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Total Synthesis of Plukenetione A

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Abstract: We describe an alkylative dearomatization/acid-mediated adamantane annulation sequence that allows facile access to type A polyprenylated acylphloroglucinol natural products including plukenetione A. Introduction of the 2-methyl-1-propenyl moiety was achieved via stereodivergent S_N2 and S_N1 cyclizations of allylic alcohol substrates.

Introduction

The polycyclic polyprenylated acylphloroglucinol (PPAP) plukenetione A (**1**, Figure 1)[1] was isolated by Jacobs and coworkers in 1996[2] from *Clusia plukenetii* (Guttiferae) and is the first natural product bearing an adamantane framework isolated from plant sources. In addition to its unique structure, **1** has been found to inhibit the enzymatic activities of both topoisomerase I and DNA polymerase.[3] Plukenetione A may be biogenetically derived from oxidation of 7-*epi*-nemorosone (**3**).[4,5] Further oxidation of **1** may also lead to the densely functionalized derivatives **6**[6] and **7**.[5] Compounds **1**−**3** and related derivatives[7] are described as type A PPAPs.[8] Clusianone (**4**), its C7 epimer **5**,[9] and the adamantane hyperibone K (**8**)[10] are categorized as isomeric type B PPAPs. In light of their challenging structures and promising biological activities, the synthetic chemistry community has shown significant attention to the PPAP family, with a number of chemical synthesis efforts reported to date,[11] including a recent synthesis of the plukenetione core.[11i]

We have previously reported the synthesis of the type B PPAP clusianone (**4**) employing a tandem alkylative dearomatization−annulation process (Scheme 1).[12] During these studies, we found that treatment of the acylphloroglucinol clusiaphenone B (**9**) with α-acetoxy enal **10** under basic conditions led to the production of adamantane **11** via a tandem Michael addition−elimination−Michael aldol sequence proceeding through anionic

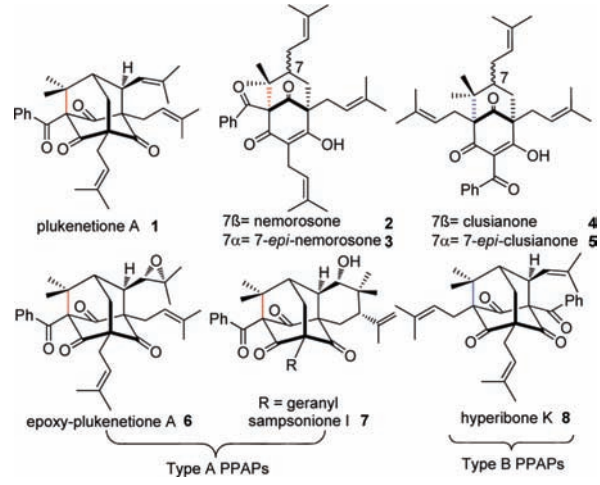
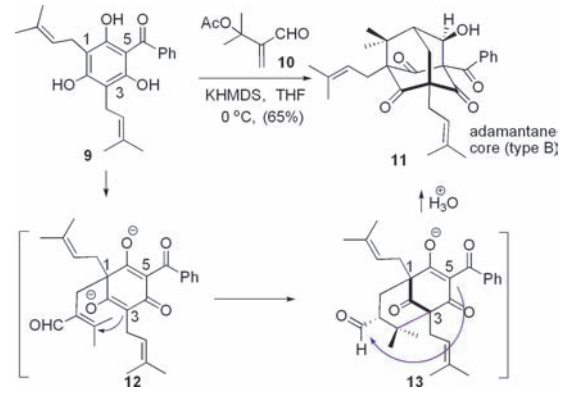


Figure 1. Polycyclic polyprenylated acylphloroglucinol (PPAP) natural products.

Scheme 1. Synthesis of the Type B Adamantane Core



intermediates **12** and **13**. In subsequent work, we developed an enantioselective variant of this transformation employing chiral phase-transfer catalysis and applied the methodology to the enantioselective synthesis of hyperibone K (**8**).[13] For acylphloroglucinol substrate **9**, alkylative dearomatization−annulation occurred chemoselectively at carbons 1 and 3. In the present work, we considered whether a protected acylphloroglucinol such as clusiaphenone methyl ether (**14**) may block initial

(1) Presented in part at the 238rd American Chemical Society National Meeting, Aug 18−23, 2009, Washington DC, ; abstract ORGN 595.
(2) Henry, G. E.; Jacobs, H.; Sean Carrington, C. M.; McLean, S.; Reynolds, W. F. *Tetrahedron Lett.* **1996**, *37*, 8663.
(3) Diaz-Carballo, D.; Malak, S.; Bardenheuer, W.; Freistuehler, M.; Peter, R. *Bioorg. Med. Chem.* **2008**, *16*, 9635.
(4) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073.
(5) Hu, L.; Sim, K. *Tetrahedron* **2000**, *56*, 1379.
(6) Christian, O. E.; Henry, G. E.; Jacobs, H.; McLean, S.; Reynolds, W. F. *J. Nat. Prod.* **2001**, *64*, 23.
(7) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279.
(8) Ciochina, R.; Grossman, R. *Chem. Rev.* **2006**, *106*, 3963.
(9) Piccinelli, A.; Cuesta-Rubio, O.; Chica, M.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206.
(10) Tanaka, N.; Takaishi, Y.; Shikishima, Y.; Nakanishi, Y.; Bastow, K.; Lee, K. H.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2004**, *67*, 1870.

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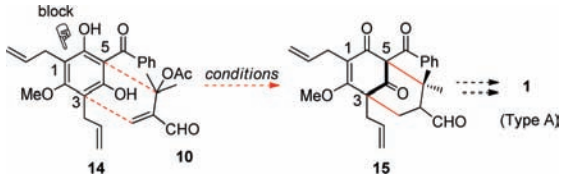
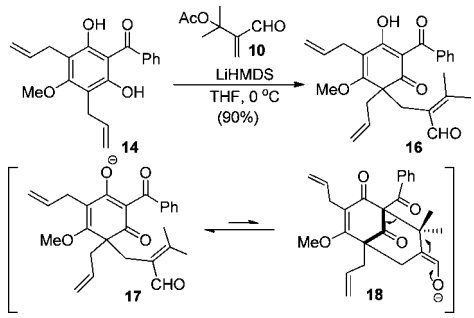


Figure 2. Alkylative dearomatization approach to type A PPAPs.

Scheme 2. Attempted Alkylative Dearomatization−Annulation



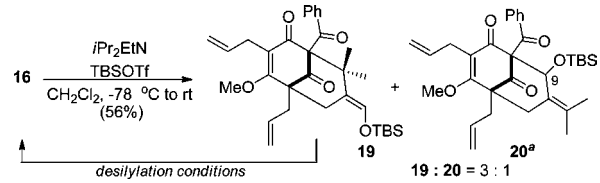
alkylative dearomatization at C1 and redirect annulation to C3 and C5 (Figure 2). Successful achievement of this approach would afford the type A PPAP framework **15** which may be further elaborated to **1** and related natural products. In this article, we report development of methodology along these lines to access the isomeric type A PPAPs, leading to the total synthesis of the complex adamantane plukenetione A (**1**).

Results and Discussion

We initiated our investigation by examining alkylative dearomatization of **14** (prepared in two steps from 5-methoxyresorcinol)[14] with α-acetoxy enal **10**[12] (Scheme 2) under basic conditions.[15] In initial studies, we found that the desired annulation product **15** was not observed, and only monodearomatized adduct **16** was obtained. The inability of enolate intermediate **17** to further cyclize to a bicyclo[3.3.1] ring system under basic conditions as previously observed in the type B series (cf. Scheme 1) is likely related to facile and reversible retro-Michael addition of **18** due to the high thermodynamic stability of enolate **17**.

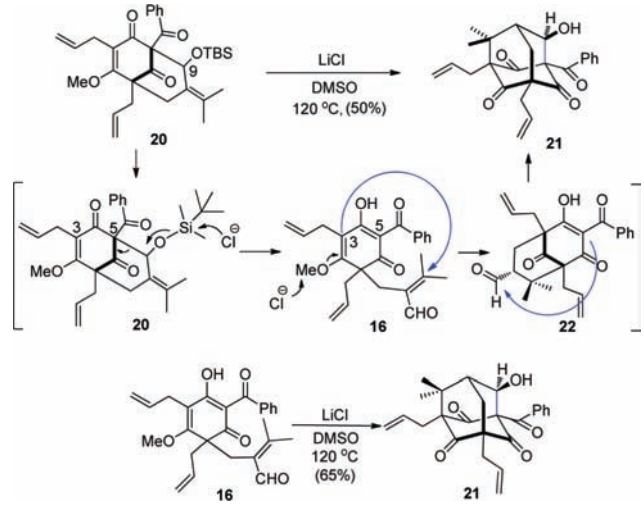
In an effort to identify irreversible cyclization conditions, silylative cyclization of **16** with TBSOTf and *N*,*N*-diisopropylethylamine (DIEA)[16] yielded the cyclized products **19** and **20** as a 3:1 mixture of structural isomers (Scheme 3). On the basis of this result, we proceeded to evaluate cyclizations of **19** and **20** under demethylation conditions to access an adamantane structure (Scheme 4). Interestingly, treatment of silyl ether **20** using conditions reported by Krapcho and co-workers[17] unexpectedly led to the formation of the type B adamantane **21**. In this case, the chloride ion may remove the silyl protecting group, thereby triggering retro-aldol fragmentation and formation of ring-opened aldehyde **16**. Further nucleophilic demethylation, followed by intramolecular Michael addition, provides aldehyde **22** which participates in intramolecular aldol cyclization to **21**. In order to further probe the proposed mechanism, treatment of dearomatized substrate **16** under identical reaction conditions led to clean formation of adamantane alcohol **21** as a single product.

Scheme 3. Silylative Cyclization to the Bicyclo[3.3.1] Ring System



[a] C9 stereochemistry unassigned. See Supporting Information.

Scheme 4. Unexpected Production of the Type B Adamantane Core



We also evaluated chlorinative cyclization[18] of silyl enol ether **19** with the expectation that this reaction mode would allow us to directly access an adamantane framework (Scheme 5). To our delight, treatment of **19** with *N*-chlorosuccinimide (NCS)[18] in the presence of LiCl to promote demethylation[17] (DMA, 60 °C) led to the formation of chloroadamantane **23** as a single diastereomer, likely through cyclization of silyloxonium (siloxycarbinyl cation)[19] **24**. Unfortunately, chloroadamantane derivative **23** was found to be resilient to desilylation and led to either no reaction or formation of byproducts under either acidic or basic fluoride-mediated reaction conditions.

(11) For select syntheses of type A PPAPs, see: (a) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (b) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619. (c) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659. (d) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (e) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895. (f) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048. (g) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840. (h) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803. (i) Takagi, R.; Inoue, Y.; Ohkata, K. *J. Org. Chem.* **2008**, *73*, 9320. (j) Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430. (k) Shimizu, Y.; Shi, S.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (l) Simpkins, N.; Taylor, J.; Weller, M.; Hayes, C. *Synlett* **2010**, *4*, 639. (m) Abe, M.; Saito, A.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 1298.

(12) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682.

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

(14) Mitasev, B.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 2285.

(15) See Supporting Information for complete experimental details.

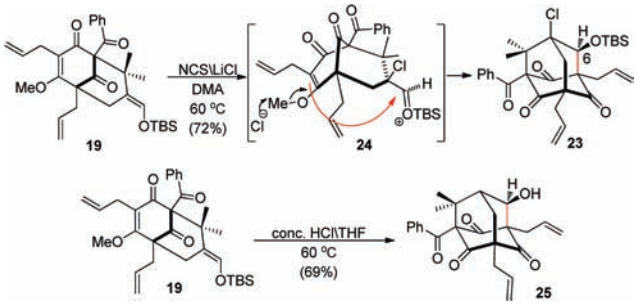
(16) Kozikowski, A. P.; Jung, S. *J. Org. Chem.* **1986**, *51*, 3400.

(17) Krapcho, A.; Weimaster, J.; Eldridge, J.; Jahngen, E.; Lovey, A.; Stephens, W. *J. Org. Chem.* **1978**, *43*, 138.

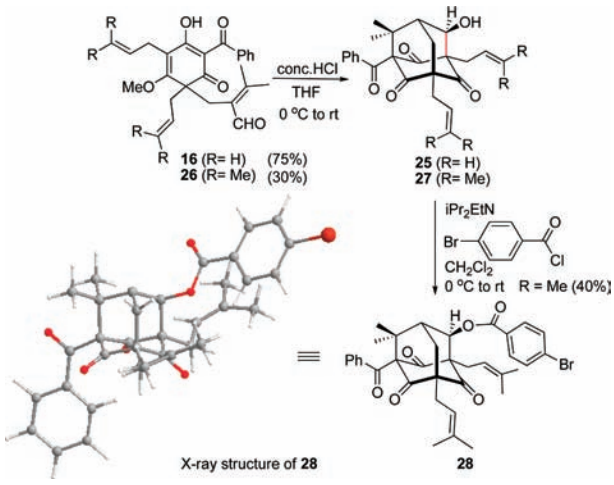
(18) For a review of NCS-mediated reactions, see: Golebiewski, W. M.; Gucma, M. *Synthesis* **2007**, *23*, 3599.

(19) (a) Hambly, G. F.; Chan, T. H. *Tetrahedron Lett.* **1986**, *27*, 2563. (b) Ohkata, K.; Mase, M.; Akiba, K. *J. Chem. Soc., Chem. Commun.* **1987**, *22*, 1727.

Scheme 5. Synthesis of the Type A Adamantane Framework



Scheme 6. Direct Access to the Adamantane Core of **1**



The latter observation led us to reevaluate the possibility for protonation/cyclization of **19** to directly access the adamantane core of plukenetione A. Subjection of silyl enol ether **19** to conventional desilylation conditions and Lewis and Brønsted acids (e.g., TFA and AcOH) generally led to formation of ring-opened product **16** or the rearomatized acylphloroglucinol **14** (Scheme 3).[20] After a survey of conditions, we found that exposure of **19** to concentrated HCl in THF (4 equiv) led to the production of adamantane alcohol **25** in 69% yield as a single diastereomer (cf. Scheme 5). As we suspected hydrolysis of **19** to enal **16** under the reaction conditions, we found that treatment of **16** or its bis-prenylated variant **26** with concentrated HCl in THF led directly to adamantanes **25** and **27** (Scheme 6),[21] enabling rapid construction of the plukenetione A core in two steps from acylphloroglucinol **14**. The structure of adamantane **27** was confirmed by acylation to *p*-bromobenzoate **28** and X-ray crystal structure analysis.[15]

Two possible pathways for the acid-mediated adamantane cyclization are shown in Figure 3. In pathway a, the protonated aldehyde **29** may undergo demethylative aldol cyclization[22] to **30** which may be followed by protonation of the tetrasubstituted alkene and cationic cyclization[11i] to afford **25**. In pathway b, the allylic cation resonance structure **31** derived from **29** may participate in cationic cyclization,[11i] leading to the production of bicyclo[3.3.1]

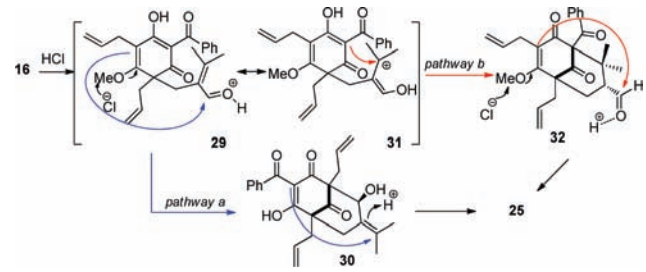
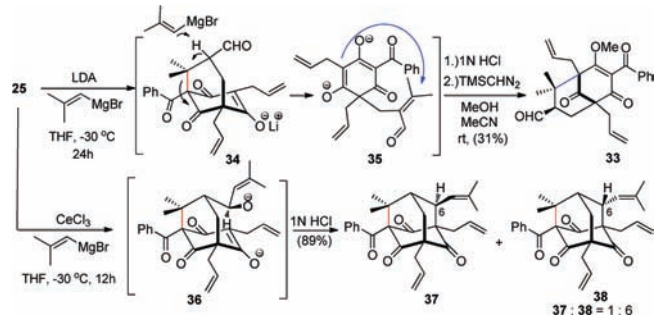


Figure 3. Possible reaction mechanisms for adamantane formation.

Scheme 7. Retro-Aldol/Organocerium Addition



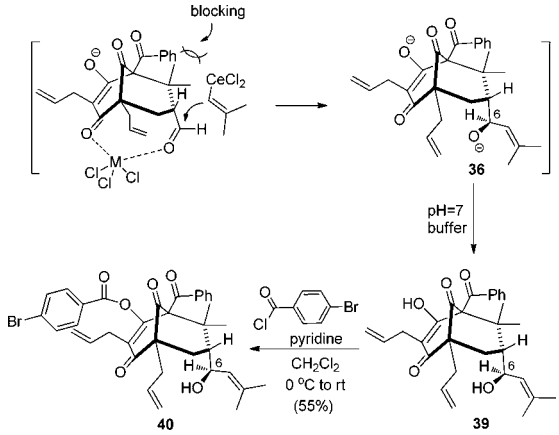
derivative **32** which may undergo final demethylative aldol cyclization[22] to afford adamantane **25**.[23]

We next investigated whether adamantane alcohol **25** could be converted to plukenetione A using the retro-aldol/alkenyl metal addition protocol employed in our hyperibone K synthesis.[13] Unexpectedly, exposure of **25** to LDA followed by addition of 2-methyl-1-propenyl magnesium bromide led to fragmentation to provide the clusianone (type B PPAP) aldehyde **33** after enol methylation of the crude product (Scheme 7). This cascade process likely occurs by deprotonation of derived aldehyde **34**, followed by retro-Michael reaction to intermediate **35**, which may undergo subsequent intramolecular Michael addition. The structure of **33** was further confirmed by treatment with $Sc(OTf)_3$ in CH_3NO_2 to afford the type B PPAP adamantane derivative **21**.[13,15] After surveying a number of base/nucleophile combinations, the fragmentation process was circumvented by cerium(III) chloride-promoted reaction of the alkenyl Grignard reagent,[24] which cleanly afforded the desired adduct **36** without noticeable side reactions. Interestingly, quenching of the organocerium reaction with 1 N HCl led to the production of adamantanes **37** and **38** as a 1:6 mixture of isomers, favoring the undesired stereoisomer **38**.

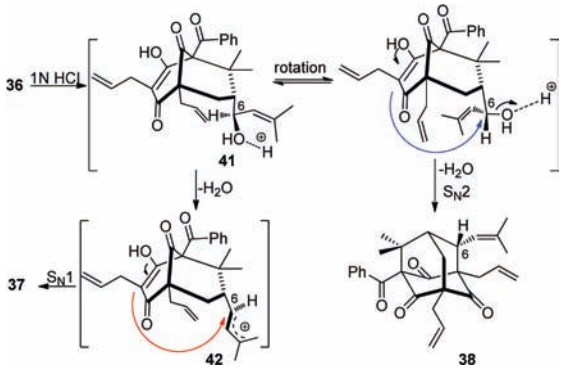
On the basis of these results, we continued to probe the reaction mechanism leading to adamantanes **37** and **38** and the possibility to reverse the selectivity. We found that quenching of organocerium addition with pH 7 buffer led to formation of an enol intermediate, **39**, which was acylated directly with *p*-bromobenzoyl chloride to provide enol ester **40** (Scheme 8) along with its enol ester isomer. The structure of **40** was confirmed by single X-ray crystal structure analysis (Figure 4).[15] Inspection of this structure indicates that the configuration at C6 of the allylic alcohol of **36** may be derived from long-range chelation between Ce(III) (or Mg (II)) of the enol/

(20) For rearomatization of dearomatized acylphloroglucinols, see: Raikar, S.; Nuhant, P.; Delpech, B.; Marazano, C. *Eur. J. Org. Chem.* **2008**, *8*, 1358.
(21) Anhydrous HCl was also examined with substrates **16** and **19** at room temperature, leading to recovery of starting materials after 2 days.
(22) For demethylative aldol reactions, see: Murakami, M.; Minamikawa, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 1051.
(23) According to the insightful recommendation of a reviewer, demethylation of intermediates **29** and **32** may also occur by hydrolysis of oxonium intermediates produced after cyclization.
(24) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

Scheme 8. Proposal for Diastereoselectivity in the Grignard Addition



Scheme 9. Rationale for Stereoselectivity

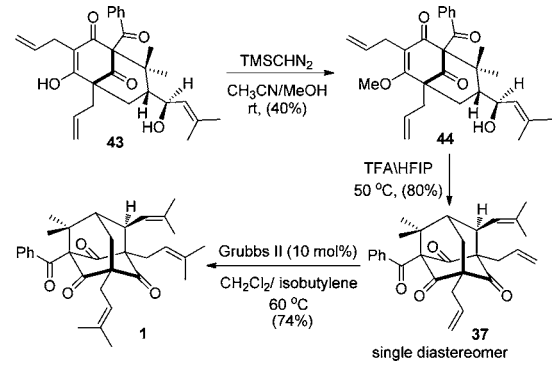


ketone[25] moiety and the aldehyde, followed by facially selective addition of the alkenyl metal reagent to the face away from the *gem*-dimethyl moiety.

On the basis of the cyclization results and the observed stereochemistry at C6, we propose a rationale for stereoselectivity of the adamantane cyclization as shown in Scheme 9. Quenching of intermediate **36** with 1 N HCl should lead to protonated enol **41**, which is properly situated for S_N2 cyclization[26] leading to formation of the C6-*epi* derivative **38**. Alternatively, ionization of allylic alcohol **41** should afford allylic cation **42** which may undergo cationic (S_N1) cyclization leading to **37**.[13]

Given the high reactivity of the free enol/allylic alcohol **39**/**43**, we proceeded to methylate the crude enols **39**/**43** in an effort to lower its nucleophilicity in the form of vinylogous ester **44** and access an S_N1 cyclization mode (Scheme 10). Gratifyingly, treatment of **44** with TFA (10 equiv) in hexafluoroisopropanol (HFIP)[27] as solvent led to selective formation of adamantane derivative **37**. Other cyclization conditions were also attempted on substrate **44**, including use of $Sc(OTf)_3$ and the cation-stabilizing solvent nitromethane ($MeNO_2$), which afforded **37** and **38** in a 1:3 ratio. Olefin cross-metathesis of **37** using isobutylene in the presence of the Grubbs II[28] metathesis catalyst afforded

Scheme 10. Completion of the Synthesis of Plukenetione A[a]



[a] For **44**, one enol ether isomer shown for clarity.

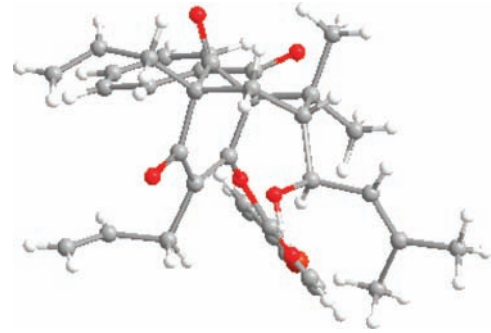


Figure 4. X-ray structure of enol ester **40**.

plukenetione A (**1**) in 74% yield. Spectral data for **1** (^1H NMR, ^{13}C NMR, mass spectrum) were in full agreement with data reported for the natural product.[2,15]

Conclusion

In summary, we have developed an expedient approach to the type A PPAP natural products including plukenetione A (**1**). The strategy relies on introduction of an ether blocking group on an acylphloroglucinol substrate to direct the regiochemistry for alkylative dearomatization−annulation and acid-mediated cyclization to construct the adamantane core. Introduction of the 2-methyl-1-propenyl moiety of **1** was achieved via stereodivergent S_N2 and S_N1 cyclizations of allylic alcohol substrates. Studies to further probe the mechanism of the acid-mediated adamantane cyclization as well as the synthesis and biological evaluation of other type A PPAP natural product targets are currently underway and will be reported in due course.

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Note Added after ASAP Publication. Schemes 1 and 6 contained errors in the version published ASAP September 15, 2010; the correct version reposted September 20, 2010.

Supporting Information Available: Experimental procedures and characterization data for all new compounds; X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA105784S

(25) For eight -membered-ring chelation using Sm(III), see: (a) Molander, G.; McKie, J. *J. Am. Chem. Soc.* **1993**, *115*, 5821. Using Mg(II): (b) Chung, K.; Chu, C.; Chang, M. *Bull. Korean Chem. Soc.* **2004**, *25*, 417.
(26) For S_N1 vs S_N2 reactivity in metal triflate-catalyzed alkylations, see: Noji, M.; Konno, Y.; Ishii, Y. *J. Org. Chem.* **2007**, *72*, 5161.
(27) For solvolytic reactions in fluorinated alcohols, see: (a) Bentley, T. W.; Llewellyn, G.; Ryu, Z. *J. Org. Chem.* **1998**, *63*, 4654. For a review on fluorinated solvents, see: (b) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925.
(28) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.