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# An enantioselective approach to (−)-platencin via catalytic asymmetric intramolecular cyclopropanation

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ABSTRACT

This Letter describes an enantioselective approach to (−)-platencin. A uniquely functionalized chiral intermediate, which was prepared via the highly enantioselective catalytic asymmetric intramolecular cyclopropanation (CAIMCP) that we have developed, was successfully transformed to Nicolaou's intermediate in his total synthesis of (−)-platencin.



The research group at Merck isolated (−)-platensimycin (**1**)[1] (Fig. 1) and (−)-platencin (**2**)[2] from *Streptomyces platensis* MA 7327 and 7339, respectively. These compounds have a 3-amino-2,4-dihydroxybenzoic acid moiety as the common structure but differ in their lipophilic and polycyclic moieties.

(−)-Platensimycin (**1**) has a tetracyclic framework including a cyclic ether while (−)-platencin (**2**) has a tricyclic framework which consists of only carbons. (−)-Platensimycin (**1**) is a potent and selective inhibitor of FabF, the condensing enzyme that catalyzes elongation in bacterial fatty acid synthesis.[1] (−)-Platencin (**2**) is a moderate inhibitor of both FabF and FabH, the enzyme catalyzing the initial condensation in bacterial fatty acid synthesis.[2] Because of their new modes of action, **1** and **2** show potent, broad-spectrum Gram-positive antibacterial activity, and also exhibit no cross-resistance to antibiotic-resistant bacteria, including MRSA and VRE.[1,2]

The unique structural features and new modes of action of these new antibiotics have attracted much attention from the synthetic and medicinal chemistry communities, and a number of total syntheses[3–5] as well as SAR studies[6] have been reported.

We were interested in the synthesis of compounds **1** and **2**, and their new derivatives because of their biological activity. Moreover, the structural similarities between **1** and **2** led us to develop enantioselective and divergent approaches to this new class of antibiotics. We herein report the enantioselective formal total synthesis of (−)-platencin (**2**) via the chiral key intermediate which was prepared via a highly enantioselective catalytic asymmetric intramolecular cyclopropanation (CAIMCP) that we have developed.

In the course of the retrosynthetic analysis of **1** and **2**, we identified a common carbon framework, a *cis*-dehydrodecalin skeleton possessing a bridgehead stereogenic quaternary carbon, which was hidden within their structures (Scheme 1). The *cis*-dehydrodecalin skeleton was also found in intermediates reported earlier by other

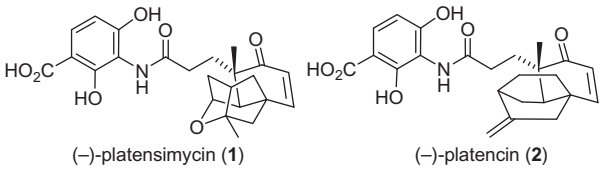
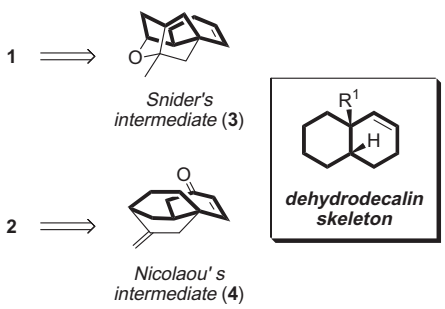



**Figure 1.** Structures of (−)-platensimycin (**1**) and (−)-platencin (**2**).

research groups, including Snider's intermediate **3**[3b] for **1** and Nicolaou's intermediate **4**[4a] for **2**. Therefore, we set **4** as the target of our formal total synthesis of (−)-platencin (**2**).

We have reported the CAIMCPs with CuOTf and bisoxazoline ligand **6**.[7] Tricyclo[4.4.0.0]decene derivatives **7** thus prepared (Scheme 2) can serve as the key synthetic intermediates because they possess useful functional groups such as a cyclopropane, an alkene, and a ketone. Hence, **7** and related derivatives prepared by the CAIMCP have been successfully utilized for the enantioselective total synthesis of natural products.[8] Moreover, compounds **7** also incorporate the *cis*-dehydrodecalin skeleton with a quater-




**Scheme 1.** *cis*-Dehydrodecalin skeleton hidden in **1** and **2**.

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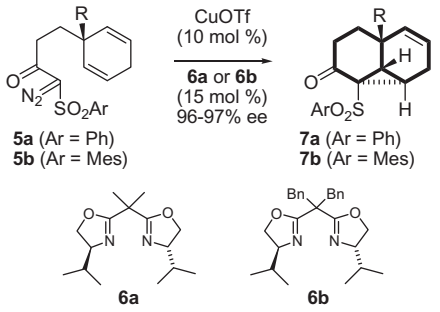
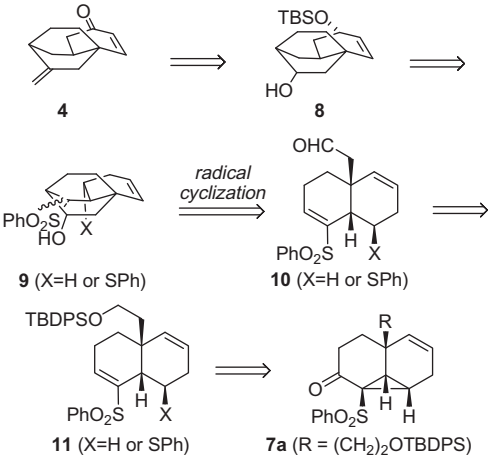


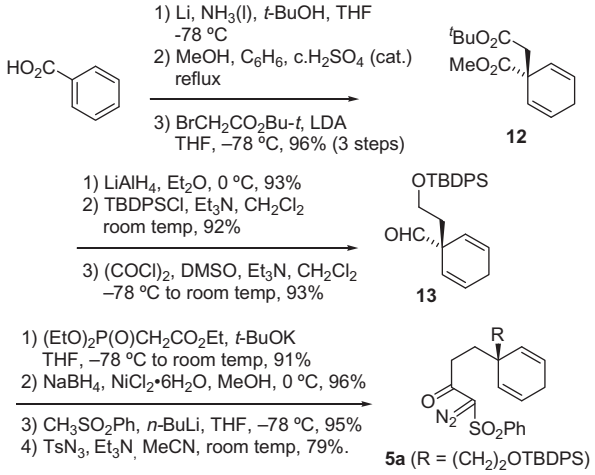

**Scheme 2.** Preparation of **7** by catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of **5**.




**Scheme 3.** Retrosynthetic analysis of **4**.

nary stereogenic center. Therefore, we surmised that **7** would be suitable for the synthesis of **4**, and we undertook the retrosynthetic analysis of **4** starting from **7**.

Compound **4** was thought to be formed from alcohol **8** via oxidation, Wittig olefination, deprotection, and oxidation (Scheme 3). Alcohol **8** would be obtained from **9** by the removal of the sulfur-containing functional group(s) and subsequent allylic oxidation. As the α,β-unsaturated sulfone is a good radical acceptor, tricyclic compound **9** could be formed by the reductive radical cyclization




**Scheme 4.** Preparation of **5a** (R = $(CH_2)_2$OTBDPS).

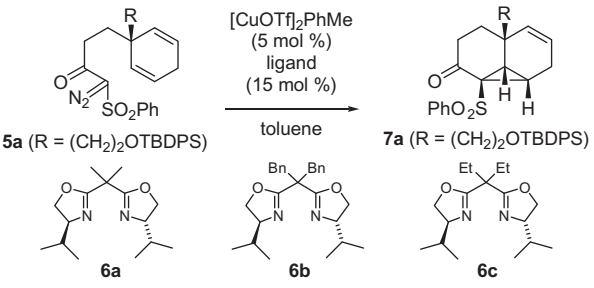
of aldehyde **10**. Finally, aldehyde **10** would be prepared from compound **11**, which was thought to be prepared by the appropriate transformations from compound **7a** (R = $(CH_2)_2$OTBDPS).

On the basis of the retrosynthetic analysis of **4** (Scheme 3), we first prepared α-diazo-β-keto sulfone **5a** (R = $(CH_2)_2$OTBDPS) to examine the CAIMCP approach for obtaining compound **7a** (R = $(CH_2)_2$OTBDPS) (Scheme 4). Birch reduction of benzoic acid, methyl ester formation, and subsequent alkylation of the enolate with *tert*-butyl bromoacetate afforded compound **12**. Reduction of ester **12** with $LiAlH_4$ afforded the corresponding diol, followed by the selective TBDPS ether formation of the less hindered hydroxyl and then Swern oxidation to afford aldehyde **13**. Aldehyde **13** was subjected to Horner–Wadsworth–Emmons reaction, followed by reduction with $NaBH_4$ in the presence of $NiCl_2$,[9] addition of methyl phenyl sulfone, and diazo transfer reaction to afford α-diazo-β-keto sulfone **5a** (R = $(CH_2)_2$OTBDPS).

The CAIMCPs of compound **5a** (R = $(CH_2)_2$OTBDPS) with CuOTf and ligand **6a–c** were examined (Table 1). The CAIMCP with ligand **6a** proceeded at room temperature to successfully afford cyclopropane **12** (72%) with 95% ee (entry 1). The CAIMCP with the more bulky ligand **6b** was slow at room temperature and required heating to afford **7a** (R = $(CH_2)_2$OTBDPS) (entry 2, 50%, 93% ee). The reaction with ligand **6c** did not improve the yield and gave the same result as that obtained with ligand **6b** (entry 3). Consequently, we decided to employ the conditions in entry 1 to prepare **7a** (R = $(CH_2)_2$OTBDPS). The absolute configuration of **7a** (R = $(CH_2)_2$OTBDPS) was not determined at this stage but was provisionally assigned as shown in Table 1 according to our transition state model.[7a]

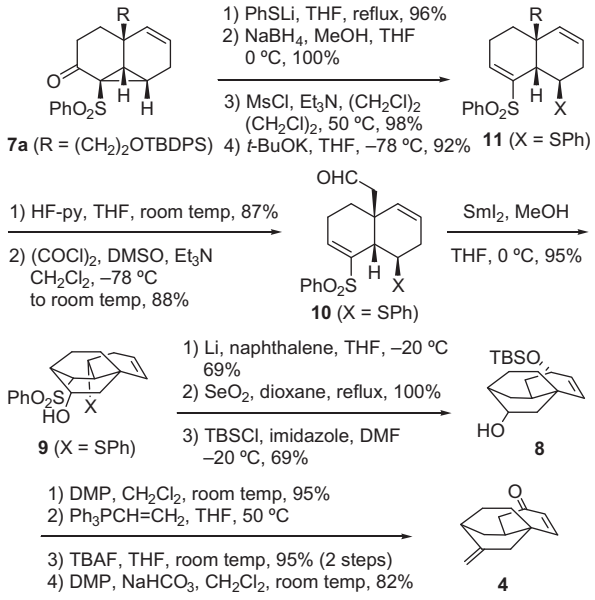
Next we examined the transformation of **7a** (R = $(CH_2)_2$OTBDPS) to **4** (Scheme 5). The ring-opening reaction of cyclopropane **7a** (R = $(CH_2)_2$OTBDPS) without removing the phenyl sulfonyl group was attempted first. However, all the reactions with various reducing agents provided a mixture of products that lacked the phenyl sulfonyl group. Consequently, we conducted the ring-opening reaction with lithium thiophenoxide[8a] with the intention of removing the phenyl sulfide at a later stage. The ring-opening reaction with lithium thiophenoxide afforded the corresponding keto

**Table 1**
CAIMCP of **5a** (R = $(CH_2)_2$OTBDPS)




| Entry | Ligand | Temp (°C) | Time (h) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **6a** | rt | 18 | 72 | 95 |
| 2 | **6b** | rt, 50[c] | 3.5, 13[c] | 50 | 93 |
| 3 | **6c** | rt, 50[c] | 3.5, 15[c] | 42 | 93 |

[a] Isolated yields.
[b] ee determined by HPLC. HPLC conditions: Daicel CHIRALCEL OD-H 0.46φ × 25 cm, hexane/2-propanol 9:1, flow rate = 0.4 ml/min, retention time 18.6 min for minor, 22.2 min for major.
[c] Reaction was carried out at the indicated temperatures for the indicated times, respectively.




**Scheme 5.** Formal total synthesis of (−)-platencin (**2**).

sulfide in high yield, and subsequent reduction with $NaBH_4$ afforded the corresponding alcohol. Unfortunately, attempts to dehydrate the resultant alcohol under various conditions produced a mixture of regioisomeric alkenes; hence, we prepared the corresponding mesylate to prepare alkene **11** (X = SPh) by the elimination reaction under basic conditions.

Although double bond isomerization of **11** (X = SPh) during the elimination reaction was a problem, when a pre-cooled (−78 °C) THF solution of potassium *tert*-butoxide was added to a solution of the mesylate in THF at −78 °C, **11** (X = SPh) was obtained in 92% yield with a trace amount of its regioisomeric alkene isomer.

With the key compound **11** (X = SPh) in hand, we examined the synthesis of compound **4**. Not only did removal of the TBDPS group in compound **11** (X = SPh) with TBAF caused migration of the double bond, but also did the use of TBAF with an acidic additive was unsuccessful. Fortunately, the reaction of **11** (X = SPh) with HF·py proceeded cleanly and kept the alkene intact, and the subsequent Swern oxidation afforded aldehyde **10** (X = SPh).

The key reductive radical cyclization of aldehyde **10** (X = SPh) with $SmI_2$ proceeded smoothly at 0 °C to afford compound **9** (X = SPh) which possessed the tricyclic core of (−)-platencin (**2**) as a single isomer. Treatment of compound **9** (X = SPh) with lithium naphthalenide removed the sulfide and sulfone simultaneously without problem. Subsequent allylic oxidation with selenium dioxide followed by selective protection of the reactive allylic hydroxyl with TBSCl at −20 °C afforded TBS ether **8**. Dess–Martin oxidation of alcohol **8**, Wittig methylenation, removal of the TBS group, and Dess–Martin oxidation in the presence of sodium bicarbonate successfully afforded compound **4**. The synthesized compound was proved to be identical in all respects to the intermediate **4** described by Nicolaou ($^1H$ and $^{13}C$ NMR, IR, MS, and $[\alpha]_D$).[10] This fact established the absolute structure of cyclopropane **7a** (R = $(CH_2)_2$OTBDPS) and verified the formal enantioselective total synthesis of (−)-platencin (**2**).

In summary, a new enantioselective approach to (−)-platencin (**2**) has been developed via the unique chiral intermediate **11** (X = SPh), possessing a useful α,β-unsaturated sulfone functionality which served as a good radical acceptor. This intermediate **11** (X = SPh) was derived from compound **7a** (R = $(CH_2)_2$OTBDPS), which was successfully prepared via the highly enantioselective CAIMCP that we have developed. Therefore, the formal enantioselective total syntheses reported herein prove the applicability of uniquely functionalized tricyclo[4.4.0.0]decene derivative **7a** (R = $(CH_2)_2$OTBDPS) as well as the usefulness of the CAIMCP in natural product synthesis. Studies on a new enantioselective approach to (−)-platensimycin (**1**) via the same intermediate prepared in this study are now underway and will be reported in due course.

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10. Compound **4**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.57 (1H, d, $J$ = 10.0 Hz), 5.88 (1H, d, $J$ = 10.0 Hz), 4.83 (1H, d, $J$ = 1.7 Hz), 4.69 (1H, d, $J$ = 1.7 Hz), 2.48–2.40 (2H, m), 2.36–2.29 (2H, m), 2.19–2.08 (2H, m), 2.03–1.96 (1H, m), 1.82–1.68 (3H, m), 1.55–1.48 (1H, m), 1.20 (1H, ddd, $J$ = 12.6, 7.8, 1.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 156.7, 148.9, 127.7, 106.9, 41.6, 40.8, 36.0, 35.5, 35.4, 34.8, 26.3, 24.5; IR (neat) $\nu_{max}$ 2939, 2866, 1684, 1429, 1273, 1236, 1167, 877, 765 cm$^{-1}$; FAB HRMS $[M+H]^+$ calcd for $C_{13}H_{17}O$: 189.1279, found: 189.1288; $[\alpha]_D^{25}$ +21.2 (*c* 0.1, $CHCl_3$) (lit.[4f] $[\alpha]_D^{25}$ +21.2 (*c* 1.0, $CHCl_3$)).