

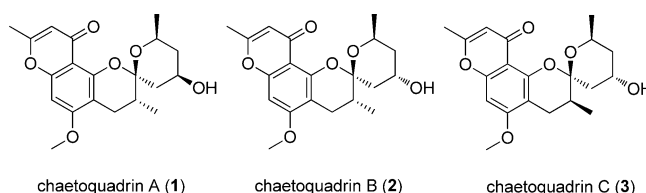
## Total Synthesis of Chaetoquadrins A–C

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## ABSTRACT



The first total synthesis of the monoamine oxidase inhibitors chaetoquadrins A–C has been accomplished. Key steps in the synthesis include an aromatic Claisen rearrangement, asymmetric boron aldol reaction and acid-mediated spiroketalization. Comparison of spectral data for the synthetic spiroketals confirmed the proposed structure for these natural products.

In 2002 Fujimoto and co-workers reported the isolation of chaetoquadrins A–C (1–3; Figure 1) from an ethyl acetate extract of the ascomycete, *Chaetomium quadrangulatum* (strain 71-NG-22). They were found to inhibit mouse liver monoamine oxidase (MAO) using the modified Kraml assay.<sup>1</sup> Recently, chaetoquadrins A (1) and B (2) were also isolated from *Chaetomium aureus* by Li and co-workers.<sup>2</sup> These novel spiroketals feature a chromone (1,4-benzopyran-4-one) fused to a substituted [6,6]-spiroketal framework, differing from each other by the stereogenic pattern around the spiroketal ring. To the best of our knowledge, syntheses of these natural products have not yet been reported. Owing to our ongoing interest in the synthesis of bioactive spiroketal-containing natural products and especially that of benzannulated spiroketals,<sup>3</sup> we were prompted to embark on a synthesis of the chaetoquadrins. Chaetoquadrin C (3), with the highest inhibitory activity against mouse liver MAO, was chosen as the initial synthetic target.

Our retrosynthetic analysis of chaetoquadrin C (3) is outlined in Scheme 1. Spiroketal 3 was envisioned to be constructed *via* an acid-mediated spiroketalization of  $\beta$ -hydroxy ketone 4, which in turn would be prepared from an aldol reaction of aldehyde 5 and its aldol partner derived from the union of bromide 6 and chiral propionate fragment 7. We thought to access bromide 6 *via* means of an aromatic Claisen rearrangement of allyl phenyl ether 8,

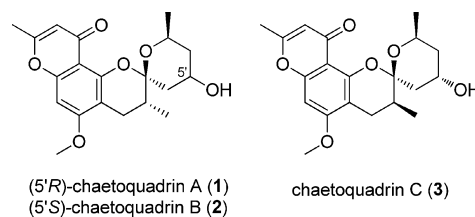


Figure 1. Structure of chaetoquadrins A–C.

which was to be accessed *via* alkylation of the known chromone, noreugenin (9).

We began our synthesis from noreugenin (9) which itself is readily accessible from 2,4,6-trihydroxyacetophenone.<sup>4</sup> Selective alkylation of the non-hydrogen bonded phenol with dimethyl sulfate proceeded smoothly to give eugenin (10)<sup>5</sup> (Scheme 2). The subsequent alkylation of the hydrogen-bonded phenol required elevated temperature, which delivered allyl phenyl ether 8 in good yield. Heating allyl ether 8 at 200 °C for 2 h effected the aromatic Claisen rearrangement,<sup>6</sup> and the resulting phenol was treated with benzyl bromide to give benzyl protected allyl chromone 11. Preliminary investigations had established that this choice

(1) Fujimoto, H.; Nozawa, M.; Okuyama, E.; Ishibashi, M. *Chem. Pharm. Bull.* **2002**, *50*, 330–336.

(2) Li, M. L.; Zou, Q.; Li, G. Y. *Chin. Chem. Lett.* **2010**, *21*, 1203–1205.

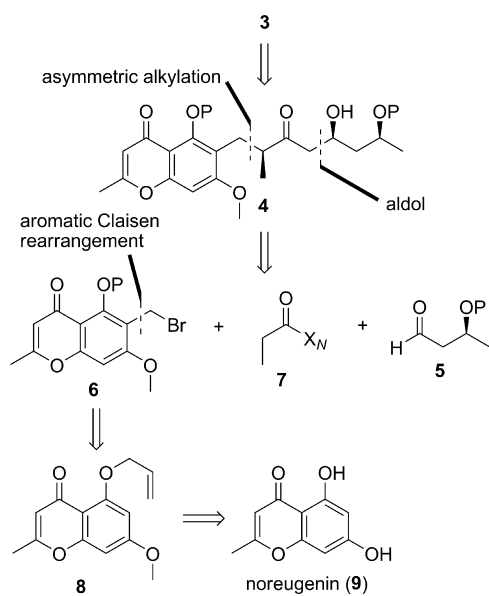
(3) For selected examples, see: Yuen, T.-Y.; Brimble, M. A. *Org. Lett.* **2012**, *14*, 5154–5157 and references within.

(4) Bruder, M.; Haseler, P. L.; Muscarella, M.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2009**, *75*, 353–358.

(5) Czepa, A.; Hofmann, T. *J. Agric. Food Chem.* **2003**, *51*, 3865–3873.

(6) *Chromenes, chromanones, and chromones*; Ellis, G. P., Ed.; Wiley: New York, 1977; Chapter 8, pp 698–699.

### Scheme 1. Retrosynthetic Analysis of Chaetoquadrin C (3)



of protecting group was more amenable to subsequent transformations than use of either the methoxy (OMe) or ethoxymethyl ether (OEM) group.

With chromone **11** in hand, we first needed to remove two terminal carbons from the C-6 allyl side chain to form the benzylic framework of bromide **12**. To this end chromone **11** was subjected to thermal isomerization with carbonylchlorohydridotris(triphenylphosphine)ruthenium(II),<sup>7,8</sup> followed by oxidative cleavage with OsO<sub>4</sub>/NaIO<sub>4</sub> to afford aldehyde **13**. Sodium borohydride reduction of **13** gave a benzylic alcohol which was treated with phosphorus tribromide to afford the desired benzylic bromide **12** in good yield.

We were now ready to investigate the key coupling of bromide **12** with a chiral propionate fragment to install the chiral center at C-2' (Table 1).<sup>9</sup> The initial alkylation with valine-derived oxazolidinone **14a**, KO<sup>t</sup>Bu, and bromide **12** was unsuccessful (entry 1);<sup>10</sup> however treatment of the same oxazolidinone with NaHMDS enabled the desired transformation to take place (entry 2). Unfortunately, the low yield of this reaction and the difficulty of the subsequent reductive cleavage step mandated use of a different auxiliary. Alkylation of phenylalanine-derived oxazolidinone **14b** was unsuccessful (entry 3), as was the alkylation with *N*-propionyl pseudoephedrine **14c** (entry 4).<sup>11</sup>

(7) Levison, J. J.; Robinson, S. D. *Inorg. Phys. Theor.* **1970**, 2947–2954.

(8) Yue, C. J.; Liu, Y.; He, R. *J. Mol. Catal. A* **2006**, 259, 17–23.

(9) There are surprisingly few general asymmetric approaches to  $\alpha$ -chiral  $\beta$ -arylated compounds. For examples, see: Molander, G. A.; Shin, I.; Jean-Gérard, L. *Org. Lett.* **2010**, 12, 4384–4387 and references within.

(10) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, 104, 1737–1739. (b) Fresno, N.; Perez-Fernandez, R.; Goya, P.; Jimeno, M.; Alkorta, I.; Elguero, J.; Menendez-Taboada, L.; Garcia-Granda, S. *Tetrahedron* **2011**, 67, 9104–9111.

(11) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496–6511. (b) Myers, A. G.; Bryant, H. Y. *Org. Synth.* **2000**, 77, 22–28.

### Scheme 2. Synthesis of the Bromide 12

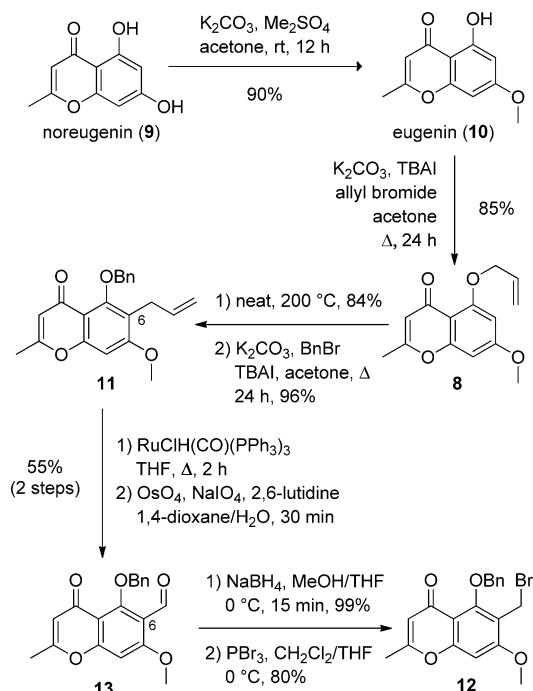
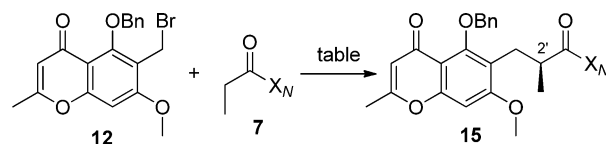
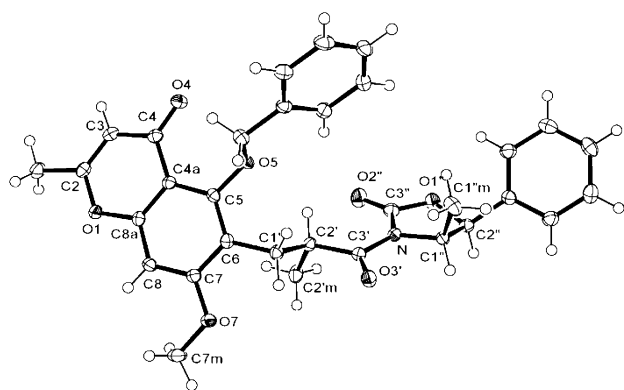


Table 1. Alkylation of Bromide **12** with a Chiral Propionate **7**



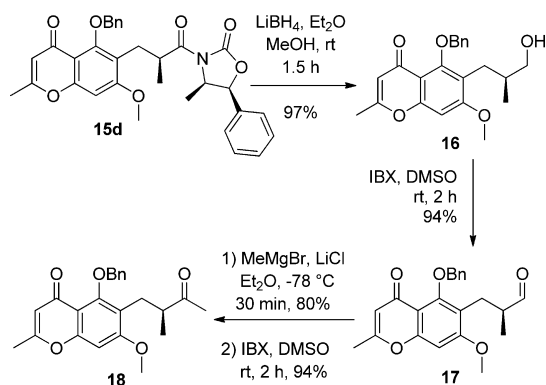
entry	chiral auxiliary	reaction conditions	yield <sup>a</sup>
1		KO <sup>t</sup> Bu, THF, -78 °C	n.r.
2	<b>14a</b>	NaHMDS, THF, -78 °C	16%
3		NaHMDS, THF, -78 °C	n.r.
4		LDA, LiCl, THF, -78 °C $\rightarrow$ 0 °C	n.r.
5		NaHMDS, THF, -78 °C	51%

<sup>a</sup> n.r. = no reaction.



**Figure 2.** X-ray crystal structure of imide **15d**.

### Scheme 3. Synthesis of Methyl Ketone **18**



Eventually, it was found that alkylation with norephedrine-derived auxiliary **14d**<sup>12</sup> with NaHMDS afforded the desired product which was readily isolated in enantiopure form by chromatography in 51% yield (entry 5). The resulting imide **15d** also had the advantage of being a highly crystalline solid, and an X-ray crystal structure was obtained, unambiguously confirming the configuration of the newly formed C-2' stereocenter to be *S* (Figure 2). In the course of this research imide **15d** was prepared and stored on multigram scale without special precautions.

Moving forward, imide **15d** was reduced with lithium borohydride to give primary alcohol **16** in excellent yield (Scheme 3). IBX oxidation gave aldehyde **17** which was treated with methyl magnesium bromide in the presence of lithium chloride to give a mixture of two epimeric methyl alcohols that was subsequently oxidized with IBX to give methyl ketone **18** in nearly quantitative yield.

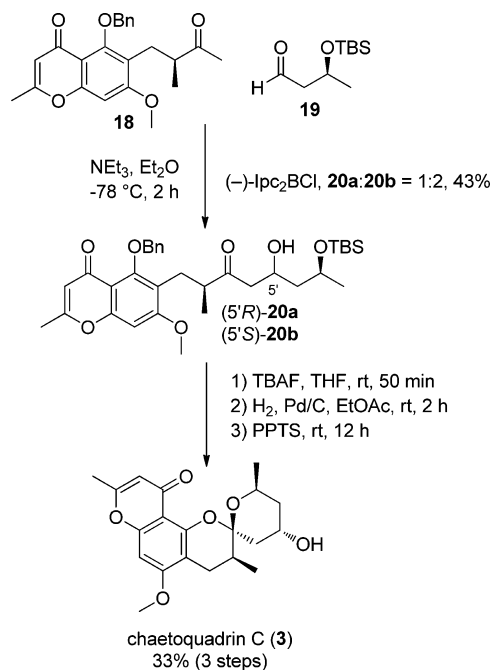
With methyl ketone **18** in hand we were now ready for the key aldol reaction with aldehyde **19**<sup>13</sup> (Scheme 4).

(12) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547–551.

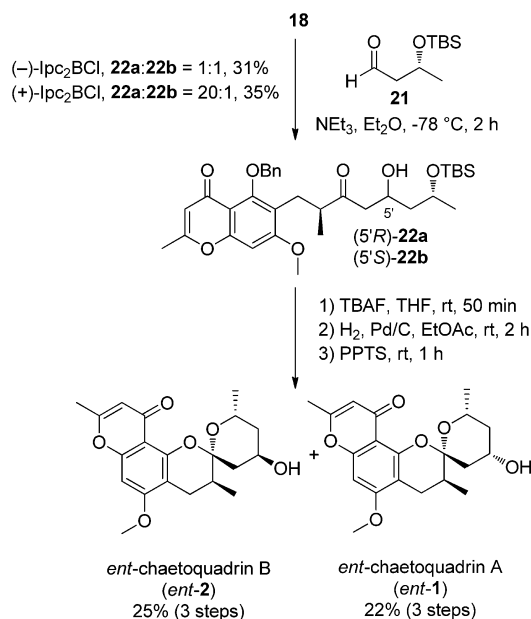
(13) Aldehyde **19** was prepared in two steps from ethyl (*S*)-3-hydroxybutyrate via known procedures. See: Fernandes, R. A.; Mulay, S. V. *J. Org. Chem.* **2010**, *75*, 7029–7032.

(14) Cergol, K. M.; Coster, M. J. *Nat. Protoc.* **2007**, *2*, 2568–2573.

### Scheme 4. Total Synthesis of Chaetoquadrin C (**3**)



### Scheme 5. Total Synthesis of *ent*-Chaetoquadrin A (*ent*-**1**) and B (*ent*-**2**)



Using Paterson aldol conditions,<sup>14</sup> the combination of ketone **18**, (-)-Ipc<sub>2</sub>BCl, and aldehyde **19** afforded the β-hydroxyketone in moderate yield and selectivity (dr 1:2, **20a:20b**) in favor of the desired diastereoisomer **20b**. To form the spiroketal, the silyl protecting group was first cleaved with tetrabutylammonium fluoride followed by hydrogenolysis of the benzyl protecting group over Pd/C.

Finally, treatment of the crude deprotected spiroketal precursor with pyridinium *p*-toluenesulfonate gave chaetoquadrin C (**3**) which gratifyingly could be purified by preparative thin layer chromatography in moderate yield (33% over three steps). Spectroscopic data and the CD spectrum of the synthetic material were in excellent agreement with the reported data.

With chaetoquadrin C (**3**) in hand, our attention next turned to chaetoquadrins A (**1**) and B (**2**), epimeric at C-5'. Accordingly, treatment of methyl ketone **18** with (–)-Ipc<sub>2</sub>BCl and aldehyde **21**<sup>15</sup> enabled access to the required β-hydroxy ketone as a 1:1 mixture of diastereoisomers **22a** and **22b**. Interestingly, use of (+)-Ipc<sub>2</sub>BCl resulted in a dramatic improvement in diastereoselectivity in favor of **22a** (dr 20:1), suggesting that this combination of starting materials and boron auxiliary is matched (Scheme 5).

Application of the deprotection/cyclization sequence used previously for **20a:20b** to the 1:1 mixture of **22a** and **22b** gave *ent*-(**1**) and *ent*-(**2**) in moderate yields. Gratifyingly, the two natural products were readily separated by

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(15) Aldehyde **21** was prepared in two steps from ethyl (*R*)-3-hydroxybutyrate *via* known procedures. See: Fernandes, R. A.; Mulay, S. V. *J. Org. Chem.* **2010**, *75*, 7029–7032.

preparative thin layer chromatography. Spectroscopic data of both *ent*-**1** and *ent*-**2** were in full agreement with those of the natural sample, and the CD spectra of the synthetic samples were a mirror image of those reported by Fujimoto *et al.*<sup>1</sup>

In conclusion, we report the first total synthesis of chaetoquadrins A, B, and C. The key steps of our synthesis include an aromatic Claisen rearrangement, boron-mediated aldol reaction, and acid-catalyzed spiroketalization reaction. Synthetic investigations into other members of the chaetoquadrin family are ongoing in our laboratories.

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**Supporting Information Available.** Experimental procedures and full spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.