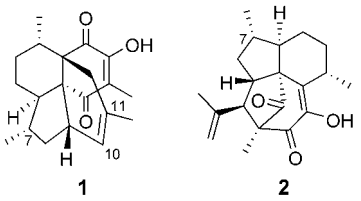
Natural Product Synthesis

Total Synthesis of (−)-Colombiasin A and (−)-Elisapterosin B**

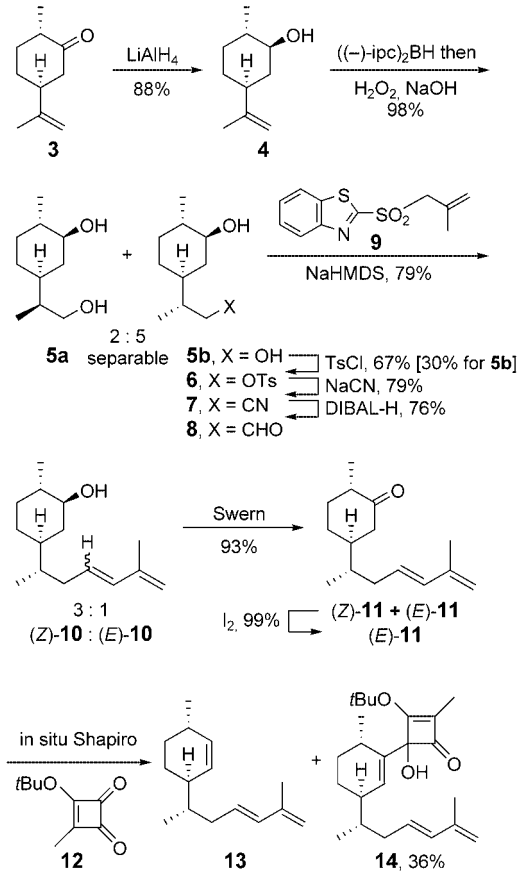
David C. Harrowven, David D. Pascoe, Daniela Demurtas, and Heather O. Bourne*

Colombiasin A (**1**) and elisapterosin B (**2**) are recent additions to the family of diterpenes from the gorgonian octacoral *Pseudopterogorgia elisabethae*.[1,2] Discovered by Rodriguez et al., their unusual molecular architecture soon attracted attention from the natural products community.[3] Initially, colombiasin A proved the more popular target,[4] with total syntheses being reported firstly by Nicolaou et al.[5] and then by Kim and Rychnovsky.[6] The latter report also describes the first total synthesis of (−)-elisapterosin B, a compound that exhibits strong antiplasmodial activity against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria.[3] A synthesis of (+)-elisapterosin B by Rawal et al. followed soon after.[7] Herein we describe total syntheses of both (−)-colombiasin A (**1**) and (−)-elisapterosin B (**2**)



in which a Moore rearrangement[8] of vinylcyclobutene **14** is used to set up intramolecular [4+2][4–6] and [5+2][7,9] cycloaddition reactions leading to the target compounds.

Our synthesis of **14** (Scheme 1) began with (−)-dihydrocarvone (**3**), which was reduced to alcohol **4** using $LiAlH_4$. Hydroboration with $((-)\text{-ipc})_2BH$,[10] followed by oxidative work-up gave diols **5** as a 5:2 mixture of diastereomers. These were separated by a combination of column chromatography and fractional crystallization. Sequential monotosylation to **6**, cyanide displacement to nitrile **7**, and DIBAL-H reduction to aldehyde **8** then allowed us to introduce the diene function by means of a Julia reaction with **9**.[11] Higher yields were obtained using the Kocienski modification,[12] these conditions giving **10** as a 3:1 mixture of *Z* and *E* isomers in 79% yield. Swern oxidation followed, and the resulting mixture of



Scheme 1. Synthesis of intermediate **14**; ipc = 2,6,6-trimethylbicyclo[3.1.1]hept-3-yl, NaHMDS = sodium hexamethyldisilazane, Ts = *p*-toluenesulfonyl, DIBAL-H = diisobutylaluminum hydride.

Z and *E* dienones **11** was equilibrated to (*E*)-**11** in near quantitative yield with catalytic iodine.

The next step, a Shapiro reaction between dienone (*E*)-**11** and squarate **12**,[13] proved troublesome.[14] Though the tosylhydrazone of (*E*)-**11** was readily formed and isolated, it gave triene **13** as the major product on treatment with butyllithium and addition of squarate **12**. By contrast, all attempts to prepare and isolate the corresponding trisylhydrazone (trisyl = triisopropylbenzenesulfonyl), either directly or indirectly,[15] met with failure. Monitoring the reaction by NMR spectroscopy showed that the formation of the trisylhydrazone was facile at room temperature in $CDCl_3$, and that it subsequently decomposed on prolonged standing. Consequently, an in situ variant of the Shapiro reaction was developed (Scheme 1). Trisylhydrazine and (*E*)-**11** in THF were first stirred at ambient temperature for 2 h before the reaction mixture was cooled to −78 °C. Four equivalents of *n*BuLi were then added and the temperature raised to −20 °C. At this juncture squarate **12** was added, giving vinylcyclobutene **14** in 36% yield.

The stage was now set for a Moore rearrangement of **14** to hydroquinone **16**,[8] a reaction that proceeded smoothly at 110 °C in THF under microwave irradiation (Scheme 2). After cooling to ambient temperature and stirring in air, quinone **18** was isolated in a satisfying 80% yield. Heating a toluene solution of **18** in the dark at 150 °C, either conven-

[*] Dr. D. C. Harrowven, D. D. Pascoe, D. Demurtas, Dr. H. O. Bourne
School of Chemistry
University of Southampton
Highfield, Southampton, SO171BJ (UK)
Fax: (+44) 2380-596-805
E-mail: dch2@soton.ac.uk

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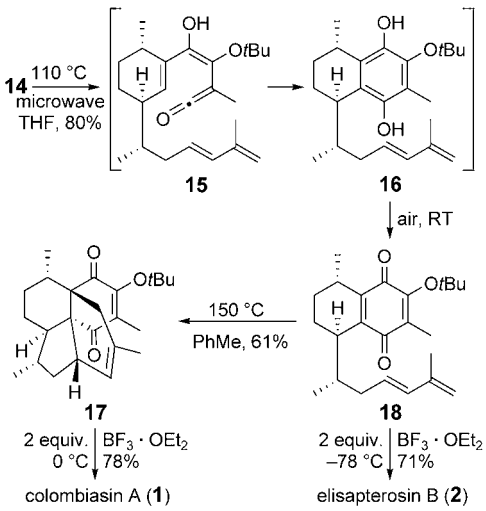

Scheme 2. Total syntheses of (−)-colombiasin A (**1**) and (−)-elisapterosin B (**2**) starting with **14**.

tionally or in the microwave oven, induced an intramolecular Diels–Alder cycloaddition to (−)-colombiasin A *tert*-butyl ether **17**.[4–6] Attempts to effect removal of the protective group with $TiCl_4$ succeeded in that task,[16] but also led to Markovnikov addition of HCl across the sensitive C10–C11 double bond.[5] Deprotection with diethyl ether–trifluoroborane however, proceeded cleanly to complete a total synthesis of (−)-colombiasin A (**1**). Notably, exposing quinone **18** to diethyl ether–trifluoroborane induced both deprotection of the *tert*-butyl ether and an intramolecular [5+2] cycloaddition to give (−)-elisapterosin B (**2**);[6] our synthetic samples of **1** and **2** exhibit physical and spectral characteristics identical to those reported for the natural products.[1,2]

In conclusion, stereocontrolled syntheses of (−)-colombiasin A (**1**) and (−)-elisapterosin B (**2**) have been achieved, in twelve and eleven steps respectively from (−)-dihydrocarvone (**3**). The problematic C7 stereocenter was established by hydroboration with $((-)\text{-ipc})_2BH$, and the use of a *tert*-butyl protective group ensured that deprotection could be accomplished in high yield without disruption of the sensitive C10–C11 double bond.[5] A distinctive feature of our approach is the use of a Moore rearrangement to set up intramolecular [4+2] and [5+2] cycloaddition reactions, leading to (−)-colombiasin A (**1**) and (−)-elisapterosin B (**2**) respectively. Studies are underway to further develop and improve the in situ Shapiro reaction and to apply the "reagent-free" rearrangement sequence in syntheses of related natural products such as elisapterosins A and D.[2,3,17]

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