Synthesis of (–)-Hennoxazole A: Integrating Batch and Flow Chemistry Methods

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Received: 11.12.2012; Accepted: 30.12.2012

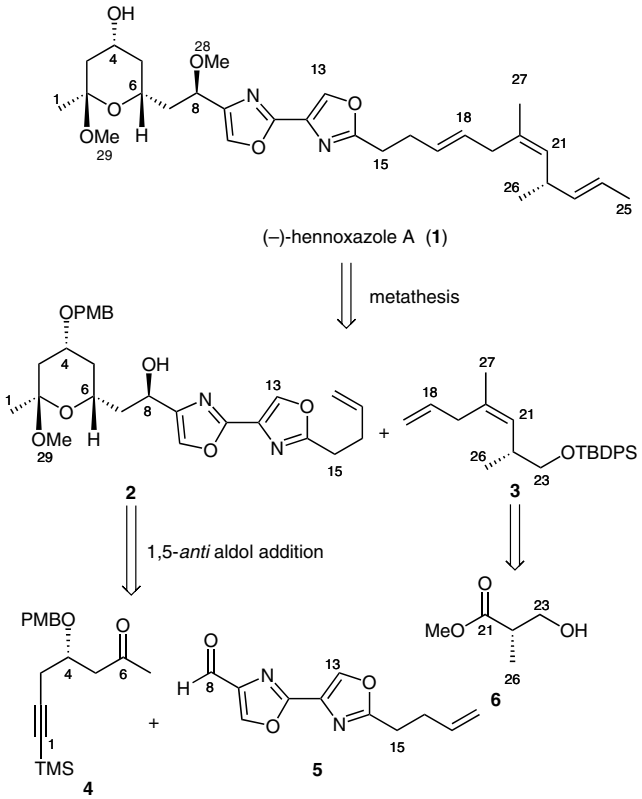
Abstract: A new total synthesis of (–)-hennoxazole A is reported. The synthetic approach is based on the preparation of three similarly sized fragments resulting in a fast and convergent assembly of the natural product. The three key reactions of the synthesis include a highly stereoselective 1,5-*anti* aldol coupling, a gold-catalyzed alkoxycyclization reaction, and a stereocontrolled diene cross-metathesis. The synthesis involves integrated batch and flow chemistry methods leading to the natural product in 16 steps longest linear sequence and 2.8% overall yield.

Key words: flow chemistry, polymer-supported reagents, metathesis, total synthesis, natural products

(–)-Hennoxazole A (**1**) was isolated in 1991 from the marine sponge *Polyfibrospongia* sp.[1] This structurally interesting natural product has succumbed to a number of total syntheses[2] over the intervening years. Given our interest in bisoxazoles[3] and in particular using the integration of batch and flow chemistry technologies,[4] (–)-hennoxazole A (**1**) presents itself as an attractive target for synthesis.

The synthesis plan relies on the preparation of three similarly sized fragments, a central bisoxazole core **5**, an alkynyl ketone **4** and a skipped diene side chain **3** (Scheme 1). In order to assemble these three fragments, a stereoselective boron-promoted aldol reaction and a cross-metathesis process are considered as key steps in the planned synthesis. Furthermore, given that flow chemistry can replace some of the labor and time-consuming processes common to traditional batch methods by improving downstream processing and reaction telescoping, this machine-assisted approach can be efficiently integrated with conventional synthesis methods.[5]

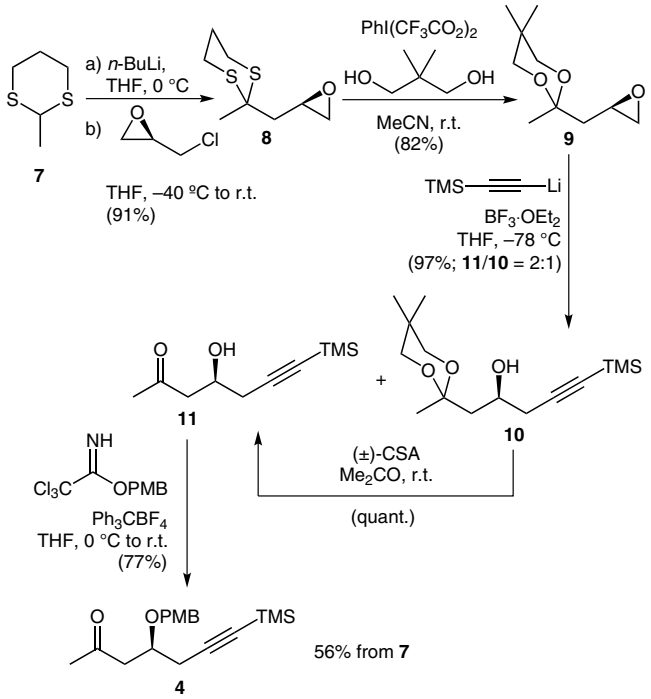
The batch preparation of ketone **4** began from commercially available (*R*)-epichlorohydrin. Treatment of this compound with the lithium anion derived from dithiane **7** gave oxirane **8** as a single regioisomer in good yield (Scheme 2).[6] However, reaction of **8** with different metalated alkynyls gave low yields of the ring-opened product, probably due to the coordinating behavior of the dithiane moiety. To overcome this problem, a change in the protecting group was required. Interconversion of dithiane **8** to the oxirane **9** allowed ring opening using lithiated trimethylsilylacetylene. The desired ketone **11** was formed as the major product together with a smaller quantity of the protected compound **10**. These two compounds were easily separated by flash column chromatography. Moreover, the minor ketal **10** was conveniently converted to the ketone **11** under acidic acetal-cleavage conditions using (±)-CSA. Finally, protection of the free hydroxy group as PMB ether[7] afforded the desired fragment **4** in 56% overall yield.



Scheme 1 Retrosynthetic analysis

For the preparation of the bisoxazole core **5** we chose to use flow-chemistry methods as these had worked well, on scale, during a synthesis of *O*-methyl siphonazole, another bisoxazole natural product.[4] Therefore, straightforward coupling between 5-pentenoic acid, in situ activated with carbonyldiimidazole (CDI), and (±)-serine methyl ester in the presence of triethylamine with subsequent cyclodehydration using diethylaminosulfur trifluoride (DAST) fur-

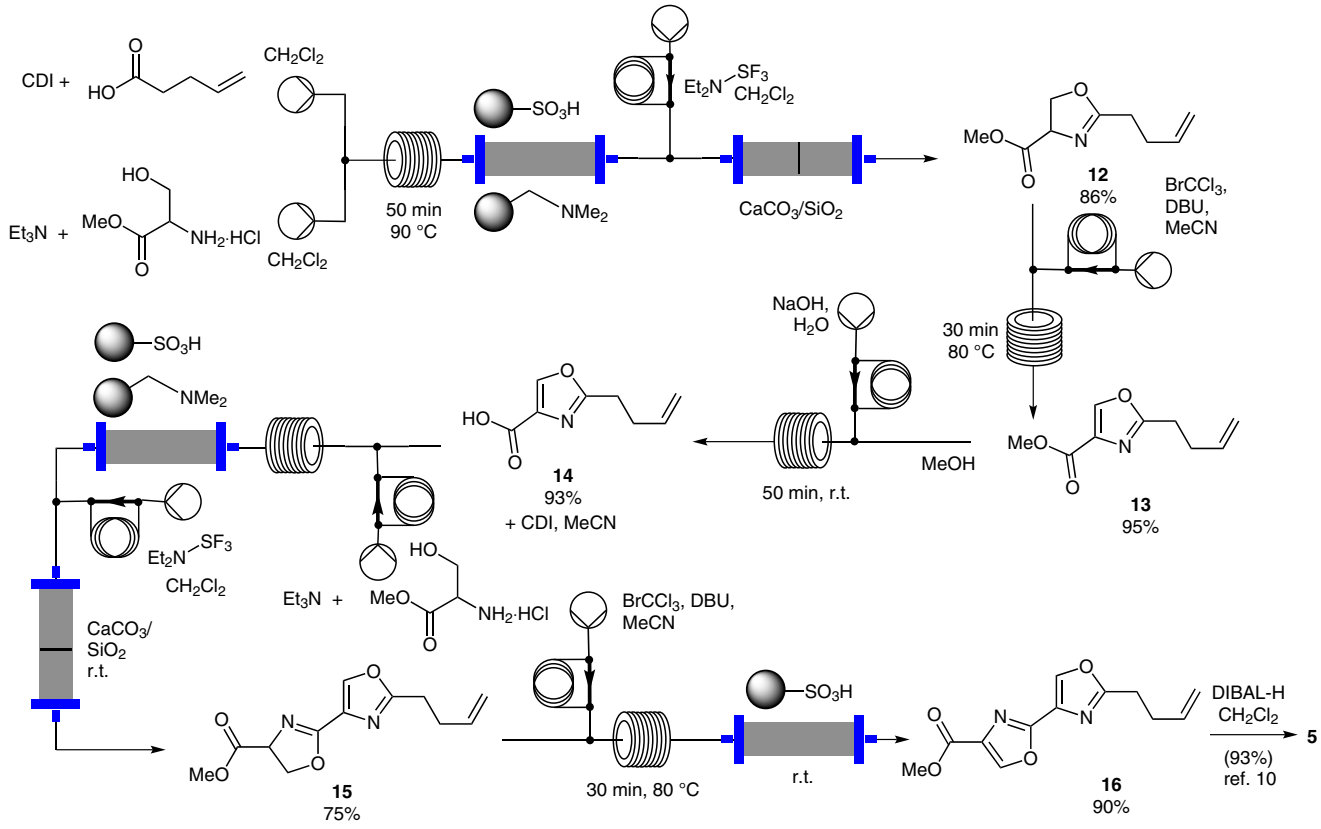
SYNLETT 2013, 24, 0514–0518
Advanced online publication: 30.01.2012
DOI: 10.1055/s-0032-1318109; Art ID: ST-2012-D1062-L



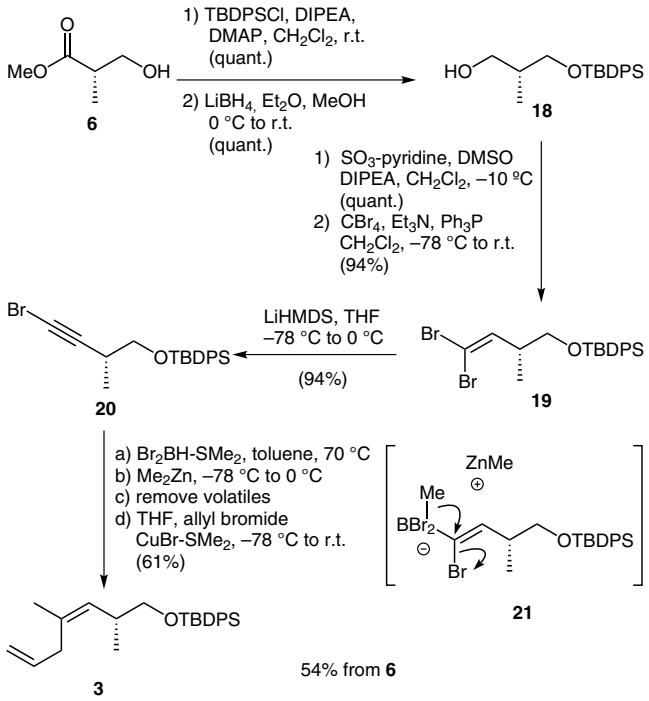
Scheme 2 Synthesis of ketone **4**

nished the corresponding oxazoline **12** in 86% yield over two steps (Scheme 3).[8] This was achieved using a similar flow-chemistry set-up to our previous oxazoline preparation.[4] It is noteworthy that a $CaCO_3/SiO_2$ scavenger was employed in this step to quench excess DAST and to trap the generated HF, improving the safety profile for this reaction set-up.[9] Intermediate **12** was oxidized using bromochloroform in the presence of DBU to form oxazole derivative **13**,[8] which was subjected to saponification with aqueous NaOH thus yielding the corresponding acid **14** in excellent yield. Utilization of the oxazole-forming process converted this precursor into the desired bisoxazole ester **16** in a notable yield (90%). The overall flow synthesis of bisoxazole **16** was carried out on multigram scales (>5 g). Furthermore, it featured the use of polymer-supported reagents and scavengers to afford clean intermediates without resource to time-consuming manual workup. The flow process also eliminates the need for aqueous extraction or column chromatography at any intermediate stage and can be carried out conveniently and safely despite the use of aggressive reagents such as diethylaminosulfur trifluoride (Scheme 3). Finally, a batch reduction of **16** using DIBAL-H afforded aldehyde **5**,[10] the core fragment of the natural product.

With efficient methods available for the preparation of these two fragments, we turned our attention to the preparation of the third coupling partner **3**. Based on earlier work by Walsh[11a] and Negishi[11b] a multicomponent approach to a skipped *Z*-diene bearing the stereogenic C22 center was investigated. The preparation of **3** in batch began with the protection of the commercially available (*S*)-Roche ester with TBDPSCl under standard conditions. Then, a reduction to alcohol **18** and reoxidation using



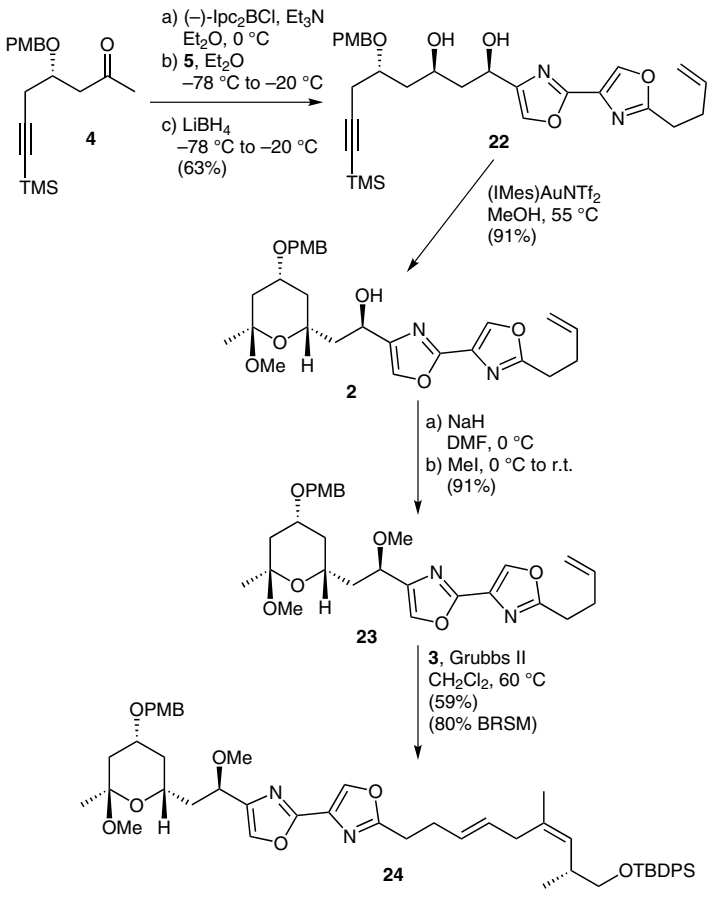
Scheme 3 Continuous-flow synthesis of bisoxazole core **5**



Scheme 4 Synthesis of diene fragment **3**

Parikh–Doering conditions gave the intermediate aldehyde ready for a subsequent Ramirez olefination to afford *gem*-dibromoalkene **19**. Elimination of **19** with a base afforded bromoalkyne **20**. Subsequent hydroboration of **20** proceeded with high regioselectivity and treatment of the bromoalkene with dimethylzinc gave the intermediate **21** which undergoes a rearrangement and further boron–zinc exchange. Finally, this organozinc intermediate could be trapped with allyl bromide in the presence of a copper source. This one-pot sequence of reactions with formation of two new C–C bonds and control of olefin geometry leading directly to the coupling fragment **3** in quantity and good overall yield is attractive and best suited to batch methods (Scheme 4).

With the three key fragments in hand and available in gram quantities, we could begin the assembly process to (–)-hennoxazole A (**1**). While many coupling options were available to us, we chose first to investigate the 1,5-*anti* aldol reaction between ketone **4** and aldehyde **5**.[12] The best results were achieved using (–)-Ipc_2BCl and an in situ reduction of the boron intermediate to afford the desired diol **22** in good yield and as a single diastereomer. Next, we studied the gold-catalyzed alkoxycyclization reaction to form the tetrahydropyran ring. After catalyst-screening studies, we were pleased to observe the formation of the desired tetrahydropyran **2** as a single diastereomer using 5 mol% of $(IMes)AuNTf_2$[13] in MeOH at 55 °C in 91% yield.[14] This intermediate was then methylated to afford **23** using a standard protocol. We next investigated the crucial cross-metathesis reaction. The best conditions

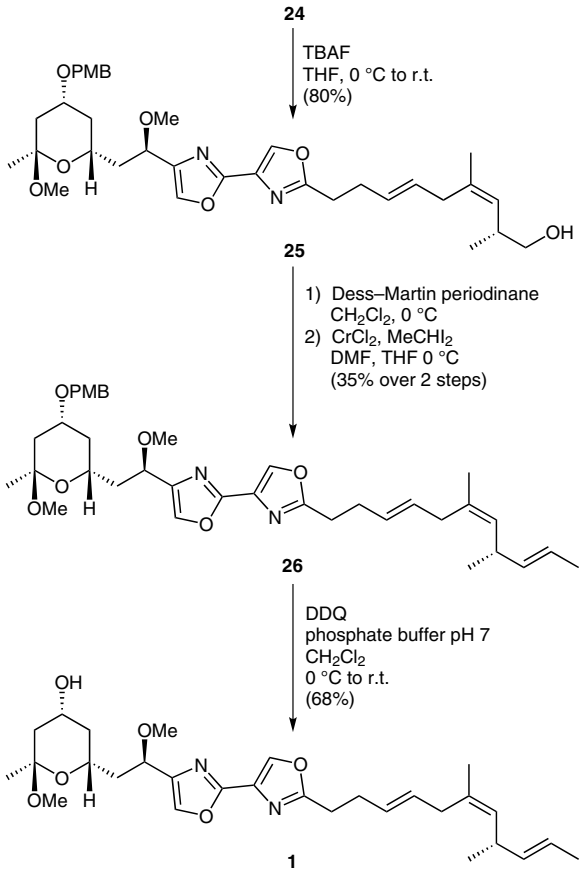


Scheme 5 Assembly of the key fragments

for this process employed the second-generation Grubbs catalyst and CH_2Cl_2 as solvent, while heating at 60 °C in a sealed tube which furnished **24** in 59% yield or 80% based on recovered starting material (Scheme 5).

Final elaboration of **24** to the natural product involved deprotection using TBAF and oxidation of the resulting free alcohol **25** to the intermediate aldehyde using Dess–Martin periodinane. It is noteworthy that the aldehyde was not isolated due to its potential to epimerize; rather it was used directly in the next step.

This involved a modified Takai olefination with 1,1-diiodoethane, giving **26** in moderate 35% yield over two steps as a single *E*-stereoisomer. Finally, cleavage of the PMB ether using DDQ[2c] in a buffered solution was achieved in good yield affording the natural product (–)-hennoxazole A identical to an authentic sample (Scheme 6).[15]



Scheme 6 Final steps

In summary, the total synthesis of (–)-hennoxazole A has been completed in 16 steps longest linear sequence and 26 steps overall. Highlights of this work include the development of a new flow process for the synthesis of the bisoxazole core in concert with traditional batch methods, an efficient assembly of the three similarly sized fragments taking advantage of organometallic processes, cross-metathesis, a highly stereocontrolled boron-promoted aldol reaction, and a stereoselective gold-promoted alkoxycyclization process.

Acknowledgment

We are grateful to the Marie Curie Intra-European Fellowship within the 7th European Community Framework Programme (A.F.), the Williams College for a Dr Herchel Smith Fellowship (Z.G.L), the Ralph Raphael studentship award (M.B.), the Swiss National Science Foundation (S.S.-M. and C.S.), the Royal Society (I.R.B.), the BP Endowment (S.V.L.), and the EPSRC EP/F0693685/1 for financial support. Dr. Matthew L. Maddess, Dr. Malte Brasholz, and Antti Kataja are acknowledged for alternative approaches not reported here.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Data for Compound 2**
Mp 74–79 °C. R_f = 0.34 (EtOAc–PE, 1:1); $[\alpha]_D^{29.4}$ –23 (*c* 0.13, $CHCl_3$). IR (neat): 3464, 2984, 2932, 2837, 2365, 2337, 1639, 1615, 1578, 1512, 1449, 1380, 1362, 1302, 1247, 1171 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (1 H, s), 7.61 (1 H, s), 7.24 (2 H, d, *J* = 8.7 Hz), 6.86 (2 H, d, *J* = 8.7 Hz), 5.84 (1 H, ddt, *J* = 17.0, 10.3, 6.6 Hz), 5.08 (1 H,

dq, J = 17.1, 1.6 Hz), 5.01 (1 H, dq, J = 10.2, 1.4 Hz), 4.97 (1 H, d, J = 9.7 Hz), 4.46 (2 H, d, J = 2.7 Hz), 4.18 (1 H, s), 3.94–3.83 (2 H, m), 3.79 (3 H, s), 3.21 (3 H, s), 2.93 (2 H, t, J = 7.6 Hz), 2.56 (2 H, q, J = 7.1 Hz), 2.26–2.19 (2 H, m), 2.03–2.00 (1 H, m), 1.90 (1 H, dt, J = 14.6, 10.2 Hz), 1.42–1.39 (1 H, m), 1.36 (3 H, s), 1.26 (1 H, q, J = 11.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5, 159.1, 155.3, 144.8, 137.8, 136.1, 134.1, 130.6, 129.7, 116.1, 113.8, 100.1, 70.8, 70.4, 69.7, 68.5, 55.2, 47.8, 42.1, 41.8, 37.7, 30.7, 27.5, 23.6. ESI-HRMS: *m/z* calcd for $C_{27}H_{34}N_2NaO_7^+$ $[M + Na]^+$: 521.2258; found: 521.2250.

(15) An authentic sample of (–)-hennoxazole A was kindly provided by Prof. Thomas E. Smith (Williams College).

