Towards an enantiospecific total synthesis of garsubellin A and related phloroglucin natural products: the α-pinene approach

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Abstract—The first enantiospecific approach to garsubellin A and related phloroglucin natural product nemorosone, of contemporary interest from (−)-α-pinene, has been delineated. Through a series of stereospecific operations, the requisite stereochemistry of the prenyl groups has been secured. Kende cyclization has been employed as the key step to construct the functionalized bicyclo[3.3.1]nonane core.

In 1997, Fukuyama et al. reported the isolation of a novel polyprenylated phloroglucin natural product garsubellin A **1** from the wood of *Garcinia subelliptica* (Guttiferae).[1] These authors also reported that **1** enhanced in vitro choline acetyltransferase (ChAT) activity in P10 rat septal neuron cultures by 154% at 10 μM concentration.[1] This was a very significant observation as many neurodegenerative disorders of intense contemporary concern like Alzheimer's disease have been attributed to deficiencies in the levels of neurotransmitter acetylcholine (ACh).[2] Consequently, inducers of the enzyme (ChAT), which is involved in the biosynthesis of ACh, have potential in developing therapies for Alzheimer's disease. Structurally, garsubellin A **1** (Fig. 1) belongs to a small but growing family of phloroglucins, characterized by the presence of a highly oxygenated and densely functionalized bicyclo[3.3.1]- nonane-1,3,5-trione core embellished with one or more hydrophobic prenyl groups. Other prominent members of this structural class are hyperforin[3] from *Hypericum perforatum* and nemorosone **3**[4] from the floral resins of several *Clusia* species and among them, the former is widely recognized as the beneficial ingredient of St. John's wort. On the other hand, nemorosone **3** has been shown to exhibit a promising activity profile against epitheloid carcinoma (HeLa), epidermoid carcinoma (Hep-2), prostate cancer (PC-3) and CNS cancer (U251).[4c]

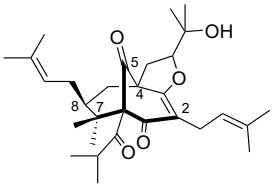
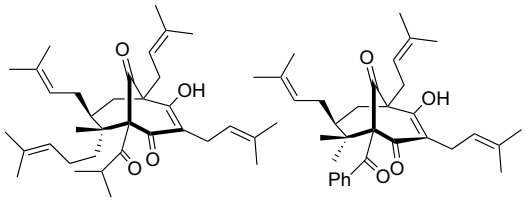


Figure 1. Structure of garsubellin A **1**.



2 Hyperforin **3 Nemorosone**

It is therefore hardly surprising that both on account of structural complexity and biological potential, these polyprenylated pholoroglucins have received considerable attention from synthetic organic chemists in the past few years.[5] However, to date no total synthesis of any member of this natural product family has been achieved though many interesting and novel strategies have been described towards garsubellin A **1** and related compounds.[5a–d] We report here the first enantiospecific approach to garsubellin A **1** and nemorosone **3** from the

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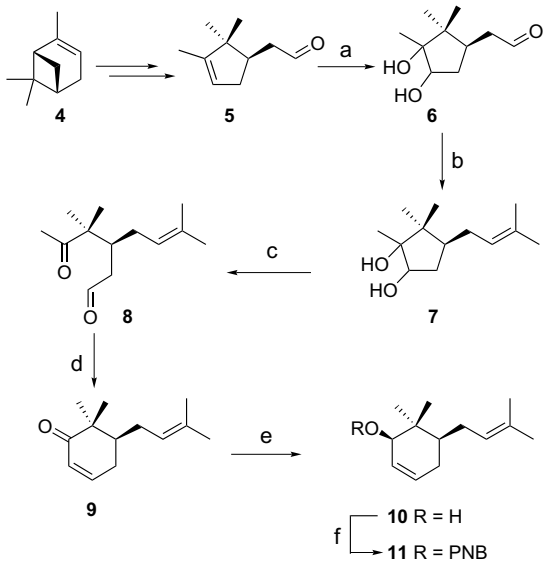
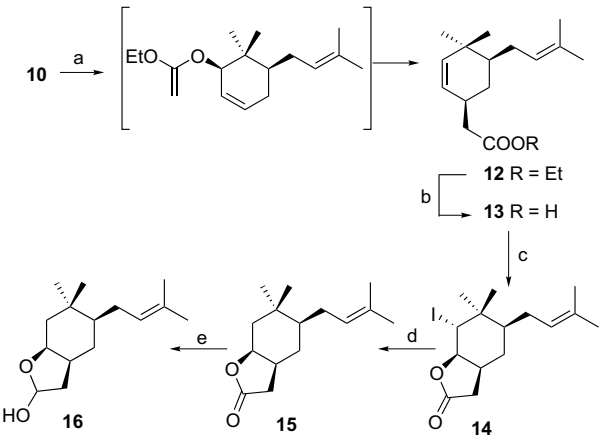


Scheme 1. Reagents and conditions: (a) OsO_4, NMMO, $(CH_3)_2CO$–H_2O–^{t}BuOH (5:5:2) rt, 3 days; 70%; (b) $Ph_3P^+CH(CH_3)_2Br^-$, KO^{t}Bu, THF, 0 °C, 1 h, 65%; (c) $NaIO_4$, THF–H_2O (1:1), 0 °C, 1 h, 88%; (d) 1 N KOH, MeOH, 0 °C, 1 h, 60%; (e) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 10 min, 82%; (f) *p*-$NO_2C_6H_4COCl$, pyridine, DMAP, DCM, rt, 80%.

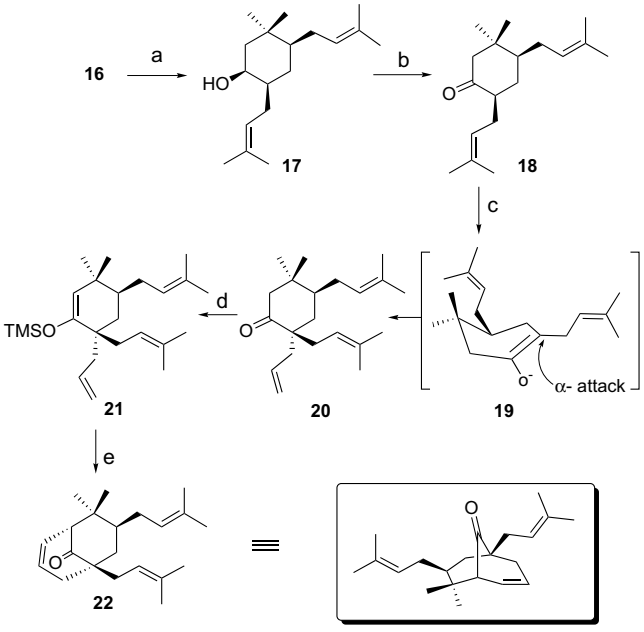
readily and abundantly available monoterpene chiron (−)-α-pinene **4** that has culminated in the generation of the bicyclo[3.3.1]nonane core and the stereoselective installation of the key prenyl subunits. To the best of our knowledge, the absolute configuration of garsubellin A **1** and related phloroglucins has not been determined. Thus, the choice of α-pinene, available in both enantiomeric forms, as the starting material for synthesis is particularly appropriate.

(−)-α-Pinene **4** was converted into (+)-campholenic aldehyde **5** through epoxidation and Lewis acid mediated fragmentation as described in the literature,[6] and this aldehyde served as the starting point of our synthesis. Catalytic OsO_4-mediated dihydroxylation of **5** furnished **6** as a single diastereomer (Scheme 1). Wittig olefination on **6** led to **7**[7] and installed the key C(8) prenyl side arm (see numbering in **1**). The *cis*-diol moiety in **7** was cleaved with periodate and the resulting 1,5-dicarbonyl compound **8** on base mediated intramolecular aldol cyclization furnished the cyclohexenone **9**. Luche reduction[8] of **9** was stereoselective and exclusively delivered the β-hydroxy compound **10** with hydride addition from the α-face opposite to the bulky prenyl side-chain.[7] The stereochemical assignment in **10** was secured through a single crystal X-ray structure determination[9] of the *p*-nitrobenzoate ester **11** prepared from **10** (Scheme 1).

Allylic alcohol **10** was subjected to a stereospecific orthoester Claisen rearrangement (Johnson modification)[10] to install the second prenyl unit and it smoothly delivered **12** (Scheme 2).[7] Further hydrolysis of ester **12** to the acid **13** and iodolactonization led to **14**. Reductive deiodination of **14** with TBTH was straightforward and furnished the bicyclic lactone **15**.[7] Dibal-H reduction of



Scheme 2. Reagents and conditions: (a) $CH_3C(OEt)_3$, CH_3CH_2-COOH, 180 °C, 24 h, 75%; (b) 1 N KOH, MeOH–H_2O, 60 °C, 6 h, 80%; (c) I_2, KI, $NaHCO_3$, THF–H_2O, 0 °C, 12 h, 85%; (d) ^{n}Bu_3SnH, AIBN, C_6H_6, 80 °C, 1 h, 95%; (e) DIBAL-H,THF, −78 °C, 1 h, 78%.



Scheme 3. Reagents and conditions: (a) $Ph_3PCH(CH_3)_2^+Br^-$, KO^{t}Bu, THF, 0 °C, 1 h, 65%; (b) PCC, DCM, 0 °C, 1 h, 98% (c) NaH, allyl bromide, THF, 60 °C, 4 h, 70%; (d) LDA, TMSCl, THF, −78 °C, 1 h; (e) $Pd(OAc)_2$, CH_3CN–DCM, rt, 12 h, 30% from **20** after two steps.

15 provided the lactol **16** with a masked aldehyde functionality required for the generation of the C(4) prenyl moiety (Scheme 2). Wittig isopropenylation of the bicyclic lactol proceeded as planned to yield **17** and installed the second prenyl unit (Scheme 3). PCC oxidation of **17** gave **18** and set the stage for the introduction of the allyl side chain required for the generation of the bridged bicyclo[3.3.1]nonane framework. Allylation of **18**, employing NaH as the base was stereoselective and furnished a single diastereomer **20**.[7] The enolate **19** derived from **18** encounters considerable

steric hindrance on the top face due to the *gem*-dimethyl substitution and α-face attack to give **20** is clearly favored (Scheme 3).

In our synthetic strategy, Kende cyclization[11] had been identified as the pivotal step to construct the bicyclo[3.3.1]nonane framework. Consequently, cyclohexanone **20** was transformed to the TMS enol ether **21** then $Pd(OAc)_2$ mediated cyclization was gratifyingly successful to furnish **22** in modest yield (Scheme 3).[7] The structure of **22** was in full conformity with its spectral characteristics and its bicyclic skeleton and prenyl and *gem*-dimethyl substitution pattern correspond to that present in garsubellin A **1** and nemorosone **3**. Further efforts are ongoing to adapt this sequence to build the functionalization pattern of the natural products on to the bicyclo[3.3.1]nonane core.

In short, employing (−)-α-pinene as the chiron, we have achieved the first enantiospecific construction of the bicyclic core present in garsubellin A and nemorosone **3** with appropriate positioning of the C(4) and C(8) prenyl chains. Kende cyclization has been employed as the key step for the generation of the functionalized bicyclo[3.3.1]nonane core.

Acknowledgements

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7. All new compounds were fully characterized on the basis of IR, ^1H and ^{13}C NMR and HRMS data. Selected spectral data for key compounds: **10**: IR (cm^{-1}): 3391; ^1H NMR (300 MHz, $CDCl_3$): δ 5.72–5.68 (m, 1H), 5.50 (d, $J = 9.9$ Hz, 1H), 5.12–5.06 (m, 1H), 3.87 (br s, 1H), 2.25–2.05 (m, 2H), 1.84–1.67 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.43–1.37 (m, 1H), 1.06 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6, 130.3, 128.8, 123.8, 76.5, 43.1, 37.7, 29.3, 28.1, 26.2, 25.1, 18.2, 13.5. (+)-**12**: IR (cm^{-1}): 1738; $[\alpha]_D^{25}$ +13.9° (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.41–5.33 (m, 2H), 5.11 (br s, 1H), 4.14 (q, $J = 6.9$ Hz, 2H), 2.55–2.49 (m, 1H), 2.24–2.22 (m, 2H), 2.14–2.05 (m, 1H), 1.70 (s, 3H), 1.59 (s, 3H), 1.36–1.19 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.01 (s, 3H), 0.97–0.85 (m, 2H) 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 139.8, 132.2, 127.1, 124.0, 60.2, 44.6, 41.1, 34.8, 34.0, 30.8, 28.7, 28.5, 25.8, 22.8, 17.8, 14.2; HRMS (ES) *m/z* calcd for $C_{17}H_{28}NaO_2$ $[M+Na]^+$: 287.1987 found: 287.2016; (+)-**15**: IR (cm^{-1}): 1773; $[\alpha]_D^{25}$ +42.7° (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.08–5.03 (m, 1H), 4.50 (br s, 1H), 2.65 (dd, $J = 16.5$, 6.6 Hz, 1H), 2.35–2.01 (m, 4H), 1.72–1.61 (m, 2H), 1.7 (s, 3H), 1.58 (s, 3H), 1.46–1.4 (m, 1H), 1.13–0.91 (m, 2H), 0.96 (s, 3H), 0.87(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4, 132.7, 123.5, 80.0, 44.8, 41.9, 38.2, 35.6, 31.9, 30.7, 28.7, 28.1, 25.8, 20.8, 17.8; HRMS (ES) *m/z* calcd for $C_{15}H_{24}NaO_2$ $[M+Na]^+$: 259.1674 found: 259.1689; (+)-**17**: IR (cm^{-1}): 3488; $[\alpha]_D^{25}$ +32.2° (*c* 1.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.14–5.12 (m, 2H), 3.89 (s, 1H), 2.14–1.96 (m, 3H), 1.70 (br s, 6H), 1.67–1.66 (m, 2H), 1.63 (s, 3H), 1.59 (s, 3H), 1.42–1.34 (m, 4H), 1.20–1.07 (m, 1H), 0.97 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.4, 131.7, 124.4, 122.8, 69.7, 48.0, 47.7, 42.5, 33.0, 31.2, 28.8, 28.3, 25.8 (2C), 22.4, 17.8 (2C); HRMS calcd (ES) *m/z* for $C_{18}H_{32}NaO$ $[M+Na]^+$: 287.2351, found: 287.2339; (+)-**18**: IR (cm^{-1}): 1713; $[\alpha]_D^{25}$ 33.9° (*c* 0.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.15–5.08 (m, 2H), 2.40–2.19 (m, 4H), 2.08–2.03 (m, 2H), 1.95–1.85 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.68–1.59 (m, 2H), 1.58 (s, 6H), 1.15–1.11 (m, 1H), 1.06 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.4, 132.7, 132.5, 123.5, 122.1, 56.6, 50.4, 46.7, 39.5, 34.9, 29.8 (2C), 28.2, 27.5, 25.8, 25.7, 19.9, 17.8; HRMS (ES) *m/z* calcd for $C_{18}H_{30}NaO$: 285.2194 $[M+Na]^+$, found: 285.2194. (+)-**20**: IR (cm^{-1}): 1706; $[\alpha]_D^{25}$ +56.9° (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.65–5.51 (m, 1H), 5.12–4.98 (m, 4H), 2.46–2.38 (m, 2H), 2.22–2.06 (m, 4H), 2.00–1.96 (m, 1H), 1.76–1.64 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.41–1.25 (m, 2H), 1.04 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.0, 134.3, 133.5, 132.8, 123.9, 120.4, 118.3, 54.3, 52.6, 42.7, 41.2, 39.0, 37.8, 33.3, 30.1, 28.7, 26.4, 26.2, 20.5, 18.4, 18.2; HRMS calcd for $C_{21}H_{34}NaO$: 325.2507 $[M+Na]^+$, found: 325.2509. **22**: IR (cm^{-1}): 1718; $[\alpha]_D^{25}$ −22.2° (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 5.83 (dt, $J = 9.3$, 3.3 Hz, 1H), 5.64–5.57 (m, 1H), 5.18–5.08 (m, 2H), 2.41–2.39 (m, 3H), 2.23–2.06 (m, 4H), 1.92–1.87 (m, 1H), 1.84–1.78 (m, 1H), 1.71 (s, 6H), 1.57 (s, 6H), 0.98 (s, 3H), 0.9–0.78 (m, 1H), 0.8 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.4, 133.7, 132.3, 129.9, 126.3, 123.7, 119.9, 60.1, 49.2, 43.5, 42.9, 42.4, 38.9, 35.1, 28.0, 26.1, 26.0, 25.8, 20.8, 17.9, 17.8; HRMS (ES) *m/z* calcd for $C_{21}H_{32}NaO$: 323.2351 $[M+Na]^+$, found: 323.2354.
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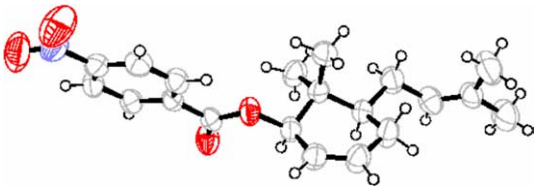
9. Crystal data: X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite

monochromated MoKα radiation ($\lambda = 0.7103$ Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. Compound **11**: $C_{20}H_{25}NO_4$ MW = 343, Crystal system: triclinic, space group: P-1, cell parameters: $a = 6.169$ (4) Å, $b = 11.196$ (6) Å, $c = 14.154$ (8) Å, $\alpha = 89.277$ (9)°, $\beta = 82.668$ (10)°, $\gamma = 77.000$ (9)°, $V = 944.57$ Å^3, $Z = 2$, $D_c = 1.207$ g cm^{-3}, $F(000) = 367.9$, $\mu = 0.08$ mm^{-1}. Total number of l.s. parameters = 326, R1 = 0.0500 for 2742 Fo > 4sig(Fo) and 0.0625 for all 3457 data. GOF = 1.042, Restrained GOF = 1.042 for all data. An ORTEP drawing of compound **11** with 50% ellipsoidal probability has been shown below. Crystallographic data is deposited with the Cambridge Crystallographic Data Centre, CCDC 220642.



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