Domino Reactions

A 4-*exo*-dig Cyclocarbopalladation/ 8π Electrocyclization Cascade: Expeditious Access to the Tricyclic Core Structures of the Ophiobolins and Aleurodiscal**

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The design and elaboration of complex molecules from simple starting materials in the minimum number of synthetic steps is one of the most challenging goals in organic synthesis today.[1] Towards this end, transition-metal-catalyzed processes have become a powerful tool for the construction of sensitive functionalized polycyclic molecules under very mild conditions.[2] A particularly attractive goal in this field is the development of new methodologies for synthesizing cyclo-

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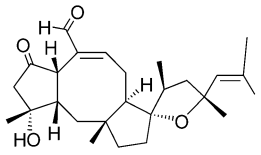
octanoid ring systems.[3] This substructure is present in over 100 different natural products, many of which exhibit exceptional and broad-ranging biological activity. One of the most notable examples is the diterpene paclitaxel (taxol).[4] However, because of the high degree of ring strain, transannular interactions, and unfavorable entropic and enthalpic factors, the synthesis of compounds with eight-membered rings remains difficult. Several authors have reported elegant approaches to such systems based on transition-metal catalysis.[5] The most recent reports[5h–i] described the formation of bicyclic structures by using a rhodium catalyst in a one-pot operation. However, none of these approaches involved the direct formation of a 5,8,5-tricyclic skeleton. Ophiobolin A (**1**)[6] and aleurodiscal (**2**)[7] are natural compounds that



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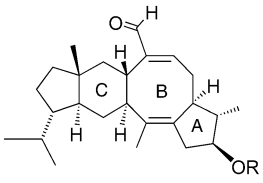

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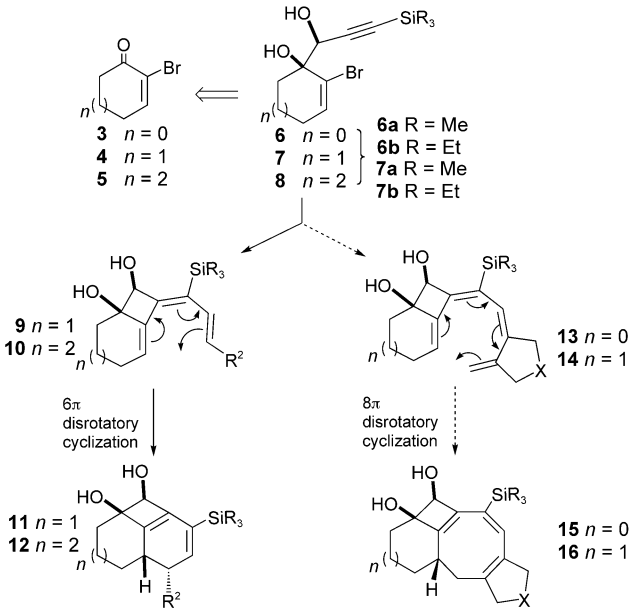
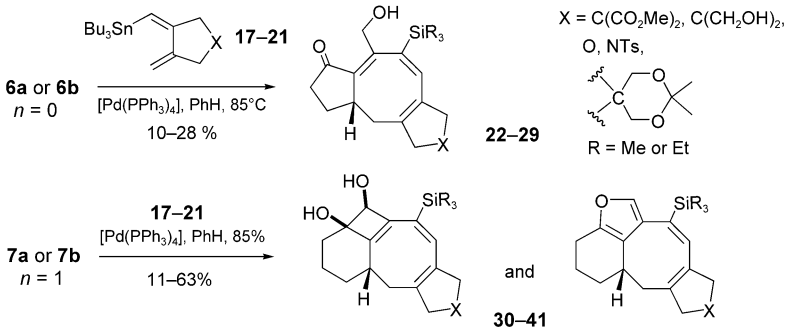


Scheme 1. 4-*exo*-dig cyclocarbopalladation/6π electrocyclization cascade extended to 8π electrocyclization.

contain a 5,8,5-tricyclic and 5,6,8,5-tetracyclic core, respectively. Ophiobolins have a broad spectrum of biological activity against nematodes, fungi, and bacteria,[8,9] as well as potent antitumor activity.[10] Aleurodiscal is an antifungal antibiotic produced by mycelial cultures of *Aleurodiscus mirabilis* collected from the bark of *Cinnamonum camphora*, which is endemic to Japan. Extensive studies toward these polycyclic skeletons have been carried out by several research groups,[11] and the total synthesis of ophiobolin C was completed by Kishi and co-workers in 1989.[12]

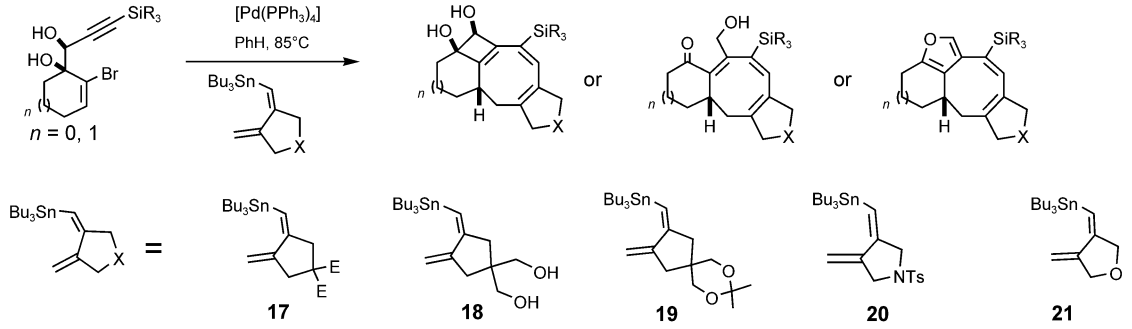
We recently disclosed an efficient reaction that led to the formation of unusual polycyclic compounds through an initial 4-*exo*-dig cyclocarbopalladation of propargylic diols.[13] In a one-pot operation, the products of this reaction can undergo reaction with a suitable vinyl stannane, followed by a disrotatory 6π electrocyclization to give unusual tricyclic systems of the type **11** and **12**, which contain a new six-membered ring and a cyclobutene ring whose double bond is located at the junction of the three rings (Scheme 1). These were the first examples of a metal-catalyzed exclusively 4-*exo*-dig cyclization. The process has been applied to a wide variety of propargylic diols and tributylstannane derivatives and can be scaled up to afford multigram quantities of new highly strained compounds. One limitation was the failure of the diols **6**, which contain a five-membered ring, to undergo the desired reaction. Instead only decomposition of the starting material was observed, probably because of the highly strained nature of the [3.2.0] bicyclic system in the hypothetical intermediate.

During our studies towards the extension of this new methodology to the synthesis of other valuable polycyclic structures, such as those present in the biologically active natural products mentioned above, we decided to examine the possibility of including a conrotatory 8π electrocyclization in the reaction sequence. It was proposed that the functionalized tetracyclic trienes **15** and **16**, which contain an eight-membered ring, could be formed from the potential tetraene intermediates **13** and **14** (Scheme 1). The two diols **6** and **7**, which contain a five- and a six-membered ring, respectively, were tested as substrates in presence of the stannylated dienes **17**–**21**. The stannanes were prepared by a straightforward method developed by Lautens et al.[14] We describe herein a new cascade reaction based on three consecutive transformations starting from these two types of diol: An initial 4-*exo*-dig cyclocarbopalladation followed by a Stille cross-coupling reaction and finally a concerted conrotatory 8π electrocyclization allows the preparation of highly functionalized tetracyclic compounds. Three main types of product were obtained in this reaction, depending on the ring size of the substrate (Scheme 2). The first product type (**22**–**29**, Table 1) was generated from the cyclopentene diols **6a** or **6b** in a sequence of four reactions. The other two product types (**30**–**41**, Table 1) resulted from a cascade of three or five consecutive reactions starting from



Scheme 2. Access to the core skeleton of the ophiobolins and aleurodiscal. Ts = *p*-toluenesulfonyl.

Table 1: Synthesis of various 5,8,5- and 6,4,8,5-polycyclic systems.

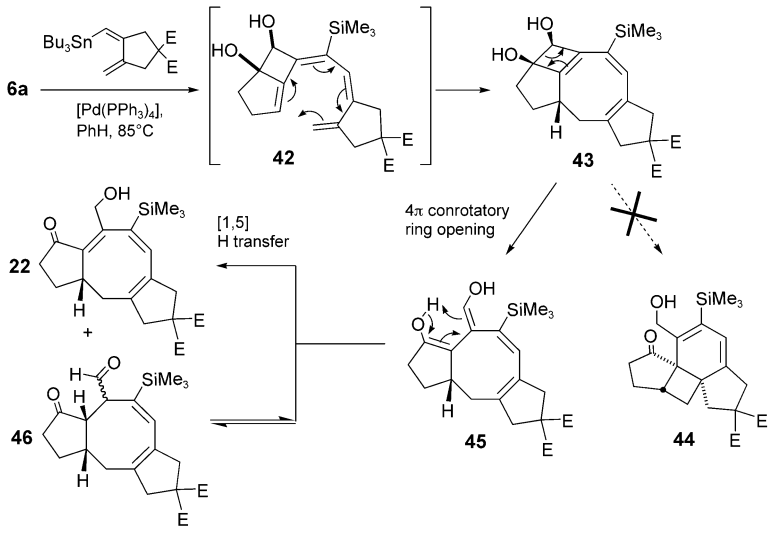


Entry	Starting diol	Products (yield [%])				
		(with **17**)	(with **18**)	(with **19**)	(with **20**)	(with **21**)
1	**6a**: R = $SiMe_3$	**22** (20)	–	**25** (16)	**27** (16)	**28** (24)
2	**6b**: R = $SiEt_3$	**23** (28)	**24** (21)	**26** (11)	–	**29** (10)
3	**7a**: R = $SiMe_3$	**30** (26)	**32**	**34** (15)	**36**	**40** (11)
4	**7b**: R = $SiEt_3$	**31** (21/35[a])	–	**35** (53)	**37**	**41** (37)
			+		+	
	7a: R = $SiMe_3$		**33**		**38**	
	7b: R = $SiEt_3$		–		**39**	
			32:**33** = 59:41 (61[b])		**36**:**38** = 48:52 (56[b])	
					37:**39** = 34:66 (41[b])	

[a] Reaction conducted in toluene as the solvent at 110 °C. [b] Combined yield.

the cyclohexene diols **7a** or **7b**. All reaction sequences proceeded in a one-pot operation without isolation of the intermediates.

This reaction cascade facilitates the expeditious preparation of 5,8,5-tricyclic structures of the ophiobolane family and new 6,4,8,5-tetracyclic structures, which include the ABC core of aleurodiscal. The polycyclic products are produced in just two steps from the readily available bromocyclopentenone **3** or bromocyclohexenone **4** (Scheme 1). To our knowledge, this is the shortest reported route to functionalized polycyclic structures of this type and degree of complexity.[11] The starting *anti* diols **6** and **7** were prepared on a large scale by the addition of a suitably protected metalated propargylic alcohol to **3** and **4**, respectively, followed by deprotection and chromatographic separation of the *anti* and *syn* diastereomers.[13a] When the diol **6a** was treated with the tributylstannyldiene **17** (X = $C(CO_2Et)_2$) in the presence of $[Pd(PPh_3)_4]$ (5 mol%) in benzene at 85 °C, an exclusively 4-*exo*-dig cyclocarbopalladation gave the bicyclic [4.2.0] product **42**, which could not be isolated, but underwent a rapid 8π electrocyclization to afford the tetracyclic derivative **43** in 16% yield after 2 h (Scheme 3). Pericyclic reactions of this type have few precedents in the synthesis of natural products.[15,16] One of the most well-known examples was described in the total synthesis of endiandric acids A and B by Nicolaou et al. in 1982.[15]



Scheme 3. Formation of the 5,8,5-tricyclic structure of the ophiobolane family.

The 1,3,5-cyclooctatriene **43** thus obtained did not undergo the usual subsequent 6π electrocyclization[17] to the corresponding tetracyclic diene **44**, because of the unlikely formation of this very strained spirocyclic diene. The stereospecificity of the conrotatory 8π electrocyclization allowed the synthesis of **43** as a single diastereomer. Each of the 1,3,5-cyclooctatrienes **30**–**41**, derived from the diols **7a** and **7b**, were also formed as a single diastereomer. Whereas the diols **7a** and **7b** reacted to give a stable 6,4,8,5-tetracyclic system, the initial products of the reactions of **6a** and **6b**, when heated for several hours, underwent opening of the cyclobutene ring to give the ketoallylic alcohol **22** and ketoaldehyde **46**. The formation of **22** and **46** can be explained by a 4π electrocyclic ring opening of **43** to the intermediate bis(enol) **45**, which can either undergo a 1,5-hydrogen shift to give **22** or tautomerization to its γ-ketoaldehyde form **46** (Scheme 3). At 85 °C the ketoaldehyde **46** undergoes thermal decomposition, and none of it was isolated after 6 h in the crude reaction mixture. The generality of this new expeditious process was explored by using several stereodefined cyclic stannanes (Table 1).

In two cases the yields of the 6,4,8,5-polycyclic systems were limited by the formation of furanyl derivatives, which probably result from a rearrangement of the corresponding cyclobutenediol. The yields observed (10–53 %) were modest to acceptable if the complexity of the new products formed in just one step from readily prepared diols is considered. The most efficient cascade process started from the diol **7b** (R = $SiEt_3$) and the dienyl stannane **19** and afforded the tetracycle **35** in 53 % yield. The exact influence of the silyl group on the reaction has not been yet clarified, as no clear trend was observed in the results (compare entries 1 and 2 with entries 3 and 4 of Table 1). The structures of all compounds were proposed based on ^{13}C and 2D ^{1}H NMR spectroscopy, including NOESY, COSY, HMQC, and HSQC experiments, and mass spectral analysis. Finally, these structures were unambiguously confirmed by X-ray crystal-structure analysis on two compounds,[18] the tetracycles **30** and **38** (Figure 1).

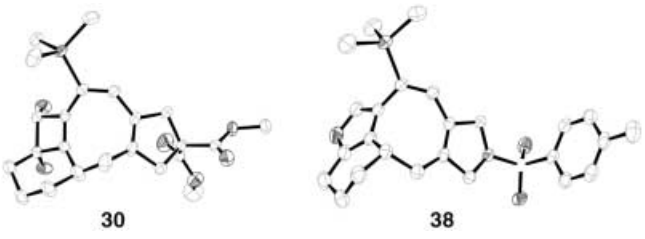


Figure 1. X-ray crystal structures of compounds **30** and **38**.

In conclusion, we have reported the direct synthesis of 5,8,5- and 6,4,8,5-polycyclic systems in one operation from readily prepared substrates. The modest yields observed are compensated by the structural complexity of the final products obtained and the limited number of steps in the reaction sequence. The strategy developed is based on a cascade reaction consisting of a 4-*exo*-dig cyclocarbopalladation, Stille cross-coupling reaction, and conrotatory 8π electrocyclization. To date, only rare examples of this pericyclic reaction for the direct formation of eight-membered rings have been described. Thus, we have shown that its potential as an efficient route to stable cyclooctatrienes should be reconsidered. Further extension of this chemistry to the rapid synthesis of compounds of biological importance is underway.

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Keywords: domino reactions · electrocyclic reactions · medium-ring compounds · polycycles · Stille reaction

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[18] Crystal data for **30**: $C_{23}H_{32}O_6Si$, $M_r = 432.59$, monoclinic, space group $P2/c$, $a = 19.1201(5)$, $b = 12.9474(4)$, $c = 21.2609(6)$ Å, $\beta = 116.360(5)°$, $V = 4716.0(2)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.22$ g cm^{-3}, $\mu = 0.134$ mm^{-1}, 10841 data (3161 reflections with $I > 3\sigma(I)$), $R = 0.055$, $wR = 0.065$, residual electron density maxima 0.47 e Å^{-3}. Crystal data for **38**: $C_{25}H_{31}NO_3SSi$, $M_r = 453.68$, orthorhombic, space group $Pbca$, $a = 8.0812(1)$, $b = 38.0184(2)$, $c = 15.5969(6)$ Å, $V = 4791.9(2)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.26$ g cm^{-3}, $m = 0.211$ mm^{-1}, 13493 data (3007 reflections with $I > 3\sigma(I)$), $R = 0.042$, $wR = 0.062$, residual electron density maxima 0.34 e Å^{-3}. Measurements were made on a Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromated, $\lambda = 0.71073$ Å). These structures were solved by using direct methods. After refinement of the non-hydrogen atoms, difference Fourier maps revealed maxima of residual electron density close to positions expected for hydrogen atoms. Hydrogen atoms were introduced as fixed contributors at calculated positions (C–H = 0.95 Å, B(H) = 1.3 Beqv(C)). All calculations were made by using the Nonius OpenMoleN package.[19] Neutral atom-scattering-factor coefficients and anomalous dispersion coefficients were taken from a standard source.[20] CCDC 228625 (**30**) and 228626 (**38**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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