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Unified enantioselective total synthesis of 3,6-dioxygenated diketopiperazine natural products, diatretol and lepistamides A, B and C

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ABSTRACT

The concise enantioselective total synthesis of Diatretol (1) has been achieved *via* 9 steps with 30% yield. The synthetic approach involves stereoselective oxidation and regioselective transacetalization utilizing a folded conformation induced by an intramolecular CH/π interaction. In addition, we have also achieved total synthesis of three diketopiperazine natural products, Lepistamides A (2), B (3) and C (4).

Introduction

Malaria, which is caused by species of *Plasmodium* parasites, is one of the world's three gravest infectious diseases, and according to the 2019 World Malaria Report, in 2018 there were an estimated 228 million cases of malaria and 405,000 deaths [1]. Antimalarial drugs are the main weapon to combat malaria, either for prophylaxis or treatment. The WHO now recommends artemisinin-based combination therapies as the preferred treatment option. However, malaria parasites have historically developed resistance to all newly introduced antimalarials extremely quickly, and so drug resistance has remained a continuous problem [2]. For example, artemisinin is one of the major antimalarial drug. However, plasmodium falciparum has evolved resistance to Artemisinin [3]. Consequently, there has always been a need to find new antimalarial drugs, preferably those that have a unique or different structure or mode of action, to try and offset or delay the emergence of drug resistance. Therefore, novel antimalarial drugs with new modes of action are urgently and constantly required to tackle the disease.

Our research group has strived to develop new medicines from microbial metabolite. Through the screening of antimalarial agents from our natural product library in the Kitasato institute, we identified the potent antimalarial activity of Diatretol (**1**), [4] originally isolated from a culture broth of the fungus *Clitocybe diatreta* by Arnone and co-workers in 1996 [5]. Other members of the 3,6-dioxygenated diketopiperazine (DKP) family, similar compounds, such as the Lepistamides (**2**–**4**) [6], don't demonstrate antimalarial activity (Fig. 1). The structure of (+)-**1** has been clarified by X-ray crystallography, and the benzyl and methoxy moieties in the DKP ring show a characteristic folded conformation [7,8] (Fig. 1). Additionally, the C6 methoxy group in the ^{1}H NMR of (+)-**1** was significantly shifted to lower ppm value (1.97 ppm in DMSO d_6) in ^{1}H NMR analysis data, while the methoxy group is within the shielding region of the phenyl group due to an intramolecular CH/π interaction [9,10]. Thereby, the methoxy and benzyl moieties are cis positioned at the DKP ring. However, the absolute configuration of (+)-**1** remains unknown.

In terms of antimalarial activity, (+)-**1** displayed potent *in vitro* antimalarial activity against the *Plasmodium falciparum* K1 strain, with an IC_{50} value of 378 ng/ml, as well as *in vivo* efficacy in a *P. berghei*-infected mouse model, with ca. 50% inhibition at 30 mg/kg (p.o.) [4]. Thus, we envisioned the enantioselective total synthe-

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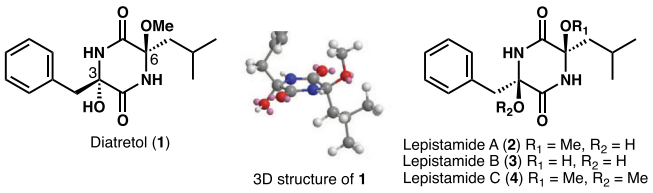


Fig. 1. Structures of Diatretol (1) and Lepistamides (2–4).

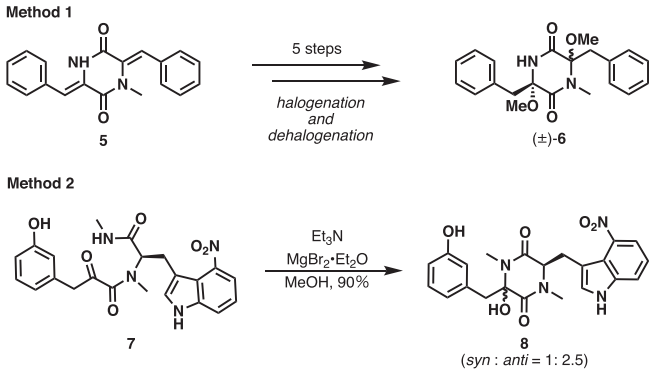
sis of (+)-**1** to determine its absolute configuration and clarify of its Structure/Activity relationship (SAR).

Results and discussion

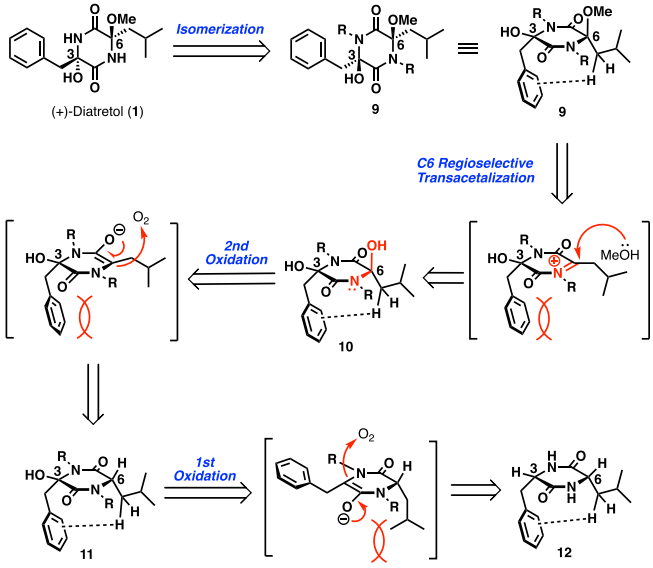
As for the construction of oxygenated DKP skeletons, two general methods have been reported (Scheme 1). Method 1 features halogenation and dehalogenation processes from the dehydrated intermediate **5** [11], while method 2 afford the *N,O*-acetal product **8** as a diastereomeric mixture via intramolecular cyclization from the ketoamide **7** [12]. However, when these methods are applied for the enantioselective synthesis of (+)-**1**, induction of the stereocenters at C3 and C6, and the chemoselective introduction of the C6 methoxy group, are problematic tasks. Due to limitations of the known protocols, we pursued a new synthetic approach for **1** (as shown retrosynthetically in Scheme 2), which features the isomerization of the *syn* compound **9** to a thermodynamically stable *anti* compound, followed by removal of *N*-protection groups to afford (+)-**1**. The C6 regioselective transacetalization of **10** using a folded conformation induced by an CH/π interaction, and the stereoselective stepwise oxidation of the known DKP **12** could be expected to produce the optically active **10**. DKP **12** was prepared from commercially available starting materials by using Xue's one-pot procedure [13]. To the best of our knowledge, the use of a folded conformation induced by an CH/π interaction is unprecedented in natural product synthesis.

Our synthesis began with N—H protection of **12** with a BOM group to give **13** (Scheme 3). Subsequently, we attempted the stereoselective oxidation of **13**. In the oxidation of the DKP ring, which consists of phenylalanine as one of amino acid residues, the corresponding C3 position tends to be predominantly oxidized over the C6 position [14], due to the lower bond dissociation energy of the C3-H, which is influenced by the benzyl moiety [15]. On the basis of this unique chemo selectivity, we postulated that the diol **10** would be obtained with high enantioselectivity via a stepwise oxidation process. Prior to the stepwise oxidation of **13**, we undertook a deuterium labeling experiment for the selective deprotonation of the C3 position. Interestingly, even with the use of excess amount of KHMDS only the C3 labeled product **14** was obtained as a single isomer, presumably due to the instability of the corresponding dienolate.

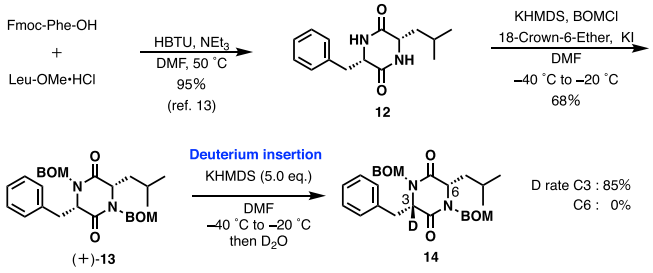
With a regio and stereoselective deprotonation product in hand, we extended the oxidation of **13**. Screening various oxidants, it was progressed under O_2 condition with high enantioselectivity. Based on this expected result, a plausible mechanistic pathway became clear (Scheme 4). The regio and stereoselective deprotonation at the C3 position proceeded to generate the enolate **15**, which underwent stereoselective oxidation to afford **16**, due to the steric repulsion of the isobutyl group. Progression of the 2nd oxidation subsequently afforded the optical active diol **20**, following the reduction of the peroxide **19**. As mentioned above, due to the relative instability of the dienolate, this remarkable double oxidation was achieved in a highly enantioselective fashion [16].



Scheme 1. Reported *N,O*-acetal construction methods for DKP.

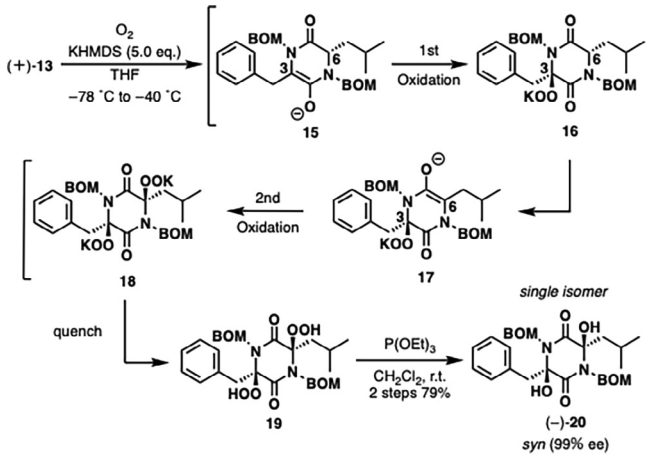


Scheme 2. Synthetic strategy for Diatretol (1).

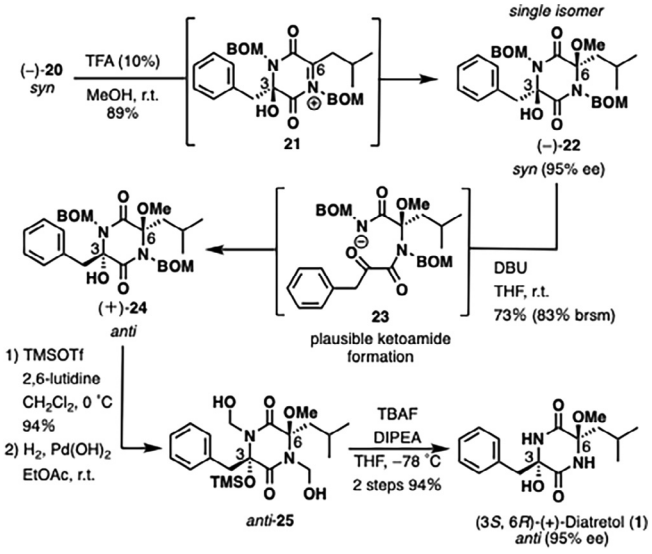


Scheme 3. Synthesis of DKP 13 and deuterium insertion.

In our scenario, *syn*-**20** would take a folded conformation due to a CH/π interaction, and the lone pair of the C6 adjacent nitrogen and the C6-OH moiety would adopt an antiperiplanar arrangement. This effect would lead to the regio selective iminium cation formation, followed by the stereoselective addition of MeOH from the opposite side of the benzyl moiety to afford the desired transacetalization product *syn*-**22** as a kinetic product. After testing a variety of conditions, the regio and diastereoselective transacetalization was produced under 10% TFA in MeOH at room temper-



Scheme 4. Regio and stereoselective sequential oxidation to produce the optically active diol (−)-20.

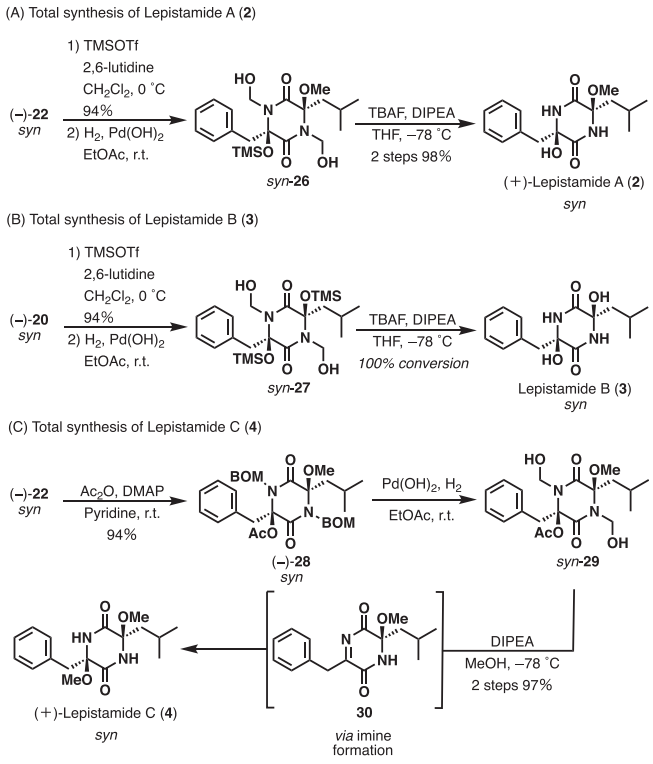


Scheme 5. Synthesis of (+)-Diatretol (1).

ature to give *syn*-**22** as a single diastereomer in high yield and 95% ee [17] (Scheme 5). Racemization occurred slightly during this conversion from (−)-**20** (99% ee) to (−)–**22** (95% ee), and we therefore presumed that there was slight equilibrium between *N,O*-acetal and ring-opened form (keto-amide form) at the iminium intermediate **21**. To prove our concept, this transacetalization was carried out using a substrate manipulated cyclohexyl moiety instead of phenyl moiety of (−)-**20** (see SI for the preparation of the cyclohexyl derivative). As a result, the regioselectively at C6 was cancelled and two corresponding mono-methoxy *N,O*-acetal products (1.1 : 1 as an inseparable mixture) were obtained [18]. This result indicated that the CH/π interaction has a significant influence on the regioselectivity in this transacetalization process.

In the end game for the synthesis of (+)-**1**, the isomerization of the C6 position was needed. We carried out the structure optimization and calculated single point energy of the both *syn*-**22** and *anti*-**24** by DFT calculation at B3LYP/6-31G* level, and concluded that the *anti*-**24** is −3.5 kcal/mol more stable than *syn*-**22** [19]. This calculation indicated that the CH/π interaction between benzyl and methoxy is stronger than that between benzyl and isobutyl. After adjusting the conditions, DBU was found to be most effective for the isomerization via the ketoamide intermediate **23** to afford the desired *anti*-**24** as a thermodynamic stable conformer. Then, *anti*-**24** was protected with TMSOTf and the cleavage of benzyl moieties was performed to give the hydroxymethyl *anti*-**25**. Finally, an optimized combination of TBAF and DIPEA for global deprotection provided Diatretol (**1**) in 9 steps with 30% overall yield (Scheme 5). Although the NMR spectral data from our synthetic sample of (+)-**1** ($[\alpha]_D$ = +7.4 in MeOH) were in reasonable agreement with those reported for the natural product, the optical rotation data were not identical with the reported data ($[\alpha]_D$ = +44.0 in MeOH) [5]. However, the optical rotation data of the natural sample ($[\alpha]_D$ = +7.8 in MeOH) which was obtained by us is in good agreement with that of the synthetic one. Furthermore, further support for the absolute configuration of natural (+)-**1** was obtained by comparison with the chiral HPLC ret ention analysis with the synthetic (+)-**1** (3*S*, 6*R*) [20]. Furthermore, the synthetic (+)-**1** (3*S*, 6*R*) and natural (+)-**1** showed comparable activity in the comparison of antimalarial activity *in vitro* and *in vivo* [4].

This divergent synthesis route allows for production of the three DKP natural products, Lepistamides A (**2**), B (**3**) and C (**4**) (Scheme 6). Silylation of *syn*-**22**, followed by the manipulations of *syn*-**22**, followed by the manipulations of *syn*-**22**, followed by the manipulations of the protecting group afforded **2**, double silylation of *syn*-**20** followed by stepwise deprotections gave **3**. Although the final deprotection step proceeded successfully, the target product **3** could not be isolated as a pure form due toinstability of **3**. Hence, we confirmed the formation of **3** by the comparison with the reported ^{1}H NMR data of **3** [6] without further purification. In contrast, acylation of *syn*-**22**, with subsequent introduction of a methoxy group gave *syn*-**28**. Removal of the hydroxymethyl group provided **4** via imine formation. Intriguingly, Lepistamides A (**2**), B (**3**) and C (**4**) were isolated as racemic natural products [6], whereas our synthetic route enabled to access to each enantiomer [21].



Scheme 6. Synthesis of Lepistamides A (2), B (3) and C (4).

Conclusions

In conclusion, the first and facile enantioselective total synthesis of Diatretol (**1**) has been achieved in 9 steps with 30% yield, and the absolute configuration of **1** was determined. The synthetic approach involves the stereoselective oxidation and regioselective transacetalization taking full advantage of a folded conformation. In addition, we applied the newly established synthetic route to the total synthesis of three analogs, Lepistamides A (**2**), B (**3**) and C (**4**). We are currently undertaking SAR studies and creating a library of derivatives and analogs for further biological evaluations. The results will be reported in due course. Our findings may facilitate the development of much needed novel antimalarial agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152895.

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[16] See the ESI for the chiral HPLC analytical conditions and chromatograms of (−)-20 and (+)-20.
[17] See the ESI for the chiral HPLC analytical conditions and chromatograms of (−)-22 and (+)-22.
[18] Compound 31 (see the ESI), having no CH/π interaction between C3 and C6 sidechains, gave two isomers 32 and 33 as an inseparable mixture under transacetalization condition (10% TFA in MeOH, r.t.).
[19] See the ESI for the DFT calculations by Gaussian 03.
[20] See the ESI for the chiral HPLC analytical conditions and chromatograms of natural (1), (+)-1 and (−)-1.
[21] See the ESI for the optical rotation data.