Communication

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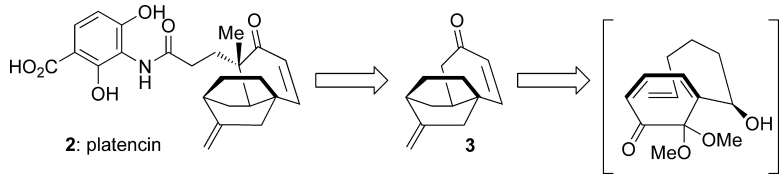

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An Expedient Asymmetric Synthesis of Platencin

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Fatty acid biosynthesis (FAS) is an essential metabolic process for all living organisms.[1] As such, selective intervention of fatty acid metabolism constitutes a useful means to treat disease. Indeed, inhibitors of certain steps of the bacterial fatty acid biosynthetic pathway have been targeted as potential antibacterial agents to treat infections.[2] The recent discovery of the broad-spectrum antibiotics platensimycin (**1**, Figure 1)[3] and platencin (**2**, Figure 1)[4] by a Merck team represents a milestone in the search for novel FAS inhibitors. Through application of RNA silencing technologies, platensimycin and platencin were identified from a high-throughput screening of natural product extracts. While platensimycin is a selective inhibitor of the fatty acid condensing enzyme FabF, platencin exhibits dual activity, inhibiting both FabF and FabH. As these enzymes are highly conserved among the clinically relevant pathogens, these antibiotics display broad-spectrum antibacterial properties, including activities against the drug resistant strains MRSA (methicillin-resistant *S. aureus*) and VRE (vancomycin-resistant *enterococci*). The promising therapeutic potentials and intriguing molecular architectures of platensimycin (**1**) and platencin (**2**) have instigated significant research activities in scientific and medical circles, and a number of chemical syntheses of platensimycin,[5] platencin,[6] and rationally designed analogues of platensimycin have been reported.[7] Herein we disclose an expedient and asymmetric synthetic route to enone **3** that constitutes a formal total synthesis of platencin (**2**), since **3** has been previously converted to this natural product.[6]

As outlined in Figure 1, retrosynthetic simplification of platencin (**2**) began with the initial detachment of the two side chains of the molecule from its tricyclic core structure as shown to unravel cyclohexenone **3**, a known precursor of the target.[6] Inspired by the work of Liao and co-workers in the cycloaddition reactions of masked *o*-benzoquinones,[8] an intramolecular Diels−Alder reaction of 6,6-dimethoxy-cyclohexa-2,4-dienone **4** bearing a pendent terminal alkene was defined as the means to cast the tricyclic core of enone **3**. The stereochemical requirements of the tricyclic scaffold of enone **3** were expected to arise from the sole stereocenter within benzylic alcohol **5**, whose absolute stereochemistry was to be derived from an asymmetric reduction of the corresponding carbonyl compound.

The synthesis of enone **3** commenced with silyl protection (TBDPSCl, imidazole, DMAP, 95%) of guaiacol (**6**)[9] and proceeded as shown in Scheme 1. *ortho*-Lithiation of the TBDPS-protected guaiacol (*s*-BuLi, TMEDA)[10] followed by treatment of the resulting aryl lithium species with alkenyl Weinreb amide **7**[11] gave ketone **8** in 51% yield (90% based on 57% conversion). Catalytic asymmetric reduction of ketone **8** under the Corey−Bakshi−Shibata (CBS) conditions[12] delivered benzyl alcohol **5** in 78% yield[13] and 90% ee (as determined by ^{1}H NMR analysis of the Mosher ester derivative). Desilylation of **5** through exposure to TBAF (92% yield) provided phenol **9**, setting the stage for the generation and intramolecular Diels−Alder trapping of the targeted monoprotected *o*-benzoquinone. Pleasingly, treatment of a methanolic solution of

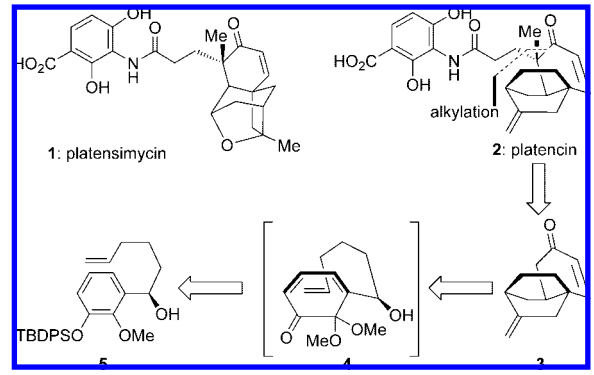

Figure 1. Structures of platensimycin (**1**) and platencin (**2**) and retrosynthetic analysis of **2** leading, sequentially, to tricyclic enone **3**, dienone **4**, and benzyl alcohol **5**. TBDPS = *tert*-butyldiphenylsilyl.

phenol **9** with 1.1 equiv of $PhI(OAc)_2$ followed by solvent exchange from methanol to toluene and refluxing led, via the intermediacy of 6,6-dimethoxy-cyclohexa-2,4-dienone derivative **4**, to Diels−Alder adduct **10** in 75% yield and 15:1 dr (as determined by ^{1}H NMR spectroscopic analysis). The remarkably high degree of stereocontrol by the lone stereocenter within precursor **4** in forming the three additional stereocenters in product **10** (*endo*) was both interesting and gratifying.[14] Catalytic hydrogenation (Pd/C cat., H_2) of **10** gave hydroxy ketone **11** in essentially quantitative yield. The desired elimination of the equatorially disposed secondary hydroxyl group within **11** posed an initial challenge that was ultimately overcome by a three-step procedure involving (i) oxidation of the secondary hydroxyl group to the corresponding ketone (PCC);[15] (ii) enol triflate formation ($PhNTf_2$, KHMDS); and (iii) reductive detriflation [$Pd(PPh_3)_2Cl_2$, HCO_2H, n-Bu_3N; 80% overall yield]. Further reductive processing with SmI_2 cleaved the gem-dimethoxy moiety from **12** providing keto-olefin **13** in 72% yield. Addition of MeMgBr to the latter compound furnished an inconsequential mixture of tertiary alcohols (**14**, *ca.* 1:1) which were subjected, without separation, to the allylic oxidation conditions described by Shing et al. [$Mn(OAc)_3$, t-BuOOH, O_2][16] to afford enone **15**, as a mixture of diastereoisomers, in 70% yield over the two steps. Finally, Martin's sulfurane-mediated elimination of the tertiary hydroxyl group from **15** resulted in the exclusive formation of the desired exocyclic olefin (90% yield), completing the synthesis of the targeted tricyclic enone **3** and, thus, the formal total synthesis of platencin (**2**). Enone **3** exhibited identical physical properties (^{1}H and ^{13}C NMR spectra, $[\alpha]_D$, and MS) to those previously reported for this compound.[6]

Commencing with a readily available and inexpensive starting material, and based on a highly efficient and stereoselective intramolecular Diels−Alder reaction, the described chemistry offers an expedient catalytic asymmetric route to platencin and provides an opportunity for rapid construction of analogues of this new antibiotic for biological and pharmacological studies.

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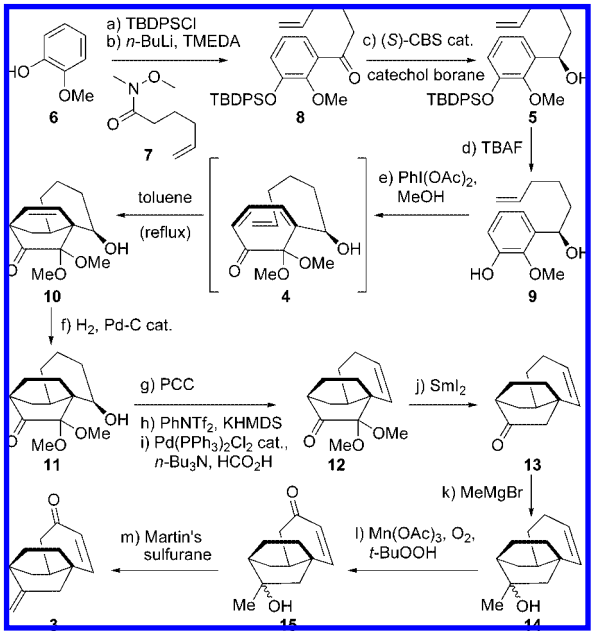
Scheme 1. Synthesis of Enone **3** [a]



[a] Reagents and conditions: (a) TBDPSCl (1.5 equiv), imidazole (4.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 → 23 °C, 16 h, 95%; (b) *sec*-BuLi (1.4 M in cyclohexane, 1.2 equiv), TMEDA (1.5 equiv), THF, −78 °C, 45 min; then **7** (1.0 equiv), −78 °C, 2 h, 51% (90% based on 57% conversion); (c) (*S*)-(−)-2-methyl-CBS-oxazaborolidine (0.2 equiv), catechol borane (1.0 equiv), toluene, 0 °C, 2 h, 78% (90% ee) (92% based on 85% conversion); (d) TBAF (1.0 M in THF, 1.5 equiv), THF, 0 → 23 °C, 2 h, 92%; (e) $PhI(OAc)_2$ (1.1 equiv), $KHCO_3$ (2.0 equiv), MeOH, 0 → 23 °C, 30 min; then toluene, reflux, 4 h, 75% (15:1 dr); (f) Pd−C (0.25 equiv), H_2, MeOH, 23 °C, 30 min, 100%; (g) PCC (1.6 equiv), CH_2Cl_2, 23 °C, 16 h, 97%; (h) $PhNTf_2$ (1.4 equiv), KHMDS (0.5 M in toluene, 2.3 equiv), THF, −78 → 0 °C, 30 min; (i) $Pd(PPh_3)_2Cl_2$ (0.36 equiv), *n*-Bu_3N (2.7 equiv), HCO_2H (1.8 equiv), DMF, 70 °C, 16 h, 82% for the two steps; (j) SmI_2 (0.1 M in THF, 10 equiv), THF/MeOH (20:1), 0 °C, 15 min, 72%; (k) MeMgBr (1.0 M in THF, 2.0 equiv), THF, 0 → 23 °C, 30 min, 87% (ca. 1:1 mixture of diastereoisomers); (l) $Mn(OAc)_3$ (0.35 equiv), *t*-BuOOH (5.0 M in decane, 4.8 equiv), O_2, EtOAc, 23 °C, 16 h, 80%; (m) Martin's sulfurane (2.0 equiv), CH_2Cl_2, 23 °C, 2 h, 90%. 4-DMAP = 4-dimethylaminopyridine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TBAF = tetra-*n*-butylammonium fluoride; PCC = pyridinium chlorochromate; Tf = trifluoromethanesulfonyl; KHMDS = potassium hexamethyldisilazide; DMF = *N*,*N*′-dimethylformamide.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via Internet at http://pubs.acs.org.

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(13) A reverse addition protocol (see Supporting Information) was adopted for optimal overall conversion/ee and minimal side reactions (including undesired hydroboration of terminal olefin).

(14) A similar Diels−Alder reaction using racemic **9** was first demonstrated by Liao and co-workers; see ref 8. The preference for the *endo* product can be attributed to the severe steric congestion experienced by the *exo* transition state as revealed by manual molecular models.

(15) Alcohol **11** derived from the major diastereoisomer of the Diels−Alder reaction oxidizes faster than the minor diastereoisomer, allowing further enantiomeric enrichment of the product through kinetic resolution. A single recrystallization (hexane) of the resulting ketone afforded essentially optically pure material (by optical rotation measurement).

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