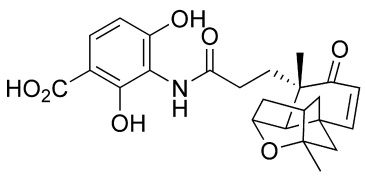
Communication

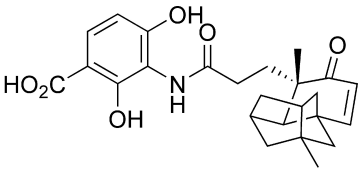
Total Synthesis and Antibacterial Properties of Carbaplatensimycin

K. C. Nicolaou, Yefeng Tang, Jianhua Wang, Antonia F. Stepan, Ang Li, and Ana Montero

J. Am. Chem. Soc., **2007**, 129 (48), 14850-14851 • DOI: 10.1021/ja076126e



platensimycin



carbaplatensimycin

More About This Article

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

- Supporting Information
- Links to the 25 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

J|A|C|S
COMMUNICATIONS

Published on Web 11/08/2007

Total Synthesis and Antibacterial Properties of Carbaplatensimycin

K. C. Nicolaou,* Yefeng Tang, Jianhua Wang, Antonia F. Stepan, Ang Li, and Ana Montero

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received August 14, 2007; E-mail: kcn@scripps.edu

The recent isolation of platensimycin (**1**, Figure 1)[1] has attracted considerable interest from both biological and chemical circles due to its unique pharmacological profile. Indeed, platensimycin is the first antibiotic discovered in over 40 years that exerts its antibacterial effect through a novel mechanism of action, manifested by its impressive activity against a variety of drug-resistant bacteria, including methicilin- and vancomycin-resistant strains.[1] As such, platensimycin represents a unique opportunity for the development of critically needed antibiotics. The complex molecular architecture and exquisite antibacterial activity render platensimycin a worthy target for chemical synthesis, and syntheses of both the racemate and natural (−)-enantiomer have been reported.[2] Additionally, its first bioactive designed analogue, adamantaplatensimycin (**2**, Figure 1), has been disclosed from these laboratories.[3] In this communication, we report the total synthesis and antibacterial properties of carbaplatensimycin (**3**, Figure 1), the all-carbon-cage isostere of the natural product.

Platensimycin eradicates bacteria through the selective inhibition of the elongation-condensing enzyme β-ketoacyl-(acyl carrier protein) synthases I/II (Fab F/B) in the type II bacterial fatty acid biosynthetic pathway. X-ray crystallographic analysis of the platensimycin complex with its target FabF protein indicates a hydrogen bonding interaction between the ether oxygen of the molecule and the T270 threonine residue of its target. It was with the aim of investigating the effect of this ethereal hydrogen bond acceptor on the platensimycin bioactivity that the synthesis of carbaplatensimycin (**3**) was undertaken.

For the chemical synthesis of carbaplatensimycin, we made use of aldehyde **4**, an intermediate employed in the asymmetric synthesis of platensimycin,[2b] which was readily obtained in enantiomerically enriched form (ee > 98%) in eight steps (42% overall yield) from known 3-(2-dioxolanyl)propionic acid. This intermediate was first converted to carbocycle **15** as shown in Scheme 1. Thus, addition of TMSCN to intermediate **4** in the presence of Et_3N furnished TMS-protected cyanohydrin **5**.

Subsequent removal of the silyl protecting group, followed by treatment of the resulting free cyanohydrin with ethyl vinyl ether in the presence of PPTS furnished 1-ethoxyethyl (EE) ether **7** in 80% overall yield for the three steps (and as an inconsequential 1:1:1:1 mixture of epimers at C10 and the acetal carbon of the EE group). Treatment of **7** with KHMDS at low temperature, followed by warming to 0 °C, induced intramolecular conjugate addition of the transient anion so generated onto the bisenone subunit to afford tricycle **8** in 70% yield and as a single epimer at C10. Wittig olefination of the latter intermediate gave triene **9** (92% yield), the newly introduced double bond serving as a temporary protecting device for the required carbonyl functionality.[4]

Reduction of the nitrile moiety present in **9** with Red-Al ensured the formation of aldehyde **10** (90% yield), from which the EE-protected alcohol was excised through the action of SmI_2. Pleasingly, this reaction proceeded smoothly and with inversion of configuration at the formyl-bearing stereocenter to afford aldehyde **11** as the desired C10 epimer in high yield (92%). Reduction of this aldehyde to alcohol **12** ($NaBH_4$, 99% yield) was followed by a Barton−McCombie deoxygenation[5] of the corresponding xanthate ester (**13**) to furnish hydrocarbon **14** in 65% overall yield for the two steps. Finally, a two-step protocol involving regioselective dihydroxylation (cat. OsO_4, NMO) of the exocyclic olefin, followed by oxidative cleavage of the resulting diol with $NaIO_4$, revealed key carbocyclic enone **15** in 72% overall yield.

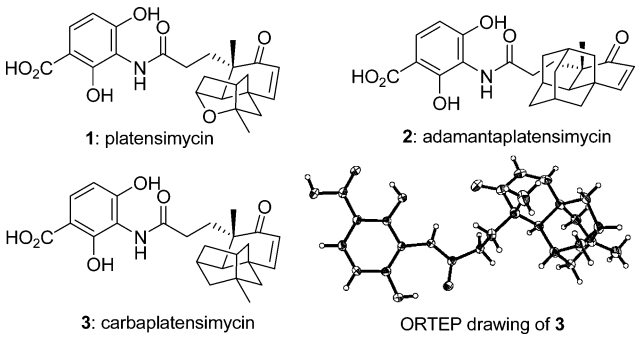


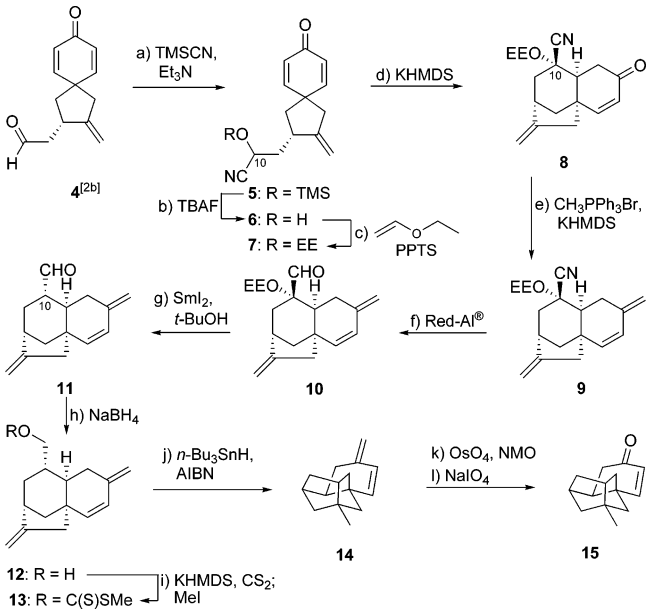
Figure 1. Structures of platensimycin (**1**), adamantaplatensimycin (**2**), and carbaplatensimycin (**3**) and ORTEP view of **3** with the thermal ellipsoids at 30% probability level.

The completion of the synthesis of carbaplatensimycin (**3**) followed a similar pathway to that previously employed in the syntheses of platensimycin and adamantaplatensimycin (Scheme 2).[2a,b,3] Thus, enone **15** was sequentially alkylated with MeI (92% yield) and allyl iodide (87% yield) [KHMDS, THF/HMPA (5:1), −78 → −10 °C] to afford advanced intermediate **16**. Cross-metathesis of the latter compound with excess boronate **17** was achieved using Grubbs' second generation catalyst to furnish vinyl boronate **18** in 85% yield (and as a 6:1 mixture of *E*:*Z* isomers).[6] Boronate cleavage using Me_3NO as the oxidant led to clean formation of aldehyde **19** (85% yield),[6a] which was subsequently transformed into carboxylic acid **20** through a Pinnick oxidation (95%). Finally, coupling of acid **20** with aniline **21**[2a] gave protected intermediate **22** (80% yield), which, after sequential treatment with aqueous LiOH and aqueous HCl, yielded the targeted compound, carbaplatensimycin (**3**), in 82% overall yield. Crystallization of carbaplatensimycin from acetone/hexanes gave colorless crystals (mp 217−219 °C) that were used to prove unambiguously its structure by X-ray crystallographic analysis (see ORTEP drawing, Figure 1).

The antibacterial activity of carbaplatensimycin (**3**) against an array of bacterial strains, including methicilin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), was determined and compared to those of platensimycin (**1**) and adamantaplatensimycin (**2**). As shown in Table 1, the minimum inhibitory activities (MIC) for the new

 10.1021/ja076126e CCC: $37.00

Scheme 1. Construction of Carbocyclic Core Intermediate **15**[a]



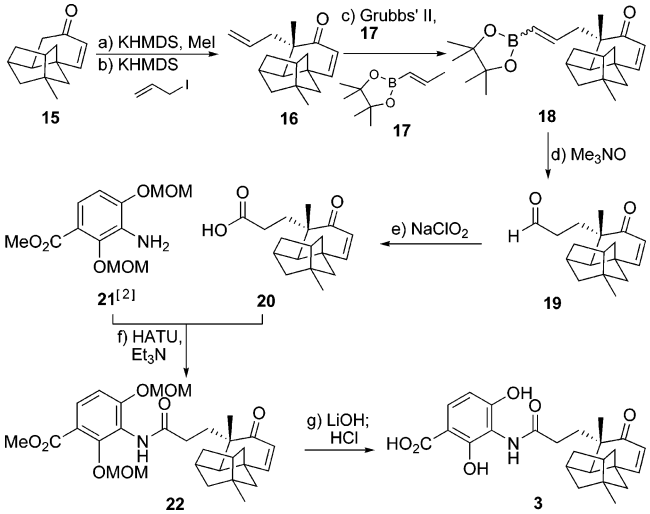
[a] Reagents and conditions: (a) TMSCN (1.5 equiv), Et_3N (0.5 equiv), CH_2Cl_2, 25 °C, 1 h; (b) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 1 h; (c) ethyl vinyl ether (excess), PPTS (0.5 equiv), CH_2Cl_2, 25 °C, 12 h, 80% over 3 steps; (d) KHMDS (0.5 M in toluene, 1.5 equiv), THF, −78 → 25 °C, 0.5 h, 70%; (e) CH_3PPh_3Br (2.5 equiv), KHMDS (0.5 M in toluene, 2.0 equiv), THF, −78 → 0 °C, 1 h, 92%; (f) Red-Al (3.5 M in toluene, 5.0 equiv), THF, −20 → 25 °C, 6 h, 90%; (g) SmI_2 (0.1 M in THF, 2.5 equiv), THF:*t*-BuOH (10:1), −10 → 25 °C, 2 h, 92%; (h) $NaBH_4$ (1.5 equiv), THF:CH_3OH (2:1), 0 → 25 °C, 30 min, 99%; (i) CS_2 (3.0 equiv), KHMDS (0.5 M in toluene, 3.0 equiv), THF, −78 → 25 °C, 1 h; then MeI (3.0 equiv), THF, 25 °C, 1 h, 99%; (j) *n*-Bu_3SnH (1.5 equiv), AIBN (0.75 equiv), benzene, 80 °C, 0.5 h, 65%; (k) OsO_4 (2.5 wt % in ^{t}BuOH, 5 mol %), NMO (50 wt % in H_2O, 2.0 equiv), acetone:H_2O (8:1), 0 °C, 4 h, 80%; (l) $NaIO_4$ (2.0 equiv), THF:H_2O (1:1), 25 °C, 1 h, 92%.

analogue (**3**) against a number of Gram-positive bacteria lie in the same order of magnitude as those of the natural product (**1**) and adamantaplatensimycin (**2**). For example, the MIC values for **1**, **2**, and **3** against MRSA were found to be 0.2−0.4, 1.3−1.8, and 1.1−2.2 μg mL^{-1}, respectively, while the corresponding values against VREF for these compounds are 0.4−0.8, 1.3−1.8, and 1.1−2.2 μg mL^{-1}. However, the similar potency of carbaplatensimycin (**3**) against these bacteria to that of adamantaplatensimycin (**2**) indicates the important contribution of the ether oxygen of the natural product to its antibacterial activity. All three platensimycins (**1**−**3**) were tested and found inactive (MIC > 88 μg mL^{-1}) against the following Gram-negative bacterial strains: *E. coli*, *B. cepacia*, *S. typhimurium*, *P. aeruginosa*.

The reported synthesis of carbaplatensimycin (**3**) adds a new, bioactive platensimycin analogue to this promising class of antibiotics. At the same time, these investigations confirmed the positive role that the ether oxygen plays in the biological activity of platensimycin. This information may prove useful in the rational design of new antibacterial agents based on the platensimycin lead structure.

Acknowledgment. We thank Drs. D. H. Huang, G. Siuzak, and R. Chadha for NMR spectroscopic, mass spectrometric, and for X-ray crystallographic assistance, respectively. This material is based upon work supported by the National Science Foundation under Grant No. 0603217, as well as the Skaggs Institute for Chemical Biology, and fellowships from Bristol-Myers Squibb (to A.L.), Schering AG (to A.F.S.), and the Spanish Ministry of Science and Education (MEC/Fulbright, to A.M.).

Scheme 2. Completion of the Synthesis of Carbaplatensimycin (**3**)[a]



[a] Reagents and conditions: (a) KHMDS (0.5 M in toluene, 2.0 equiv), MeI (8.0 equiv), THF:HMPA (5:1), −78→−10 °C, 1 h, 92%; (b) KHMDS (0.5 M in toluene, 4.0 equiv), allyl iodide (8.0 equiv), THF:HMPA (5:1), −78→−10 °C, 1 h, 87%; (c) Grubbs gen. II (10 mol %), **17** (5.0 equiv), benzene, 80 °C, 1 h, 85%; (d) Me_3NO (6.0 equiv), THF, 65 °C, 2 h, 85%; (e) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (7.0 equiv), 2,3-dimethylbutene (10 equiv), *t*-BuOH:H_2O (1:1), 25 °C, 1 h, 95%; (f) **20** (1.0 equiv), **21** (3.0 equiv), HATU (4.0 equiv), Et_3N (6.0 equiv), DMF, 25 °C, 20 h, 80%; (g) 2 N aq. LiOH (30 equiv), THF, 45 °C, 6 h; then 2 N aq. HCl (60 equiv), THF, 45 °C, 24 h, 82% overall yield.

Table 1. Minimum Inhibitory Concentration (MIC) Values (μg mL^{-1}) of **1**, **2**, and **3** against a Variety of Bacterial Strains[a]

	1	**2**	**3**
MRSA	0.2−0.4	1.3−1.8	1.1−2.2
VREF	0.4−0.8	1.3−1.8	1.1−2.2
Staphylococcus aureus	0.2−0.6	1.1−2.2	0.4−1.1
Staphylococcus epidermidis	<0.2	0.5−1.1	0.2−0.5
Bacillus cereus	2.2−4.4	8.8−11.1	17.6−22.0
Lysteria monocytogenes	<0.2	3.3−4.4	1.1−2.2

[a] The antibacterial activity was determined by National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution methods. Inocula of MRSA (ATCC 33591), VREF (ATCC 51575), *S. aureus* (ATCC 29213), *S. epidermidis* (ATCC 35989), *B. cereus* (ATCC 11778), and *L. monocytogenes* (ATCC 10115) were prepared and treated as described in the Supporting Information.

Supporting Information Available: Complete ref 1, experimental procedures, and compound characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Wang, J.; et al. *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.

(2) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086. (b) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4016. (c) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825. (d) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922. (e) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417. (f) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534.

(3) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712.

(4) Dai, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 3498.

(5) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1571.

(6) (a) Njardarson, J. T.; Biswas, K.; Danishefsky S. J. *Chem. Commun.* **2002**, 2759. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

JA076126E