A facile synthesis of (+)/(−)-pentenomycin I and analogs, and their antimicrobial evaluation

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A facile synthesis of (+)/(−)-pentenomycin I and analogs, and their antimicrobial evaluation

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Keywords

Pentenomycin, Total synthesis, Antimicrobial susceptibility testing, Structure-activity relationships

Abstract

This study reported a stereoselective synthesis of (+)/(+)-pentenomycin I in 4−5 steps through regioselective silylation, optical resolution and dihydroxylation, followed by an olefin formation, from a known racemic cyclopentenone prepared from 2-deoxy-D-glucose. We also accomplished the transformation of a common intermediate into a variety of analogs. In addition, the antimicrobial activities of the pentenomycin analogs were evaluated, which revealed important structural factors of pentenomycins for the antimicrobial activities.

Introduction

In general, the molecules having a cyclopentenone framework also possess an important function as the Michael acceptors for a variety of cellular nucleophiles, due to their highly reactive α,β-unsaturated carbonyl centers.[1] Thus, the cyclopentenone framework is usually used as a basic core to prepare natural and unnatural products.[2,3] In addition, highly oxygenated cylopentenoids are known to exhibit promising antimicrobial activity.[4] In particular, pentenomycins exhibit moderate activity against both Gram-positive and Gram-negative bacterial species (Figure 1).[5–7] Pentenomycin I (**1**) was isolated by Umino *et al.* in 1973 from a culture strain of *Streptomyces eurythermus*. The unique structures of pentenomycins having various reactive functional groups and quaternary chiral center are especially interesting for its synthesis. Furthermore, pentenomycins with biological properties have also attracted attention in recent years. Various methods have been reported for the total syntheses, both enantioselective and racemic, of pentenomycins.[8–19] In recently, total synthesis of (−)-pentenomycin I (**1**), a natural product, from D-mannose, and (+)-**1** from D-ribose were reported by Rao group.[18] In later years, Pal group

reported the the syntheses of both enantio isomers of **1** from D-ribose as the single starting material, via stereoselective hydroxymethylation, Grignard reaction and ring-closing metathesis as key reactions.[19] While the synthetic methods reported to date are very interesting, many of those require multiple steps, especially the ones that are stereo- and enantioselective. The shortest process for the synthesis of (+)-**1** were reported by Elliott group.[20] In this case, however, the required starting material was prepared from quinic acid in more than ten steps.[21,22] In addition, pentenomycin analogs could not be efficiently synthesized from pentenomycin (**1**) because multi-hydroxy groups inhibit selective modification of functional groups. Despite numerous efforts on the synthesis of **1**, there are few reports of antimicrobial evaluation. Therefore, the development of synthetic routes of pentenomycin analogs and investigation of their antimicrobial activities would be beneficial. Herein, we report the enantioselective synthesis of (+)/(−)-pentenomycin I (**1**) and their analogs prepared from a key intermediate in a short overall process, and their antimicrobial evaluation.

Results and discussion

Recently, we reported a facile method for the preparation of cyclopentenone **4** from 2-deoxy-D-glucose (2-DG) by a hydrothermal reaction under mild condition,[23] and **4** could be replaced with the starting material used by Elliott *et al*. The synthetic plan of (+)/(−)-pentenomycin I (**1**) is shown in Scheme 1. At the beginning, the primary hydroxy group in **4** is protected regioselectively, then the optical resolution by enzymes results in the separation of the (+)/(−)-enantiomers. After that, the basic pentenomycins skeleton is formed by dihydroxylation and formation of the olefin by E_1cb elimination. Finally, protective group is removed to produce **1**.

According to the synthetic plan, the synthesis of (+)/(−)-**1** were achieved as follows (Scheme 2). The regioselective silylation of primary hydroxy group was carried out by a non-nucleophilic base under catalyst-free conditions.[24] In this case, with the presence of the catalyst, 4-dimethylaminopyridine (DMAP), the major product in which both hydroxy groups protected was produced and also, the regioselectivity was reduced when nucleophilic bases were used.[25] Subsequent optical resolution was succeeded by using Lipase amano series.[26,27] When **5** was treated with vinyl acetate and Lipase AK amano, **6** and (*S*)-**5** were obtained in equivalent yield. The absolute configuration of each compound was determined by comparing to the optical resolution of the chiral compounds prepared from the (*R*)-**4** (99% *ee*) and (*S*)-**4** (99% *ee*) (both were supplied by the FromSeeds Corporation). After that, the olefination and the subsequent dihydroxylation were proceeded in one-pot in which **6** was treated with osmium catalyst and *N*-methylmorpholine oxide at room temperature. However, compound **6** has not consumed completely and recovered in 28% yield. In this case, we found that compound **7** decomposed and a lower yield was obtained when the reaction time exceeded 2 h. The pentenomycin skeleton could be constructed at once, however the enatiopurity of **7** was moderate (56% *ee*, determined by chiral-phase high performance liquid chromatography (HPLC)). In addition, the enatiopurity of (–)-**7** prepared from (*R*)-**4** (99% *ee*) was also moderate. Therefore, the stereoselective formation of the osmate ester intermediate was not completely controlled due to the less steric hindrance of the acetoxy group.[20] Finally, desilylation through treatment with aqueous 3 M HCl produced (–)-pentenomycin I (**1**). Under the same conditions, (+)-**1** was produced from (*S*)-**5**. The spectroscopic properties of **1** were identical to those reported previously. The optical rotation of synthetic (+)-1, $[\alpha]_D^{23}$ = + 13.2 (c = 0.36, EtOH), matched with the literature value of $[\alpha]_D$ = +30.1 (c 0.1, EtOH)[19].

And also, the optical rotation of (–)-1, $[\alpha]_D^{23}$ = –19.6 (c = 0.35, EtOH) matched with a previous report of $[\alpha]_D$ = −30.2 (c 0.29, EtOH)[19].

Previously, Umino *et al.* reported that several pentenomycin analogs were produced from an isolated **1**, however the overall yield was very low. On the other hand, we believe that the intermediate **7** is suitable to promote to analogs. We have also demonstrated the syntheses of several analogs of natural type from (−)**-7,** as shown in Scheme 3. Initially, the secondary hydroxyl group of (−)**-7** was modified with benzoic ester **8** through treatment with benzoic anhydride under basic condition, pyridine and DMAP. The reaction was required longer time to reach completion when benzoyl chloride was used instead of benzoic anhydride. Benzoic pentenomycin **9** was prepared by treatment of **8** with 6 M HCl, because the starting material **9** was not completely consumed under 3 M HCl. I_2 in the presence of pyridine provided the α-iodide derivatives **10** and **11**. Hydrogenation of **9** over Pd/C catalyst subjected compound **12**.Compound **13** could be obtained in 64% yield from **11** in two steps: Suzuki-Miyaura coupling reaction which was carried out with $PhB(OH)_2$, K_2CO_3, and a catalytic amount of $Pd(PPh_3)_2Cl_2$, followed by desilylation.[17] We have succeeded in synthesizing several pentenomycin analogs, so as the next target, we attempted their antimicrobial evaluation. The synthesized analogs **9**, **10**, **12** and **13** were tested for their antimicrobial activity. Antimicrobial susceptibility was tested by broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) recommendations. It was performed on seven bacterial species of the most common pathogens in the clinical settings, and the minimum inhibitory concentration (MIC) values are summarized in Table 1. Compound **9** and **10** had moderate antimicrobial activities for either organisms. On the other hand, the activities of compound **11** and **13** were remarkably decreased. These results suggested that the cyclopentenone framework, α,β-unsaturated carbonyl, in pentenomycins would be responsible for the pronounced

antimicrobial activity. In addition, it was revealed that when there is bulky and non-liberating substituent, such as phenyl group, in α position of cyclopentenone, its antimicrobial activity was remarkably attenuated. To the best of our knowledge, the antimicrobial activity of compound **10**, **11** and **13** has not been previously reported in literature; while the MIC value of compound **9** was reported elsewhere.[7] These findings provide new knowledge for designing new pentenomycin derivatives, more active synthetic antimicrobial compounds.

Conclusion

We have achieved the enantioselective synthesis of (+)/(−)-Pentenomycin I (**1**) in a liner sequence of four steps, starting from cyclopentenone **4** which could be prepared from 2-DG. In addition, the analogs could be obtained successfully in a less complicated method from intermediate **7**. A preliminary antibiological activity of pentenomycin analogs **10**, **11** and **13** was also investigated, which provided some structure-activity relationship insight. We believe that these findings will be useful for the design and development of new pentenomycins for antimacrobial agents. Now we are promoting the syntheses of the highly enantioselective pentenomycin analogs.

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Supplementary information

Supplementary date that the experimental and material data to this article can be found at.

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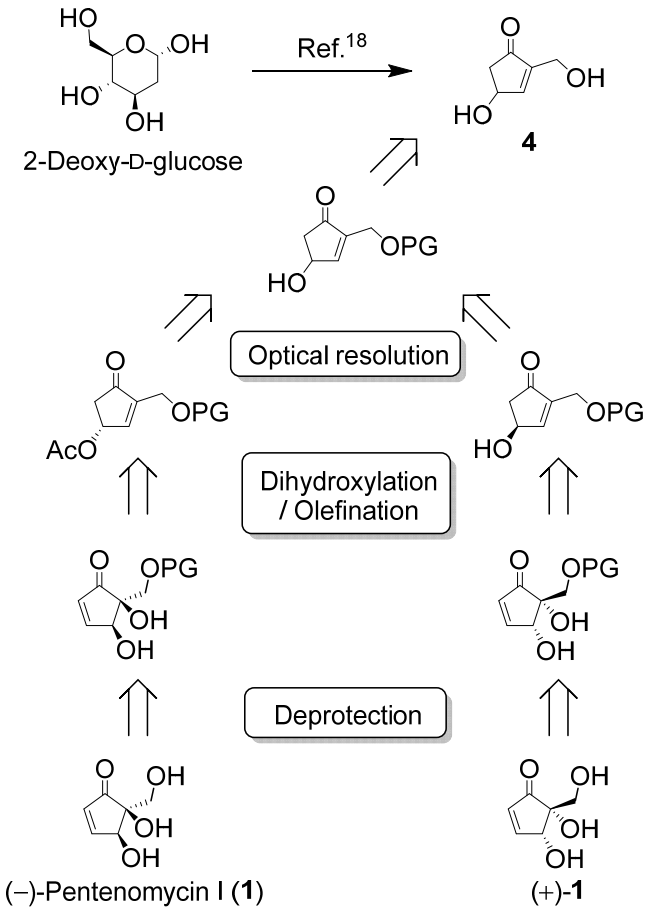
Figure 1.

Pentenomycin I (**1**) R = H
Pentenomycin II (**2**) R = Ac

Dehydropentenomycin (**3**)

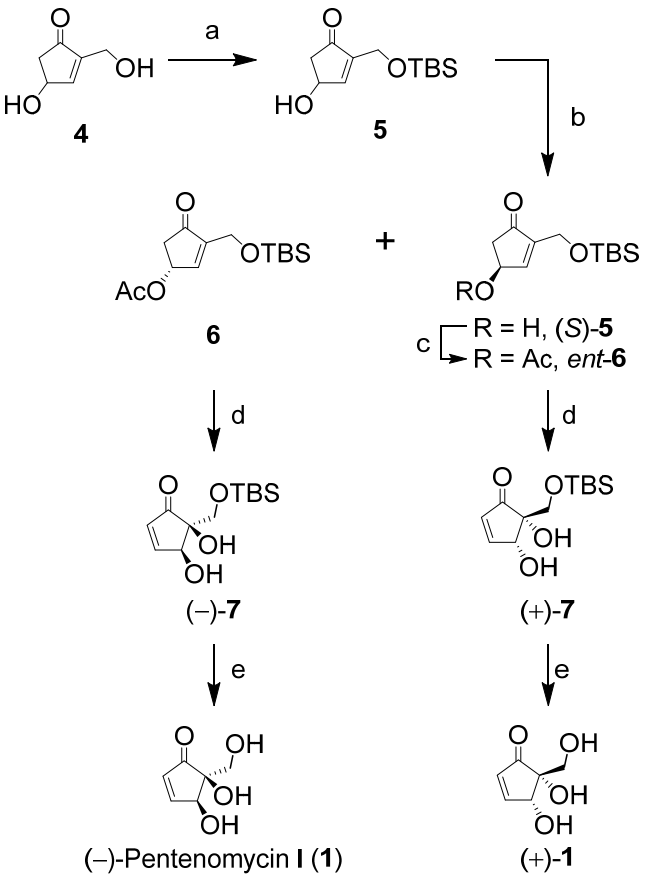
Figure 1. Structures of pentenomcyins

Scheme 1.



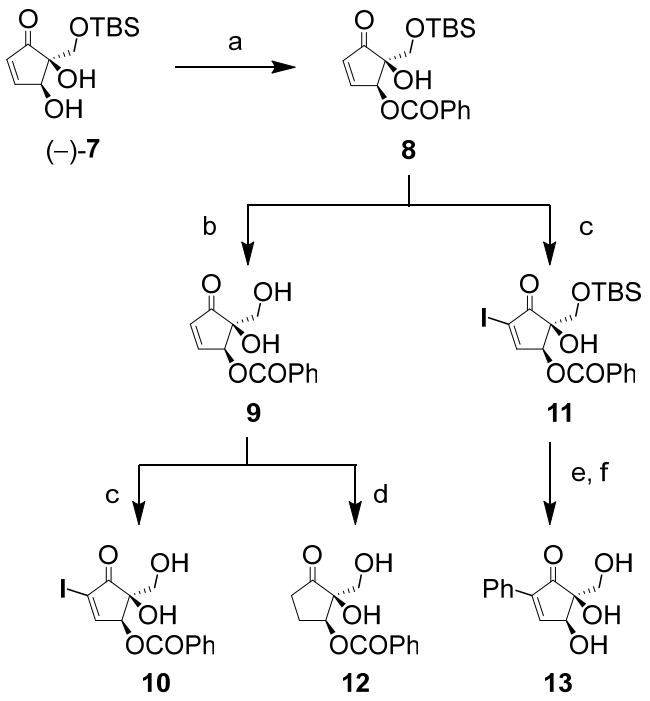
Scheme 1. Retrosynthesis of (+)/(–)-pentenomycin I (1). PG: protective group.

Scheme 2.



Scheme 2. Syntheses of (+)/(–)-pentenomycin I (**1**). Reagents and conditions: (a) TBSCl (tert-butyldimethylsilyl), Et_3N, THF, room temperature (r.t.), overnight, 82%; (b) Lipase AK amano, vinlyacetate-acetone (1:1), r.t., overnight, 48% for **6**, 50% for (*S*)-**5**; (c) Ac_2O, pyridine, 4-Dimethylaminopyridine (DMAP), r.t., overnight, 72%; (d) $K_2OsO_2(OH)_2$, *N*-methylmorpholine oxide (NMO), acetone-H_2O (2:1), r.t., 2 h, 61% for (–)-**7**, 55% for (+)-**7**; (e) 3 M HCl, THF, r. t., 0.5 h, 48 % for (–)-**1**, 57% for (+)-**1**.

Scheme 3.



Scheme 3. Syntheses of pentenomycin analogs. Reagents and Conditions: (a) $(PhCO)_2O$, pyridine, 4-Dimethylaminopyridine (DMAP), THF, room temperature (r.t.), 1 h, 95%; (b) 6 M HCl, THF, r.t., 1 h, 100 %; (c) I_2, CH_2Cl_2-pyridine (2:1), 1 h, r.t., 47% for **10**; (d) H_2 (balloon), Pd/C, MeOH, r.t., 1 h, 100 %; (e) K_2CO_3, $PhB(OH)_2$, $Pd(PPh_3)_2Cl_2$, THF-H_2O (2:1), 60 ° C, overnight; (f) 3 M HCl, THF, r.t., 1 h, 64 % (2 steps from **11**).

Table 1.

Table 1. Antimicrobial evaluation of pentenomycin analogs

Organisms	MIC test (μg/mL)[a, b]			
	9	**10**	**12**	**13**
S. aureus ATCC29213	64	128	>1024	1024
E. faecium ATCC35667	64	64	>1024	1024
E. coli DH5alpha	128	128	>1024	256
K. pneumoniae ATCC10031	64	64	>1024	256
E. cloacae ATCC13047	128	128	>1024	256
P. aeruginosa PAO1	512	128	>1024	1024
A. baumannii ATCC17978	64	32	>1024	256

(a) Determined by CLSI broth marcodilution methods; (b) Measured concentration (0.5-1024 ug/mL); *Stapylococcus aureus; S. aureus, Enterococcus faecium; E. faecium, Escherichia coli; E. coli, Klebsiella pneumonia; K. pneumoniae, Enterobacter cloacae; E. cloacae, Pseudomonas aeruginosa; P. aeruginosa, Acinetobacter baumannii; A. baumannii.*