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Total Synthesis of Plukenetione A

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Abstract

We describe an alkylative dearomatization/acid-mediated adamantane annulation sequence which allows facile access to type A polyprenylated acylphloroglucinol (PPAP) 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** 1 (Figure 1) was isolated by Jacobs and coworkers in 19962 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 derivatives7 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 (MEM)-aldol sequence proceeding through anionic intermediates **12** and **13**. In subsequent work, we have developed an enantioselective variant of this transformation employing chiral phase transfer catalysis and have 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 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**.

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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.

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 mono-dearomatized 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 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). Based on 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 coworkers 17 unexpectedly led to the formation of the type B adamantane **21**. In this case, the chloride ion may remove the silyl protecting group 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.

We also evaluated chlorinative cyclization18 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 demethylation17 (DMA, 60 °C) led to the formation of chloroadamantane **23** as a single diastereomer, likely thru 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.

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, Lewis, and Bronsted acids (*e.g*. TFA and AcOH) generally led to formation of ring-opened product **16** or rearomatized acylphloroglucinol **14** (Scheme 3).20 After a survey of conditions, we found that exposure of **19** to conc. HCl in THF (4 equiv) led to the production of adamantane alcohol **25** in 69% yield as a single diastereomer (*cf*. Scheme 1). As we suspected hydrolysis of **19** to enal **16** under the reaction conditions, we found that treatment of both **16** or its the *bis*-prenylated variant **26** with conc. 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 cyclization22 to **30** which may be followed by protonation of the tetrasubstituted alkene and cationic cyclization11i to afford **25**. In pathway b, the allylic cation resonance structure **31** derived from **29** may participate in cationic cyclization11i leading to the production of bicyclo [3.3.1] derivative **32** which may undergo final demethylative aldol cyclization22 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 reagent24 which cleanly afforded the desired adduct **36** without noticeable side reactions. Interestingly, quenching of the organocerium reaction with 1N HCl led to the production of adamantanes **37** and **38** as a 1 to 6 mixture of isomers favoring the undesired stereoisomer **38**.

Based on 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.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/ketone25 moiety and the aldehyde followed by facially selective addition of the alkenyl metal reagent to the face away from the *gem*-dimethyl moiety.

Based on the cyclization results and the observed stereochemistry at C6, we propose a rationale for stereo-selectivity of the adamantane cyclization as shown in Scheme 9. Quenching of intermediate **36** with 1N HCl should lead to protonated enol **41** which is properly situated for S_N2 cyclization26 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 enol **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 II28 metathesis catalyst afforded plukenetione A **1** in 74% yield. Spectral data for **1** (^{1}H 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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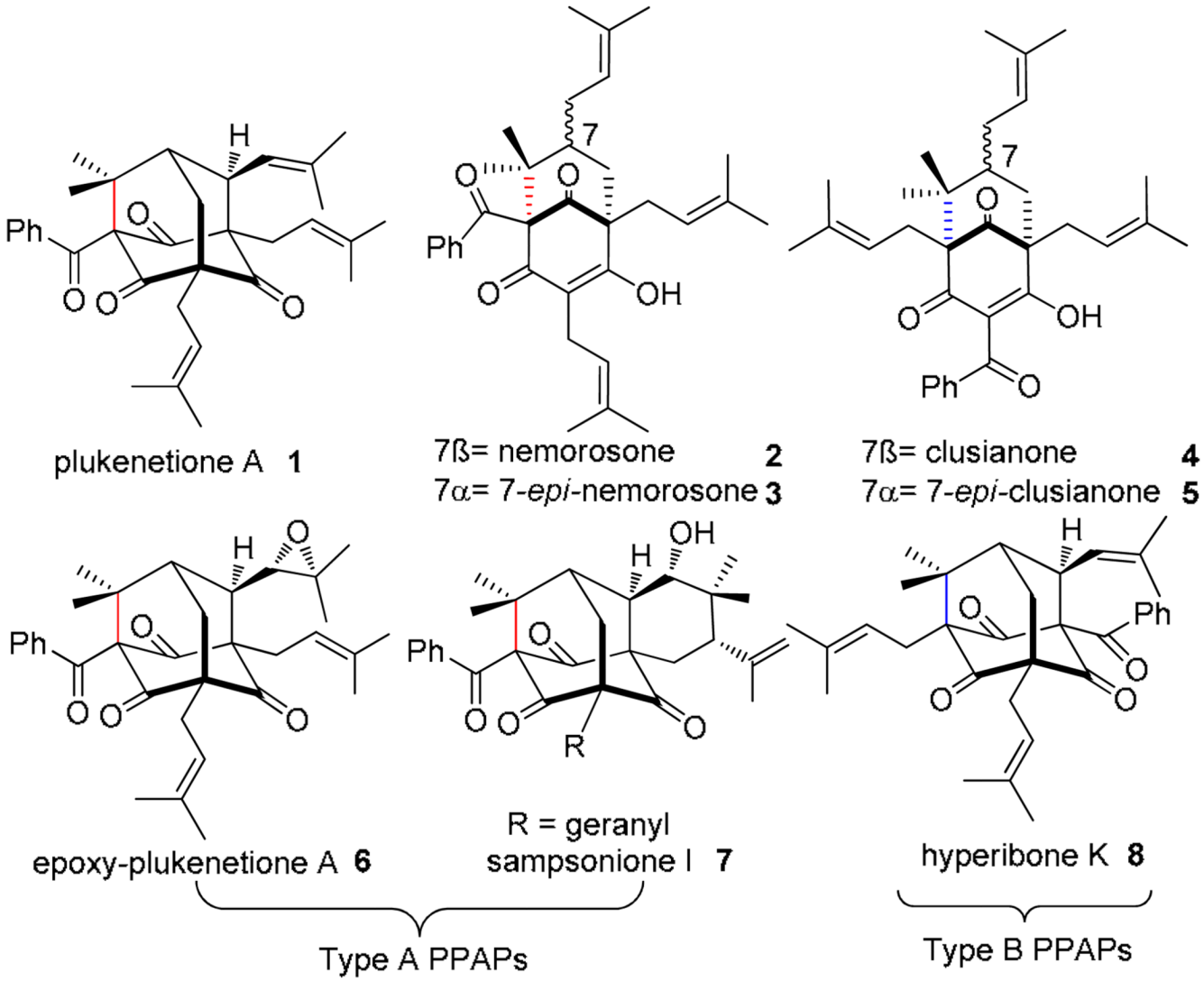


Figure 1.
Polycyclic polyprenylated acylphloroglucinol natural products

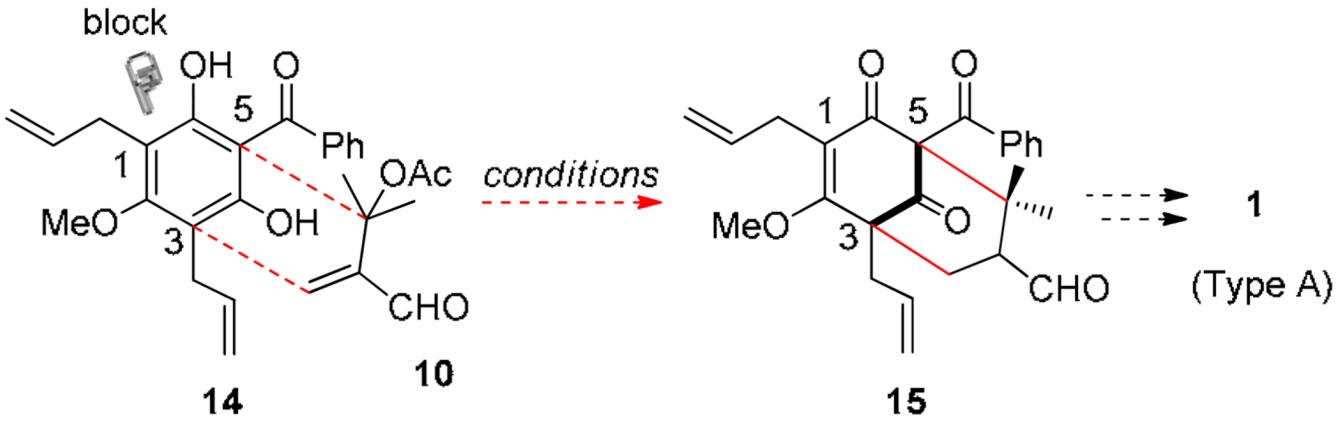


Figure 2.
Alkylative Dearomatization Approach to type A PPAPs

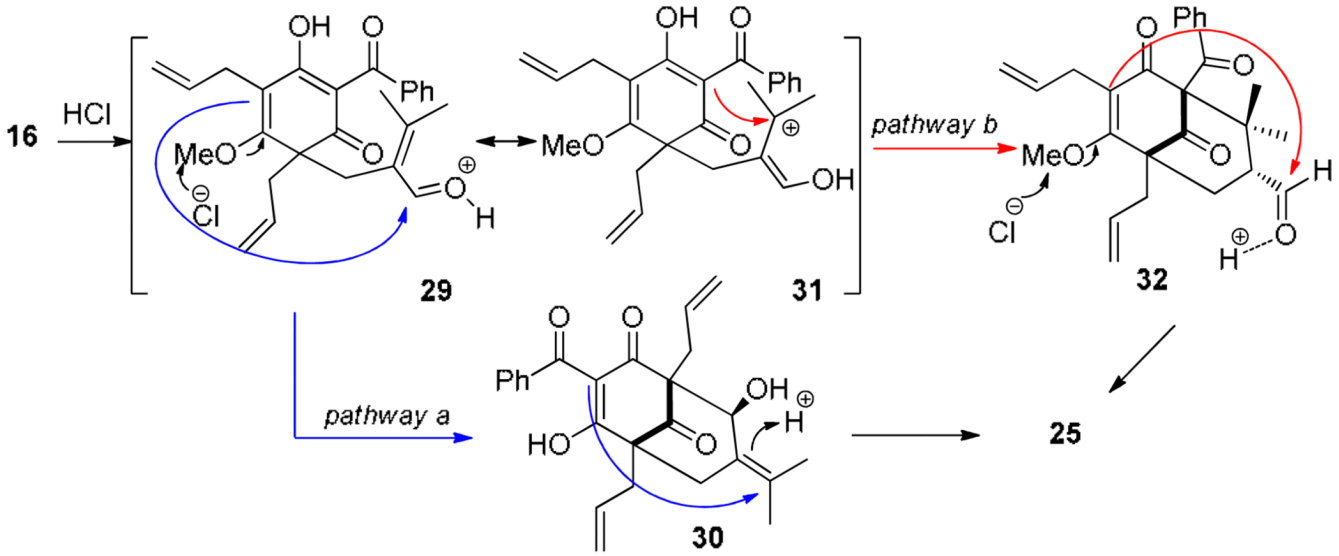


Figure 3.
Possible reaction mechanisms for adamantane formation

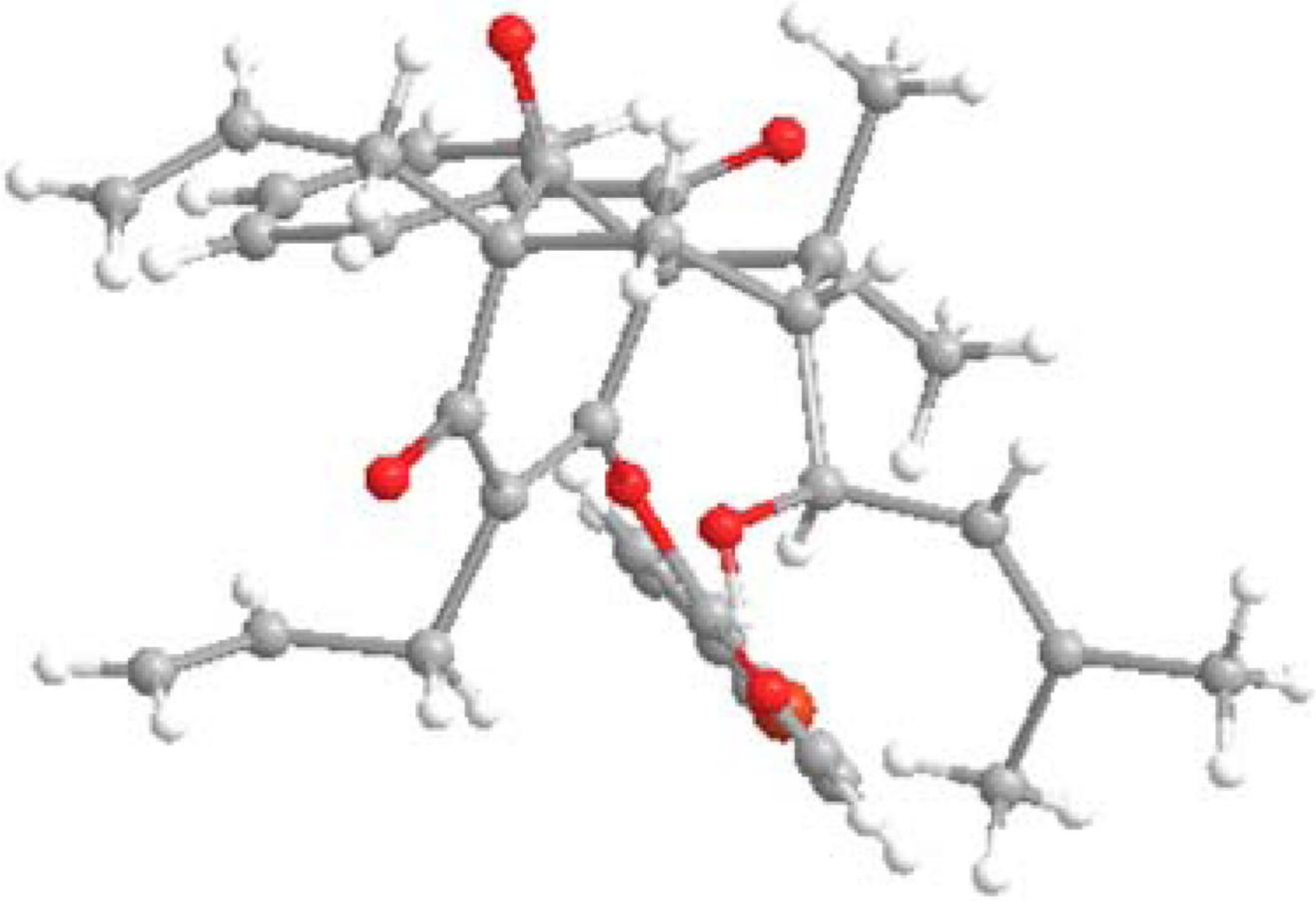
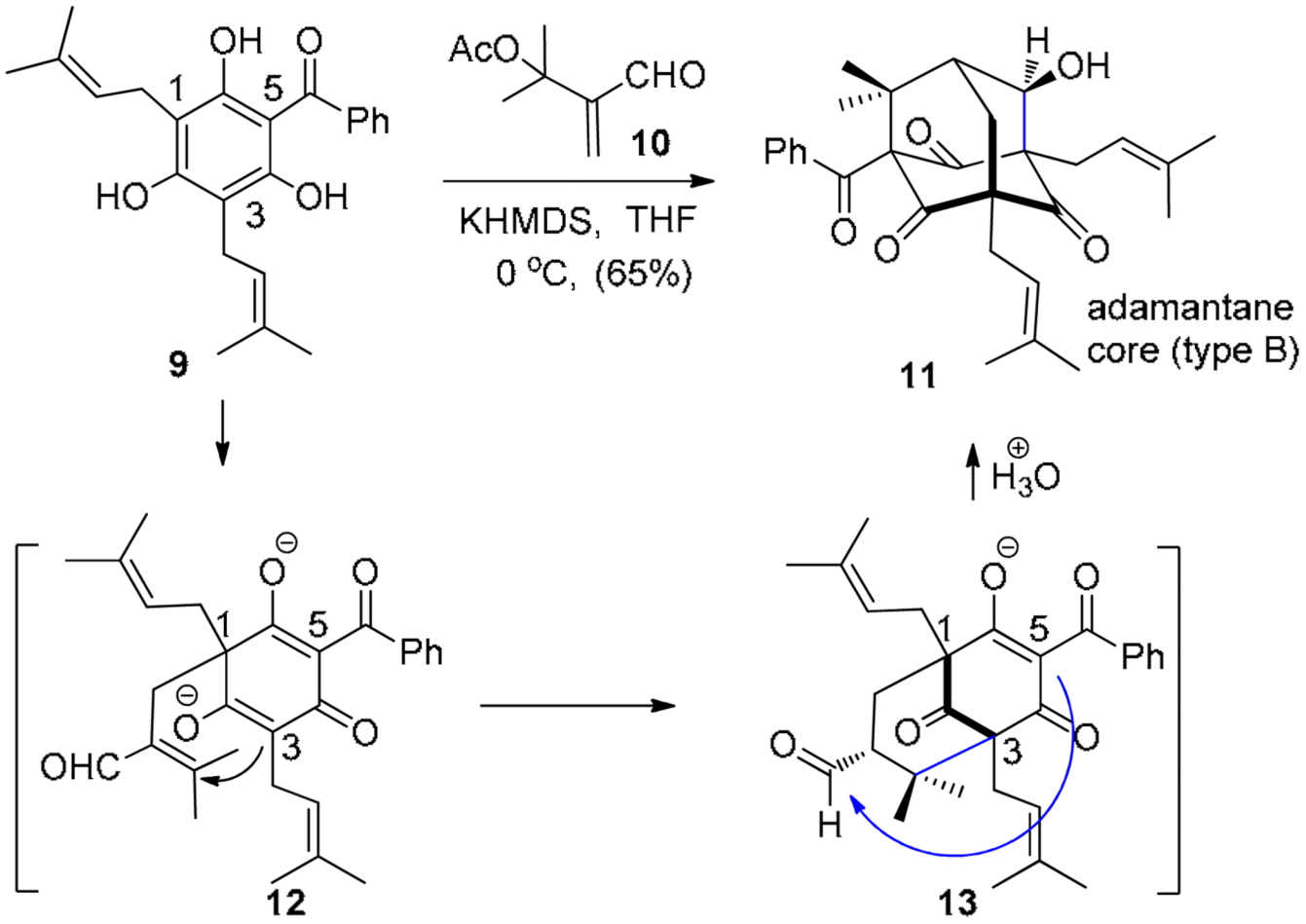
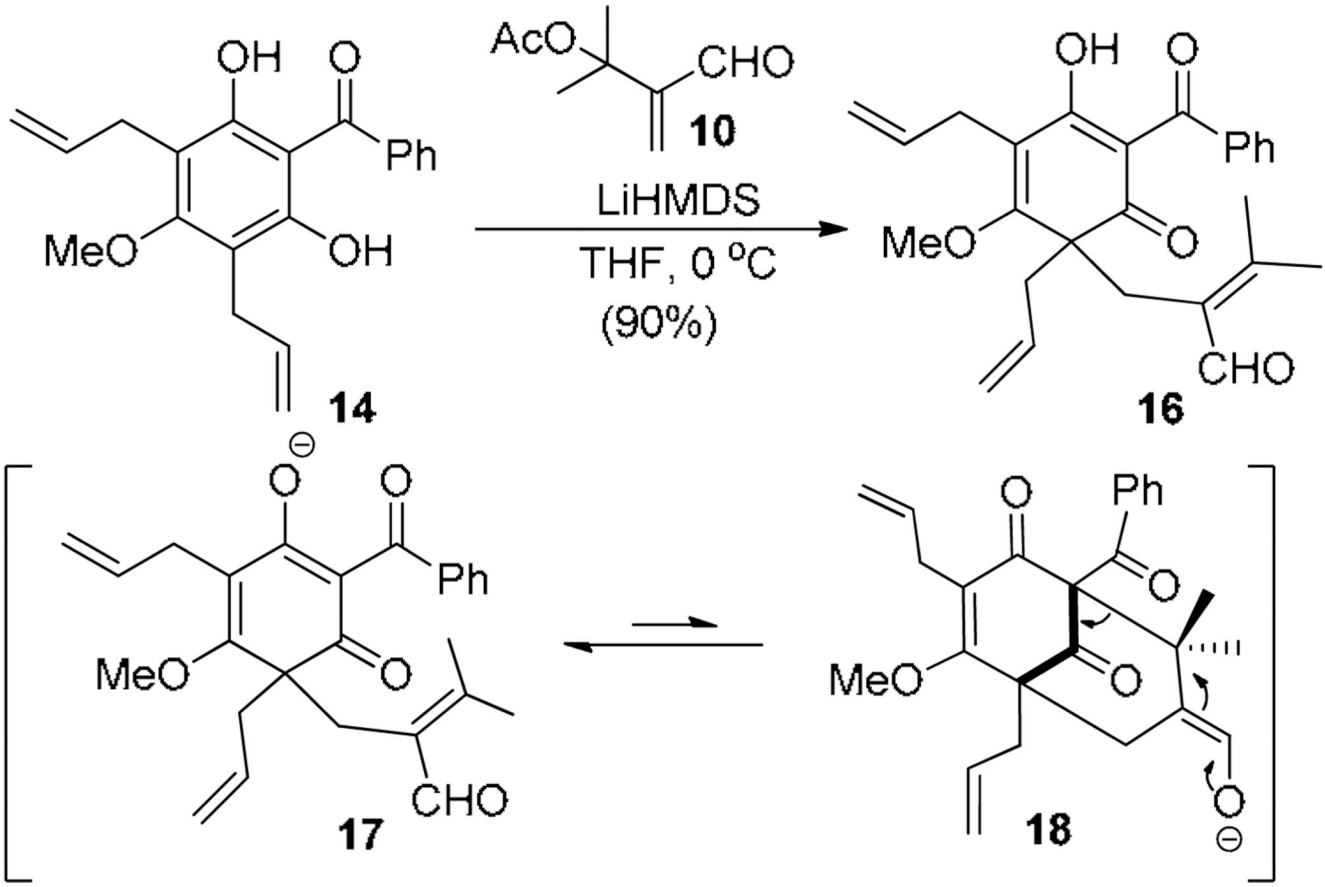


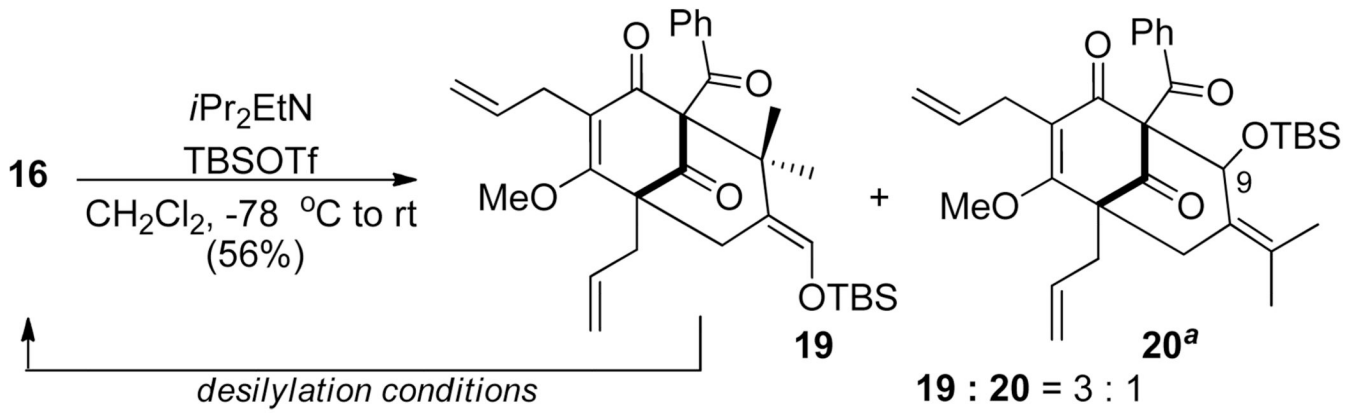
Figure 4.
X-ray structure of enol ester **40**



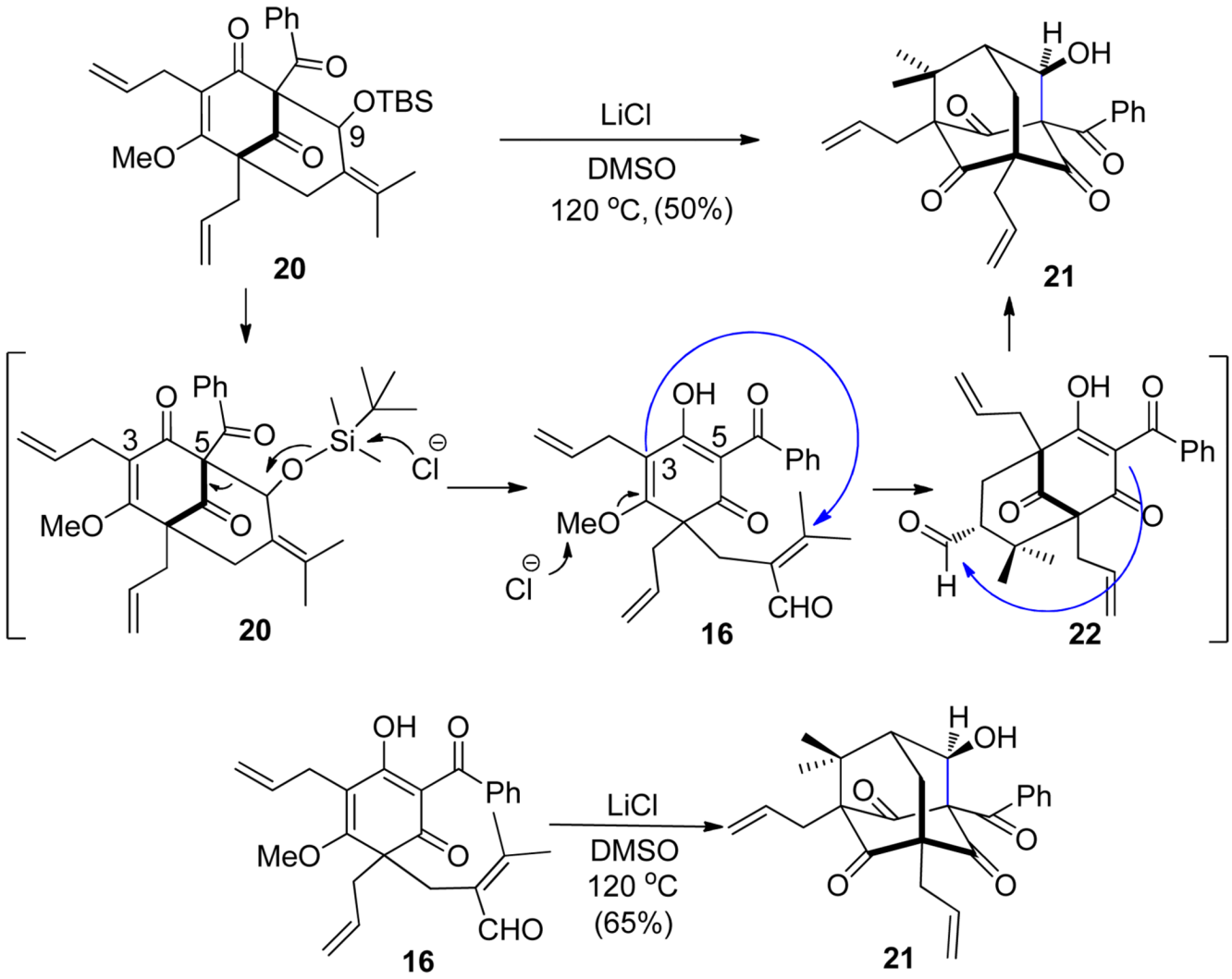
Scheme 1.
Synthesis of the type B adamantane core



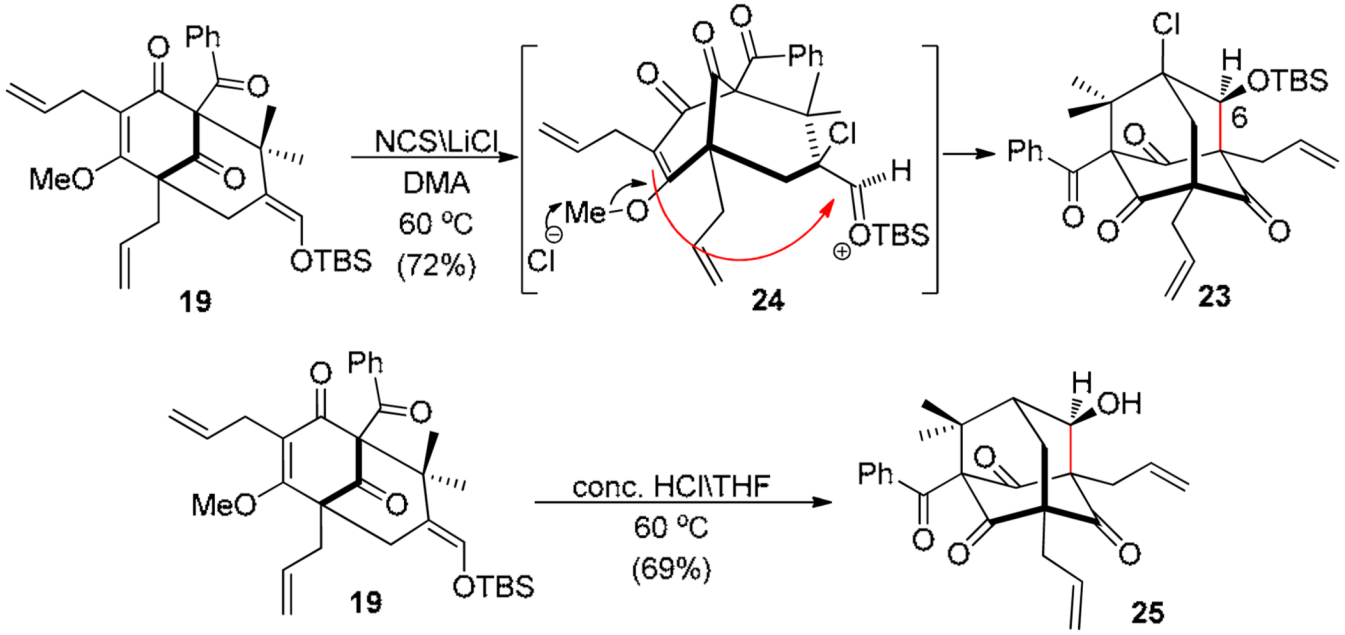
Scheme 2.
Attempted alkylative dearomatization/annulation



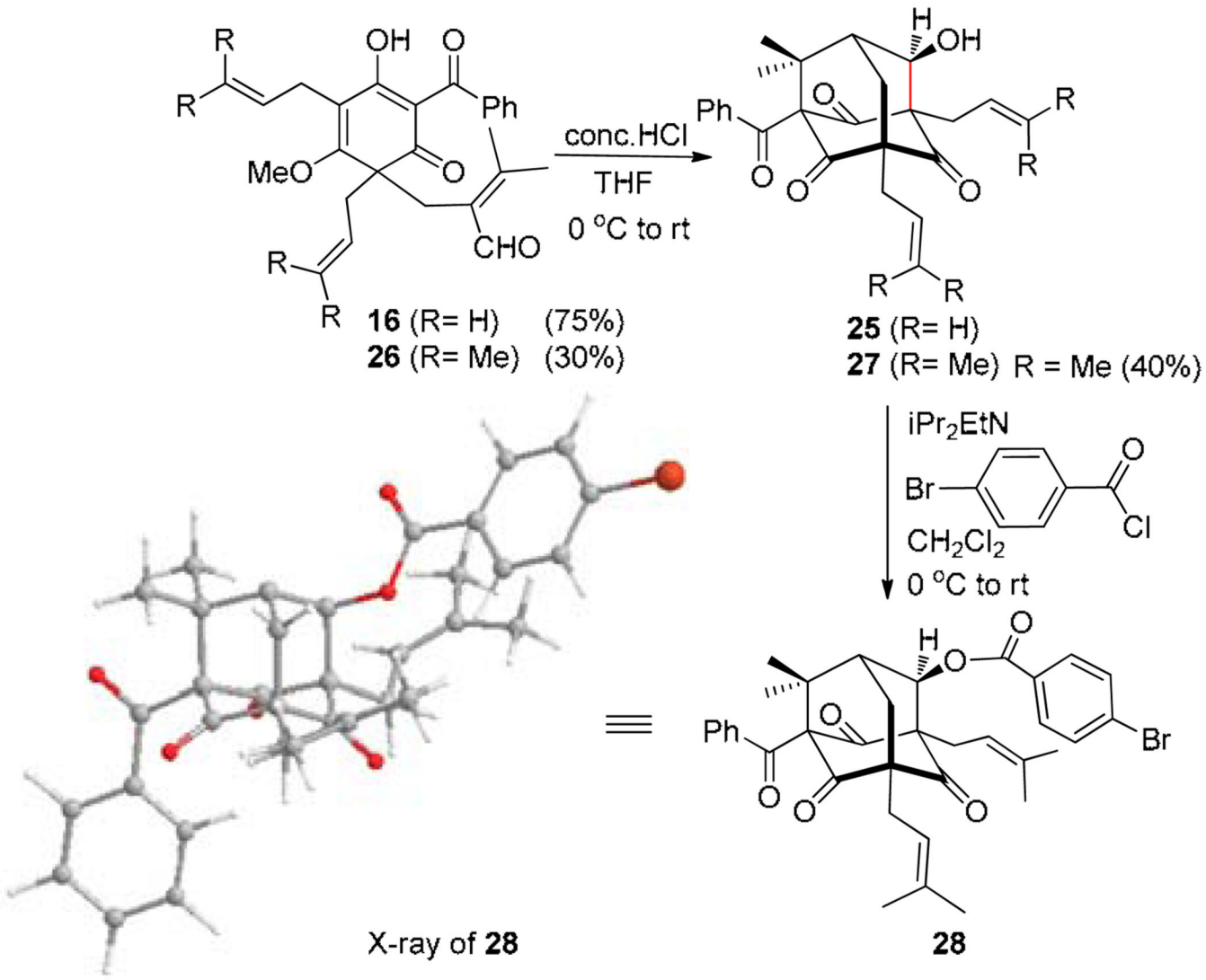
Scheme 3.
Silylative cyclization to the bicyclo [3.3.1] ring system
[a] C9 stereochemistry unassigned. See Supporting Information



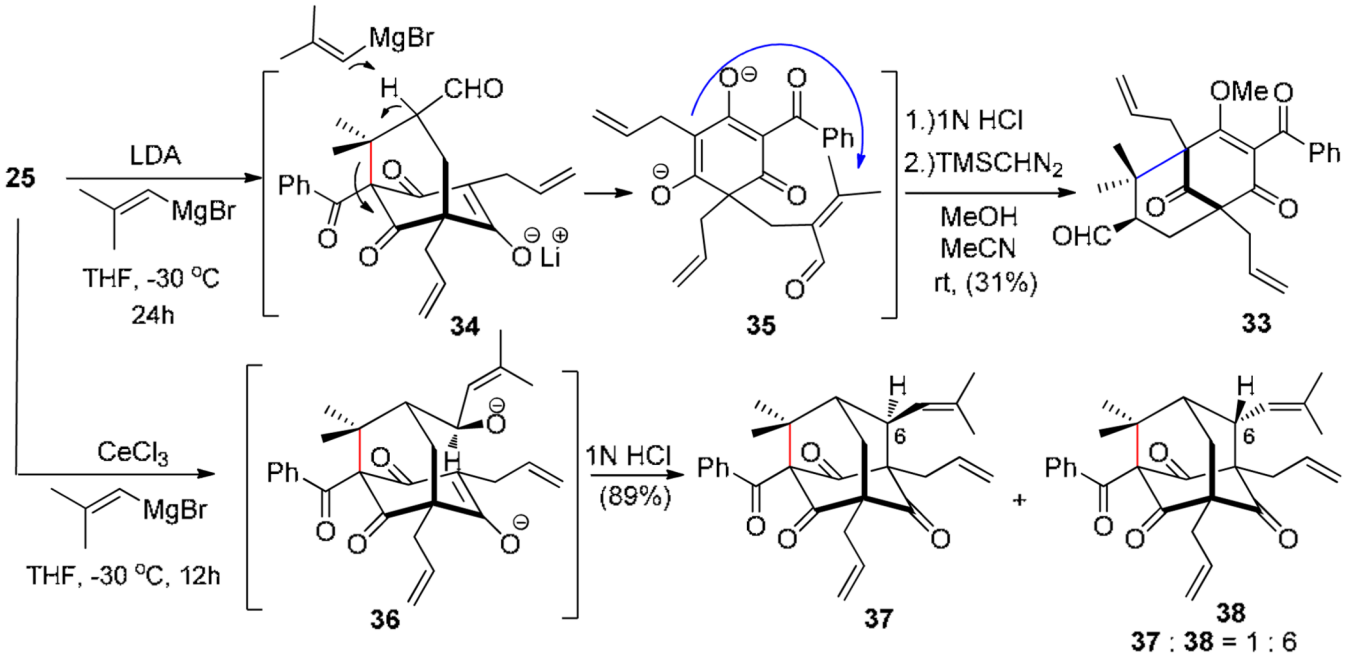
Scheme 4.
Unexpected production of the type B adamantine core



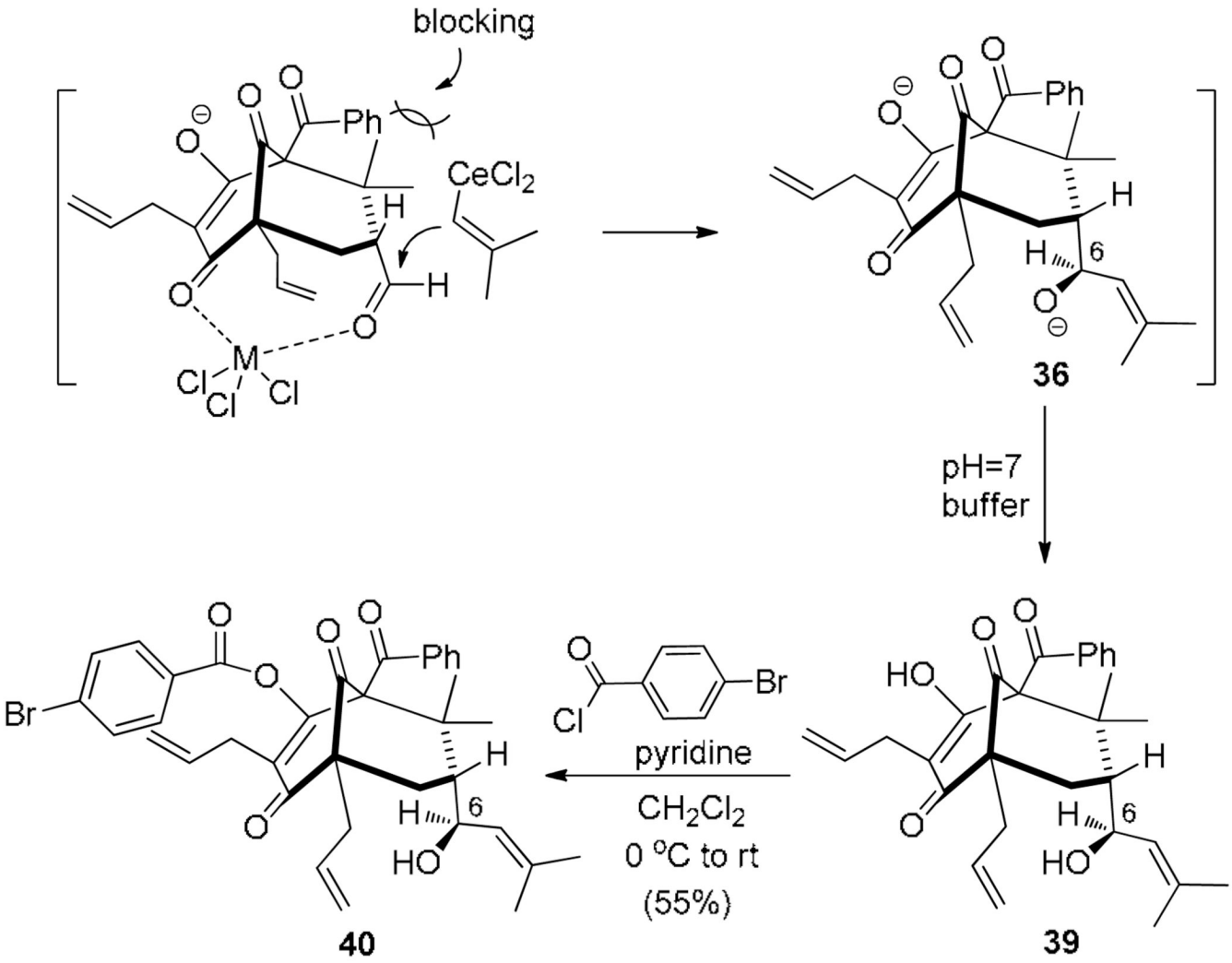
Scheme 5.
Synthesis of the type A adamantane framework



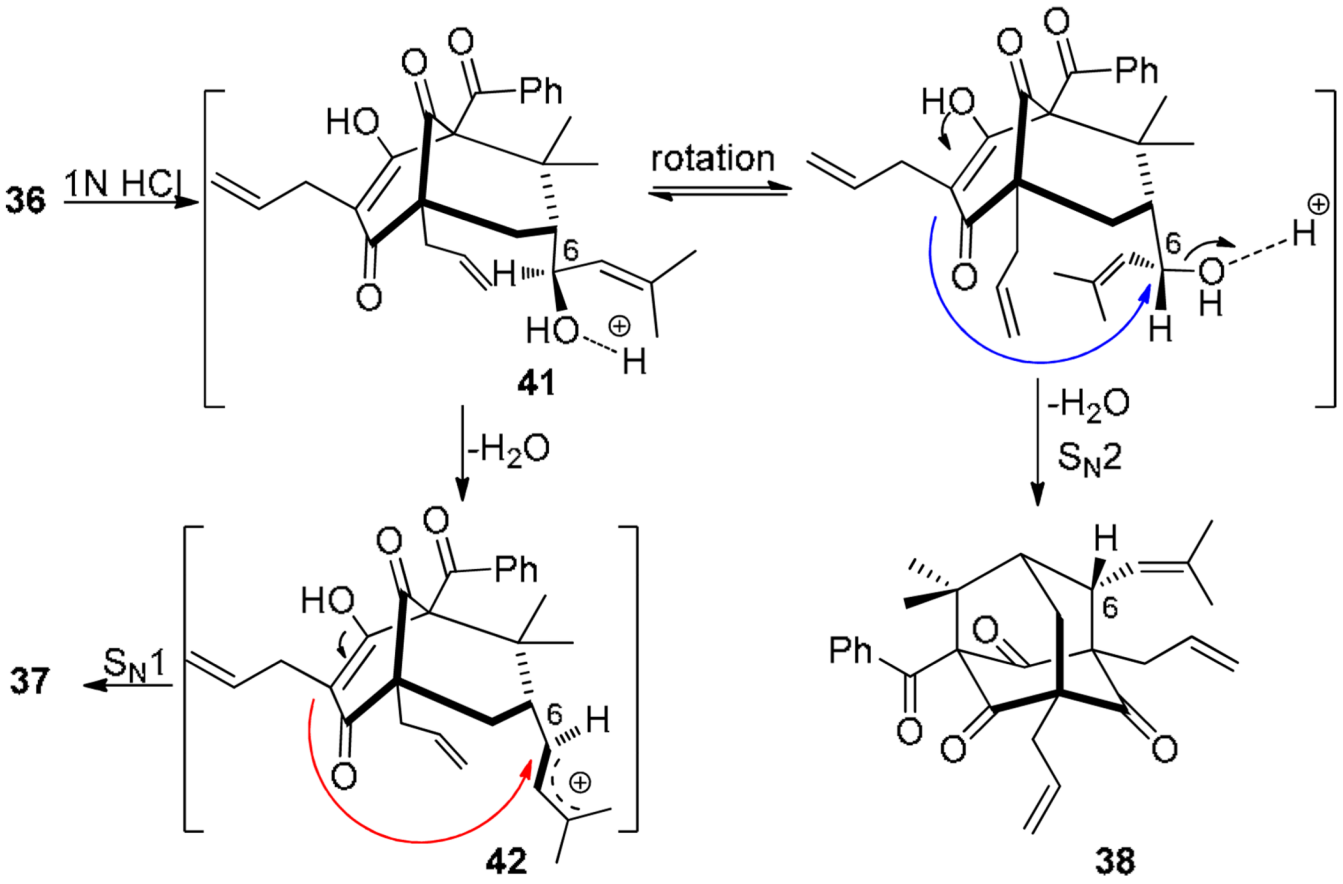
Scheme 6.
Direct access to the adamantane core of **1**.



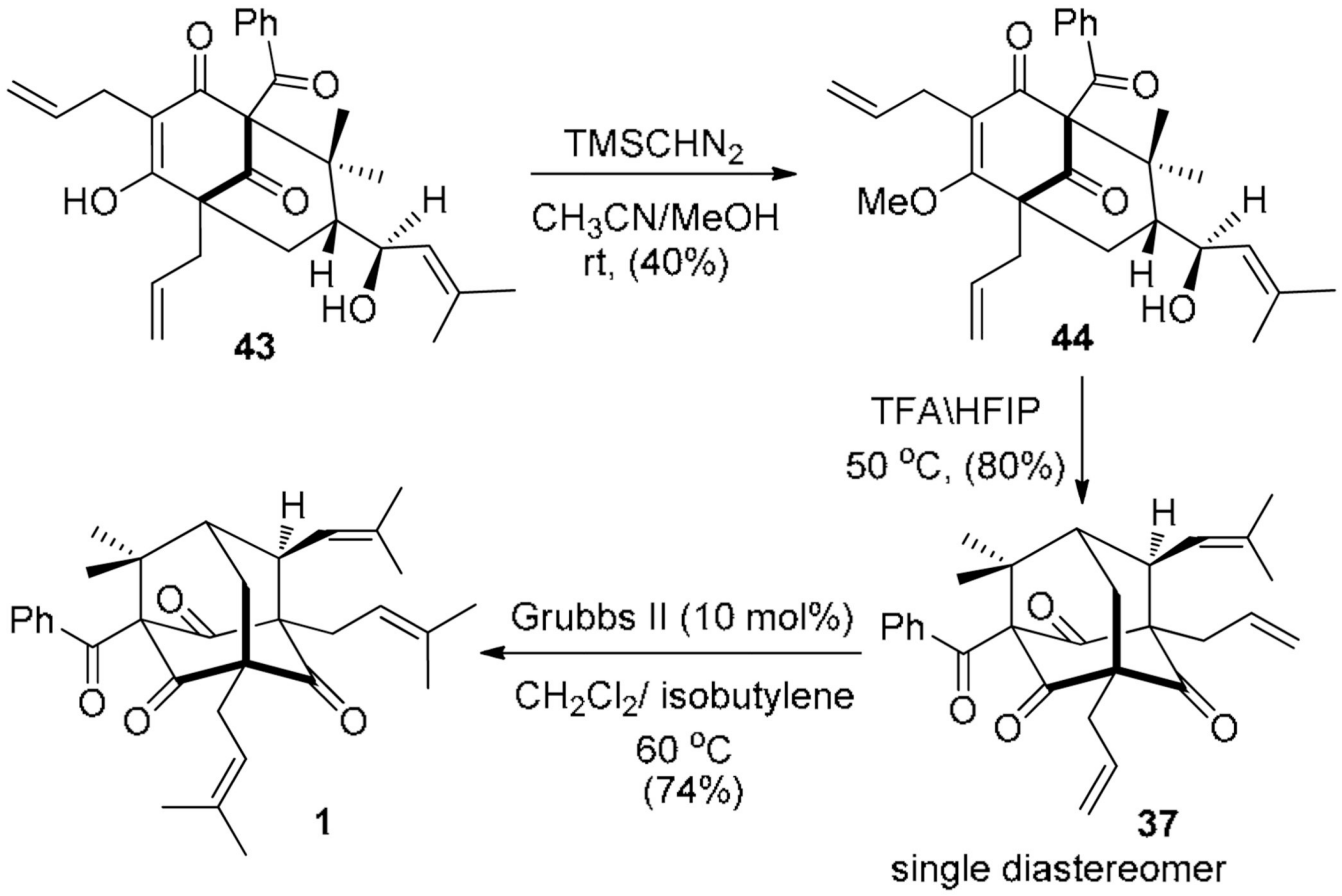
Scheme 7.
Retro-aldol/organocerium addition



Scheme 8.
Proposal for diastereoselectivity in the Grignard addition



Scheme 9.
Rationale for stereoselectivity



Scheme 10.
Completion of the synthesis of plukenetione Aa
[a] For **44**, one enol ether isomer shown for clarity.