Platensimycin

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Adamantaplatensimycin: A Bioactive Analogue of Platensimycin**

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Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Antibacterial resistance is recognized as a worldwide problem in the management of infectious disease. Moreover, during the last two decades the number of new antibacterial agents that have reached the marketplace has decreased whilst resistance to existing antibiotics has increased. Thus, there is an urgent need for new types of antibiotics that exert their activity through novel mechanisms of action.

Isolated from a strain of *Streptomyces platensis*, platensimycin ((−)-**1**, Figure 1)[1,2] is a newly discovered antibiotic that displays potent activity against Gram-positive bacterial strains that include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin intermediate *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium* (VREF). Platensimycin operates through a novel mechanism of action that involves inhibition of 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.[1] The synthetic challenge posed by the cagelike domain of (−)-**1**[3,4] led us to design adamantaplatensimycin ((−)-**2**), in which the adamantyl moiety represents an approximately isosteric, but more synthetically accessible cage of the ketolide domain of the molecule. Herein we report the synthesis and biological evaluation of racemic adamantaplatensimycin ((±)-**2**) and each of its pure enantiomers (−)-**2** and (+)-**2**.

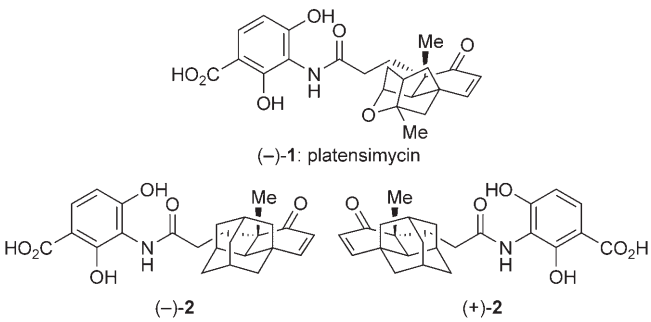
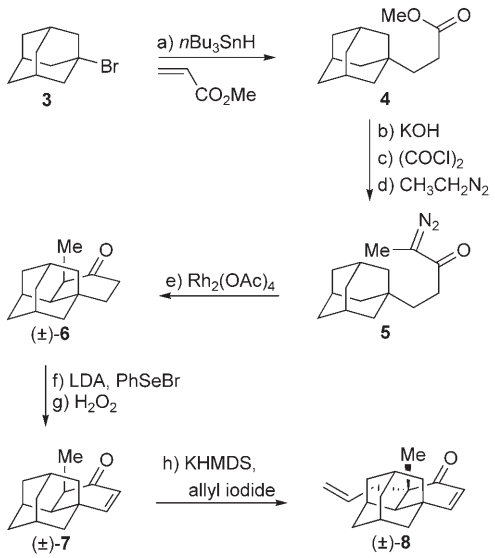


Figure 1. Structures of platensimycin ((−)-**1**) and adamantaplatensimycins (−)-**2** and (+)-**2**.

The synthesis of (±)-**2** began with the radical conjugate addition of commercially available bromoadamantane (**3**) to methyl acrylate to afford the adamantyl ester **4** as shown in Scheme 1.[5] Conversion of **4** into the requisite symmetric diazoketone **5** was then carried out by saponification, acyl chloride formation, and treatment of the latter intermediate with freshly prepared diazoethane[6] (51%, over four steps). Decomposition of diazoketone **5** in the presence of a catalytic amount of $Rh_2(OAc)_4$ provided the expected C–H bond insertion product (±)-**6** as a single diastereoisomer in 65%



Scheme 1. Synthesis of the adamantyl cage alkene (±)-**8**. Reagents and conditions: a) methylacrylate (2.0 equiv), AIBN (0.05 equiv), nBu_3SnH (1.2 equiv), toluene, reflux, 2 h; b) KOH (6.0 equiv), MeOH/H_2O (10:1), 22 °C, 12 h; c) $(COCl)_2$ (1.2 equiv), DMF (1 drop), CH_2Cl_2, 0→22 °C, 2 h; d) CH_3CHN_2 (excess), THF, 0 °C, 30 min, 51% over 4 steps; e) $Rh_2(OAc)_4$ (3 mol%), CH_2Cl_2, 22 °C, 12 h, 65%; f) LDA (1.2 equiv), THF, −78 °C, 30 min; then PhSeBr (1.2 equiv), −78 °C, 30 min; g) H_2O_2 (30% aq, excess), pyridine (excess), CH_2Cl_2, 22 °C, 2 h, 88%; h) KHMDS (4.0 equiv), HMPA (excess), THF, −78 °C; then allyliodide (8.0 equiv), −78→−10 °C, 1 h, 86%. AIBN = 2,2′-azobisisobutyronitrile, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethyl phosphoramide, LDA = lithium diisopropylamide, KHMDS = potassium bis(trimethylsilyl)amide.

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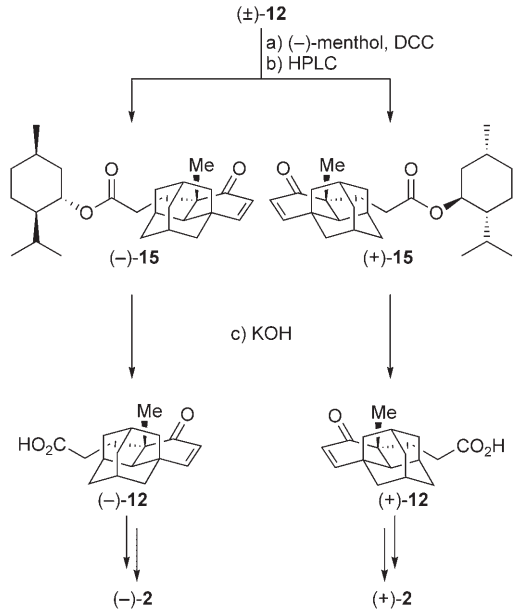
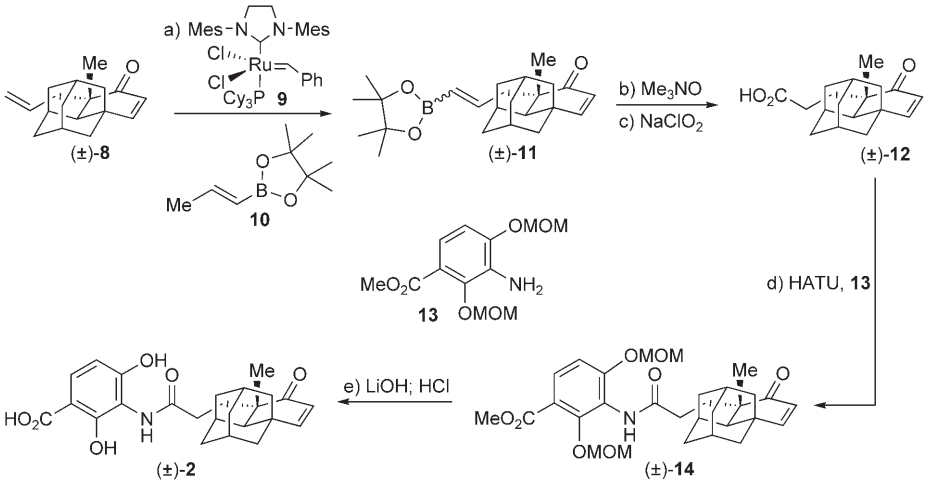
yield. Conversion of this intermediate into the corresponding enone (±)-**7** was straightforward and involved α selenylation (PhSeBr) of its kinetic lithium enolate (LDA, −78 °C), followed by oxidation/*syn* elimination of the selenide so obtained (88% overall yield). Finally, allylation of (±)-**7** through the corresponding potassium enolate (KHMDS, −78 °C) with allyliodide gave the adamantaplatensimycin cage (±)-**8** as a single diastereoisomer in 86% yield.

The completion of the synthesis of (±)-**2** was carried out in an analogous manner to that reported for platensimycin (**1**),[3] as shown in Scheme 2. Thus, formation of the carboxylic acid coupling partner (±)-**12** was achieved in three steps and 75% overall yield through 1) cross-metathesis of (±)-**8** with vinyl boronate **10**,[7] and 2) oxidation of the so-derived alkenylboronate esters (±)-**11** (ca. 3:1 mixture of *E*/*Z* isomers), first with Me_3NO to afford the corresponding aldehyde, and then with $NaClO_2$. HATU-induced coupling of the carboxylic acid (±)-**12** with aniline **13**[3] afforded the protected adamantaplatensimycin (±)-**14**, which was converted into racemic (±)-**2** (m.p. 213–217 °C, EtOAc/hexanes) by the indicated one-pot sequence, which involved ester hydrolysis (LiOH) and cleavage of the MOM groups (aq HCl; 65% for two steps).

The resolution of the carboxylic acid (±)-**12** and the synthesis of both enantiomers of adamantaplatensimycin in pure form is described in Scheme 3. Thus, formation of the menthol esters derived from (±)-**12** (DCC, DMAP, (−)-menthol, 88% combined yield), and separation of the diastereoisomers so obtained by HPLC on a chiral stationary phase, followed by ester cleavage, led to the enantiomerically pure carboxylic acids (−)-**12** ($[\alpha]_D = -30.9$ ($c = 0.11$, MeOH) and (+)-**12** ($[\alpha]_D = +31.2$, $c = 0.13$, MeOH). Coupling of each of these acids with aniline **13**,[3] followed by further elaboration in accordance with the conditions described above, led to (−)-**2** (m.p. 213–215 °C, EtOAc/hexanes, $[\alpha]_D = -75.9$, $c = 0.10$, MeOH; Table 2) and (+)-**2** (m.p. 214–216 °C, EtOAc/hexanes, $[\alpha]_D = +76.2$, $c = 0.13$, MeOH) in similar yields to those described for (±)-**2**. The structure of (−)-adamantaplatensimycin ((−)-**2**) was proved unambiguously by X-ray analysis (Figure 2).[8]



Scheme 3. Resolution of carboxylic acid (±)-**12** and synthesis of (+)-**2** and (−)-**2**. Reagents and conditions: a) DCC (1.2 equiv), (−)-menthol (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 22 °C, 1 h; b) Chiralcel OD-H, 0.5% isopropyl alcohol/hexanes; c) aq KOH (1 N, 6.0 equiv), MeOH/H_2O (10:1), 22 °C, 6 h, 85% over 3 steps. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.



Scheme 2. Synthesis of racemic adamantaplatensimycin ((±)-**2**). Reagents and conditions: a) **9** (5 mol%), **10** (5.0 equiv), benzene, reflux, 30 min; b) Me_3NO (5.0 equiv), THF, 65 °C, 2 h; c) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (5.0 equiv), 2,3-dimethylbutene (10 equiv), *t*BuOH/H_2O (1:1), 22 °C, 10 min, 75% over 3 steps; d) **13** (2.0 equiv), HATU (4.0 equiv) Et_3N (6.0 equiv), DMF, 22 °C, 12 h; e) aq LiOH (2 N, 30 equiv), THF, 22 °C, 3 h; then aq HCl (2 N, 60 equiv), THF, 22 °C, 12 h, 65% over 2 steps. Cy = cyclobutyl, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, Mes = 2,4,6-trimethylphenyl, MOM = methoxymethyl.

The synthesized adamantaplatensimycins were tested against MRSA and VREF, and their minimum inhibitory concentrations (MIC) are displayed in Table 1. As can be seen from Table 1, (−)-**2** exhibits activity of the same order of magnitude (1.3–1.8 $\mu g\,mL^{-1}$) against MRSA and VREF as (−)-platensimycin ((−)-**1**, 0.2–0.4 for MRSA and 0.4–0.8 for VREF), while (+)-**2** shows no activity against these bacterial strains at concentrations up to 88 $\mu g\,mL^{-1}$. Racemic adamantaplatensimycin ((±)-**2**) exhibited half the activity of its biologically active enantiomer (−)-**2**. It should be noted that the potency of (−)-**2** against MRSA and VREF is comparable to that reported for linezolid (2–4 $\mu g\,mL^{-1}$),[9] a widely used antibacterial agent.

Table 1: Minimum inhibitory concentration values ($\mu g\,mL^{-1}$) of (−)-**2**, (+)-**2**, and (±)-**2** against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VREF), and *E. coli*.[a]

	(+)-**2**	(−)-**2**	(±)-**2**	(−)-**1**[b]	(±)-**1**[c]
MRSA	>88	1.3–1.8	2.6–3.6	0.2–0.4	0.4–0.8
VREF	>88	1.3–1.8	2.6–3.6	0.4–0.8	0.8–1.6
E. coli	>88	>88	>88	>88	>88

[a] Inocula of MRSA (ATCC 33591), E. coli (ATCC 29425), and VREF (ATCC 51575) were prepared using overnight cultures of microorganisms grown in either nutrient broth (Difco, Detroit, MI) or brain heart infusion (BHI; Difco, Detroit, MI) in the case of VREF. The inocula were then diluted to an approximate concentration of 5×105 cfu mL^{-1} in cation-adjusted Mueller–Hinton broth II (Becton Dickinson, Sparks, MD), or BHI in the case of VREF, as determined by a colony count on a nutrient agar plate. Cells (80 μL) were dispensed into the 96-well microtitre plates that contained serial dilutions of the tested compounds (20 μL) or known antibacterial agent (vancomycin for MRSA, streptomycin for *E. coli*, and daptomycin for VREF). Plates were incubated with gentle agitation at 37 °C for 24 h. The minimum inhibitory concentration was determined as the lowest concentration at which no bacteria were observed to grow. [b] Synthetic (−)-platensimycin.[4] [c] Synthetic (±)-platensimycin.[3]

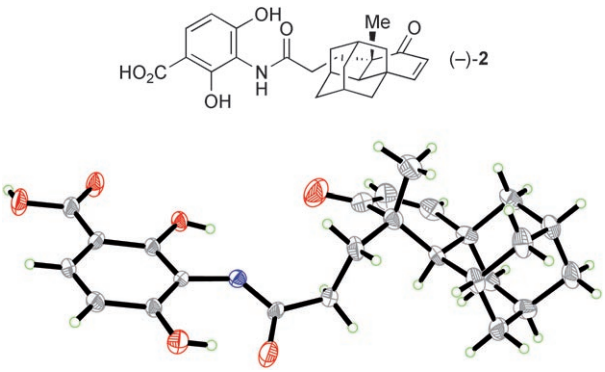


Figure 2. ORTEP view of (−)-adamantaplatensimycin ((−)-**2**) with the thermal ellipsoids at the 30% probability level.

Based on these biological results and the sign of optical rotation exhibited by (−)-**2**, we have tentatively assigned the absolute stereochemistry of (−)-adamantaplatensimycin to be the same as that of platensimycin ((−)-**1**).

In conclusion we have described the synthesis and biological activity of adamantaplatensimycin ((−)-**2**), a novel analogue of platensimycin ((−)-**1**), and demonstrated its potent activity against the drug-resistant strains MRSA and VREF. Further investigations with this novel platensimycin analogue and related compounds are in progress.[10]

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Table 2: Selected physical properties for compound (−)-**2**.

(−)-**2**: $R_f=0.18$ (silica gel, acetone/hexanes/AcOH 70:30:0.1); $[\alpha]_D^{22}=-75.9$ ($c=0.10$, MeOH); IR (film): $\tilde{\nu}=3281$brm, 2909m, 2854m, 2577brm, 1653s, 1599m, 1535m, 1462m, 1446 m, 1376m, 1294, 1245m, 1216m, 1183w, 1155m, 1117w, 1090w, 1059m, 1023w, 834w, 791m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=11.73$ (m, 1H), 11.25 (m, 1H), 8.27 (s, 1H), 7.63 (d, $J=9.2$ Hz, 1H), 6.58 (d, $J=10.0$ Hz, 1H), 6.51 (d, $J=9.2$ Hz, 1H), 5.92 (d, $J=10.0$ Hz, 1H), 2.46–2.34 (m, 2H), 2.31–2.22 (m, 2H), 2.12–2.01 (m, 6H), 1.91–1.85 (m, 1H), 1.82–1.69 (m, 6H), 1.65–1.61 (m, 2H), 1.34 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=206.2$, 174.2, 172.8, 159.2, 155.4, 154.4, 128.3, 125.4, 114.4, 111.2, 103.5, 48.6, 46.5, 46.4, 40.5, 37.2, 36.5, 36.4, 32.9, 32.7, 32.5, 29.7, 28.3, 27.2, 24.8 ppm; HRMS (ESI TOF): m/z calcd for $C_{25}H_{29}NO_6$ [M+H$^+$]: 440.2068; found 440.2065.

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[10] Preliminary experiments to induce asymmetry in the C–H bond insertion step of the synthesis by employing the terminal diazo counterpart of substrate **5** and tetrakis(4-methoxycarbonyl-2-oxyoxazolidinyl)dirhodium(II) (Rh_2[MEOX]$_4$)[11] yielded the desmethyl equivalent of (±)-**6** in 70% *ee*. Further studies to improve this catalytic asymmetric reaction as a means to achieve an asymmetric synthesis of (−)-adamantaplatensimycin are in progress.

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