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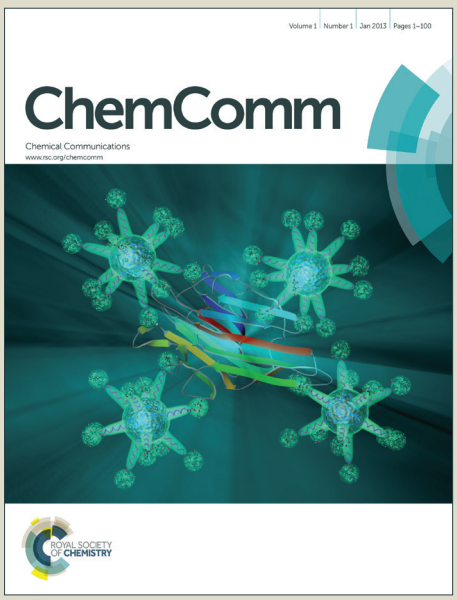

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Stereoselective Construction of a Key Hydroindole Precursor of Epidithiodiketopiperazine (ETP) Natural Products

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An asymmetric synthetic strategy for constructing the divergent-synthesis monomer of Epidithiodiketpipeazine (ETP) natural products has been successfully achieved. The functionalized 2,3,3a,4,7,7a-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 range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties.[1] ETPs, characterized by sulfur atoms[2] and a diketopiperazine structure, have led to 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 their elegant total syntheses of ETP molecules containing indole moiety. Among the ETP family, there are also lots of members incorporated with the hydroindole scaffolds (perhydroindole, 2,3,7,7a-tetrahydroindole, 2,3,3a,4,7,7a-hexahydroindole) structure (Figure 1).

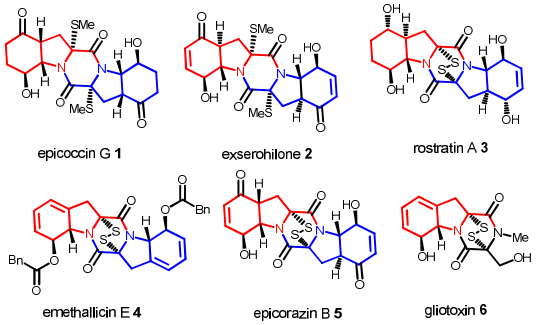
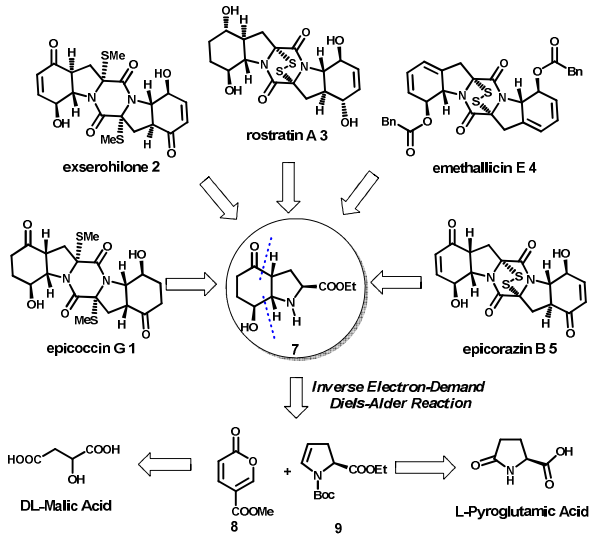


Figure 1. Representative ETP family members containing hydroindole scaffolds

Although numerous synthetic approaches were investigated, there were only a limited number of strategies for the preparation of the highly functionalized hydroindole scaffolds. The first synthesis of the related compound, glitoxin **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 2,3,7,7a-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 2,3,3a,4,7,7a-hexahydroindole core.[5] Recently, several fantastic works were achieved by Nicolaou and co-workers in 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 their synthesis of ETPs. A similar strategy to construct the hydroindole scaffold was also used in the total synthesis of acetylaranotin, another member of ETPs, 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 their key monomer **7**, which was found to be the key monomer accessed to most of ETPs, due to the C_2-symmetric structure (Scheme1). Thus, a reliable approach to access key monomer **7** was urgent to be developed. The hydroindole core was envisaged to be prepared through an inverse electron-demand Diels-Alder reaction (IEDDA).[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.

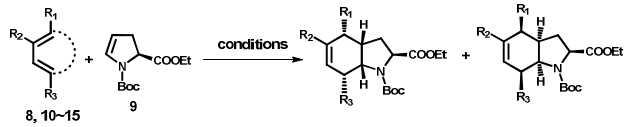


Scheme 1. Retrosynthetic Plan for Synthesis of ETPs

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 react with the electron-rich dienophile **9**. Different Lewis acids, such as BF_3•Et_2O and Et_2AlCl, were

attempted to promote the reaction. Unfortunately, dienophile **9** was found to be decomposed quickly in Lewis acidic conditions, even at low temperature. The dienes containing 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 unsuitable partner, either. To increase the electron deficiency of the diene, electron-withdrawing groups were then installed into the diene. The diene **13**, containing one bromine atom in position 5, reacted with dienophile **9**, affording the expected product in a 54% yield and the ratio of the *exo*/*endo* products was 3:1. Encouraged by this result, two bromine atoms (positions 3 and 5) installed diene **14** was tested. However, the yield was lower, presumably due to the steric hindrance of the bromine atom on the bridge of the product. After carboxyl group was introduced into position 5, only trace amounts of the product could be obtained due to the poor solubility of the diene **15**. To our satisfaction, after ester was introduced into position 5, the reaction afforded the desired product in 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.

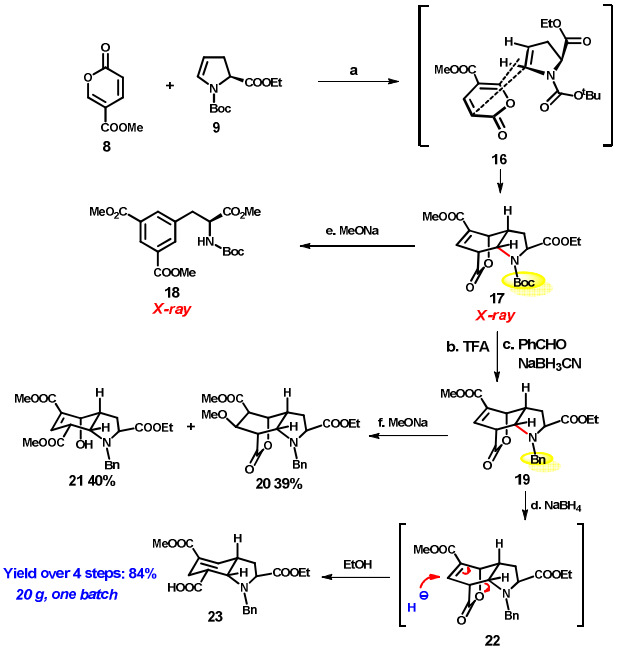
Table 1. Exploration of Stereoselective IEDDA Reaction.[a]



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[d]	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.

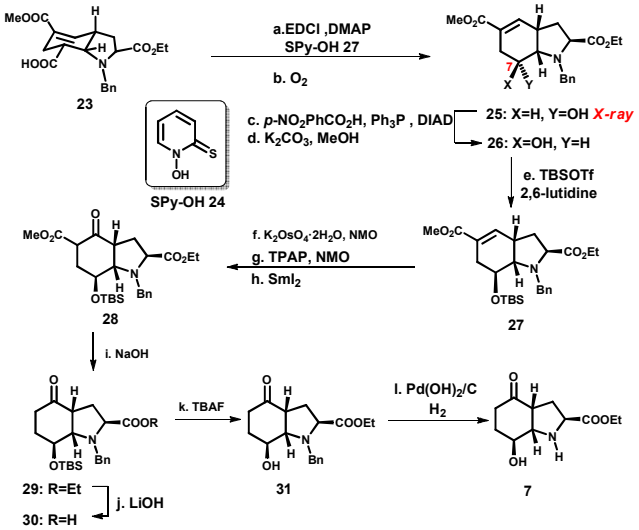
The relative stereochemistry of the IEDDA product **17** was comfirmed by X-ray crystallography (please see ESI). The stereoselectivity corresponds to an *exo*-approach of the diene **8** from the less hindered side of the dienophile **9**, pointing ethoxycarbonyl group in the opposite direction of the ring (**16**, Scheme 2). The endeavor on opening bridged-lactone ring in saponification conditions was invalid, due to the weakness of the C-N bond of *t*-butoxycarbonyl protecting IEDDA product **17**. Most of basic conditions afforded the C-N bond cleavage products, such as **18**, which was identified by X-ray crystallography. Considering the influence of the protecting group of amino, *t*-butoxycarbonyl protection was altered to benzyl protection. After treated with MeONa, benzyl protecting intermediate **19** was converted to the desired product **21** in 40% yield with 39% of Michael addition byproduct **20**. These negative results compelled us to abandon the attempts of ring opening in saponification conditions. In order to reduce the bridged-lactone ring to the corresponding alcohol or aldehyde, a variety of reducing reagent was investigated. To our delight, the ring-opened carboxylic acid **23** was achieved in quantitative yield via an S_N2' (conjugate reduction/elimination process) process (**22**) when treated with $NaBH_4$. Under the optimized conditions, the first three steps could be carried out in sequence without purification. And carboxylic acid **23** could be prepared in twenty grams, which demonstrated the efficiency of the approach.



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%.

With abundant 2,3,3a,6,7,7a-hexahydroindole core **23** in hand, we forwarded to 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] Alcohol **26** and **25** were isolated as diastereoisomers (*dr* = 3:1). Furthermore, the minor product **25** with the opposite configuration of hydroxyl group in position **7**, characterized by X-ray crystallography, could be transformed to **26** with the desired configuration by 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 benzyl protection (98%) affording key monomer **7**. Meanwhile, carboxylic acid **30** could be obtained by saponification of **29** in excellent yield (95%) as well.



Scheme 3.*Conditions*: (a) EDCl, 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•$2H_2O$, 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 (1M aq.)/THF, EtOH, rt, 95%; (k) TBAF, THF, rt. 92%; (l) $Pd(OH)_2$/C, H_2, EtOAc, rt, 98%.

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 2,3,3a,6,7,7a-hexahydroindole core could be prepared by the reliable approach, which should provide a solid basis for synthesis of other natural products featuring the hydroindole structure. Monomer **7** represents a key intermediate in divergent synthetic strategy for natural products of ETP family, further progress towards divergent total synthesis of ETPs and related natural products will be reported in the future.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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