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Total Synthesis of (±)-Platencin

Takehiko Yoshimitsu,* Shoji Nojima, Masashi Hashimoto, and Tetsuaki Tanaka

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

yoshimit@phs.osaka-u.ac.jp

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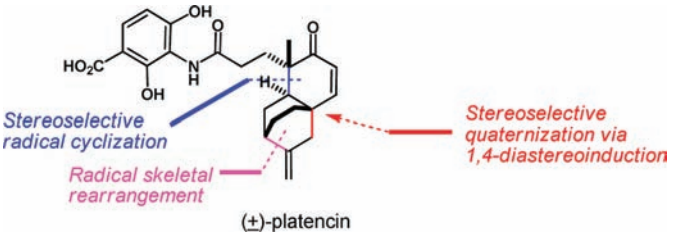
ABSTRACT



A novel route to (±)-platencin is reported, in which the highly stereoselective alkylative quaternization of a cyclohexenone scaffold via 1,4-diastereoinduction and two radical carbon−carbon bond-forming reactions that involve titanium(III)-mediated cyclization and stannyl-radical-mediated skeletal rearrangement are utilized.

Drug resistance that results from genetic mutations in bacterial strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA), is one of the most pressing concerns in the clinical environment. Massive effort to screen natural resources that would potentially overcome the drug resistance has led to the discovery of platencin (**1**)[1−3] and platensimycin (**2**),[1,4] both of which are highly potent antibiotics with a novel chemical scaffold, from the strains of *Streptomyces platensis* (Figure 1).

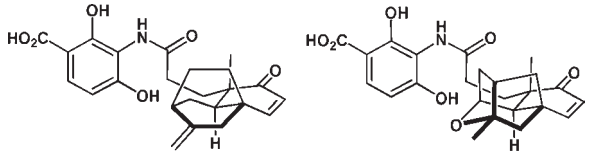


Figure 1. Platencin and platensimycin.

These compounds share a 3-amino-β-resorcylic acid anilide linkage that attaches similar complex terpenoid motifs with unique bond connectivity. Although they are structurally similar, they differ in the mode of action that is responsible for their antibiotic activities. Platencin (**1**) blocks two proteins essential for bacterial fatty acid biosynthesis, β-ketoacyl−acyl carrier protein (ACP) synthase II (FabF) and III (FabH)[5] whereas platensimycin (**2**) selectively inhibits FabF. As platencin (**1**) and platensimycin (**2**) potently inhibit the growth of antibiotic-resistant bacteria fatal to humans through their unique mechanisms, both compounds have caught the attention of the scientific community with the prospect that they would serve as new antibiotics. Nevertheless, despite these attractive properties, their clinical application is still fraught with many hurdles due to poor in vivo efficacy that stems from rapid clearance from tissues. Therefore, intensive effort is being made to solve these problems, including chemical modification of the natural compounds and wide-range screening for natural platencin/platensimycin congeners with a view to discovering potent analogues with improved pharmacokinetic properties suitable for clinical trials. In this context, chemical access to these potent antibiotic leads that would allow us to design and, create new platencin/platensimycin analogues is highly demanded.[6] In this paper, we disclose a new route to (±)-platencin (**1**), which features the stereoselective preparation of a quaternized cyclohexenone scaffold via 1,4-diastereoinduction followed by two radical transformations that involve a titanium(III)-mediated cyclization[7] and a homoallylic radical rearrangement.[8]

In our retrosynthetic analysis, platencin (**1**) was dissected to platencinic acid (**3**) that would be accessible from tricyclic intermediate **4** in a few steps involving radical skeletal rearrangement (Scheme 1). Intermediate **4** that possesses vicinal tertiary−quaternary stereocenters would

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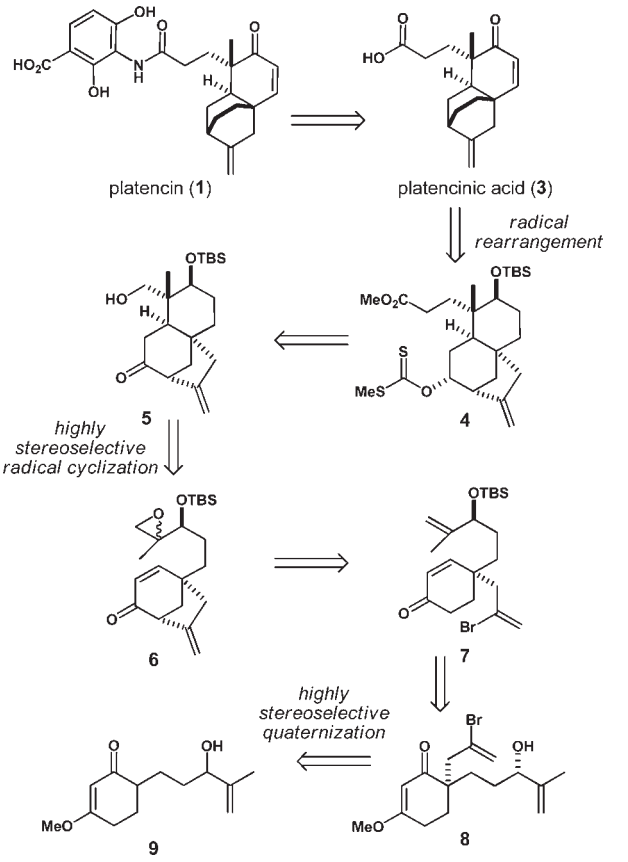
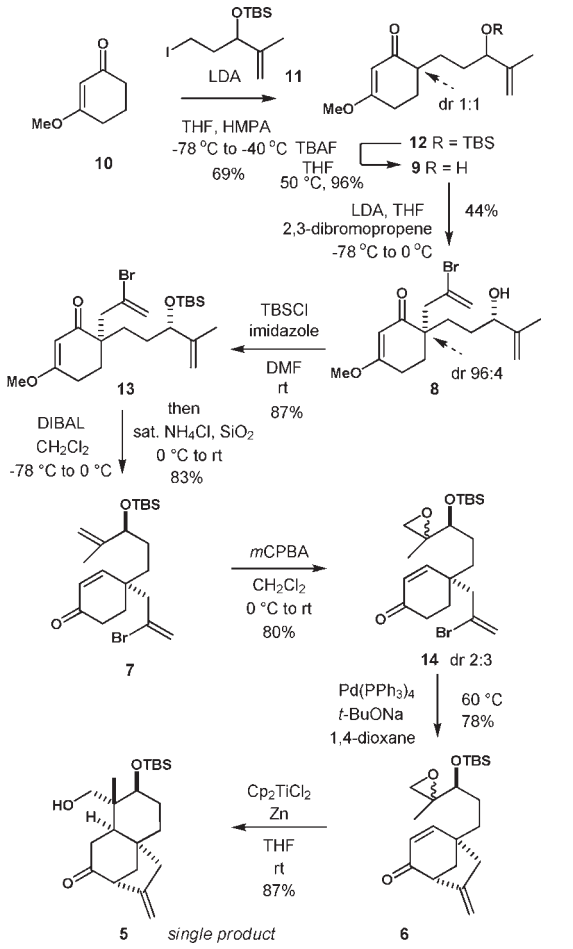
Scheme 1. Retrosynthesis of Platencin (**1**)



be traced back to epoxide **6**, with the prospect that epoxide **6** would undergo radical cyclization with a low valent organotitanium(III)[7] species to afford tricyclic ketone **5**, a suitable precursor for compound **4**. Epoxide **6** would reasonably be obtained from enone **7** that is accessible from alcohol **8**, which in turn would be prepared by the alkylative quaternization of alcohol **9**. As will be seen, our approach in this line features highly stereoselective processes that involve the transformation of epoxy enone **6** into tricyclic compound **5** through the thermodynamic epimerization of the radical center as well as the quaternization of compound **9** via the alkoxy-directed 1,4-diastereoinduction. It should be mentioned that the stereocenter of the hydroxyl group of **9**, despite its disappearance at the later stage of the synthesis, plays a pivotal role in forming other requisite stereocenters relevant to those of the target natural product.

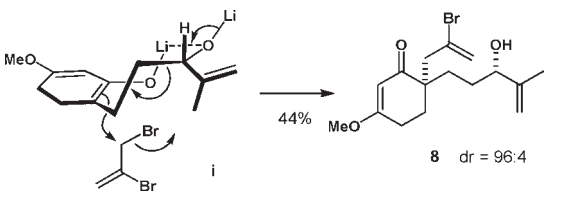
The synthesis commenced with the alkylation of known enone **10**[9] with iodide fragment **11** that was prepared from 1,3-propanediol[10] to provide compound **12** as a 1:1 diastereomeric mixture in 69% yield (Scheme 2). The next task was the quaternization of compound **12** by alkylation of the corresponding enolate with 2,3-dibromopropene. Although the alkylation of compound **12** with 2,3-dibromopropene was found to provide a mixture of nearly equal amounts of two diastereomers with respect to the quaternary stereocenter, it occurred to us that if free alcohol **9** was used as the substrate a chelation-controlled alkylation could be operative to possibly allow stereoselective construction of the quaternary carbon.[11]

Scheme 2. Stereoselective Synthesis of Tricyclic Motif **5** via Radical Cyclization



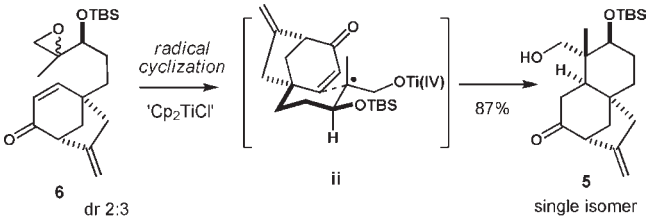
To our delight, the prospect was indeed found to be realizable. Thus, alcohol **9** that was derived by desilylation of compound **12** with TBAF was subjected to alkylation with 2,3-dibromopropene using 3 equiv of LDA to furnish compound **8** in a highly stereoselective manner (ca. 96:4) along with a small amount of regioisomer.[12] The stereochemical outcome may be rationalized by a chelating model, in which the conformation of lithium alkoxide intermediate **i** is fixed to allow the alkylation to stereoselectively take place from the less hindered site (Scheme 3). This represents a rare instance of a highly stereoselective direct quaternization of an enolate having "fixed geometry".

Scheme 3. Proposed Rationale for Highly Stereoselective Quaternization of Compound **9**



Then, alcohol **8** was again protected as TBS ether **13**, which was subjected to reductive enone carbonyl transposition with DIBAL followed by acid treatment to furnish enone **7** in 83% yield. Regioselective epoxidation of enone **7** with mCPBA took place smoothly to give epoxide **14** in 80% yield as a diastereomeric mixture (dr = 2:3).[13] Then, epoxide **14** was transformed into compound **6** in 78% yield by treatment with *t*-BuONa in the presence of $Pd(PPh_3)_4$ in heated 1,4-dioxane. With bicyclic compound **6**, the key radical cyclization was examined by using a low-valent titanium(III) reagent generated in situ under Nugent–RajanBabu conditions.[7a] The cyclization of epoxide **6** that constitutes two diastereomers (ca. 2:3) under the conditions was found to successfully provide the desired tricyclic compound **5** as a single stereoisomer in 87% yield, indicating that both diastereomeric epoxides were transformed into compound **5** irrespective of their original stereochemistry.[14] This result is attributable to the intermediacy of diastereomerically single radical **ii** that arose by rapid epimerization of the carbon radical center: the thermodynamically preferential conformation of **ii** in which the bulky TBS group is situated at the equatorial position allows intermediate **ii** to undergo stereoselective cyclization (Scheme 4).

Scheme 4. Plausible Mechanism for Highly Stereoselective Radical Cyclization of Epoxy Enone **6** to Yield Single Tricycle **5**



(1) For selected reviews on the chemistry of platencin and platensimycin, see: (a) Palanichamy, K.; Kaliappan, K. P. *Chem. Asian J.* **2010**, *5*, 668–703. (b) Lu, X.; You, Q. *Curr. Med. Chem.* **2010**, *17*, 1139–1155. (c) Harsh, P.; O'Doherty, G. A. *Chemtracts* **2009**, *22*, 31–40. (d) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548–2555.

(2) Selected papers on isolation of platencin and its congeners: (a) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 4684–4688. (b) Wang, J.; Kodali, S.; Lee, S. H.; Galgoci, A.; Painter, R.; Dorso, K.; Racine, F.; Motyl, M.; Hernandez, L.; Tinney, E.; Colletti, S.; Herath, K.; Cummings, R.; Salazar, O.; Gonzalez, I.; Basilio, A.; Vicente, F.; Genilloud, O.; Pelaez, F.; Jayasuriya, H.; Young, K.; Cully, D.; Singh, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 7612–7616. (c) Singh, S. B.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Jayasuriya, H.; Zink, D. L.; Parthasarathy, G.; Becker, J. W.; Wang, J.; Soisson, S. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4756–4759. (d) Zhang, C.; Ondeyka, J.; Dietrich, L.; Gailliot, F. P.; Hesse, M.; Lester, M.; Dorso, K.; Motyl, M.; Ha, S. N.; Wang, J. *Bioorg. Med. Chem.* **2010**, *18*, 2602–2610. (e) Yu, Z.; Smanski, M. J.; Peterson, R. M.; Marchillo, K.; Andes, D.; Rajski, S. R.; Shen, B. *Org. Lett.* **2010**, *12*, 1744–1747. (f) Zhang, C.; Ondeyka, J.; Herath, K.; Jayasuriya, H.; Guan, Z.; Zink, D. L.; Dietrich, L.; Burgess, B.; Ha, S. N.; Wang, J. *J. Nat. Proc.* **2011**, *74*, 329–340. (g) Herath, K.; Attygalle, A. B.; Singh, S. B. *Tetrahedron Lett.* **2008**, *49*, 5755–5758.

(3) Syntheses of platencin: (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780–1783. (b) Hayashida, J.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4373–4376. (c) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6199–6200. (d) Yun, S. Y.; Zheng, J.-C.; Lee, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 6201–6203. (e) Waalboer, D. C. J.; Schaapman, M. C.; Van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6576–6578. (f) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292–11293; addition/correction: *J. Am. Chem. Soc.* **2008**, *130*, 14016. (g) Austin, K. A. B.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2008**, *10*, 4465–4468. (h) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937–2941. (i) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3685–3688. (j) Ghosh, A. K.; Xi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5372–5375. (k) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909–15917. (l) Hirai, S.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 5076–5079. (m) Hirai, S.; Nakada, M. *Tetrahedron* **2011**, *67*, 518–530. (n) Singh, V.; Sahu, B. C.; Bansal, V.; Mobin, S. M. *Org. Biomol. Chem.* **2010**, *8*, 4472–4481. (o) Li, P.; Yamamoto, H. *Chem. Commun.* **2010**, *46*, 6294–6295.

(4) (a) 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.; Tormo, J. R.; Genilloud, 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.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *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; addition/correction: *J. Am. Chem. Soc.* **2006**, *128*, 15547.

(5) For reviews on fatty acid synthesis, see: (a) Wright, H. T.; Reynolds, K. A. *Curr. Opin. Microbiol.* **2007**, *10*, 447–453. (b) Goodman, C. D.; McFadden, G. I. *Curr. Pharm. Des.* **2008**, *14*, 901–916. (c) Häebich, Dieter; von Nussbaum, F. *Chem. Med. Chem.* **2006**, *1*, 951–954. (d) Johansson, P.; Wiltschi, B.; Kumari, P.; Kessler, B.; Vonrhein, C.; Vonck, J.; Oesterhelt, D.; Grininger, M. *Proc. Natl. Acad. Sci. U.S. A.* **2008**, *105*, 12803–12808.

(6) Selected papers on synthesis of platencin analogues: (a) Barykina, O. V.; Rossi, K. L.; Rybak, M. J.; Snider, B. B. *Org. Lett.* **2009**, *11*, 5334–5337. (b) Waalboer, D. C. J.; Leenders, S. H. A. M.; Schuelin-Casonato, T.; van Delft, F. L.; Rutjes, F. P. J. T. *Chem.—Eur. J.* **2010**, *16*, 11233–11236. (c) Tiefenbacher, K.; Gollner, A.; Mulzer, J. *Chem.—Eur. J.* **2010**, *16*, 9616–9622. (d) Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2011**, 183–196.

(7) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562. (b) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000–1003. (c) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525–4527. For pertinent reviews, see: (d) Barrero, A. F.; Quilez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627–1641. (e) Cuerva, J. M.; Justicia, J.; Oller-Lopez, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63–91. For some recent reports on Ti(III)-mediated cyclization of epoxides with alkenes, see: (f) Mandal, S. K.; Paira, M.; Roy, S. C. *J. Chem. Sci.* **2010**, *122*, 423–426. (g) Fernández-Mateos, A.; Madrazo, S. E.; Teijón, P. H.; González, R. R. *J. Org. Chem.* **2009**, *74*, 3913–3918. (h) Mandal, S. K.; Paira, M.; Roy, S. C. *J. Org. Chem.* **2008**, *73*, 3823–3827. (i) Chakraborty, T. K.; Samanta, R.; Das, S. *J. Org. Chem.* **2006**, *71*, 3321–3324.

(8) (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916–4925. Also see ref 3k. For selected reviews, see: (b) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347–359. (c) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091–2115.

(9) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 7187–7188.

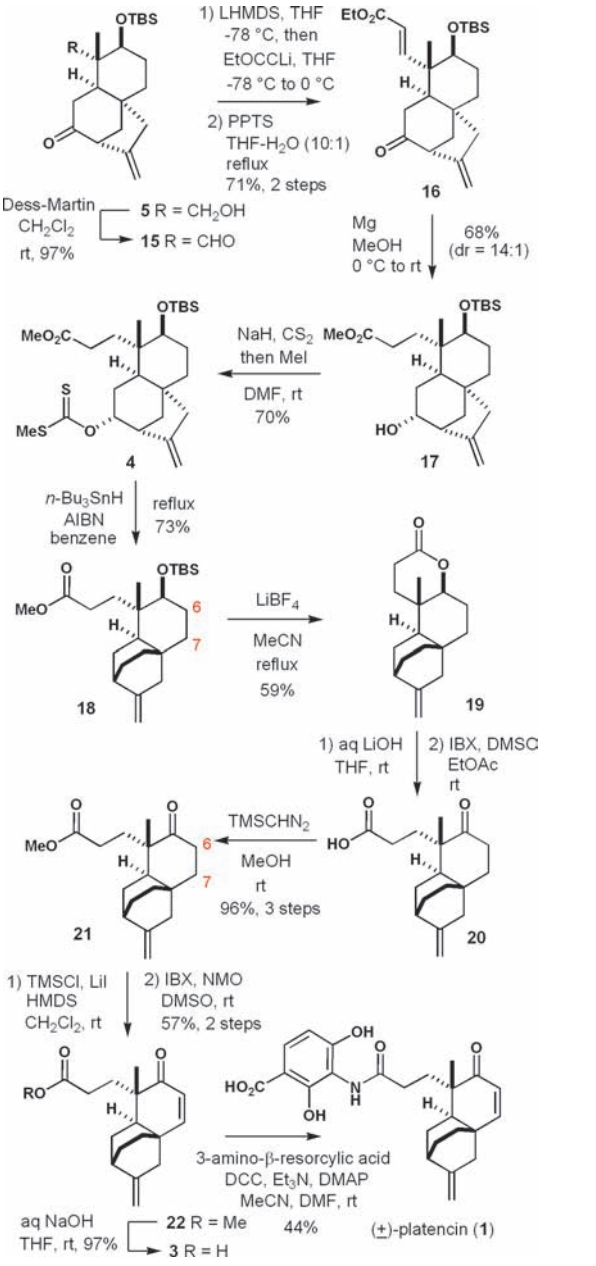
(10) For details, see Supporting Information.

(11) The pioneering work on 1,4-chiral induction of δ-hydroxyl acyclic esters, in which a tertiary stereocenter α to the ester carbonyl group is successfully created by δ-hydroxyl directed alkylation or aldolization, has been reported. (a) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc., Jpn.* **1987**, *60*, 1457–1464. (b) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81–84. (c) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Chem. Lett.* **1986**, 1755–1758.

(12) A small amount (11%) of a regioisomer, which may be produced via γ-deprotonation followed by α-alkylation–isomerization reactions, was obtained together with unreacted starting material **9** (13%). Two authentic diastereomers **8** and *epi*-**8** were derived from the corresponding products obtained by alkylation of compound **12** with 2,3-dibromopropene, followed by desilylation with TBAF. The selective production of compound **8** was unambiguously confirmed by careful analyses of TLC and ^1H NMR spectra of the two diastereomers. For details, see Supporting Information.

(13) No stereochemical assignment of the isomers was made.

Scheme 5. Completion of Total Synthesis of (±)-Platencin (**1**)



Next, tricyclic compound **5** was subjected to side-chain elongation (Scheme 5). Compound **5** was first oxidized with Dess-Martin periodinane to afford aldehyde **15** quantitatively. Then, aldehyde **15** was alkynylated with lithium ethoxy acetylide to give alcohol as a diastereomeric mixture (dr = 1:2; structure not shown), which, in turn, was subjected to dehydration with PPTS to provide α,β-unsaturated ester **16** in 71% yield in two steps.

It should be mentioned that pretreatment of **15** with LHMDS to form a ketone lithium enolate was quite important to avoid undesired alkynylation at the ketone carbonyl group. The Mg-mediated transformation of ester **16** in MeOH gave methyl ester **17** that was produced via reduction of the carbon−carbon double bond and the ketone carbonyl group concomitant with transesterification with the solvent.[15] Then, ester **17** was transformed into xanthate **4** in 70% yield, a material suitable for radical skeletal rearrangement.[8] Xanthate **4**, when reacted with *n*-Bu_3SnH in the presence of AIBN, underwent radical rearrangement to furnish desired compound **18** in 73% yield. With this architecture relevant to platencin, installation of the double bond at the C6 position (platencin numbering) was then examined. Desilylation of compound **18** with $LiBF_4$ afforded lactone **19** via facile cyclization of the resultant hydroxyl ester.[16] Although the hydrolysis of lactone **19** was found to be problematic because the resultant hydroxyl carboxylic acid (structure not shown) readily underwent lactonization during workup processes to regenerate lactone **19**, careful treatment of the crude carboxylic acid with IBX allowed us to successfully deliver keto carboxylic acid **20** without the accompanying undesired lactonization.[17] Compound **20** was then esterified with trimethylsilyldiazomethane in MeOH to provide ketone **21** in 96% yield over three steps from **19**. Next, ketone **21** was converted into the corresponding TMS enol ether, which was successfully oxidized with IBX-NMO in DMSO to provide enone **22** in 57% yield in two steps.[18] Hydrolysis of enone **22** with aq NaOH afforded platencinic acid (**3**) quantitatively, which, by subjecting to the known amidation reaction with 3-amino-β-resorcylic acid,[3b] eventually furnished (±)-platencin (**1**). The spectroscopic and analytical data of synthetic platencin exactly matched those reported in the literature.

In conclusion, we have established a new route to (±)-platencin that features the stereoselective quaternization of a cyclohexenone motif through chelation-controlled alkylation followed by two successful radical reactions, i.e., highly stereoselective radical cyclization as well as skeletal rearrangement. It should be noted that the present route is applicable to the asymmetric production of platencin simply by switching racemic fragment **11** to chiral **11**. On the basis of the present route, the derivatization of new platencin analogues is underway with a view to discovering potent antibiotic leads through structure−activity relationship studies.

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Supporting Information Available. Experimental procedures, characterization data, and $^1H/^{13}C$ NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) At this stage, a tiny amount of the minor product that was generated from a minor diastereomer (4%) could be completely separated by silica gel column chromatography.

(15) In this reaction, 5% of minor β-hydroxy diastereomer was formed and could be separated from the desired isomer by silica gel chromatography. For details, see Supporting Information.

(16) Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35–36. either TBAF nor HF·Py, a common desilylating agent, gave the desired compound.

(17) For details, see Supporting Information.

(18) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996–1000.