An efficient synthesis of (±)-frondosin B using a Stille–Heck reaction sequence†

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A concise, convergent synthesis of (±)-frondosin B has been developed based on the application of a Stille–Heck reaction sequence of 2-chloro-5-methoxybenzo[*b*]furan-3-yl triflate and 2-(3-butenyl)-3-(trimethylstannyl)cyclohex-2-enone giving the racemic natural product in a 34% overall yield.

Frondosins A–E, **1–5** (Fig. 1), are a family of related marine sesquiterpenoids isolated from the marine sponges *Dysidea frondosa* (**1–5**) and *Eurospongia* (**1** and **4**).[1] Interestingly, those isolated from *Dysidea frondosa* are in the *dextro*-rotary form and those from *Eurospongia* in the *levo*-rotatory form. 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 anti-inflammatory,[2a] anti-HIV,[1b,2b] and antitumor[2c–f] properties. The biological activities of the frondosins thus warrant further investigation and medicinal chemistry studies. While a number of syntheses of the frondosins have been reported,[3] they are either low yielding or lack the generality required for structure–activity relationship studies. Recently, we reported that the sequential Stille–Heck coupling of 2-bromo (or chloro)-alkenyl triflates **6** with alkenyl tethered vinylstannanes **7** (Stille–Heck acceptor) may provide a useful and modular method for obtaining carbocycles **8** (Scheme 1), including the bicyclo[5.4.0]undecane ring system that is common to all frondosins A–E.[5] Herein we report the application of this reaction to a high yielding, flexible approach to (±)-frondosin B.

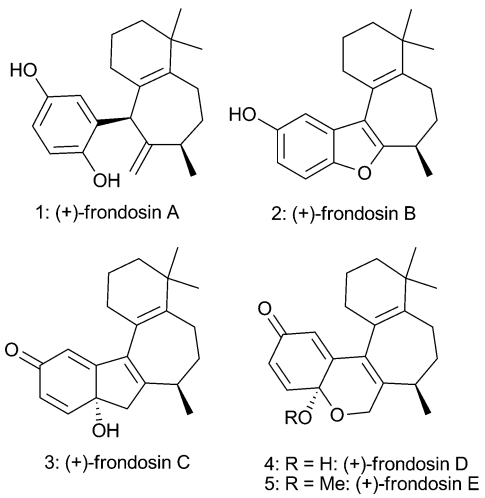
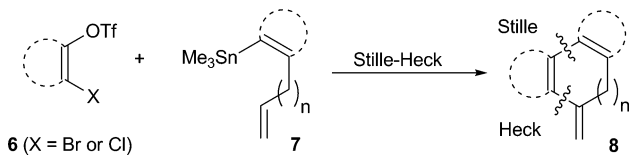
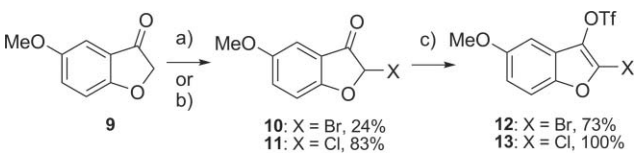


Fig. 1 (+)-Frondosins A–E.[4]



Scheme 1 Stille–Heck reaction.

The planned approach to frondosin B required the initial preparation of 2-halo-5-methoxybenzo[*b*]furan-3-yl-triflates, namely bromide **12** and chloride **13** (Scheme 2). Despite their potential utility in the synthesis of 2,3-disubstituted benzo[*b*]furans, there have been no prior reports on the preparation of 2-halo-benzo[*b*]furan-3-yl-triflates.[6] We envisaged that these potentially useful benzo[*b*]furan derivatives could be prepared by α-halogenation and enoltriflation of the corresponding benzo[*b*]furan-3-one. Accordingly, we sought to α-brominate and α-chlorinate commercially available 5-methoxybenzo[*b*]furan-3-one **9** using $CuBr_2$ and SO_2Cl_2, respectively (Scheme 2).[5] The best yield obtained for 2-bromo-5-methoxybenzo[*b*]furan-3-one **10** was 24% with competitive decomposition of **9** and dibromination being the key limiting factors. The corresponding 2-chloro-5-methoxybenzo[*b*]furan-3-one **11**, was obtained in a good yield (83%). Enol-triflation of **10** and **11** was readily achieved using triethylamine and triflic anhydride at low temperature giving **12** (73%) and **13** (quantitative), respectively, (Scheme 2).[6]



Scheme 2 Synthesis of 2-halobenzo[*b*]furan-3-yl triflates. Conditions: a) $CuBr_2$, EtOAc, $CHCl_3$; b) SO_2Cl_2, $CHCl_3$; c) Et_3N, Tf_2O, CH_2Cl_2, −78 °C to RT.

The Stille–Heck acceptor **14** was prepared from 1,3-dimethoxybenzene in four steps as previously described (Scheme 3).[5a] Reaction of the 2-bromo-5-methoxybenzo[*b*]furan-1-yl triflate **12** with **14** under our previously developed domino Stille–Heck reaction conditions, involving $Pd(dba)_2$, tri-(2-furyl)phosphine (TFP), $ZnCl_2$ and copper(I) thiophenecarboxylate (CuTC) in *N*-methylpyrrolidine (NMP),[5] gave the two

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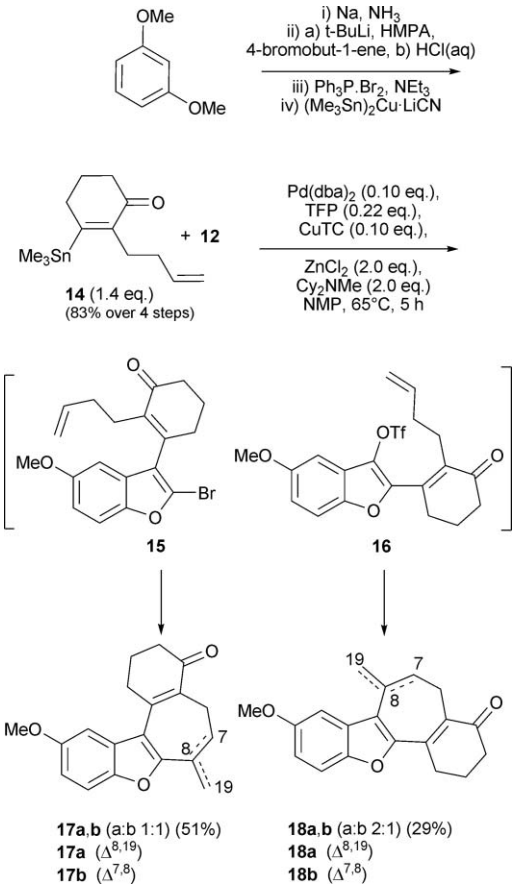
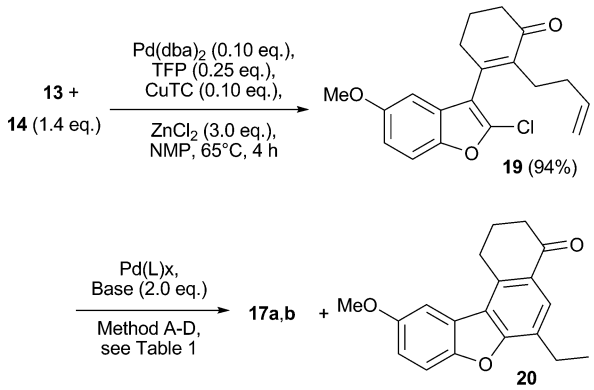


Scheme 3 Domino Stille–Heck reaction of triflate **12** and stannane **14**.

regioisomers **17** (51%) and **18** (29%), which could be separated by chromatography, but were each isolated as a mixture of inseparable double-bond isomers **a** and **b**. The two regiosiomers **17** and **18** appear to have resulted from competitive oxidative insertion of the palladium(0) catalyst into the *C3*-OTf and *C2*-Br bonds, giving initially the two Stille intermediates **15** and **16** (not isolated), respectively. This is opposed to the previous examples of regioselective Stille–Heck reaction processes involving 2-bromoalkenyl triflates,[5] which show highly selective reaction initially at the triflate. Presumably, the increased reactivity of the bromide in a 2-bromobenzo[*b*]furan reduces this regioselectivity.

When the 2-chloro-5-methoxybenzo[*b*]furan-1-yl triflate **13** and **14** were subjected to the same reaction conditions as used above for the domino Stille–Heck, only the Stille reaction was observed, which proceeded entirely through the triflate moiety to give **19** in an excellent yield (94%, Scheme 4). As with other 2-chloroalkenyl triflates under these conditions,[5] the reaction stopped after the Stille coupling and further heating did not lead to any intramolecular-Heck product. In other systems, we had been successful in achieving intramolecular-Heck reactions of alkenyl chlorides in an efficient manner with Pd(*t*-$Bu_3P)_2$ and Cs_2CO_3 in NMP at 85 °C,[5] however, when applied to **19** this only gave a low yield of **17a**,**b** (31%) (**a** : **b** 1 : 1) and returned mostly starting material (Method A, Table 1). Increasing the reaction time did not improve the outcome (not shown) and the low conversion of substrate was attributed to competitive decomposition of the catalyst. Interestingly, the use of microwave irradiation (MWI)



Scheme 4 Two step Stille–Heck reaction of **13** and **14**.

altered the outcome substantially (Method B, Table 1).[7] The extent of the Heck reaction was considerable, with all of the starting material converted to Heck cyclised products **17a**,**b** (41%) and **20** (59%).

Heck product **20** presumably arises from initial migration of the terminal olefin (internalisation), followed by 1,6-Heck reaction and aromatization. One possible explanation is that the thermally induced burst of catalytic activity generated under MWI may in turn lead to a rapid accumulation of HPdCl(*t*-$Bu_3P)_2$, which results from the *β*-hydride elimination step in the catalytic cycle and that this Pd(II) species catalyses double-bond isomerism at a faster rate than the biphasic, base (Cs_2CO_3) mediated reductive elimination of HCl from the catalyst.[8] Accordingly, the homogeneous base dicyclohexylmethylamine was used to replace the heterogeneous base Cs_2CO_3 in order to increase the rate of catalyst regeneration (Method C, Table 1). While these conditions had the desired effect of reducing the amount of 1,6-Heck product **20** (not observed), the overall reaction was less efficient, giving a modest yield of **17a**,**b** (13%) and starting material **19** (87%).

Based on recent reports on the use of 2′,4′,6′-diisopropyl-1,1′-biphenyl-2-yldicyclohexylphosphine (X-Phos, Fig. 2) in promoting the intramolecular arylation of aryl bromides and in the intermolecular Heck reaction of arylchlorides we utilised this ligand and MWI in the intramolecular Heck reaction of **19** and obtained an excellent yield of **17a**,**b** (83%, **a** : **b** 9 : 1) (Table 1, Method D).[9] In this case, double-bond isomerism in **19** and subsequent cyclisation to give **20** was avoided. Possibly the acetate anions, introduced as the pre-catalyst $Pd(OAc)_2$, may have provided sufficient basicity to prevent accumulation of HPdCl(*t*$Bu_3P)_2$, effectively acting as a phase-transfer catalyst for K_2CO_3.

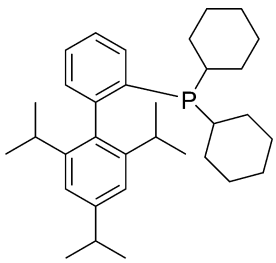


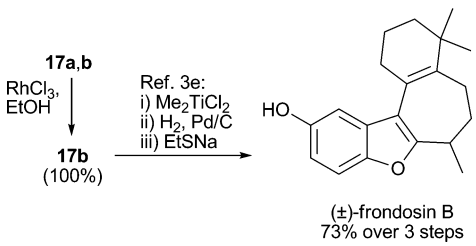
Fig. 2 X-Phos.

Table 1 Intermolecular Heck reaction of chloride **19** (Scheme 4)

Method	Catalyst, Base, Solvent	Heating Method/°C	Time/h	Product (Yield%)
A	Pd(*t*-$Bu_3P)_2$, [a] Cs_2CO_3, NMP	Bath (85)[c]	6	**17a,b** (31) **19** (69)
B	Pd(*t*-$Bu_3P)_2$, [a] Cs_2CO_3, NMP	MWI (85)[d]	1	**17a,b** (41) **20** (59)
C	Pd(*t*-$Bu_3P)_2$, [a] Cy_2NMe, NMP,	MWI (85)[d]	1	**17a,b** (13) **19** (87)
D	Pd(X-Phos)$_2$, [b] K_2CO_3, DMA	MWI (100)[d]	0.5	**17a,b** (83)

[a] Preformed catalyst (0.2 eq.). [b] Catalyst formed *in situ* by addition of $Pd(OAc)_2$ (0.10 equiv.) and X-Phos (0.20 eq.) to reaction mixture. [c] External mercury thermometer in oil bath. [d] Internal infrared thermometer.

Mixtures of double-bond isomers **17a**,**b** were quantitatively converted to the thermodynamically more stable internal double-bond isomer, **17b**, upon reaction with $RhCl_3$ in ethanol (Scheme 5).[5a] Tetracycle **17b** is a common intermediate with our previously described total synthesis of (±)-frondosin B.[3e] It is converted into (±)-frondosin B through a sequence of *gem*-dimethylation of the ketone (Me_2TiCl_2), chemoselective hydrogenation of the $\Delta^{7,8}$ double-bond and cleavage of the methylphenyl ether. In its longest linear sequence, 9 steps from 1,3-dimethoxybenzene, this synthesis gives frondosin B in an overall 34% yield and 47% yield (8 steps) from commercially available **9**.



Scheme 5 Formal synthesis of (±)-frondosin B.

In conclusion, an efficient synthesis of (±)-frondosin B has been achieved that utilises functional-group tolerant Stille and Heck reaction protocols as key steps, providing an excellent opportunity to explore different substituents and ring sizes in SAR studies of the frondosins. The capacity to access both double isomers, **17a** and **17b**, in this synthesis will improve our chances of achieving an enantioselective hydrogenation using chiral catalysts, which is currently under investigation. Furthermore, the preparation of the 2-chlorobenzo[*b*]furan-1-yl triflates and the selective substitution of its OTf and Cl moieties using palladium catalysis is likely to have broad applicability in the preparation of other 2,3-disubstituted benzo[*b*]furans. In particular, the combination of MWI and X-Phos ligands in promoting palladium mediated reactions of aryl/alkenyl chlorides is also likely to find broader applicability.

Notes and references

1 (*a*) A. D. Patil, A. J. Freyer, L. Killmer, P. Offen, B. Carte, A. J. Jurewicz and R. K. Johnson, *Tetrahedron*, 1997, **53**, 5047–5060; (*b*) Y. F. Hallock, J. H. Cardellina II and M. R. Boyd, *Nat. Prod. Lett.*, 1998, **11**, 153–160.
2 (*a*) M. Seitz, B. DeWald, N. Gerber and M. Baggioni, *J. Clin. Invest.*, 1991, **87**, 463–469; (*b*) B. R. Lane, K. L. Paul, J. Block, J. Andersson, M. J. Coffey, R. M. Strieter and D. M. Markovitz, *J. Virol.*, 2001, **75**, 8195–8202; (*c*) T. Karashima, P. Sweeney, A. Kamat, S. Huang, S. J. Kim, M. Bar-Eli, D. J. McConkey and C. P. Dinney, *Clin. Cancer Res.*, 2003, **9**, 2786–2797; (*d*) Y. M. Zhu, S. J. Webster, D. Flower and P. J. Woll, *Br. J. Cancer*, 2004, **91**, 1970–1976; (*e*) B. M. Mian, C. P. Dinney, C. E. Bermejo, P. Sweeney, C. Tellez, X. D. Yang, J. M. Gudas, D. J. McConkey and M. Bar-Eli, *Clin. Cancer Res.*, 2003, **9**, 3167–3175; (*f*) D. J. Brat, A. C. Bellail and E. G. Van-Meir, *Neuro-Oncology*, 2005, **7**, 122–133.
3 (*a*) M. Inoue, A. J. Frontier and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2000, **39**, 761–764; (*b*) M. Inoue, M. W. Carson, A. J. Frontier and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 1878–1889; (*c*) C. C. Hughes and D. Trauner, *Angew. Chem., Int. Ed.*, 2002, **41**, 1569–1572; (*d*) C. C. Hughes and D. Trauner, *Tetrahedron*, 2004, **60**, 9675–9686; (*e*) D. J. Kerr, A. C. Willis and B. L. Flynn, *Org. Lett.*, 2004, **6**, 457; (*f*) I. Martínez, P. E. Alford and T. V. Ovaska, *Org. Lett.*, 2005, **7**, 1133–1135; (*g*) X. Li, R. E. Kyne and T. V. Ovaska, *Org. Lett.*, 2006, **8**, 5153; (*h*) X. Li, R. E. Kyne and T. V. Ovaska, *Tetrahedron*, 2007, **63**, 1899–1906; (*i*) B. M. Trost, Y. Hu and D. M. Horne, *J. Am. Chem. Soc.*, 2007, **129**, 11781–11790; (*j*) X. Li and T. V. Ovaska, *Org. Lett.*, 2007, **9**, 3837–3840; (*k*) G. Mehta and N. S. Likhite, *Tetrahedron Lett.*, 2008, **49**, 7113–7116.
4 The absolute stereochemistry depicted for (+)-frondosins is tentatively depicted as (*S*)- based on previous asymmetric synthesis efforts, see ref. 3*i*,*j* and references cited therein.
5 (*a*) K.-S. Masters and B. L. Flynn, *J. Org. Chem.*, 2008, **73**, 8081–8084; (*b*) K.-S. Masters and B. L. Flynn, *Adv. Synth. Catal.*, 2009, **351**, 530–536.
6 For a previous report of benzo[*b*]furan-3-yl-triflates see: C. Morice, F. Garrido, A. Mann and J. Suffert, *Synlett*, 2002, 501–503.
7 For previous reports on the application of MWI to Heck reactions see: (*a*) G. K. Datta, K. S. A. Vallin and M. Larhed, *Mol. Diversity*, 2003, **7**, 107; (*b*) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2002, **124**, 14127; (*c*) K. Dahlén, E. A. A. Wallén, M. Grøtli and K. Luthman, *J. Org. Chem.*, 2006, **71**, 6863.
8 Fu has previously described accumulation of HPdCl(*t*-$Bu_3P)_2$ in the Heck reaction of alkenyl chlorides with Cs_2CO_3 where the Pd-hydride becomes the resting-state in the catalytic cycle; (*a*) I. D. Hills and G. C. Fu, *J. Am. Chem. Soc.*, 2004, **126**, 13178–9; (*b*) A. F. Littke and G. C. Fu, *J. Org. Chem.*, 1999, **64**, 10–11.
9 (*a*) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; (*b*) J.-P. Ebran, H. L. Hansen, T. M. Ggsig and T. Skrydstrup, *J. Am. Chem. Soc.*, 2007, **129**, 6931.

