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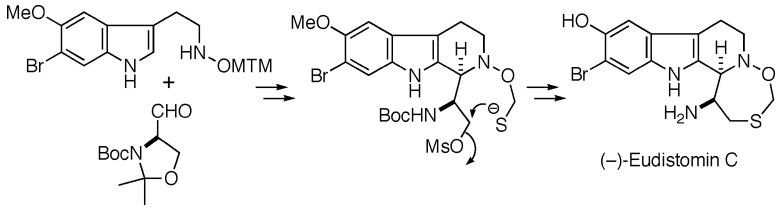

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Stereocontrolled Total Synthesis of (−)-Eudistomin C

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Eudistomins, isolated from a Caribbean tunicate (*Eudistoma olivaceum*) by Rinehart and co-workers in 1984,[1,2] are members of the tetrahydro-β-carboline family of marine alkaloids. Among eudistomins, eudistomin C (**1**), E (**2**), K (**3**), L (**4**), and F (**5**), possessing the hitherto unknown oxathiazepine ring, have displayed extremely potent antiviral activity against both DNA and RNA viruses as well as antitumor and antimicrobial activity[1c,2c] (Figure 1). Therefore, this class of compounds has attracted a great deal of attention as a synthetic target, and two examples of total syntheses[3,4] and several synthetic approaches[5] have been described to date. We disclose herein the stereocontrolled total synthesis of (−)-eudistomin C (**1**), featuring the highly efficient formation of the oxathiazepine ring.

In previous synthetic studies,[3−5] considerable difficulties were encountered in the construction of an oxathiazepine ring containing three heteroatoms and two chiral centers. Thus, ring closure by the intramolecular alkylation of hydroxylamine oxygen with halomethyl sulfide (i.e., disconnection at bond-***a***) has proved difficult[3b] presumably due to alkylation at the nitrogen of the *N*,*N*-dialkylhydroxylamine to form *N*-oxide.[6] The other successful strategy utilizing the intramoleculer Pictet−Spengler reaction based on disconnection at bond-***b*** provided an undesired diastereomer as the major product.[4] Instead of using these problematic ring-closing reactions, we planned to construct an oxathiazepine ring via the intramoleculer alkylation of thiol **6** even though, to the best of our knowledge, such transformation was unprecedented. The generation of the thiol would be possible from MTM ether through the formation of chloromethyl ether,[7] followed by the introduction of the sulfur atom. The diastereoselective construction of tetrahydro-β-carboline could be made possible by the Pictet−Spengler reaction[3] between tryptamine derivative **7** and Garner aldehyde **8**.[8]

The synthesis of indole segment **9** started from nitroaniline **10**, which was readily prepared from *m*-anisidine in four steps (Scheme 2).[9] The conversion of **10** to iodoaniline derivative **11** was conducted by a three-step sequence that included the Sandmyer reaction, the selective reduction of the nitro group with Fe/$FeCl_2$, and trifluoroacetylation. Then, Mitsunobu reaction with TBS-protected *cis*-butene diol (**12**) provided indole precursor **13**,[10] which was subjected to the intramolecular Heck reaction conditions reported by Macor and co-workers[11] to give the desired tryptophol derivative **14**. After protection of indole NH with the Boc group and desilylation of the TBS ether, hydroxylamine functionality was then incorporated by the Mitsunobu reaction of **15** with *N*-Ns-*O*-MTM hydroxylamine[12] (**16**), which was derived from *N*-hydroxyphthalimide in two steps. Finally, deprotection of the Boc and Ns groups[13] under conventional conditions furnished the desired tryptamine derivative **9**.

We then focused our attention on the crucial Pictet−Spengler reaction with Garner aldehyde **8**. Since an initial attempt using a model substrate of **9** lacking the bromo and methoxy groups gave the undesired diastereomer as the major product (3:1) under standard conditions (TFA in CH_2Cl_2, −78 °C), we conducted extensive screening of the solvents and acid catalysts. Surprisingly, we found that the reaction in the presence of a catalytic amount of chloroacetic acid or dichloroacetic acid in toluene proceeds smoothly at 0 °C to afford the desired diastereomer **18** with high selectivity (11:1) (Scheme 3).

The next task was to transform the *O*-MTM ether to the corresponding *O*-methylthiol. After the protection of indole NH of **18** with the α-chloroethoxycarbonyl (ACE) group,[14] MTM ether **19** was treated with SO_2Cl_2 to give chloromethyl ether **20**[7] (Scheme 3). Due to its instability, the crude **20** was immediately treated with AcSH in the presence of Hunig's base to furnish thiol acetate **21** in excellent yield. Then, removal of the acetonide and mesylation of the resultant alcohol afforded cyclization precursor **22**. To our great satisfaction, upon heating with K_2CO_3 in MeOH, thiol acetate **22** underwent facile methanolysis and the subsequent ring-closing alkylation took place smoothly to furnish the desired oxathiazepine ring with the concomitant deprotection of the ACE group. It should be emphasized that appreciable formation of the isoxazolidine ring by the release thioformaldehyde followed by intramolecular cy-

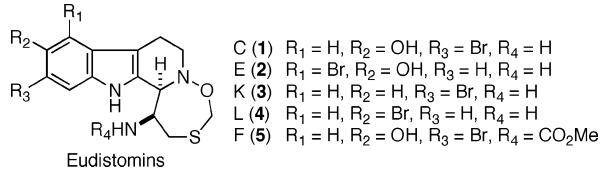
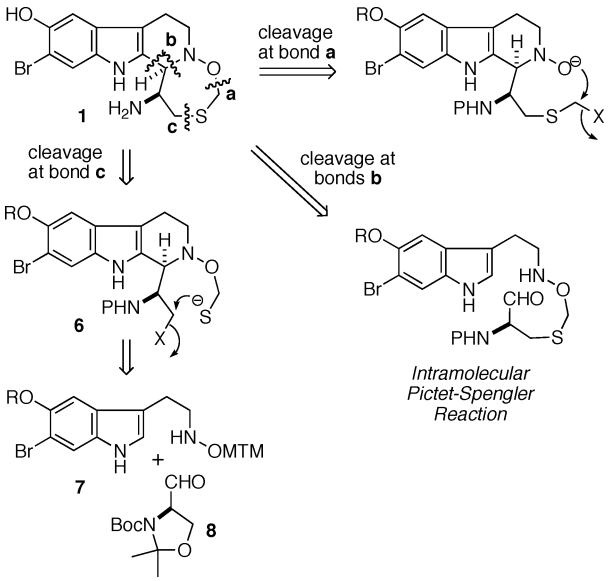


Figure 1. Structures of the eudistomins.

Scheme 1 Retrosynthetic Analysis



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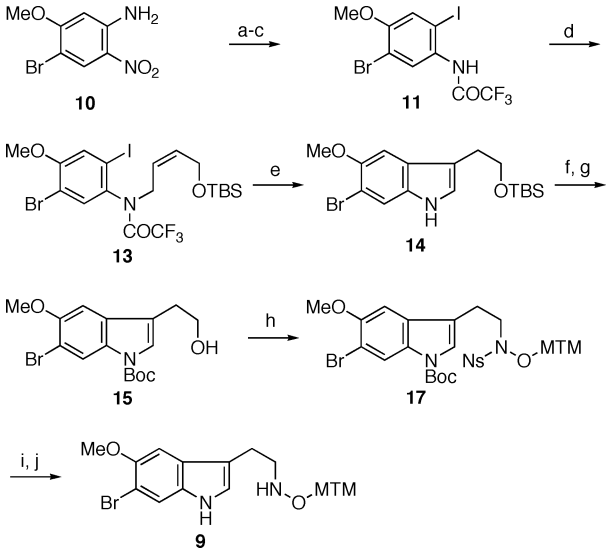
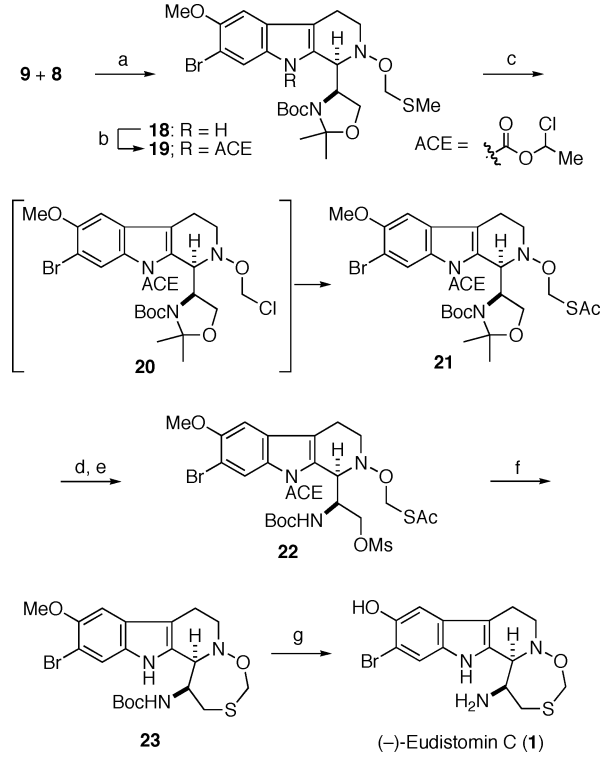
Scheme 2. Preparation of the Indole Segment[a]



[a] Reagents and conditions: (a) $NaNO_2$, H_2SO_4, CH_3CN, H_2O; KI; (b) Fe, $FeCl_2$, 1 N HCl, EtOH, reflux; (c) TFAA, Py, CH_2Cl_2, 62% (three steps); (d) (*Z*)-$HOCH_2CH{=}CHCH_2OTBS$ (**12**), DEAD, PPh_3, PhH, 90%; (e) cat. $Pd(OAc)_2$, Et_3N, $BnEt_3NCl$, DMF, 80 °C, 66%; (f) Boc_2O, DMAP, CH_2Cl_2; (g) CSA, MeOH, 97% (two steps); (h) Ns-NH−OMTM (**16**), DEAD, PPh_3, PhH; (i) Me_2S, TFA, CH_2Cl_2, 97% (two steps); (j) PhSH, K_2CO_3, DMF, 94%.

Scheme 3. Formation of the Oxathiazepine Ring and the Completion of the Total Synthesis of (−)-Eudistomin C[a]



[a] Reagents and conditions: (a) cat. Cl_2CHCO_2H, toluene (11:1 dr), 0 °C; (b) *n*-BuLi, THF, −78 °C; ACE-Cl, 89% (two steps); (c) SO_2Cl_2, CH_2Cl_2, −78 °C to room temperature; AcSH, *i*-Pr_2NEt, 95%; (d) aq AcOH, THF, 80°C, 61%; (e) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 98%; (f) K_2CO_3, MeOH, reflux, 65%; (g) BBr_3, CH_2CH_2, −78 °C to room temperature, 78%.

clization at hydroxylamine oxygen was not observed. Finally, the Boc group and methyl group on phenolic oxygen were removed by treatment with BBr_3 to obtain (−)-eudistomin C (**1**). All of the spectral data of the synthetic compound were identical to those of natural (−)-eudistomin C.[1,3]

In conclusion, we have accomplished the stereocontrolled total synthesis of (−)-eudistomin C (**1**) based on the development of the Brønsted acid-catalyzed diastereoselective Pictet−Spengler reaction and the unprecedented construction of an unusual oxathiazepine ring. The 18-step sequence with an overall yield of 7.7% has allowed us to conduct the gram-scale preparation of eudistomin C as well as variety of its derivatives. Biological studies on the natural and unnatural compounds will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compound **16** was prepared from *N*-hydroxyphthalimide in a three-step sequence. For details, see Supporting Information.

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