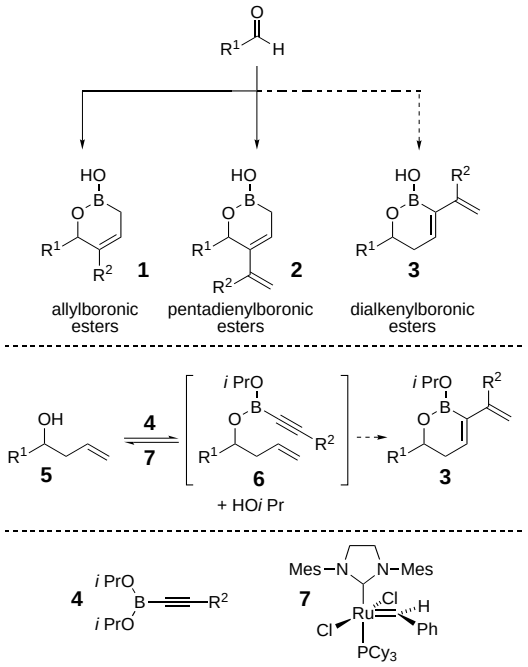
[11] T. J. Kidd, D. A. Leigh, A. J. Wilson, *J. Am. Chem. Soc.* **1999**, *121*, 1599.
[12] a) S. Wylie, D. H. Macartney, *J. Am. Chem. Soc.* **1992**, *114*, 3136; b) M. Fujita, F. Ibukuro, H. Seki, O. Kamo, M. Imanari, K. Ogura, *J. Am. Chem. Soc.* **1996**, *118*, 899.
[13] Crystal data for **4a***·6 H_2O ($C_{100}H_{100}F_{16}N_{12}O_{26}Pd_2$, $M_W = 2402.72$):[19] orthorhombic, *Pbcn*, $a = 37.176(3)$, $b = 15.2673(11)$, $c = 18.2484(13)$ Å, $V = 10357.5(13)$ Å^3, $T = 193$ K, $Z = 4$, $R = 0.0526$, $R_W = 0.1364$, GOF = 0.929. Catenane **4a*** was obtained by the reaction of an alkoxy-attached derivative ligand **1a*** with **2a** in D_2O.
[14] Very similar orientations were observed in optimized structures which follow annealing by molecular dynamics simulations. Thus, the chiral orientation is considered to be unaffected by crystal-packing effects.
[15] The chiral orientation was not observed by NMR spectroscopy, which indicates that two enantiomeric *P* and *M* forms rapidly interconvert in solution.
[16] A single crystal of (*R*,*R*)-**3c** was obtained by slow diffusion of diethyl ether into the DMF/MeOH solution. Crystal data for **3c**·1.5 dmf·0.5 MeOH ($C_{53}H_{50.5}F_8N_{7.5}O_8Pd$, $M_W = 1178.91$):[19] triclinic, *P*1, $a = 11.6595(14)$, $b = 12.0387(14)$, $c = 20.209(2)$ Å, $\alpha = 82.508(2)$, $\beta = 83.352(2)$, $\gamma = 68.841(2)°$, $V = 2615.5(5)$ Å^3, $T = 193$ K, $Z = 2$, $R = 0.0883$, $R_W = 0.2154$, GOF = 1.560.
[17] CD spectra of monomer ring (*R*,*R*)-**3c** and [2]catenane (*R*,*R*,*R*,*R*)-**4c** were measured in DMF (0.125 mM) and D_2O/[D_7]DMF 2:1 (0.056 mM), respectively, at 25.0 °C.
[18] The optical purity of the catenane has been not determined.
[19] CCDC-189501 (**3c**·1.5 dmf·0.5 MeOH), CCDC-189502 (**3a′**·2 H_2O), and CCDC-189503 (**4a***·6 H_2O) 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 CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

An Alkynylboronic Ester Annulation: Development of Synthetic Methods for Application to Diversity-Oriented Organic Synthesis**

Glenn C. Micalizio and Stuart L. Schreiber*

Dedicated to Professor William R. Roush

Diversity-oriented synthesis aims to prepare complex and diverse small molecules efficiently. These molecules can be used to explore biology—our goal is to be able to do so in a systematic way.[1] Whereas complex molecules can be synthesized efficiently using coupled complexity-generating reactions,[2] the goal of developing diversity-generating pathways yielding products with a high degree of skeletal diversity has not yet been realized. The development of synthetic pathways incorporating branch points holds promise as an effective route to skeletal diversity.[1] One such pathway, which diverges from common starting materials, aims to exploit the diverse reactivity of alkyl-, allyl-, pentadienyl-, alkenyl- and dialkenylboronic acids (Scheme 1).[3] This approach should enable the branching architecture of diversity-oriented synthesis pathways by using the diverse reactivity associated with these classes of reagents.[4]



Scheme 1. Development of branching reaction pathways for diversity-oriented organic synthesis; proposed alkynyl-boronic ester annulation. Mes = 2,4,6-trimethylphenyl, Cy = cyclohexyl.

Previously we reported annulation reactions of allylboronic esters with allylic and propargylic alcohols that stereospecifically provide allylboronic acids **1** and pentadienylboronic acids **2**.[3] Here we report new annulation reactions of electron-deficient alkynylboronic esters with homoallylic alcohols that provide functionalized dialkenylboronic acids **3**. In addition, we demonstrate oxidation and allene-forming hydroxyalkylation reactions of the resulting cyclic alkenyl boronic acids that further illustrate diversity-generating, branching reaction pathways.

Based on our earlier work on the allylboronic ester annulation,[3] we anticipated that the transesterification of an alkynylboronic ester **4** and a homoallylic alcohol **5** would afford a transient, mixed organoboronic ester **6** (Scheme 1), which could be trapped using ring-closing ene-yne metathesis to afford cyclic dialkenylboronic esters **3**. As expected, treatment of the homoallylic alcohol **8** with the *n*-propyl-substituted alkynylboronic ester **9** [5] and the Grubbs catalyst **7**[6] in benzene at 65 °C afforded the cyclic dialkenylboronic acid **12** in 69 % yield (Table 1, entry 1). The annulation

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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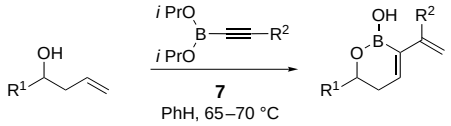
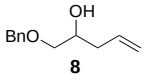
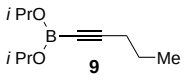
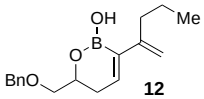
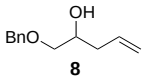
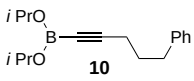
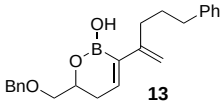
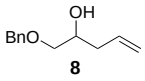
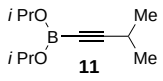
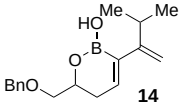
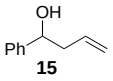
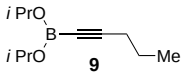
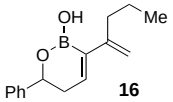
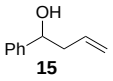
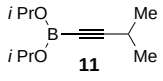
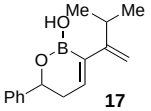
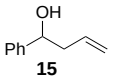
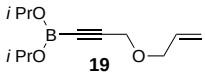
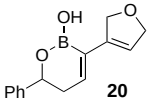
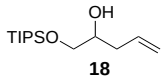
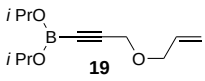
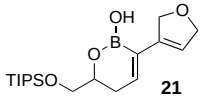
Table 1. Alkynylboronic ester annulation.



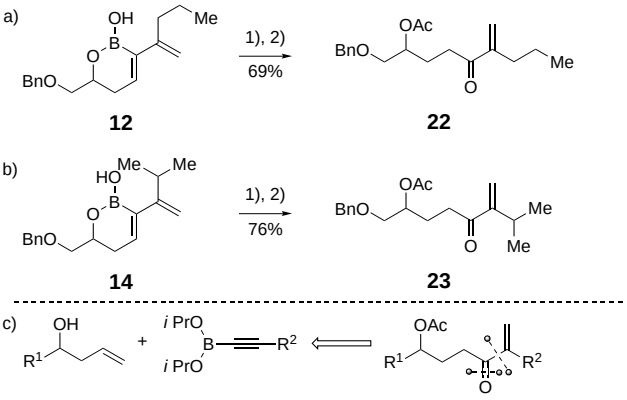
Entry	Substrate	Alkynylboronic ester	Annulation product	Yield [%]
1	 **8**	 **9**	 **12**	69
2	 **8**	 **10**	 **13**	66
3	 **8**	 **11**	 **14**	73
4	 **15**	 **9**	 **16**	72
5	 **15**	 **11**	 **17**	72
6	 **15**	 **19**	 **20**	66
7	 **18**	 **19**	 **21**	67

[a] TIPS = triisopropylsilyl.

reaction was similarly effective with the substituted alkynylboronic esters **10**[5] and **11**[5] (Table 1, entries 2 and 3).[7] Aromatic substitution on the homoallylic alcohol is tolerated in the reaction, as annulation with the benzylic homoallylic carbinol **15** provided the substituted dialkenylboronic acids **16** and **17** (Table 1, entries 4 and 5).

Coupling of the alkynylboronic ester annulation with an additional ring closing ene-yne metathesis[8] affords bicyclic dialkenylboronic acids. For example, annulation of the homoallylic alcohols **15** and **18** with the allyloxy-substituted alkynylboronic acid **19**[5] provides the bicyclic heterocycles **20** and **21** in 66% and 67% yield respectively (Table 1, entries 6 and 7).

We anticipated that oxidative cleavage of the dialkenylboronic acid products would provide a transient enol which, after tautomerization, would yield substituted enones.[9] As expected, oxidation of the cyclic dialkenylboronic acids **12** and **14** afforded the sensitive γ-hydroxy enones which, following acetylation afforded the γ-acetoxy enones **22** and **23** (Scheme 2a,b).[10] Overall, the two-step sequence of alkynylboronic ester annulation followed by oxidation represents a new convergent strategy for the transformation of homoallylic alcohols to functionalized enones (Scheme 2c).



Scheme 2. Manipulation of the cyclic vinylboronic acids via oxidation—acetylation. 1) H_2O_2, NaOH, THF; 2) Ac_2O, DMAP, Et_3N. DMAP = 4-dimethylaminopyridine. a) and b) show formation of specific functionalized enones, while c) is a retrosynthetic analysis of the product type.

The cyclic dialkenylboronic acids can be transformed efficiently into small molecules with completely different skeletons. For example, when the annulation products **14** and **16** are heated with trioxane they are converted into the trisubstituted allenes **24** and **25** ($\geq$78%; d.r. 4–6:1) (Sche-

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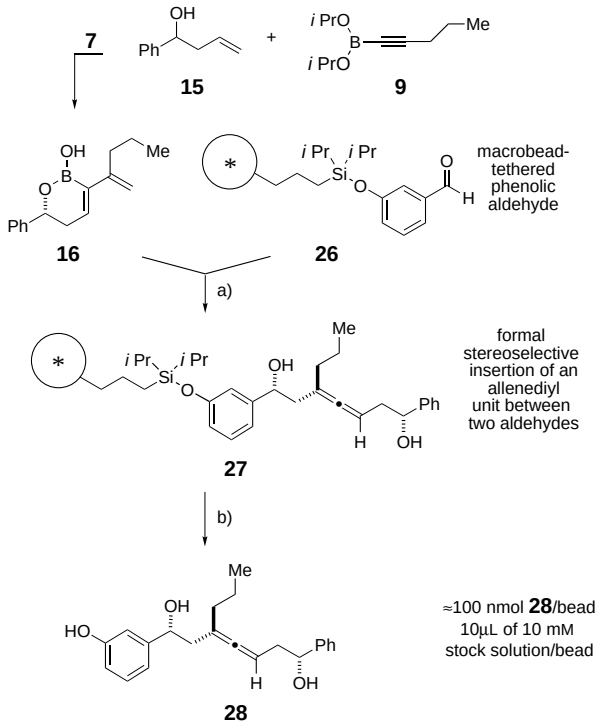
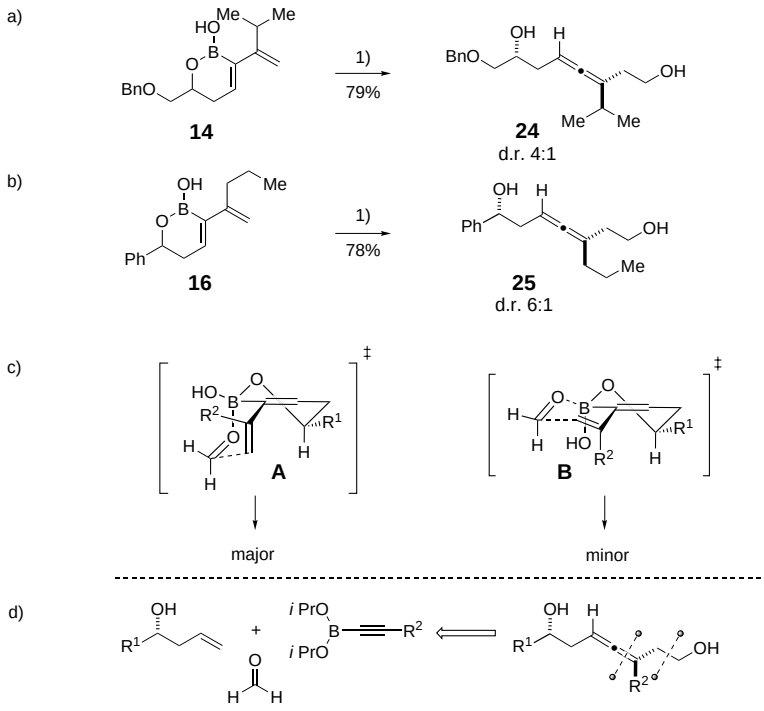
me 3a,b).[11,12] The major product observed in this allenylation process is consistent with reaction via the closed transition structure **A**.[13] We note that in the closed transition structure leading to the major product (**A**), the developing $\sigma_{B\text{-}O}$ bond is stabilized by two anomeric interactions, whereas in the closed transition structure **B** (leading to the minor diastereomer) the developing $\sigma_{B\text{-}O}$ bond is stabilized by a single anomeric interaction. The new allenylation reaction can be performed without purification of the intermediate cyclic dialkenylboronic acid. For example, following alkynylboronic ester annulation of homoallylic alcohol **15** and hydrolysis of the boronic acid with an aqueous wash, the resultant crude boronic acid **16** was hydroxymethylated to yield the trisubstituted allene **25** (see Scheme 3b, 56% yield, d.r. 6:1).[14] This two-step sequence (alkynylboronic ester annulation—allenylation) provides a new convergent approach to the diastereoselective synthesis of trisubstituted allenes from homoallylic alcohols (Scheme 3d).[15]

The allenylation reaction leading to **28**[16] was performed efficiently using phenolic aldehyde-loaded macrobeads (Scheme 4). This is an especially promising result as it demonstrates the feasibility of performing this chemistry on the high-capacity macrobead-linker reagent used in a one-bead, one-stock solution platform for chemical genetics.[17]

The goal of diversity-orientated synthesis is to synthesize complex and diverse small molecules efficiently. Herein, we have demonstrated the development of a new alkynylboronic ester annulation that provides mono- and bicyclic dialkenylboronic acids. Oxidation of the dialkenylboronic acid products provides a new route to functionalized enones, whereas treatment with trioxane promotes a novel and diastereoselective allene-forming reaction. Together with our previous study, we demonstrate the design of synthetic pathways that diverge from readily available aldehydes in just two steps and provide stereospecific access to allylboronic, pentadienylboronic, and dialkenylboronic acids. Exploiting the reactivity differences inherent to these classes of compounds provides access to saturated and unsaturated diols (including allenic diols), acyclic enones, and polycyclic heterocycles (Scheme 5).



Scheme 4. Allenylation reaction performed on the high capacity bead-linker reagent used in a one-bead, one-stock solution platform for chemical genetics. a) PhMe, 80°C; b) HF·pyr/pyr, THF.



Scheme 3. Allenylation reaction of cyclic boronic acids. a) Reaction conditions: 1) 1,3,5-trioxane, PhMe, 80°C; b) reaction conditions: 1) 1,3,5-trioxane, PhMe, 60°C; c) rationalization of d.r. obtained from proposed transition states; d) retrosynthetic analysis.

This study is indicative of many diversity-oriented synthesis pathways that are being driven by our knowledge of synthetic chemistry and yet that have not taken into account the range of anticipated molecular properties of the products. To address this shortcoming, we are integrating information science with this diversity-oriented synthesis network, first to populate multidimensional descriptor space ("chemical space") in a more targeted way. We ultimately hope to populate the chemical space which is likely to overlap effectively with the biological descriptor space most relevant to a given area of biological interest.[18] This future challenge aside, the reported studies already highlight several issues of relevance to synthetic chemistry. Consideration of the goals of diversity-oriented synthesis provides an intellectual framework for the development of novel synthetic methods. Investigations of diversity-oriented synthesis pathways provide opportunities to discover new patterns of reactivity in organic chemistry. We hope that the current study, together with our earlier report, specifically illustrates these

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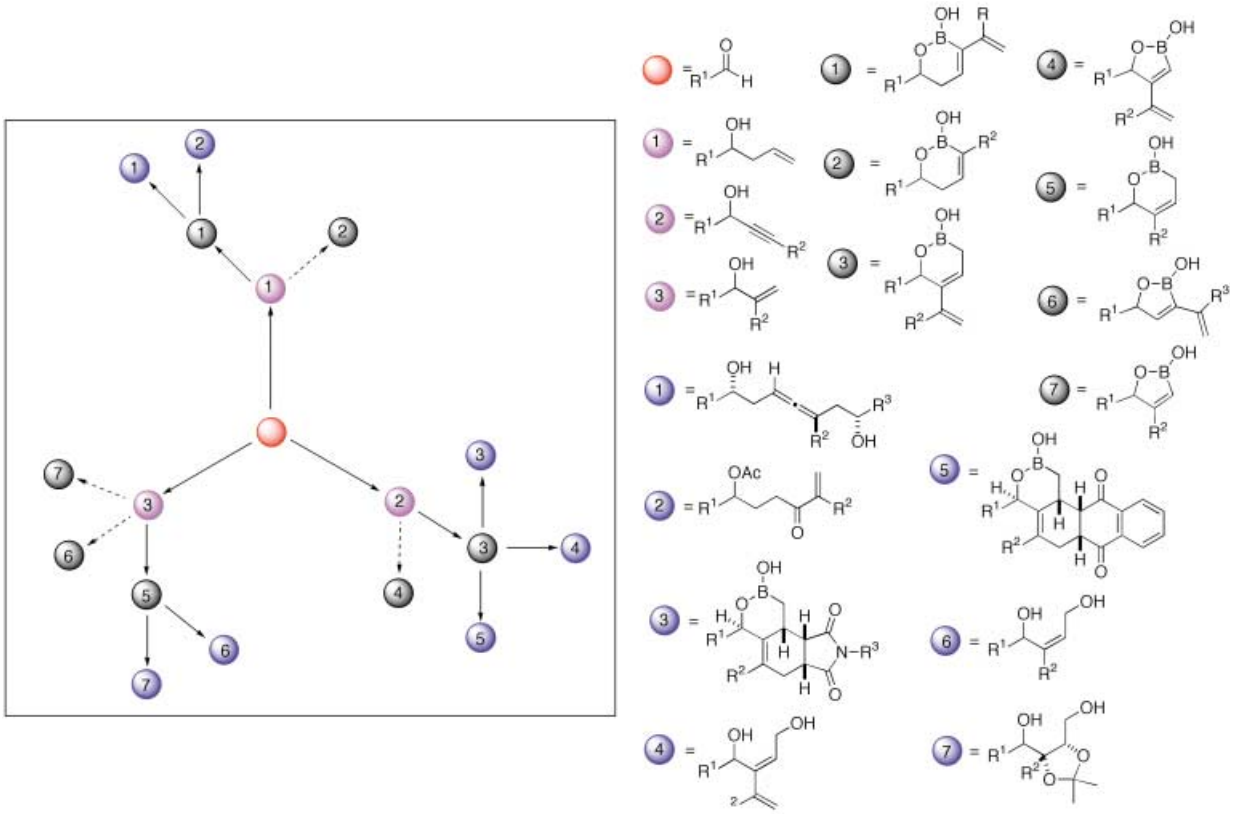

Scheme 5. Synthetic pathway incorporating a branched network of reactions based on the boronic ester annulation chemistry presented here and in our earlier report.[3]

points and generally illustrates the use of branched networks of reactions as a step toward realizing the goals of diversity-oriented synthesis in the context of chemical genetics (Scheme 5).

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[2] D. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, *2*, 709 – 712.

[3] G. C. Micalizio, S. L. Schreiber, *Angew. Chem.* **2002**, *114*, 160 – 162; *Angew. Chem. Int. Ed.* **2002**, *41*, 152 – 154.

[4] For a general review of organoboronic ester chemistry in organic synthesis, see a) D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**, p. 405; b) B. M. Mikhailov, Yu. N. Bubnov, *Organoboron Compounds in Organic Synthesis*, Harwood Academic, Chur, **1984**, p. 781.

[5] Prepared by addition of the alkynyl lithium to triisopropyl borate. See Supporting Information for details.

[6] For recent reviews of olefin metathesis, see a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413 – 4450; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140 – 3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043.

[7] The alkynylboronic ester derived from phenyl acetylene did not provide the annulation product with homoallylic alcohol **8** (**7**; 10 mol %, PhH, 70 °C).

[8] For an example of an intramolecular ene-yne metathesis of a pinacol-derived alkynylboronic ester see: J. Renaud, C.-D. Graf, L. Oberer, *Angew. Chem.* **2000**, *112*, 3231 – 3234; *Angew. Chem. Int. Ed.* **2000**, *39*, 3101 – 3104.

[9] For an alternative synthesis of functionalized enones employing a siloxyalkyne–alkene metathesis see: M. P. Schramm, D. S. Reddy, S. A. Kozmin, *Angew. Chem.* **2001**, *113*, 4404 – 4407; *Angew. Chem. Int. Ed.* **2001**, *40*, 4274 – 4277.

[10] The oxidation/acetylation sequence was not effective for the conversion of the bicyclic boronic acid **20** into the corresponding γ-acetoxy enone.

[11] For reviews concerning allene synthesis, see a) C. J. Elsevier in *Methods Org. Chem. (Houben-Weyl), 4th ed. 1952–, Vol. E21a*, **1995**, pp. 537 – 566; b) S. R. Landor, *The Chemistry of the Allenes*, Academic Press, New York, **1982**; c) H. Yamamoto in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**; p. 81 – 98. For allene synthesis via a 2-stannyl-1,3-butadiene, see d) C. Nativi, M. Taddei, *Tetrahedron* **1989**, *45*, 1131 – 1144; via propargylic boronic esters, see e) E. Favre, M. Gaudemar, *J. Organomet. Chem.* **1974**, *76*, 297 – 304; via propargylic boranes, see f) S. S. Nikam, K. K. Wang, *J. Org. Chem.* **1985**, *50*, 2193 – 2195; via propargylic silanes, see g) S. Kobayashi, K. Nishio, *J. Am. Chem. Soc.* **1995**, *117*, 6392 – 6393; h) J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1997**, *62*, 8976 – 8977; via an enyne-titanium alkoxide complex, see i) T. Hamada, R. Mizojiri, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **2000**, *122*, 7138 – 7139; via propargylic titanium alkoxide, see j) C. Schultz-Fademrecht, B. Wibbeling, R. Fröhlich, D. Hoppe, *Org. Lett.* **2001**, *3*, 1221 – 1224; via allenylstannanes, see k) J. A. Marshall, J. Perkins, *J. Org. Chem.* **1994**, *59*, 3509 – 3511; l) J. A. Marshall, R. H. Yu, J. F. Perkins, *J. Org. Chem.* **1995**, *60*, 5550 – 5555; via vinyl sulfoxides, see m) T. Satoh, Y. Kuramochi, Y. Inoue, *Tetrahedron Lett.* **1999**, *40*, 8815 – 8818; via sigmatropic rearrangements, see n) J. A. Marshall, X. Wang, *J. Org. Chem.* **1991**, *56*, 4913 – 4918; o) Y. Nishibayashi, J. D. Singh, S. Fukuzawa, S. Uemura, *J. Org. Chem.* **1995**, *60*, 4114 – 4120; p) R. J. D. Evans, S. R. Landor, J. P. Regan, *J. Chem. Soc. Chem. Commun.* **1965**, 397 – 398; q) K. Mori, T. Nukada, T. Ebata, *Tetrahedron*, **1981**, *37*, 1343 – 1347; r) A. G. Myers, B. Zheng, *J. Am. Chem. Soc.* **1996**, *118*, 4492 – 4493; s) G. A. Moniz, J. L. Wood, *J. Am. Chem. Soc.* **2001**, *123*, 5095 – 5097; via palladium-catalyzed alkylation, see t) M. Ogasawara, H. Ikeda, T. Nagano, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 2089 – 2090; u) Y. Imada, K. Ueno, K. Kutsuwa, S.-I. Murahashi, *Chem. Lett.* **2002**, 140 – 141; v) P. H. Dixneuf, T. Guyot, M. D. Ness, S. M. Roberts, *Chem. Commun.* **1997**, 2083 – 2084.

[12] The stereochemistry of the major product was determined by NOE analysis after Hg^{II}-promoted conversion of **25** into a dihydropyran; see Supporting Information for experimental details.

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[13] A closed transition state has been assumed in accord with the precedented reactivity patterns of allylboronic esters. For a review of the chemistry of allylboronic esters, see W. R. Roush In *Methods. Org. Chem. (Houben-Weyl), 4th ed. 1952–, Vol. E21b*, **1995**, pp. 1410 – 1486.
[14] See Supporting Information for experimental details.
[15] Preliminary results indicate that the allenylation reaction is also effective with aldehydes, as heating a solution of the cyclic vinylboronic acid **14** and α-triisopropylsilyloxy acetaldehyde in toluene at 60 °C provides the homologated trisubstituted allene (ca. 50 % yield, d.r. ca. 5:1:0:0).
[16] For the allene **28**, d.r. $\approx$3:1:0:0; the stereochemistry of the major diastereomer was assigned by analogy to **25**; transition state **A** (Scheme 3c) was used as a predictive model, with the aldehyde substituent placed in an equatorial position about the bicyclic transition structure.
[17] a) J. A. Tallarico, K. D. Depew, H. E. Pelish, N. J. Westwood, C. W. Lindsley, M. D. Shair, S. L. Schreiber, M. A. Foley, *J. Comb. Chem.* **2001**, *3*, 312 – 318; b) H. E. Blackwell, L. Pérez, R. A. Stavenger, J. A. Tallerico, E. Cope Etough, M. A. Foley, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1167 – 1182; c) P. A. Clemons, A. N. Koehler, B. K. Wagner, T. G. Sprigings, D. R. Spring, R. W. King, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1183 – 1195.
[18] P. Clemons, G. C. Micalizio, S. L. Schreiber, unpublished results.

The Total Synthesis of Coleophomones B and C**

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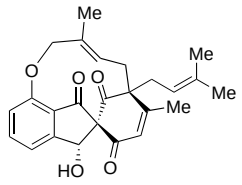
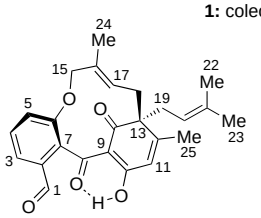
Dedicated to Professor Thomas J. Katz on the occasion of his 65th birthday

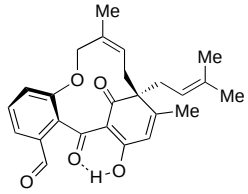
In 1998, a patent[1] from a group at Shionogi disclosed the structures and biological activity of three novel natural products, designated I-1 (**1**), I-2 (**2**), and I-3 (**3**), which had been isolated from a broth produced by the fungus *Stachybothys cylindrospora* RF-5900. Two of these compounds later re-emerged in the literature when a group at Merck discovered them in extracts from the fermentation of *Coleophoma* sp. fungi and named them coleophomones A (**1**) and B (**2**).[2] The biological profile of the coleophomone family includes



1: coleophomone A



2: coleophomone B



3: coleophomone C

antifungal activity,[1] inhibition of human heart chymase,[1,3] and antibiotic properties.[2] In addition, their unique molecular architectures are laden with unusual and challenging features: The strained and rigid framework of the coleophomones possesses a sensitive tricarbonyl moiety tethered into an 11-membered macrocycle whose strain is derived from the incorporation of a fused aryl ring and a highly unsaturated bridging six-membered carbocycle with the point of attachment being a quarternary carbon atom. Herein we report the total synthesis of coleophomones B (**2**) and C (**3**)[4] by a route that pushes the frontiers of the olefin metathesis reaction as a means to construct challenging molecular complexity.

Coleophomone A (**1**) is related to coleophomone B (**2**) by an aldol reaction that affords, from the latter, the unique spirocycle seen in the former. In view of the reported[2] interconversion of **1** and **2**, our approach to the coleophomone family initially focused on the total synthesis of **2** and **3**. These differ only in the configuration of the double bond ($\Delta^{16,17}$) that is *E* in **2** and *Z* in **3**. From all the possible retrosynthetic disconnections we therefore chose the one dissecting this double bond by the olefin metathesis reaction (Scheme 1). This disconnection, which led to the general precursor **I**, promised an exciting synthetic adventure because of the unprecedented nature of the challenge, made even more acute by the requirement to control the geometrical outcome of the projected ring-closing metathesis to deliver either isomer at will and the possible occurrence of atropisomers within the targeted frameworks. Our second major retrosynthetic disconnection operated on precursor **I** at the C8–C9 bond to generate the key building blocks **II** and **III**. This left the considerable hurdle of their union to be negotiated in the synthetic direction.

Scheme 2 summarizes the construction of the requisite aromatic building block **7**. The preference for the cyano group in **7** was based upon literature precedent regarding our subsequent intentions to effect preferential C-acylation over the usually more facile O-acylation in the coupling step,[5] while the *p*-bromobenzoate group was chosen as a protecting group to enhance the chances for crystalline derivatives to be obtained for X-ray crystallographic analysis purposes. Thus, beginning with commercially available 2,3-dimethyl phenol (**4**) and following a five-step literature procedure,[6] we arrived at hydroxy acetonide **5**, whose conversion to benzaldehyde

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