Natural Products

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A Concise Ring-Expansion Route to the Compact Core of Platensimycin**

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Recently, researchers at Merck disclosed a new natural product, platensimycin (**1**; Figure 1),[1] which was obtained by screening a large collection of South African soil samples

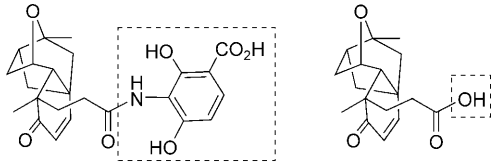


Figure 1. The structures of platensimycin and platensic acid.

using a novel antibiotic assay approach. Characterization revealed a unique compact core connected to a highly oxygenated and unusual aromatic ring through a propionate tether. Platensimycin has a novel mechanism of action, inhibiting the β-ketoacyl-(acyl carrier protein) synthase (FabF) in the bacterial fatty acid synthetic pathway.[2] Several new members of this class have since been reported.[3] These differ only in functionalization of the carboxylate terminus. This attractive natural product target has also encouraged researchers to engineer strains to improve its production.[4]

Despite a flurry of synthetic activity, only two groups have completed the total syntheses of platensimycin (**1**).[5] All other reported efforts have focused on constructing the platensimycin core **3**.[6] To highlight the diversity of these synthetic approaches we have chosen to emphasize the last bond formed to complete the platensimycin core as reported by each research group (Figure 2). Recently, a series of derivatives obtained by modifying platensimycin have been reported.[7] Alternatively, several research groups have developed analogues of platensimycin,[8] some of which were equipotent with the natural product.[8a–c] These results bode well for analogue approaches utilizing diverted total synthetic strategies.[9]

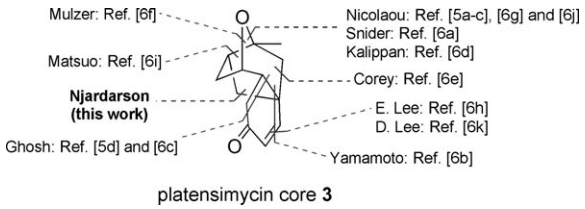
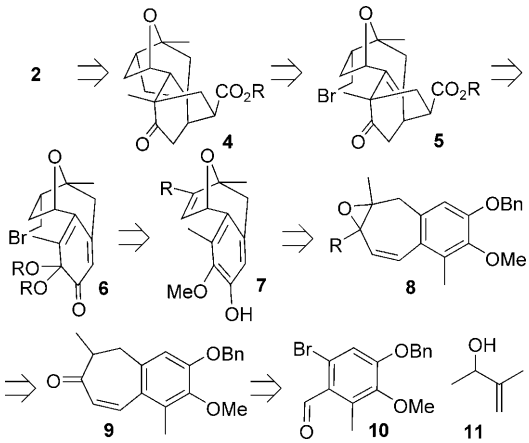


Figure 2. Synthetic approaches to complete the platensimycin core.

We envisioned a concise retrosynthetic plan for the total synthesis of platensimycin (Scheme 1). Platensic acid (**2**) was our immediate target as it serves later as the branch point for accessing all the other members of this natural product family. We proposed that **2** could be accessed from **4** by a *retro*-



Scheme 1. Platensimycin retrosynthetic analysis. Bn = benzyl.

Michael ring-opening reaction and subsequent hydrolysis of the resulting ester. Radical cyclization of bromide **5** would then be expected to afford the platensimycin carbocyclic core **4**. Oxidative dearomatization of **7** and in situ trapping of the ketal **6** with methyl acrylate was expected to provide **5** as the only cycloadduct. In this one remarkable transformation, the aromatic core would be unraveled and primed for the subsequent cyclization step. At the same time, the quaternary center bearing the side chain with the desired oxidation state would be installed by a substrate and regiocontrolled Diels–Alder cycloaddition. Oxatropane **7** would originate from vinyl oxirane **8** using our newly described copper-catalyzed ring-expansion protocol.[10] Epoxidation of the diene obtained from enone **9** could also serve as the asymmetric entry point for this synthesis, which in turn would be assembled in two steps from **10**[11] and **11** using a Heck coupling and then an intramolecular condensation.

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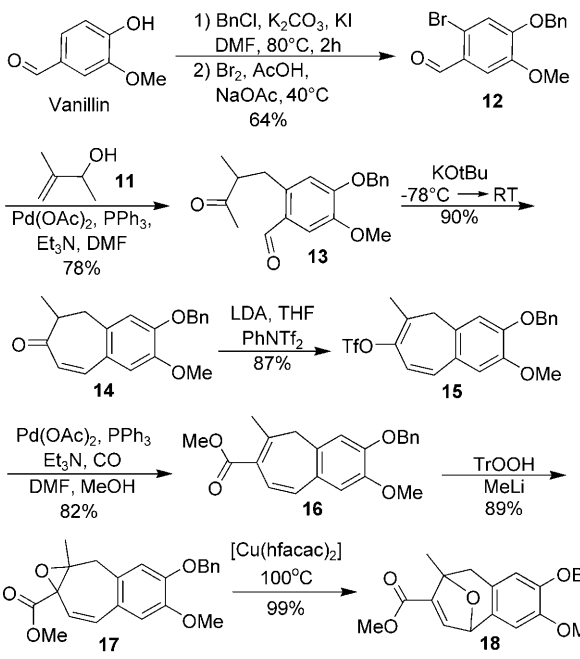
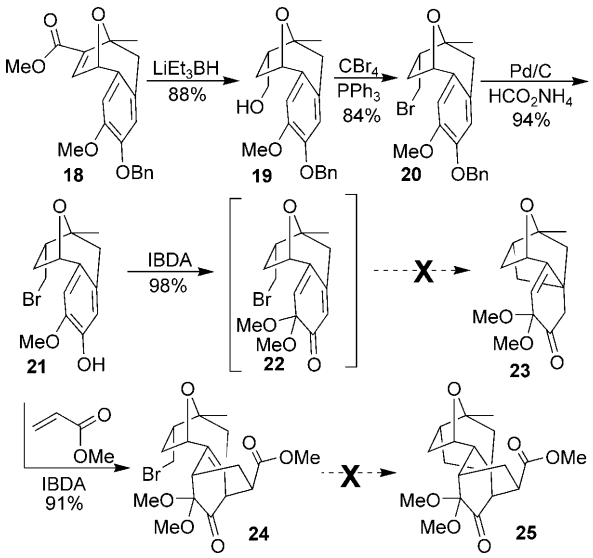
Our synthetic efforts commenced with vanillin[12] which was regioselectively brominated and protected by using known procedures (**12**, Scheme 2).[13] This substrate was



Scheme 2. Synthesis of the functionalized aryl-fused oxatropane. DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, Tf = trifluorosulfonyl, Tr = triphenylmethyl, hfacac = hexafluoroacetyl acetonate.

subjected to Heck coupling conditions in the presence of allylic alcohol **11**, which furnished keto aldehyde **13**.[14] The methyl branching is key to the rapid assembly of the fused ring system **14**, ensuring that under the thermodynamic conditions employed, the initial five-membered ring aldol product cannot dehydrate and instead undergoes a retro aldol to give exclusively the seven-membered ring enone. Triflate formation to give **15** was accomplished by deprotonation with LDA[15] and trapping of the resulting enolate with *N*-phenyltriflamide. Palladium-mediated carbonylation afforded dienoate **16** in excellent yield.[16] Regioselective epoxidation was accomplished using the highly reactive trityl hydroperoxide,[17] and our new copper-catalyzed ring-expansion protocol formed oxatropane **18**.

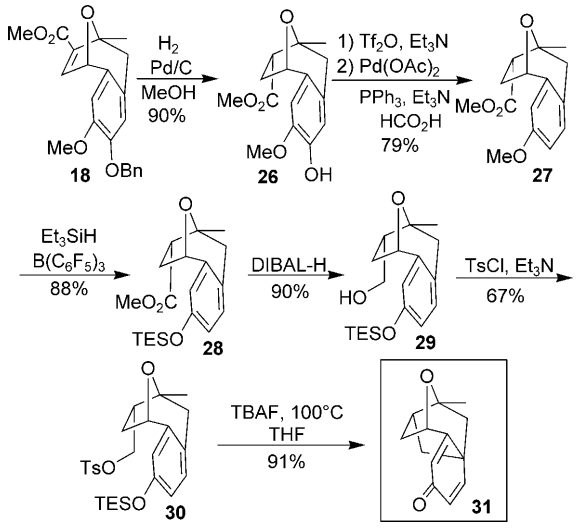
Methyl enolate **18** (Scheme 3) was fully reduced stereoselectively to form **19** using lithium triethyl borohydride. Primary bromide **20** was accessed using carbon tetrabromide and triphenylphosphine, and the arylbenzyl ether was removed by employing a transfer-hydrogenolysis protocol. Oxidation of **21** using IBDA afforded dimethyl ketal **22** which underwent a facile Diels–Alder dimerization. This process was slow enough, however, to test the proposed cyclization. Unfortunately, all efforts to access **23** using either radical or anionic conditions did not form the desired core, giving instead only the product of bromide reduction and no C–C bond formation.[18] Regardless, diene **22** could be trapped in situ after oxidative dearomatization with methyl acrylate to



Scheme 3. Oxidative dearomatization/cyclization attempts. IBDA = iodobenzene diacetate.

give the desired cycloadduct **24**. Our calculations had indicated that the structure of the new six-membered ring would bring the radical-accepting olefin into closer proximity with the primary radical, and therefore make the cyclization more likely. Unfortunately all attempts to form **25** were not successful, again giving only the product of bromide reduction.

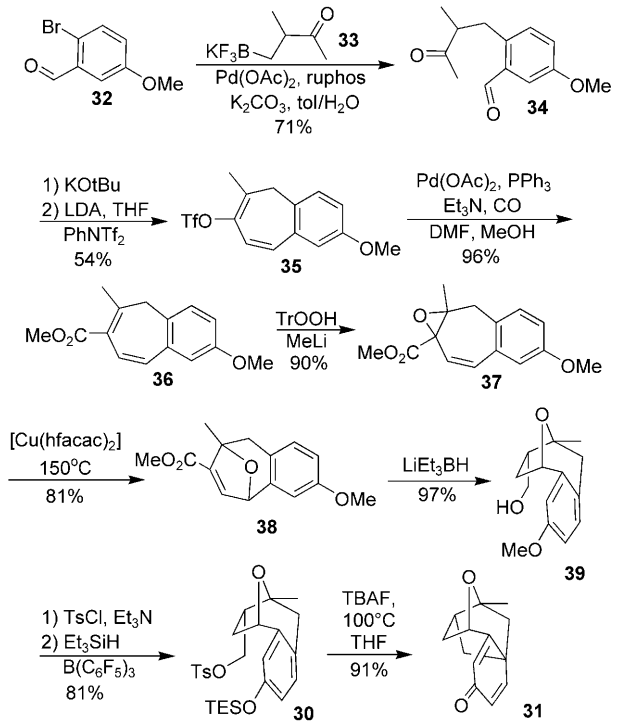
We decided to evaluate a slightly different substrate to determine whether our proposed C–C cyclization strategy to form the platensimycin core was feasible (Scheme 4). To this end oxatropane **18** was converted into **26** by alkene reduction and hydrogenolysis of the benzyl protecting group. Deoxygenation was then accomplished by converting **26** into an aryl triflate and then effecting reductive cleavage using palladium and formic acid to give **27**. A remarkably mild phenolic



Scheme 4. Intramolecular alkylative dearomatization. DIBAL-H = diisobutylaluminum hydride, TES = triethylsilyl, Ts = 4-toluenesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.

silylation of the remaining arylmethyl ether with triethylsilane and tris(pentafluorophenyl)borane furnished TES-protected phenol **28**.[19] The ester was reduced with DIBAL-H to give primary alcohol **29**, which was directly activated for displacement by conversion into the tosylate **30**. When this cyclization precursor was heated with TBAF it rapidly underwent the alkylative cyclization in excellent yield to form the platensimycin core **31**. The ^{1}H and ^{13}C NMR spectra of **31** are identical to those previously reported,[6e,f] thus completing our formal synthesis of platensimycin.

This success inspired us to improve the synthetic approach by starting with brominated anisaldehyde **32** rather than the vanillin analogue **12** (Scheme 5). This approach would allow



Scheme 5. Efficient synthesis of the platensimycin core. ruphos = 2-dicyclohexylphosphino-2′,6′-diisopropoxylbiphenyl.

us to alleviate the steps associated with the late stage deoxygenation necessary in Scheme 4. To that end, commercially available bromide **32** was converted into **34**, using the cross-coupling strategy reported by Molander and Petrillo, to directly install the requisite ketone chain.[20] This keto aldehyde cleanly underwent the analogous condensation, triflate formation, and carbonylation using the previously optimized conditions to give **36**. Nucleophilic epoxidation with trityl hydroperoxide allowed access to vinyl oxirane **37**, which subsequently ring-expanded to oxatropane **38** when subjected to our $[Cu(hfacac)_2]$ conditions. Substrate-controlled reduction afforded primary alcohol **39** which was converted into the tosylate and again hydrosilated to give TES-protected phenol **30**. The platensimycin core **31** was again accessed by alkylative dearomatization, this time completing the formal synthesis in only ten steps from commercially available precursor **32**.

In summary, we have developed a very efficient route to the compact platensimycin core. Our architectural assembly relied on the use of a new copper-catalyzed oxirane ring-expansion in combination with an alkylative dearomatization to complete the core. Other notable features of this synthetic approach include an underutilized phenol ether deprotection, nucleophilic enoate epoxidation, and a mild introduction of a substituted alkyl ketone using a trifluoroborate cross-coupling.

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