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# Enantioselective Synthesis of (−)-Platensimycin Oxatetracyclic Core by Using an Intramolecular Diels−Alder Reaction

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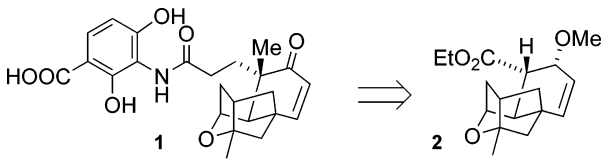
## ABSTRACT




(-)-Platensimycin

**An enantioselective route to the oxatetracyclic core of (−)-platensimycin (1) has been investigated by using an intramolecular Diels−Alder reaction as the key step. The thermal reaction of *E*/*Z* mixture (1:1) provided oxatetracyclic core 2 from the *E*-diene and the *Z*-diene was recovered unchanged. The Diels−Alder substrate was conveniently assembled in optically active form with use of (*S*)-carvone as the starting material.**

Antibiotic resistance has become an increasingly alarming public health concern worldwide. The problem continues to worsen as first-line antibiotic drugs are becoming less effective due to the emergence of a range of lethal resistant strains.[1] This raises serious issues with respect to future treatments and prevention of infectious diseases. Consequently, discovery and development of new antibiotics with a novel mechanism of action are critically important. In 2006, a novel class of antibiotic, platensimycin (**1**, Figure 1), was isolated from a strain of *Streptomyces platensis* by a Merck research group.[2,3] Platensimycin shows strong, broad-spectrum Gram positive antibacterial activity. This compound can selectively inhibit bacterial cellular lipid biosynthesis by targeting the $\beta$-ketoacyl-acyl-carrier-protein synthase I/II (FabF/B) in the synthetic pathway of fatty acids which are important components of cell membranes and cell envelopes.[3] The discovery of platensimycin and its novel mechanism of action have identified a new promising target for treatment of bacterial infections.

The structure of platensimycin was elucidated by use of 2-D NMR techniques. The X-ray crystallographic analysis of the bromo derivative further confirmed its relative and absolute stereochemistry.[3a] Platensimycin consists of a hydrophobic oxatetracyclic core and a polar 3-amino-2,4-dihydroxybenzoic acid side chain. The chemistry and biology of platensimycin have logically attracted considerable interest in its synthesis and structure−activity studies. The first total synthesis of racemic platensimycin[4a] and subsequently asymmetric synthesis of (−)-platensimycin[4b] were reported by

(1) Walsh, C. *Antibiotics*: *actions*, *origins*, *resistance*; ASM Press: Washington, DC, 2003.

(2) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, A. Ä.; Tormo, J. R.; Enilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Chmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358.

(3) (a) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am Chem. Soc.* **2006**, *128*, 11916. (b) Häbich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951.

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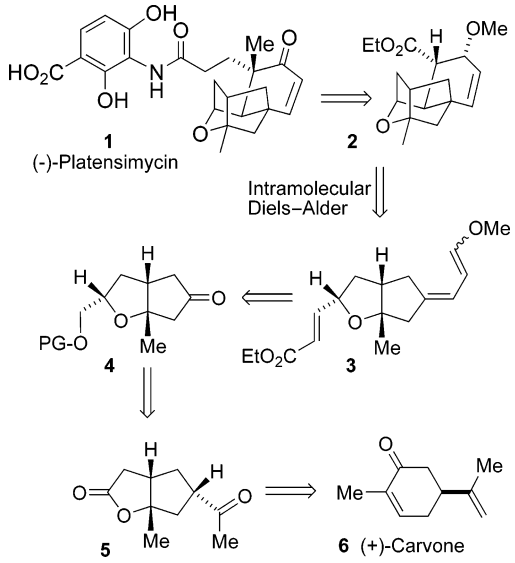
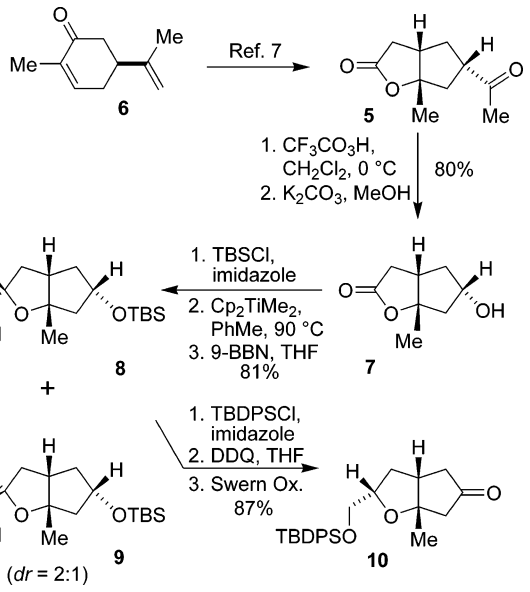



**Figure 1.** Retrosynthetic analysis of (−)-platensimycin.

Nicolaou and co-workers. They reported the synthesis of its analogue adamantaplatensimycin recently.[4c] Two other racemic syntheses[5a,b] and a related structure of the oxatetracyclic core have also been reported.[5c] The above-mentioned syntheses utilized an intramolecular etherification reaction to construct the hydrophobic core of platensimycin. Very recently, Yamamoto and co-workers reported an elegant enantioselective route to (−)-platensimycin using an intramolecular Robinson annulation as the key step.[6] This report has prompted us to publish our preliminary results toward the total synthesis of (−)-platensimycin.

Our strategy, however, is based upon an intramolecular Diels−Alder reaction of an appropriately functionalized substrate to construct the oxatetracyclic core in a stereocontrolled manner. As shown in Figure 1, the oxatetracyclic core **2** can be formed by an intramolecular Diels−Alder reaction of substrate **3**. For preliminary investigation, we planned to examine a Diels−Alder reaction with the mixture of *E*/*Z* isomers as shown in **3**. In principle, both expected products can be converted to the oxatetracyclic core enone derivative. Diels−Alder substrate **3** can be synthesized from ketone **4** by constructing the diene and dienophile moiety at each side of the bicyclic ketone **4**. Ketone **4** can be derived from the lactone **5** by olefination of the lactone carbonyl followed by hydroboration of the resulting olefin to set up the required stereocenter. Lactone **5** will be synthesized starting from commercially available (+)-carvone **6**.

**Scheme 1.** Synthesis of Ketone **5**




As shown in Scheme 1, commercially available (+)-carvone **6** was transformed to the known lactone **5** by slight modification of a literature procedure.[7] Our initial Baeyer−Villiger oxidation of lactone **5** with *m*CPBA proceeded very slowly and the corresponding oxidation product was obtained in poor yield (20%). However, lactone **5** was successfully transformed into the corresponding ester in 89% yield by using trifluoroperoxyacetic acid formed *in situ* from trifluoroacetic anhydride and the urea hydrogen peroxide complex (UHP) at 0 °C for 5 h.[8] Saponification of the resulting ester furnished alcohol **7** in 90% yield. Protection of the alcohol **7** with TBSCl gave the silyl ether in quantitative yield. The lactone was subjected to the Petasis olefination[9] with $Cp_2TiMe_2$ in toluene at 90 °C to provide the corresponding enol ether. Hydroboration of the resulting enol ether with 9-BBN provided the desired primary alcohol **8** and its diastereomer **9** as a 2:1 mixture of diastereomers in 81% yield.[10] The diastereomers were separated by flash chromatography. The major diastereomeric alcohol **8** was protected as the TBDPS group to provide the corresponding bis-silyl ether in 98% yield. Selective cleavage of the secondary TBS ether with a catalytic amount of DDQ in 9:1 THF and water afforded the secondary alcohol in 93% yield.[11] Swern oxidation of this alcohol provided ketone **10** in 96% yield.

The synthesis of substrate **3** is outlined in Scheme 2. Installation of diene from ketone **10**, required an olefin

(4) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086. (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (c) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712.

(5) (a) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825. (b) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922. (c) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417.

(6) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534.

(7) (a) Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883. (b) Weinges, K.; Reichert, H. *Synlett* **1991**, 785. (c) Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H. *Liebigs Ann. Chem.* **1993**, 403. (d) Weinges, K.; Reichert, H.; Braun, R. *Chem. Ber.* **1994**, *127*, 549.

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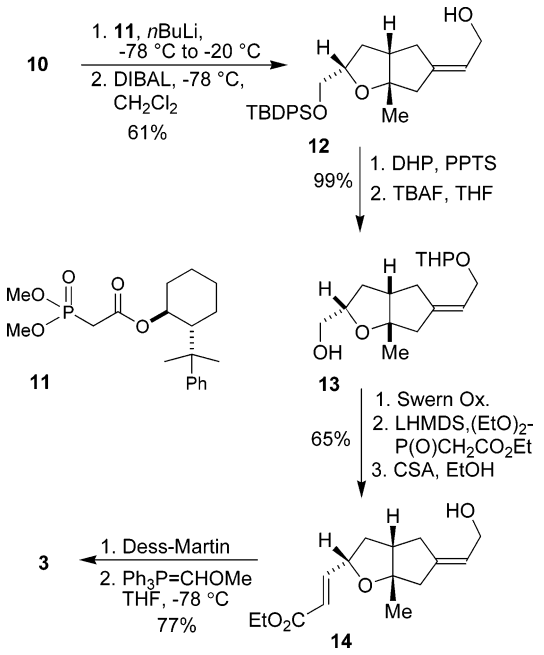
(9) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Dollinger, L. M.; Ndakala, A. J.; Hasshemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R. *J. Org. Chem.* **1999**, *64*, 7074.

(10) Lambert, W. M.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382.

(11) (a) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833. (b) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997.

**Scheme 2.** Synthesis of Diels−Alder Substrate **3**

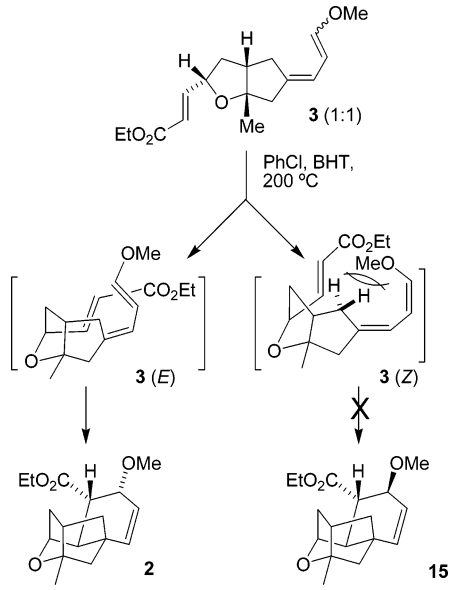



with an *E*-configuration. The ketone carbonyl possesses an α-methylene group on each side and the steric differentiation is marginal. The presence of a ring junction methyl group may be utilized to build selectivity. Our initial attempt at selective olefination using Horner−Emmons olefination with lithium hexamethyldisilazide and triethyl phosphonoacetate provided only marginal selectivity (3:2, by $^1$H NMR analysis) for the *E*-olefin. Thus, we relied upon asymmetric olefination with a chiral phosphonoacetate reagent **11**.[12] Chiral phosphonate **11** was synthesized from transesterification of trimethylphosphonoacetate with (+)-phenylnormenthol.[13] The Horner−Emmons reaction of **10** with chiral phosphonoacetate at −78 to −20 °C furnished a mixture (3.2:1 by $^1$H NMR analysis) of the corresponding unsaturated *E*- and *Z*-esters in 93% yield. The *E*,*Z* mixture can be separated by flash chromatography on silica gel with 10% $Et_2O$ in hexanes as the eluent. DIBAL reduction of the *E*-unsaturated ester afforded the desired allylic alcohol **12** in 86% yield. The chiral ligand, (+)-phenylnormenthol, was recovered in 95% yield. The protection of the allylic alcohol **12** as THP ether followed by removal of the TBDPS group with TBAF in THF generated alcohol **13** in 99% yield over 2 steps. Alcohol **13** was subjected to a Swern oxidation to provide the corresponding aldehyde. Horner−Emmons olefination with triethylphosphonoacetate furnished the dienophile moiety as a mixture (5:1) of *E*/*Z*-unsaturated esters. Removal of the THP group with camphorsulfonic acid in EtOH afforded alcohol **14** in 65% overall yield. Alcohol **14** was converted to the Diels−Alder substrate **3** in two steps involving (1) Dess−Martin oxidation of the allylic alcohol to the corresponding aldehyde and (2) Wittig olefination of the aldehyde at −78 °C for 30 min. Triene derivative **3** was obtained in 77% yield over 2 steps as an inseparable mixture (1:1) of *E*/*Z* enol ethers. This mixture was utilized for preliminary investigation of the intramolecular Diels−Alder reaction.

(12) (a) Hatakeyama Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713. (b) Gais, H.-J.; Schmiedl, G.; Ossenkamp, R. K. L. *Liebigs Ann.* **1997**, 2419.

(13) Refluxing a solution of (+)-phenylnormenthol (1 equiv), trimethylphosphonoacetate (3 equiv), and DMAP (0.3 equiv) in toluene for 3 days provided **11** in 99% yield.

**Scheme 3.** The Intramolecular Diels−Alder Reaction




As shown in Scheme 3, triene **3** was then subjected to a thermal intramolecular Diels−Alder reaction. A dilute solution of substrate **3** in chlorobenzene (0.005 M) in the presence of a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the radical inhibitor[14] was heated in a sealed tube at 200 °C for 2 h. The reaction was cooled to 23 °C, solvent was evaporated, and silica gel chromatography provided the Diels−Alder product **2** as a single isomer in 39% isolated yield. The corresponding *Z*-enol ether (**3**-*Z*) was recovered in 38% isolated yield. As shown in Scheme 3, the *E*-enol ether substrate (**3**-*E*) successfully underwent a Diels−Alder reaction to provide the oxatetracyclic core **2**. The corresponding *Z*-enol ether (**3**-*Z*) did not provide the Diels−Alder product, presumably due to the developing nonbonded

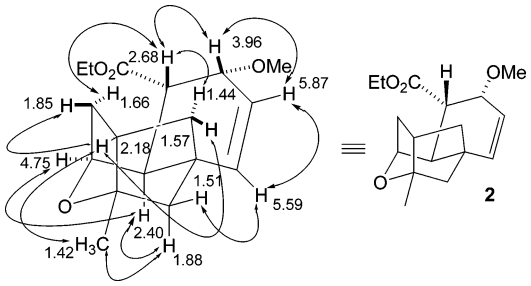



**Figure 2.** The NOESY of compound **2**.

interactions between the terminal methoxy group and one of the methylene hydrogens on the bicyclic ring. The stereochemistry of oxatetracyclic core **2** was confirmed by extensive NMR experiments ($^1$H, $^{13}$C, COSY, NOESY, HMQC, HMBC). The results of the 2-D NMR experiments (NOESY) are summarized in Figure 2. The observed NOESY among the protons are consistent with the assigned stereochemistry of structure **2**.

In summary, an enantioselective synthesis of the oxatetracyclic core of (−)-platensimycin has been achieved using an intramolecular Diels−Alder reaction. Further optimizations of the Diels−Alder substrate, reaction conditions, and completion of the total synthesis are currently in progress.

**Acknowledgment.** Financial support of this work was provided in part by the National Institutes of Health and Purdue University.

**Supporting Information Available:** Experimental procedures, spectral data, copies of $^1$H NMR, $^{13}$C NMR, and NOESY spectra for compounds **2**−**3**, **3**-*Z*, **7**−**10**, and **12**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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