JOC Featured Article

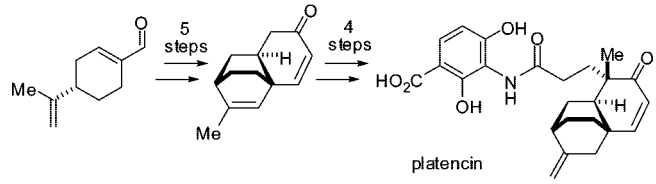
A Nine-Step Total Synthesis of (−)-Platencin

Konrad Tiefenbacher* and Johann Mulzer*

Institute of Organic Chemistry, University of Vienna, Währingerstrasse 38, 1090 Vienna, Austria

johann.mulzer@univie.ac.at; konrad.tiefenbacher@univie.ac.at

Received January 28, 2009



Within 1 year, platencin, a recently discovered antibiotic, has become a highly competitive synthetic target, due to its promising bioactivity and its unusual complex molecular architecture. Herein, a particularly concise total synthesis of platencin starting from inexpensive perillaldehyde is described. The key features of this approach are (1) a highly diastereoselective Diels−Alder reaction with Rawal's diene—forming the first all-carbon quaternary center, (2) a ring-closing metathesis to generate the strained tricylic skeleton, (3) a hydration/dehydration strategy to efficiently shift the endocyclic alkene to the exoposition, and (4) a 1,4-addition of a hindered ketone enolate to methyl acrylate to create the second all-carbon quaternary center. In view of the brevity (nine linear steps) and the overall yield of 10%, our synthesis compares favorably with all the previous ones.

Introduction

The rise of multiresistant bacteria is a serious and urgent threat, especially in hospitals, where antibiotics are permanently used and bacteria strains easily evolve that withstand multiple antibiotic classes. Infections by gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumonia* (PRSP) are especially worrying.[1] From these observations, the urgency to develop new antibiotics is obvious. Since novel antibiotics usually address well-known targets just at different binding sites or through new binding modes, the discovery of platensimycin[2] (**1**) and platencin[3] (**2**, Figure 1) is a breakthrough in antibiotics research.

This is due to the fact that compounds **1** and **2** address an apparently ideal biological target. They are the first potent inhibitors of bacterial fatty acid biosynthesis (Fab), which is essential to the survival of the pathogens, distinct from the mammalian pathway and generally highly conserved among bacteria. While platensimycin is blocking the fatty acid condensing enzyme FabF selectively, platencin is inhibiting the enzymes FabF and FabH. These compounds thus display a broad-spectrum antibiotic activity against many drug-resistant pathogens such as methycillin-, macrolide-, and linezolid-resistant *S. aureus*, vancomycin intermediate *S. aureus*, vancomycin-resistant enterococci, and *Streptococcus pneumoniae*.[3] Just recently, platensimycin B_1-B_3, less biologically active natural derivatives of platensimycin, have been discovered.[4]

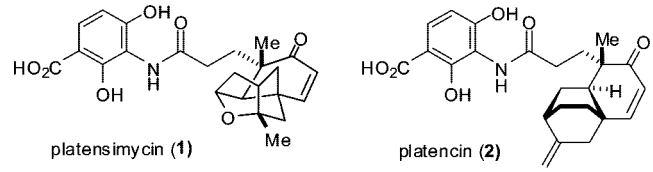


FIGURE 1. Structures of platensimycin (**1**) and platencin (**2**).

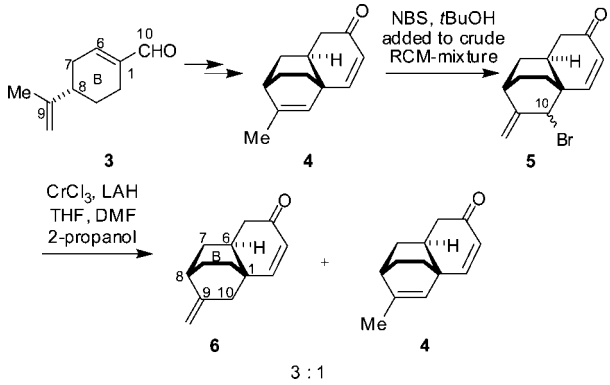
Owing to the unique mode of action, no cross-resistances to existing drugs have been observed so far. In addition, the toxicity profile seems to be good. However, the in vivo efficacy is low, due to the limited metabolic stability, so that suitable synthetic derivatives will have to be prepared and investigated to find more promising drug candidates.[1]

(1) (a) Häbich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951. (b) Holzgrabe, U.; Dingermann, T.; Zündorf, I. *Pharm. Unserer Zeit* **2006**, *35*, 388.

(2) (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. (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; *J. Am. Chem. Soc.* (Addition/Correction) **2006**, *128*, 15547. (c) Singh, S. B.; Herath, K. B.; Wung, J.; Tsou, N.; Ball, R. G. *Tetrahedron Lett.* **2007**, *48*, 5429. (d) Singh, S. B.; Wang, J.; Basilio, A.; Genilloud, O.; Hernandez, P.; Tormo, J. R. WO 2005009391, 2005 (CAN 142: 196607).

10.1021/jo9001855 CCC: $40.75 © 2009 American Chemical Society
Published on Web 03/04/2009

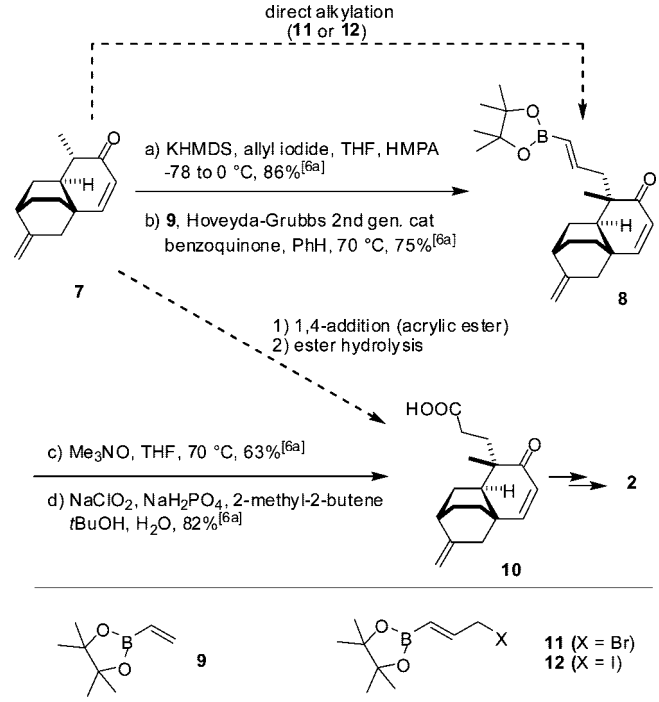
SCHEME 1. First-Generation Synthesis of the Core Fragment 6 of Platencin (2)



Not surprisingly, the unusual structure and the promising biological activity have attracted great interest from the scientific community, leading to one total and eight formal syntheses[5] of **1** during the last 2 years and two total and five formal syntheses[6] of **2**—all published in 2008. Our goal was to develop a short total synthesis of platencin based on our previous five-step formal synthesis (Scheme 1).[6c]

Perillaldehyde (**3**) was chosen as the starting material because it is inexpensive and can be converted to the advanced core system **4** in three steps. The disadvantage of this first-generation approach is the shift of the *endo*-cycloalkene (in **4**) to the thermodynamically less favored *exo* position (in **6**). As this operation furnished a 3:1 mixture of **6** and **4** and required 2.5 equiv of chromium reagent, we decided to replace it with a more suitable methodology. Another issue is the endgame, that is, the conversion of intermediate **6** into platencin (**2**). In Nicolaou's benchmark approach[6a] (Scheme 2), **6** was first methylated to **7** and then converted to **8** via allylation and cross metathesis with

SCHEME 2. Nicolaou's Endgame[6a] and Potential Alternatives



vinyl boronate **9**. A two-step oxidation furnished carboxylic acid **10**. We envisioned a more convergent route from **7** to **10** either by alkylation with the appropriately functionalized allyl halides **11** or **12** or by a conjugate enolate 1,4-addition to an acrylic ester. We are now pleased to note that due to the improvements reported in this full account our new synthesis produces substantial amounts of pure **2** in only nine linear steps with satisfactory stereo- and regiocontrol.

Results and Discussion

Synthesis of the Core Fragment 6: The first step in the synthesis is the Diels–Alder reaction between perillaldehyde (**3**) and a suitable diene. The traditional Danishefsky diene (**13a**) fails to react with poor dienophiles such as cyclohex-1-enecarbaldehydes under regular conditions. Therefore, we decided to use the much more reactive Rawal diene (**13b**),[7] which after exposure to **3** in refluxing toluene for 4.5 h, followed by acidic treatment, furnished the desired cycloadduct **14** in 68% yield and excellent diastereoselectivity (20:1, Scheme 3). Later, the Rutjes group did add **13a** to **3**; however, as expected, high pressure conditions (15 kbar), which traditionally limit the scale up of a reaction, had to be used.[6e]

The selective methylenation of the neopentylic aldehyde function of **14** in the presence of the unsaturated ketone was unproblematic if just a slight excess of the Wittig reagent was used at 0 °C. Under these conditions, triene **15** was obtained in 80% yield. Ring-closing metathesis (RCM) of **15** with Grubbs' second-generation catalyst[8] (7 mol %) in refluxing CH_2Cl_2 led to **4** in 90% isolated yield. Since the reaction was slow, the catalyst was added in three portions over 36 h. As expected,

(3) (a) 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. (b) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Teresa Diez, M.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 4684.

(4) Zhang, C.; Ondeyka, J.; Zink, D. L.; Burgess, B.; Wang, J.; Singh, S. S. *Chem. Commun.* **2008**, 5034.

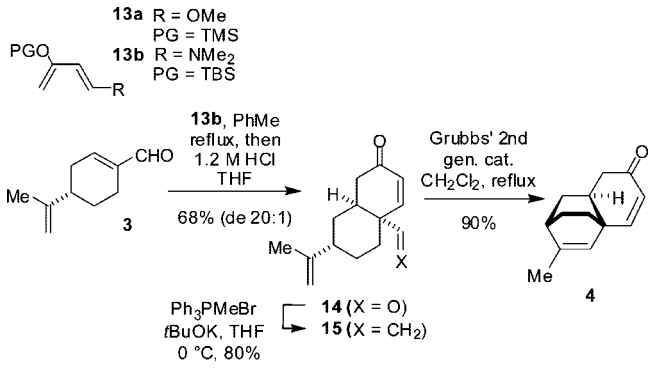
(5) Review on the synthesis of platensimycin: (a) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548. Total synthesis of platensimycin: (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086. Formal synthesis of platensimycin: (c) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (d) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825. (e) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922. (f) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534. (g) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8074. (h) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921. (i) Nicolaou, K. C.; Pappo, D.; Tsang, K. Y.; Gibe, R.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 944. (j) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4009. Derivatives of platensimycin: (k) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712. (l) Nicolaou, K. C.; Tang, Y.; Wang, J.; Stepan, A. F.; Li, A.; Montero, A. *J. Am. Chem. Soc.* **2007**, *129*, 14850. (m) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417. Synthetic studies toward the tetracyclic core system: (n) Ghosh, A. K.; Xi, K. *Org. Lett.* **2007**, *9*, 4013. Short synthesis of the aromatic part: (o) Heretsch, P.; Giannis, A. *Synthesis* **2007**, *17*, 2614.

(6) (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780. (b) Hayashida, J.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4373. (c) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6199. (d) Yun, S. Y.; Zheng, J.-C.; Lee, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 6201. (e) Waalboer, D. C. J.; Schaapman, M. C.; Van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6576. (f) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292; *J. Am. Chem. Soc.* (Addition/Correction) **2008**, *130*, 14016. (g) Austin, K. A. B.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2008**, *10*, 4465.

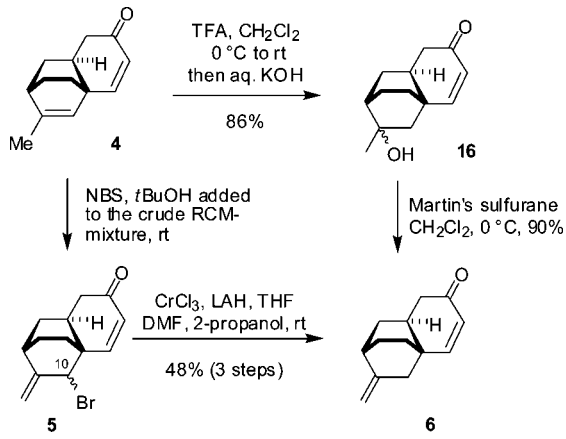
(7) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039.

(8) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.

SCHEME 3. Synthesis of Tricycle 4



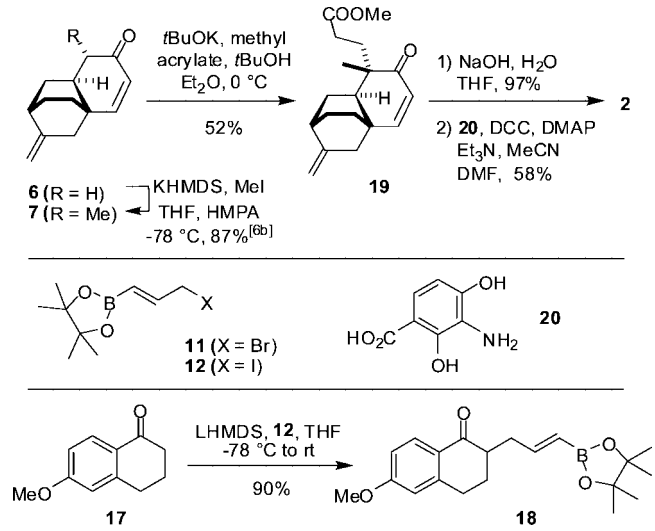
SCHEME 4. Conversion of the Endocyclic to the Exocyclic Alkene via Bromination or Hydration



Grubbs' first-generation catalyst under the same conditions did not furnish any product.

For the isomerization of **4** to **6** (Scheme 4), we first tried to improve our initial Mori-type[9] bromination/chromium(II) reduction sequence. As the allylic bromination under literature conditions (NBS, MeOH, CH_2Cl_2, 0 °C) saddled us with considerable amounts of undesired bromoethers, we explored a series of other bromination and chlorination protocols (for instance, NBS, $(BzO)_2$, CCl_4, reflux; NCS, $Yb(OTf)_3$, TMSCl;[10a] NBA, acetone, water, rt;[10b] NBS, CH_2Cl_2, silica gel, rt;[10c] NaOCl, H_3PO_4, hexane, 0 °C),[10d] which all yielded complex product mixtures. Without an alcohol additive, no reaction was observed. Finally, after a lot of experimentation, we found that the bromoether formation we observed under our standard conditions (NBS, MeOH, CH_2Cl_2, 0 °C) could be suppressed by replacing methanol with the much bulkier *t*BuOH. Nevertheless, the yield was unsatisfying and variable, until we discovered that the reaction proceeded smoothly when impure, dark samples of **4** (obtained from cursorily performed column chromatography of the RCM mixture) were used. Assuming that the dark impurity is some ruthenium species which catalyzes the allylic bromination, we skipped the chromatography and added NBS and *t*BuOH directly to the crude RCM reaction mixture. Indeed,

SCHEME 5. Completion of the Total Synthesis of Platencin (2)



clean and reproducible formation of **5** was achieved. On second sight, this is not so surprising, as Ru(II) species are known to act as Lewis acid catalysts in several transformations, such as (hetero)-Diels−Alder reactions, Mukaiyama aldol reactions, oxa-ene reactions, and Claisen rearrangements.[11] With allylic bromide **5** finally in hand, chromium(II) reduction furnished a separable 3:1 mixture of **6** and **4**. Several other reduction conditions were explored, but to no avail. For instance, Zn, AcOH, MeOH, 22 °C resulted in an unfavorable 1:0.7 ratio of **6** and **4**; for $Pd(dba)_3$, PBu_3, Et_3N, HCOOH, THF, reflux,[6e] the ratio was 1:0.8, whereas $NaBH_4/CeCl_3$, MeOH or LAH, Et_2O furnished complex product mixtures.

Finally, to avoid the use of stochiometric amounts of chromium and to increase the **6**/**4** ratio, a concise hydration/dehydration strategy was devised. Thus, our RCM product **4** was hydrated to **16** (formed as an inconsequential 1.5:1 diastereomeric mixture) via the trifluoroacetate and subsequent saponification. The following dehydration was performed with a selection of dehydrating reagents, which varied considerably with respect to their regioselectivity. Thus, whereas Burgess reagent[12] (THF, CH_2Cl_2) or $SOCl_2$, pyridine[13] gave ca. 1:1 mixtures of **6** and **4**, Martin's sulfurane led to satisfactory results (7:1 at 20 °C and 10:1 at 0 °C). Although this selectivity was somewhat lower than that which the Nicolaou group had reported,[6f] this method proved highly practical for procuring the desired *exo*-olefin.

Completion of the Total Synthesis: After having established an exceptionally direct and selective access to the core fragment **6**, we decided to keep the endgame as short and convergent as possible. Thus, after methylation of **6** to **7** (Scheme 5),[6a,b] we tried the alkylation of **7** with known allylic bromide **11**[14] or the easily accessible iodide **12** under various conditions, but only starting material could be isolated in all cases. With 6-methoxy-1-tetralone (**17**) as a simple test substrate, alkylation to **18** with

(9) (a) Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* **2001**, *42*, 939. (b) Abad, A.; Agullò, C.; Cunat, A. C.; Marzal, I. A.; Gris, A.; Navarro, I.; Ramirez de Arellano, C. *Tetrahedron* **2007**, *63*, 1664.

(10) (a) Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2002**, *43*, 2403. (b) Hiranuma, S.; Shimizu, T.; Yoshioka, H. *Chem. Pharm. Bull.* **1991**, *39*, 2167. (c) Since it was observed that silica gel (TLC) accelerates the reaction in the presence of an alcohol additive. (d) Nussbaumer, C.; Frater, G.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1016.

(11) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.

(12) Reviews on the chemistry of the Burgess reagent: (a) Taibe, P.; Mobashery, S. In *Encyclopedia of Reagents for Organic Synthesis*; PaquetteL. A., Ed.; John Wiley & Sons: Chichester, UK, 1995; Vol. 5, pp 3345−3347. (b) Burckhardt, S. *Synlett* **2000**, 559.

(13) Margaros, I.; Vassilikogiannakis, G. *J. Org. Chem.* **2007**, *72*, 4826.

(14) Pergament, I.; Reich, R.; Srebnik, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1215.

iodide **12** could be achieved in 90% yield, while bromide **11** failed. Although not successful for **7**, this result at least indicated that, in principle, iodide **12** could be a useful alkylation agent to form tertiary carbon centers, with the advantage of further functionalization by oxidation or coupling at the vinyl boronate position. Fortunately, our second approach, conversion of **7** into the enolate followed by 1,4-addition to methyl acrylate, worked and gave us an easily separable 4:1 mixture of **19** and its diastereomer. Interestingly, the diastereomeric ratio was not affected by lowering the temperature—even at −78 °C, the same ratio was observed. The synthesis was completed by ester hydrolysis and direct coupling[6b] of the carboxylic acid with the unprotected aniline **20**.[5o,15] In contrast to previous endgames,[6a,b] this protocol is atom economical and does not need cross metathesis and dummy atoms such as boron or silicon, which have to be removed oxidatively.

The spectral data (^{1}H, ^{13}C NMR) of **2** perfectly matched those in the literature.[6a,b] Moreover, the OH and NH signals were unambiguously assigned in the ^{1}H NMR spectrum by D_2O exchange (see Supporting Information).

Conclusion

In summary, a nine-step, protecting-group-free total synthesis of natural (−)-platencin (**2**) has been accomplished. We obtained 36 mg of **2** with ee >92% (limited only by the optical purity of the perillaldehyde) in nine linear steps and 10% overall yield. As a consequence, we have an efficient route at our disposal, which should also allow the fast and concise synthesis of derivatives, required for the development of antibiotics with more suitable pharmacological characteristics.

Experimental Section

(2*S*,4a*R*,8a*S*)-2-Isopropenyl-7-oxo-1,3,4,7,8,8a-hexahydro-2*H*-naphthalene-4a-carbaldehyde (14): To a refluxing solution of (−)-perillaldehyde (4.37 g, 29.1 mmol) in anhydrous toluene (82 mL) was added Rawal diene (4.41 g, 19.4 mmol) in three portions every 30 min. After the last addition, the reaction mixture was refluxed for another 3 h, cooled to rt, and the solvent removed under vacuum. The oily residue was dissolved in THF (108 mL); 1.2 M aqueous HCl (44 mL) was added, and the mixture was stirred at rt for 16 h. After addition of brine (385 mL), the aqueous layer was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Purification by column chromatography (130 g silica gel) using hexane/ethyl acetate = 3:1 as an eluent yielded aldehyde **14** (2.86 g, 68%) as a slightly yellow oil: R_f = 0.32 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ = +170.3 (c = 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1H), 6.60 (d, J = 10.1 Hz, 1H), 6.08 (d, J = 10.1 Hz, 1H), 4.75 (s, 1H), 4.69 (s, 1H), 2.85−2.76 (m, 1H), 2.71−2.60 (m, 1H), 2.43−2.35 (m, 1H), 2.26−2.18 (m, 1H), 2.16−2.06 (m, 1H), 1.79−1.56 (m, 4H), 1.69 (s, 3H), 1.31−1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.6 (CH), 198.5 (C), 148.2 (C), 147.9 (CH), 129.9 (CH), 109.7 (CH_2), 52.7 (C), 39.2 (CH_2), 38.0 (CH), 32.8 (CH_2), 32.6 (CH), 28.1 (CH_2), 27.1 (CH_2), 20.9 (CH_3); IR (film) $\tilde{\nu}$ = 2931, 1726, 1676, 1452, 1251, 890 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{18}O_2$ [M$^+$] 218.1307, found 218.1300.

(4a*R*,7*S*,8a*S*)-7-Isopropenyl-4a-vinyl-4a,5,6,7,8,8a-hexahydro-1*H*-naphthalen-2-one (15): To a suspension of *t*BuOK (2.11 g, 18.8 mmol) in THF (42 mL) was added PPh_3MeBr (8.39 g, 23.5 mmol) and stirred for 25 min at rt. At this time, 30 mL of this yellow suspension was quickly added to a solution of aldeyde **6** (1.71 g, 7.83 mmol) in THF (100 mL) at 0 °C. After stirring for 20 min at this temperature, water (500 mL) was added and the aqueous layer was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, silica gel (6 g) was added, and the solvent was carefully removed under vacuum. Purification of the adsorbed material by column chromatography (60 g silica gel) using hexane/ethyl acetate = 10:1 as an eluent yielded triene **15** (1.36 g, 80%) as a colorless oil: R_f = 0.46 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ = +88.2 (c = 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.58 (d, J = 10.1 Hz, 1H), 5.96−5.86 (m, 2H), 5.26 (d, J = 10.8 Hz, 1H), 5.17 (d, J = 17.6 Hz, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 2.69−2.57 (m, 1H), 2.41−2.28 (m, 2H), 2.20−2.09 (m, 1H), 1.84−1.72 (m, 2H), 1.72 (s, 3H), 1.69−1.60 (m, 2H), 1.57−1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.2 (C), 157.2 (CH), 148.8 (C), 143.3 (CH), 127.0 (CH), 115.8 (CH_2), 109.4 (CH_2), 42.3 (C), 40.0 (CH_2), 38.3 (CH), 38.1 (CH), 32.0 (CH_2), 30.6 (CH_2), 25.9 (CH_2), 21.1 (CH_3); IR (film) $\tilde{\nu}$ = 2930, 1674, 1450, 884 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{20}O$ [M$^+$] 216.1516, found 216.1504.

(1*R*,6*S*,8*S*)-9-Methyltricyclo[6.2.2.0^{1,6}]dodeca-2,9-dien-4-one (4): A solution of triene **15** (609 mg, 2.82 mmol) and Grubbs' second-generation catalyst (72 mg, 0.085 mmol) in degassed (pump, freeze, and thaw technique) CH_2Cl_2 (56 mL) was refluxed overnight. Two times additional catalyst (48 mg, 0.057 mmol) was added, and the mixture was refluxed for 8−12 h. After the reaction was finished, air was blown into the reaction vessel and stirring was continued for 30 min. Silica gel (4 g) was added, and the solvent was carefully removed under vacuum. Purification of the adsorbed material by column chromatography (50 g silica gel) using hexane/ethyl acetate = 7:1 as an eluent yielded tricycle **4** (478 mg, 90%) as colorless oil: R_f = 0.43 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ = −71.3 (c = 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (d, J = 10.0 Hz, 1H), 5.93 (dd, J = 10.0, 0.9 Hz, 1H), 5.80 (s, 1H), 2.57−2.48 (m, 1H), 2.42−2.27 (m, 2H), 2.00−1.89 (m, 1H), 1.82 (d, J = 1.7 Hz, 3H), 1.80−1.69 (m, 2H), 1.62−1.53 (m, 1H), 1.41−1.23 (m, 2H), 1.02 (ddd, J = 12.6, 6.3, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.4 (C), 157.1 (CH), 142.7 (C), 128.6 (CH, 2C), 41.7 (CH_2), 39.2 (C), 38.5 (CH), 35.9 (CH), 32.1 (CH_2), 27.0 (CH_2), 25.6 (CH_2), 20.2 (CH_3); IR (film) $\tilde{\nu}$ = 2938, 2861, 1682, 1250, 1202, 766 cm^{-1}; HRMS(EI) calcd for $C_{13}H_{16}O$ [M$^+$] 188.1201, found 188.1205.

(1*R*,6*S*,8*S*)-9-Hydroxy-9-methyltricyclo[6.2.2.0^{1,6}]dodec-2-en-4-one (16): Trifluoroacetic acid (1.9 mL) was added to a solution of **4** (320 mg, 1.70 mmol) in CH_2Cl_2 (5.6 mL) at 0 °C. After 15 min, the cooling bath was removed and stirring continued for 2 h. The reaction mixture was diluted with diethyl ether (20 mL), and aqueous KOH (10%, 20 mL) was slowly added at 0 °C. The cooling bath was removed, and rigorous stirring continued for 14 h. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Purification by column chromatography (18 g silica gel) using hexane/ethyl acetate = 1:1 as an eluent yielded alcohol **16** (302 mg, 86%) as a colorless oil: R_f = 0.24/0.29 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.52 (d, J = 10.1 Hz, 0.4H), 6.47 (d, J = 10.1 Hz, 0.6H), 5.85 (dd, J = 10.1, 1.0 Hz, 0.6H), 5.84 (dd, J = 10.1, 1.0 Hz, 0.4H), 2.49−1.98 (m, 4.4H), 1.74−1.40 (m, 7H), 1.36 (s, 1.8H), 1.34 (s, 1.2 H), 1.33−1.27 (m, 0.6H), 1.15−1.09 (m, 0.4H), 1.00−0.92 (m, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.3 (C), 200.0 (C), 157.2 (CH), 156.7 (CH), 127.7 (CH), 127.7 (CH), 71.6 (C), 70.9 (C), 49.3 (CH_2), 49.2 (CH_2), 41.5 (CH_2), 41.5 (CH_2), 37.6 (CH), 37.0 (CH), 35.5 (C), 35.3 (C), 34.3 (CH), 34.2 (CH), 31.2 (CH_2), 30.8 (CH_3), 30.0 (CH_2), 29.9 (CH_3), 23.8 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 21.2 (CH_2); IR (film) $\tilde{\nu}$ = 3449, 2926, 1676, 1258, 1121, 779, 611 cm^{-1}; HRMS(EI) calcd for $C_{13}H_{18}O_2$ [M$^+$] 206.1307, found 206.1297.

(1*R*,6*S*,8*S*)-9-Methylenetricyclo[6.2.2.0^{1,6}]dodec-2-en-4-one (6): To a solution of alcohol **16** (279 mg, 1.35 mmol) in CH_2Cl_2 (8 mL) was added a solution of Martin's sulfurane (1.0 g, 1.49 mmol)

(15) Coupling of **20** with the acyl chloride[16] led to decomposition.

(16) Lee, K.; Lee, J. H.; Boovanahalli, S. K.; Jin, Y.; Lee, M.; Jin, X.; Kim, J. H.; Hong, Y.-S.; Lee, J. J. *J. Med. Chem.* **2007**, *50*, 1675.

in CH_2Cl_2 (2.5 mL) at 0 °C. After 1.5 h, additional Martin's sulfurane (300 mg, 0.45 mmol) in CH_2Cl_2 (2.5 mL) was added and stirring continued for 1 h at 0 °C. The reaction mixture was concentrated under vacuum, and the residue was purified by column chromatography (30 g silica gel) using hexane/diethyl ether = 4:1 as an eluent to yield **6** (229 mg, 90%) as a colorless oil: $R_f = 0.38$ (hexane/EtOAc 3:1); $[\alpha]^{20}_D = +27.5$ ($c = 0.83$, $CHCl_3$); $[\alpha]^{35}_D = +22.2$ ($c = 0.68$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.55$ (d, $J = 10.1$ Hz, 1H), 5.86 (d, $J = 10.1$ Hz, 1H), 4.84−4.80 (m, 1H), 4.69−4.66 (m, 1H), 2.49−2.38 (m, 2H), 2.36−2.26 (m, 2H), 2.20−2.06 (m, 2H), 2.03−1.94 (m, 1H), 1.82−1.63 (m, 3H), 1.54−1.45 (m, 1H), 1.23−1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 200.0$ (C), 156.6 (CH), 148.9 (C), 127.7 (CH), 106.9 (CH_2), 41.6 (CH_2), 40.9 (CH_2), 36.0 (CH), 35.6 (C), 35.5 (CH), 34.9 (CH_2), 26.4 (CH_2), 24.5 (CH_2); IR (film) $\tilde{\nu} = 2939$, 2866, 1683, 1429, 1392, 1273, 877 cm^{-1}; HRMS(EI) calcd for $C_{13}H_{16}O$ [M^+] 188.1201, found 188.1206.

(1*S*,5*S*,6*S*,8*S*)-5-Methyl-9-methylenetricyclo[6.2.2.0^{1,6}]dodec-2-en-4-one (7): Preparation was according to Rawal et al:[6b] $R_f = 0.41$ (hexane/EtOAc 5:1); $[\alpha]^{20}_D = -19.5$ ($c = 0.75$, $CHCl_3$); $[\alpha]^{35}_D = -18.0$ ($c = 0.75$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.49$ (d, $J = 10.0$ Hz, 1H), 5.87 (d, $J = 10.0$ Hz, 1H), 4.83−4.81 (m, 1H), 4.68−4.66 (m, 1H), 2.39 (dt, $J = 16.4$, 2.7 Hz, 1H), 2.36−2.32 (m, 1H), 2.27 (hex, $J = 6.6$ Hz, 1H), 2.16−2.10 (m, 1H), 2.04−1.95 (m, 1H), 1.83−1.67 (m, 4H), 1.53−1.46 (m, 1H), 1.29 (ddd, $J = 12.6$, 8.3, 1.3 Hz, 1H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 202.0$ (C), 155.4 (CH), 148.9 (C), 127.2 (CH), 106.7 (CH_2), 43.7 (CH), 42.6 (CH), 41.2 (CH_2), 36.0 (C), 35.6 (CH), 34.3 (CH_2), 26.4 (CH_2), 24.9 (CH_2), 11.3 (CH_3); IR (film) $\tilde{\nu} = 2937$, 2867, 1676, 1452, 1392, 1375, 1206, 1166 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{18}O$ [M^+] 202.1358, found 202.1352.

3-[(1*S*,5*S*,6*R*,8*S*)-5-Methyl-9-methylene-4-oxotricyclo[6.2.2.0^{1,6}]-dodec-2-en-5-yl]propionic acid methyl ester (19): To a solution of **7** (95 mg, 0.47 mmol) in diethyl ether (1.4 mL) and *t*BuOH (1.4 mL) was added *t*BuOK (105 mg, 0.94 mmol) at 0 °C. After stirring at this temperature for 5 min, methyl acrylate (0.34 mL, 3.76 mmol) was added. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Purification by column chromatography (10 g silica gel) using hexane/ethyl acetate = 7:1 as an eluent yielded a crude diastereomeric mixture of esters (123 mg, dr 4:1) as colorless oil. Purification by HPLC yielded ester **19** (71 mg, 52%) as an analytically pure material: $R_f = 0.23$ (hexane/EtOAc 5:1); $[\alpha]^{20}_D = +22.7$ ($c = 0.60$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.46$ (d, $J = 10.1$ Hz, 1H), 5.83 (d, $J = 10.1$ Hz, 1H), 4.85−4.83 (m, 1H), 4.69−4.67 (m, 1H), 3.64 (s, 3H), 2.44−2.40 (m, 1H), 2.35−2.28 (m, 1H), 2.24−2.03 (m, 4H), 2.01−1.93 (m, 2H), 1.76−1.65 (m, 3H), 1.63−1.43 (m, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 204.0$ (C), 174.0 (C), 154.3 (CH), 148.8 (C), 126.2 (CH), 107.3 (CH_2), 51.6 (CH_3), 47.2 (C), 44.5 (CH_2), 39.5 (CH), 36.1 (C), 35.9 (CH), 29.8 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 26.6 (CH_2), 25.8 (CH_2), 21.1 (CH_3); IR (film) $\tilde{\nu} = 2935$, 2867, 1739, 1675, 1436, 1306, 1195, 1173, 827 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{24}O_3$ [M^+] 288.1725, found 288.1729.

3-[(1*S*,5*S*,6*R*,8*S*)-5-Methyl-9-methylene-4-oxotricyclo[6.2.2.0^{1,6}]-dodec-2-en-5-yl]propionic acid (10): To a solution of ester **19** (41 mg, 0.14 mmol) in THF (1.7 mL) was added 1 M aqueous NaOH (1.7 mL), and the mixture was stirred for 23 h at rt. After the addition of water (16 mL) and brine (8 mL), the mixture was washed with diethyl ether twice. The aqueous phase was acidified with 1.2 M HCl (formation of a white precipitate) and extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum to give acid **10** (38 mg, 97%): $R_f = 0.32$ (hexane/EtOAc 3:1); $[\alpha]^{20}_D = +22.6$ ($c = 0.50$, $CHCl_3$); $[\alpha]^{35}_D = +20.6$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 6.47$ (d, $J = 10.1$ Hz, 1H), 5.85 (d, $J = 10.1$ Hz, 1H), 4.86−4.84 (m, 1H), 4.70−4.68 (m, 1H), 2.45−2.41 (m, 1H), 2.34−2.29 (m, 1H), 2.29−2.22 (m, 2H), 2.15−2.10 (m, 1H), 2.10−2.05 (m, 1H), 2.01−1.94 (m, 2H), 1.76−1.66 (m, 3H), 1.63−1.56 (m, 1H), 1.56−1.46 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 204.2$ (C), 178.7 (C), 154.4 (CH), 148.7 (C), 126.2 (CH), 107.4 (CH_2), 47.1 (C), 44.5 (CH_2), 39.5 (CH), 36.1 (C), 35.8 (CH), 29.4 (CH_2), 29.1 (CH_2), 28.0 (CH_2), 26.6 (CH_2), 25.8 (CH_2), 21.1 (CH_3); IR (film) $\tilde{\nu} = 2925$, 1707, 1675, 1653, 1457, 1294, 1125, 887, 826 cm^{-1}. HRMS(EI) calcd for $C_{17}H_{21}O_3$ [$M - H]^-$ 273.1496, found 273.1493.

Platencin (2): According to Rawal et al,[6b] to a solution of acid **10** (40 mg, 0.146 mmol) in MeCN (1.4 mL) were added DMAP (36 mg, 0.292 mmol), Et_3N (61 μL, 0.438 mmol), and DCC (190 μL, 0.190 mmol, 1 M in CH_2Cl_2). The mixture was stirred for 7.5 h. To the resulting mixture was added a solution of 3-amino-2,4-dihydroxybenzoic acid **20** (49 mg,0.292 mmol) in DMF (0.40 mL) and stirred for additional 40 h. The mixture was directly charged on a silica gel column (10 g) and purified using EtOAc/hexane/AcOH/MeOH/H_2O = 80:20:0.5:1.0:0.5 as an eluent to yield **2** (36 mg, 58%) as a white solid: $R_f = 0.20$ (EtOAc/hexane/AcOH/MeOH/H_2O = 80:20:0.5:1.0:0.5); $[\alpha]^{20}_D = -15.0$ ($c = 0.24$, MeOH); $[\alpha]^{23}_D = -15.4$ ($c = 0.24$, MeOH); $[\alpha]^{35}_D = -17.4$ ($c = 0.24$, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 11.7$ (s, 1H), 11.2 (s, 1H), 8.24 (s, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 6.58 (d, $J = 10.1$ Hz, 1H), 6.51 (d, $J = 9.1$ Hz, 1H), 5.93 (d, $J = 10.1$ Hz, 1H), 5.30 (s, 1H), 4.88−4.86 (m, 1H), 4.70−4.68 (m, 1H), 2.50−2.32 (m, 4H), 2.19−2.13 (m, 1H), 2.13−2.08 (m, 1H), 2.04−1.98 (m, 2H), 1.86−1.73 (m, 4H), 1.61−1.52 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 205.9$ (C), 174.1 (C), 172.5 (C),156.0 (CH), 155.4 (C), 154.4 (C), 148.3 (C), 128.2 (CH), 126.0 (CH), 114.4 (C), 111.3 (CH), 107.7 (CH_2), 103.3 (C), 47.7 (C), 44.4 (CH_2), 39.4 (CH), 36.3 (C), 35.8 (CH), 32.3 (CH_2), 31.0 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 25.7 (CH_2), 21.2 (CH_3); IR (film) $\tilde{\nu} = 2930$, 1652, 1538, 1456, 1373, 1282 cm^{-1}; HRMS(EI) calcd for $C_{24}H_{26}NO_6$ [$M - H]^-$ 424.1760, found 424.1766.

Acknowledgment. We thank Lothar Brecker, Susanne Felsinger, and Hanspeter Kählig for NMR spectroscopic assistance, and Peter Unteregger for mass spectroscopy.

Supporting Information Available: Experimental details for compounds **6** (via bromide **5**), **12**, and **18** and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9001855