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Total Synthesis of (±)-7-*epi*-Nemorosone

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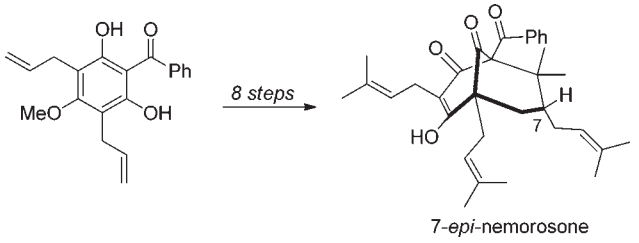
ABSTRACT



A concise total synthesis of (±)-7-*epi*-nemorosone is reported. Our synthetic approach establishes a viable route to polycyclic polyprenylated acylphloroglucinol natural products (PPAP's) bearing a C-7 *endo* prenyl side chain. Key steps include retro-aldol-vinyl cerium addition to a hydroxy adamantane core scaffold and palladium-mediated deoxygenation.

Polycyclic polyprenylated acylphloroglucinol natural products (PPAPs) are a class of compounds that have attracted significant attention in the synthetic chemistry community, largely due to their challenging structures and biological activities.[1] PPAPs generally possess a bicyclo-[3.3.1]nonane-1,3,5-trione core structure which is comprised of a highly oxygenated framework and vicinal quaternary carbon centers (Figure 1). Recent biological studies have showed promising results for PPAPs. For example, nemorosone (**1**) and its C-7 epimer 7-*epi*-nemorosone (**2**) both show antibacterial activity[2] and potent activity against the malaria parasite *P. falciparum*.[3] In addition, **1** and **2** exhibit cytotoxicity against a number of human cancer cell lines[4] including breast, colon, brain, ovary, liver, and lung carcinomas.[5] Recently, nemorosone (**1**) was found to be a potent protonophoric mitochondrial uncoupler which may form the basis of its cytotoxicity to cancer cells.[6]

The type A[7] PPAP nemorosone (**1**) has a C-7 *exo* prenyl moiety whereas 7-*epi*-nemorosone (**2**) bears a C-7 *endo*-prenyl substituent. The *O*-methyl ether of **2** was first isolated by Marsaioli and co-workers in 1999[8] but was assigned as an isomeric structure. In 1999, Jacobs and co-workers reported the isolation of the enol ester isomers plukenetiones D and E (**3** and **4**). These compounds were found to have the same framework as nemorosone, but the C-7 stereocenter was unassigned.[9] In 2000, Jacobs and Grossman[10] analyzed NMR data for **3** and **4** and proposed that these compounds were enol acetates of 7-*epi*-nemorosone (**2**). Subsequently, Marsaioli and co-workers reisolated the compound and corrected its structure to **2**.[11] Despite numerous synthetic efforts concerning type A PPAPs,[12] few have targeted construction of the C-7 *endo* prenyl moiety as found in **2** with the exception of a recent successful example reported by Plietker and co-workers.[12l] Herein, we report the first total synthesis of

(1) For a recent review of synthetic efforts toward PPAPs, see: Njardarson, J. T. *Tetrahedron* **2011**, *67*, 7631.
(2) de Castro Ishida, V. F.; Negri, G.; Salatino, A.; Bandeira, M. F. C. L. *Food Chem.* **2011**, *125*, 966.
(3) Monzote, L.; Cuesta-Rubio, O.; Matheeussen, A.; Van Assche, T.; Maes, L.; Cos, P. *Phytother. Res.* **2011**, *25*, 458.
(4) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramírez-Apan, T.; Cárdenas, J. *Z. Naturforsch.* **2002**, *57c*, 372.
(5) (a) Díaz-Carballo, D.; Malak, S.; Bardenheuer, W.; Freistuehler, M.; Reusch, H. P. *Bioorg. Med. Chem.* **2008**, *16*, 9635. (b) Popolo, A.; Piccinelli, A. L.; Morello, S.; Sorrentino, R.; Osmany, C. R.; Rastrelli, L.; Aldo, P. *Can. J. Physiol. Pharmacol.* **2011**, *89*, 50.
(6) (a) Pardo-Andreu, G. L.; Nuñez-Figueredo, Y.; Tudella, V. G.; Cuesta-Rubio, O.; Rodrigues, F. P.; Pestana, C. R.; Uyemura, S. A.; Leopoldino, A. M.; Alberici, L. C.; Curti, C. *Mitochondrion* **2011**, *11*, 255. (b) Holtrup, F.; Bauer, A.; Fellenberg, K.; Hilger, R. A.; Wink, M.; Hoheisel, J. D. *Br. J. Pharmacol.* **2011**, *162*, 1045.
(7) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.
(8) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073.
(9) Reynolds, W. F.; McLean, S.; Carrington, C. M. S.; Jacobs, H.; Henry, G. E. *Tetrahedron* **1999**, *55*, 1581.
(10) Grossman, R. B.; Jacobs, H. *Tetrahedron Lett.* **2000**, *27*, 5165.
(11) Bittrichb, V.; Amaralb, M. C. E.; Machado, S. M. F.; Anita, J.; Marsaioli, A. J. *Z. Naturforsch.* **2003**, *58*, 643.

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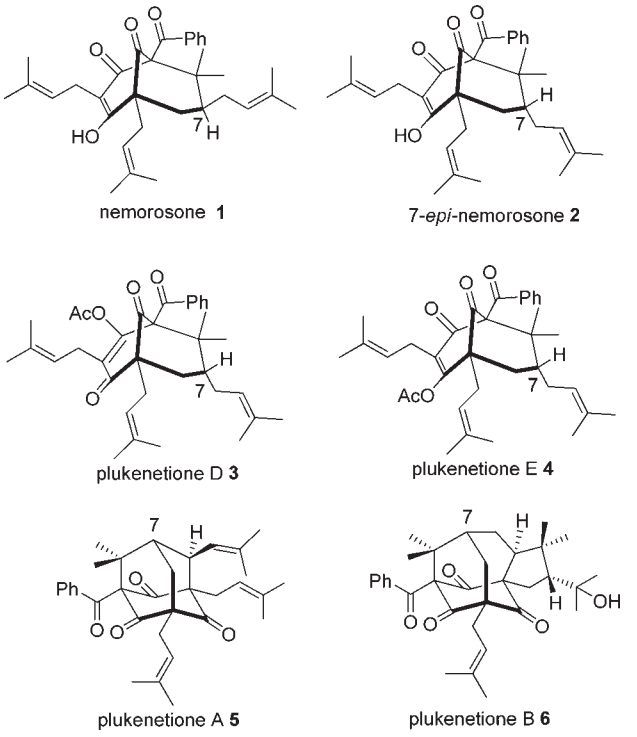


Figure 1. Representative type A polycyclic polyprenylated acylphloroglucinols (PPAPs).

(±)-7-*epi*-nemorosone (**2**) *via* elaboration of a hydroxy adamantane core scaffold.[13]

Retrosynthetically, we envisioned that 7-*epi*-nemorosone (**2**) may be derived from the *bis*-*O*-acylated bicyclo-[3.3.1]nonane **7** after palladium(0)-mediated reduction (Figure 2). Bicyclic intermediate **7** may be derived from organocerium-mediated retro-aldol/vinyl metal addition to adamantane alcohol **8**.[13] Finally, adamantane **8** may be obtained from the readily available α-acetoxy enal **9** and acylphloroglucinol **10** using an alkylative dearomatization–annulation sequence.[13]

The synthesis commenced with treatment of acylphloroglucinol **10** with aldehyde **9** under basic conditions to afford the dearomatized adduct in high yield[13] (Scheme 1). The crude product was directly subjected to acidic conditions

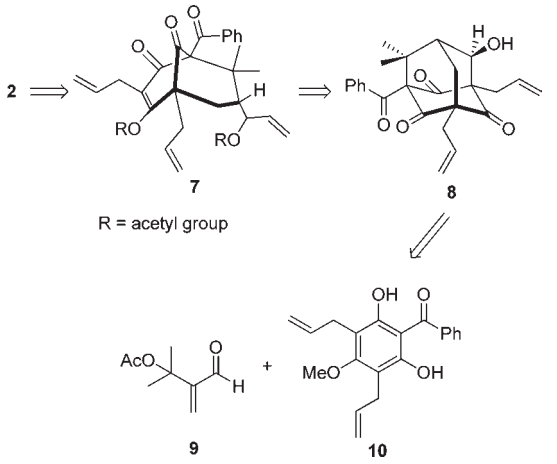
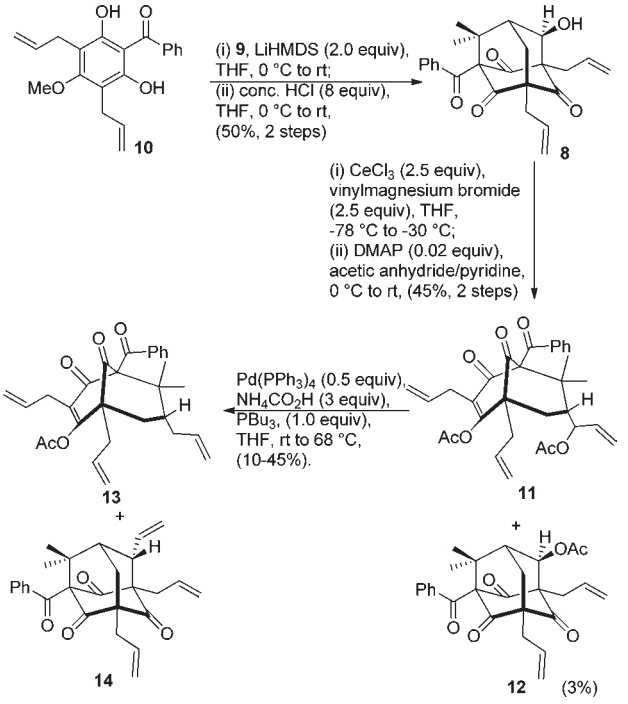


Figure 2. Retrosynthetic analysis for (±)-7-*epi*-nemorosone **2**.

Scheme 1. Synthesis of the 7-*epi*-Nemorosone Core



(conc. HCl, THF, rt) to yield adamantane alcohol **8** (50% yield, two steps).[13] Exposure of adamantane **8** to a preactivated $CeCl_3$/vinylmagnesium bromide mixture led to tandem retro-aldol condensation/Grignard addition.[14] The crude product mixture was subjected to standard esterification conditions (Ac_2O/pyridine/DMAP) which afforded *bis*-acylated compound **11** as the major product (45% yield, two steps). A small amount of adamantane acetate **12** (3%) was

(12) For recent syntheses of PPAPs, see: (a) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (b) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048. (c) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283. (d) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840. (e) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287. (f) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (g) Shimizu, Y.; Shi, S.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (h) Simpkins, N.; Taylor, J.; Weller, M.; Hayes, C. *Synlett* **2010**, *4*, 639. (i) Qi, J.; Beeler, A. B; Zhang, Q.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 13642. (j) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234. (k) McGrath, N. A.; Binner, J. R.; Markopoulos, G.; Brichacek, M.; Njardarson, J. T. *Chem. Commun.* **2011**, *47*, 209. (l) Biber, N.; Möws, K.; Plietker, B. *Nat. Chem.* **2011**, *9*, 938. (m) Garnsey, M. R.; Matous, J. A.; Kwiek, J. J.; Coltart, D. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2406.

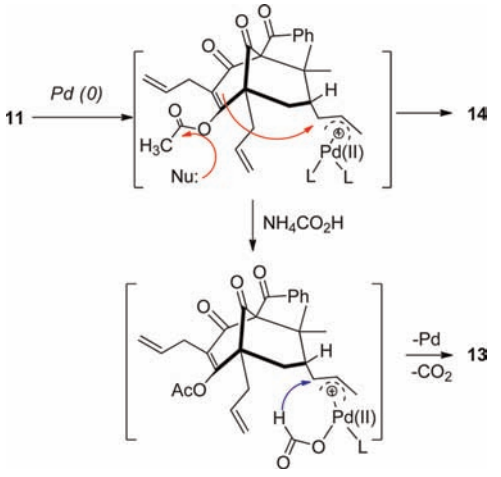
(13) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212.

(14) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

also isolated *via* acylation of unreacted adamantane alcohol **8**.

Efforts to convert the *bis*-acetate **11** to its reduced form **13** were problematic as a competing pathway leading to the formation of the undesired adamantane **14** was generally observed. This can presumably be attributed to a facile intramolecular cyclization which occurred prior to reduction (Scheme 2). After evaluation of reaction conditions including palladium(0) and hydride sources,[15] an optimized yield (45%) for **13** was obtained using $Pd(Ph_3P)_4$ with added PBu_3[15c] using NH_4CO_2H at 68 °C and a reaction concentration of 0.2 M. A relatively high Pd(0) catalyst loading (50%) was found to be necessary to reduce the reaction time and avoid decomposition of product **13** under the reaction conditions. In addition, under these conditions adamantane product **14** was also produced (~10%). Finally, alkene cross metathesis of **13** with isobutylene catalyzed by the Grubbs II catalyst[16] afforded plukenetione E acetate (**4**) albeit in inconsistent yield, likely due to cleavage of the labile enol acetate protecting group under thermal conditions.[17] Analytical data for synthetic **4** were in agreement with the data reported by Jacobs and co-workers.[9,17]

Scheme 2. Cyclization *vs* Reduction Processes



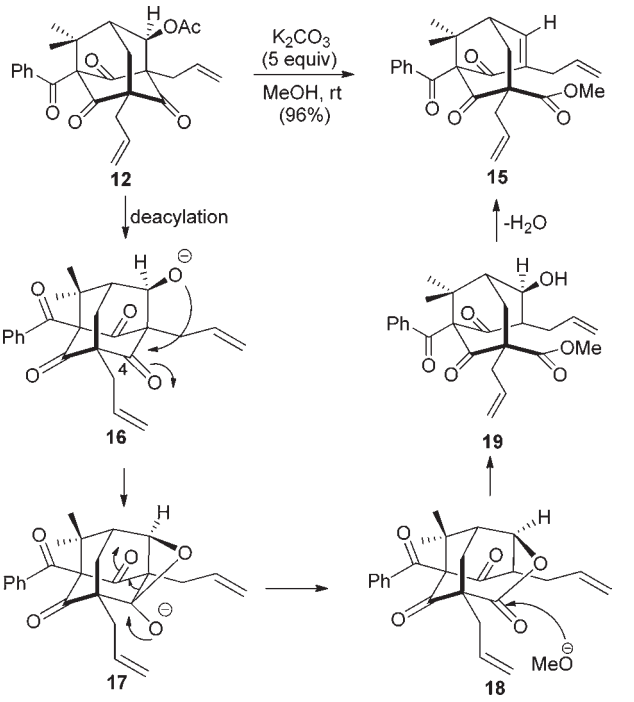
Interestingly, treatment of acylated adamantane **12** with K_2CO_3/MeOH led to unexpected formation of the fragmentation product **15** in nearly quantitative yield. The structure of **15** was confirmed by X-ray analysis (Figure 3).[17] A proposed mechanism is shown in Scheme 3. Adamantane acetate **12** may be initially deacylated by methoxide to generate alkoxide **16**. The proximity between the emerged alkoxide and C-4 ketone (~2.9 Å) should facilitate formation of the oxetane intermediate **17**.

(15) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1. (b) Forsyth, D. A.; Estes, M. R.; Lucas, P. *J. Org. Chem.* **1982**, *47*, 4380. (c) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107.

(16) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

(17) Please see the Supporting Information for complete experimental details.

Scheme 3. An Unexpected Fragmentation Process



Fragmentation of **17** followed by protonation may then lead to formation of lactone **18** which may subsequently undergo ring opening by methoxide to afford **19**. Finally, dehydration of alcohol **19** *via* β-elimination may afford bicyclic product **15**. A similar fragmentation process was reported by Nicolaou and co-workers en route to the PPAP natural product hyperforin.[18]

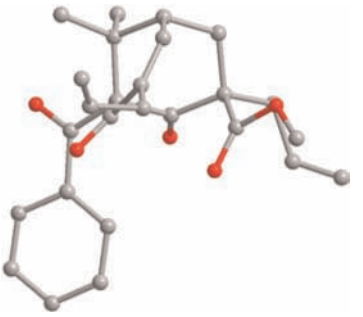
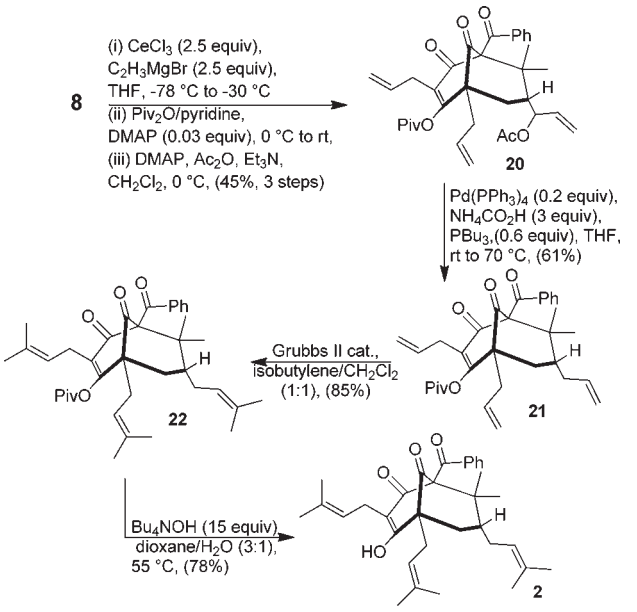


Figure 3. X-ray crystal structure of fragmentation product **15**.

Due to inconsistent yields observed for reduction of **11** and in the cross metathesis of derived product **13**, we considered altering the protecting group for the vinylogous acid moiety in order to increase its stability. After considerable experimentation, we found the pivalate group to be an excellent candidate for the sequence. Starting from

(18) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895.

Scheme 4. Synthesis of (±)-7-*epi*-Nemorosone



adamantane **8**, tandem retro-aldol/vinyl Grignard addition followed by sequential acylations led to the formation of **20** (45% yield, 3 steps) as a single enol pivalate[17,19] isomer with only a single purification required (Scheme 4). Palladium-mediated deoxygenation of **20** occurred smoothly to generate **21** in consistent overall yield (61%). Moreover, due to the increased stability of the pivalate protecting group, adamantane byproduct **14** (cf. Scheme 1) was not observed.

In the final stages of the synthesis, global cross metathesis of **21** afforded the triprenylated 7-*epi*-nemorosone core structure **22** in high yield (Scheme 4). Tetrabutylammonium hydroxide-mediated deprotection of **22** effected removal of the pivalate protecting group affording the natural product **2**. Attempted purification of the crude product mixture *via* conventional silica gel chromatography led to the unexpected decomposition of **2**.[12d,h] Fortunately, purification of synthetic **2** using preparative HPLC was successful employing 99:1 CH_3CN/H_2O with 0.01% TFA[20] in the eluant buffer leading to the production of (±)-7-*epi*-nemorosone (**2**) (78%). Analytical data including ^1H and ^{13}C NMR analyses for **2** were in agreement with those obtained from a sample provided by the Jacobs group.

In conclusion, we have achieved the first total synthesis of (±)-7-*epi*-nemorosone, a type A PPAP natural product bearing a C-7 *endo* prenyl side chain. Key steps include retro-aldol-vinyl cerium addition to a hydroxy adamantane core structure and palladium-mediated deoxygenation. The use of an enol pivalate protecting group for a vinylogous acid moiety was found to be helpful in order to prevent undesirable cyclizations. Further studies on the synthesis of PPAPs and their chemical reactivity are ongoing in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(19) For enol pivalates of 1,3-cyclohexanediones, see: (a) Boeckman, R. K., Jr.; Sum, F. W. *J. Am. Chem. Soc.* **1982**, *104*, 4604. (b) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

(20) Trace amounts of TFA were required for preparative HPLC purification of synthetic **2** in order to match spectral data for natural **2** provided by the Jacobs group.

The authors declare no competing financial interest.