ORIGINAL ARTICLE

Stereoselective total synthesis of garsubellin A

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The stereoselective total synthesis of garsubellin A is described. The total synthesis was achieved through the stereoselective construction of a bicyclo[3.3.1]nonane derivative via a three-step sequence: intramolecular cyclopropanation, formation of a germinal dimethyl group, and regioselective ring opening of cyclopropane. To complete the total synthesis of garsubellin A, chemo- and stereoselective hydrogenation to generate the C8 stereogenic center is followed by the formation of the fused tetrahydrofuran ring by a regioselective epoxide-opening reaction with C3 ketone, and finally cross metathesis to construct two prenyl groups.

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INTRODUCTION

Garsubellin A, which was originally isolated from the wood of *Garcia subelliptica* by Fukuyama *et al.*¹ has been identified as a potent inducer of choline acetyltransferase, which is a key enzyme for the biosynthesis of an important neurotransmitter, acetylcholine. Atrophy of cholinergic neurons and corresponding deficiencies in acetylcholine are believed to be associated with the dementia of Alzheimer disease. Therefore, garsubellin A is surmised to be a promising compound for Alzheimer's therapeutics.

Garsubellin A possesses a trioxygenated bicyclo[3.3.1]nonane skeleton with a gem-dimethyl group at C9, prenyl groups at C2 and C8, a fused tetrahydrofuran ring with stereogenic centers at C4 and C18, and an isobutyryl group at the bridgehead, C6.

The fascinating structural features and biological activity of garsubellin A have made it an attractive synthetic target; accordingly, many synthetic studies^{2,3} including two total syntheses^{4,5} and one formal synthesis⁶ have been reported this far. As a component of the collective total synthesis of polycyclic polyprenylated acylphloroglucinols (PPAPs), the total synthesis of garsubellin A via a new approach that can be made to be enantioselective is herein reported.

RESULTS AND DISCUSSION

The PPAP family features complex and diverse structures that comprise a highly oxygenated and densely substituted bicyclo[3.3.1]nonane (Figure 1) or bicyclo[3.2.1]octane core with prenyl or geranyl side chains, among others.⁷ The family currently includes more than 110 compounds and the number of members is still increasing. Some PPAPs feature the same scaffold-bearing different substituents and show diverse biological activities. For example, hyperforin shows

antidepressant and antitumor activities,⁸ whereas nemorosone exhibits antiHIV and antitumor activities.⁹

Therefore, we envisioned that the development of a synthetic strategy for the bicyclo[3.3.1]nonane derivative would facilitate structure–activity relationship studies on PPAPs, with the potential of the discovery of new drug candidates. Some PPAPs, for example, the three compounds shown in Figure 1 have the same bicyclo[3.3.1]nonane core with stereogenic centers and oxygen functionalities incorporated at the same positions. Considering these structural

Figure 1 Structures of hyperforin, nemorosone, garsubellin A and bicyclo[3.3.1]nonane skeleton.

features and the hidden symmetry of the structure, we developed a new approach to bicyclo[3.3.1]nonane derivative **4** that is useful for the synthesis of PPAPs in general; accordingly, we recently reported the stereoselective total synthesis of nemorosone.¹⁰

As shown in Scheme 1, our approach to bicyclo[3.3.1]nonane derivative **4** comprises a three-step sequence: intramolecular cyclopropanation (IMCP) of **1** (step I),^{11,12} followed by stereoselective alkylation of the cyclopropane **2** (step II) and finally, regioselective ring opening of the cyclopropane moiety in **3** (step III). As the desymmetrization occurs in step I, the reaction could be made enantioselective by using a chiral catalyst. Step II would allow the introduction of two different substituents at the C9 position by stereoselective alkylation from the less-hindered convex face to generate the all-carbon quaternary stereogenic center that is required for the synthesis of hyperforin (Figure 1). Step III leads to **4** because the electron-donating methoxy group on cyclopropane and the electron-withdrawing ketone moiety cooperatively enhance regioselective ring opening under acidic conditions.

α -Diazo- β -ketone **1**, which is required for IMCP, was prepared from 2,6-dimethoxybenzoic acid methyl ester **5** in seven steps (Scheme 2). Compound **5** was subjected to Birch reduction followed by a one-pot reaction with allylbromide, reduction with lithium aluminum hydride and protection of the primary hydroxyl group as a TIPS ether to afford **6**. Selective dihydroxylation of **6** and subsequent 1,2-diol cleavage resulted in aldehyde **7**, which was converted to **8** by a one-pot methylation¹³-Oppenauer oxidation¹⁴ protocol developed by

our group. Finally, methyl ketone **8** was successfully converted to **1** in a one-pot reaction with an 85% yield.¹⁰

IMCP of **1** afforded cyclopropane **2** (Scheme 3), which was dimethylated and treated with acid to afford diketone **9** as a single isomer (58% yield over three steps). Conversion of **9** to the corresponding enol triflate and subsequent palladium-mediated carbonylation afforded **10**. Chemo- and stereoselective hydrogenation of **10** with Crabtree's catalyst (0.5 mol%),¹⁵ which is thought to proceed via the directing effect of the internal methoxyalkene, afforded **11** as a single isomer. Reduction of **11** with DIBAL-H, subsequent selective acetylation of the primary hydroxyl and oxidation of the secondary hydroxyl afforded **12**. Subsequent allylic oxidation at the C4 position of **12** successfully afforded **13**;¹⁶ this was followed by removal of the acetate, formation of the triflate and a coupling reaction with divinylcuprate to afford **14**.

Compound **14** was predicted to be a key intermediate for the total synthesis of garsubellin A. Therefore, further treatment of **14** toward the total synthesis of garsubellin A was investigated. The fused tetrahydrofuran ring in garsubellin A was envisioned to form via an internal reaction of the epoxide and ketone group in **15** (Scheme 4). Compound **15** was predicted to be obtained from the regioselective prenylation and subsequent chemoselective epoxidation of **14**. We observed that no allylation occurred at the C2 position of **14** under the conditions described in Scheme 4 during our research on the total synthesis of nemorosone; additionally, epoxidation of the prenyl group was expected to be faster than that of the C8 allyl group

Scheme 1 Our approach to bicyclo[3.3.1]nonane derivative **4** by a three-step sequence: intramolecular cyclopropanation, construction of a germinal dimethyl group and regioselective ring opening of cyclopropane.

Scheme 2 Preparation of **1** (Uwamori *et al.*¹⁰).

Scheme 3 Preparation of **14** (Uwamori *et al.*¹⁰).

Scheme 4 Total synthesis of garsubellin A.

because the prenol group includes a more electron-rich trisubstituted alkene.

Indeed, prenylation of **14** proceeded only at the C4 position and subsequent epoxidation with mCPBA occurred only at the prenol group to afford **15** as an inseparable mixture of diastereomers (*dr* = 1.5: 1). The formation of the tetrahydrofuran ring by an internal reaction of **15** was examined under varying conditions. The reaction of **15** with TMSCl afforded **16** as a separable mixture of isomers (*dr* = 6.3: 1),⁶ and the major isomer was identified as the desired compound, **16**, by NMR analysis. The different isomer ratios of **15** and **16** were attributed to the different rate of cyclization of the diastereomers of **15**. To enable allylation at the C2 position of **16**, the C19 tertiary hydroxyl of **16** was protected as a TMS ether, and subsequent allylation using the conditions that were optimized during the total synthesis of nemorosone^{10,17} quantitatively afforded **17**. All the silyl groups of **17** were removed by TBAF and subsequent Dess–Martin oxidation gave aldehyde **18**. The reaction of **18** with isopropylmagnesium chloride reduced the C1 ketone, but the reaction with the corresponding cerium reagent successfully afforded the desired product without forming the reduced product.¹⁸ Subsequent Dess–Martin oxidation and cross metathesis;¹⁹ with Grubbs II catalyst and 2-methylpropene at 60 °C in a sealed tube afforded the final product, which spectroscopically matched garsubellin A in all respects (that is, ¹H- and ¹³C-NMR, IR and HRMS),² thereby confirming the total synthesis of garsubellin A.

In summary, we accomplished the total synthesis of garsubellin A via a bicyclo[3.3.1]nonane derivative prepared by a three-step sequence: IMCP, construction of a germinal dimethyl group and subsequent regioselective ring opening of cyclopropane. Further treatment to obtain garsubellin A from the versatile intermediate includes chemo- and stereo-selective hydrogenation to generate the

C8 stereogenic center and formation of the fused tetrahydrofuran ring via a regioselective epoxide-opening reaction with the C3 ketone. The IMCP can be enantioselective by using a chiral catalyst. Therefore, the catalytic asymmetric IMCP of **1** and its derivatives are now under investigation, and the results will be reported in due course.

EXPERIMENTAL SECTION

General methods

¹H and ¹³C NMR spectra were recorded on 400 MHz or 500 MHz spectrometer. ¹H and ¹³C chemical shifts are reported in p.p.m. downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; brs, broad; Cq, quaternary carbon; CH, methine carbon; CH₂, methylene carbon; CH₃, methyl carbon. IR spectra were recorded on a FT/IR spectrometer. To confirm the ¹H and ¹³C NMR peak assignments (Supporting Information) and carbon multiplicities, 1H NMR, BCM, DEPT, COSY, HMQC, HMBC and NOESY methods were used. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by TLC carried out on 0.25 mm silica gel plates using UV light as visualizing agent, and phosphomolybdic acid and heat as developing agents. Silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative TLC (PTLC) separations were carried out on self-made 0.3 mm silica gel plates. THF and Et₂O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. MeOH was distilled with a small amount of magnesium and **12**. Benzene and MeCN were distilled from CaH₂, and all commercially available reagents were used without further purification. Optical rotations were measured on a polarimeter at a wavelength of 589 nm. HR-MS were obtained by either an ESI recorded in a Time-of-Flight mass spectrometer or a fast atom bombardment (FAB) recorded in a DFMS (double-focusing mass spectrometer), and theoretical monoisotopic molecular masses were typically ≤ 5 p.p.m. The mp was uncorrected. TLC R_Fs of purified compounds were included.

(4*R**,6*R**,8*S**)-8-allyl-9,9-dimethyl-1-methoxy-4-prenyl-6-((triisopropylsilyloxy)methyl)bicyclo[3.3.1]non-1-ene-3,5-dione (14-1)

To a solution of **14** (100 mg, 0.230 mmol) in THF (2.0 ml) was added HMPA (0.4 ml) at room temperature. The mixture was then cooled to −78 °C, and LiTMP (4.6 ml, 0.5 M, 2.30 mmol, 10 equiv) was added to the solution. After the resulting reaction mixture was stirred at the same temperature for additional 1 h, prenol bromide (0.27 ml, 2.30 mmol, 10 equiv) was added to the reaction mixture. After the reaction was completed, saturated aqueous NH₄Cl solution (10 ml) was added to the reaction mixture and the aqueous layer was extracted with Et₂O (10 ml $\times$ 3). The combined organic layers were washed with brine (20 ml $\times$ 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 5/1) to afford **14-1** (73.1 mg, 63%) as a white powder.

R_F = 0.25 (hexanes/ethyl acetate = 2/1); ¹H NMR (400 MHz, CDCl₃) δ 5.89 (1H, s), 5.70–5.50 (1H, m), 5.01–4.91 (3H, m), 4.90–4.80 (1H, brs), 4.41 (1H, d, *J* = 8.0 Hz), 4.09 (1H, d, *J* = 8.0 Hz), 3.76 (3H, s), 2.24 (1H, dd, *J* = 14.4, 7.0 Hz), 2.37 (1H, dd, *J* = 14.4, 6.4 Hz), 2.24–2.12 (1H, brs), 1.95 (1H, dd, *J* = 13.2, 4.0 Hz), 1.81–1.65 (3H, m), 1.66 (3H, s), 1.55 (3H, s), 1.24 (1H, t, *J* = 13.2 Hz), 1.08–0.94 (24H, brs), 0.68 (3H, s); ¹³C (100 MHz, CDCl₃) δ 206.3, 196.8, 175.9, 136.7, 133.1, 120.1, 116.7, 108.2, 65.8, 63.7, 58.3, 56.0, 43.6, 42.0, 40.9, 33.9, 29.9, 25.7, 24.3, 18.0, 17.9, 17.8, 16.3, 12.0; IR (neat) ν_{max} 2942, 2865, 1731, 1656, 1603, 1463, 1241, 1108 cm^{−1}; HRMS (ESI) [*M* + Na]⁺ calculated for C₃₀H₅₀NaO₄Si 525.3376, found 525.3372; mp 157–158 °C.

(4*S**,6*R**,8*S**)-3-(8-allyl-9,9-dimethyl-1-methoxy-6-((triisopropylsilyloxy)methyl)bicyclo[3.3.1]non-1-ene-3,5-dione-4-yl)methyl-2,2-dimethyloxirane (15)

To a stirred solution of **14-1** (26.4 mg, 0.0525 mmol) in CH₂Cl₂ (1.0 ml) was added NaHCO₃ (13.2 mg, 0.158 mmol) and then mCPBA (18.1 mg,

0.0788 mmol) at 0 °C. After the reaction was completed, saturated aqueous NaHCO₃ (10 ml) and saturated aqueous Na₂S₂O₃ (10 ml) were added successively to the reaction mixture, and the aqueous layer was extracted with Et₂O (15 ml × 2). The combined organic layers were washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was used for the next step without further purification.

(4S*,6R*,8S*,18S*)-8-allyl-18-(1-hydroxy-1-methylethyl)-9,9-dimethyl-6-((triisopropylsilyloxy)methyl)-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (16)

To a crude solution of **15** in CH₂Cl₂ (1 ml) was added TMSCl (67.1 μl, 0.525 mmol, 10 equiv) at 0 °C. After the reaction was completed, saturated aqueous NaHCO₃ (10 ml) was added to the reaction mixture, and the aqueous layer was extracted with Et₂O (10 ml × 2). The combined organic layers were washed with brine (10 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 10/1) to afford **16** (9.3 mg, 35%) as a white powder.

R_F = 0.50 (hexanes/ethyl acetate = 1/1); ¹H NMR (400 MHz, CDCl₃) δ 5.81 (1H, s), 5.68–5.52 (1H, m), 5.05–4.85 (1H, brs), 4.49 (1H, dd, *J* = 10.8, 6.0 Hz), 4.23 (1H, d, *J* = 8.0 Hz), 4.19 (1H, d, *J* = 8.0 Hz), 2.69 (1H, dd, *J* = 13.2, 10.8 Hz), 2.33–2.20 (1H, brs), 2.10 (1H, dd, *J* = 13.6, 4.4 Hz), 1.92–1.79 (1H, brs), 1.75 (1H, dd, *J* = 13.2, 6.0 Hz), 1.69–1.52 (1H, m), 1.44 (1H, t, *J* = 13.6 Hz), 1.29 (3H, s), 1.16 (3H, s), 1.06 (3H, s), 1.05–0.81 (23H, brs), 0.71 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 204.6, 195.5, 176.3, 136.7, 116.9, 104.9, 90.0, 71.2, 71.0, 59.1, 58.7, 44.1, 40.3, 38.9, 33.0, 30.2, 26.3, 23.7, 22.7, 17.9, 16.8, 12.0; IR (neat) ν_{max} 3408, 2941, 2865, 1736, 1637, 1463, 1366, 1161 cm^{−1}; HRMS (ESI) [M + Na]⁺ calculated for C₂₉H₄₈NaO₅Si 527.3169, found 527.3148; mp 162–164 °C.

(4S*,6R*,8S*,18S*)-8-allyl-18-(1-methyl-1-trimethylsilyloxyethyl)-9,9-dimethyl-6-((triisopropylsilyloxy)methyl)-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (16-1)

To a solution of **16** (8.8 mg, 0.0175 mmol) in DMF (1.0 ml) was added imidazole (11.9 mg, 0.175 mmol, 10 equiv), DMAP (0.21 mg, 1.75 μmol) and TMSCl (11.3 μl, 0.0875 mmol, 5 equiv) at 0 °C. After the reaction was completed, saturated aqueous NaHCO₃ (5 ml) was added to the reaction mixture, and the aqueous layer was extracted with Et₂O (10 ml × 2). The combined organic layers were washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 20/1) to afford **16-1** (8.9 mg, 88%) as an oil.

R_F = 0.25 (hexanes/ethyl acetate = 2/1); ¹H NMR (400 MHz, CDCl₃) δ 5.76 (1H, s), 5.70–5.52 (1H, m), 5.00 (1H, s), 4.97 (1H, d, *J* = 8.8 Hz), 4.36 (1H, d, *J* = 10.4, 6.0 Hz), 4.23 (1H, d, *J* = 8.0 Hz), 4.19 (1H, d, *J* = 8.0 Hz), 2.64 (1H, dd, *J* = 13.2, 10.4 Hz, 1H), 2.29 (1H, brs), 1.82–1.71 (1H, brs), 1.69 (1H, dd, *J* = 13.2, 6.0 Hz), 1.69–1.52 (1H, m), 1.43 (1H, t, *J* = 14.3 Hz), 1.28 (3H, s), 1.18 (3H, s), 1.06 (3H, s), 1.03–0.90 (23H, brs), 0.71 (3H, s), 0.05 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 204.8, 195.4, 176.9, 136.8, 116.8, 104.6, 90.5, 73.4, 71.1, 59.0, 58.6, 44.1, 40.3, 39.0, 33.1, 29.9, 26.8, 25.8, 22.7, 17.9, 16.7, 12.0, 2.3; IR (neat) ν_{max} 2941, 2865, 1735, 1639 cm^{−1}; HRMS (ESI) [M + Na]⁺ calculated for C₃₂H₅₆NaO₅Si 599.3564, found 599.3544.

(4S*,6R*,8S*,18S*)-2,8-diallyl-18-(1-methyl-1-trimethylsilyloxyethyl)-9,9-dimethyl-6-((triisopropylsilyloxy)methyl)-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (17)

To a stirred solution of **16-1** (8.9 mg, 0.0155 mmol) in THF (1.0 ml) was added LiTMP (0.16 ml, 0.5 M, 0.0775 mmol, 5.0 equiv) at −78 °C. After the resulting reaction mixture was stirred at the same temperature for additional 30 min, (2-Th)Cu(CN)Li (0.78 ml, 0.1 M, 0.0775 mmol, 5.0 equiv) was added to the reaction mixture. After the resulting mixture was stirred at the same temperature for additional 30 min, to the mixture was added allyl bromide (6.7 μl, 0.0775 mmol, 5.0 equiv). After the reaction was completed, 30% aqueous NH₄OH solution (5 ml) was added to the reaction mixture and the aqueous layer was extracted with Et₂O (10 ml × 3). The combined organic layers were

washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 20/1) to afford **17** (9.6 mg, quant) as an oil.

(2-Th)Cu(CN)Li was prepared according to the literature method.¹⁷

R_F = 0.20 (hexanes/ethyl acetate = 15/1); ¹H NMR (400 MHz, CDCl₃) δ 5.88–5.72 (1H, m), 5.68–5.51 (1H, m), 5.04–4.93 (3H, m), 4.91–4.84 (1H, m), 4.37 (1H, dd, *J* = 10.4, 5.6 Hz), 4.25 (1H, d, *J* = 8.0 Hz), 4.20 (1H, d, *J* = 8.0 Hz), 3.11 (1H, dd, *J* = 14.8, 6.4 Hz), 3.04 (1H, dd, *J* = 14.8, 6.4 Hz), 2.64 (1H, dd, *J* = 13.2, 10.4 Hz), 2.33–2.21 (1H, brs), 2.09 (1H, dd, *J* = 13.6, 4.4 Hz), 1.76–1.52 (3H, brs), 1.42 (1H, t, *J* = 12.4 Hz), 1.26 (3H, s), 1.21 (3H, s), 1.06 (3H), 1.02–0.93 (21H, brs), 0.72 (3H, s), 0.07 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 204.8, 194.2, 172.6, 136.9, 135.7, 116.7, 114.5, 90.0, 73.7, 70.9, 59.3, 58.4, 44.1, 40.5, 39.2, 33.0, 30.4, 27.6, 26.5, 25.5, 22.7, 17.9, 16.8, 12.0, 2.3; IR (neat) ν_{max} 2942, 2865, 1736, 1638, 1364 841 cm^{−1}; HRMS (ESI) [M + Na]⁺ calculated for C₃₅H₆₀NaO₅Si₂ 639.3877, found 639.3879.

(4S*,6R*,8S*,18S*)-2,8-diallyl-18-(1-hydroxy-1-methylethyl)-6-hydroxymethyl-9,9-dimethyl-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (17-1)

To a stirred solution of **17** (10.1 mg, 0.0164 mmol) in THF (1 ml) was added TBAF (0.082 ml, 1.0 M in THF, 0.0820 mmol, 5.0 equiv) at room temperature. After the reaction was completed, saturated aqueous NH₄Cl (5 ml) was added to the reaction mixture, and the aqueous layer was extracted with Et₂O (10 ml × 2). The combined organic layers were washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude **17-1** was used for the next step without further purification.

(4S*,6R*,8S*,18S*)-2,8-diallyl-18-(1-hydroxy-1-methylethyl)-9,9-dimethyl-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione-6-carbaldehyde (18)

To a stirred solution of crude **17-1** in CH₂Cl₂ (0.16 ml) was added Dess–Martin periodinane (13.8 mg, 0.0328 mmol, 2.0 equiv) and NaHCO₃ (9.6 mg, 0.115 mmol, 7.0 equiv) at room temperature. After the reaction was completed, Et₂O (10 ml) and a mixture of saturated aqueous NaHCO₃ solution (10 ml) and saturated aqueous Na₂S₂O₃ solution (10 ml) were added to the reaction mixture. The aqueous layer was extracted with Et₂O (10 ml × 2). The combined organic layers were washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 10/1) to afford **18** (5.1 mg, 81%) as an oil.

R_F = 0.60 (hexanes/ethyl acetate = 2/3); ¹H NMR (400 MHz, CDCl₃) δ 9.46 (1H, s), 5.87–5.71 (1H, m), 5.69–5.54 (1H, m), 5.10–4.91 (4H, m), 4.58 (1H, dd, *J* = 11.0, 6.0 Hz), 3.15 (1H, dd, *J* = 14.4, 6.0 Hz), 3.06 (1H, dd, *J* = 14.4, 6.8 Hz), 2.69 (1H, dd, *J* = 13.6, 11.2 Hz), 2.35 (1H, brs), 2.09 (1H, dd, *J* = 13.6, 4.0 Hz), 1.78 (1H, dd, *J* = 13.6, 6.0 Hz), 1.78–1.61 (3H, m), 1.54 (1H, dd, *J* = 13.6, 12.4 Hz), 1.34 (3H, s), 1.23 (3H, s), 1.18 (3H, s), 1.06 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 202.8, 194.3, 191.7, 175.1, 136.3, 135.0, 117.3, 115.2, 115.0, 90.7, 79.3, 70.8, 59.6, 45.6, 40.9, 37.3, 32.5, 29.6, 27.1, 26.7, 24.1, 23.0, 16.4; IR (neat) ν_{max} 3478, 2976, 2922, 2853, 1744, 1725, 1618, 1366, 1232 cm^{−1}; HRMS (ESI) [M + Na]⁺ calculated for C₂₃H₃₀NaO₅ 409.1991, found 409.1975.

(4S*,6R*,8S*,18S*)-2,8-diallyl-18-(1-hydroxy-1-methylethyl)-6-(1-hydroxy-2-methylpropyl)-9,9-dimethyl-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (18-1)

To a stirred solution of **18** (3.2 mg, 8.29 μmol) was added CeCl₃ • 2LiCl in THF (0.33 ml, 0.25 M, 8.29 μmol, 10 equiv) at room temperature. After the resulting reaction mixture was stirred at the same temperature for additional 1 h, the mixture was cooled to −78 °C, and iPrMgCl (0.51 ml, 0.5 M, 0.249 mmol, 30 equiv) was added to the reaction mixture. After the resulting mixture was stirred at the same temperature for additional 30 min, temperature of the reaction mixture was gradually warmed up to −20 °C. After the reaction was completed, saturated aqueous NH₄Cl solution (10 ml) was added to the reaction mixture and the aqueous layer was extracted with Et₂O (10 ml × 3). The combined organic layers were washed with brine (20 ml × 1), dried

(Na₂SO₄), filtered and concentrated under reduced pressure. The crude **18-1** was used for the next step without further purification.

(4S*,6R*,8S*,18S*)-2,8-diallyl-18-(1-hydroxy-1-methylethyl)-6-isobutyryl-9,9-dimethyl-31-oxatricyclo[6.3.1.0^{3,4}]dodec-2-ene-1,5-dione (18-2)

To a stirred solution of **18-1** in CH₂Cl₂ (1.0 ml) was added Dess–Martin periodinane (7.0 mg, 16.6 μmol, 2.0 equiv) and NaHCO₃ (4.9 mg, 58.0 μmol, 7.0 equiv) at room temperature. After the reaction was completed, Et₂O (10 ml) and a mixture of saturated aqueous NaHCO₃ solution (10 ml) and saturated aqueous Na₂S₂O₃ solution (10 ml) were added to the reaction mixture. The aqueous layer was extracted with Et₂O (10 ml × 2). The combined organic layers were washed with brine (20 ml × 1), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate = 10/1) to afford **18-2** (3.4 mg, 96%) as an oil.

R_f = 0.50 (hexanes/ethyl acetate = 3/2); ¹H NMR (400 MHz, CDCl₃) δ 5.85–5.70 (1H, m), 5.68–5.52 (1H, m), 5.08–4.85 (4H, m), 4.55 (1H, dd, *J* = 10.8, 5.6 Hz), 3.22 (1H, dd, *J* = 14.4, 6.0 Hz), 3.04 (1H, dd, *J* = 14.4, 6.8 Hz), 2.68 (1H, dd, *J* = 13.2, 10.8 Hz), 2.35 (1H, brs), 2.07 (1H, dd, *J* = 13.6, 3.6 Hz), 1.98 (1H, m), 1.79 (1H, dd, *J* = 13.2, 5.6 Hz), 1.75–1.54 (2H, m), 1.50 (1H, t, *J* = 12.8 Hz), 1.36 (3H, s), 1.25 (3H, s), 1.19 (3H, s), 1.07 (3H, d, *J* = 6.4 Hz), 1.02 (3H, s), 0.96 (3H, d, *J* = 6.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 208.7, 204.3, 192.4, 173.9, 136.6, 135.1, 117.0, 114.9, 114.6, 90.3, 82.2, 70.8, 59.7, 46.3, 42.1, 41.3, 38.2, 32.6, 30.1, 27.1, 26.9, 24.1, 22.7, 21.4, 20.5, 16.0; IR (neat) ν_{max} 3468, 2975, 2927, 1732, 1625, 1472, 1367, 1231 cm^{−1}; HRMS (ESI) [*M* + Na]⁺ calculated for C₂₆H₃₆NaO₅ 451.2460, found 451.2455; mp 148–149 °C.

Garsubellin A

Compound **18-2** (3.2 mg, 7.46 μmol) and Grubbs II catalyst (0.633 mg, 0.746 μmol, 10 mol%) was added to a sealed tube. Isobutene (5 ml) was condensed into the tube at −78 °C. The tube was sealed and allowed to slowly warm up to 60 °C. After stirring for 4 h, the bottle was removed from the oil bath and allowed to cool to −78 °C. The isobutene was slowly vented off at room temperature. The residue was purified by flash chromatography (hexanes/ethyl acetate = 20/1) to afford garsubellin A (3.2 mg, 88%) as an oil.

R_f = 0.50 (hexanes/ethyl acetate = 2/1); ¹H NMR (500 MHz, C₆D₆) δ 5.38 (1H, m), 4.96 (1H, brs), 3.93 (1H, dd, *J* = 11.0, 5.5 Hz), 3.36 (1H, dd, *J* = 14.0, 7.5 Hz), 3.19 (1H, dd, *J* = 14.0, 8.0 Hz), 2.73 (1H, dd, *J* = 13.0, 10.5 Hz), 2.24 (1H, dq, *J* = 6.5, 6.5 Hz), 2.09 (1H, m), 1.93 (1H, dd, *J* = 14.0, 4.5 Hz), 1.74 (1H, m), 1.69 (3H, s), 1.60 (3H, s), 1.58 (1H, m), 1.58 (3H, s), 1.57 (3H, s), 1.44 (3H, s), 1.34 (3H, d, *J* = 6.5 Hz), 1.28 (3H, d, *J* = 6.5 Hz), 1.23 (3H, s), 0.95 (3H, s), 0.79 (3H, s); ¹³C NMR (125 MHz, C₆D₆) δ 208.6, 204.7, 193.0, 173.3, 133.2, 132.4, 123.3, 122.1, 116.7, 90.2, 82.7, 70.3, 59.9, 46.7, 43.1, 42.7, 39.1, 30.3, 27.1, 26.4, 26.0, 25.8, 24.5, 23.2, 22.7, 21.9, 20.9, 17.94, 17.90, 16.5; IR (neat) ν_{max} 3458, 2969, 2926, 2856, 1731, 1626, 1456, 1362, 1211 cm^{−1}; HRMS (ESI) [*M* + Na]⁺ calculated for C₃₀H₄₄NaO₅ 507.3086, found 507.3072.

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- 1 Numbering of compounds corresponds to Fukuyama's report, see: Fukuyama, Y., Kuwayama, A. & Minami, H. Garsubellin A, a novel polyprenylated phloroglucin derivative, increasing choline acetyltransferase (ChAT) activity in postnatal rat septal neuron cultures. *Chem. Pharm. Bull.* **45**, 947–949 (1997).
- 2 Njardarson, J. T. Synthetic efforts toward [3.3.1] bridged bicyclic phloroglucinol natural products. *Tetrahedron* **67**, 7631–7666 (2011).
- 3 Richard, J. A., Pouwer, R. H. & Chen, D. Y. -K. The chemistry of the polycyclic polyprenylated acylphloroglucinols. *Angew. Chem. Int. Ed.* **51**, 4536–4561 (2012).
- 4 Kuramochi, A., Usuda, H., Yamatsugu, K., Kanai, M. & Shibasaki, M. Total synthesis of (±)-garsubellin A. *J. Am. Chem. Soc.* **127**, 14200–14201 (2005).
- 5 Siegel, D. R. & Danishefsky, S. J. Total synthesis of garsubellin A. *J. Am. Chem. Soc.* **128**, 1048–1049 (2006).
- 6 Ahmad, N. M., Rodeschini, V., Simpkins, N. S., Ward, S. E. & Blake, A. J. Synthesis of polyprenylated acylphloroglucinols using bridgehead lithiation: total synthesis of racemic clusianone and a formal synthesis of racemic garsubellin A. *J. Org. Chem.* **72**, 4803–4815 (2007).
- 7 Ciochina, R. & Grossman, R. B. Polycyclic polyprenylated acylphloroglucinols. *Chem. Rev.* **106**, 3963–3986 (2006).
- 8 Bystrov, N. S., Chernov, B. K., Dobrynin, V. N. & Kolosov, M. N. The structure of hyperforin. *Tetrahedron. Lett.* **16**, 2791–2794 (1975).
- 9 Cuesta-Rubio, O., Frontana-Urbe, B. A., Ramírez-Apan, T. & Cárdenas, J. Z. Polyisoprenylated benzophenones in cuban propolis; biological activity of nemorosone. *Naturforsch. C* **57**, 372–378 (2002).
- 10 Uwamori, M., Saito, A. & Nakada, M. Stereoselective total synthesis of nemorosone. *J. Org. Chem.* **77**, 5098–5107 (2012).
- 11 Honma, M. *et al.* Asymmetric catalysis on the intramolecular cyclopropanations of α-diazo-β-keto sulfones. *J. Am. Chem. Soc.* **125**, 2860–2861 (2003).
- 12 Honma, M., Takeda, H., Takano, M. & Nakada, M. Development of catalytic asymmetric intramolecular cyclopropanation for α-diazo-β-keto sulfones and applications to natural product synthesis. *Synlett* 1695–1712 (2009).
- 13 Ashby, E. C. & Noding, S. A. Alkylation of enones and ketones using substituted alkyl- and arylaluminum compounds. *J. Org. Chem.* **44**, 4792–4797 (1979).
- 14 Graves, C. R., Zeng, B.-S. & Nguyen, S. T. Efficient and selective Al-catalyzed alcohol oxidation via Oppenauer chemistry. *J. Am. Chem. Soc.* **128**, 12596–12597 (2006).
- 15 Crabtree, R. H. *et al.* Dihydrido olefin and solvent complexes of iridium and the mechanisms of olefin hydrogenation and alkane dehydrogenation. *J. Am. Chem. Soc.* **104**, 6994–7001 (1982).
- 16 Yu, J.-Q. & Corey, E. J. A mild, catalytic, and highly selective method for the oxidation of α, β-enones to 1,4-enediones. *J. Am. Chem. Soc.* **125**, 3232–3233 (2003).
- 17 Lipshutz, B. H., Koerner, M. & Parker, D. A. 2-Thienyl(cyano)copper lithium. a lower order, stable “cuprate in a bottle” precursor to higher order reagents. *Tetrahedron. Lett.* **28**, 945–948 (1987).
- 18 Krasovskiy, A., Kopp, F. & Knochel, P. Soluble lanthanide salts (LnCl₃•2LiCl) for the improved addition of organomagnesium reagents to carbonyl compounds. *Angew. Chem. Int. Ed.* **45**, 497–500 (2006).
- 19 Chatterjee, A. K., Sanders, D. P. & Grubbs, R. H. Synthesis of symmetrical trisubstituted olefins by cross metathesis. *Org. Lett.* **4**, 1939–1942 (2002).