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A Bismuth(III)-Catalyzed Friedel−Crafts Cyclization and Stereocontrolled Organocatalytic Approach to (−)-Platensimycin

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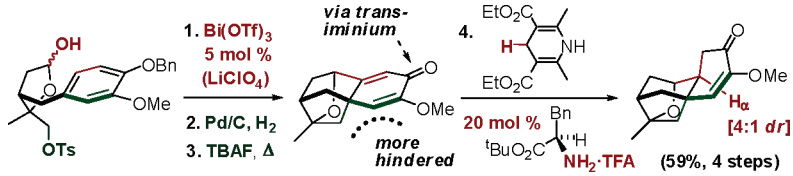
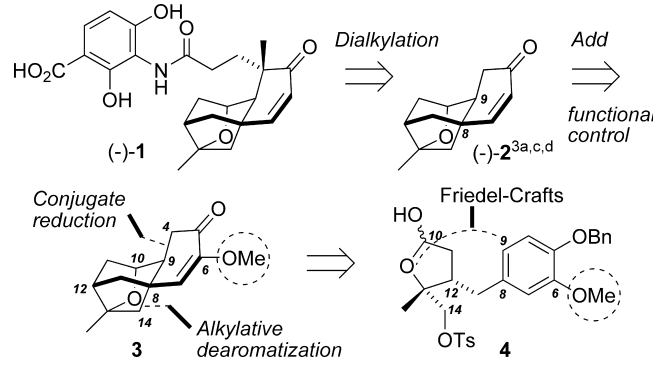
ABSTRACT



A high yielding route to the (−)-platensimycin core is communicated. This entailed the discovery of $Bi(OTf)_3$ to catalyze a Friedel−Crafts cyclization of a free lactol, supplemented by $LiClO_4$ to suppress the Lewis basicity of the sulfonate group. After TBAF-promoted cyclodearomatization, a diastereoselective conjugate reduction of a dienone was achieved by adopting amine-based organocatalytic rationales to reverse the inherent steric control of the substrate.

Natural products continue to challenge even our most established and advanced synthetic methods. They also inspire new methods and new strategies. Platensimycin (−)-**1** is a prime example. Since its antisense/RNA-based identification from a *Streptomyces platensis* strain, and structural disclosure by Merck researchers in 2006,[1] this potent broad-spectrum antibiotic has succumbed to several total, formal, and analog syntheses.[2−5] Amid a majority of chiral pool and racemic routes, the catalytic Rh(I)/BINAP-based and Brønsted/Lewis acid Diels−Alder methods stand out to be highly enantioselective in forming intermediates to (−)-**1**.[3] A common such intermediate is Nicolaou's tetracyclic enone **2**[2,3a,c,d] (Scheme 1).

Scheme 1. Retrosynthetic Analysis of (−)-Platensimycin (**1**)



Installation of the required C8/C9 relative stereochemistry has, however, been nontrivial under chiral reagent control,[4]

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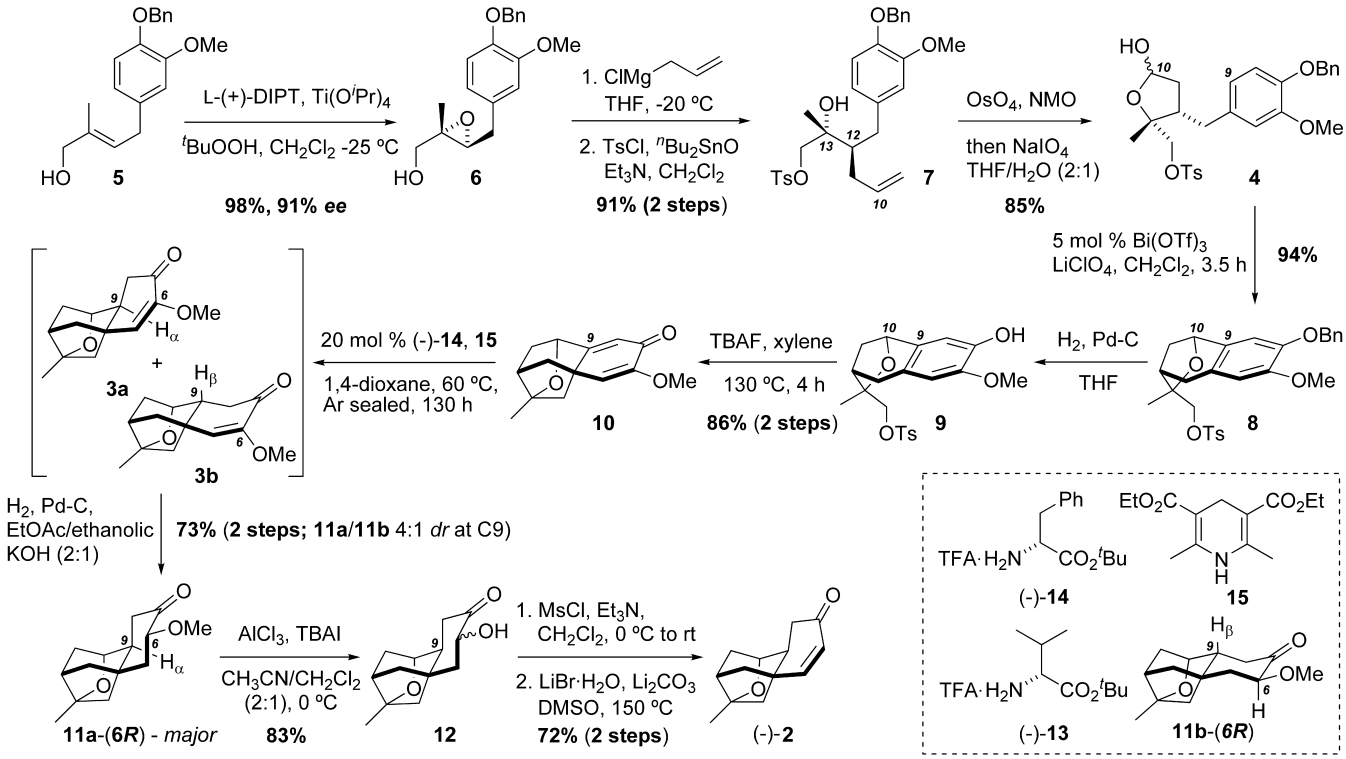
Scheme 2. Stereocontrolled Assembly of the Tetracyclic Enone Core **2** of (−)-Platensimycin



although high diastereoselectivity has been achieved under high pressure hydrogenation conditions.[3b,5g] Herein, we describe an enantioselective synthesis of (−)-**2**[3a,c,d] through the development of a direct Bi(III)-catalyzed Friedel−Crafts cyclization of the free lactol **4** and a stereocontrolled iminium-mediated conjugate reduction of a 6-methoxy-4,6-dienone precursor of **3** from the sterically more congested α-face.

Retrosynthetically, the 6-methoxy version of **2**[3a,c,d] (**3**) was anticipated to impart greater electronic and steric control in securing the *cis*-C8/C9-ring juncture (vide infra). This would necessitate the realization of a diastereoselective Friedel−Crafts (FC) cyclization[6] of the lactol **4** to an oxabicyclo[3.2.1]octane (**8**) via Marson-type oxocarbenium chemistry.[7] A Masamune-inspired intramolecular alkylative dearomatization strategy[8] would then complete the cage-like core. A concise and enantioselective assembly of the tetracyclic enone **2** is outlined in Scheme 2.

Beginning with allyl alcohol **5**,[9] a catalytic Sharpless epoxidation with L-(+)-DIPT afforded the epoxy alcohol **6** in 98% yield and 91% ee.[10] Regioselective epoxide opening with allyl magnesium chloride[11] established the desired stereocenter at C12, after which Martinelli's regioselective catalytic monotosylation[12] provided **7**. Oxidative double-bond cleavage with concomitant cyclization then furnished the *cis*-tosyl lactol **4** in 85% yield.

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Under Marson-type FC conditions, initial efforts to cyclize **4** to the benzotetrahydrofuran **8** with $BF_3{\cdot}Et_2O$ were met with limited success.[7b,c,13] After screening, a large excess of $SnCl_4$ was found to give optimal results at −78 °C.[6a,d] Notably, this intramolecular arylation step proceeded with high stereo- and regioselectivity at C9/C10. The alternative C7/C10-regioisomer and C8/C10 *ipso*-isomer were not detected. Quenching the reaction was, however, problematic. Typical aqueous protocols led to significant decomposition of **8**, with significant reversion back to **4**. After considerable experimentation, quenching the remaining $SnCl_4$ by pouring into half-saturated Rochelle salt solution suppressed these side-reactions and reliably provided **8** in good yields.[14] As much as 8 equivalents of $SnCl_4$ were, however, required for the conversion, suggesting a possible retardation of Lewis acid reactivity by the sulfonate group.[15]

To further improve practical issues, we next decided to develop a direct catalytic FC method to **8**. Having screened several oxophilic Lewis acids, a new catalytic combination of 5 mol % $Bi(OTf)_3$ with 3 equiv of $LiClO_4$ as a cocatalyst[16] was eventually discovered to drive the FC cyclization to furnish **8** in 94% yield within 3.5 h.[15] Interestingly, $LiClO_4$ alone was incapable of effecting the cyclization and one equivalent of $Bi(OTf)_3$ without $LiClO_4$ gave inefficient conversions for tosylates. In Mukaiyama's $SbCl_5/LiClO_4$-catalyzed Friedel−Crafts acylation,[16a] the formation of an active oxocarbenium perchlorate species is suggested between $SbCl_5$ and $LiClO_4$ with acid anhydrides.[15] Likewise, the combination of $Bi(OTf)_3$ and $LiClO_4$ could generate a more reactive cationic species with the lactol **4** toward nucleophilic ring closure. From our findings, we also reason that Li^+ can compete for the Lewis basic sulfonate group and release any trapped Bi(III), thereby allowing a catalytic cycle to persist.

Having secured reliable FC cyclization conditions, the benzyl deprotected tosyl-phenol **9** was freshly formed (see Supporting Information for single-crystal X-ray data) and directly subjected to intramolecular alkylative dearomatization conditions. Boger's methods were initially examined.[8b,c] DBU in refluxing CH_3CN or NaH in DMF/THF (and methods such as Na in ^{t}BuOH or LDA in THF) gave poor conversions with **9**. Eventually, without the need to resort to better leaving groups or phenyl silyl ether activation methods,[3b,5e,8b,d] the treatment of **9** with TBAF in xylene (at ambient pressures) or THF (in a sealed-tube) at 130 °C efficiently afforded the dienone caged-core **10** in 86% yield over two steps.

As introduced earlier, a chemo- and stereocontrolled conjugate reduction at the electron-deficient C4−C9 olefin of **10** to the enone **3a** (versus its C9-epimer **3b**) was anticipated to be achievable by virtue of the C6-methoxy group. A method to control the stereochemical outcome was, however, difficult to achieve (Table 1, entries 1−3). Atmospheric hydrogenation of **10** over catalytic Pd/C afforded a 1:3 diastereomeric ratio (dr) in favor of undesired **11b** over **11a** (entry 1). Buchwald's *in situ* prepared (*R*)-*p*-*tol*-BINAP-stabilized Cu−H complex[17] gave a 1:4 dr in favor of **3b** over **3a** (entry 2) and alternative Cu−H conditions with (*S*)-BINAP[18] favored the undesired **3b** exclusively (entry 3).

Table 1. Conjugate Reduction Study of α-Methoxydienone **10**

entry	conditions	yield (%)	**3a**:**3b**[a]
1	Pd−C cat., H_2, EtOAc/ethanolic KOH (2:1), 2 h	70	1:3[b]
2	(i) CuCl/NaO^{t}Bu/(*R*)-tol-BINAP (20 mol %), PMHS[c] (2 equiv), toluene, 132 h; then (ii) DMP[d] (3 equiv), CH_2Cl_2, 7 h	56	1:4
3	(*S*)-BINAP/Cu(OAc)$_2$ (0.5 equiv), PMHS[c] (6 equiv), ^{t}BuOH/THF, 36 h	17	0:1
4	(−)-**13** (1 equiv), **15** (2.4 equiv), dioxane, 60 °C, 48 h	30	3.5:1
5	20 mol % (*S*)-TRIP[23]/ D-Val-O^{t}Bu, **15** (5 equiv), ^{n}Bu$_2$O, 70 °C, 120 h	10	1.2:1
6	20 mol % (−)-**14**, **15** (3.2 equiv), dioxane, 60 °C, 130 h	61	8:1[e]

[a] Based on ^{1}H NMR dr at C9. [b] **11a/11b** isolated (1:3). [c] Polymethylhydrosiloxane. [d] Dess−Martin periodinane. [e] **11a/11b** also isolated in 17% yield (∼1:1).

Collectively, these results suggest an over-riding substrate-controlled steric effect enforcing β-facial attack. They are also consistent with Mulzer's first investigation on using Crabtree's Ir-catalyst, which furnished a 1.3:1 C8/C9-*cis*/*trans* decalin mixture at best from a C6-demethoxy analog of **10** under 1 atm of H_2.[4a] Nevertheless, exceptions to substrate control have been achieved under high pressures and with optimized chiral reagents. These include Corey's 600-psi Rh(I)/DIOP-catalyzed hydrogenation[3b] and, recently, Mulzer and Pfaltz optimized their Ir(I)/*P*,*N*-ligand-catalyzed hydrogenation[5g] procedure at 50 bar of pressure. Neither possessing the specialized apparatus nor reagents, we pursued alternative methods to affect a stereocontrolled reduction process (Table 1, entries 4−6).

Inspired by amine-based organocatalytic mechanistic rationales, we explored the possibility of reversing the facial preference of **10** toward hydride delivery by relaying steric information via a C6-methoxy group-directed putative *trans*-iminium species **16** (Figure 1). Although MacMillan-type catalysts in the presence of Hantzsch hydride donors like

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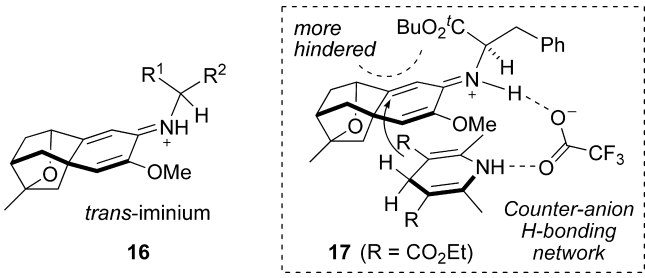

Figure 1. Proposed *trans*-iminium intermediate **16** and mechanistic rationale[20] for π-facial selectivity via **17**.

15 were found unreactive,[19] List's D-valine TFA salt **13**[20,21] with **15**[22] gave a 3.5:1 dr in favor of desired **3a** over **3b**, albeit in low yield (entry 4). List's optimal antipodal catalyst combination, the (*S*)-TRIP[23] salt of D-valine *tert*-butyl ester, gave poor conversions and 1.2:1 dr (**3a/3b**), suggesting competing steric effects came into operation (entry 5). Eventually,[15] higher catalytic activity and selectivity were achieved with the unreported *tert*-butyl ester[21] of D-phenylalanine **14**, although further reduction of **3a/3b** to **11a/11b** could not be avoided (entry 6).

To optimize the isolated yield of desired **11a**, the sequential Hantzsch-based and Pd/C-mediated reduction of **10** via **3a/3b** to a separable mixture of C9-epimeric 6-methoxyketones **11a/b** was found favorable. This gave a 73% yield over two steps and 4:1 dr at C9. The methoxyketones, however, proved unstable on silica and **11a** was best separated from **11b** with 90−95% purity under N_2 through Et_3N-deactivated silica. Original dr ratios at C6 could not be determined on crude mixtures of **11a/b**. Although minor amounts of **11a**-(***6S***) could be isolated and characterized, the newly formed C6 chiral center of **11a** readily epimerized to the major diastereomer **11a**-(***6R***) during silica gel chromotography. The C6 epimer of **11b**-(***6R***) was never detected.

Finally, demethylation of **11a** with $AlCl_3$/TBAI,[24] followed by mesylation of **12** and heating with $LiBr/Li_2CO_3$ in DMSO,[25] furnished the targeted tetracyclic enone (−)-**2**. The ^1H and ^{13}C NMR spectra of (−)-**2** were found identical to those reported by Nicolaou.[3d]

The π-facial selectivity observed in the Hantzsch ester (**15**) hydride delivery to the 6-methoxydienone **10** can be rationalized to occur via a phenylalanine-derived *trans*-iminium intermediate (**17**), probably aided by an additional counteranion hydrogen bonding network[20] (Figure 1). Conceivably, the sterically more congested face of **10** would preferentially relay the benzyl and *tert*-butyl ester groups to the opposite face in **17**, thereby making the bottom face more sterically accessible. This steric reversal reasoning can account for the low reactivity and diastereoselectivity of List's TRIP[23] catalyst, but also that the reduction of **10** gave similar yields and selectivities irrespective of using (+)-, (−)- or (±)-forms of phenylalanine **14**.

In summary, we achieved a new stereocontrolled route to the tetracyclic enone (−)-**2** of (−)-platensimycin (**1**) in 12 steps, 21% overall yield from the readily available allylic alcohol **5**.[9] The tactic of employing a methoxy group to impart needed electronic and steric control helped advance three key transformations to **2**: (1) a direct *para*-arylation of an oxocarbenium species in a $Bi(OTf)_3$-catalyzed Marson-type FC cyclization of the free lactol **4**; (2) a direct TBAF-mediated alkylative dearomatization on the free phenol **9**, without silyl preactivation; and (3) a chemo- and diastereoselective conjugate reduction of the 6-methoxydienone **10** mediated by TFA salts of phenylalanine using readily available laboratory resources and techniques. While total synthesis efforts to (−)-**1** are ongoing, nonchiral primary amines are also being explored to further improve the π-facial selectivity of this latter step.[15]

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, synthesis of allyl alcohol **5**, and X-ray characterization of tosyl-phenol **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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