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Asymmetric Syntheses and Wnt Signal Inhibitory Activity of Melleumin A and Four Analogues of Melleumins A and B

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Abstract: The first total synthesis of melleumin A and four analogues of melleumins A and B is described. The *N*-acyl L-Thr-Gly/β-hydroxy-γ-amino acid coupling/macrolactamization strategy allowed the efficient assembly of the three segments being free of epimerization. While the Jouin–Castro method with minor modification allows a rapid entrance to the key *syn*-β-hydroxy-γ-amino acid segment, required for the synthesis of melleumin A, an extension of our malimide-based methodology using a changed *N*-protecting group affords a flexible access to several *anti*-β-hydroxy-γ-amino acids, and hence analogues of melleumins A and B. Among them, unnatural 4-*epi*-melleumin B (**2a**) exhibits a modest inhibitory activity on Wnt signaling. The total synthesis of melleumin A allowed confirmation of its full structure.

Keywords: asymmetric synthesis · biological activity · natural products · total synthesis · Wnt signal inhibition

Introduction

Natural products are not only important sources for drug discovery and development, many natural products have also become indispensable tools for biological studies.[1,2] Since the emergence of combinatorial chemistry in the 1980s,[3] their importance in drug development has widely been ignored. However, in recent years there has been a renaissance of natural products as drug candidates.[4] Among various sources of natural products, slime molds (myxomycetes), a group of fungus-like organisms usually present in terrestrial ecosystems, have been shown to be a valuable source of new biological active metabolites (natural products).[5] The myxomycete life cycle involves two very different trophic (feeding) stages, one consisting of uninucleate amoebae and the other consisting of a distinctive multinucleate structure, the plasmodium.[5b] Although chemical studies on the secondary metabolites of the myxomycetes have so far been limited, more than 100 secondary metabolites have been investigated.[5b]

In 2005, Ishibashi and co-workers reported the isolation of a novel peptide lactone melleumin A (**1**) and its seco acid methyl ester, melleumin B (**2**) (Figure 1), from the cultured plasmodium of the *myxomycete physarum melleum*.[6] In a subsequent study, through the synthesis of the segments, the full absolute stereochemistry of melleumin A (**1**) and melleumin B (**2**) was determined, jointly by a modification of Mosher's method and chiral HPLC analysis, as 3*S*,4*S*,10*S*, and 11*R*.[7] The total synthesis of melleumin B confirmed this absolute stereochemistry. Interestingly, while melleumin B is inactive, the 10*R*-, and 3*R*-epimers, as well as (3*R*,4*S*,10*R*,*11R*)-epimer of melleumin B (**2**) show a moder-

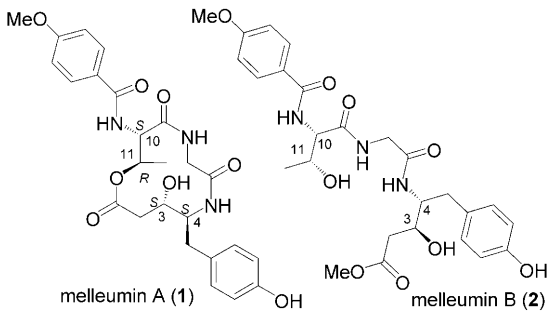

Figure 1. Structure of melleumin A (**1**) and B (**2**) (the stereochemistry at the C-4 position of melleumin A was confirmed in this study).

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Table 1. *Syn*- and *anti*-β-hydroxy-γ-amino acid residues and the parent natural products.

Entry	R	Absolute Configuration	Parent Natural Products	Bioactivity
1	*i*Bu	(3*S*,4*S*)-statine	pepstatins[11]	peptide mimetics
2	*i*Bu	(3*S*,4*R*)-statine	spiruchostatin[12]	potent histone deacetylase inhibitor
3	Bn	(3*S*,4*S*)-AHPPA	ahpatinins[13]	peptide mimetics
4	*c*-hexCH_2	(3*S*,4*S*)-ACHPA	unnatural[14]	peptide mimetics
5	Bn	(3*R*,4*S*)-AHPPA	hapalosin[15]	MDR-reversing activity
6	Me	(2*S*,3*S*,4*R*)-AHMPA	bleomycins 1[16,17] phleomycins[16]	antitumor antibiotic
7	*s*Bu	(3*S*,4*R*,5*S*)- isostatine	didemnine B[18]	antiviral, cytotoxic immunsuppressive
8	*i*Pr	(3*S*,4*R*)- norstatine	nordidemnines A–C[19]	antiviral, cytotoxic immunsuppressive
9	*s*Bu	(3*R*,4*S*,5*S*)-*N*,*O*-dimethyl-isostatine	dolastatin 10[20] simplostatin 1[21]	phase I/II (anticancer) cytotoxicity

ate Wnt signal inhibitory activity.[7,8] Wnt proteins, derived from the Drosophila Wingless (Wg) and the mouse Int-1 genes, play important roles in embryogenesis and carcinogenesis.[9] The Wnt signaling pathway has been identified as a proto-oncogene in mammary tumors with links to tumorgenesis such as adenomatous polyposis, colon carcinoma, medulloplastoma, tuberous sclerosis as well as lung cancer. The study of Wnt and its signaling pathways may open new avenues for disease treatment.

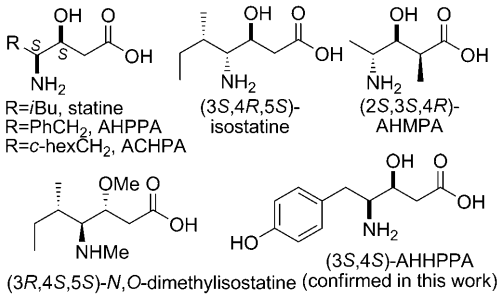


Figure 2. *Syn*- and *anti*-β-hydroxy-γ-amino acid residues found in bioactive natural products.

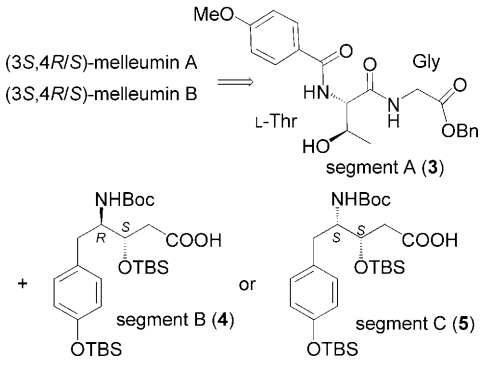
Results and Discussion

In connection with a related program,[10] we now report the first total syntheses of melleumin A, 4-*epi*-melleumin A, 4-*epi*-melleumin B, 4-*epi*-deoxymelleumin A, and 4-*epi*-deoxymelleumin B.

Melleumins A and B consist of three amino acid residues, namely *N*-acylated L-threonine, glycine, and a hitherto unknown β-hydroxy-γ-amino acid. The key to the synthesis of these molecules and of their analogues resided on a flexible approach to the β-hydroxy-γ-amino acid residue. At the time when this work began, the first challenge for synthesis was that the stereochemistry at C-4 of melleumins A and B was unknown. Because both *syn*- and *anti*-β-hydroxy-γ-amino acids are found in several natural products as relevant substructures (see Figure 2 and Table 1),[11–21] we decided first to synthesize (3*S*,4*R*)-melleumins A and B bearing an *anti*-β-hydroxy-γ-amino acid segment. The second challenge was the incorporation of the β-hydroxy-γ-amino acid segment into the target molecule, which might be complicated by side reactions such as β-elimination,[22] protecting group migration, γ-lactam formation,[12,15] as well as saponification of the ester.

Synthesis of (3*S*,4*R*)-Melleumin A (1a) and (3*S*,4*R*)-Melleumin B (2a)

As can be seen from the retrosynthetic analysis shown in Scheme 1, (3*S*,4*R/S*)-diastereomers of melleumins A and B can be synthesized from segment A (**3**) and segment B (**4**) or segment C (**5**). For the construction of the macrocyclic



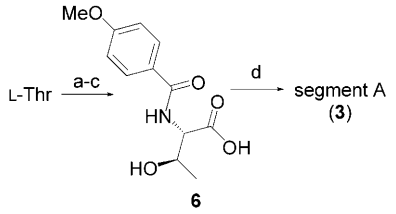
Scheme 1. Retrosynthetic analysis of (3*S*,4*R/S*)-diastereomers of melleumins A and B.

Abstract in Chinese:

本文报道 melleumin A 及其四个类似物/立体异构体的首次全合成。通过 *N*-酰基 L-苏-甘/β-羟基-γ-氨基酸偶联/大环内酰胺化策略，不但可有效地连接三个片段，且可避免外消旋化。合成 melleumin A 所需的同侧-β-羟基-γ-氨基酸系通过稍作改良的 Jouin-Castro 方法合成，而通过本实验室发展的基于苹果酰亚胺的方法，及改良的 *N*-保护基的策略，可用于灵活地合成多个反侧-β-羟基-γ-氨基酸片段，从而合成 melleumins A, B 的多个类似物。通过 melleumin A 的全合成，确证了该天然产物的结构。生物活性研究表明非天然的 4-*epi*-melleumin B 具有一定的 Wnt 信号抑制活性。

system, we elected to explore a macrolactamization instead of a macrolactonization strategy.[12]

The segment A (**3**) was synthesized from L-Thr by methyl esterification, *N*-acylation, saponification, and EDCI/HOBt-mediated coupling of *N*-acylated L-Thr **6** with glycine benzyl ester tosylic acid salt at 0 °C (Scheme 2).

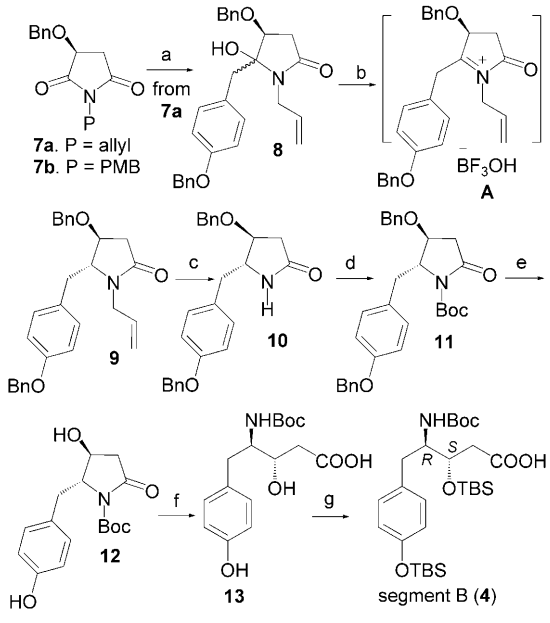


Scheme 2. The synthesis of segment A (**3**). Reagents and conditions: a) $SOCl_2$, MeOH, 100%; b) 4-methoxybenzoyl chloride, Et_3N, CH_2Cl_2, 86%; c) LiOH, THF/MeOH/H_2O, 100%; d) H-Gly-OBzl·TsOH, EDCI, HOBt, NMM, DMF, 87%.

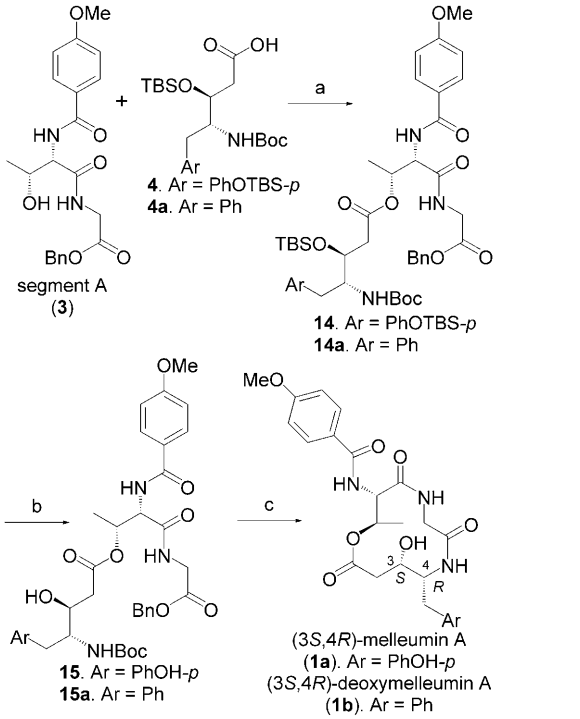
The (3*S*,4*R*)-β-hydroxy-γ-amino acid segment B (**4**) was synthesized starting from *N*-allyl (*S*)-malimide **7a**,[10] in which an allyl group[23] was selected as the *N*-protecting group.[24] The requisite malimide **7a** was prepared from (*S*)-malic acid in a three-pot manner,[10] which provided malimide **7a** with an overall yield of 77% (Scheme 3). Stepwise reductive alkylation of malimide **7a** led, regio- and diastereo-selectively, to lactam **9** with an overall yield of 79%. The origin of the observed high regioselectivity in the Grignard addition was revealed by calculation.[10c] The reductive dehydroxylation of the hemiacetal **8** was assumed to proceed via the *N*-acyliminium ion intermediate **A**.[25] While a working model was proposed to explain the highly *trans*-diastereoselective reduction of the *N*-acyliminium ion intermediate similar to **A**,[10d] a computational study is required to fully understand the origin of the stereoselectivity.

Treatment of lactam **9** with $RhCl_3$ hydrate[23] in ethanol under reflux for 2 h, followed by treatment of the resulting enamide with AcOH/H_2O under reflux for 20 h produced the desired lactam **10** with an overall yield of 77%. Reaction of lactam **10** with di-*tert*-butyl dicarbonate gave imide **11** with a yield of 90%. Catalytic transfer hydrogenolysis of **11** produced the bis-debenzylated product **12** in 85% yield, which was hydrolyzed (LiOH, THF, H_2O) to give **13**, and then to segment B (**4**) by successive *O*-silylation and hydrolysis of the concomitantly formed acid silyl ester.

Coupling of segments A (**3**) and B (**4**) using Yamaguchi's reagent[26] furnished the desired product **14** in 70% yield (Scheme 4). To avoid any complication after the macrolactamization, we decided to first remove the *O*-protecting group (TBS), expecting that the nitrogen is more nucleophilic than the oxygen, and macrolactamization would dominate over the competing macrolactonization. Indeed, after desilyation with tetrabutylammonium fluoride (60% yield), followed by *N*-deprotection with trifluoroacetic acid, and catalytic hydrogenolysis of the crude product yielded, the resulting **15** was treated with DPPA (*i*Pr_2NEt, DMF)[27] to give the macrolactamized product (3*S*,4*R*)-melleumin A (**1a**) in



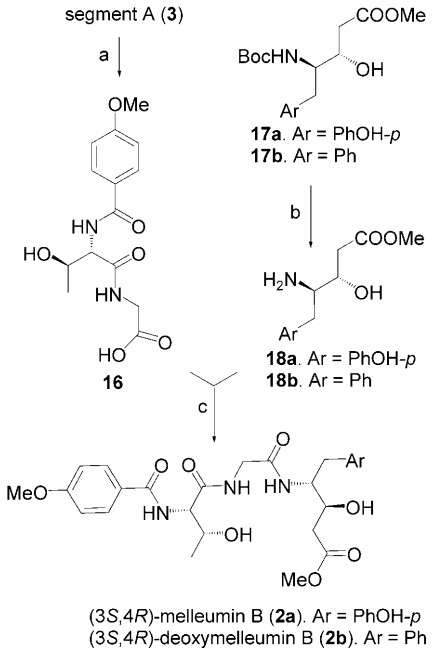
Scheme 3. The synthesis of segment B (**4**). Reagents and conditions: a) *p*-$BnOC_6H_4CH_2MgCl$, THF, 85%; b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C–RT, 91%; c) $RhCl_3{\cdot}nH_2O$, EtOH, refl. 2 h; AcOH, H_2O, refl. 20 h, 77%; d) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 90%; e) 10% Pd/C, HCO_2H, MeOH, 85%; f) LiOH, THF, H_2O, 100%; g) TBSCl, imid., DMAP, DMF; K_2CO_3, MeOH, THF, H_2O, 90%.



Scheme 4. Reagents and conditions: a) $Cl_3C_6H_2COCl$, Et_3N, DMAP, 70% (for **14**); 82% (for **14a**); b) TBAF, THF, RT, 60% (for **15**); 85% (for **15a**); c) TFA, CH_2Cl_2; H_2, 10% Pd/C, EtOH; DPPA, *i*Pr_2NEt, DMF, 30% (for **1a**); 58% (for **1b**).

an overall yield of 30% from **15**. The differences between the ^{1}H NMR and ^{13}C NMR data of (3*S*,4*R*)-melleumin A (**1a**) and those of the natural melleumin A (**1**),[6] allowed us to deduce that this compound is the 4-*epi*-melleumin A (**1a**), namely, the natural product is (3*S*,4*S*)-melleumin A (**1**).

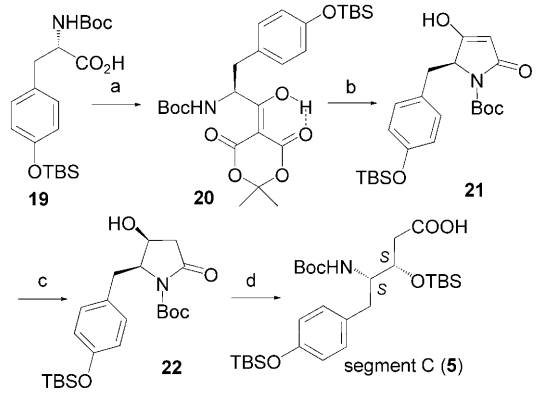
We then synthesized (3*S*,4*R*)-melleumin B (**2a**). Thus, on the one hand benzyl ester **3** was cleaved to give the corresponding acid **16** by catalytic hydrogenolysis and on the other hand, cleavage of Boc in compound **17a** (obtained by cyanide-promoted methanolysis[28] of imide **12**) with TFA gave the β-hydroxy-γ-amino acid ester **18a** (Scheme 5). Coupling of these two fragments (EDCI, HOBt, NMM, DMF) gave (3*S*,4*R*)-melleumin B (**2a**) with a yield of 60%. The difference in ^{1}H NMR and ^{13}C NMR spectra of synthetic (3*S*,4*R*)-melleumin B (**2a**) compared to those of the natural melleumin B (**2**)[6] led us to deduce that this compound is the 4-*epi*-melleumin B (**2a**), namely, the natural product is (3*S*,4*S*)-melleumin B (**2**).



Scheme 5. The synthesis of (3*S*,4*R*)-melleumin B (**2a**) and (3*S*,4*R*)-deoxymelleumin B (**2b**). Reagents and conditions: a) H_2, 10% Pd/C, EtOH, 80%; b) TFA, CH_2Cl_2, 0°C, 82%; c) EDCI, HOBt, NMM, DMF, 60% (for **2a**); 54% (for **2b**).

Synthesis of Melleumin A (1)

To confirm the stereochemistry at C-4 of melleumin A, we decided to synthesize (3*S*,4*S*)-melleumin A (**1**). The requisite (3*S*,4*S*)-*syn*-β-hydroxy-γ-amino acid **5** was synthesized by the method of Jouin and Castro[29] with minor modification. Thus the phenol hydroxyl group of *N*-Boc-(*S*)-tyrosine was first protected as silyl ether **19** (Scheme 6). Condensation of **19** with Meldrum's acid followed by refluxing the product in ethyl acetate led to the desired tetramic acid **21**. Reduction of **21** with sodium borohydride in the presence of 10% HOAc at −10°C gave *cis*-**22** as the only observable diastereomer in an overall yield of 50% from **19**. Hydrolysis of the imide **22** under basic conditions (LiOH, THF, H_2O), followed by *O*-silylation (TBSCl, imid., DMAP, DMF), and treatment of the resulting silylated product with aqueous K_2CO_3 produced the desired segment C (**5**).

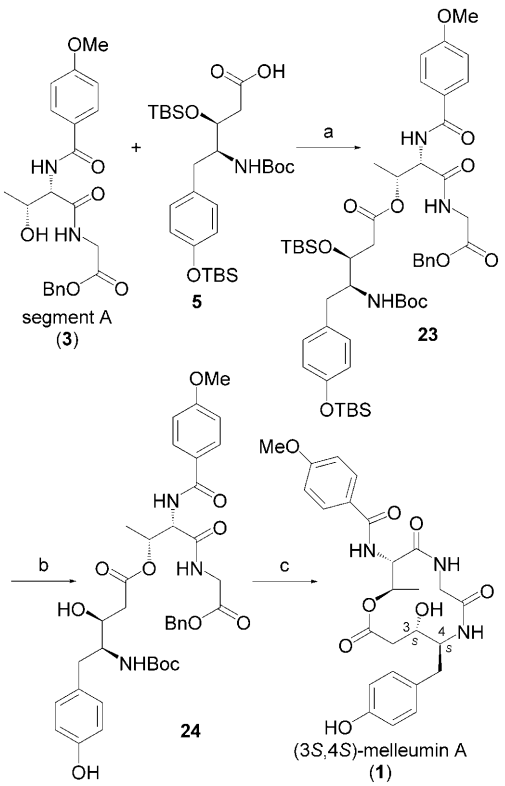


Scheme 6. Synthesis of segment C (**5**). Reagents and conditions: a) Meldrum's acid, *iso*-propyl chloroformate, DMAP, CH_2Cl_2; b) EtOAc, refl. 1 h; c) $NaBH_4$, CH_2Cl_2, CH_3COOH, −10°C, two steps 50%; d) LiOH, THF, H_2O; TBSCl, imid., DMAP, DMF; K_2CO_3, MeOH, THF, H_2O, 85%.

Coupling of segment A (**3**) with segment C (**5**) using Yamaguchi's reagent[26] produced the desired product **23** in 70% yield (Scheme 7). *O*-Desilylation with tetrabutylammonium fluoride yielded **24** in 60% yield. *N*-Deprotection of **24** with trifluoroacetic acid followed by catalytic hydrogenolysis and macrolactamization (DPPA, *i*Pr$_2$NEt, DMF)[27] gave (3*S*,4*S*)-melleumin A (**1**) in an overall yield of 30% from **24**. The ^{1}H and ^{13}C NMR spectral data of our synthetic material are identical with those of the natural product.[6] The optical rotation of synthetic (3*S*,4*S*)-melleumin A (**1**) shows the same sense as the natural one {$[\alpha]_D^{20} = +43.3$ (c = 0.15, CH_3OH); $[\alpha]_D^{20} = +44.1$ (c = 1.17, CH_3OH) lit.[6] $[\alpha]_D^{20} = +27$ (c = 0.15, CH_3OH)}. The difference in the values is likely a result of only a minute amount of the natural product (only 1.6 mg) being available for measuring the optical rotation.

At this point in time, Ishibashi et al. reported the total synthesis of melleumin B (**2**),[7] and they deduced the absolute stereochemistry of melleumin A (**1**) to be (3*S*,4*S*). Our synthesis of (3*S*,4*S*)-melleumin A (**1**) confirmed this assignment.

The study by Ishibashi and co-workers also demonstrated that while melleumins A (**1**) and B (**2**) are inactive, the 10*R*-,[7] and 3*R*-epimers, as well as the (3*R*,4*S*,10*R*,11*R*)-epimer[8] of melleumin B (**2**) show moderate Wnt signal inhibitory activity. We decided to synthesize the deoxy analogues of (3*S*,4*R*)-melleumins A (**1b**) and B (**2b**), and test their Wnt signal inhibitory activity.



Scheme 7. Reagents and conditions: a) **3**, $Cl_3C_6H_2COCl$, Et_3N, DMAP, 70%; b) TBAF, THF, RT, 60%; c) TFA, CH_2Cl_2; H_2, 10% Pd/C, EtOH; DPPA, iPr_2NEt, DMF, 30%.

Synthesis of (3*S*,4*R*)-Deoxymelleumin A (1b) and (3*S*,4*R*)-Deoxymelleumin B (2b)

For the synthesis of (3*S*,4*R*)-deoxymelleumins A and B, the β-hydroxy-γ-amino acid segment **4a** was synthesized[30] in the similar way as described for the synthesis of **4** (Scheme 3), except (*S*)-malimide **7b**[10] was used as the building block, and ceric ammonium nitrate (CAN)[31] was used to cleave the *N*-protecting group (PMB). Coupling of segment **4a** with segment B (**3**) furnished the desired product **14a** in 82% yield (Scheme 4). *O*-Desilylation with tetrabutylammonium fluoride yielded **15a** in 85% yield. Cleavage of both *O*- and *N*-protecting groups (Bn; Boc) was achieved by successive treatment with trifluoroacetic acid and catalytic hydrogenolysis, which after a simple filtration to give the deprotected compound, which was subjected to DPPA-mediated macrolactamization to give (3*S*,4*R*)-deoxymelleumin A (**1b**) with an overall yield of 58% from **15a**.

Following the sequence developed for the synthesis of (3*S*,4*R*)-melleumin B (**2a**), and using (3*S*,4*R*)-**17a** as the β-hydroxy-γ-amino acid segment, (3*S*,4*R*)-deoxymelleumin B (**2b**) was synthesized with similar efficiency (Scheme 5).

Wnt Signal Inhibitory Activity

We next examined the inhibitory effect of the synthesized compounds on Wnt signaling by using the luciferase reporter gene TOP-Flash,[32] a β-catenin-responsive reporter plasmid with multiple TCF-binding sites (CCTTTGATC). As a control, we used FOP-Flash that has eight mutated TCF-binding sites (CCTTTGGCC) and has no response to Wnt signaling, as previously described.[33] Briefly, HEK293T cells were cultured in 60 mm plates at 60% confluency and each plate was transfected with 0.5 μg of TOP-Flash luciferase reporter plasmid. At 16 h posttransfection, three plates were treated with 30 μM of each drug; 20 h later, cells were harvested and luciferase activity was determined. As shown in Figure 3, 4-*epi*-melleumin B (**2a**) exhibited a moderate inhibition on the reporter gene activity, with a reduction of approximately 23% compared to that from the untreated cells (Ctrl).

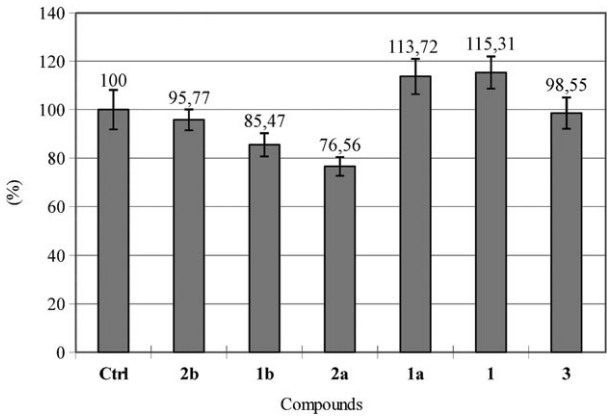


Figure 3. TOP/FOP-Flash reporter activation ratio of Melleumin A and four derivatives of Melleumins A and B. TOPFLASH and FOPFLASH = two commercial products of affinity purified DNA. TCF = Transfection grade T cell factor. HEK293T cells were transfected with Topflash or Fopflash luciferase reporter and three plates were then treated with 30 μM of each drug for 20 h before harvest. The experiment was repeated three times. The luciferase activity from the untreated cells (Ctrl) was defined as 100%.

Since few small molecules are known as Wnt signal inhibitors, we believe that these results are interesting for the identification of Wnt signal inhibitors from natural products. The novel derivative of the melleumin group may offer a potential candidate as a small-molecule inhibitor for Wnt signaling.

Conclusions

In summary, starting from L-tyrosine, we accomplished the first total synthesis of melleumin A (**1**) in 8 steps with an overall yield of 4.6%, which allowed us to confirm the full absolute configuration of natural melleumin A (**1**). By using our malimide-based synthetic methodology, the asymmetric synthesis of 4-*epi*-deoxymelleumin A (**1b**) and 4-*epi*-deoxymelleumin B (**2b**) were also achieved in 10 and 8 steps from (*S*)-malimide **7b** with overall yields of 19.1% and 31.2%, respectively. Extending the scope of this methodology by

using the allyl group as imide/amide *N*-protecting group allowed the asymmetric synthesis of 4-*epi*-melleumins A (**1a**) and B (**2a**) in 9 and 7 steps from (*S*)-malimide **7a** with overall yields of 5% and 14%, respectively. Compared with the method used for the synthesis of the β-hydroxy-γ-amino acid segment[7,8] and the strategy for the synthesis of melleumin B,[7,8] our approaches are both highly diastereoselective and free of epimerization. The Wnt signal inhibitory activity exhibited by 4-*epi*-melleumin B (**2a**) demonstrates a potential value of our flexible and epimerization-free, yet highly diastereoselective, method for developing more active melleumin A and B analogues.

Experimental Section

General

Optical rotations were recorded on a Perkin–Elmer 341 automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer. ^{1}H NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection), HRFABMS spectra were recorded by a Bruker APEX-FTMS apparatus. Elemental analyses were performed using a Vario RL analyzer. Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected.

Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide. Dimethylformamide was distilled from calcium hydride. Silica gel (Zhifu, 300–400 mesh) from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture.

Syntheses

16: 2-((2*S*,3*R*)-3-Hydroxy-2-(4-methoxybenzamido)butanamido)acetic acid: Compound **3** (110 mg, 0.275 mmol) was dissolved in EtOH (6 mL), and hydrogenated under an atmosphere of H_2 with 10% Pd/C (42 mg). After stirring overnight at RT, the suspension was filtered through a short pad of Celite. After being concentrated in vacuum, the crude product was purified by flash chromatography (EtOAc/PE 4:1, a little acetic acid was added) to afford **16** as a colourless liquid (70 mg, yield 82%). $[\alpha]_D^{20} = +16.6$ ($c = 0.5$ in CH_3OH); IR (film): $\tilde{\nu} = 3326, 2972, 1726, 1641, 1606, 1503, 1257, 1181, 1022\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (brs, 3H), 2.05 (s, 1H), 3.64 (s, 3H), 3.92 (m, 2H), 4.35 (m, 1H), 4.67 (m, 1H), 6.76 (m, 2H), 7.64–7.86 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.7, 41.5, 49.4, 55.4, 67.6, 113.8, 125.2, 129.3, 162.6, 168.2, 171.8, 172.6$ ppm; MS (ESI): *m*/*z* (%): 333 (100) $[M+Na^+]$, 349 (13.5) $[M+K^+]$; HRESIMS calcd for $[C_{14}H_{18}N_2O_6+Na]^+$: 333.1057; found: 333.1059.

17a: (3*S*,4*R*)-methyl 4-(tert-butoxycarbonylamino)-3-hydroxy-5-(4-hydroxyphenyl) pentanoate: THF (5 mL) and MeOH (5 mL) were added to a mixture of compound **12** (418 mg, 1.36 mmol) and KCN (9 mg, 0.14 mmol). After stirring for 60 h at RT, the volatile was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE 1:5) to afford **17a** as white crystals (322 mg, yield 70%). M.p. 149 °C; $[\alpha]_D^{20} = +13.6$ ($c = 1.0$ in CH_3OH); IR (film): $\tilde{\nu} = 3400, 2919, 1738, 1651, 1556, 1384, 1253, 1161\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.37 (s, 9H), 2.50 (dd, $J = 8.8, 16.4$ Hz, 1H), 2.57 (brd, $J = 15.6$ Hz, 1H), 2.74 (dd, $J = 8.0, 14.0$ Hz, 1H), 2.87 (dd, $J = 4.0, 14.0$ Hz, 1H), 3.65 (brs, 1H), 3.71 (s, 3H), 3.81 (brs, 1H), 3.98 (brs, 1H), 4.61 (d, $J = 8.0$ Hz, 1H), 5.83 (brs, 1H), 6.73 (d, $J = 7.6$ Hz, 2H), 7.05 ppm (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3, 35.1, 38.0, 52.0, 55.5, 70.1, 79.9, 115.4, 129.2, 130.5, 154.6, 156.0, 173.4$ ppm; MS (ESI): *m*/*z* (%): 362 (100) $[M+Na^+]$; elemental analysis: calcd (%) for $C_{17}H_{25}NO_6$: C 60.16, H 7.42, N 4.13; found: C 60.43, H 7.67, N 3.97.

2a: 4-*epi*-Melleumin B: TFA (0.40 mL) was added dropwise to a cooled (0 °C) solution of compound **17a** (30 mg, 0.088 mmol) in CH_2Cl_2 (1.5 mL). After stirring at RT for 2 h, the reaction mixture was concentrated under reduced pressure to afford compound **18a**, which was used directly for the next step without further purification. To a cooled (−20 °C) solution of compound **16** (33 mg, 0.106 mmol) in DMF (1 mL) in the presence of HOBt (20 mg, 0.150 mmol) was added EDCI (19 mg, 0.097 mmol). The resulting mixture was stirred at −20 °C for 0.5 h. To the resulting solution was added dropwise compound **18a** in DMF (1 mL) at 0 °C in the presence of NMM (24 μL). After stirring at 0 °C for 5 h and then at RT overnight, the reaction mixture was diluted with ethyl acetate (30 mL) and washed successively with 1 N HCl, 10% Na_2CO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/methanol 20:1) to give 4-*epi*-melleumin B (**2a**) as a colourless oil (16 mg, yield, 60%). $[\alpha]_D^{20} = +10.0$ ($c = 0.3$ in CH_3OH); IR (film): $\tilde{\nu} = 3339, 2918, 1727, 1642, 1595, 1536, 1498, 1258, 1123, 1031\ cm^{-1}$; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.12$ (d, $J = 6.4$ Hz, 3H), 2.19 (dd, $J = 9.6, 16.4$ Hz, 1H), 2.44 (dd, $J = 9.2, 13.6$ Hz, 1H), 2.55 (m, 1H), 2.90 (dd, $J = 2.8, 12.4$ Hz, 1H), 3.54 (s, 3H), 3.59 (m, 1H), 3.61 (m, 1H), 3.76 (m, 2H), 3.82 (s, 3H), 4.07 (m, 1H), 4.29 (dd, $J = 4.8, 7.2$ Hz, 1H), 5.04 (d, $J = 6.4$ Hz, 1H), 5.09 (d, $J = 6.4$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 9.6$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 2H), 7.96 (d, $J = 7.6$ Hz, 1H), 8.24 (brt, $J = 5.6$ Hz, 1H), 9.09 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 20.0, 34.9, 38.9, 42.2, 51.1, 55.3, 55.4, 60.0, 66.6, 69.8, 113.5, 114.8, 126.1, 129.2, 129.5, 129.9, 155.4, 161.8, 166.4, 168.4, 170.8, 172.0$ ppm; MS (ESI): *m*/*z* (%): 554 (100) $[M+Na^+]$; HRESIMS calcd for $[C_{26}H_{33}N_3O_9+H]^+$: 532.2290; found: 532.2298.

22: (4*S*,5*S*)-*tert*-Butyl 5-(4-(*tert*-Butyldimethylsilyloxy)benzyl)-4-hydroxy-2-oxopyrrolidine-1-carboxylate: Meldrum's acid (200 mg, 1.40 mmol) and DMAP (386 mg, 3.16 mmol) were added to a stirred solution of **19** (500 mg, 1.27 mmol) in dry methylene chloride (15 mL) at 0 °C under nitrogen. A solution of isopropyl chloroformate in toluene (1.8 mL, 1.90 mmol) was then added dropwise over 1 h, and the reaction mixture was stirred for 3 h at 0 °C. The mixture was washed twice with 15% $KHSO_4$ (5 mL), the organic layer was dried over Na_2SO_4, and the solution was concentrated to afford the crude acylated Meldrum's acid. This material was then refluxed in ethyl acetate (15 mL) for 1 h, and the solution was concentrated to afford the crude product. The crude product was dissolved in a mixture of CH_2Cl_2 (20 mL) and AcOH (2.0 mL), then cooled to −10 °C and stirred vigorously while being treated in portions with $NaBH_4$ (143 mg, 3.8 mmol). The mixture was then stirred for 4 h at 0 °C. Cooled saturated $NaHCO_3$ (5 mL) was added to the mixture. The resulting mixture was extracted with CH_2Cl_2, the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum. The crude product was purified by chromatography on silica gel (EtOAc/PE = 1:5) to give (4*S*,5*S*)-**22** (266 mg, 50%) as white crystals. M.p. 148 °C; $[\alpha]_D^{20} = +22.1$ ($c = 1.7$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3458, 2957, 2930, 2858, 1777, 1510, 1256, 1157\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.17$ (s, 6H), 0.96 (s, 9H), 1.51 (s, 9H), 2.35 (dd, $J = 8.4, 17.2$ Hz, 1H), 2.57 (dd, $J = 7.6, 17.2$ Hz, 1H), 3.07 (d, $J = 6.0$ Hz, 2H), 4.38 (dd, $J = 6.0, 6.9$ Hz, 1H), 4.48 (ddd, $J = 6.9, 7.6, 8.4$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 2H), 7.14 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5, 18.1, 25.6, 28.0, 33.0, 40.1, 62.6, 65.6, 83.3, 120.1, 130.1, 130.7, 149.8, 154.3, 171.7$ ppm; MS (ESI): *m*/*z* (%): 422 (100) $[M+H^+]$; elemental analysis: calcd (%) for $C_{22}H_{35}NO_5Si$: C 62.67, H 8.37, N 3.32; found: C 62.91, H 8.77, N 3.08.

5: (3*S*,4*S*)-4-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-(4-(*tert*-butyldi-methylsilyloxy)phenyl)pentanoic acid: Lithium hydroxide monohydrate (48 mg, 1.14 mmol) was added to a solution of compound **22** (240 mg, 0.57 mmol) in a mixed solvent (THF/H_2O v/v = 3:1, 12 mL) in one portion at 0 °C. After stirring at the same temperature for 1 h, the reaction mixture was diluted with ice water (10 mL), then acidified to pH 2–3 with 1 M HCl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to give a colorless oil, which was used in the following reaction without further purification. The crude product, TBSCl (214 mg, 1.43 mmol), imidazole (155 mg, 2.28 mmol) and DMAP (10 mg, 0.09 mmol) in DMF (7 mL) was stirred 48 h at RT. The resulting

mixture was diluted with water (40 mL) and extracted with ether (5× 20 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. After concentration under reduced pressure, the residue was dissolved in a mixed solvent (MeOH/THF v/v = 3:1, 12 mL). To the solution K_2CO_3 (236 mg, 1.71 mmol) was added in one portion at 0 °C. After stirring at RT for 30 min, the reaction mixture was concentrated under reduced pressure, diluted with brine (15 mL), then acidified to pH 4–5 with 1 M $KHSO_4$. The mixture was extracted with ether (5×10 mL). The combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4 and filtered. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:10) to afford **5** (268 mg, yield 85%) as a pale yellow solid. M.p. 179 °C; $[\alpha]_D^{20} = -17.8$ (c = 1.9 in $CHCl_3$); IR (film): $\tilde{\nu}$ = 3320, 2950, 2930, 1710, 1510, 1408, 1370, 1260, 1170, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) arising from the presence of two rotamers, signals in ^1H NMR spectrum were broadened: δ = 0.09 (s, 3H), 0.13 (s, 3H), 0.16 (s, 6H), 0.93 (s, 9H), 0.97 (s, 9H), 1.27–1.35 (m, 9H), 2.47–2.67 (3H, complex), 2.82 (1H, complex), 3.76–4.66 (2H, complex), 5.79 (brs, 1H), 6.75 (d, J = 8.3 Hz, 2H), 7.05 ppm (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.5, −4.3, 18.1, 18.2, 25.7, 25.9, 28.1, 28.3, 29.7, 36.7, 37.6, 38.9, 40.0, 55.3, 57.6, 70.1, 79.8, 80.3, 120.0, 129.9, 130.1, 130.6, 131.4, 154.1, 156.2, 156.7, 174.9, 175.6 ppm; MS (ESI): m/z (%): 576 (100) $[M+Na^+]$; elemental analysis: calcd (%) for $C_{28}H_{51}NO_6Si_2$: C 60.72, H 9.28, N 2.53; found: C 60.63, H 9.55, N 2.35.

23: (3*S*,4*S*)-((2*R*,3*S*)-4-(2-(Benzyloxy)-2-oxo-ethylamino)-3-(4-methoxybenzamido)-4-oxobutan-2-yl)-4-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-(4-(*tert*-butyldimethylsilyloxy)phenyl)pentanoate: Triethylamine (110 μL, 0.79 mmol) and 2,4,6-trichlorobenzoyl chloride (110 μL, 0.66 mmol) were added sequentially to a solution of acid **5** (364 mg, 0.66 mmol) in anhydrous THF (3 mL). After stirring at RT for 40 min, a solution of compound **3** (369 mg, 0.92 mmol) and DMAP (160 mg, 1.32 mmol) in anhydrous THF (9 mL) was added. The reaction mixture was stirred at RT for 18 h and then quenched with aqueous NH_4Cl. Volatiles were removed under reduced pressure and the remaining aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/PE 1:2) afforded **23** (433 mg, yield 70%) as a colourless oil. $[\alpha]_D^{20} = -6.9$ (c = 1.7 in $CHCl_3$); IR (film): $\tilde{\nu}$ = 3350, 2950, 2930, 1740, 1690, 1640, 1610, 1509, 1390, 1255, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3H), 0.10 (s, 3H), 0.15 (s, 6H), 0.93 (s, 9H), 0.96 (s, 9H), 1.25 (s, 9H), 1.30 (d, J = 6.4 Hz, 3H), 2.34 (dd, J = 2.8, 14.0 Hz, 1H), 2.66 (m, 2H), 2.72 (m, 1H), 3.85 (s, 3H), 4.00–4.05 (m, 3H), 4.11 (dd, J = 5.4, 18.7 Hz, 1H), 4.77 (brd, J = 10.1 Hz, 1H), 4.90 (m, 1H), 5.14 (s, 2H), 5.50 (brs, 1H), 6.70 (d, J = 8.2 Hz, 2H), 6.86–7.05 (m, 5H), 7.30–7.36 (m, 5H), 7.69–7.88 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8, −4.5, −4.2, 16.2, 18.1, 18.2, 25.7, 25.9, 28.2, 38.6, 40.3, 41.4, 54.6, 55.4, 56.9, 67.0, 70.2, 70.6, 79.4, 113.7, 113.8, 120.1, 125.6, 128.3, 128.4, 128.5, 128.6, 129.5, 129.9, 130.7, 135.2, 154.2, 156.0, 162.5, 167.5, 169.1, 169.4, 169.5 ppm; MS (ESI): m/z (%): 958 (100) $[M+Na^+]$; HRESIMS calcd for $[C_{49}H_{73}N_3O_{11}Si_2+Na]^+$: 958.4676; found: 958.4685.

24: (3*S*,4*S*)-((2*R*,3*S*)-4-(2-(Benzyloxy)-2-oxo-ethylamino)-3-(4-methoxybenzamido)-4-oxobutan-2-yl)-4-(*tert*-butoxycarbonyl)-3-hydroxy-5-(4-hydroxyphenyl)pentanoate: TBAF (1 M in THF, 2.0 mL) was added to a solution of compound **23** (310 mg, 0.332 mmol) in anhydrous THF (4.0 mL) at 0 °C. After stirring at RT for 20 h, the reaction mixture was diluted with ethyl acetate (40 mL), washed successively with water (2 mL), brine (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to afford **24** (141 mg, yield 60%) as a colourless oil. $[\alpha]_D^{20}$ = +2.6 (c = 1.7 in MeOH); IR (film): $\tilde{\nu}$ = 3350, 2975, 2926, 1740, 1642, 1609, 1520, 1501, 1260, 1176 cm^{-1}; ^1H NMR (400 MHz, MeOD): δ = 1.26 (d, J = 6.4 Hz, 3H), 1.29 (s, 9H), 2.40 (dd, J = 8.0, 15.2 Hz, 1H), 2.47 (dd, J = 5.4, 15.2 Hz, 1H), 2.57 (dd, J = 8.8, 13.7 Hz, 1H), 2.72 (dd, J = 6.3, 13.7 Hz, 1H), 3.72 (m, 1H), 3.81 (s, 3H), 3.96 (d, J = 8.2 Hz, 2H), 4.25 (m, 1H), 4.79 (d, J = 4.9 Hz, 1H), 5.12 (s, 2H), 5.38 (m, 1H), 6.15 (d, J = 9.7 Hz, 1H), 6.63 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 7.25–7.33 (m, 5H), 7.81 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, MeOD): δ = 17.3, 28.8, 38.1, 40.5, 42.3, 56.0, 57.2, 58.4, 68.0, 69.9, 71.7, 80.2, 114.9, 116.1, 126.9, 129.3, 129.6, 130.6, 131.3, 137.1, 157.0, 164.4, 171.0, 172.6 ppm; MS (ESI): m/z (%): 730 (100) $[M+Na^+]$; HRESIMS calcd for $[C_{37}H_{45}N_3O_{11}+H]^+$: 708.3127; found: 708.3118.

1: Melleumin A: TFA (1.6 mL) was added dropwise to an ice-cold solution of compound **24** (120 mg, 0.17 mmol) in CH_2Cl_2 (6 mL). After stirring at 0 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOH (6 mL), and hydrogenated under an atmosphere of H_2 using 10% Pd/C (120 mg) at RT for 2.5 h. The reaction mixture was flash-filtered through a short column and the filtrate evaporated under reduced pressure. The residue was dissolved in DMF (120 mL). To this cooled (0 °C) solution diphenylphosphoryl azide (110 μL, 0.51 mmol) and *di-iso*-propylethylamine (170 μL, 1.02 mmol) were added dropwise. After stirring at 0 °C for 5 h and then at RT for 2 d, the reaction mixture was diluted with ethyl acetate (800 mL) washed with water (5×100 mL), brine (2×60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give melleumin A (**1**) (25 mg, yield 30%) as a pale yellow amorphous solid. $[\alpha]_D^{20}$ = +44.1 (c = 1.17 in CH_3OH) {lit.[6] $[\alpha]_D^{26}$ = +27 (c = 0.15 in CH_3OH)}; IR (film): $\tilde{\nu}$ = 3350, 2920, 2855, 1724, 1657, 1615, 1502, 1360, 1255, 1179, 1059 cm^{-1}; ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.21 (d, J = 6.3 Hz, 3H), 2.37 (m, 1H), 2.56 (m, 1H), 2.59 (m, 1H), 2.87 (dd, J = 2.1, 14.3 Hz, 1H), 3.48 (m, 2H), 3.75 (m, 1H), 3.82 (s, 3H), 4.13 (m, 1H), 5.01 (dd, J = 3.5, 8.9 Hz, 1H), 5.45 (d, J = 4.4 Hz, 1H), 5.65 (qd, J = 3.6, 6.3 Hz, 1H), 6.20 (d, J = 10.0 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.9 Hz, 1H), 8.52 (brt, J = 5.6 Hz, 1H), 9.16 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 16.2, 30.8, 38.7, 44.4, 54.8, 54.9, 55.4, 69.6, 71.7, 113.5, 115.0, 126.0, 129.3, 129.4, 129.6, 155.5, 161.8, 166.6, 169.1, 169.2, 170.8 ppm; MS (ESI): m/z (%): 522 (100) $[M+Na^+]$; HRESIMS calcd for $[C_{25}H_{29}N_3O_8+H]^+$: 500.2027; found: 500.2022.

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