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Enantioselective Route to Platensimycin: An Intramolecular Robinson Annulation Approach

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Platensimycin (**1**) (Scheme 1) is a novel antibiotic lead compound recently discovered by Merck scientists from a strain of *Streptomyces platensis*.[1a,b] The potential medicinal applications[1c,d] and challenging structure motif, especially the cage-like tetracyclic core with several stereogenic centers, made this compound very attractive as a target for chemical synthesis. To this end, total synthesis of its racemic form was first reported by Nicolaou and co-workers,[2a] and later they also reported corresponding asymmetric versions.[2b] More recently, two other routes to the tetracyclic core structure (±)-**9**[2c,d] and synthesis of a related structure[2e] have been reported. Whereas these reported routes all utilized intramolecular etherification reactions[2a] between the alcohol motifs and the alkene parts as key steps, an alternative intramolecular Robinson annulation approach seems to be more straightforward. Herein, we describe our efforts in the enantioselective synthesis of the key cage-like tetracyclic core structure of platensimycin.

The retrosynthetic analysis presented in Scheme 1 envisions a Robinson annulation event[3] of bicyclic compound **8** to give the tetracyclic core structure **9**.[2a] Specifically, we expect that by using proline-type catalysts, high diastereoselectivity will be obtained.[4] Compound **8** could be constructed from bicyclic lactone **4** by adding two appendages in an appropriate manner. Lactone **4** has turned out to be a known compound, which was encountered in the total synthesis of a series of natural products in the hirsutene family.[5] In contrast to the methods in the literature, we believe the potential precursor of lactone **4** could be ketone **3**, through a Baeyer-Villiger oxidation/rearrangement sequence.[6] And by utilizing our recently developed Brønsted acid-assisted chiral Lewis acid (BLA)[7] catalyzed highly enantio- and regioselective Diels-Alder reaction,[8] and subsequent *N*-nitroso aldol addition/decarboxylation sequence,[9] enantiomerically pure ketone **3** could be easily prepared from inexpensive, commercially available starting materials.

The implementation of the above mentioned approach is outlined in Scheme 2. BLA catalyst (2 mol%) prepared *in situ* from oxazaborolidine[10] **10** and carbon-based Brønsted acid[11] **11** promoted the Diels-Alder reaction between methyl acrylate and methyl cyclopentadiene to give adduct **2** in 92% yield with essentially complete regio-, diastereo- and enantiocontrol. The Diels-Alder adduct **2** was transformed to the desired ketone **3** in a one-pot procedure: nitroso aldol reaction of lithium enolate of **2** gave the *N*-nitroso adduct exclusively, which upon treatment with lithium hydroxide in dioxane/H_2O underwent oxidative decarboxylation to give **3** in 75% yield after hydrolysis during work-up.[12] Baeyer-Villiger oxidation of ketone **3** under basic hydrogen peroxide conditions[13] gave lactone **4** in 68% yield**,** presumably through hydrolysis of the initially formed Baeyer-Villiger product followed by dehydrative lactonization.[6]

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Addition of vinyl cuprate reagent[14] to lactone **4** led to the corresponding carboxylic acid, which underwent an acid catalyzed lactonization with a catalytic amount of trifluoromethanesulfonimide[15] to give vinyl lactone **5** as an inconsequential diastereomeric mixture (*ca.* 10:1 d.r.) in 81% yield over two steps.[16] DIBAL-H reduction of **5** was followed by Lewis acid mediated cyanation in one pot, giving desired cyanide **6** and undesired cyanide **6′** as a separable diastereomeric mixture in 1:1 ratio with 85~95% yield. This one-pot sequence eliminated the need to go through corresponding acetate intermediates as is often seen in the literature.[17] The undesired cyanide **6′** can be converted back to a 2:3 mixture of **6** and **6′** by deprotonation with LiHMDS followed by aqueous work-up. Cyanide **6** was reduced by DIBAL-H/*n*-BuLi to the corresponding aldehyde,[18] which was immediately subjected to Wadsworth-Emmons conditions[19] to give enone **7** in 65% yield over two steps. The protocol of ruthenium catalyzed oxidative cleavage of terminal olefins[20] chemoselectively gave aldehyde **8** in 59% yield (86% based on recovered **7**).

Gratifyingly, the key Robinson annulation event was accomplished in one pot by using L-proline as the chiral control element to mediate the initial intramolecular Michael addition, followed by sodium hydroxide treatment to finish the aldol dehydration. The tetracyclic core structure **9** and its C-9 epimer (platensimycin numbering[1b]) **9′** was obtained with 5:1 d.r. favoring the desired isomer. The observed preference for the enone's *si* face being attacked (Figure 1) can be understood by the stereoelectronic reasons previously proposed.[21] With L-proline as the matched chiral control element, such intrinsic preference is reinforced to give higher diastereoselectivity than the mismatched D-proline (3:1 d.r., favoring **9**).[22,23] The ^{1}H and ^{13}C NMR spectra of **9** are identical to those previously reported[2a,c,d]. Thus, our formal synthesis of platensimycin is finished.

In conclusion, an enantioselective route to the tetracyclic core structure of platensimycin is accomplished in ten steps from simple commercially available starting materials. A number of the steps in this synthesis are noteworthy or novel: (1) the regio- and enantioselective Diels-Alder reaction between methyl acrylate and methyl cyclopentadiene with only 2 mol% catalyst loading; (2) the one-pot conversion from ester **2** to ketone **3** using nitrosobenzene under mild conditions; (3) the one-pot reductive cyanation of lactone **4**; (4) the stereoselective intramolecular Michael addition[24] between the α-branched aldehyde moiety and the β-substituted enone part of bicyclic compound **8**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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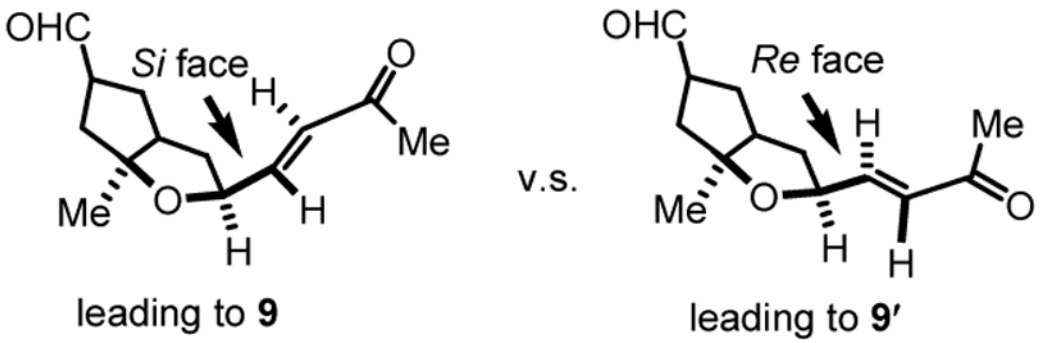
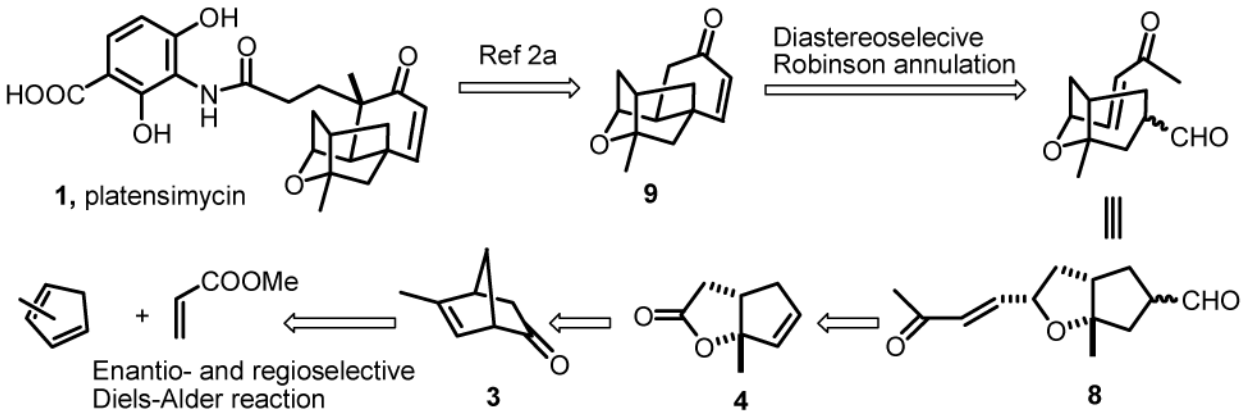
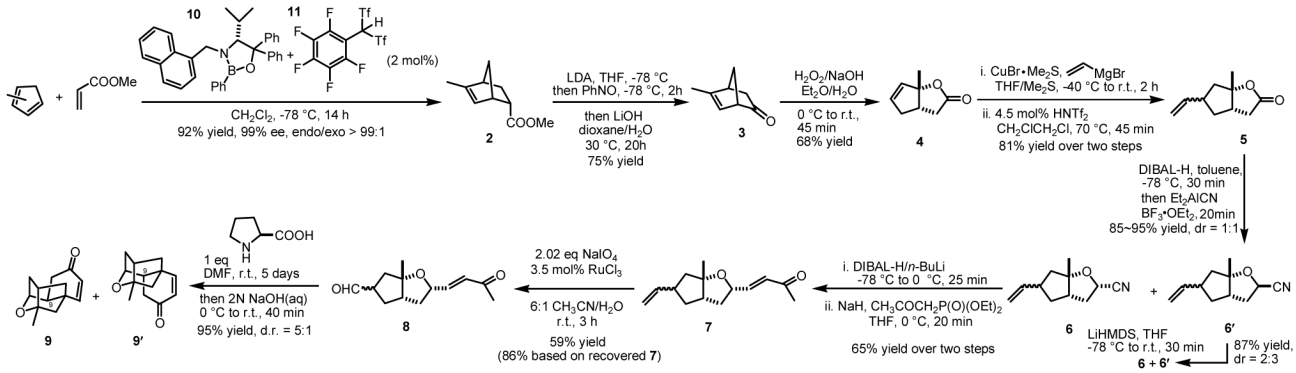


Figure 1.
Facial selectivity for the intramolecular Michael addition.



Scheme 1.
Retrosynthetic analysis.



Scheme 2.
Synthetic route toward tetracyclic compound **9**.