Asymmetric Synthesis of Ampelomin A and *ent*-Epiampelomin A

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Abstract: We synthesized the naturally occurring carbasugar ampelomin A and its epimer from a common starting material. The enantiomerically pure starting material was obtained by base-catalyzed asymmetric Diels–Alder reaction of 3-hydroxy-2-pyrone and chiral acrylate. The total yield of ampelomin A was 14% in seven synthetic steps. The key step of the synthesis of ampelomin A was inversion of the stereochemistry at the C-6 position, which was achieved by stereoselective catalytic hydrogenation of the corresponding methyldene group. Further synthesis of the epimer was straightforward, because all stereogenic centers had already been introduced on the starting material; the total yield was 44% in four synthetic steps. Both the final products were obtained in pure form without contamination with undesired isomers. The reported ^1H NMR chemical shift of the C-7 methyl protons and the H-5_{axial} coupling pattern of natural ampelomin A were inconsistent with those of our synthetic product. After careful comparison of the spectra and examination of the stable conformation obtained through MM2 calculations, we present revised NMR data for ampelomin A.

Key words: ampelomin family, carbasugar, asymmetric synthesis, base-catalyzed Diels–Alder reaction

1 INTRODUCTION

Carbasugars are sugar-like structures possessing polyfunctionalized cycloalkanes such as cyclohexanes or cyclopentanes^{1,2)}. They are relatively small compounds, but play various and important roles in living systems. For example, the most common simple carbasugar, inositol, is a vitamin B-like compounds recognized as an important component of cell membranes and signaling molecules³⁾. In addition, due to their structural similarities with sugars, carbasugars frequently exhibit inhibitory activity toward enzymes such as glycosidases and/or glycotransferases, which are involved in antibacterial or antiviral processes²⁾.

In 2009, the novel naturally occurring carbasugar ampelomin A (**1**) and six related compounds, ampelomins B–G (Fig. 1), were isolated from the soil-derived fungal strain *Ampelomyces* sp. SC0307⁴⁾. The stereochemistry of **1** was assigned as 4*R*,6*S* using the modified Mosher's method⁵⁾. Although the absolute configurations of the other ampelomins were not established, they were presumed to be as shown in Fig. 1, based on the well accepted biogenetic pathway via a polyketide intermediate of natural polyoxygenated methylcyclohexanoids, such as theobroxide and epoformin^{6,7)}. Although the biological activities of the ampelomins have not been fully tested, antibacterial activity

against *S. aureus*, *E. coli*, *P. vulgaris*, and *P. aeruginosa* and moderate inhibitory activity against β -glucosidase have been observed for **1** and some other ampelomins⁴⁾.

Our group is interested in developing concise syntheses of biologically active small molecules such as carbasugars and cyclohexene oxides^{8–14)}. The ampelomins possess a wide range of functional groups and diverse stereochemistries, making them attractive targets for our synthetic studies. The proposed biosynthetic pathway⁴⁾ suggested that **1** and its corresponding 4-epimer, epiampelomin A (**2**), yet to be isolated as a natural product, were considered to be the parent compounds of the entire ampelomin family.

Compounds **1** and **2** are also known as attractive building blocks for polyoxygenated natural products and have previously been synthesized as important intermediates by several research groups. Carreño et al. introduced the *tert*-butyldimethylsilyl ether of *ent*-**1** as an intermediate for quinone antibiotics¹⁵⁾. O'Doherty's group prepared *ent*-**1** and **2** from D-(–)-quinic acid as precursors of carbasugar phosphates¹⁶⁾. Taylor et al. reported a mixture of **1** and **2** as an intermediate of biologically active γ -butyrolactone¹⁷⁾. In 2012 and in 2013, Bräse's group developed two different approaches for producing enantiopure **1** and **2** as an inseparable mixture^{18,19)}.

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Fig. 1 Naturally occurring ampelomin family and epiampelomin A.

Scheme 1 Base-catalyzed Diels-Alder reaction of 3 and 4.

All of these syntheses require multi-step procedure and/or difficult separation processes for the diastereomers, and thus development of a simple and efficient method for preparing 1 and 2 would be valuable for synthesizing various natural products. Therefore, we sought to develop a brief and stereocontrolled synthesis of these compounds.

In our previous syntheses of carbasugars and cyclohexene oxides^{9–14}, we used a base-catalyzed Diels-Alder (DA) reaction of 3-hydroxy-2-pyrone (3) and electron deficient dienophiles as the key reaction for constructing the polyfunctionalized six-membered rings (Scheme 1)^{20–23}. Diene 3 is relatively unreactive because of its aromatic character, and the resulting cycloadducts are unstable on heating. Therefore, the DA adducts were difficult to obtain under thermal reaction conditions²⁴. Consequently, we developed a base-catalyzed DA reaction that activates dienes with acidic hydroxyl groups, such as 3, and affords the corresponding DA adducts in good to excellent yields under mild conditions^{20–23}. The enantiomerically pure adducts have also been obtained through a base-catalyzed asymmetric DA reaction using the chiral dienophile 4, which is suitable for the asymmetric synthesis of carbasugars^{10–13}.

2 EXPERIMENTAL PROCEDURES

2.1 Materials and General Experimental Procedure

Rf values were measured using Merck TLC Aluminium Sheets 1.05554.0009 (20 × 50 mm). IR spectra were recorded using a JASCO FT/IR 5300 spectrometer. NMR spectra were measured using a JEOL GSX400 spectrometer. FAB mass spectra were obtained using a JEOL JMX-SX/SX 102A spectrometer. All reagents were commercially available and used without further purification. Silica gel 60 (0.063–0.200 mm, Merck) was used for column chromatography.

2.2 (1*S*,5*R*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methylene-7-oxabicyclo[4.1.0]heptan-2-one [(+)-6]

Compound (+)-6 was prepared by the same synthetic protocol as its enantiomer used in the synthesis of phyllostine^{10,11}.

2.3 (1*S*,3*S*,5*R*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-7-oxabicyclo[4.1.0]heptan-2-one [(–)-7]

Finely powdered Pd/C (5.0% Pd in active charcoal, 10 mg) was added to a solution of (+)-6 (50 mg, 0.20 mmol) in ethyl acetate (4.0 mL) and subjected to H₂ (1 atm) provided by a rubber balloon. After stirring for 24 h at rt, the reaction mixture was filtered through a pad of Celite and evaporated. The resulting residue was purified by silica gel column chromatography (hexane:diethylether = 9:1) to give 7 (46 mg, 92%) as a colorless oil. $[\alpha]_D^{24} -15$ (c 0.43, CHCl₃); IR (film): 3476, 1721, 1462, 1260, 1100 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.11 (3H, s), 0.13 (3H, s), 0.99 (9H, s), 1.03 (3H, d, *J* = 6.5), 1.57–1.61 (1H, m), 2.20 (1H, ddt, *J* = 1.4, 5.5, 13.7 Hz), 2.68 (1H, ddd, *J* = 1.4, 6.5, 12.7 Hz), 3.31 (1H, d, *J* = 3.9 Hz), 3.48 (1H, dt, *J* = 3.9, 1.4 Hz), 4.36 (1H, dt, *J* = 1.4, 5.5); ¹³C NMR (100 MHz, CDCl₃): δ –4.8, –4.7, 15.2, 18.1, 25.8, 34.7, 41.1, 55.5, 63.4, 65.9, 139.5, 208.4; HREIMS *m/z* 256.1490 [M]⁺ (calculated for C₁₃H₂₄O₃Si, 256.1495).

2.4 Ampelomin A[(+)-1]

Compound **7** (42 mg, 0.16 mmol), sodium thiosulfate pentahydrate (480 mg, 1.9 mmol), and Amberlyst® 15 (40 mg) were added to a solution of NaI (92 mg, 0.61 mmol) in acetone (4.0 mL) at rt. After stirring for three days, the mixture was poured into aq. Na₂S₂O₃ solution (5.0%, 10 mL) and extracted with ethyl acetate (15 mL, three times). The combined organic layer was dried over MgSO₄, filtered through a glass filter, and evaporated. The residue was purified by silica gel column chromatography (hexane:ether = 9:1) to give α , β -unsaturated ketone (14 mg, 35%).

Pyridinium *p*-toluenesulfonate (1.1 mg, 0.0042 mmol) was added to a solution of an aliquot of the above product (10 mg, 0.042 mmol) in methanol (2.0 mL). After stirring for one day at 40°C, the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (CH₂Cl₂: MeOH = 9:1) to give **1** (5.0 mg, 95%) as a colorless oil. [α]_D²⁴ 62 (c 0.080, MeOH) (lit. value [α]_D²⁰ 50.1 (c 1.6, MeOH)⁴⁷); IR (film): 3383, 1678, 1671, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): see Table 1; ¹³C NMR (100 MHz, CDCl₃): see Table 1; HREIMS m/z 126.0678[M]⁺ (calculated for C₇H₁₀O₂, 126.0681).

2.5 [(1*R*,4*S*,8*S*)-4-Hydroxy-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-8-yl]methyl 4-methylbenzenesulfonate[(−)-8]

To a solution of **5** (115 mg, 0.35 mmol) in THF (5.0 mL), LiBH₄ (6.8 mg, 0.31 mmol) was carefully added at rt, and the reaction mixture was stirred for 40 min. The mixture was quenched with a few drops of aq. H₃PO₄ solution (5.0%) and water (ca. 15 mL), and the entire mixture was extracted with ethyl acetate (15 mL, three times). The combined organic layer was dried over MgSO₄, filtered through a glass filter, and evaporated under reduced pressure. Purification by silica gel column chromatography (AcOEt) gave a crude product (ca. 64 mg).

DMAP (5.0 mg, 0.038 mmol), Et₃N (116 μ L, 0.83 mmol), and tosyl chloride (86 mg, 0.45 mmol) were added to a solution of the obtained product (ca. 64 mg) in CH₂Cl₂ (6.0 mL). After stirring for 6 h, the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (10 mL, three times). The combined organic layer was dried over MgSO₄, filtered through a glass filter, and evaporated. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:1) to give **8** (83 mg, two steps 73%) as a yellowish oil. [α]_D²⁴ −40 (c 0.90, CHCl₃); IR (film): 3474, 1759, 1360, 1175, 979 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.70 (1H, ddd, *J* = 1.4, 4.1, 13.4 Hz), 2.23 (1H, ddd, *J* = 4.8, 8.6, 13.4 Hz), 2.46 (3H, s), 2.46–2.50 (1H, m), 3.64 (1H, s),

Table 1 NMR spectra of natural and synthetic ampelomin A and its epimer in CDCl₃.

position	natural Ampelomin A ^{a)}		synthetic 1		<i>ent</i> - 2	
	¹ H NMR	¹³ C NMR	¹ H NMR	¹³ C NMR	¹ H NMR	¹³ C NMR
1		201.6		201.0		201.9
2	6.85, dt (<i>J</i> = 10.0, 2.0 Hz)	128.4	6.88, dt (<i>J</i> = 10.4, 2.3 Hz)	129.0	6.87, dd (<i>J</i> = 10.1, 4.1 Hz)	129.3
3	5.95, dd (<i>J</i> = 10.0, 2.0 Hz)	153.5	5.97, dd (<i>J</i> = 10.4, 2.3 Hz)	152.6	5.97, dd (<i>J</i> = 10.1, 1.4 Hz)	148.4
4	4.64, ddt (<i>J</i> = 10.2, 4.8, 2.0 Hz)	67.2	4.66, br d (<i>J</i> = 10.3 Hz)	67.6	4.57, m	63.6
5	H-5 _{eq} 2.35–2.40, m	41.2	H-5 _{eq} 2.38–2.42, m	41.6	H-5 _{eq} 2.15, dt (<i>J</i> = 13.4, 5.6 Hz)	38.9
	H-5 _{ax} 1.72, tdd (<i>J</i> = 12.2, 10.2, 2.0 Hz)		H-5 _{ax} 1.74, ddd (<i>J</i> = 14.7, 13.3, 10.3 Hz)		H-5 _{ax} 2.08, ddd (<i>J</i> = 13.4, 8.3, 4.8 Hz)	
6	2.35–2.40, m	40.1	2.38–2.42, m	40.2	2.77, ddq (<i>J</i> = 8.3, 5.6, 7.3 Hz)	37.9
7	1.45, d (<i>J</i> = 6.5 Hz)	14.8	1.17, d (<i>J</i> = 6.9 Hz)	15.0	1.18, d (<i>J</i> = 7.3 Hz)	15.4

a) Cited from Ref 4.

3.87 (1H, t, $J=9.5$ Hz), 4.29 (1H, dd, $J=4.1, 9.5$ Hz), 5.24 (1H, t, $J=4.8$ Hz), 6.24 (1H, d, $J=7.8$ Hz), 6.44 (1H, dd, $J=4.8, 7.8$ Hz), 7.35 (2H, d, $J=8.3$ Hz), 7.77 (2H, d, $J=8.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.8, 30.7, 37.1, 70.6, 73.7, 74.9, 128.0, 130.1, 130.3, 132.6, 134.7, 145.3, 175.1 Hz.

2.6 *ent*-Epiampelomin A [(+)-*ent*-2]

To a solution of **8** (154 mg, 0.48 mmol) in THF (10 mL), LiAlH_4 (54 mg, 1.43 mmol) was carefully added at 0°C , and the reaction mixture was stirred for 24 h at rt. The reaction was quenched with a few drops of aq. H_3PO_4 solution (5.0%). Powdered NaIO_4 (153 mg, 0.71 mmol) was added to the resulting mixture, stirred for 3 h at rt, and then filtered through a pad of Celite to remove insoluble residues. The filtrate was diluted with water (ca. 15 mL), and the entire mixture was extracted with CH_2Cl_2 (15 mL, three times). The combined organic layer was dried over MgSO_4 , filtered through a glass filter, and evaporated. The residue was purified by silica gel column chromatography (AcOEt :hexane = 3:1 to 4:1) to give *ent*-**2** (36 mg, two steps 60 %) as a colorless oil. $[\alpha]_D^{24}$ 122 (c 0.49, MeOH) (lit. value of $2[\alpha]_D^{20} - 144.76$ (c 1.72, CHCl_3)¹⁶); IR (film): 3396, 1672, 1380, 1259, 1056 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): see Table 1; ^{13}C NMR (100 MHz, CDCl_3): see Table 1; HREIMS m/z 126.0671 $[\text{M}]^+$ (calculated for $\text{C}_7\text{H}_{10}\text{O}_2$, 126.0681).

3 RESULTS AND DISCUSSIONS

Synthesis of **1** was started from the DA adduct **5** (Scheme 2). The cyclohexene framework and the stereogenic center at the C-4 position in **1** can be directly introduced from the starting material, although the stereochemistry of the C-6 position is opposite that of the corresponding substituent in **5**. Thus we planned to introduce the stereochemistry by stereoselective reduction of the corresponding methylidene **6** that had already been prepared by our group as an intermediate of epiepoformin and related compounds^{10, 11}. Stereoselective reduction of the methylidene group successfully proceeded by catalytic hydrogenation to yield diastereomer **7** as a single product. The stereoselectivity of this reduction can be attributed to the steric effect of the bulky OTBS group at the C-4 position. Deoxygenation of the epoxide²⁵ and subsequent deprotection of the TBS group gave **1** in moderate yield. The total yield was 14% in seven steps from **5**.

Further synthesis of *ent*-epiampelomin A (*ent*-**2**) was straightforward because the both of the stereogenic centers at the C-4 and C-6 positions had already been introduced in the DA adduct **5** (Scheme 2). Chemoselective reduction of **5** was readily achieved using LiBH_4 to give a hydroxymethylbicyclic lactone that was subsequently

a) H_2 , Pd/C, MeOH, rt, 92%; b) NaI, amberlyst X, MeOH, rt; c) PPTS, MeOH, rt, 33% for two steps; d) LiBH_4 , THF, 0°C ; e) TsCl, DMAP, Et_3N , CH_2Cl_2 , rt, 73% for two steps; f) LAH, THF, rt; g) NaIO_4 , THF- H_2O , rt, 60% for two steps.

Scheme 2 Synthesis of **1** and **2**.

derived to the tosylate derivative **8**. Typically, reductive removal of a sulfonyloxy group or halogen substituent using hydride reducing agents has been known to be difficult, often requiring harsh reaction conditions, and giving low yields^{26, 27}. However, LAH reduction of **8** easily removed the tosyloxy group and reduced the lactone ring at ambient temperature, likely due to the formation of the reactive oxetane intermediate **9** that was immediately opened by the hydride to give **10**. The 1,2-diol moiety of the resultant triol was then cleaved using NaIO_4 to give the target compound *ent*-**2** in good yield. The total yield was 44% in four steps from **5**.

The ^1H and ^{13}C NMR signals for natural⁴ and synthetic ampelomin A (**1**) and *ent*-**2** are listed in Table 1. Although the ^{13}C NMR signals for natural ampelomin A showed fair agreement with those for **1**, the ^1H NMR chemical shift for the C-7 methyl protons (δ 1.45 for natural ampelomin A, and δ 1.17 for synthetic **1**) were obviously inconsistent. The previously reported NMR spectra for synthetic **1** (including its enantiomer) showed good agreement with our data^{16–19}. Subsequently, we obtained the ^1H NMR spectrum of natural ampelomin A and upon comparison with that of synthetic **1**, we found that the spectra were essentially superimposable. Therefore, we concluded that the reported δ value for the methyl signal of natural ampelomin A should be revised to 1.17.

The coupling pattern of H-5_{ax} of synthetic **1** that was assigned as ddd, was also inconsistent with that for natural

ampelomin A, reported as tdd. Unfortunately, most of the ^1H NMR data in previous reports were not fully investigated³⁰⁾ and thus, we examined this assignment through conformational analysis of **1** and *ent*-**2** using MM2 calculations (Fig. 2). The H-5 methylene protons in the stable conformations of **1** and *ent*-**2**, calculated by the MM2 program in Chem3D software, were clearly oriented *pseudo*-axial and *pseudo*-equatorial. Consequently, the coupling observed for H-5_{ax} in **1** was assigned as a combination of three large couplings (one germinal and two “trans-diaxial”-like between H-5_{ax} and H-4, and H-5_{ax} and H-6). Similarly, the couplings observed for the H-5 protons in *ent*-**2** were assigned as combinations of two large couplings (one germinal and one “trans-diaxial” between H-5_{ax} and H-6) and one medium coupling (“axial-equatorial” between H-5_{ax} and H-4) for H-5_{ax}, and one large coupling (geminal) and two medium couplings (both “axial-equatorial” between H-5_{eq} and H-4, and H-5_{eq} and H-6) for H-5_{eq}. Therefore, the coupling of H-5_{ax} in **1** was corrected to ddd, and the couplings of H-5_{ax} and H-5_{eq} in *ent*-**2** were assigned as ddd and dt, respectively.

4 CONCLUSION

We developed a stereocontrolled synthesis of ampelomin A (**1**) and *ent*-epiampelomin A (*ent*-**2**) from the same starting material **5**. Because **1** and its epimer have been recognized as parent compounds in the biogenetic pathway of the ampelomin family of natural products, we believe that this method provides a good starting point for comprehensive synthesis of ampelomins. The compounds **1** and **2** are known as attractive building blocks of organic synthesis. The total yields and synthetic steps for **1** and **2** in our synthesis were 14% in seven steps, and 44% in four steps, respectively, which are better than or comparable to previously reported methods that required more synthetic steps and/or difficult separation of undesired isomers. Further synthetic studies of the ampelomin family and related com-

pounds are under way and will be reported in the future³⁰⁾.

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Supporting Information

This material is available free of charge via the Internet at <http://dx.doi.org/jos.64.10.5650/jos.ess.14212>

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Fig. 2 Stable conformations of ampelomin A (**1**) and *ent*-epiampelomin A (*ent*-**2**) obtained by MM2 calculation.

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 - 28) We are grateful to Professor Xiaoyi Wei, South China Botanical Garden, for providing the ¹H NMR spectrum chart of natural ampelomin A.
 - 29) Only O'Doherty's group reported the detailed assignment of the couplings, which shows good agreement with those of ours. See supporting information of reference 16.
 - 30) Very recently, a synthetic approach toward deoxy-carbasugars including ampelomins using stereoselective hydrogenation was reported: Lagreca, M.E.; Carrera, I.; Seoane, G.A.; Brovotto, M. Stereoselective hydrogenation of methylcyclohex-2-ene-1,4-diols used in the synthesis of ampelomins and deoxy-carbasugars. *Tetrahedron Lett.* **55**, 853-856 (2014).