Antibiotics

DOI: 10.1002/ange.200603892

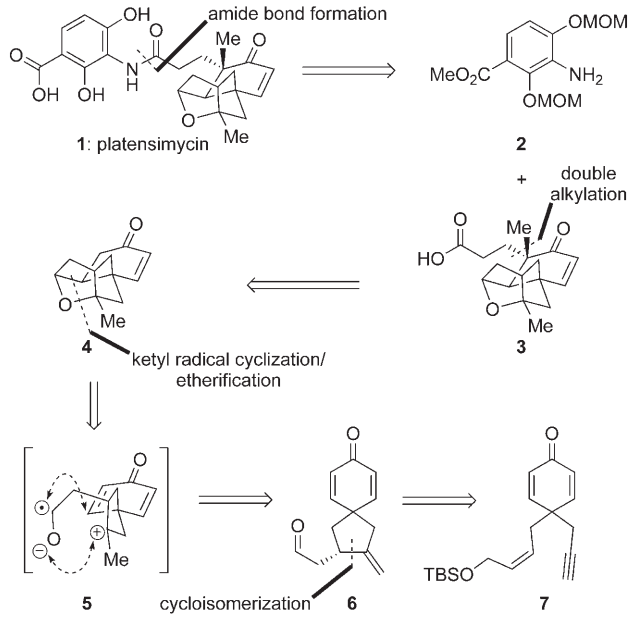
Total Synthesis of Platensimycin**

K. C. Nicolaou, Ang Li, and David J. Edmonds*

Infectious disease remains a menace to society despite the isolation of many new antibiotics over the last few decades. The drugs that are currently available to defend against such ailments are becoming progressively less effective because of the development of bacterial resistance, leading to an increase in potentially fatal, drug-resistant infections. The rather sporadic success in the development of antibiotics since the 1960s has led to a pressing need to discover new antibiotics to combat drug resistance.[1] Compounds that act through new mechanisms are particularly attractive as they offer the prospect of combating effectively infections resistant to all existing drugs. Platensimycin (**1**, Scheme 1) was isolated recently from a strain of *Streptomyces platensis* by a Merck research group as part of a high-throughput screening program of metabolites to identify inhibitors of bacterial fatty acid biosynthesis.[2] Platensimycin represents a new structural class of antibiotic, operating through a novel mechanism of action and, as such, presents a ray of hope for the development of a powerful new therapy. Specifically, the Merck research group showed that platensimycin inhibits the elongation–condensing enzymes β-ketoacyl-(acyl carrier protein) synthases I/II (FabF/B) in the type II bacterial fatty acid biosynthetic pathway by binding to the acyl–enzyme intermediate involved. These enzymes are essential for lipid biosynthesis and are found in many pathogenic species. Indeed, platensimycin was found to be the most potent inhibitor of these enzymes known to date and exhibited potent broad-spectrum antibacterial activity against Gram-positive bacterial strains, including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium*. In light of the gravity of the situation arising from drug-resistant bacteria and because of the activity and novelty

[*] Prof. Dr. K. C. Nicolaou, A. Li, Dr. D. J. Edmonds
Department of Chemistry
and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for assistance with NMR spectroscopy and mass spectrometry, respectively. We also gratefully acknowledge helpful discussions with Dr. P. G. Bulger and Dr. L. A. McAllister. Financial support for this work was provided by the National Institutes of Health (USA), the Skaggs Institute of Chemical Biology, and by Merck Sharp & Dohme (postdoctoral fellowship to D.J.E.).

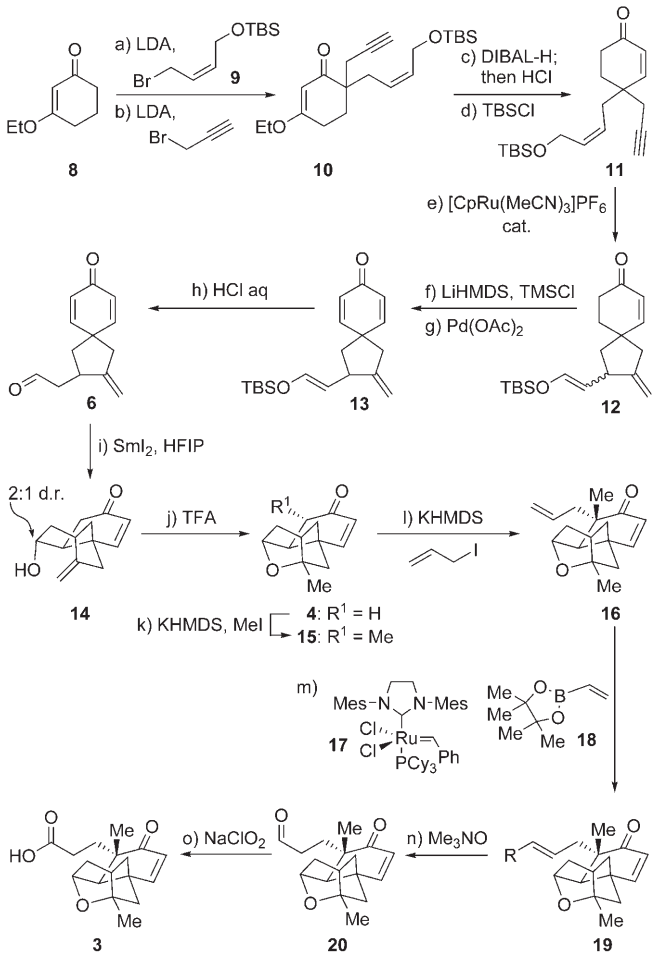


Scheme 1. Structure and retrosynthetic analysis of platensimycin (**1**). MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

of the structure of platensimycin, we undertook the total synthesis of this newly discovered antibiotic. Herein we report the first total synthesis of this potentially useful molecule in racemic form.

Platensimycin consists of an unusual 3-amino-2,4-dihydroxybenzoic acid polar domain linked through an amide bond to a relatively lipophilic, compact, pentacyclic ketolide structural motif, and thus presents an intriguing synthetic challenge. While the amide bond provides an apparent and reasonable site for coupling the two rather disparate fragments, the construction of the two domains is less predictable, despite the many possibilities that can be imagined. Scheme 1 shows the retrosynthetic analysis of one such possibility. Thus, disconnection of the amide bond reveals two subtargets: the aromatic amine **2** and the carboxylic acid **3**. The acid **3** can then be disconnected to remove the propionate and methyl substituents, leaving the cagelike core of the target molecule, compound **4**, as the next subtarget. Of the many disconnections possible for the further retrosynthesis of **4**, the one involving cleavage of the ether bond to leave a tertiary carbocation synthon, followed by rupture of the carbon–carbon bond adjacent to the generated secondary alcohol to reveal a spirocyclic cyclohexadienone (see structures **4** and **5**, Scheme 1) appealed to us because of its potential expediency. The proposed synthetic sequence at this juncture would involve selective generation of a ketyl radical from the corresponding aldehyde, stereoselective conjugate addition of the carbon-centered radical onto one side of the bis-enone, and regioselective ether formation between the hydroxy group of the resultant secondary alcohol and the proximal *exo*-methylene group to give the desired cagelike structure. The substrate for this key step, the spirocyclic cyclohexadiene **6**, can then be further disconnected to reveal the simple enyne **7** as a potential precursor.

The synthesis of the pentacyclic carboxylic acid **3** began with the preparation of enone **11** from **8**[3] in a manner analogous to that recently employed by Hayashi et al.,[4] and proceeded as shown in Scheme 2. Thus, sequential alkylation of **8** with allylic bromide **9**[5] (LDA, 92%) and propargyl

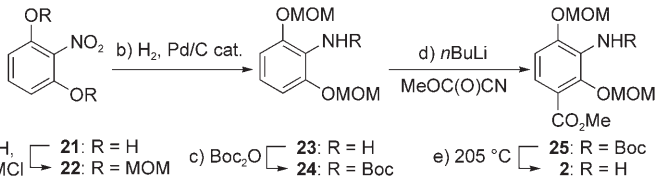


Scheme 2. Construction of the pentacyclic carboxylic acid **3**. Reagents and conditions: a) LDA (1.2 equiv), **9** (1.5 equiv), THF, −78→22 °C, 6 h, 92%; b) LDA (1.4 equiv), propargyl bromide (3.0 equiv), THF, −78→22 °C, 13 h, 97%; c) DIBAL-H (1.2 equiv), toluene, −78→−20 °C, 2 h; then MeOH, 2 N aq HCl, −20→22 °C, 2 h; d) TBSCl (1.2 equiv), imidazole (3.0 equiv), DMF, 22 °C, 20 min, 84% (two steps); e) $[CpRu(MeCN)_3]PF_6$ (0.02 equiv), acetone, 22 °C, 1.5 h, 92%, 1:1 diastereomeric mixture; f) LiHMDS (2.0 equiv), TMSCl (1.5 equiv), THF, −78 °C, 2 h; g) $Pd(OAc)_2$ (1.1 equiv), MeCN, 22 °C, 1.5 h, 68% (two steps); h) 1 N aq HCl/THF (1:1), 22 °C, 2 h, 85%; i) SmI_2 (0.1 M in THF, 2.2 equiv), HFIP (1.5 equiv), THF/HMPA (10:1), −78 °C, 1 min, 46%, ca. 2:1 d.r.; j) TFA/CH_2Cl_2 (1.8:1), 0 °C, 1.5 h, 87%; k) KHMDS (0.5 M in toluene, 1.5 equiv), MeI (8.0 equiv), THF/HMPA (5:1), −78→−10 °C, 2 h, 88%; l) KHMDS (0.5 M in toluene, 4.0 equiv), allyl iodide (8.0 equiv), THF/HMPA (5:1), −78→−10 °C, 2 h, 79%; m) **18** (6.0 equiv), **17** (0.25 equiv), CH_2Cl_2, 40 °C, 6 h, 85%, ca. 6:1 *E*/*Z*; n) Me_3NO (5.0 equiv), THF, 65 °C, 2 h, 95%; o) $NaClO_2$ (3.0 equiv), 2-methyl-2-butene (10 equiv), NaH_2PO_4 (5.0 equiv), *t*BuOH/H_2O (1:1), 22 °C, 15 min, 95%. Cp = cyclopentadienyl, Cy = cyclohexyl, DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol, HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, Mes = mesityl = 2,4,6-trimethylphenyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

bromide (LDA, 97%) afforded the bis-alkylated enone **10** as a single regioisomer. Reduction of **10** using DIBAL-H followed by acidic hydrolysis and reintroduction of the TBS ether gave enone **11** in 84% overall yield. Cycloisomerization of **11** was achieved by using the method of Trost et al., which involved exposure of the substrate to the catalyst $[CpRu(MeCN)_3]PF_6$ in an acetone solution[6] to give spirocycle **12** in 92% yield as an inconsequential 1:1 mixture of diastereoisomers. The bis-enone **13** was then generated from mono-enone **12** through the oxidation ($Pd(OAc)_2$) of the intermediate TMS enol ether (LiHMDS, THF, −78°C) in 68% overall yield.[7] Finally, the anticipated aldehyde **6** was unmasked by acidic hydrolysis of the TBS enol ether in 85% yield.

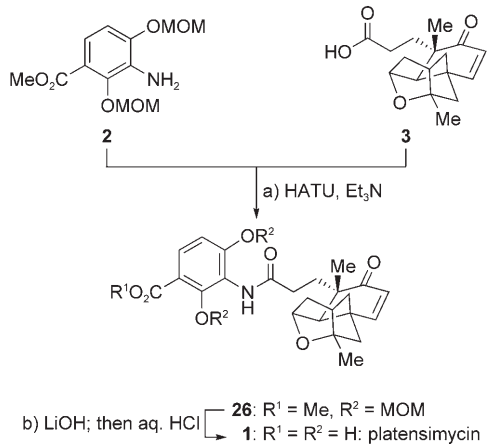
Rapid addition of a solution of the single-electron reductant samarium(II) iodide[8,9] to a dilute, solution of **6** and HFIP in THF/HMPA (10:1) at −78°C, followed by immediate quenching with saturated aqueous NH_4Cl solution, gave an approximately 2:1 mixture (as indicated by ^{1}H NMR spectroscopy) of secondary alcohol **14** and its diastereoisomer in 46% combined yield. Treatment of this inseparable mixture with TFA led to smooth etherification, thus reflecting the proximity of the hydroxy group of the desired diastereoisomer to the exocyclic olefin, and thereby gave the cagelike structure **4** in 87% yield based on the quantity of the correct isomer of **14** present. The undesired alcohol diastereoisomer was recovered unchanged from the etherification reaction. It was surmised from these experiments that the major isomer generated in the SmI_2-mediated cyclization reaction had the desired stereochemistry (**14**, Scheme 2). The conversion of **6** into **4** could also be achieved in a single reaction vessel by quenching the excess SmI_2 with oxygen at −78°C followed by addition of TFA to the resulting mixture and stirring at ambient temperature. This one-pot procedure allowed the isolation of **4** in around 25% overall yield, and streamlines to some extent this segment of the synthetic sequence. The required alkyl substituents adjacent to the carbonyl group were then stereoselectively and efficiently installed by treatment of **4** with KHMDS and MeI (88%) followed by KHMDS and allyl iodide (79%). In each case, the diastereomeric products were undetectable (<2%) in the crude reaction mixture by ^{1}H NMR spectroscopy. The use of allyl bromide in the second alkylation gave lower yields of **16**, accompanied by significant quantities of the O-alkylated isomer. The excellent stereocontrol observed in the alkylation sequence is rationalized by inspection of molecular models of ketones **4** and **15**, in which the rigid cage structure effectively shields the top face of the corresponding enolate. The conversion of terminal olefin **16** into the required carboxylic acid **3** was carried out through two different pathways, both involving aldehyde **20**. In the first case, hydroboration of **16** gave a diol (resulting from concomitant 1,2-reduction of the enone), which could be oxidized to give aldehyde **20** using excess Dess–Martin reagent[10] in CH_2Cl_2 (ca. 40% from **16**). The disappointing yield of this sequence and the low reactivity of the terminal olefin towards hydroboration led us to seek an alternative route for the conversion of **16** into **20**. The preferred method involved olefin cross-metathesis between **16** and vinyl pinacol boronate under the influence of the Grubbs second-generation catalyst **17**,[11] which furnished vinyl boronate **19** in 85% yield as a mixture of *E* and *Z* isomers (ca. 6:1).[12] This intermediate underwent smooth oxidation[13] upon treatment with trimethylamine *N*-oxide to give **20** in 95% yield, which was further oxidized to furnish the desired carboxylic acid **3** in excellent yield (95%) by using the Pinnick protocol.[14]

The synthesis of the aromatic amine, fragment **2**, proceeded smoothly from 2-nitroresorcinol (**21**) as outlined in Scheme 3. Protection of **21** as the bis-MOM ether (NaH, MOMCl, 82%) followed by catalytic hydrogenation (99%) of the resulting compound gave aniline **23**. Protection of the amino group of **23** with a Boc group was achieved by stirring the neat amine with Boc_2O at 40°C to furnish **24** in 99% yield. Interestingly, treatment of **23** with Boc_2O in CH_2Cl_2 in the presence of a catalytic amount of 4-dimethylaminopyridine led to formation of the corresponding isocyanate. Compound **24** was successfully carboxymethylated by using in situ silylation of the carbamate (*n*BuLi, TMSCl), followed by lithiation of the aromatic ring (*n*BuLi), and quenching with methyl cyanoformate (54% overall yield). Finally, thermolysis of the Boc group under microwave radiation (1,2-dichlorobenzene) promoted clean conversion into the required aniline **2** in 83% yield.



Scheme 3. Construction of the aromatic amine fragment **2**. Reagents and conditions: a) NaH (2.5 equiv), MOMCl (2.3 equiv), THF, 0→22°C, 1.5 h, 82%; b) H_2 (balloon), 10% Pd/C (0.1 equiv), MeOH/EtOAc (10:1), 22°C, 12 h, 99%; c) Boc_2O (3.0 equiv), 40°C, 4 h, 99%; d) *n*BuLi (2.2 M in pentane, 1.0 equiv), TMSCl (1.0 equiv), −78°C, 15 min; then *n*BuLi (2.2 M in pentane, 2.2 equiv), methyl cyanoformate (1.0 equiv), THF, −78°C, 30 min; then 1 N aq HCl, 22°C, 30 min, 54%; e) 1,2-dichlorobenzene, 205°C (microwave), 5 min, 83%. Boc = *tert*-butoxycarbonyl.

The total synthesis of platensimycin was completed as shown in Scheme 4. Coupling of carboxylic acid **3** with aniline **2** was achieved by treatment with HATU in 85% yield. The methyl ester of **26** was then hydrolyzed on exposure to aqueous LiOH. Following complete hydrolysis of the ester as determined by TLC analysis, 2N aqueous HCl was added to effect cleavage of the MOM ethers, thus furnishing (±)-platensimycin (±)-**1** in excellent overall yield (ca. 90%). The spectral data for (±)-**1** were consistent with the reported data[2a,b] and its structure (Table 1). The possibility of achieving an enantioselective synthesis of platensimycin exists at the cycloisomerization stage, where in principle a chiral, enantiomerically pure organometallic species, such as a rhodium catalyst,[15] could be employed to induce asymmetric induction. Alternatively, a resolution, either by classical means or by HPLC on a chiral stationary phase, at the carboxylic acid stage, may be used to provide the enantiomerically pure form



Scheme 4. Total synthesis of platensimycin. Reagents and conditions: a) **3** (1.0 equiv), **2** (2.0 equiv), HATU (4.0 equiv), Et_3N (5.9 equiv), DMF, 22 °C, 26 h, 85%; b) LiOH (55 equiv), THF:H_2O (4:1), 45 °C, 2 h; then 2 N aq HCl, THF:H_2O (3:1) 45 °C, 10 h, ca. 90% overall. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.

of platensimycin. Further improvements of this route to platensimycin are envisaged.

The described chemistry renders platensimycin (**1**) readily available by chemical synthesis in its racemic form and sets the stage for the synthesis of designed analogues for structure-activity relationship (SAR) studies in search of new antibacterial agents. Certainly, numerous other synthetic sequences to this molecule can be imagined and no doubt many total syntheses will be reported following this one.

Received: September 21, 2006
Published online: September 29, 2006

Keywords: antibiotics · drug resistance · natural products · samarium diiodide · total synthesis

Table 1: Selected physical properties for compounds **1**, **3**, **4**, and **6**.

1: R_f = 0.11 (silica gel, acetone/hexane/AcOH 60:40:1); IR (film): $\tilde{\nu}$ = 3316br m, 2961m, 2921m, 2870w, 1664s, 1656s, 1605s, 1534m, 1448m, 1400m, 1380m, 1282m, 1218m, 1150m, 1102m, 1091m, 1072m, 953w, 831m, 786m cm^{-1}; ^1H NMR (500 MHz, C_5D_5N): δ = 8.12 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 10.0 Hz, 1H), 5.95 (d, J = 10.0 Hz, 1H), 4.50 (br s, 1H), 2.84 (ddd, J = 14.6, 11.7, 5.3, Hz, 1H), 2.76 (ddd, J = 14.3, 11.4, 4.6 Hz, 1H), 2.72–2.66 (m, 1H), 2.45 (s, 1H), 2.20 (t, J = 6.5 Hz, 1H), 2.08–2.02 (m, 1H), 1.94–1.90 (m, 1H), 1.82 (d, J = 11.6 Hz, 2H), 1.73 (dd, J = 11.2, 3.0 Hz, 1H), 1.58 (dd, J = 11.6, 6.9 Hz, 1H), 1.49 (d, J = 10.9 Hz, 1H), 1.40 (s, 3H), 1.15 ppm (s, 3H); ^{13}C NMR (150 MHz, C_5D_5N): δ = 203.7, 175.2, 174.9, 158.8, 158.5, 154.4, 129.9, 127.7, 115.7, 110.4, 107.5, 87.3, 76.9, 55.4, 47.2, 47.0, 46.6, 45.5, 43.5, 41.2, 32.6, 32.2, 24.9, 23.7 ppm; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.61 (d, J = 8.9 Hz, 1H), 6.55 (d, J = 10.0 Hz, 1H), 6.51 (d, J = 8.9 Hz, 1H), 5.97 (d, J = 10.0 Hz, 1H), 4.64 (br s, 1H), 2.68–2.63 (m, 1H), 2.52–2.46 (m, 4H), 2.19–2.15 (m, 1H), 2.11 (dd, J = 12.0, 3.4 Hz, 1H), 2.07 (d, J = 11.7 Hz, 1H), 1.96 (dd, J = 11.4, 3.4 Hz, 1H), 1.88 (td, J = 11.4, 5.0 Hz, 1H), 1.84 (dd, J = 11.7, 7.2 Hz, 1H) 1.69 (d, J = 11.4 Hz, 1H), 1.57 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 203.8, 173.4, 172.2, 155.1, 154.2, 153.9, 128.2, 127.2, 114.3, 111.1, 103.7, 88.0, 76.4, 54.7, 46.5, 46.1, 45.9, 44.7, 42.9, 40.4, 31.5, 31.2, 24.4, 22.7; HR-MS (ESI TOF): m/z calcd for $C_{24}H_{28}NO_7$ $[M+H]^+$: 442.1860; found 442.1853.

3: R_f = 0.35 (silica gel, EtOAc); IR (film): $\tilde{\nu}$ = 2968br m, 1719s, 1657s, 1469w, 1445w, 1410w, 1297m, 1231m, 1183s, 1164m, 1151m, 1104m, 1095m, 953m, 831s, 758m cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.48 (d, J = 10.1 Hz, 1H), 6.90 (d, J = 10.1 Hz, 1H), 4.43 (br s, 1H), 2.41 (t, J = 6.5 Hz, 1H), 2.37 (br s, 1H), 2.35–2.24 (m, 3H), 2.10–2.07 (m, 1H), 2.04–2.00 (m, 2H), 1.88 (dd, J = 11.2, 3.5 Hz, 1H), 1.79–1.73 (m, 2H), 1.62 (d, J = 11.2 Hz, 1H), 1.45 (s, 3H), 1.24 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 203.4, 178.5, 153.6, 127.3, 87.1, 76.5, 54.9, 46.5, 46.0, 45.9, 44.6, 43.2, 40.5, 30.6, 29.0, 24.5, 23.0 ppm; HR-MS (ESI TOF): m/z calcd for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591; found 291.1581.

4: R_f = 0.20 (silica gel, EtOAc/hexane 3:7); IR (film): $\tilde{\nu}$ = 2951m, 1677s, 1448w, 1379w, 1327w, 1282w, 1248w, 1138w, 1082w, 1037w, 993w, 820w, 778w cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.62 (d, J = 10.0 Hz, 1H), 5.94 (d, J = 10.0 Hz, 1H), 4.17 (t, J = 3.4 Hz, 1H), 2.43–2.29 (m, 4H,), 1.97–1.94 (m, 2H), 1.90 (d, J = 11.6 Hz, 1H), 1.79–1.74 (m, 2H), 1.66 (d, J = 11.2 Hz, 1H), 1.45 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.1, 155.2, 128.9, 87.2, 79.0, 51.7, 46.2, 44.2, 42.7, 42.2, 37.9, 37.5, 23.1 ppm; HR-MS (ESI TOF): m/z calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 205.1223; found 205.1216.

6: R_f = 0.31 (silica gel, EtOAc/hexane 1:1); IR (film): $\tilde{\nu}$ = 2831w, 2725w, 1718s, 1657s, 1621s, 1406m, 1284w, 1259m, 1180w, 1090w, 1059w, 1023w, 888w, 858s, 706w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.83 (t, J = 1.3 Hz, 1H), 6.98–6.96 (m, 1H), 6.79–6.76 (m, 1H), 6.27–6.23 (m, 2H), 5.11–5.09 (m, 1H), 4.99–4.97 (m, 1H), 3.31–3.23 (m, 1H), 2.85 (ddd, J = 17.9, 4.9, 1.2 Hz, 1H), 2.68 (dq, 16.0, 2.4 Hz, 1H), 2.64 (ddd, J = 17.8, 8.3, 1.4 Hz, 1H), 2.47 (dd, J = 16.0, 1.6 Hz, 1H), 2.15 (ddd, J = 13.0, 8.0, 1.6 Hz, 1H), 1.69 ppm (dd, J = 13.0, 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.5, 185.8, 154.2, 152.1, 151.2, 128.7, 127.7, 108.5, 49.2, 46.8, 44.4, 43.7, 36.2 ppm; HR-MS (ESI TOF): m/z calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067; found 203.1067.

[1] a) H. Pearson, *Nature* **2002**, *418*, 469; b) C. T. Walsh, *Nat. Rev. Microbiol.* **2003**, *1*, 65–70; c) S. B. Singh, J. Barrett, *Biochem. Pharmacol.* **2006**, *71*, 1006–1015.

[2] a) J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, A. Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, S. B. Singh, *Nature* **2006**, *441*, 358–361; b) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920. For a discussion of the activity and possible origins of platensimycin, see: c) D. Häblich, F. von Nussbaum, *ChemMedChem* **2006**, *1*, 951–954.

[3] Compound **8** is commercially available from a number of sources. Alternatively, it can be prepared according to: W. F. Gannon, H. O. House, *Org. Synth.* **1960**, *40*, 41–42.

[4] Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui, M. Shoji, *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029.

[5] M. Sun, Y. Deng, E. Batyreva, W. Sha, R. G. Salomon, *J. Org. Chem.* **2002**, *67*, 3575–3584.

[6] a) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 714–715; b) B. M. Trost, J.-P. Surivet, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15592–15602. For a review of Ru-catalyzed reactions, see: B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788–6825; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630–6666.

[7] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.

[8] For similar conditions that have been used, see: H. Hagiwara, H. Sakai, T. Uchiyama, Y. Ito, N. Morita, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc. Perkin Trans. 1* **2002**, 583 – 591.

[9] For selected reviews of the use of SmI_2 in organic synthesis, see: a) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29 – 68; b) G. A. Molander, *Org. React.* **1994**, *46*, 211 – 367; c) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307 – 338; d) G. A. Molander, C. R. Harris, *Tetrahedron* **1998**, *54*, 3321 – 3354; e) H. B. Kagan, J.-L. Namy, *Lanthanides: Chemistry and Use in Organic Synthesis* (Ed.: S. Kobayashi), Springer, Berlin, **1999**, pp. 155 – 198; f) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351 – 10372; g) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3372 – 3404.

[10] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156.

[11] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956; b) T. M. Trnka, J. P. Morgan, M. S. Sanford, T. E. Wilhelm, M. Scholl, T.-L. Choi, S. Ding, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 2546 – 2558.

[12] C. Morrill, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031 – 6034.

[13] G. W. Kabalka, H. C. Hedgecock, Jr., *J. Org. Chem.* **1975**, *40*, 1776 – 1779.

[14] B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091 – 2096.

[15] A. Lei, M. He, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 8198 – 8199.

