Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 689–692
Tetrahedron Letters

# A rapid acquisition of the bicyclo[3.3.1]nonan-9-one core present in garsubellin A and related phloroglucins

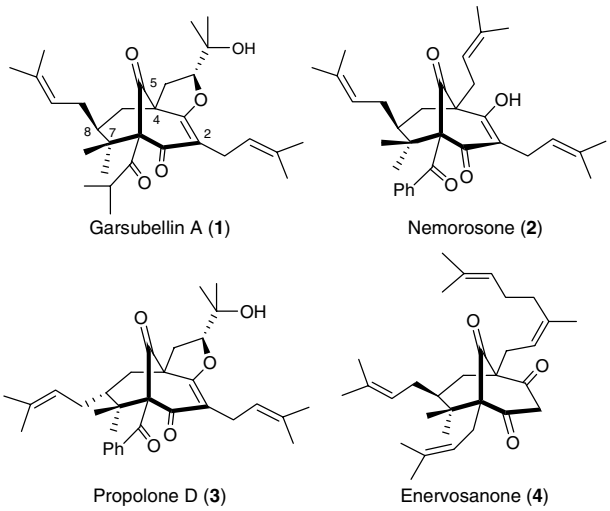
Goverdhan Mehta* and Mrinal K. Bera

*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India*

Received 26 September 2005; revised 15 November 2005; accepted 23 November 2005

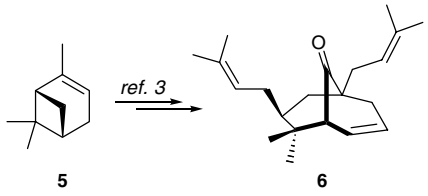
**Abstract**—An exceptionally concise and stereoselective route to the prenylated bicyclo[3.3.1]nonan-9-one core present in garsubellin A and related phloroglucin natural products from the readily available precursor dimedone is delineated.


A range of polyisoprenylated phloroglucinol derivatives (phloroglucins) with increasing levels of structural complexity are often being reported in the contemporary literature from diverse plant sources.[1] Typical examples of this growing family of natural products, based on bicyclo[3.3.1]nonane framework and generously embodying isoprene derived fragments and a dense oxygenation pattern, are garsubellin A **1**,[1b] nemorosone **2**,[1e,r] propolone D **3**[1r] and enervosanone **4**[1s] to name but a few. Besides their complex, enchanting framework and functionalization pattern, these pholoroglucinol derived natural products exhibit wide ranging biological activity profiles, which include cytotoxicity against several human cancer cell lines and antibacterial activity.[1] Among these pholoroglucins, garsubellin A **1**, isolated by the group of Fukuyama[1b] in 1997 from the wood of *Garcinia subelliptica* (Guttiferae) holds special appeal. These authors also made an important observation that **1** enhanced in vitro choline acetyltransferase (ChAT) activity in P10 rat septal neuron cultures by 154% at 10 μM concentration.[1b] This finding is of much significance as a deficiency in the levels of the neurotransmitter acetylcholine (ACh) has been implicated in several neurodegenerative disorders such as Alzheimer's disease. Thus, inducers of the enzyme (ChAT), which is involved in the biosynthesis of ACh have implications in developing Alzheimer therapeutics. Such a potential has evoked a great deal of synthetic interest in garsubellin A **1**, which, in addition, is endowed with a very challenging molecular architecture and several groups have entered the fray. These synthetic efforts have understandably focused on the synthesis of bicyclo[3.3.1]nonane core with varying degrees of functionalization for further elaboration to the natural product and several innovative strategies have been devised in this context.[2] We too have recently delineated an enantiospecific approach to **1** emanating from monoterpene α-pinene **5** that has resulted in the synthesis of the bicyclic core **6**, Scheme 1.[3] Concurrently, we have also been exploring an alternative synthetic approach that could provide a short access to the core structure present in phloroglucins. In this letter, we disclose an exceptionally short and simple acquisition of the prenylated bicyclo[3.3.1]-nonane fragment from the readily available dimedone **7**, setting the stage for further elaboration to the natural product garsubellin A **1** and for generating diversity based on this scaffold.



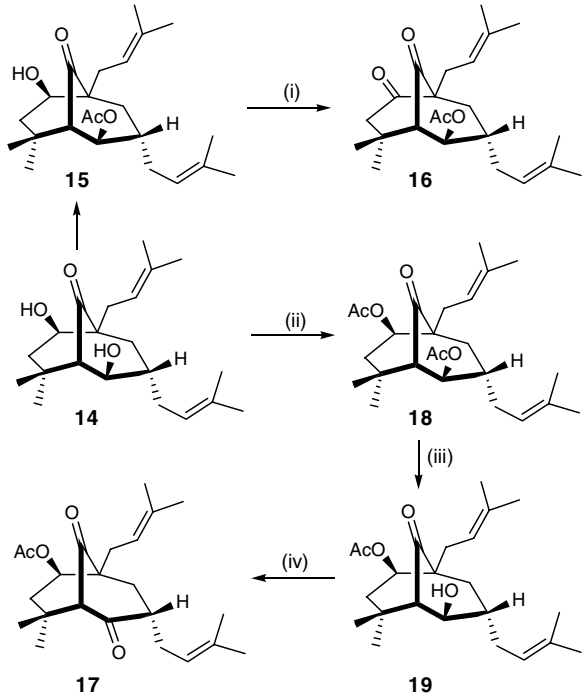

* Corresponding author. Tel.: +91 8023 600367; fax: +91 8023 600283; e-mail: gm@orgchem.iisc.ernet.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.120

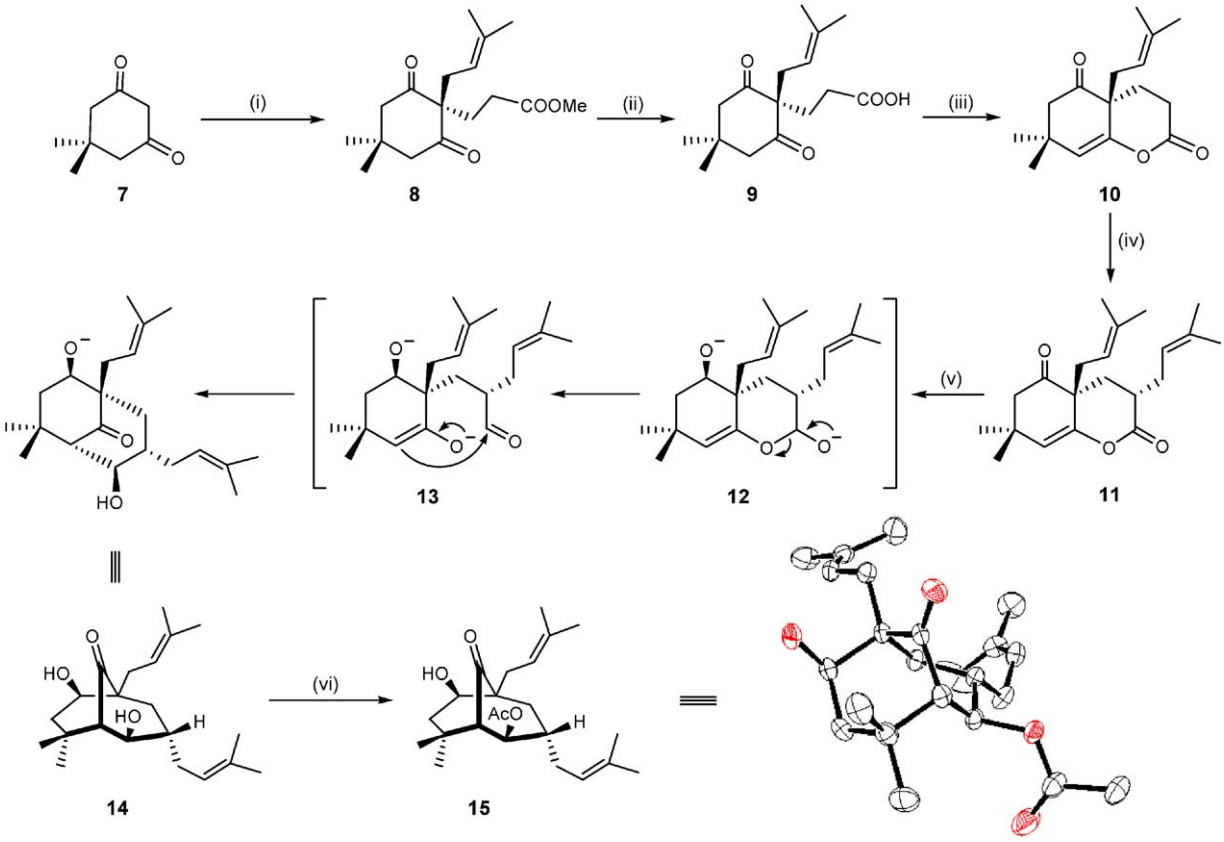



**Scheme 1.**

Sequential addition of methyl acrylate and prenyl bromide to dimedone **7** in the presence of DBU led to the formation of **8** in a single-pot operation.[4,5] Hydrolysis of **8** to lactone carboxylic acid **9**[4] and enol-lactonization furnished δ-lactone **10**[4] in excellent yield, Scheme 2. Quenching the kinetic enolate derived from **10** with prenyl bromide introduced the second prenyl group and stereoselectively delivered **11**.[4] DIBAL-H reduction of **11** led to the desired structural reconstitution along with the concomitant stereoselective reduction of the bystander carbonyl group and directly furnished the bicyclic *exo*,*exo*-diol **14**[4] through the intermediacy of the initially formed lactol anion **12** and aldol cyclization product **13**, Scheme 2. Interestingly, *exo*,*exo*-keto-diol **14** was obtained as a single diastereomer during the aldolization process and was further regioselectively converted into the crystalline monoacetate **15**. An X-ray crystal struc-




**Scheme 3.** Reagents and conditions: (i) PCC, DCM, rt, 1 h, 95%; (ii) $Ac_2O$, $Et_3N$, DMAP, rt, 12 h, 85%; (iii) $K_2CO_3$, MeOH, rt, 1 h, 70%; (iv) PCC, DCM, rt, 1 h, 94%.




**Scheme 2.** Reagents and conditions: (i) (a) $CH_2{=}CHCO_2Me$, DBU, THF, rt, 3 h, (b) $Me_2C{=}CHCH_2Br$, DBU, THF, rt, 3 h, 70% over two steps; (ii) $H_2SO_4$, acetone–water (5:1), reflux, 12 h, 87%; (iii) $CH_3COONa$ (1.2 equiv), $Ac_2O$, reflux, 2 h, 92%; (iv) $Me_2C{=}CHCH_2Br$, LHMDS, THF, −78 °C, 1 h, 62%; (v) DIBAL-H (2.5 equiv), DCM, 0 °C, 3 h, 52%; (vi) $Ac_2O$, $Et_3N$, DMAP, DCM, rt, 3 h, 92%.

ture determination of **15** secured its formulation and the ORTEP diagram with 50% thermal ellipsoidal probability is shown in Scheme 2 (hydrogen atoms not shown for clarity).[6]

In **14**, two of the three prenyl units present in the phloroglucins were in place and all the three bridges of bicyclo[3.3.1]nonane moiety had functionality and in routine transformations it was further shown that the carbonyl group, required for further elaboration could be positioned on either of the two bridges (Scheme 3) to furnish either of diketones **16** and **17**. While **16** was prepared from keto-diol **14** through regioselective monoacetate **15** and PCC oxidation, the diketone **17** was obtained from **14** by conversion to diacetate **18**, regioselective hydrolysis to **19**[4] and oxidation with PCC, Scheme 3.

In summary, we have described a very concise (five steps, 18% overall yield) and promising synthetic strategy for the rapid acquisition of the polyprenylated bicyclo[3.3.1] nonan-9-one core, present in phloroglucin natural products, from the commercially available diketone dimedone.[7]

## Acknowledgements

One of us, M.K.B., thanks UGC for the award of a research fellowship. We thank the CCD facility at IISc for the single crystal X-ray diffraction data.

## References and notes

1. (a) Karanjgoakar, C. G.; Rama Rao, A. V.; Venkataraman, K.; Palmer, K. J. *Tetrahedron Lett.* **1973**, *14*, 4977; (b) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947; (c) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853; (d) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073; (e) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cárdenas, J. *Phytochemistry* **2001**, *57*, 279; (f) Shan, M. D.; Hu, L. H.; Chen, Z. L. *J. Nat. Prod.* **2001**, *64*, 127; (g) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701; (h) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramírez-Apan, T.; Cárdenas, J. *Z. Naturforsch.* **2002**, *57c*, 372; (i) Wu, J.; Cheng, X.-F.; Harrison, L. J.; Goh, S.-H.; Sim, K.-Y. *Tetrahedron Lett.* **2004**, *45*, 9657; (j) Verotta, L.; Lovaglio, E.; Sterner, O.; Appendino, G.; Bombardelli, E. *J. Org. Chem.* **2004**, *69*, 7869; (k) Šavikin-Fodulović, K.; Aljančić, I.; Vajs, V.; Menković, N.; Macura, S.; Gojgić, G.; Milosavljević, S. *J. Nat. Prod.* **2003**, *66*, 1236; (l) Weng, J.-R.; Tsao, L.-T.; Wang, J.-P.; Wu, R.-R.; Lin, C.-N. *J. Nat. Prod.* **2004**, *67*, 1796; (m) Wu, C.-C.; Weng, J.-R.; Won, S.-J.; Lin, C.-N. *J. Nat. Prod.* **2005**, *68*, 1125; (n) Gartner, M.; Müller, T.; Simon, J. C.; Giannis, A.; Sleeman, J. P. *ChemBioChem* **2005**, *6*, 171; (o) Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Guan, Z.; Borris, R. P.; Stijfhoorn, E.; Stevenson, D.; Wang, J.; Sharma, N.; Macnaul, K.; Menke, J. G.; Ali, A.; Schulman, M. J.; Singh, S. B. *J. Nat. Prod.* **2005**, *68*, 617; (p) Baggett, S.; Protiva, P.; Mazzola, E. P.; Yang, H.; Ressler, E. T.; Basile, M. J.; Weinstein, I. B.; Kennelly, E. J. *J. Nat. Prod.* **2005**, *68*, 354; (q) Massoit, G.; Long, C.; David, B.; Serrano, M. J.; Daubie, F.; Alby, F.; Ausseil, F.; Knibiehler, M.; Moretti, C.; Hoffmann, J. S.; Cazaux, C.; Lavaud, C. *J. Nat. Prod.* **2005**, *68*, 979; (r) Hernandez, I. M.; Fernandez, M. C.; Cuesta-Rubio, O.; Piccinelli, A. N.; Rastrelli, L. *J. Nat. Prod.* **2005**, *68*, 931; (s) Taher, M.; Idris, M. S.; Ahmad, F.; Arbain, D. *Phytochemistry* **2005**, *66*, 723.
2. (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724; (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859; (c) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621; (d) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943; (e) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134; (f) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659; (g) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401.
3. Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113.
4. All new compounds were fully characterized on the basis of their IR, $^1$H NMR, $^{13}$C NMR and mass spectral data. Selected spectral data for key compounds: **8**: IR (neat): $\nu_{max}$ 1738, 1693 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.89–4.84 (1H, m), 3.64 (3H, s), 2.65 (2H, d, $J = 14.7$ Hz), 2.49–2.38 (4H, m), 2.21–2.15 (2H, m), 2.09–2.03 (2H, m), 1.65 (3H, s), 1.59 (3H, s), 1.06 (3H, s), 0.89 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 208.9 (2C), 173.4, 136.4, 116.9, 67.9, 51.6 (3C), 35.9, 30.6, 29.7, 29.3, 27.5, 26.7, 25.9, 17.9. HRMS (ES): $m/z$ calculated for $C_{17}H_{26}O_4Na$: 317.1729 $(M+Na)^+$, found: 317.1729. Compound **9**: IR (neat): $\nu_{max}$ 1714, 1693 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.90–4.85 (1H, m), 2.72–2.64 (2H, m), 2.49–2.44 (4H, m), 2.26–2.21 (2H, m), 2.09–2.04 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.08 (3H, s), 0.89 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 208.9 (2C), 178.4, 136.6, 117.6, 67.9, 51.5 (2C), 36.2, 30.6, 29.8, 29.2, 27.4, 26.1, 25.9, 18.0. HRMS (ES): $m/z$ calculated for $C_{16}H_{24}O_4Na$: 303.1572 $(M+Na)^+$, found: 303.1572. Compound **10**: IR (neat): $\nu_{max}$ 1766, 1718, 1678 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.46 (1H, s), 4.99–4.94 (1H, m), 2.68–2.49 (4H, m), 2.38–2.27 (2H, m), 2.02–1.89 (2H, m), 1.68 (3H, m), 1.58 (3H, s), 1.15 (3H, s), 1.02 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 208.6, 168.1, 148.2, 136.4, 118.4, 118.3, 117.4, 50.6, 48.8, 33.5, 33.2, 30.2, 27.4, 25.8, 24.9, 17.9. HRMS (ES): $m/z$ calculated for $C_{16}H_{22}O_3Na$: 285.1467 $(M+Na)^+$, found: 285.1460. Compound **11**: IR (neat): $\nu_{max}$ 1764, 1715 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.40 (1H, s), 5.07–4.94 (2H, m), 2.78–2.68 (1H, m), 2.59–2.52 (3H, m), 2.38–2.26 (3H, m), 2.20–2.13 (1H, dd, $J = 13.8$, 7.5 Hz), 1.68 (6H, s), 1.61 (3H, s), 1.57 (3H, s), 1.51 (1H, dd, $J = 13.8$, 10.8 Hz), 1.15 (3H, s), 1.03 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 208.9, 170.1, 148.4, 136.3, 135.3, 119.6, 117.5, 116.8, 50.6, 48.8, 38.5, 33.2, 32.8, 31.0, 30.9, 30.3, 30.2, 25.8 (2C), 17.9 (2C). HRMS (ES): $m/z$ calculated for $C_{21}H_{30}O_3Na$: 353.2093 $(M+Na)^+$, found: 353.2094. Compound **14**: IR (thin film): $\nu_{max}$ 3437, 1699 cm$^{-1}$; $^1$H NMR (300 MHz,$CDCl_3$):$\delta$ 5.18–5.06 (2H, m), 3.95 (1H, bs), 3.76–3.73 (1H, m), 2.43–2.35 (2H, m), 2.21–2.14 (1H, m), 2.07 (1H, t, $J = 1.8$ Hz), 2.03–1.96 (1H, m), 1.91–1.81 (1H, m), 1.77–1.76 (1H, m), 1.73 (3H, s), 1.70 (3H, s), 1.65 (3H, s), 1.62 (3H, s), 1.51–1.50 (1H, m), 1.26–1.19 (2H, m), 1.15 (6H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 215.5, 135.1, 133.9, 121.4, 118.7, 78.4, 75.0, 68.3, 51.7, 41.0, 39.3, 37.8, 34.9, 30.9, 30.2, 29.4, 27.9, 26.1, 25.9, 17.9 (2C). HRMS (ES): $m/z$ calculated for $C_{21}H_{34}O_3Na$: 357.2406 $(M+Na)^+$, found: 357.2410.
5. To a solution of dimedone (1.0 g, 7.1 mmol) in dry THF (15 mL) was added DBU (3.4 mL, 21.4 mmol) at room temperature and the mixture was allowed to stir for 15 min. Then methyl acrylate (1.0 mL, 10.7 mmol) was added and

the reaction mixture was stirred for 3 h. When the starting material was fully consumed, prenyl bromide (1.3 mL, 10.7 mmol) was added at rt and after an additional 3 h, the reaction was quenched with water (5 mL) and the product extracted with EtOAc ($30 \times 3$ mL). The combined organic extract was washed with brine and dried over anhydrous $Na_2SO_4$. Removal of the solvent produced a yellow oil, which was filtered through a silica gel column to furnish pure **8** (1.47 g, 70%). For the IR, $^1$H NMR, $^{13}$C NMR and mass spectral data of **8**, see Ref. 4.

6. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 292 K. The X-ray generator was operated at 50 kV and 35 mA using Mo $K_\alpha$ radiation. The data was collected with a $\omega$ scan width of 0.3°. A total of 606 frames per set were collected using SMART in three different settings of $\varphi$ (0°, 90° and 180°) keeping the sample detector distance at 6.062 cm and the $2\theta$ value fixed at −25°. The data were reduced by SAINTPLUS; an empirical absorption correction was applied using the package SADABS, and XPREP was used to determine the space group. The structures were solved using SIR92 and refined using SHELXL97. Crystal data for compound **15**: $C_{23}H_{36}O_4$, $M = 376.52$, monoclinic, space group $P2_1/c$, $a = 12.8517(17)$ Å, $b = 15.222(2)$ Å, $c = 11.8734(16)$, $\beta = 108.021(2)°$, $V = 2208.9(5)$ Å$^3$, $Z = 4$, $\rho_{calcd} = 1.132$ g cm$^{-3}$, $F(000) = 824$, $\mu = 0.076$ mm$^{-1}$, number of l.s. parameters = 252, $R = 0.0670$, $R_w = 0.1437$, GOF = 1.108 for 3889 reflections with $I > 2\sigma(I)$. The CIF file has been submitted to the Cambridge Crystallographic Data Centre and assigned the corresponding depository number (CCDC 286618).
7. While this manuscript was being reviewed, a total synthesis of garsubellin A **1** by the group of Shibasaki came to our attention (Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, *ASAP*).