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Isoplatensimycin: Synthesis and biological evaluation

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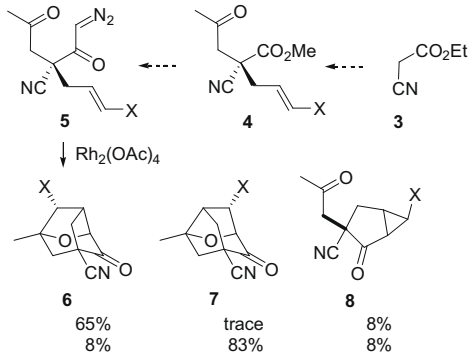
ABSTRACT

Isoplatensimycin, a novel analog of platensimycin, was synthesized via intramolecular dipolar cycloaddition of a carbonyl ylide. Isoplatensimycin showed little activities against strains of *Staphylococcus aureus*, but exhibited activities against some vancomycin-resistant enteroccoci.

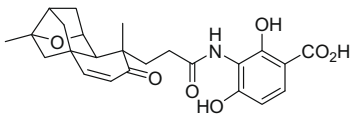
Platensimycin (**1**) is a broad spectrum antibiotic against Gram-positive bacteria, which was isolated from *Streptomyces platensis* by Merck scientists. It inhibits bacterial growth by selectively inhibiting the condensing enzyme FabF in the bacterial fatty acid synthesis pathway.[1] Platensimycin (**1**) shows no cross-resistance to methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant enterococci. Due to the remarkable biological profile, intense activities were directed to the synthesis of platensimycin (**1**)[2] and its analogs.[3]

Recently, we reported an efficient and concise approach to **1**, in which the key tricyclic intermediate **7** (X = I) was prepared via intramolecular dipolar cycloaddition of the carbonyl ylide generated from the halogen-substituted olefinic intermediate **5** (X = I).[2f] In the absence of halogen substitution, regioselectivity in this key step is reversed, and an isomeric tricycle **6** (X = H) was obtained from **5** (X = H) (Scheme 1). Overall, the structure of tricycle **6** closely resembled that of tricycle **7**, and we were intrigued by the possibility of using **6** in the preparation of isoplatensimycin **2** (Fig. 1), a novel analog of **1** with subtle structural differences.

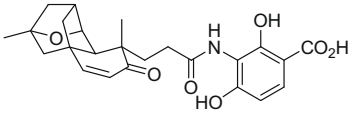
Horner–Emmons reaction of **6** (X = H) proceeded smoothly to produce enone **9**. The hydrosilylation in the presence of catalyst **10**[4] followed by DIBAL reduction, imine hydrolysis under one-pot reactions, and silyl enol ether hydrolysis furnished the synthesis of **11** in 51% yield. The epimeric byproduct was also isolated (17% yield). Under acidic conditions, the tetracyclic enone intermediate **12** was prepared from **11** in high yield. The methylation product of **12** was reacted with acrylonitrile under basic conditions in *t*-butanol to produce nitrile **13**,[5] which was converted into the carboxylic acid **14** under alkaline conditions. The conventional



Scheme 1. Regioselective carbonyl ylide [3+2] cycloaddition reactions.[2f]



1 Platensimycin



2 Isoplatensimycin

Figure 1. Platensimycin (**1**) and isoplatensimycin (**2**).

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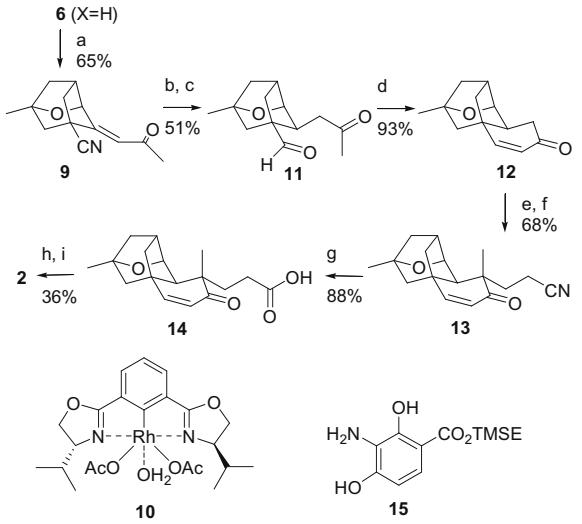

Scheme 2. Reagents and conditions: (a) $MeCOCH_2PO(OMe)_2$, NaH, LiCl, 4 Å MS, THF; (b) Me_2PhSiH, 2 mol % [Rh{(*R*,*R*)-Phebox-*i*Pr}$(OAc)_2$]·H_2O (**10**), toluene, 60 °C; DIBAL, toluene, −40 °C; AcOH–H_2O (1:1), 0 °C; (c) 2 N HCl, THF, 0 °C; (d) *p*-TsOH, toluene, reflux; (e) KHMDS, THF–HMPA (5:1), −78 °C; MeI, −10 °C; (f) KOH, acrylonitrile, *t*-BuOH, 60 °C; (g) 20% aq KOH, MeOH, reflux; (h) **15**, HATU, TEA, DMF, 24 °C; (i) TASF, DMF, 40 °C.

Table 1
Bioassay of platensimycin (**1**) and isoplatensimycin (**2**)

No.	Strain name	Drug sensitivity	MIC (μg/ml)			
			(±)-**1**	(±)-**2**	Oxa[a]	Van[b]
1	*S. aureus*	MSSA	4	128	0.125	—
2	*S. aureus*	MSSA	64	>128	0.5	—
3	*S. aureus*	MSSA	128	>128	0.125	—
4	*S. aureus*	MSSA	2	128	0.5	—
5	*S. aureus*	MRSA	4	>128	>128	—
6	*S. aureus*	MRSA	4	>128	>128	—
7	*S. aureus*	MRSA	16	>128	16	—
8	*S. aureus*	MRSA	4	>128	>128	—
9	*S. aureus*	VISA	4	>128	>128	—
10	*S. aureus*	VISA	4	>128	>128	—
11	*E. faecalis*	VSE	2	16	—	2
12	*E. faecalis*	VRE	1	64	—	32
13	*E. faecalis*	VRE	1	32	—	128
14	*E. faecium*	VRE	0.5	2	—	>128
15	*E. faecium*	VRE	0.5	4	—	>128

MSSA: Methicillin-sensitive *Staphylococcus aureus*.
MRSA: Methicillin-resistant *Staphylococcus aureus*.
VISA: Vancomycin-insensitive *Staphylococcus aureus*.
VSE: Vancomycin-sensitive *Enterococcus*.
VRE: Vancomycin-resistant *Enterococcus*.
[a] Oxacillin.
[b] Vancomycin.

coupling reaction between **14** and amine **15**[6] followed by fluoride-assisted hydrolysis led to isoplatensimycin (**2**)[7] (Scheme 2).

In vitro bioassay for testing isoplatensimycin (**2**) was carried out using strains of *S. aureus* and *Enterococcus faecalis* and *Enterococcus faecium*. Oxacillin and vancomycin were also tested as reference compounds for comparison (Table 1).

Isoplatensimycin (**2**) showed little activities against all strains of *S. aureus*. However, **2** displayed moderate to weak activities against *E. faecalis* strains, and relatively strong activities against vancomycin-resistant *E. faecium*, although it was less active than platensimycin (**1**). It is very interesting that a subtle structure modification resulted in a dramatic change in the antibacterial activity. Future studies will focus on the development of other novel analogs of platensimycin.

Acknowledgments

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7. *Compound* (±)-**2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.78 (s, 1H), 11.05 (s, 1H), 8.07 (s, 1H), 7.59 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 10.0 Hz, 1H), 6.48 (d, J = 8.9 Hz, 1H), 5.96 (d, J = 10.0 Hz, 1H), 4.79 (d, J = 4.9 Hz, 1H), 2.95 (s, 1H), 2.77–2.65 (m, 1H), 2.62–2.52 (m, 2H), 2.22–2.05 (m, 3H), 1.85 (d, J = 2.9 Hz, 2H), 1.83–1.75 (m, 3H), 1.36 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.0, 173.3, 172.3, 155.2, 154.2, 153.6, 128.2, 127.8, 114.2, 111.2, 103.6, 82.7, 81.9, 59.2, 48.3, 47.0, 46.4, 45.7, 44.7, 43.1, 36.9, 31.9, 23.1, 22.8. MS m/z (EI, relative intensity): 441 (M^+, 25), 379 (13), 273 (100), 255 (38), 237 (14), 218 (25), 213 (21), 169 (28), 151 (37). HRMS (EI): Calcd for $C_{24}H_{27}O_7N$ (M^+) 441.1787. Found 441.1788.