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Synthetic Studies Towards the Core Tricyclic Ring System of Pradimicin A

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Pradimicins are structurally intriguing natural products that possess potent biological activity as antifungal and antiviral agents through a unique mode of action as carbohydrate binding agents. A preliminary synthetic approach towards pradimicin A has focused on a model study of the core tricyclic ring system. The route features an alkoxyallylboration/cycloisomerization/Diels–Alder cycloaddition sequence as the key steps. The alkoxyallylboration was critical for differentiating the hydroxy groups in the central cyclohexadienediol unit of pradimycins, which will ensure a regiocontrolled glycosylation. For the cycloisomerization reaction, various substrates and conditions were tested for a ring-closing enyne metathesis reaction. With enyne substrate **23**, dimerization-prone bicyclic diene **24** was isolated as the major product under the conditions of both ruthenium-catalyzed metathesis and palladium-catalyzed cycloisomerization. In the end, the optimal route found for the synthesis of the model functionalized tricyclic ring system **31** features a one-pot sequential palladium-catalyzed cycloisomerization, Diels–Alder reaction, and oxidative aromatization.

Introduction

In 1988, efforts to discover novel microbial metabolites led to the isolation of a new class of natural products, called pradimicins and benanomicins, by Oki and Takeuchi and their co-workers.[1–6] Oki and co-workers found that a cultured broth of *Actinomadura hibisca* bacteria, isolated from a Fiji Island soil sample, contained red pigments that precipitated from the broth at pH = 5, and these were purified by column chromatography.[3] The components were later identified and characterized to be pradimicins A, B, and C (Table 1) and were shown to be active against various fungi, yeasts, and viruses.[5] Takeuchi and co-workers isolated benanomicin A and B from a cultured broth of *Actinomadura species* in the same year.[2,4] The unique biological activity that this class of compounds exhibits and the ongoing need for antifungal and antiviral treatments makes it a valuable target in synthetic chemistry. The structures of the pradimicins and benanomicins consist of an amino acid, a disaccharide, and a benzo[*a*]naphthacenequinone core. There are approximately 20 congeners in this family to date, and their specific structures vary according to their amino acid and disaccharide components (Table 1). Pradimicin A (PRM-A), one of the first and most abundant congeners isolated, was initially subjected to biological testing, but was claimed to have limited solubility in water (≤50 μM).[7] To overcome this issue, testing was also performed with the analogues BMY-28864, BMS-181184, and, more recently, PRM-S, which have different and more water-soluble amino acid and disaccharide functionalities (Table 1).[7–13]

Pradimicins and benanomicins exhibit their antifungal and antiviral biological activities by acting as carbohydrate-binding agents (CBAs). As low-molecular-weight natural products, the ability of pradimicins to bind to carbohydrates is very rare, proving them to be unique and with great potential for antifungal and antiviral applications. Aside from avoiding some of the disadvantages of protein-based CBAs, such as cost and lower stability, the main advantage of non-proteinageneous CBAs is their low molecular weight, which is beneficial in scale-up, purification, and production.[14]

The pradimicins show specificity towards high-mannose-type glycans. The molecular architecture of pradimicins is proposed to be crucial, with the aglycon core, the amino acid, and the disaccharide all involved in the binding mechanism.[15–18] According to a study conducted by Oki and co-workers, a calcium ion coordinates to two molecules of pradimicin A (PRM-A) through the carboxylic acid groups, and the other two moieties are involved in binding to the target oligomannan.[15–18] This model correlates with the finding that when the carboxylic acid is methylated, PRM-A loses its biological activity.[15–18] It is unclear whether the function of calcium is solely to bridge two PRM-A units or whether it plays a role in coordinating mannose to the antibiotic.[19]

Pradimicins have shown activity against numerous pathogens, including systemic fungal infections and, potentially more importantly, against the human immunodeficiency virus (HIV).[1,7,8,14,20–22] It prevents viral entry into the host cell by binding to gp120, a glycoprotein present on the

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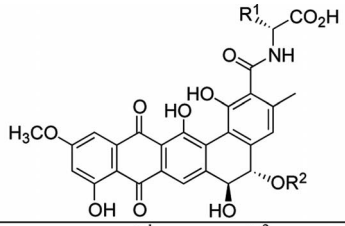
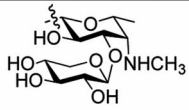
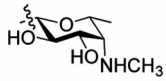
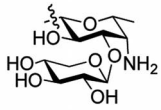
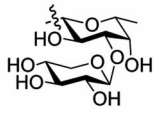
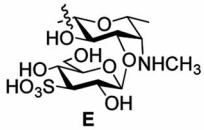
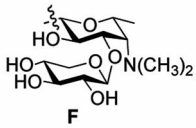
Table 1. Pradimicin and benanomicin analogues.



Name	R^1	R^2 sugar moiety
Pradimicin A (**1**)	CH_3	 **A**
Pradimicin B	CH_3	 **B**
Pradimicin E	H	 **C**
Benanomicin A	CH_3	 **D**
Pradimicin S	CH_3	 **E**
BMY-28864	CH_2OH	 **F**
Pradimicin D	H	**A**
Pradimicin FA-1	CH_2OH	**A**
Pradimicin FA-2	CH_2OH	**C**
Benanomicin B	CH_3	**C**
BMS-181184	CH_2OH	**D**

HIV envelope that mediates entry into the host cell.[7,8] The glycans that make up gp120 have been found to contain a large amount of mannose and, as previously mentioned, pradimicins have a specific binding affinity towards mannose.[7] Mammalian cells have a significantly lower amount of high-mannose-type glycans on the cell surface, which results in little to no binding with mannose-targeting CBAs. This implies that pradimicin CBAs could be selective towards the viral cells with little toxicity towards the host.[8]

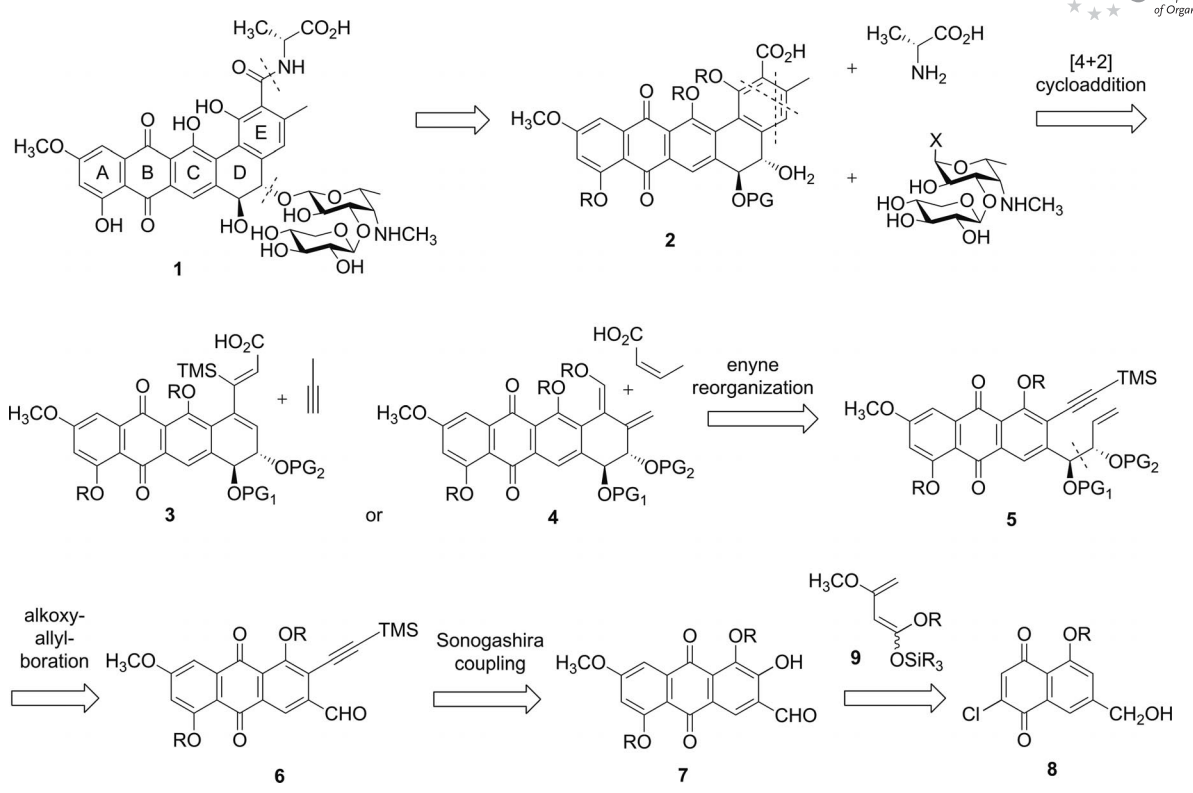
Owing to our interest in synthetic CBAs,[23–26] we were interested in developing a synthetic strategy that would eventually enable the design of a receptor library approach to target various cell-surface oligosaccharides. A number of factors must be taken into consideration when designing a synthetic route towards the pradimycin/benanomycin family of natural products. The main challenges associated with this molecule include a highly substituted pentacyclic core, a *trans*-1,2-diol, and a disaccharide that requires regioselective introduction. The core C, D, and E rings of pradimicin A (see Scheme 1) would therefore require the most consideration. In fact, most of the previous synthetic efforts of Suzuki,[27–30] Krohn,[31,32] Hauser,[33,34] and other groups,[35–37] as well as the work reported herein, have been directed towards this tricyclic system. The key to the synthesis lies in the formation and functionalization of the D ring. It would be ideal if the diol were introduced in a manner that would afford different protecting groups on each alcohol. Sequential deprotection of the alcohol would then allow glycosylation to occur chemoselectively and therefore increase the efficiency of the overall synthetic plan.

There is only one total synthesis to date of the pradimicin and benanomicin family,[30] but there have also been a few interesting partial syntheses that have targeted variations of the aglycon core.[31–37] In 1999, Suzuki and co-workers published the first synthesis of pradimicinone, an aglycon of the pradimicins and benanomicins that lacks the disaccharide moiety and contains a free *trans*-diol.[28,30] They completed the first total synthesis of benanomicin B in 2005 by a Bringmann-type asymmetric ring-opening of a biaryl lactone instead of having to resort to optical resolution to acquire the required enantioenriched biaryl aldehyde precursor.[29,30] Suzuki and co-workers successfully synthesized three naturally occurring congeners, benanomicin B, benanomicin A, and pradimicin A, by the introduction of the appropriate amino acid and disaccharide functionalities.[30]

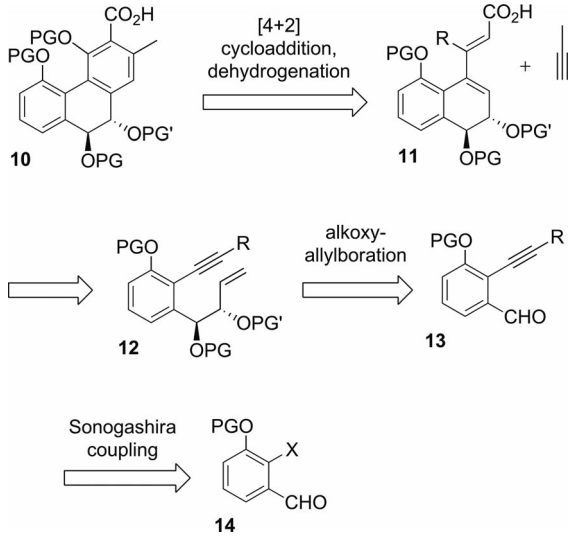
We became interested in developing an alternative and efficient synthetic route to the pradimicin/benanomicin natural products that would allow access to analogues and the design of libraries of synthetic CBAs. In particular, we hoped to achieve a more direct and enantioselective route towards the differentiated *trans*-diol compared with the synthesis of Suzuki and co-workers, which requires several manipulations.[30] Our proposed retrosynthetic analysis is presented in Scheme 1. The introduction of the amine and disaccharide onto pentacycle **2** was envisioned to occur in the later stages of the synthesis to allow an easily accessible route to analogues. The projected intramolecular metathesis of enyne **5** followed by a Diels–Alder reaction via diene **3** or **4** to close rings D and E would be an interesting, new, and expedient approach towards the synthesis of these natural products. The enyne **5** was envisioned to be synthesized by a Brown alkoxyallylboration of aldehyde **6**, which would derive from precursors **7**–**9**.

Results and Discussion

A model study was proposed to test the key reactions involved in the synthesis of the C–D–E tricyclic ring system **10** from precursors **11**–**14** (Scheme 2). Our efforts in this synthesis began by designing a route towards enyne precursor **12** from aldehyde **14**. The chosen route involved an alkoxyallylboration to directly introduce both the diol and



Scheme 1. Proposed retrosynthesis of pradimycin A (PRM-A).



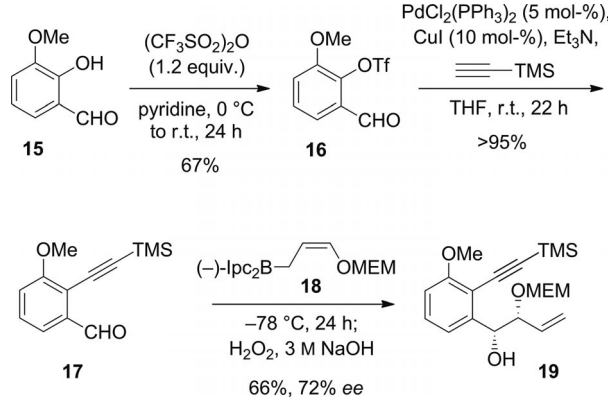
Scheme 2. Retrosynthetic rourte to the target C–D–E tricyclic core of PRM-A.

terminal alkene functionalities in alkyne **13** in one step. To this end, our initial objective was to prepare trisubstituted arene **14**.

Synthesis of Enyne Substrate 19

Synthesis of Trisubstituted Benzaldehyde 17

An inexpensive and high-yielding synthetic route towards aldehyde **14** was preferable in order to obtain the product on a large scale. The synthesis of **14** by halogenation of 3-alkoxybenzaldehydes proved to be more troublesome than anticipated. We therefore looked towards introducing a triflate group at the *ortho* position as a pseudohalide for the required Sonogashira cross-coupling reaction. Thus, triflation of commercially available phenol **15** with triflic anhydride afforded product **16** in a 67% yield (Scheme 3). To avoid the formation of Heck products between the aryl triflate and a pendent alkene, we opted to introduce the alkyne prior to the Brown alkoxyallylboration. To this end, a Sonogashira reaction was performed on **16** to obtain alkyne **17** in excellent yield (Scheme 3).[38]



Scheme 3. Preparation of key enyne intermediate **19**.

Alkoxyallylboration of Aldehyde 17

The main advantage associated with the preparation of precursor **19** by an alkoxyallylboration resides in the introduction of the monoprotected diol and terminal alkene into the aldehyde in one step. The allylboration reaction is a widely used reaction for the formation of homoallylic alcohols by an allyl transfer reaction between an allylic borane or boronate and carbonyl compounds.[39] It is a useful process, because a new C–C bond is formed as well as up to two stereogenic centers with high diastereoselectivity. We planned to utilize the stoichiometric chiral allylborane **18** (Scheme 3) derived from α-pinene developed by Brown et al.[40] This alkoxyallylboration can be applied to a wide range of aldehyde substrates, and the syntheses of several higher-order alkoxyallylboranes in situ are well known.[39] The preparation of the allylboration reagent (–)-[(*Z*)-γ-alkoxyallyl](diisopinocampheyl)borane **18** is followed by in situ addition to the aldehyde.[40] The 1,2-*syn*-alkoxy homoallylic alcohol products are obtained with high *ee* and *dr*. In 2002, Ramachandran et al. reported an alkoxyallylboration between **18** and benzaldehyde, which afforded the α-alkoxy homoallylic alcohol product in 71% yield and 98% *ee*.[41] By using similar conditions with aldehyde **17**, homoallylic alcohol product **19** was obtained in 66% yield and 72% *ee* (Scheme 3). Various reaction conditions were altered, including increasing the equivalents of borane as well as other workup conditions, but it did not significantly impact the outcome of the reaction. The *ee* was lower than expected, possibly due to our substrate. 9-Methoxy-9-borabicyclo[3.3.1]nonane (9-MeO-9-BBN) was used to form the racemic homoallylic alcohol product *rac*-**19** for an HPLC standard to determine the *ee* when using **18**. Because larger quantities are readily available, this racemic product was used to test future cyclization reactions.

Formation of the D and E Rings

Introduction to Enyne Metathesis

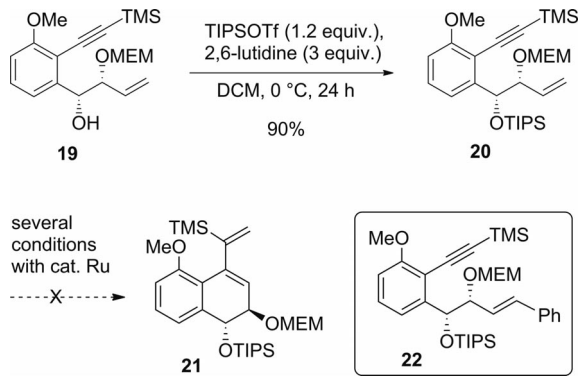
A transition-metal-induced cycloisomerization of a 1,7-enyne would be both a unique and attractive strategy for the construction of the D ring of pradimicin A. This process gives access to the 1,3-dienes required for the construction of the E ring by an intermolecular Diels–Alder reaction. Our initial attempts at ring-closing enyne metathesis (RCEM)[42–45] of precursor **19** utilized the Grubbs ruthenium–carbene system. The mechanism of enyne metathesis is not as well studied as that of diene metathesis.[42] The low-valent-transition-metal-catalyzed and metal–carbene-catalyzed systems operate through different mechanisms. The ability of the ruthenium atom to complex to either the alkene or alkyne results in different mechanistic pathways leading to two different isomeric diene products.[42] The cyclization is known to proceed successfully with alkyl groups on the alkyne and particularly well with esters of boronic acids, silyl ethers, and silyl groups.[46–49]

Enyne Metathesis for the Preparation of the D and E Rings

As seen in the proposed retrosynthesis (Scheme 2), tricycle **10** was to be obtained from an enyne of type **12**. It was envisioned that the E ring would be formed from the Diels–Alder cycloaddition of diene **11**. Diene **11** was designed to be more activated by introducing a carboxylic acid on to the terminal alkene by a cross-metathesis reaction that would lead to a more regioselective inverse-demand Diels–Alder reaction with the dienophile. It also allowed the desired substitution to occur on ring E. Diene **11** was envisioned to arise from a ruthenium–carbene-catalyzed enyne metathesis reaction with precursor **12/19**. The decision to introduce a trimethylsilyl group on the alkyne arose from the idea of first testing the tolerability of a silyl group and later replacing it with a dimethyl(phenyl)silyl group that would be capable of undergoing Tamao–Fleming oxidation to form the requisite E ring phenol in **10** (Scheme 2).

Enyne Metathesis with Substrate 19

Initial attempts towards the enyne metathesis of **19** began with the most often used Grubbs I and II catalysts. Although previous evidence suggested that a free alcohol may hinder the enyne metathesis by coordinating to the catalyst, Granja and co-workers in 2001 showed metathesis occurring in the presence of a free homoallylic alcohol.[50] Thus, the cyclization reaction was performed on alcohol **19** in dichloromethane at reflux as well as in toluene at room temperature and at 80 °C, but no conversion was observed. It was therefore assumed that the enyne metathesis reaction was not tolerated by the free alcohol in enyne **19**, probably as a result of intramolecular coordination of the homoallylic alcohol to the catalyst. The next step was to protect the alcohol in **19** to enable the metathesis reaction. A silyl protecting group was chosen in order to differentiate the protecting group from the MEM group and to prevent any interference in the cyclization reaction. The silylation reaction gave **20** in an excellent 90% yield at 0 °C in 24 h (Scheme 4). Enyne **20** was then subjected to various metathesis conditions with ruthenium–carbene, Grubbs I, Grubbs II, and Hoveyda–Grubbs II catalysts. Disappoint-

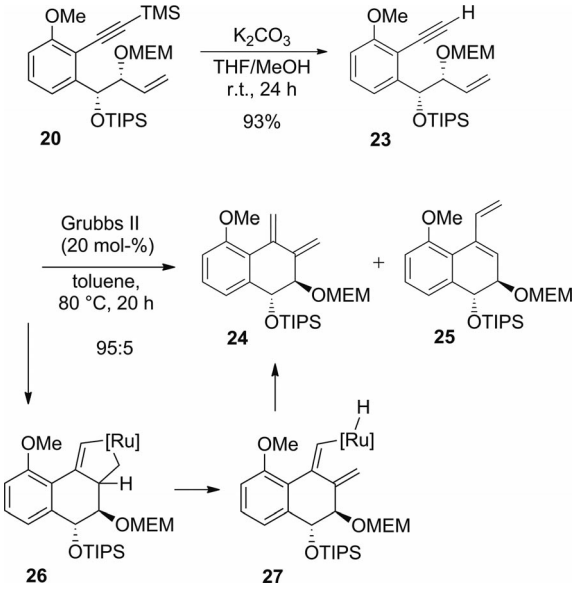


Scheme 4. Attempted enyne metathesis with substrate **20**.

ingly, at temperatures ranging from 23 to 80 °C in both toluene and dichloromethane, the enyne metathesis did not occur to produce the desired product **21**. In all cases, starting material was recovered at the end of the reaction as well as an undesired product later characterized as **22** (Scheme 4). A number of other catalysts were tested for the cyclization of substrate **20**, including $PtCl_2$ and $AuCl_3$, but complex mixtures were obtained with no indication of the desired diene product. It was concluded that the alkyne is not in close enough proximity to the alkene to react or is sterically hindered by either the *ortho*-methoxy group or the TMS substituent.

Enyne Metathesis with Modified Substrate 23

The next step was to test the enyne metathesis in the absence of the TMS group on the alkyne to see whether it was this group that hindered the reaction. As shown in Scheme 5, the silyl-capped alkyne was successfully cleaved with potassium carbonate to give **23** in 89% yield at room temperature. Although removal of the TMS group was not ideal for forming the desired substitution on ring E, we believed that the ring E phenol (e.g., as in **10**, Scheme 2) could be introduced by catalytic C–H borylation/oxidation[51] or *ortho*-lithiation/borylation at a later stage. After obtaining terminal alkyne **23**, the enyne metathesis was conducted again under the previous conditions in toluene at 80 °C. A new alkene product was formed, based on initial ^{1}H NMR data, and all the starting material was consumed. However, further analysis showed that diene **24** was unexpectedly formed along with the predicted **25** in a ratio of 95:5 (Scheme 5). The low-yielding mixture could not be isolated due to the instability of the products over time and when subjected to column chromatography. Mechanistically, diene **24** was an unexpected product from this catalytic system. The formation of a ruthenacyclopentene intermediate



Scheme 5. Enyne metathesis with terminal alkyne **23**.

is possible with a variety of transition metals and unsaturated partners, and it has been generated in the presence of an Ru^{II} catalyst.[52,53] In 1994, Murai and co-workers observed the first example of a 1,7-enyne undergoing skeletal reorganization in the presence of the catalyst $[RuCl_2(CO_3)]_2$ to form a vinylcyclohexene product.[54] They did not, however, postulate a mechanism. Given that the catalyst system is different, metallacyclopentene **26** was considered to be a possible intermediate in the formation of diene **24**. In this case, the metal atom would first coordinate to both points of unsaturation and then undergo oxidative coupling to form metallacyclopentene **26**. β-Hydride elimination to form **27** and reductive elimination would lead to the 1,3-diene **24**. The exact cause of the formation of diene product **24** over **25** is unclear.

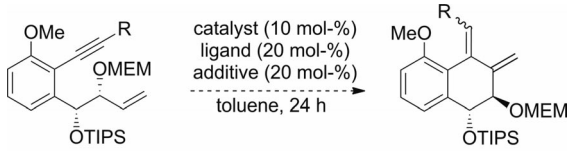
Owing to the unexpected formation of diene **24** over **25**, we were interested to see which diene would be favored by the use of low-valent-transition-metal catalysts. We then looked towards various palladium catalysts as a less expensive and potentially more efficient alternative.

Palladium-Catalyzed Cycloisomerization of Substrate 23

Palladium-catalyzed enyne reorganization has undergone extensive studies since the first Alder-ene reaction reported by Trost and co-workers in 1985.[55] It has led to numerous useful cycloisomerization reactions as well as tandem transformations with cycloaddition reactions.[52,53] In 1994, Trost and co-workers proposed a mechanism for the Pd-catalyzed cycloisomerization transformation proceeding through a palladacyclopentene intermediate. Typical Pd sources include $Pd(OAc)_2$ and $[Pd_2(dba)_3]$.[56] Trost and co-workers had previously shown that the ligand *N*,*N*-dibenzylideneethylenediamine (BBEDA) can increase catalytic activity for sluggish enyne cycloisomerization reactions. Therefore, this ligand was synthesized and employed here.[56] An alternative catalytic system was also employed in which acetic acid was used to oxidatively add to a Pd^0 source to form an H–Pd^{II}–OAc species.[57] In this case, the cycloisomerization occurred by a slightly different mechanism.

The palladium-catalyzed cycloisomerization was initially tested on substrate **20** in which the alkyne is substituted with TMS. However, only the starting material was obtained in the reaction under a variety of conditions (Table 2, Entries 1–5), including with the use of both sources of Pd, the BBEDA ligand, and acetic acid as the additive. Substrate **23** was then subjected to the same reaction conditions and actually provided more promising results. In the presence of the catalyst $Pd(OAc)_2$ at room temperature, a minimal amount of starting material was converted into the desired diene **24**. At this stage, the temperature was raised to 60 °C, and this resulted in a 100% conversion of the starting material into the product, based on ^{1}H NMR analysis (Entry 7). The reaction was also performed with $Pd(OAc)_2$, PPh_3, and the acetic acid additive at room temperature and resulted in a cleaner crude product than that obtained at the higher temperature (Entry 8). Therefore, these reaction conditions were used in all subsequent cycloisomerization reactions.

Table 2. Conditions for the Pd-catalyzed cycloisomerization of enynes **20** and **23**.



23 R = H
20 R = TMS

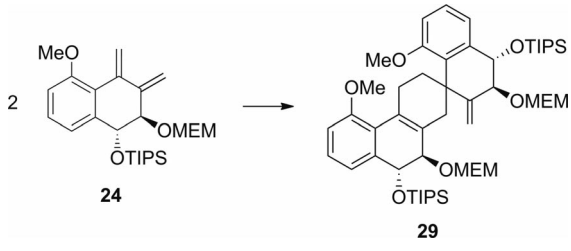
24 R = H
28 R = TMS

Entry	Catalyst/ligand[a]	Additive	R	*T* [°C]	Conversion [%][b]
1	$Pd(OAc)_2$	–	TMS	r.t.	0
2	$Pd(OAc)_2$/BBEDA	–	TMS	60	0
3	$Pd(OAc)_2$/BBEDA	–	TMS	110	0
4	$Pd_2(dba)_3/PPh_3$	AcOH	TMS	r.t.	0
5	$Pd_2(dba)_3/PPh_3$	AcOH	TMS	80	0
6	$Pd(OAc)_2$	–	H	r.t.	<10 (**24**)
7	$Pd(OAc)_2$	–	H	60	100 (**24**)
8	$Pd(OAc)_2/PPh_3$	AcOH	H	r.t.	100 (**24**)

[a] Entries 3, 6–8: 15 mol-% Pd catalyst. BBEDA: *N*,*N*-dibenzylideneethylenediamine. MEM: (2-methoxyethoxy)methyl. TIPS: triisopropylsilyl. [b] Determined by ^{1}H NMR analysis of the crude reaction product.

Isolation of Diene 24 and Dimer 29

During the preparation of diene **24**, it was noted that when the product was subjected to purification by column chromatography, a decomposition or alternative product seemed to be formed. Furthermore, after a period of approximately 24 h in solvent ($CDCl_3$), new peaks appeared in the ^{1}H NMR spectra. After the crude diene had completely converted (at room temperature for several days, based on ^{1}H NMR spectra), the unknown compound was purified by column chromatography and characterized. The ^{1}H and ^{13}C NMR spectra of the final product were not entirely clean due to the presence of numerous diastereomers; however, mass spectrometry revealed the presence of putative dimer **29** (Scheme 6). The probable formation of this particular isomer was established based on the findings of Vogel and co-workers in 2002.[58] This group reported the [4+2] formation of a dimer like **29** as the sole isomer from the corresponding diene based on a diradical intermediate.[58]



24 **29**

Scheme 6. Proposed dimer formed from diene **24**.

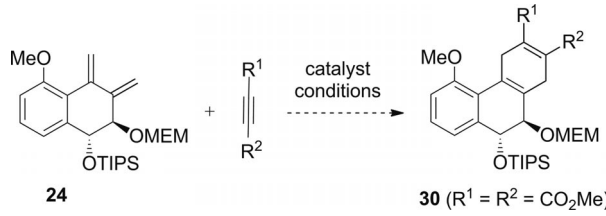
Diels–Alder Cycloaddition with Crude Substrate 24

Having successfully synthesized diene **24**, we then investigated potential routes that would use this intermediate. The potential to perform a Diels–Alder cycloaddition with diene **24** and a nonsymmetric dienophile proved attractive for the formation of ring E. However, this theory is dependent on which regioisomer is formed from the Diels–Alder reaction, as it would be hard to predict molecular orbital coefficients on the diene carbon atoms of **24**. Furthermore, because diene **24** is unstable and dimerized easily after a short period of time, we then explored the potential of a one-pot or tandem Pd-catalyzed cycloisomerization and Diels–Alder cycloaddition. To further examine this possibility, the Diels–Alder reaction was first tested by using the fairly pure, crude diene **24** to determine whether the reaction would proceed at all, and with which dienophiles. As previously mentioned, an asymmetric alkynic dienophile such as methyl 2-butynoate would be ideal for introducing methyl and ester groups into the E ring. Therefore, during preliminary testing of the Diels–Alder reaction, various asymmetric dienophiles were tested.

The conditions that were first examined included thermal, Lewis acid catalyzed, and boronic acid catalyzed Diels–Alder cycloadditions, as illustrated in Table 3. The Lewis acid catalyzed Diels–Alder reaction proved to be unsuccessful, as shown in Entries 1–3. With scandium triflate as catalyst (Entry 1) at room temperature, diene **24** dimerizes instead of reacting with the dienophile, which indicates the possible need for higher temperatures. The addition of catalytic aluminium chloride resulted in immediate decomposition (Entries 2 and 3). In the boronic acid catalyzed cycloaddition, a method developed by Zheng and Hall, with 2-alkynoic acids, a complex mixture was obtained (Entries 4 and 5).[59] As seen in Entry 6, the use of a base as additive was tested in the hope that it would act as a scavenger of possible adventitious acid, but also only led to a complex mixture. After many failed attempts, the use of a cobalt-catalyzed system developed by Hilt and Danz produced the desired tricycle **30** in 22% yield at room temperature (Entry 7).[60] Furthermore, a thermal Diels–Alder reaction at higher temperatures proved promising, giving the desired product in a yield of 32% (Entry 8). Butylated hydroxytoluene (BHT) was added as a potential radical scavenger, but it had no effect on the reaction (Entries 8 vs. 9). Because the crude cycloisomerization product was employed as a substrate, the yields obtained are for both the cycloisomerization and Diels–Alder cycloaddition steps. Unfortunately, a nonsymmetric monoactivated dienophile failed to give the desired product under similar thermal conditions, giving the dimer **29** as the only product (Entry 10).

In the hope of increasing the yield of the Diels–Alder cycloaddition step, the use of microwave heating was considered. This would allow higher temperatures to be reached in a shorter time, potentially resulting in less dimerization of the unstable diene. Some of the microwave conditions that were examined are shown in Table 4. The cycloisomerization reactions were performed in the microwave tube so that the dienophile could be added directly to the crude product to undergo the cycloaddition reaction. The use of a higher temperature, 140 °C, for both 5 min and 30 s resulted in lower yields (Entries 2 and 3). The ideal

Table 3. Study of the Diels–Alder cycloaddition reactions of substrate **24**.



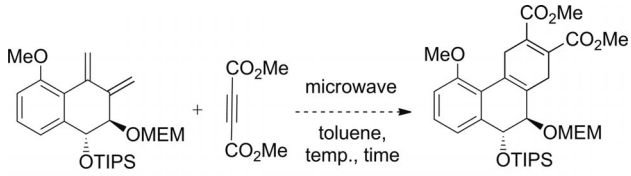
24 **30** ($R^1 = R^2 = CO_2Me$)

Entry	Catalyst or additive	R^1	R^2	Conditions	Result[a]
1	$Sc(OTf)_3$ (20 mol-%)	CO_2Me	CO_2Me	THF, r.t., 48 h	dimer **29**
2	$AlCl_3$ (2 equiv.)	CO_2Me	CO_2Me	CH_2Cl_2, RT	decomp.
3	$AlCl_3$ (2 equiv.)	H	CO_2Me	CH_2Cl_2, RT	decomposition
4	*o*-$BrC_6H_4B(OH)_2$ (20 mol-%)	H	CO_2H	CH_2Cl_2, r.t., 26 h	complex mixture
5	o-$NO_2C_6H_4B(OH)_2$ (20 mol-%)	H	CO_2H	CH_2Cl_2, r.t., 26 h	complex mixture
6	Et_3N	CO_2Me	CO_2Me	toluene, 80 °C, 24 h	complex mixture
7	[$CoCl_2$dppe] (10 mol-%), ZnI_2 (20 mol-%), Zn (10 mol-%)	CO_2Me	CO_2Me	toluene, r.t., 24 h	**30** (22%)
8	none	CO_2Me	CO_2Me	toluene, 80 °C, 24 h	**30** (32%)
9	BHT (20 mol-%)	CO_2Me	CO_2Me	toluene, 80 °C, 24 h	**30** (29%)
10	none	Me	CO_2Me	toluene, 50 °C, 24 h	dimer **29**

[a] Determined by ^{1}H NMR analysis of the crude reaction product. dppe: 1,2-bis(diphenylphosphanyl)ethane. BHT: 2,6-di-*tert*-butyl-4-methylphenol.

microwave conditions were found to be 120 °C for 1 min as these produced the highest yield over the two steps (Entry 4). Again, the BHT additive was tested, but it had no effect under microwave conditions (Entry 5).

Table 4. Diels–Alder cycloaddition reaction of substrate **24b** under microwave reaction conditions.



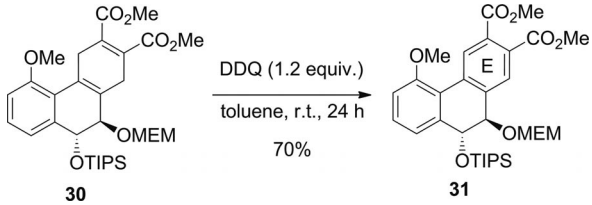
24 **30**

Entry	*T* [°C]	Time [min]	Yield [%][a]
1	80	3	33
2	140	5	<10
3	140	0.5	22
4	120	1	44
5[b]	120	1	42

[a] Isolated yield after chromatographic purification. [b] With 20 mol-% BHT.

Oxidative Aromatization of Tricycle 30

The next step in the synthesis of the C–D–E tricycle needed to be addressed, namely the aromatization of the newly formed cyclohexadiene ring E in **30** (Scheme 7). Treatment of **30** with DDQ at room temperature for 24 h provided a 70% yield of tricycle **31**.

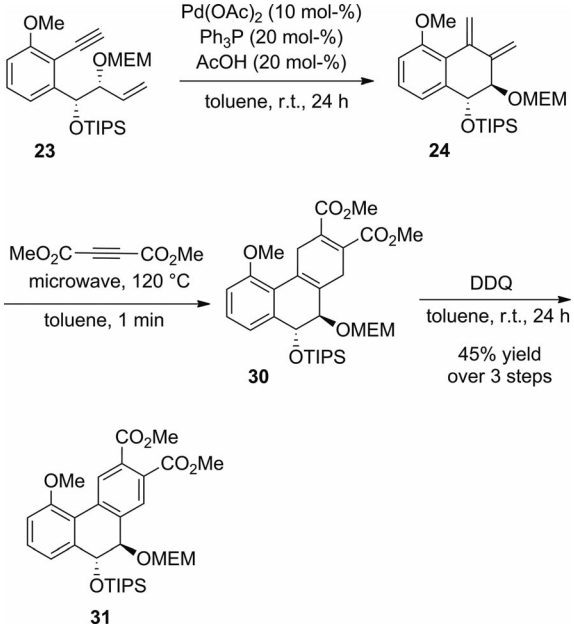


30 **31**

Scheme 7. Aromatization of diene **30**.

One-Pot Cycloisomerization/Diels–Alder Cycloaddition/Aromatization

A tandem reaction strategy to access tricycle **31** in which the enyne precursor **23**, catalyst, and dienophile are all present at the beginning of the reaction would be an elegant route towards the desired tricycle **31**. Up to this stage, diene **30** was purified prior to subjecting it to DDQ aromatization. Considering that the first two steps, cycloisomerization and Diels–Alder cycloaddition, were performed in toluene, the possibility arose of performing the DDQ-promoted oxidation reaction on the same crude mixture directly after the cycloaddition, because it is proven to work in toluene as well. A one-pot reaction was tested in which the DDQ was added at the same time as the reactants for the Diels–Alder cycloaddition step and subjected to the microwave conditions. However, this only resulted in a complex mixture. Therefore, an alternative one-pot procedure in which the DDQ was added directly to the crude mixture after the Diels–Alder reaction was examined, as illustrated in Scheme 8. This sequence worked quite well and produced **31** in an overall yield of 45% for the three steps, which compares with the 44% yield obtained previously for just the first two steps. This sequence averaged to a yield of approximately 77% per step, with the stability of diene **24** under the thermal Diels–Alder cycloaddition conditions being the limiting factor. The benefits of this process include minimizing solvent waste, eliminating purification steps, and maximizing the yield through the use of crude products. This one-pot procedure provides an efficient and unique route to tricycle **31** that may be applied in the synthesis of the core ring system of pradimicin A.



Scheme 8. One-pot, three-step reaction for the synthesis of tricycle **31**.

Conclusions

A model study towards the synthesis of the carbohydrate binding agent, pradimicin A, has led to the synthesis of tricycle **31** by a one-pot palladium-catalyzed cycloisomerization/Diels–Alder cycloaddition/aromatization. The initial synthetic route involving a Grubbs II-catalyzed enyne metathesis failed with TMS-alkyne substrate **20**, but it proceeded efficiently once the TMS group had been removed to yield the unexpected diene **24** as the major product. With the formation of this new diene came an alternative synthetic route to the tricyclic target in which **24** was applied. Other catalysts were tested to determine which product was produced under different catalyst systems. A palladium-catalyzed cycloisomerization was the most efficient and clean reaction to yield diene **24**. Diene **24** proved to be difficult to work with, because it spontaneously dimerizes to product **29**. At this point, a one-pot process combining the cycloisomerization and Diels–Alder reaction was developed to ensure quick reaction of the crude diene. A one-pot tandem process in which each reaction was performed directly on the crude material in the same reaction flask produced final tricycle **31** in a 45% yield over three steps. Ideally, if this route were to be applied to the synthesis of pradicimin A, an alternative dienophile would be required to access the specific substitution pattern of ring E. Another option would be to enhance the reactivity of the diene by substituting it with an electron-donating group, allowing regioselective access to the desired trisubstituted ring at the same time.

Experimental Section

General: Unless otherwise noted, all the reactions were performed under argon or nitrogen in flame-dried glassware. Toluene, hexanes, and CH_2Cl_2 were distilled from CaH_2. THF and Et_2O were distilled from sodium/benzophenone ketyl. THF, toluene, dichloromethane, and methanol were also used following treatment with the Fisher Scientific-MBraun MB SPS* solvent system. Molecular sieves were prepared by heating under vacuum at 130 °C (overnight) and then stored inside an oven maintained at 125 °C. TLC was performed on Merck silica gel 60 F254 plates and visualized with UV light and $KMnO_4$. NMR spectra were recorded with Varian INOVA-300, INOVA-400, INOVA-500, or Unity 500 instruments. The residual solvent protons (^1H) or the solvent carbon atoms (^{13}C) were used as internal standards. The ^1H NMR spectroscopic data are presented as follows: chemical shift in ppm relative to tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; app. dt, apparent doublet of triplets; m, multiplet. HR mass spectra were recorded by using either EI or ES ionization techniques at the University of Alberta Mass Spectrometry Services Laboratory. IR spectra and optical rotations were recorded at the University of Alberta Spectral Services. The optical purities of α-alkoxy homoallylic alcohol products were measured by chiral HPLC (Daicel OD Column, 0.46 × 25 cm) or by formation of Mosher esters and subsequent ^1H or ^{19}F NMR analysis of the crude product. Specific details are indicated in the Experimental Section for each individual product. Compound **17**[38] was synthesized according to the literature. For microwave-promoted reactions, a Biotage Initiator SW reactor was employed (2.5 mL vials).

Synthesis of Enyne Precursors

(1*R*,2*R*)-2-[(2-Methoxyethoxy)methoxy]-1-{3-methoxy-2-[(trimethylsilyl)ethynyl]phenyl}but-3-en-1-ol (19): 3-[(2-Methoxyethoxy)methoxy]prop-1-ene (0.79 g, 5.4 mmol, 1.1 equiv.) was added to a long-necked round-bottomed flask along with THF (9 mL). The solution was cooled to –78 °C, *s*BuLi (4.9 mL, 5.4 mmol, 1.1 equiv.) was added dropwise, and the mixture stirred for 30 min to form a yellow solution. (+)-Ipc_2BOMe (3.4 g, 9.8 mmol, 2.0 equiv.) dissolved in THF (5 mL) was added dropwise to form a colorless solution that was stirred for 1 h. $BF_3{\cdot}OEt_2$ (1.2 mL, 9.8 mmol, 2.0 equiv.) was then added dropwise followed directly by aldehyde **17** (1.1 g, 4.9 mmol, 1.0 equiv.) dissolved in THF (2 mL). The reaction mixture was stirred at –78 °C for 24 h at which point it was quenched by the addition of 30% H_2O_2 (5 mL) and 2 M NaOH (5 mL) and warmed to room temperature. The reaction mixture was stirred at room temperature for 12 h. The aqueous layer was washed with diethyl ether (2 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$. The solution was filtered, concentrated in vacuo, and purified by column chromatography (10% ethyl acetate/DCM). The product (1.22 g) was obtained as a yellow oil in 66% yield and 72% *ee*. $[\alpha]_D^{25}$ = 139.5 (*c* = 0.28, DCM). IR (cast film): $\tilde{\nu}$ = 3448, 2957, 2893, 2151, 1596, 1574, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.1 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 6.72 (dd, *J* = 0.8, 8.3 Hz, 1 H), 5.75–5.82 (m, 1 H), 5.17 (m, 2 H), 5.15 (m, 1 H), 4.66 (d, *J* = 6.9 Hz, 1 H), 4.54 (d, *J* = 6.9 Hz, 1 H), 4.26 (m, 1 H), 3.81 (s, 3 H), 3.44 (m, 1 H), 3.31–3.37 (m, 3 H), 3.29 (s, 3 H), 0.22 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 145.3, 134.4, 129.2, 118.9, 110.7, 109.3, 104.5, 98.9, 93.1, 81.2, 73.6, 71.6, 67.0, 58.9, 55.9, 0.1 ppm. HRMS (EI): calcd. for $C_{20}H_{30}NaO_5Si$ 401.1755; found 401.1750.

(8*R*,9*R*)-11,11-Diisopropyl-9-{3-methoxy-2-[(trimethylsilyl)ethynyl]phenyl}-12-methyl-8-vinyl-2,5,7,10-tetraoxa-11-silatridecane (20): In a round-bottomed flask, alcohol **19** (1.16 g, 3.06 mmol, 1.00 equiv.) was dissolved in DCM (7 mL). The solution was cooled

to 0 °C, and 2,6-lutidine (1.07 mL, 9.18 mmol, 3.00 equiv.) was slowly added. TIPSOTf (1.00 mL, 3.76 mmol, 1.20 equiv.) was then added dropwise to the solution, which was stirred at 0 °C for 24 h. The solution was warmed to room temperature and diluted with diethyl ether (5 mL). The organic layer was washed with $NaHCO_3$ (2 × 10 mL) and brine (10 mL) and dried with $MgSO_4$. The solution was gravity-filtered and concentrated in vacuo to produce the crude material, which was purified by column chromatography (20% ethyl acetate/hexane). The product (1.25 g) was obtained as a yellow oil in 90% yield. $[\alpha]_D^{25}$ = 32.44 (*c* = 0.27, DCM). IR (cast film): $\tilde{\nu}$ = 2944, 2891, 2867, 2153, 1575, 1471 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (app. t, *J* = 7.9 Hz, 1 H), 7.17 (dd, *J* = 0.9, 7.7 Hz, 1 H), 6.72 (dd, *J* = 1.2, 8.0 Hz, 1 H), 5.68–5.80 (m, 1 H), 5.45 (d, *J* = 6.0 Hz, 1 H), 5.11 (m, 1 H), 5.05–5.08 (m, 1 H), 4.74 (s, 2 H), 4.18 (t, *J* = 6.5 Hz, 1 H), 3.85 (s, 3 H), 3.39–3.55 (m, 4 H), 3.35 (s, 3 H), 1.02–1.05 (m, 21 H), 0.25 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 146.5, 134.9, 128.8, 120.4, 118.3, 110.9, 108.8, 103.7, 99.2, 93.6, 81.7, 74.5, 71.7, 66.5, 58.9, 55.8, 18.1, 18.0, 17.9, 17.7, 12.4, 12.3, 0.0 ppm. HRMS (EI): calcd. for $C_{20}H_{30}NaO_5Si$ 557.3089; found 557.3084.

(8*R*,9*R*)-11,11-Diisopropyl-9-{3-methoxy-2-[(trimethylsilyl)-ethynyl]phenyl}-12-methyl-8-styryl-2,5,7,10-tetraoxa-11-silatridecane (22): Side-product of attempted metathesis of **20**. IR (cast film): $\tilde{\nu}$ = 2924, 2866, 2153, 1735, 1575, 1470 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.37 (m, 7 H), 6.78 (d, *J* = 7.4 Hz, 1 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 6.25 (dd, *J* = 7.9, 16.0 Hz, 1 H), 5.63 (d, *J* = 5.2 Hz, 1 H), 4.84 (d, *J* = 6.9 Hz, 1 H), 4.78 (d, *J* = 6.9 Hz, 1 H), 4.45 (t, *J* = 6.4 Hz, 1 H), 3.90 (s, 3 H), 3.56–3.67 (m, 2 H), 3.42–3.51 (m, 2 H), 3.40 (s, 3 H), 1.02–1.10 (m, 21 H), 0.33 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 146.5, 137.0, 133.3, 128.8, 128.5, 127.4, 126.9, 126.6, 120.6, 110.9, 109.2, 103.6, 99.3, 93.4, 80.9, 74.7, 71.7, 66.5, 58.9, 55.9, 29.8, 18.1, 17.9, 12.5, 0.1 ppm. HRMS (EI): calcd. for $C_{35}H_{54}NaO_5Si_2$ 633.3402; found 633.3392.

(8*R*,9*R*)-9-(2-Ethynyl-3-methoxyphenyl)-11,11-diisopropyl-12-methyl-8-vinyl-2,5,7,10-tetraoxa-11-silatridecane (23): In a round-bottomed flask, enyne **20** (7.68 g, 14.4 mmol, 1.00 equiv.) was dissolved in THF (50 mL) and MeOH (50 mL). K_2CO_3 was then added to the solution, which was stirred at room temperature for 24 h. The solution was then concentrated in vacuo, the residue dissolved in diethyl ether (20 mL), and purified through a plug of silica gel by using diethyl ether as the eluent to obtain the product (6.19 g) as a yellow oil in 93% yield. $[\alpha]_D^{25}$ = 25.64 (*c* = 0.45, DCM). IR (cast film): $\tilde{\nu}$ = 3295, 2943, 2890, 2867, 2103, 1577, 1471 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 7.9 Hz, 1 H), 7.17 (dd, *J* = 0.7, 7.7 Hz, 1 H), 6.76 (dd, *J* = 1.0, 8.2 Hz, 1 H), 5.70–5.82 (ddd, *J* = 7.5, 11.1, 16.7 Hz, 1 H), 5.45 (d, *J* = 6.0 Hz, 1 H), 5.11 (m, 1 H), 5.07 (ddd, *J* = 0.9, 1.9, 8.1 Hz, 1 H), 4.73 (s, 2 H), 4.27 (t, *J* = 6.4 Hz, 1 H), 3.88 (s, 3 H), 3.54–3.58 (m, 2 H), 3.52 (s, 1 H), 3.42–3.45 (m, 2 H), 3.36 (s, 3 H), 0.99–1.05 (m, 21 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 146.5, 134.6, 129.0, 120.5, 110.7, 118.5, 109.9, 108.9, 93.4, 86.1, 81.3, 78.3, 71.7, 66.6, 58.9, 55.8, 16.0, 17.7, 12.4 ppm. HRMS (EI): calcd. for $C_{26}H_{42}NaO_5Si$ 485.2694; found 485.2689.

Dimerization of Diene 24. Formation of Compound 29: Diene **24** spontaneously dimerized at room temperature after a period of approximately 24 h or when subjected to column chromatography. The ^1H and ^{13}C NMR spectra were not clean enough to fully distinguish all the necessary peaks due to the presence of numerous diastereomers. IR (cast film): $\tilde{\nu}$ = 2942, 2889, 2866, 1577, 1467 cm^{-1}. HRMS (EI): calcd. for $C_{52}H_{84}NaO_{10}Si_2$ 947.5495; found 947.5488.

One-Pot Cycloisomerization and Diels–Alder Cycloaddition

Dimethyl (9*R*,10*R*)-5-Methoxy-10-[(2-methoxyethoxy)methoxy]-9-(triisopropylsilyloxy)-1,4,9,10-tetrahydrophenanthrene-2,3-dicarboxylate (30): The following procedure applies to the synthesis of diene **24** by using the palladium catalyst followed directly by subjecting the crude product to the Diels–Alder reaction. Enyne **23** (0.10 g, 0.22 mmol, 1 equiv.) was dissolved in toluene (1.2 mL) in a 2.5 mL microwave tube. $Pd(OAc)_2$ (8.6 mg, 33 μmol, 15 mol-%), PPh_3 (9.9 mg, 44 μmol, 20 mol-%), and AcOH (5.3 μL, 88 μmol, 40 mol-%) were added to the reaction flask. The reaction mixture was stirred at room temperature for 24 h at which point the dienophile, dimethyl butynedioate (0.27 mL, 2.2 mmol, 10 equiv.), was added. The reaction vessel was sealed under nitrogen and subjected to microwave heating at 120 °C at a normal absorbance level for 1 min. The solution was then concentrated in vacuo and purified by quick column chromatography (30% ethyl acetate/hexane). The one-pot reaction yielded 58.5 mg (44% yield) of **30** as a yellow oil.

As a result of its instability and tendency to dimerize, compound **24** was employed immediately after its isolation and only partially characterized. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7 Hz, 1 H), 6.98 (d, *J* = 7 Hz, 1 H), 6.91 (d, *J* = 7.3 Hz, 1 H), 6.29 (s, 1 H), 5.89 (s, 1 H), 5.78 (s, 1 H), 5.20 (s, 1 H), 4.93 (d, 1 H), 4.84 (d, 1 H), 4.64 (d, 1 H), 4.50 (d, 1 H), 3.85 (s, 3 H), 3.55 (m, 4 H), 3.40 (s, 3 H), 1.09 (d, 18 H), 1.01 (m, 3 H) ppm.

The following procedure applies to the synthesis of diene **24** by using Grubbs II ruthenium catalyst followed by subjection of the crude product to the Diels–Alder reaction conditions. Enyne **23** (0.20 g, 0.43 mmol, 1 equiv.) was dissolved in toluene (10 mL) in a round-bottomed flask equipped with a condenser. Grubbs II catalyst (73 mg, 86 μmol, 20 mol-%) was subsequently added to the reaction mixture. The solution was stirred at 80 °C for 24 h, then cooled to room temperature, transferred to a 2.5 mL microwave tube, and the dienophile, dimethyl butynedioate (0.55 mL, 4.3 mmol, 10 equiv.), was added. The reaction vessel was sealed under nitrogen and subjected to microwave heating at 120 °C at a normal absorbance level for 1 min. The solution was then concentrated in vacuo and purified by column chromatography (30% ethyl acetate/hexane). The one-pot reaction yielded 27.5 mg and a 10% yield of **30** as a yellow oil. IR (cast film): $\tilde{\nu}$ = 2945, 2890, 2866, 1725, 1578, 1471 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 7.5 Hz, 1 H), 6.91 (dd, *J* = 0.9, 7.3 Hz, 1 H), 6.84 (dd, *J* = 0.9, 8.4 Hz, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.75 (d, *J* = 7.2 Hz, 1 H), 4.72 (d, *J* = 4.1 Hz, 1 H), 4.01–4.14 (m, 1 H), 3.91–3.94 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 6 H), 3.48–3.60 (m, 6 H), 3.37 (s, 3 H), 3.05–3.15 (m, 1 H), 0.93–1.07 (m, 21 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 167.5, 156.9, 138.1, 136.1, 128.9, 128.1, 127.1, 125.7, 121.9, 121.7, 112.7, 95.4, 78.5, 71.6, 67.1, 59.0, 55.5, 52.3, 52.1, 32.5, 31.9, 18.1, 18.0, 12.7 ppm. HRMS (EI): calcd. for $C_{32}H_{48}NaO_9Si$ 627.2960; found 627.2941.

Dimethyl (9*R*,10*R*)-5-Methoxy-10-[(2-methoxyethoxy)methoxy]-9-(triisopropylsilyloxy)-9,10-dihydrophenanthrene-2,3-dicarboxylate (31): Diene **30** (0.10 g, 0.16 mmol, 1.0 equiv.) was dissolved in toluene (2 mL) in a round-bottomed flask. DDQ (44 mg, 0.19 mmol, 1.2 equiv.) was then added to the solution, and the mixture was stirred at room temperature for 24 h. The crude material was concentrated in vacuo and purified by column chromatography to produce 67.5 mg of the product as a yellow oil in 70% yield. IR (cast film): $\tilde{\nu}$ = 2944, 2892, 2866, 1729, 1612, 1598 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 7.82 (s, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 4.93 (d, *J* = 4.5 Hz, 1 H), 4.79 (d, *J* = 7.0 Hz, 1 H), 4.75 (m, 2 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.67–3.71 (m, 1 H), 3.52–

3.58 (m, 3 H), 3.40 (s, 3 H), 0.98–1.06 (sept., J = 7.6 Hz, 3 H), 0.88–0.96 (m, 18 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 167.5, 157.3, 135.6, 132.6, 129.7, 129.0, 128.6, 119.9, 112.4, 71.5, 67.1, 59.0, 55.7, 52.6, 52.5, 18.0, 17.9 ppm. HRMS (EI): calcd. for $C_{32}H_{47}O_9Si$ 603.2984; found 603.2984.

Synthesis of Product 31 by a One-Pot Cycloisomerization/Diels–Alder/Aromatization: The following procedure was performed in the same reaction vessel and the same solvent. No concentration or purification was performed between the steps. Enyne **23** (0.10 g, 0.22 mmol, 1 equiv.) and toluene (1.2 mL) were added to a 2.5 mL microwave tube. Next, $Pd(OAc)_2$ (8.6 mg, 33 µmol, 15 mol-%), PPh_3 (9.9 mg, 44 µmol, 20 mol-%), and AcOH (5.3 µL, 88 µmol, 40 mol-%) were added to the reaction mixture, which was then stirred for 24 h. The dienophile, dimethyl butynedioate (0.27 mL, 2.2 mmol, 10 equiv.), was added to the mixture and subjected to microwave heating at 120 °C at normal absorbance for 1 min (not including preheating time). Once cooled to room temperature, DDQ (59 mg, 0.26 mmol, 1.2 equiv.) was added to the reaction flask, and the mixture was stirred for 24 h. Upon completion of the reaction, the solution was concentrated in vacuo and purified by column chromatography (30% ethyl acetate/hexane) to give 59.7 mg of the product as a light-yellow oil in 45% yield over the three steps.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectral reproductions for new compounds.

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[1] T. Oki, M. Konishi, K. Tomatsu, K. Tomita, K. Saitoh, M. Tsunakawa, M. Nishio, T. Miyaki, H. Kawaguchi, *J. Antibiot.* **1988**, *41*, 1701–1704.
[2] T. Takeuchi, T. Hara, H. Naganawa, M. Okada, M. Hamada, H. Umezawa, S. Gomi, M. Sezaki, S. Kondo, *J. Antibiot.* **1988**, *41*, 807–811.
[3] M. Tsunakawa, M. Nishio, H. Ohkuma, T. Tsuno, M. Konishi, T. Naito, T. Oki, H. Kawaguchi, *J. Org. Chem.* **1989**, *54*, 2532–2536.
[4] S. Gomi, M. Sezaki, S. Kondo, T. Hara, H. Naganawa, T. Takeuchi, *J. Antibiot.* **1988**, *41*, 1019–1028.
[5] M. Kakushima, Y. Sawada, M. Nishio, T. Tsuno, T. Oki, *J. Org. Chem.* **1989**, *54*, 2536–2539.
[6] A. Tanabe, H. Nakashima, O. Yoshida, N. Yamamoto, O. Tenmyo, T. Oki, *J. Antibiot.* **1988**, *41*, 1708–1710.
[7] J. Balzarini, K. O. Francois, K. Van Laethem, B. Hoorelbeke, M. Renders, J. Auwerx, S. Liekens, T. Oki, Y. Igarashi, D. Schols, *Antimicrob. Agents Chemother.* **2010**, *54*, 1425–1435.
[8] J. Balzarini, K. Van Laethem, D. Daelemans, S. Hatse, A. Bugatti, M. Rusnati, Y. Igarashi, T. Oki, D. Schols, *J. Virol.* **2007**, *81*, 362–373.
[9] Y. Sawada, T. Tsuno, T. Ueki, H. Yamamoto, Y. Fukagawa, T. Oki, *J. Antibiot.* **1993**, *46*, 507–510.
[10] T. Furumai, K. Saitoh, M. Makushima, S. Yamamoto, K. Suzuki, C. Ikeda, S. Kobaru, M. Hatori, T. Oki, *J. Antibiot.* **1993**, *46*, 265–274.
[11] K. Numata, T. Ueki, N. Naito, N. Yamada, N. Kamasawa, T. Oki, M. Osumi, *J. Electron Microsc.* **1993**, *42*, 147–55.
[12] T. Furumai, T. Hasegawa, M. Kakushima, K. Suzuki, H. Yamamoto, S. Yamamoto, M. Hirano, T. Oki, *J. Antibiot.* **1993**, *46*, 589–597.
[13] K. Saitoh, T. Tsuno, M. Kakushima, M. Hatori, T. Furumai, T. Oki, *J. Antibiot.* **1993**, *46*, 406–411.
[14] J. Balzarini, *Antiviral Chem. Chemother.* **2007**, *18*, 1–11.
[15] F. Helle, C. Wychowski, N. Vu-Dac, K. R. Gustafson, C. Voisset, J. Dubuisson, *J. Biol. Chem.* **2006**, *281*, 25177–25183.
[16] Y. Fukagawa, T. Ueki, K. Numata, T. Oki, *Actinomycetologica* **1993**, *7*, 1–22.
[17] T. Ueki, K. Numata, Y. Sawada, T. Nakajima, Y. Fukagawa, T. Oki, *J. Antibiot.* **1993**, *46*, 149–161.
[18] T. Ueki, K. Numata, Y. Sawada, M. Nishio, H. Ohkuma, S. Toda, H. Kamachi, Y. Fukagawa, T. Oki, *J. Antibiot.* **1993**, *46*, 455–464.
[19] Y. Nakagawa, T. Doi, Y. Masuda, K. Takegoshi, Y. Igarashi, Y. Ito, *J. Am. Chem. Soc.* **2011**, *133*, 17485–17493.
[20] T. Ueki, M. Oka, Y. Fukagawa, T. Oki, *J. Antibiot.* **1993**, *46*, 465–467.
[21] M. Watanabe, T. Hiratani, K. Uchida, K. Ohtsuka, H. Watabe, S. Inouye, S. Kondo, T. Takeuchi, H. Yamaguchi, *J. Antimicrob. Chemother.* **1996**, *38*, 1073–1077.
[22] A. Tanabe-Tochikura, T. S. Tochikura, J. R. J. Blakeslee, R. G. Olsen, L. E. Mathes, *Antiviral Res.* **1992**, *19*, 161–172.
[23] S. Manku, D. G. Hall, *Aust. J. Chem.* **2007**, *60*, 824–828.
[24] M. Dowlut, D. G. Hall, *J. Am. Chem. Soc.* **2006**, *128*, 4226–4227.
[25] M. Bérubé, M. Dowlut, D. G. Hall, *J. Org. Chem.* **2008**, *73*, 6471–6479.
[26] A. Pal, M. Bérubé, D. G. Hall, *Angew. Chem.* **2010**, *122*, 1534; *Angew. Chem. Int. Ed.* **2010**, *49*, 1492–1495.
[27] K. Ohmori, M. Kitamura, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1304; *Angew. Chem. Int. Ed.* **1999**, *38*, 1226–1229.
[28] M. Kitamura, K. Ohmori, T. Kawase, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1308; *Angew. Chem. Int. Ed.* **1999**, *38*, 1229–1232.
[29] K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui, K. Suzuki, *Angew. Chem.* **2005**, *117*, 3939; *Angew. Chem. Int. Ed.* **2005**, *44*, 3871–3874.
[30] M. Tamiya, K. Ohmori, M. Kitamura, H. Kato, T. Arai, M. Oorui, K. Suzuki, *Chem. Eur. J.* **2007**, *13*, 9791–9823.
[31] K. Krohn, S. Bernhard, *Eur. J. Org. Chem.* **1999**, 3099–3103.
[32] K. Krohn, S. Bernhard, U. Floerke, N. Hayat, *J. Org. Chem.* **2000**, *65*, 3218–3222.
[33] F. M. Hauser, H. Liao, Y. Sun, *Org. Lett.* **2002**, *4*, 2241–2243.
[34] F. M. Hauser, W. A. Dorsch, D. Mal, *Org. Lett.* **2002**, *4*, 2237–2239.
[35] T. R. Kelly, W. Xu, Z. Ma, Q. Li, V. Bhushan, *J. Am. Chem. Soc.* **1993**, *115*, 5843–5844.
[36] G. Stavrakov, M. Keller, B. Breit, *Eur. J. Org. Chem.* **2007**, 5726–5733.
[37] A. Baranczak, G. A. Sulikowski, *Angew. Chem.* **2009**, *121*, 6119; *Angew. Chem. Int. Ed.* **2009**, *48*, 6005–6007.
[38] N. Nicolaus, S. Strauss, J. Neudörfl, A. Prokop, H. Schmalz, *Org. Lett.* **2009**, *11*, 341–344.
[39] H. Lachance, D. G. Hall, *Org. React.* **2008**, *73*, 1–573.
[40] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538.
[41] P. V. Ramachandran, J. S. Chandra, M. V. Ram Reddy, *J. Org. Chem.* **2002**, *67*, 7547–7550.
[42] C. S. Poulsen, R. Madsen, *Synthesis* **2003**, 1–18.
[43] S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382.
[44] J. Li, D. Lee, *Eur. J. Org. Chem.* **2011**, 4269–4287.
[45] M. Mori, *Materials* **2010**, *3*, 2087–2140.
[46] S. C. Schurer, S. Gessler, N. Buschmann, S. Blechert, *Angew. Chem.* **2000**, *112*, 4062; *Angew. Chem. Int. Ed.* **2000**, *39*, 3898–3901.
[47] J. Renaud, C. Graf, L. Oberer, *Angew. Chem.* **2000**, *112*, 3231; *Angew. Chem. Int. Ed.* **2000**, *39*, 3101–3104.
[48] J. S. Clark, F. Elustondo, G. P. Trevitt, D. Boyall, J. Robertson, A. J. Blake, C. Wilson, B. Stammen, *Tetrahedron* **2002**, *58*, 1973–1982.

[49] T. Kitamura, Y. Sato, M. Mori, *Adv. Synth. Catal.* **2002**, *344*, 678–693.
[50] E. M. Codesido, L. Castedo, J. R. Granja, *Org. Lett.* **2001**, *3*, 1483–1486.
[51] R. E. Maleczka, Jr., F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793.
[52] V. Michelet, P. Y. Toullec, J. Genet, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315.
[53] C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834.
[54] N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050.
[55] B. M. Trost, M. Lautens,*J. Am. Chem. Soc.* **1985**, *107*, 1781–1783.
[56] B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. MacPherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255–4267.
[57] B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.* **1994**, *116*, 4268–4278.
[58] E. Roversi, P. Vogel, K. Schenk, *Helv. Chim. Acta* **2002**, *85*, 1390–1398.
[59] H. Zheng, D. G. Hall, *Tetrahedron Lett.* **2010**, *51*, 3561–3564.
[60] G. Hilt, M. Danz, *Synthesis* **2008**, 2257–2263.

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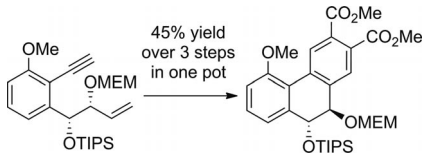
A model study towards the synthesis of the C–D–E tricyclic core of the carbohydrate binding agent, pradimicin A, is described. Alkoxyallylboration provided the differentially protected diol unit of the central ring. Optimization of a key enyne cycloisomerization reaction led to the synthesis of the tricycle by a one-pot Pd-catalyzed cycloisomerization/Diels–Alder cycloaddition/aromatization.



Keywords: Allylboration / Aromatization / Cycloaddition / Metathesis / Natural products / Synthesis design

