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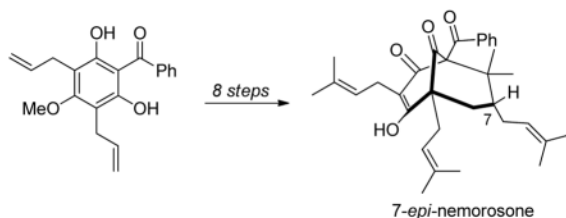
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Total Synthesis of (\pm)-7-*epi*-Nemorosone

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Abstract



A concise total synthesis of (\pm)-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 sidechain. Key steps include retro-aldol-vinyl cerium addition to a hydroxy adamantane core scaffold and palladium-mediated deoxygenation.

Polycyclic polyprenylated acylphloroglucinol natural products (PPAP's) 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 PPAP's 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 PPAP's. For example, nemorosone (**1**) and its C-7 epimer 7-*epi*-nemorosone (**2**) both show antibacterial activity² and potent activity against the malaria parasite *P. falciparum*.³ In addition, (**1**) and (**2**) exhibit cytotoxicity against a number of human cancer cell lines⁴ 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 A⁷ 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 coworkers in 1999⁸ but was assigned as an isomeric structure. In 1999, Jacobs and coworkers 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 Grossman¹⁰ analyzed NMR data for **3** and **4** and proposed that these compounds were enol acetates of 7-*epi*-nemorosone (**2**). Subsequently, Marsaioli and coworkers 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 coworkers.¹² Herein, we report the first total

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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>

synthesis of (\pm)-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 (conc. HCl, THF, rt) to yield adamantane alcohol **8** (50% yield, two steps).¹³ Exposure of adamantane **8** to a pre-activated CeCl₃/vinylmagnesium bromide mixture led to tandem retro-aldol condensation / Grignard addition.¹⁴ The crude product mixture was subjected to standard esterification conditions (Ac₂O/pyridine/DMAP) which afforded *bis*-acylated compound **11** as the major product (45% yield, two steps). A small amount of adamantane acetate **12** was also isolated in 3% yield *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(Ph₃P)₄ with added PBu₃15c using NH₄CO₂H 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 catalyst¹⁶ 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 coworkers.^{9,17}

Interestingly, treatment of acylated adamantane **12** with K₂CO₃/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**. 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 coworkers enroute to the PPAP natural product hyperforin.¹⁸

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 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 unexpected decomposition of **2**.^{12d,h} Fortunately, purification of synthetic **2** using preparative HPLC was successful employing 99:1 CH₃CN: H₂O = with 0.01% TFA20 in the eluant buffer leading to the production of (±)-7-*epi*-nemorosone (**2**) (78%). Analytical data including ¹H and ¹³C 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 sidechain. 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 PPAP's and their chemical reactivity are ongoing in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For a recent review of synthetic efforts toward PPAP's, see: Njardarson JT. *Tetrahedron*. 2011; 67:7631.
2. de Castro Ishida VF, Negri G, Salatino A, Bandeira MFCL. *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. [PubMed: 21259352]
4. Cuesta-Rubio O, Frontana-Urbe BA, Ramírez-Apan T, Cárdenas J. *Z Naturforsch*. 2002; 57c:372.
5. (a) Díaz-Carballo D, Malak S, Bardenheuer W, Freistuehler M, Reusch HP. *Bioorg Med Chem*. 2008; 16:9635. [PubMed: 18951805] (b) Popolo A, Piccinelli AL, Morello S, Sorrentino R, Osmany CR, Rastrelli L, Aldo P. *Can J Physiol Pharmacol*. 2011; 89:50. [PubMed: 21186377]
6. (a) Pardo-Andreu GL, Nuñez-Figueroa Y, Tudella VG, Cuesta-Rubio O, Rodrigues FP, Pestana CR, Uyemura SA, Leopoldino AM, Alberici LC, Curti C. *Mitochondrion*. 2011; 11:255. [PubMed: 21044702] (b) Holtrup F, Bauer A, Fellenberg K, Hilger RA, Wink M, Hoheisel JD. *Br J Pharmacol*. 2011; 162:1045. [PubMed: 21091652]
7. Ciochina R, Grossman RB. *Chem Rev*. 2006; 106:3963. [PubMed: 16967926]
8. de Oliveira CMA, Porto ALM, Bittrich V, Marsaioli AJ. *Phytochemistry*. 1999; 50:1073.
9. Reynolds WF, McLean S, Carrington CMS, Jacobs H, Henry GE. *Tetrahedron*. 1999; 55:1581.
10. Grossman RB, Jacobs H. *Tetrahedron Lett*. 2000; 27:5165.
11. Bittrich V, Amaral MCE, Machado SMF, Anita J, Marsaioli AJ. *Z Naturforsch*. 2003; 58:643.

12. For select, recent syntheses of PPAP's, see: (a) Kuramochi A, Usuda H, Yamatsugu K, Kanai M, Shibasaki M. *J Am Chem Soc.* 2005; 127:14200. [PubMed: 16218611] (b) Siegel DR, Danishefsky SJ. *J Am Chem Soc.* 2006; 128:1048. [PubMed: 16433500] (c) Rodeschini V, Ahmad NM, Simpkins NS. *Org Lett.* 2006; 8:5283. [PubMed: 17078698] (d) Tsukano C, Siegel DR, Danishefsky SJ. *Angew Chem Int Ed.* 2007; 46:8840. (e) Nuhant P, David M, Pouplin T, Delpech B, Marazano C. *Org Lett.* 2007; 9:287. [PubMed: 17217286] (f) Qi J, Porco JA Jr. *J Am Chem Soc.* 2007; 129:12682. [PubMed: 17902679] (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 AB, Zhang Q, Porco JA Jr. *J Am Chem Soc.* 2010; 132:13642. [PubMed: 20831187] (j) Garnsey MR, Lim D, Yost JM, Coltart DM. *Org Lett.* 2010; 12:5234. [PubMed: 20977254] (k) McGrath NA, Binner JR, Markopoulos G, Brichacek M, Njardarson JT. *Chem Commun.* 2011; 47:209. (l) Biber N, Möws K, Plietker B. *Nat Chem.* 2011; 9:938. [PubMed: 22109273] (m) Garnsey MR, Matous JA, Kwiek JJ, Coltart DM. *Bioorg Med Chem Lett.* 2011; 21:2406. [PubMed: 21414776]
13. Zhang Q, Mitasev B, Qi J, Porco JA Jr. *J Am Chem Soc.* 2010; 132:14212. [PubMed: 20843036]
14. Imamoto T, Takiyama N, Nakamura K, Hatajima T, Kamiya Y. *J Am Chem Soc.* 1989; 111:4392.
15. (a) Tsuji J, Mandai T. *Synthesis.* 1996:1. (b) Forsyth DA, Estes MR, Lucas P. *J Org Chem.* 1982; 47:4380. (c) Hughes G, Lautens M, Wen C. *Org Lett.* 2000; 2:107. [PubMed: 10814258]
16. Chatterjee AK, Sanders DP, Grubbs RH. *Org Lett.* 2002; 4:1939. [PubMed: 12027652]
17. Please see the Supporting Information for complete experimental details.
18. Nicolaou KC, Carenzi GEA, Jeso V. *Angew Chem Int Ed.* 2005; 44:3895.
19. For enol pivalates of 1,3-cyclohexanediones, see: (a) Boeckman RK Jr, Sum FW. *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.

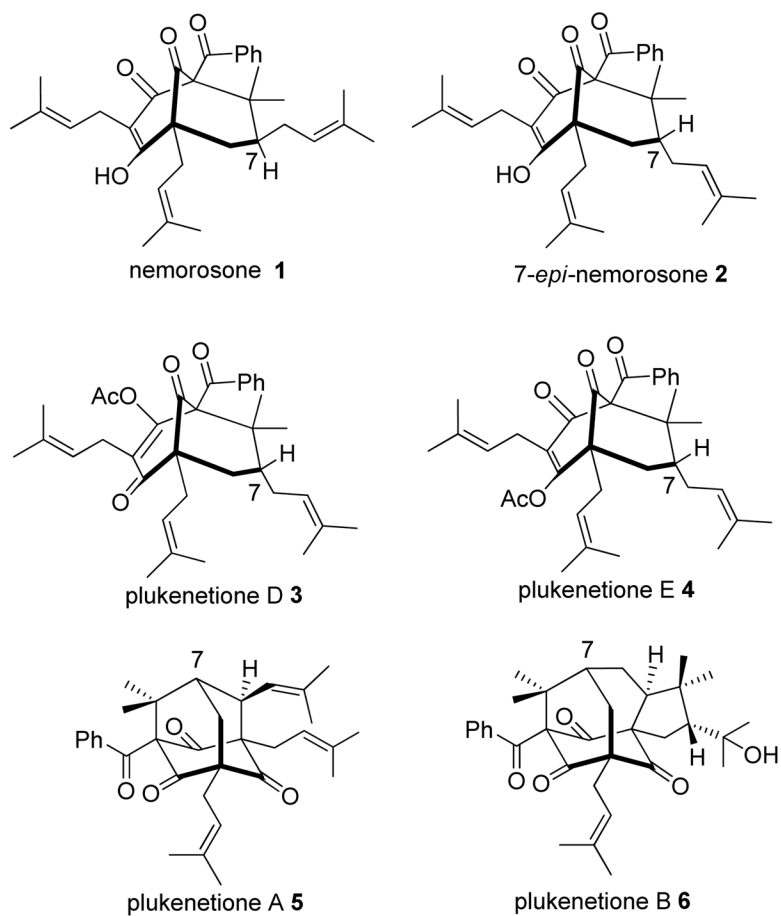


Figure 1.
Representative Type A Polycyclic Polyprenylated Acylphloroglucinols (PPAP's)

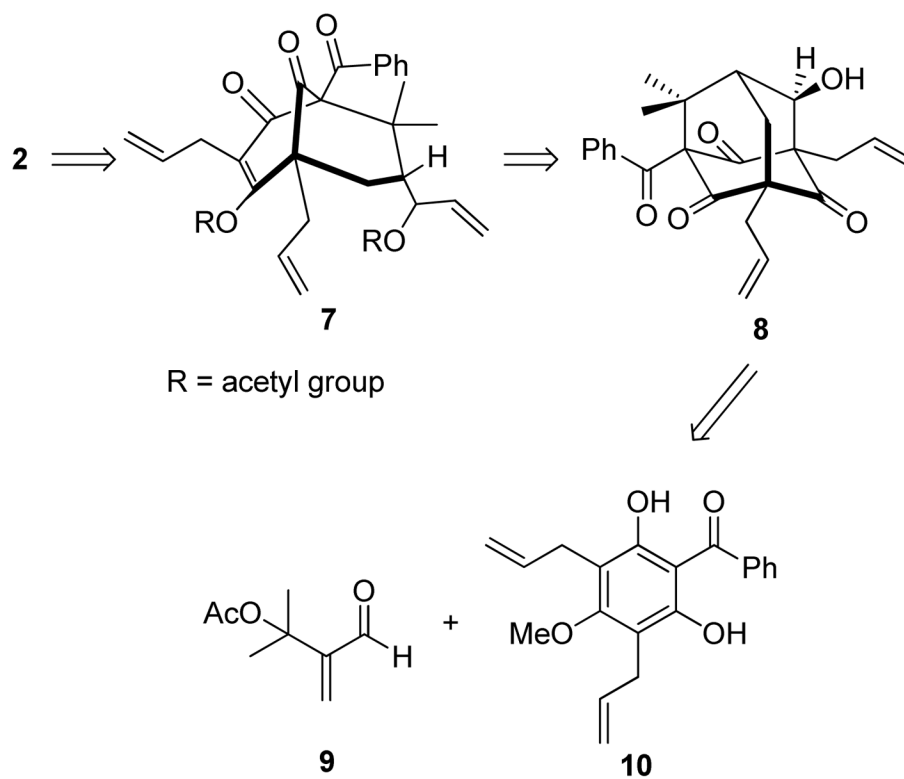


Figure 2.
Retrosynthetic analysis for (\pm)-7-*epi*-nemorosone **2**

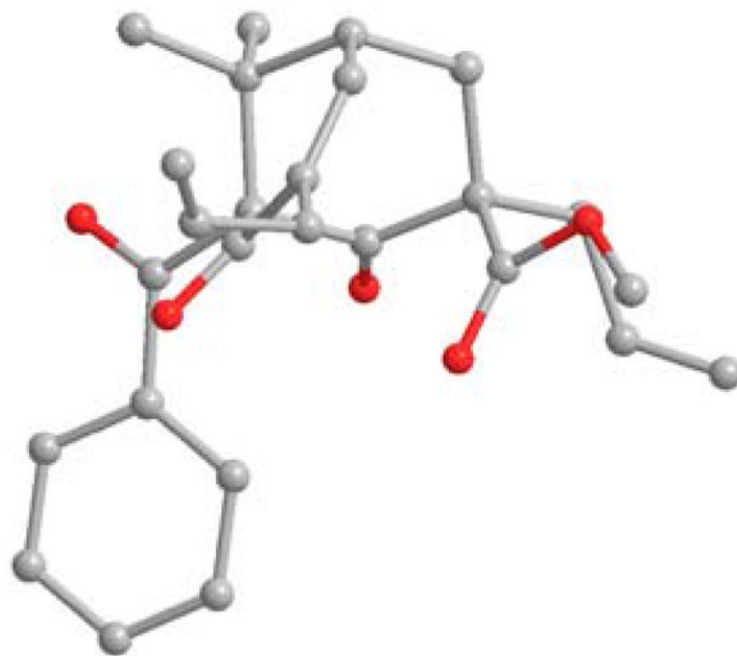
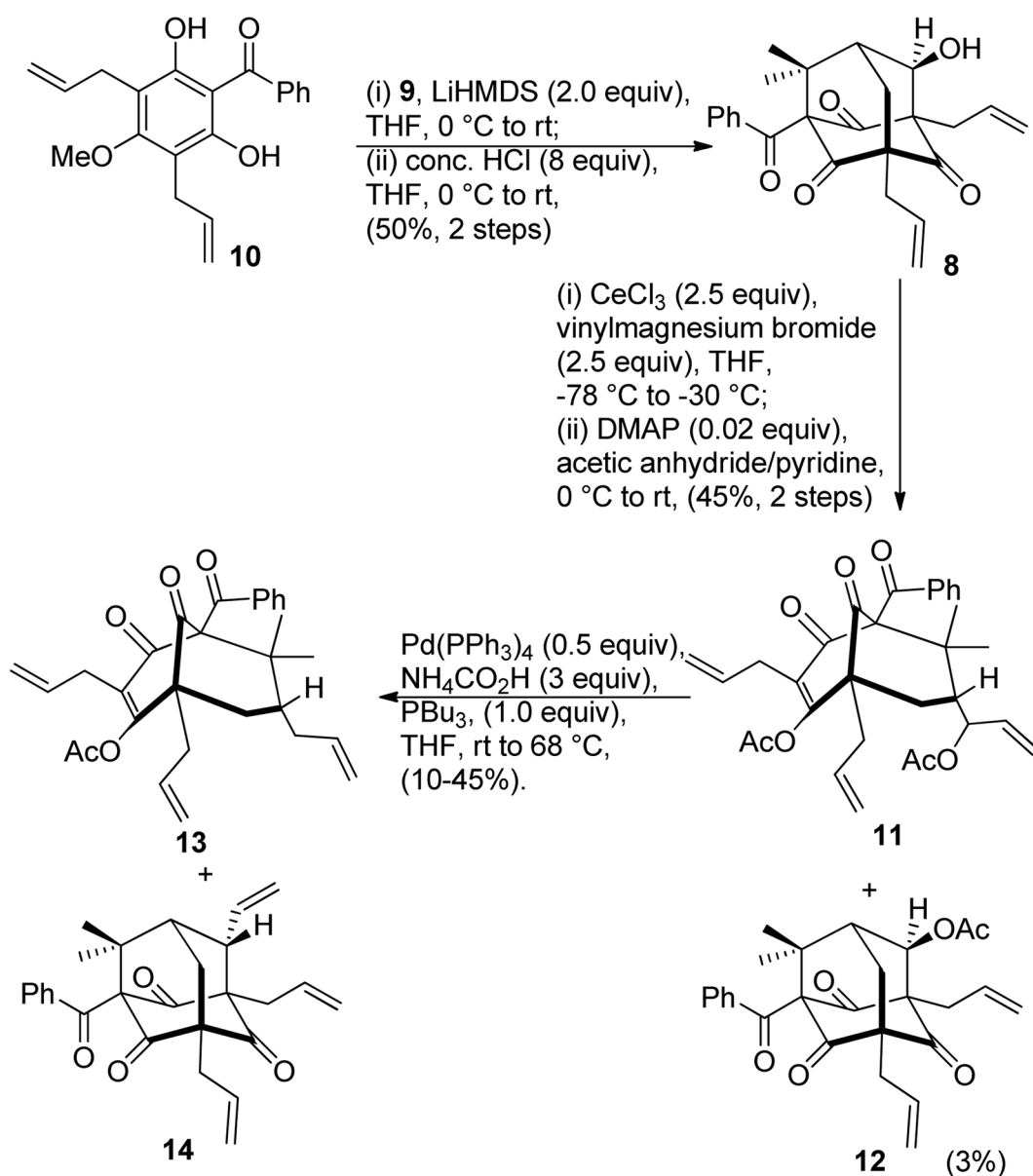
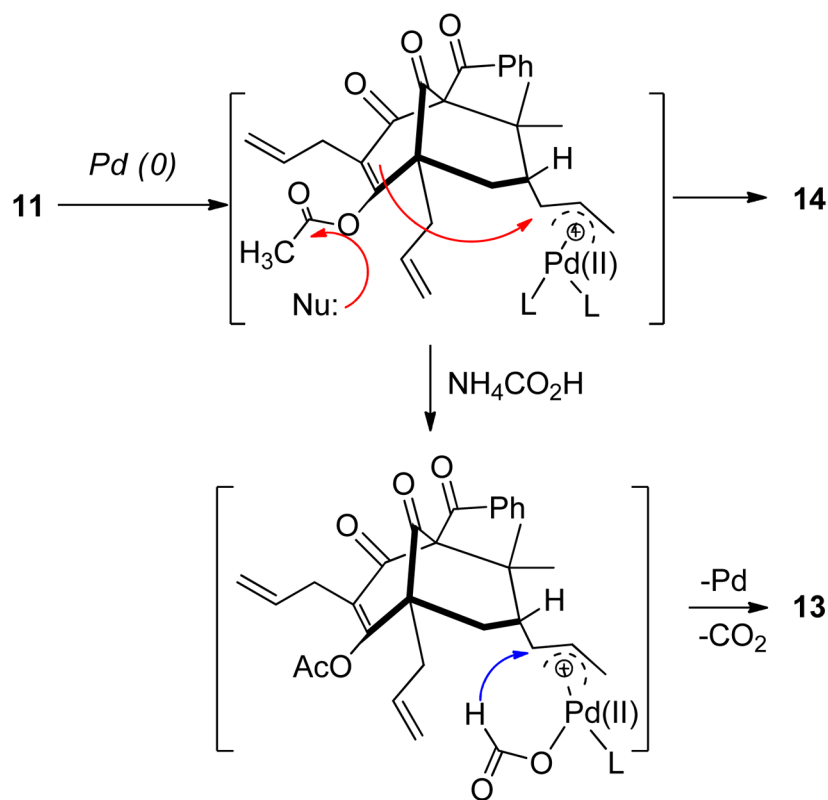


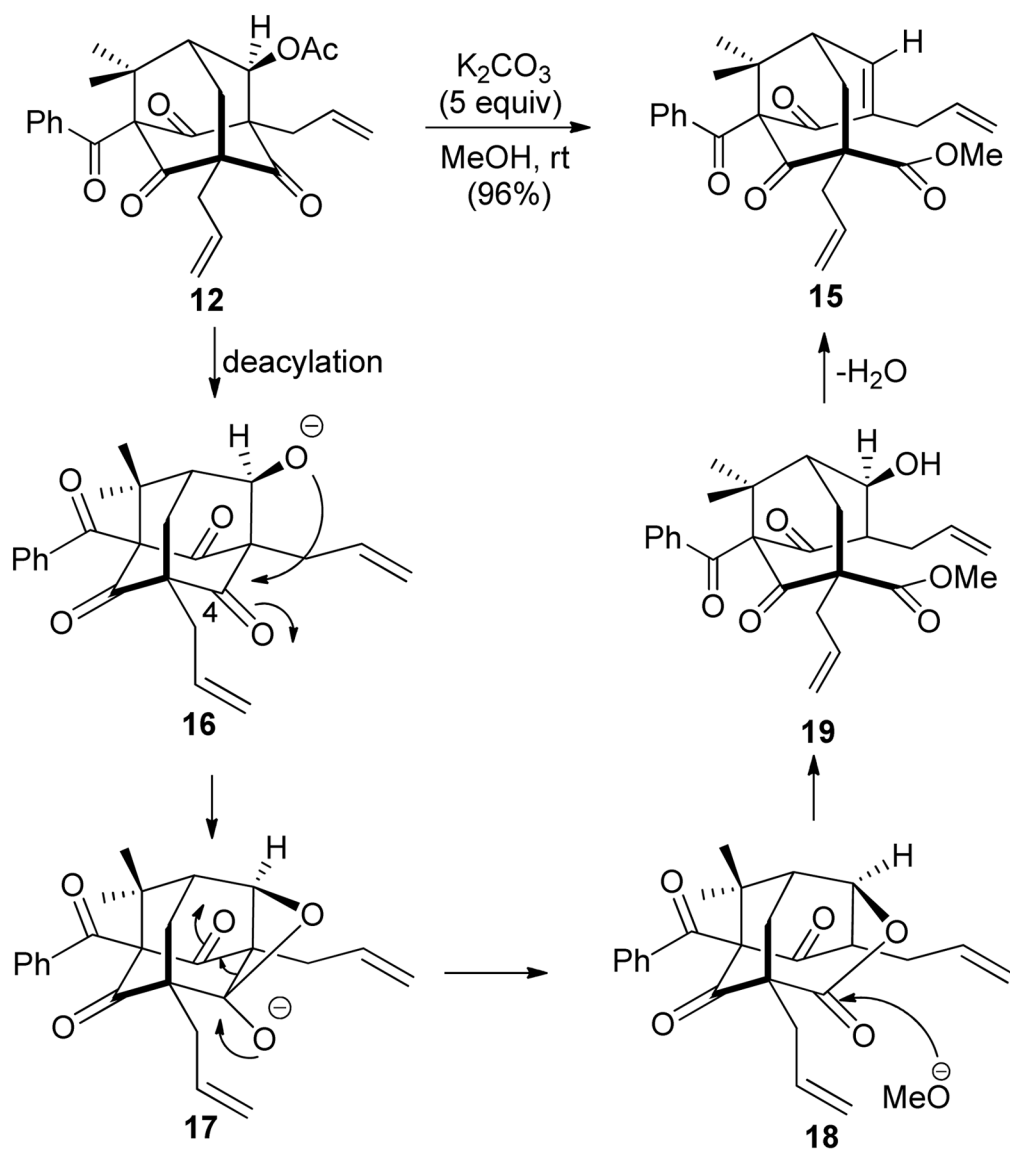
Figure 3.
X-ray crystal structure of fragmentation product **15**



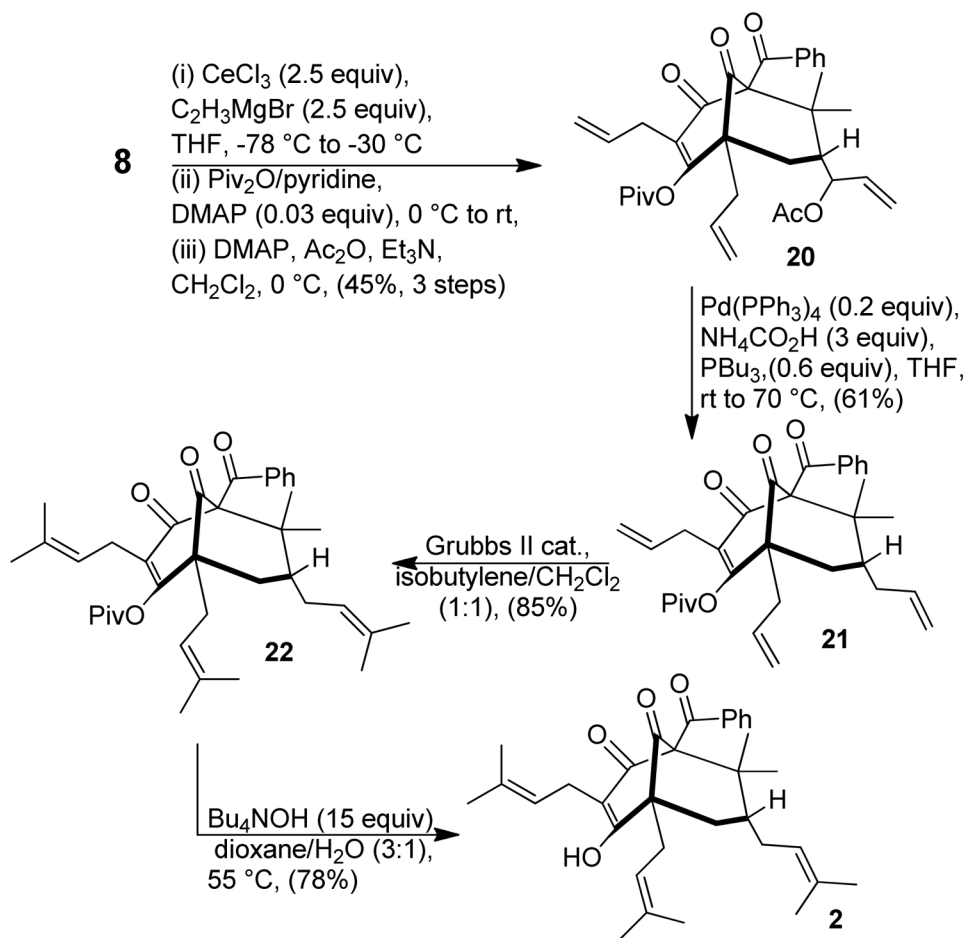
Scheme 1.
Synthesis of the 7-*epi*-nemorosone core



Scheme 2.
Cyclization vs. Reduction Processes



Scheme 3.
 An Unexpected Fragmentation Process



Scheme 4.
 Synthesis of (\pm)-7-*epi*-nemorosone