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A Concise Approach to the Polycyclic Scaffold of Frondosin D

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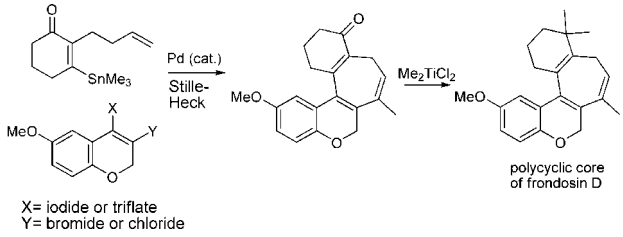

In a study directed at developing a concise approach to the polycyclic core of frondosin D, a Stille−Heck sequence has been identified that gives direct access to the trimethylbicyclo [5.4.0]undecane ring system common to all frondosins.

Frondosins A−E, **1**−**5** (Figure 1), are a family of related marine sesquiterpenoids first isolated in their *dextro*-rotatory form from the sponge *Dysidea frondosa*.[1a] Additionally, *levo*-rotatory frondosins A and D were isolated from an unidentified *Eurospongia* species.[1b] Frondosins A−E are compounds of interest due to their promising interleukin-8 (IL-8) affinity and protein kinase C inhibition.[1a] IL-8 antagonists are of particular interest in view of their antiinflammatory,[2a] anti-HIV,[1b,2b] and antitumor[2c−f] properties. To date, frondosins A, B, and C have been synthesized.[3] Notwithstanding these successes, the frondosins have proved quite a formidable synthetic challenge, and as of yet, there has been no synthesis of frondosin D or E. In this report, we describe our approaches to the molecular scaffold of frondosins D. This work has culminated in a very effective means of producing the trimethylbicyclo[5.4.0]undecane ring system common to all frondosins (shown in bold, Figure 1).

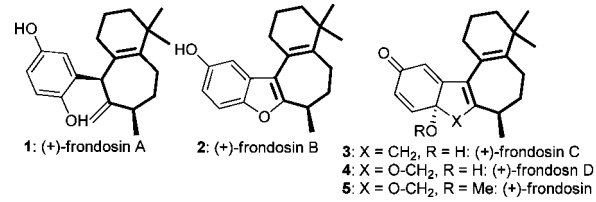

FIGURE 1. (+)-Frondosins A−E.[4]

Our retrosynthetic analysis of frondosin D focuses on accessing prochiral tetracycle **6** (Scheme 1), which could feasibly deliver frondosin D through a sequence of asymmetric double bond reduction,[5] phenylmethyl ether cleavage and oxidation.[3h] In this report, we will describe our assessment of different approaches to this key tetracycle **6**.

In our initial approach to **6**, we anticipated performing ring closing metathesis (RCM) on **7** similar to that used in our frondosin B synthesis (Scheme 1).[3e] We envisaged that chromene **7** could be accessed through Kumada−Corriu coupling of isopropenylmagnesium bromide with iodide **8**, which in turn could be formed by 1,6-*endodigonal* iodocyclization of **9**, which results from the 1,2-addition of lithium acetylide **11** to known ketone **10**,[6] followed by regioselective elimination of H_2O.[7]

A key step in our initially proposed access to frondosin D (**4**) is the 1,6-*endodigonal* iodocyclization of **9** to give **8**. At the time of conducting this work, such iodocyclizations to form 3-iodochromenes had not been reported and we undertook a brief model study to verify this key step (Scheme 2).[8] This work revealed that the sequence of 1,2-addition to give **12** (92%), followed by elimination of H_2O to give **13** (82%), albeit with a small amount of chloroallene **14** (11%) byproduct, could be readily acheived.[9] Iodocyclization of **13** was best achieved using I_2 in CH_3CN or THF with K_2CO_3 as base, affording the 1,6-*endodigonal* cyclization product, 2-iodochromene **14** in good yield (83%). However, we noted that success in this reaction was dependent on the use of anhydrous solvent, and that a specific byproduct was formed in wet solvents. This byproduct was determined to be the 1,5-*endodigonal* cyclization product **16**. This byproduct was formed as the exclusive product of the reaction when a solvent combination of THF/H_2O (99:1) was

(1) (a) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047–5060. (b) Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Nat. Prod. Lett* **1998**, *11*, 153–160.

(2) (a) Seitz, M.; DeWald, B.; Gerber, N.; Baggioni, M. *J. Clin. Invest.* **1991**, *87*, 463–469. (b) Lane, B. R.; Paul, K. L.; Block, J.; Andersson, J.; Coffey, M. J.; Strieter, R. M.; Markovitz, D. M. *J. Virol.* **2001**, *57*, 8195–8202. (c) Karashima, T.; Sweeney, P.; Kamat, A.; Huang, S.; Kim, S. J.; McConkey, D. J.; Dinney, C. P. *Clin. Cancer Res.* **2003**, *9*, 2786–2797. (d) Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer.* **2004**, *91*, 1970–1976. (e) Mian, B. M.; Dinney, C. P.; Bermejo, C. E.; Sweeney, P.; Tellez, C.; Yang, X. D.; Gudas, J. M.; McConkey, D. J.; Bar-Eli, M. *Clin. Cancer Res.* **2003**, *9*, 3167–3175. (f) Brat, D. J.; Bellail, A. C.; Van-Meir, E. G. *Neuro-oncol.* **2005**, *7*, 122–133.

(3) (a) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761–764. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878–1889. (c) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569–1572. (d) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675–9686. (e) Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457. (f) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133–1135. (g) Li, X.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, *8*, 5153. (h) Li, X.; Kyne, R. E.; Ovaska, T. V. *Tetrahedron* **2007**, *63*, 1899–1906. (i) Trost, B. M.; Hu, Y.; Horne, D. M. *J. Am. Chem. Soc.* **2007**, *129*, 11781–11790. (j) Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, *9*, 3837–3840.

(4) The absolute stereochemistry depicted for (+)-frondosins is tentatively depicted as β-methyl based on previous asymmetric synthesis efforts; see ref 3i and references cited therein.

(5) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.

(6) (a) Näf, F.; Decorzant, R. *Helv. Chim. Acta* **1974**, *57*, 1317. (b) Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.

(7) Knölker, H.-J.; Ecker, A.; Neef, G. *Tetrahedron* **1996**, *53*, 91–108.

(8) (a) Barluenga, J.; Trincado, M.; Marcos.Arias, M.; Ballestros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun.* **2005**, 2008–2010.

(9) Presumably, **14** is formed by S_N2' substitution of the intermediate sulfenate ester by a chloride ion. (a) Bhatia, Y. R.; Landor, P. D.; Landor, S. R. *J. Am. Chem. Soc.* **1959**, *81*, 24–29. (b) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273–281. (c) Soukup, M.; Widmer, E.; Lukáč, T. *Helv. Chim. Acta* **1990**, *73*, 868–873.

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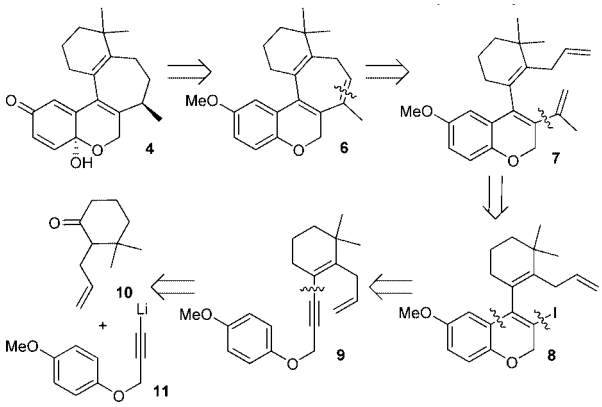
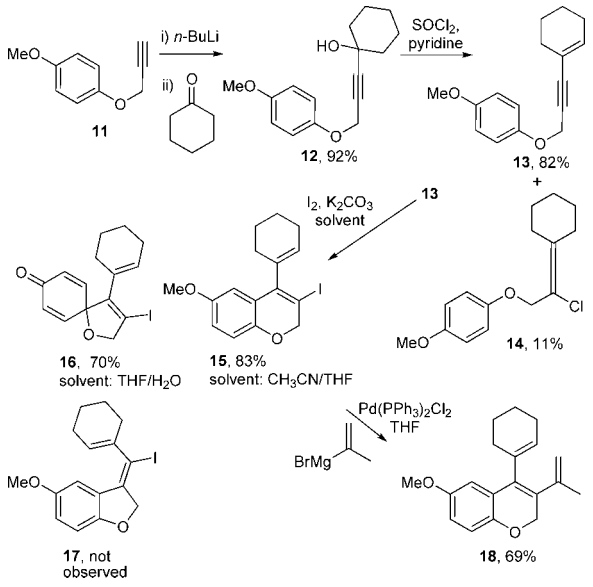
SCHEME 1. Retrosynthetic Analysis of Frondosin D



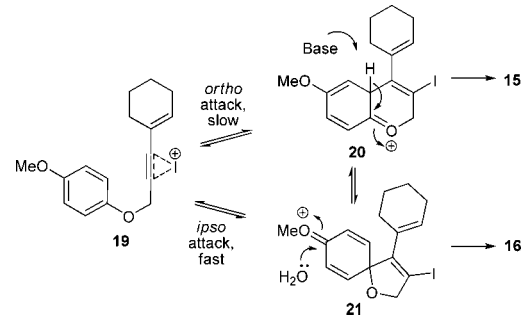
SCHEME 2. Model Iodocyclization and Coupling Study



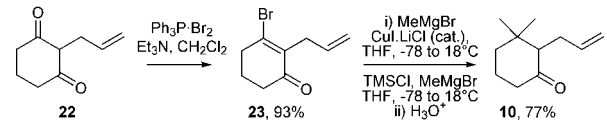
employed (70% isolated yield). At no time in this study did we detect any 1,5-*exocyclization* product **17**.

While the previous studies on 1,6-*endodigonal* iodocyclization to 2-iodochromenes did not report the formation of the 1,5-*endodigonal* product, some related cyclizations have been recently reported.[10] On the basis of these previous reports, connection of the alkyne through an electron-releasing ether group would be expected to direct nucleophilic attack of the activated alkyne through the *ortho* position of the phenyl ring in intermediate **19** to give **20** then **15** (Scheme 3). However, this *ortho*-directing effect of this ether tether appears to be overridden by the *para*-directing effect of the methoxy group, effectively giving an *ipso*-attack of the phenyl group upon the tethered alkyne, giving intermediate **21** in a 1,5-*endodigonal* cyclization. In the presence of water, **21** is "trapped", giving the spirocyclic product **16**.[10a] In the absence of water, the initially formed intermediate **21** funnels back through **19** to give the intermediate **20**, which undergoes irreversible proton elimination to give **15**. Alternatively, kinetically formed **21** migrates directly to **20** prior to trapping.

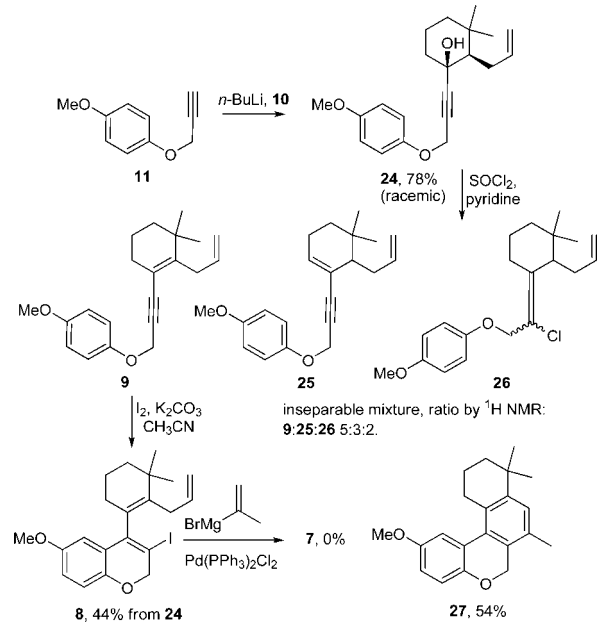
SCHEME 3. Mechanism of Formation of 15 and 16



SCHEME 4. Preparation of Cyclohexanone 10



SCHEME 5. Attempted Iodocyclization Pathway to 7



Kumada−Corriu coupling of **15** with isopropenylmagnesium bromide was successfully employed in giving **18** (69%) (Scheme 2).

On the basis of this successful access of **18**, we prepared cyclohexanone **10**, which bears the requisite substitution pattern for application to the synthesis of tetracycle **7** (Scheme 4). Compound **10** was accessed from dione **22** by initial conversion to **23**,[11] followed by a one-pot addition−elimination−addition sequence with methylcuprate, giving **10** in good yield (77%).

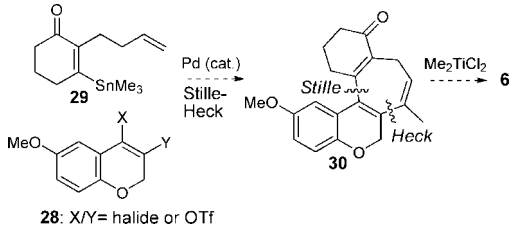
Unfortunately, application of **10** to the preparation of **7** was not successful (Scheme 5). Initial lithiation and 1,2-addition of alkyne **11** to cyclohexanone **10** proceeded well to give alcohol **24** as a single diastereomer (78%), but the elimination reaction gave an inseparable mixture of products **9**, **25**, and **26** (both diastereomers) in a 5:3:2 ratio by ^{1}H NMR.[12] Nonetheless,

(10) (a) Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47–53. (b) Barluenga, J.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Org. Lett.* **2007**, *9*, 2823–2826. (c) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231. (d) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468.

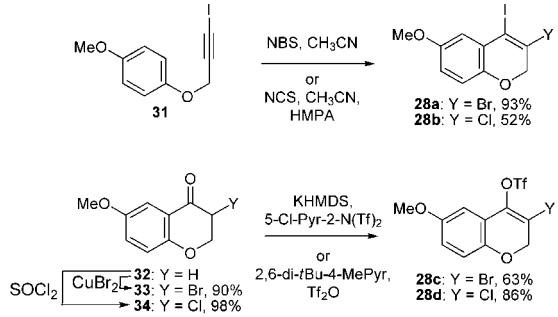
(11) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210–223.

(12) Investigation of alternative conditions included a reduction of temperature to−78 °C, which gave similar results, and the use of alternatives to SO_2Cl_2 such as $POCl_3$, TsCl, or Tf_2O led to worse outcomes.

SCHEME 6. Revised Approach to Frondosin D Core 6



SCHEME 7. Preparation of α,β-Diactivated Chromenes



treatment of the mixture with iodine gave 3-iodochromene **8** in 44% yield from **24**. Attempted Kumada−Corriu coupling of **8** with isopropenylmagnesium bromide did not yield the intended coupling product **7** but gave exclusive formation of **27**, which had resulted from an intermolecular 1,6-*exotrigonal* Heck cyclization of **8**.

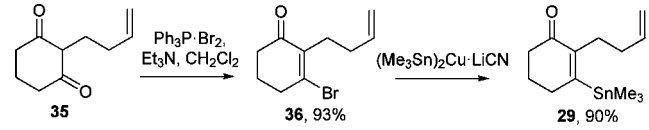
We revised our plan to take advantage of this facile Heck reaction and to avoid the requirement to prepare **9**. In the revised plan, an α,β-diactivated chromene **28** is employed in a reaction sequence involving a Stille then Heck reaction (Stille−Heck reaction) with **29** to give **30**, which is then *gem*-dimethylated to give **6** (Scheme 6).[13,14]

A considerable component of this work focused on selecting the correct arrangement of activating groups in **28**. The positioning of the functional groups, halide and triflate, in **28a−d** was based on the relative reactivity of these different groups with palladium(0) (usually I > OTf > Br ≫ Cl), such that a domino or stepwise Stille−Heck sequence with **29** will proceed with the correct regioselectivity to give **30**.

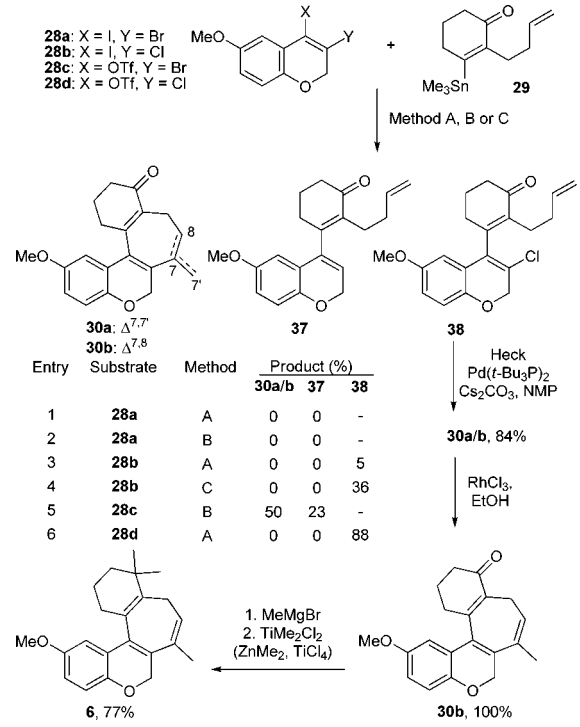
We prepared **28a** and **28b** by halocyclization of the iodoalkyne **31** using *N*-bromosuccinimde (NBS) and *N*-chlorosuccinimde (NCS), respectively (Scheme 7).[8] 1-Trifloxy-2-bromo/chlorochromenes **28c** and **28d** were both prepared from chromanone **32** by initial α-halogenation with $CuBr_2$ or SO_2Cl_2 giving **33** and **34**, respectively, followed by enoltriflation (Scheme 7).[15,16]

Stannylcyclohexenone **29** was prepared by a variation of the method previously developed by Piers et al. (Scheme 8).[17] 1,3-

SCHEME 8. Preparation of Stille−Heck Partner 29



SCHEME 9. Stille−Heck Outcomes



Entry	Substrate	Method	Product (%) 30a/b	37	38
1	**28a**	A	0	0	-
2	**28a**	B	0	0	-
3	**28b**	A	0	0	5
4	**28b**	C	0	0	36
5	**28c**	B	50	23	-
6	**28d**	A	0	0	88

Cyclohexanedione **35** was converted to bromoenone **36** (93%) and the bromo group substituted for a stannyl group using $(Me_3Sn)_2Cu\cdot LiCN$, giving **29** (90%).

We next turned to evaluating the proposed Stille−Heck sequence on the various α,β-diactivated chromene systems **28a−d** (Scheme 9). Our optimal method for performing Stille couplings involved $Pd(dba)_2$, tri-(2-furyl)phosphine (TFP), $ZnCl_2$, and copper(I) thiophenecarboxylate (CuTPC) in *N*-methylpyrrolidine (NMP) (Method A).[18,19] Also, for reactions where we anticipated that a subsequent Heck reaction may occur in situ, such as domino reaction of iodobromide **28a** or bromotriflate **28c**, we added the hindered base Cy_2NMe to ensure continual recycling of the catalyst (Method B).

In the case of the 1-iodo-2-bromochromene **28a**, the use of Method A or B led to rapid formation of a very complex reaction mixture with no discernible product formation. When the corresponding 1-iodo-2-chlorochromene **28b** was reacted with **29** using Method A, only a low yield of the coupled product **38** (<5%) was acheived. Attempted coupling of **28b** under slightly modified conditions using $Pd(PPh_3)_4$, LiCl, and CuTPC in NMP (Method C) returned a superior yet unsatisfying yield of **38** (36%). We did not further attempt to optimize coupling of either of iodochromenes **28a** or **28b** with **29** but focused instead on the more stable bromo- and chlorotriflates **28c** and **28d**. Using

(13) The use of doubly activated alkenes in sequential Stille−Heck processes has been previously reported by de Meijere and co-workers: (a) Sünnemann, H.-W.; de Meijere, A. *Angew. Chem., Int. Ed.* **2004**, *13*, 895–897. (b) Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521–1534. (c) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem.−Eur. J.* **2001**, *7*, 4035–4046.

(14) For related *gem*-dimethylations, see refs 3e and 3d.

(15) Dewald, H. A.; Heffner, T. G.; Jaen, J. C.; Lustgarten, D. M.; McPhail, A. T.; Meltzer, L. T.; Pugsley, T. A.; Wise, L. D. *J. Med. Chem.* **1990**, *33*, 445–450.

(16) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302. (b) Pal, K. *Synthesis* **1995**, 1485–1487.

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(18) (a) Farina, V.; Baker, S. R.; Sapino, C, Jr *Tetrahedron Lett.* **1988**, *29*, 6043–6046. (b) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243–4246. (c) Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.

(19) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

Method A, **28c** coupled to **29** in a domino Stille−Heck sequence to give **30** as a mixture of double bond isomers (**30a/b**) in a respectable yield (50%). Unfortunately, this material was contaminated by significant amounts of the bromo-reduced material **37** (23%), and it was not possible to separate these two products.

Using Method A with 2-chloroalkenyl triflate **28d**, we were able to achieve an excellent yield of the Stille product **38** (88%). Although alkenyl chlorides are not very reactive substrates for Heck reactions, by using $Pd^0(t\text{-}Bu_3P)_2$ as a catalyst, the 1,7-intramolecular Heck cyclization of **38** to **30a/b** (mixture of double bond isomers) was acheived in excellent yield (84%). This mixture was quantitatively converted to the thermodynamically most stable *endo*-isomer **30b** upon heating in anhydrous EtOH with catalytic $RhCl_3$.

Ketone **30b** was converted to *gem*-dimethylated tetracycle **6** using a variation of the Reetz conditions developed by Trauner and co-workers.[3c,d] This involves initial reaction of the ketone with MeMgBr to give a tertiary alchohol (not shown), followed by reaction with Me_2TiCl_2 to give **6** (77%), the structural framework of frondosins D and E (**4** and **5**, respectively).

Experimental Section

2-(But-3-enyl)-3-(3-chloro-6-methoxy-2*H*-chromen-4-yl)cyclohex-2-enone (38). $ZnCl_2$ (708 mg, 5.00 mmol) was flame dried carefully in a round-bottomed flask under vacuum and backfilled with N_2(g), then NMP (18 mL) was added, the reaction vessel was evacuated and backfilled with N_2(g), and 2-chloroalkenyl triflate **28d** (500 mg, 1.45 mmol), $Pd(dba)_2$ (83 mg, 0.145 mmol), TFP (68 mg, 0.29 mmol), CuTPC (28 mg, 0.147 mmol), and stannane **29** (654 mg, 2.03 mmol) were all added. The reaction mixture was heated to 55 °C in an oil bath under N_2(g). After 2.5 h, the starting materials were consumed (TLC analysis), the reaction was cooled to rt and poured onto a plug of alumina (neutral, Brockmann grade I), and the organics were washed through with Et_2O (100 mL). The organics were washed with H_2O (4 × 100 mL) and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Column chromatography of the brown crude on silica gel with EtOAc−PS (1:19 then 7:93) delivered chloride **38** (438 mg, 1.27 mmol, 88%) as a colorless viscous gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 8.7, 3.0 Hz, 1H), 6.45 (d, J = 3.0 Hz, 1H), 5.82−5.65 (m_c, 1H), 4.98−4.88 (m, 2H), 4.86 (d, J = 5.4 Hz, 2H), 3.78 (s, 3H), 2.65−2.55 (m, 1H), 2.59 (t, J = 6.9 Hz, 2H), 2.47−2.30 (m, 2H), 2.26−2.17 (m, 3H), 2.16−2.12 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.8 (C═O), 154.7 (C), 150.2 (C), 146.5 (C), 139.0 (C), 138.5 (CH), 132.0 (C), 121.6 (C), 121.4 (C), 116.8 (CH), 114.5 (CH_2), 114.0 (CH), 110.5 (CH), 68.7 (CH_2), 55.8 (CH_3), 38.3 (CH_2), 32.7 (CH_2), 29.9 (CH_2), 27.0 (CH_2), 22.7 (CH_2); IR (cm^{-1}) 1672; HRMS (ESI) calcd for $[C_{20}H_{22}ClO_3]^+$ ($M + H^+$) 345.1252, found 345.1244.

2-Methoxy-7-methyl-9,11,12,13-tetrahydro-6*H*-5-oxabenzo[6,7]cyclohepta[1,2-*a*]naphthalene-10-one (30b). Method A: (from alkenylchloride **38**) Cs_2CO_3 (1.25 g, 3.83 mmol) was flame dried in a Schlenk tube under vacuum and backfilled with N_2(g). NMP (7 mL) was added, and the stirring suspension was degassed [evacuated and backfilled with N_2(g)]. $Pd(t\text{-}Bu_3P)_2$ (355 mg, 0.70 mmol) was added and the suspension stirred at 85 °C for 0.2 h (catalyst dissolves), then alkenylchloride **38** (1.20 g, 3.48 mmol) was added, and the reaction was stirred for 2 h, after which time the starting material **38** was consumed by TLC. The reaction mixture was passed through a plug of alumina (neutral, Brockmann grade I) rinsing with Et_2O. The Et_2O filtrate was washed with H_2O (4 × 100 mL) and brine (50 mL) and dried with $MgSO_4$, and the volatiles were removed under reduced pressure to give a brown crude product. Column chromatography of the crude on silica gel with Et_2O−PS (9:41 then 11:39) delivered tetracycles **30a/b** (901 mg, 2.92 mmol, 84%) as a pale yellow gum.

$RhCl_3$ (3.7 mg, 5 mol %) was added to a stirred solution of tetracycles **30a/b** (57.0 mg, 0.185 mmol) in EtOH (4 mL) under N_2(g). The mixture was heated to 75 °C and stirred for 7 h, then cooled, poured into H_2O (30 mL), and extracted with Et_2O (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to deliver tetracycle **30b** (57.0 mg, 0.185 mmol, 100%) as a thick colorless gum which solidified upon standing at −20 °C. This compound was recrystallized from Et_2O−PS to pale-yellow square crystals: mp 119.5−121.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.7 Hz, 1H), 6.92 (dd, J = 8.7, 2.7 Hz, 1H), 6.59 (d, J = 2.7 Hz, 1H), 5.75 (dt, J = 7.2, 1.2 Hz, 1H), 5.07 (d, J = 14.4 Hz, 1H), 4.53 (d, J = 14.4 Hz, 1H), 3.78 (s, 3H), 3.60 (dd, J = 12.6, 8.1 Hz, 1H), 2.89 (m, 1H), 2.70−2.30 (m, 3H), 2.2−1.85 (m, 2H), 2.00 (s, 3H), 1.65 (dd, J = 12.6, 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.6 (C═O), 154.5 (C), 148.4 (C), 146.9 (C), 138.5 (C), 134.6 (C), 134.1 (C), 131.0 (C), 130.1 (CH), 124.5 (C), 117.1 (CH), 114.3 (CH), 113.2 (CH), 66.8 (CH_2), 55.8 (CH_3), 38.4 (CH_2), 29.7 (CH_2), 24.1 (CH_2), 23.7 (CH_2), 20.8 (CH_3); IR (cm^{-1}) 1671; LRMS (+ESI) calcd 308.9; HRMS (+ESI) calcd $[C_{20}H_{21}O_3]^+$ ($M + H^+$) 309.1485, found 309.1486.

Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all other compounds can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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