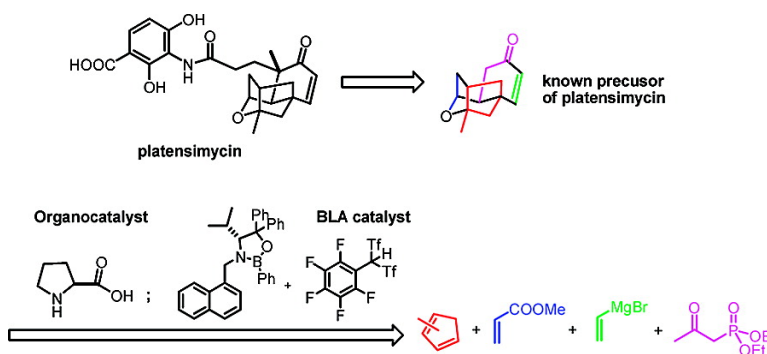


Enantioselective Route to Platensimycin: An Intramolecular Robinson Annulation Approach

Pingfan Li, Joshua N. Payette, and Hisashi Yamamoto

J. Am. Chem. Soc., **2007**, 129 (31), 9534-9535 • DOI: 10.1021/ja073547n • Publication Date (Web): 14 July 2007

Downloaded from <http://pubs.acs.org> on February 16, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 48 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)

Enantioselective Route to Platensimycin: An Intramolecular Robinson Annulation Approach

Pingfan Li, Joshua N. Payette, and Hisashi Yamamoto*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received May 23, 2007; E-mail: yamamoto@uchicago.edu

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 (\pm)-**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 event³ 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 Also, 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*-nitrosoaldol 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 oxazaborolidine¹⁰ **10** and carbon-based Brønsted acid¹¹ **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: nitrosoaldol reaction of lithium enolate of **2** gave the *N*-nitroso adduct exclusively, which upon treatment with lithium hydroxide in dioxane/H₂O underwent oxidative decarboxylation to give **3** in 75% yield after hydrolysis during workup.¹² Baeyer–Villiger oxidation of ketone **3** under basic hydrogen peroxide conditions¹³ gave lactone **4** in 68% yield, presumably through hydrolysis of the initially formed Baeyer–Villiger product followed by dehydrative lactonization.⁶

Addition of vinyl cuprate reagent¹⁴ to lactone **4** led to the corresponding carboxylic acid, which underwent an acid-catalyzed lactonization with a catalytic amount of trifluoromethanesulfonimide¹⁵ to give vinyl lactone **5** as an inconsequential diastereomeric

Scheme 1. Retrosynthetic Analysis

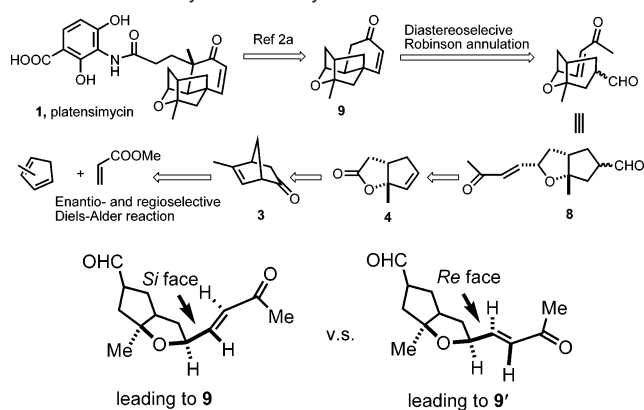


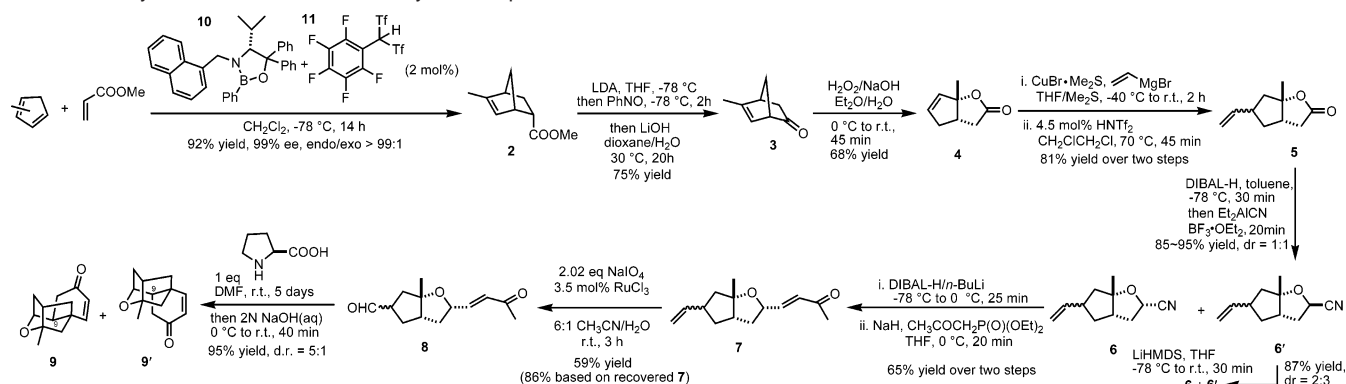
Figure 1. Facial selectivity for the intramolecular Michael addition.

mixture (ca. 10:1 dr) 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 workup. Cyanide **6** was reduced by DIBAL-H/*n*-BuLi to the corresponding aldehyde,¹⁸ which was immediately subjected to Wadsworth–Emmons conditions¹⁹ to give enone **7** in 65% yield over two steps. The protocol of ruthenium-catalyzed oxidative cleavage of terminal olefins²⁰ 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 dr, 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 dr, favoring **9**).^{22,23} The ¹H and ¹³C 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 10 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 nitrosoben-

Scheme 2. Synthetic Route toward Tetracyclic Compound 9



zene under mild conditions; (3) the one-pot reductive cyanation of lactone **4**; (4) the stereoselective intramolecular Michael addition²⁴ between the α -branched aldehyde moiety and the β -substituted enone part of bicyclic compound **8**.

Acknowledgment. This paper is dedicated to the memory of the late Professor Yoshihiko Ito. Partial financial support from the National Institute of Health (NIH, GM5-20121) is acknowledged. Special thanks to Ian Steele for X-ray analysis.

Supporting Information Available: Experiment procedures, spectral data for compounds, and complete author list of ref 1a. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Wang, J.; et al. *Nature* **2006**, *441*, 358–361. (b) 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*, 11916–11920 and 15547. (c) Pearson, H. *Nature* **2006**, *441*, 260–261. (d) Häblich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951–954.
- (2) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086–7090. (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942–3945. (c) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825–1828. (d) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922–1923. (e) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417–2419.
- (3) For a classical example of Robinson annulation in total synthesis, see: Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310–312.
- (4) (a) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958–3960. (b) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029. (c) List, B. *Chem. Commun.* **2006**, 819–824.
- (5) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3843–3958. (c) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064–5067. (d) Weinges, K.; Reichert, H. *Synlett* **1991**, 785–786. (e) Weinges, K.; Reichert, H.; Huber-Patz, U.; Irgartinger, H. *Liebigs Ann. Chem.* **1993**, 403–411. (f) Weinges, K.; Braun, R.; Huber-Patz, U.; Irgartinger, H. *Liebigs Ann. Chem.* **1993**, 1133–1140. (g) Weinges, K.; Braun, R. *Liebigs Ann. Chem.* **1994**, 99–101.
- (6) (a) Meinwald, J.; Seidel, M. C.; Cadoff, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 6303–6305. (b) Curran, D. P.; Chen, M. *Tetrahedron Lett.* **1985**, *26*, 4991–4994. (c) Corey, E. J.; Weinschenker, N. M.; Schaaf, T. M.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677. (d) Corey, E. J.; Schaff, T. K.; Huber, W.; Koelliker, V.; Weinschenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397–398. (e) Corey, E. J.; Cheng, X. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989; Chapter 11: Prostanoids. (7) For a review of combined acid catalysis, see: Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942.
- (8) (a) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, in press. (b) For an excellent review of catalytic enantioselective Diels–Alder reactions, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
- (9) Payette, J. N.; Yamamoto, H. Manuscript in preparation. For review of nitrosoaldol reactions, see: (a) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514–3525. For synthetic applications of nitrosoaldol reactions to realize mild oxidation, see: (b) Baran, P. S.; Hafenstein, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.
- (10) Futatsugi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1484–1487 and references therein.
- (11) Hasegawa, A.; Ishikawa, T.; Ishihara, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1401–1410 and references therein.
- (12) For a related oxidative decarboxylation, see: Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991**, *32*, 7517–7520.
- (13) Weinschenker, N. M.; Stephenson, R. J. *Org. Chem.* **1972**, *37*, 3741.
- (14) S_N2' type addition of organocopper reagents to compound **4** and related structures are well studied; see: Curran, D. P.; Chen, M. H.; Leszczewski, D.; Elliott, L. R.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612–1614.
- (15) Catalytic amount of silver triflate and triflic acid can also mediate this transformation, albeit in slightly lower yields. See: (a) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553–4556. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182.
- (16) Under the cyclization conditions of compound **8**, this stereocenter would be enolized to sp^2 hybridized, so both epimers could give the desired products.
- (17) For review, see: Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Exeter, 1995; Chapter 2: Electrophilic Substitutions. For a recent example, see: Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 818–820.
- (18) Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4371–4374.
- (19) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589–9598.
- (20) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814–4818.
- (21) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015–6018. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464–466. Hyperconjugation with the neighboring C–O or C–C σ bond would lead to the enone's LUMO(π^*) energy difference between the two shown conformers.
- (22) For an insightful discussion on proline catalysis, see: Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasuryswala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–470.
- (23) Extensive study of this Robinson annulation event is underway and will be reported in due course. For preliminary results, see Supporting Information.
- (24) Intermolecular reaction between such counterparts is still a remaining challenge in the area of organocatalysis; see: (a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157. (b) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599. (c) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253–4256.

JA073547N