 59.1, 59.0, 55.5, 52.5, 47.1, 44.1, 41.6, 26.0, 18.3, 18.1, 18.0, −1.18, −1.22, −3.90, −3.94, −4.8; IR (film) 2954, 2896, 1744, 1636, 1515, 1248, 1094 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{58}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 885.1980, found: 885.1970.

4.1.7. 2-{{2-[1-(*tert*-Butyldimethylsiloxy)-2-hydroxyethyl]but-3-enyl}-[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]amino}-3-methoxypropionic acid methyl ester (27). To a solution of PMB ether **24a** (10.27 g, 11.90 mmol) in 115 mL of CH_2Cl_2 and 6.8 mL of pH 7 phosphate buffer was added DDQ (3.92 g, 17.3 mmol) in one portion. The mixture turned an initial bright green color then slowly faded to a brownish-green color. After 2 h, the mixture was quenched with aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ until the washes were no longer colored yellow (4× 100 mL) and then washed with brine (100 mL). The combined aqueous layers were extracted with EtOAc (100 mL) and then the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 30% EtOAc–hexanes) gave 7.37 g (83%) of the alcohol **27** as a pale yellow oil: NMR spectra are complex due to slow rotation on the NMR timescale so only distinct resonances are noted; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50–6.70 (m, 1H), [3.74 (s), 3.72 (s), 3H], 3.52 (app t, J=8.0 Hz, 2H), [3.38 (s), 3.36 (s), 3H], 2.63–2.78 (m, 1H), [0.90 (s), 0.89 (s), 9H], 0.04–0.10 (m, 6H), [−0.01 (s), −0.02 (s), 9H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.4, 137.7, 127.9, 127.7, 99.60, 99.57, 75.6, 75.5, 74.5, 66.4, 64.5, 64.3, 59.2, 59.1, 52.6, 34.5, 26.0, 18.2, 18.1, −1.2, −4.05, −4.10, −4.57, −4.58; IR (film) 3464, 3120, 3078, 2954, 1744, 1629, 1530, 1250, 1094 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{50}Br_2N_2O_7Si_2Na$ $(M+Na)^+$: 765.1404, found: 765.1402.

4.1.8. 2,4-Bis-(*tert*-butyldimethylsiloxy)-5-{[[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]-(1-methoxycarbonylvinyl)amino]methyl}-hepta-2,6-dienoic acid methyl ester (29). To a solution of alcohol **27** (2.62 g, 3.53 mmol) in 50 mL of wet CH_2Cl_2 was added Dess–Martin periodinane (2.24 g, 5.29 mmol). A fine white precipitate quickly formed to give a milky suspension. After 30 min, the mixture was diluted with 150 mL of Et_2O and then 75 mL of a 1:1 solution of saturated aqueous $NaHCO_3$—10% (w/w) aqueous $Na_2S_2O_3$, and the mixture was allowed to stir until all of the solids had dissolved. The layers were separated and the organic layer was washed with the 1:1 solution (3×50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. The crude aldehyde was diluted in 15 mL of CH_2Cl_2 then dried (Na_2SO_4) and

concentrated to give a pale yellow oil which was immediately used in the following reaction.

This crude aldehyde and phosphonate **28** (1.65 g, 5.29 mmol) were dissolved in 70 mL of THF. Then NaO*t*-Bu (14.1 mL of a 0.5 M solution in *t*-BuOH, 7.06 mmol) was added dropwise via syringe to give a bright yellow solution. The resulting solution was poured into saturated aqueous $NaHCO_3$ (100 mL) and then diluted with Et_2O (150 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (5% EtOAc–hexanes) gave 2.30 g (73% from **27**) of the enol ether **29** as a pale yellow oil (on smaller scales the yield approached 83%): ^{1}H NMR (500 MHz, $CDCl_3$) δ [6.34 (s), 6.33 (s), 1H], [6.10 (s), 6.08 (s), 1H], [5.89 (d, J=9.0 Hz), 5.34 (d, J=9.0 Hz), 1H], 5.69–5.84 (m, 1H), 5.56–5.67 (m, 2H), [5.48 (d, J=10.5 Hz), 5.47 (d, J=10.5 Hz), 1H], [5.11 (dd, J=9.0, 6.5 Hz), 4.69 (dd, J=8.5, 5.0 Hz), 1H], 4.99–5.08 (m, 2H), 4.01–4.12 (m, 1H), [3.77 (s), 3.76 (s), 3H], [3.69 (s), 3.67 (s), 3H], 3.64–3.71 (m, 1H), 3.55–3.62 (m, 2H), 2.55–2.69 (m, 1H), [0.96 (s), 0.94 (s), 9H], [0.878 (s), 0.881 (s), 9H], 0.85–0.97 (m, 2H), −0.02−0.21 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 164.9, 164.49, 164.47, 162.0, 141.2, 140.9, 140.2, 139.7, 137.6, 137.4, 128.80, 128.76, 126.4, 122.8, 122.4, 121.7, 118.2, 118.0, 116.6, 116.4, 110.0, 109.9, 99.3, 75.6, 70.1, 69.5, 66.5, 66.4, 52.80, 52.78, 52.3, 51.9, 51.3, 49.9, 49.2, 49.1, 26.2, 26.0, 25.8, 18.9, 18.4, 18.3, 18.23, 18.17, −1.2, −3.7, −3.8, −4.09, −4.14, −4.5, −4.6, −4.8, −4.9; IR (film) 3078, 2954, 2860, 1731, 1648, 1524, 1437, 1324, 1250, 1198 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{62}Br_2N_2O_8Si_3Na$ $(M+Na)^+$: 915.2078, found: 915.2073.

4.1.9. 4-(*tert*-Butyldimethylsiloxy)-5-{[[4,5-dibromo-1-(2-trimethylsilyl ethoxymethyl)-1H-pyrrole-2-carbonyl]-(1-methoxycarbonylvinyl)-amino]methyl}-2-oxo-hept-6-enoic acid methyl ester (9). To a solution of enol ether **29** (2.30 g, 2.57 mmol) and AcOH (0.72 mL, 12.9 mmol) in 51 mL of MeCN at 0 °C was added CsF (977 mg, 6.43 mmol) in one portion. The mixture was allowed to warm to room temperature and then stirred for an additional 75 min. The reaction mixture then was diluted with 200 mL of EtOAc and 50 mL of saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 15% EtOAc–hexanes) gave 1.74 g (87%) of the α-keto ester **9** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.12 (s, 1H), 5.76 (ddd, J=17.0, 10.0, 9.0 Hz, 1H), 5.62 (s, 1H), 5.52 (AB_q, J_{AB}=10.5 Hz, $\Delta\nu_{AB}$=23.8 Hz, 2H), 5.05–5.15 (m, 2H), 4.32 (dt, J=6.5, 5.5 Hz, 1H), 3.86 (s, 3H), 3.72–3.86 (m, 2H), 3.69 (s, 3H), 3.56–3.61 (m, 2H), 3.21 (dd, J=17.5, 5.0 Hz, 1H), 3.02 (dd, J=17.5, 6.5 Hz, 1H), 2.60–2.67 (m, 1H), 0.87–0.95 (m, 2H), 0.84 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 164.3, 162.0, 161.4, 140.9, 137.0, 128.5, 122.2, 118.8, 116.6, 110.3, 99.3, 75.6, 69.7, 66.5, 53.2, 52.9, 49.3, 49.2, 44.5, 25.9, 18.2, 18.1, −1.2, −4.4, −4.5; IR (film) 2954, 2858, 1731, 1654, 1621, 1524, 1248, 1092, 1081 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{48}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 801.1213, found: 801.1237.

4.1.10. 4-[1-(*tert*-Butyldimethylsiloxy)-3-methoxycarbonyl-3-oxo-propyl]-1-[4,5-dibromo-1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrrole-2-carbonyl]-4,5-dihydro-1H-pyrrole-2-carboxylic acid methyl ester (8). A flame dried 25 mL two-neck reaction flask was equipped with a reflux condenser topped with a three-way gas flow adapter and a teflon stopcock (all ground glass connections were greased). Diene **9** (414 mg, 0.530 mmol) was transferred to the reaction apparatus in 4.3 mL of CH_2Cl_2 (degassed by sparging with Ar for 2 h) via syringe. A solution of the metathesis catalyst **15** (1.0 mL of a 0.027 M solution in CH_2Cl_2, 0.027 mmol) was added via syringe and the solution was brought to reflux. After 23 h, ^{1}H NMR analysis of an aliquot indicated the reaction had gone to about 90% completion. After 41 h, the brown solution was concentrated and purified on silica gel (gradient elution, hexanes to 5% EtOAc–hexanes to 7.5% EtOAc–hexanes to 15% EtOAc–hexanes) to give 414 mg (80%) of dihydropyrrole **8** as an oil, along with 25 mg of recovered diene **9**; keto ester **8** is a 8:1 mixture of keto and enol tautomers in $CDCl_3$. Only the keto peaks are reported in the ^{1}H NMR, but all the peaks are reported in the ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 5.99 (d, J=2.5 Hz, 1H), 5.73 (d, J=10.5 Hz, 1H), 5.61 (d, J=10.5 Hz, 1H), 4.34 (dt, J=7.0, 5.0 Hz, 1H), 4.13 (dd, J=11.0, 10.0 Hz, 1H), 4.01 (dd, J=7.0, 6.5 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.59 (app dd, J=8.5, 7.5 Hz, 2H), 3.22–3.28 (m, 1H), 3.09 (dd, J=17.0, 7.0 Hz, 1H), 2.87 (dd, J=17.0, 5.0 Hz, 1H), 0.86–0.92 (m, 2H), 0.84 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 161.5, 161.1, 160.0, 140.3, 138.7, 138.3, 127.5, 124.0, 123.3, 117.5, 117.1, 113.0, 112.0, 99.8, 75.3, 68.9, 68.6, 66.52, 66.48, 53.7, 53.45, 53.40, 52.9, 52.5, 52.4, 49.3, 48.5, 44.3, 25.9, 18.2, 18.14, 18.10, −1.0, −1.2, −1.4, −4.3, −4.4, −4.5, −4.9; IR (film) 3450, 3124, 2954, 2858, 1733, 1632, 1524, 1426, 1391, 1250, 1082 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{44}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 773.0901, found: 773.0904.

4.1.11. Azomethine imine cyclization product 31. A sealable tube was charged with α-keto ester **8** (433 mg, 0.575 mmol), thiosemicarbazide (315 mg, 3.45 mmol) and 12 mL of EtOH. The mixture was sparged with argon for 20 minutes, then the vessel was sealed and heated to 110 °C. After 2 d, the bright yellow solution was cooled to below 78 °C, the tube was opened, and the mixture was adsorbed onto silica gel with 10% CH_3OH/CH_2Cl_2 and purified on silica gel (gradient elution, 7.5% EtOAc–hexanes to 15% EtOAc–hexanes) to give 82 mg (71%) of cycloadduct **31** as a colorless solid:[§] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.65 (d, J=11.0 Hz, 1H), 5.50 (d, J=10.5 Hz, 1H), 5.35 (s, 1H), 4.41–4.47 (m, 1H), 4.08 (d, J=10.0 Hz, 1H), 4.01 (app d, J=5.0 Hz, 2H), 3.71 (s, 3H), 3.48–3.56 (m, 2H), 2.79 (ddt, J=10.5, 10.5, 5.8 Hz, 1H), 2.36 (dd, J=14.5, 5.5 Hz, 1H), 2.26 (dd, J=14.5, 7.3 Hz, 1H), 0.86–0.93

[§] Under these conditions, an unidentified by-product is isolated in approximately 5–8% yield. This product appears when the reaction is carried out at temperatures greater than 70 °C. Attempts to conduct the condensation with thiosemicarbazide at temperatures greater than 110 °C resulted in larger amounts of this byproduct.

(m, 2H), 0.89 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.4, 171.6, 168.6, 161.7, 126.5, 117.3, 112.2, 100.0, 91.2, 78.5, 78.0, 75.8, 66.7, 58.6, 54.8, 53.5, 49.8, 42.6, 25.8, 18.14, 18.07, −1.2, −4.3, −4.5; IR (film) 3272, 2954, 2858, 1773, 1750, 1640, 1426, 1252, 1200, 1094 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{44}Br_2N_5O_6SSi_2Na$ $(M+H)^+$: 792.0917, found: 792.0941.

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