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# Stereoselective construction of a key hydroindole precursor of epidithiodiketopiperazine (ETP) natural products†

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**An asymmetric synthetic strategy for constructing the divergent-synthesis monomer of epidithiodiketopiperazine (ETP) natural products has been successfully developed. The functionalized 2,3,3*a*,4,7,7*a*-hexahydroindole scaffold was constructed by a diastereoselective inverse electron-demand Diels–Alder (IEDDA) reaction.**

Epidithiodiketopiperazine (ETP) natural products comprise a large number of metabolites, which display a wide range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties.[1] ETPs, characterized by sulfur atoms[2] and a diketopiperazine structure, have gained significant interest from the synthetic community, due to their unique structural and biological properties. In this field, Kishi,[3a,b] Movassaghi,[3c,e,g,h] Sodeoka,[3d] and Overman[3f] have reported the elegant total syntheses of ETP molecules containing indole moieties. Among the ETP family, there are also lots of members containing the hydroindole scaffolds (perhydroindole, 2,3,7,7*a*-tetrahydroindole, and 2,3,3*a*,4,7,7*a*-hexahydroindole) (Fig. 1).

Although numerous synthetic approaches have been investigated, there have been only a limited number of strategies for the preparation of the highly functionalized hydroindole scaffolds. The first synthesis of a related compound, gliotoxin **6**, was reported in 1976 by Kishi and co-workers, in which a Michael addition and a nucleophilic substitution reaction were used to construct the 2,3,7,7*a*-tetrahydroindole core.[4] Thirty-three years later, Bräse and co-workers reported a short and stereoselective synthesis of the epicoccin core, using a diastereoselective [2+2] cycloaddition between a ketene and an enecarbamate, followed by an RCM reaction to provide the 2,3,3*a*,4,7,7*a*-hexahydroindole core.[5] Recently,

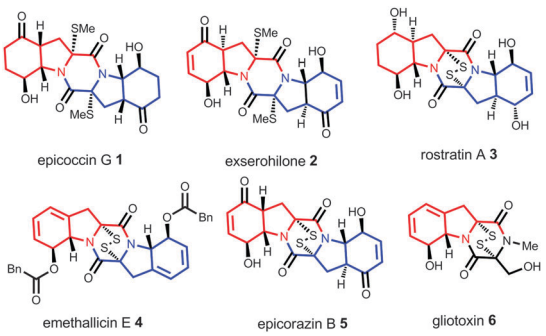


Fig. 1 Representative ETP family members containing hydroindole scaffolds.

several fantastic studies were reported by Nicolaou and co-workers on the total synthesis of epicoccin G **1**, 8,8-*epi-ent*-rostratin B, emethallicin E **4**, haematocin, gliotoxin **6** and gliotoxin G.[6] An oxidative cyclization of L-Boc-tyrosine with $PhI(OAc)_2$ followed by an intramolecular conjugate addition process was involved in the synthesis of ETPs. A similar strategy to construct the hydroindole scaffold was also used in the total synthesis of acetylaranotin, another member of the ETP family, which was achieved by Tokuyama and co-workers[7] shortly after its first total synthesis accomplished by Reisman's group.[8] Herein we present a new stereoselective approach for preparing the highly functionalized hydroindole core, which can be converted to the key divergent-synthesis monomer of ETPs.

Our synthetic plan commenced with the retrosynthetic simplification of ETPs **1–5** to **7**, which was found to be the key monomer having access to most of the ETPs, due to the $C_2$-symmetric structure (Scheme 1). Thus, a reliable approach to access key monomer **7** was needed to be urgently developed. The hydroindole core was envisaged to be prepared through an inverse electron-demand Diels–Alder (IEDDA) reaction.[9] Ultimately, **8** and **9** were chosen as two specified Diels–Alder precursors which can be prepared by naturally abundant D/L-malic acid and L-pyroglutamic acid.

Following the strategy, a variety of electron-poor dienes were synthesized to explore the IEDDA reaction (Table 1). The linear dienes **10** and **11** were demonstrated to be unsuitable partners to

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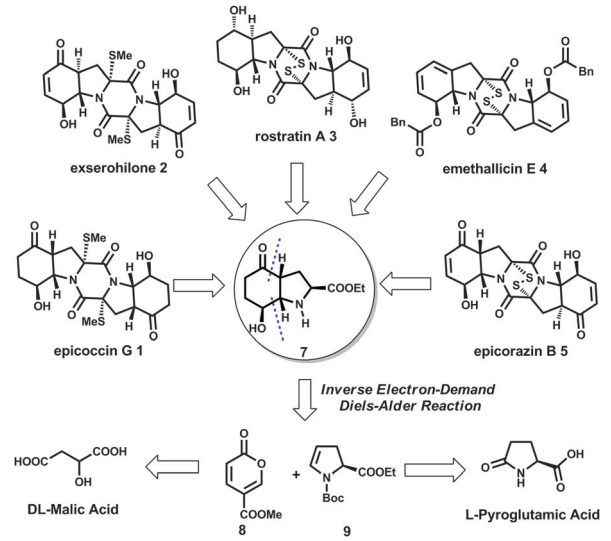
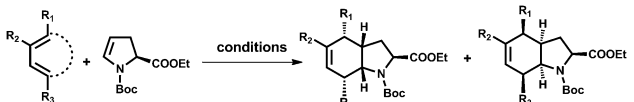
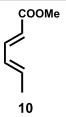
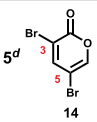
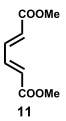
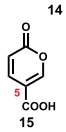
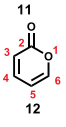
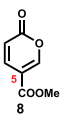
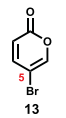
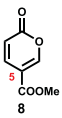



Scheme 1 Retrosynthetic plan for synthesis of ETPs.

Table 1 Exploration of the stereoselective IEDDA reaction[a]

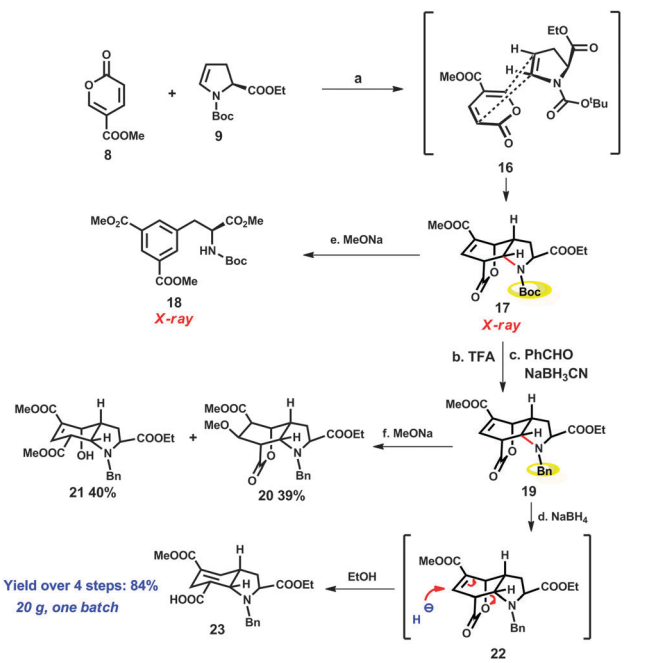



| Entry | Diene | Yield[b] (%) | *exo* : *endo*[c] | Entry | Diene | Yield[b] (%) | *exo* : *endo*[c] |
|---|---|---|---|---|---|---|---|
| 1 |  10 | NR | — | 5[d] |  14 | 48 | 3 : 1 |
| 2 |  11 | NR | — | 6 |  15 | Trace | — |
| 3 |  12 | NR | — | 7 |  8 | 52 | 7 : 1 |
| 4 |  13 | 54 | 3 : 1 | 8[e] |  8 | 95 | >10 : 1 |

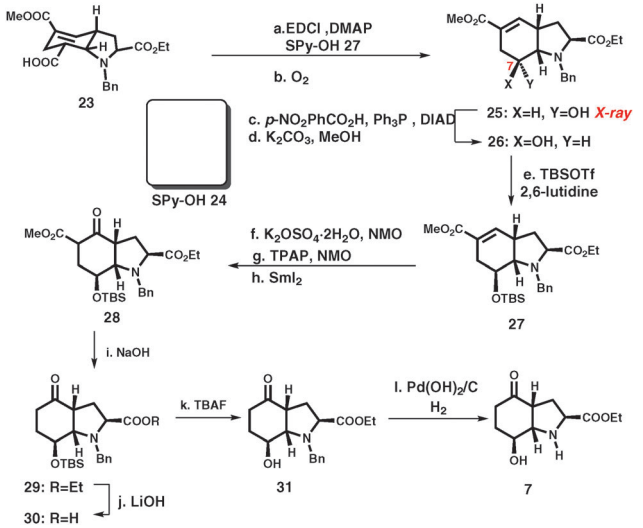
[a] Conditions: diene (0.1 mmol), enamine (0.1 mmol), toluene (1.0 mL), reflux. [b] Isolated yields. [c] Ratios determined by integration of crude $^1$H NMR. [d] Performed at 90 °C. [e] 130 °C in a sealed tube.

react with the electron-rich dienophile **9**. Different Lewis acids, such as $BF_3{\cdot}Et_2O$ and $Et_2AlCl$, were employed to promote the reaction. Unfortunately, dienophile **9** was found to decompose quickly under Lewis acidic conditions, even at low temperatures. The dienes containing the 2-pyrone moiety were then tested, because the cyclic diene may show better reactivity and selectivity in the stereoselective Diels–Alder reaction.[10] However, the non-functionalized 2-pyrone diene **12** was not a suitable partner either. To increase the electron deficiency of the diene, electron-withdrawing groups were then installed into the diene. Diene **13**, containing one bromine atom in position 5, reacted with dienophile **9**, affording the expected product in 54% yield and the ratio of the *exo*/*endo* products was 3 : 1. Encouraged by this result, diene **14** containing two bromine atoms (positions 3 and 5) was tested. However, the yield was lower, presumably due to the steric hindrance of the bromine atom on the bridge of the product. After a carboxyl group was introduced at position 5, only trace amounts of the product could be obtained due to the poor solubility of diene **15**. To our satisfaction, after an ester was introduced at position 5, the reaction afforded the desired product with a better diastereoselectivity (*exo* : *endo* = 7 : 1), although the yield was not improved. Then the temperature was raised to 130 °C in a sealed tube to enhance the efficiency; as expected, the optimized conditions afforded the IEDDA product in an excellent yield (95%) with over 10 : 1 diastereoselectivity.

The relative stereochemistry of the IEDDA product **17** was confirmed by X-ray crystallography (see ESI†). The stereoselectivity corresponds to an *exo*-approach of diene **8** from the less hindered side of dienophile **9**, pointing an ethoxycarbonyl group in the opposite direction of the ring (**16**, Scheme 2). The endeavor to open the bridged-lactone ring under saponification conditions was invalid, due to the weakness of the C–N bond of *t*-butoxycarbonyl protecting IEDDA product **17**. Most of the basic conditions afforded the C–N bond cleavage products, such as **18**, which was identified by X-ray crystallography. Considering the influence of the amino protecting group, *t*-butoxycarbonyl protection was altered to benzyl protection. After treatment with MeONa, benzyl protecting intermediate **19** was converted to the desired product **21** in 40% yield with 39% of the Michael addition byproduct **20**. These negative results compelled us to abandon the attempts of ring opening under saponification conditions. In order to reduce the bridged-lactone ring to the corresponding




Scheme 2 Conditions: (a) toluene, 130 °C, sealed operator; (b) TFA, DCM, rt; (c) PhCHO, $NaBH_3CN$, MeCN/AcOH, rt; (d) $NaBH_4$, EtOH, 0 °C, 84% over 4 steps; (e) MeONa, MeOH, 0 °C, 88%; (f) MeONa, MeOH, −10 °C, **20** 39%, **21** 40%.




Scheme 3 Conditions: (a) EDCI, DMAP, Spy-OH, DCM/toluene, rt; (b) $O_2$, 60%, **25**:**26** = 1:3; (c) *p*-$NO_2PhCOOH$, $Ph_3P$, DIAD, THF, 0 °C to rt, (d) $K_2CO_3$, MeOH, rt, 66% over 2 steps; (e) TBSOTf, 2,6-lutidine, DCM, −40 °C, 85%; (f) $K_2OSO_4{\cdot}2H_2O$, NMO, *t*-BuOH/$H_2O$, 50 °C; (g) TPAP, NMO, DCM, silica gel, rt; (h) $SmI_2$, THF, rt, 35% over 3 steps; (i) NaOH, THF/$H_2O$, 60 °C, 42% (51% b.r.s.m); (j) LiOH (1 M aq.)/THF, EtOH, rt, 95%; (k) TBAF, THF, rt. 92%; (l) $Pd(OH)_2/C$, $H_2$, EtOAc, rt, 98%.

alcohol or aldehyde, a variety of reducing reagents were investigated. To our delight, the ring-opened carboxylic acid **23** was achieved in a quantitative yield *via* an $S_N2'$ (conjugate reduction/elimination process) process (**22**) upon treatment with $NaBH_4$. Under the optimized conditions, the first three steps could be carried out in a sequence without purification. And twenty grams of carboxylic acid **23** could be prepared, which demonstrated the efficiency of the approach.

With the abundant intermediate **23**, containing the 2,3,3*a*,6,7,7*a*-hexahydroindole core, we proceeded with its conversion to the key monomer **7** (Scheme 3). First, the carboxyl group was converted to the hydroxyl group by a Barton decarboxylative oxygenation.[11] Alcohols **26** and **25** were isolated as diastereoisomers (*dr* = 3:1). Furthermore, the minor product **25** with an opposite configuration of the hydroxyl group in position 7, characterized by X-ray crystallography, could be transformed to **26** with the desired configuration by the Mitsunobu process. After *t*-butyldimethylsilyl protection of the hydroxyl group, the dihydroxylation/Ley oxidation[12]/dehydroxylation[13] sequence was performed, furnishing the β-methoxycarbonyl ketone **28**. After demethoxycarbonylation by sodium hydroxide, the *N*,*O*-protected monomer **29** was obtained, whose *t*-butyldimethylsilyl group could be easily removed in excellent yield (92%), followed by the removal of the benzyl protection (98%) affording key monomer **7**. Meanwhile, carboxylic acid **30** could be obtained by saponification of **29** in excellent yield (95%) as well.

In conclusion, a stereoselective synthesis of the key monomer of ETP natural products which involves a diastereoselective IEDDA reaction and the firstly reported $NaBH_4$ promoted bridged-lactone ring opening reaction has been successfully accomplished. The abundant intermediate **23** containing the 2,3,3*a*,6,7,7*a*-hexahydroindole core could be prepared by the reliable approach, which should provide a solid basis for the synthesis of other natural products featuring the hydroindole structure. Monomer **7** represents a key intermediate in the divergent synthetic strategy for natural products of the ETP family; further progress towards divergent total synthesis of ETPs and related natural products will be reported in the future.

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