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Modular Total Syntheses of Hyperforin, Papuaforins A, B and C via Gold(I)-Catalyzed Carbocyclization

Gabriel Bellavance[#] *and Louis Barriault**

Centre for Catalysis, Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Canada K1N 6N5.

Louis.Barriault@uottawa.ca

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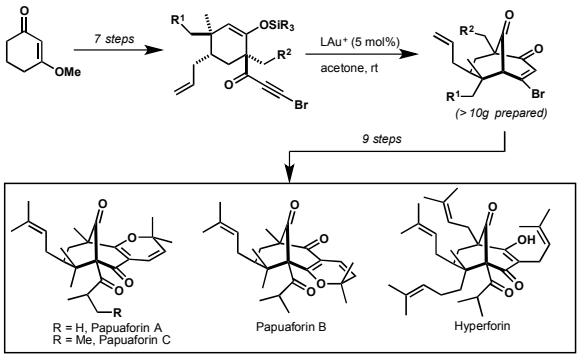


ABSTRACT: The remarkable biological activities of polyprenylated polycyclic acylphloroglucinols (PPAPs) combined with their highly oxygenated and densely functionalized frameworks have stimulated the interest of synthetic organic chemists over the last decade. Herein, we report the concise total syntheses of four natural products PPAPs of which some have antibacterial properties notably hyperforin and papuaforin A. The salient features of this strategy are the short and gram-scalable synthesis of densely substituted PPAPs scaffolds via a Au(I)-catalyzed carbocyclization and the late-stage functionalization for an unified access to a wide variety of PPAPs

INTRODUCTION

Isolated from the Guttiferae plants, polycyclic polyprenylated acylphloroglucinols (PPAPs) are naturally occurring molecules possessing a distinctive densely substituted and highly oxygenated bicyclo[3.3.1]nonanone framework. These compounds are mainly classified in three groups; A, B and C (Figure 1). The compounds in group A are characterized by an acyl moiety at C1 adjacent to an all quaternary carbon center at C8, while in group C, the acyl moiety on C5 is contiguous a methylene group. PPAPs belonging in group B are depicted with an acyl group located on C3. More than 200 members of this family have been isolated to date and most of them display a wide range of biological activities. Isolated from St. John's wort, hyperforin (**1**) is probably to most studied natural product of this family showing promising antidepressant therapeutic properties.[1] Through a unique mechanism, hyperforin (**1**) prevents the re-uptake of various neurotransmitters.[2] It was also found that **1** possesses antimalarial, antimetastatic and antibacterial activities against MRSA bacteria with a minimal inhibitory concentration of 1.86 μmol.[3] Other PPAPs such as papuaforins A, B and C (**2**-**4**) isolated from *Hypericum papuanum* found in Papua New Guinea possess modest antibacterial properties activity.[4] The structural complexity of PPAPs combined with their therapeutic profiles have stimulated the genesis of numerous synthetic strategies.[5] These strategies culminated in the successful syntheses of various PPAPs[6] including hyperforin (**1**),[7] nemorosone (**5**),[8] and garsubellin A (**6**).[9] In 2014, our group reported the modular syntheses of hyperforin (**1**) and papuaforins A-C (**2**-**4**) via a gold(I)-catalyzed cyclization.[10] In this article, a detailed investigation of the synthesis of these molecules is described.[11]

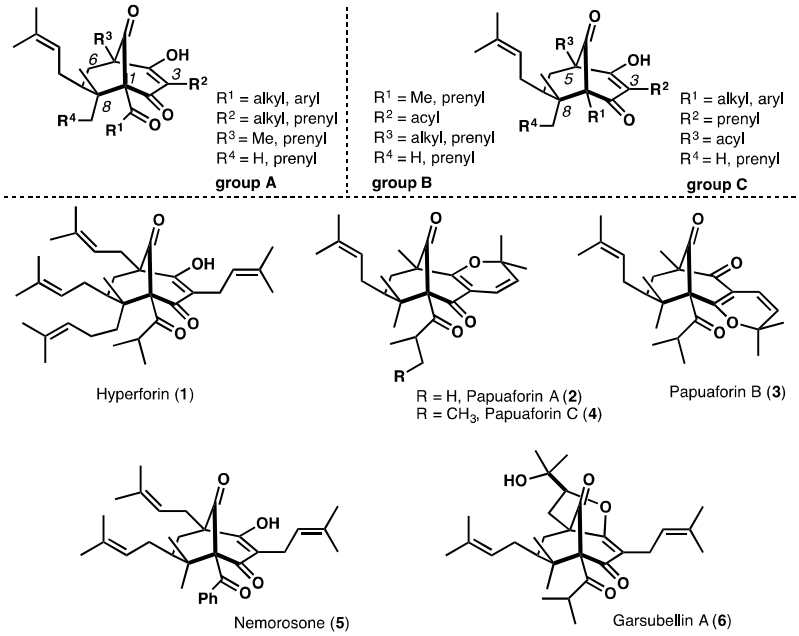
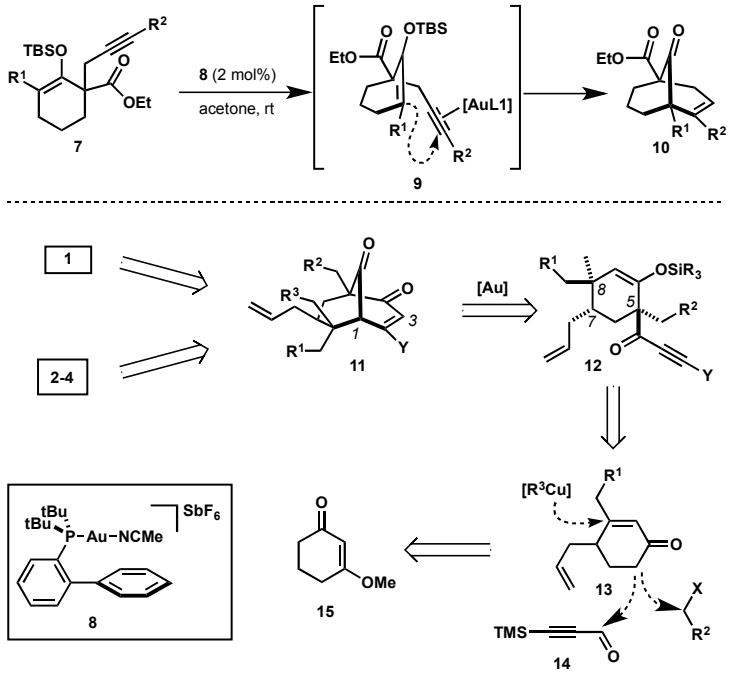


Figure 1. Structures of various PPAPs

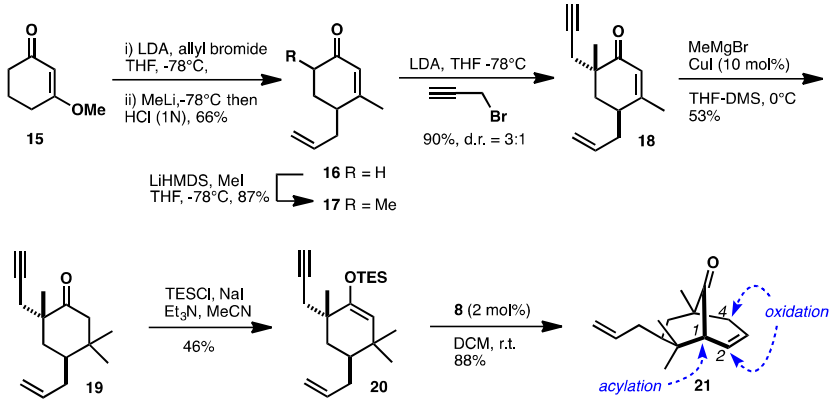
RESULTS AND DISCUSSION

Previous work from our group revealed that bicyclic ketone framework **10** can be easily synthesized through a *6-endo* dig gold(I)-catalyzed carbocyclization of 1,5-enyne **7** using catalyst **8** (Scheme 1).[12,13] Taking advantage of this method, we delineated a blueprint in which the bicyclo[3.3.1]nonenone core **11** could serve as a central intermediate for the construction various PPAPs including **1**-**4** via late-stage functionalization at C1 and C3. However, we took early cognizance that the formation of carbon-carbon at C1 bond adjacent to a quaternary carbon center (C8) might be challenging. From commercially available enone **15**, we devised a modular approach in which the functional groups at C5, C7 and C8 would be installed through a carefully coordinated sequence of stereoselective alkylation, allylation and aldol reactions (**13**→**12**). To validate our synthetic plan, a model substrate for the gold(I)-catalyzed cyclization was thus prepared.



Scheme 1. Retrosynthetic analysis

A one-pot allylation/alkylation on the commercially available ketone **15** using LDA and allylbromide followed by the addition of MeLi and subsequent addition HCl (1N) provided enone **16** in 83% yield (Scheme 2). A second alkylation with LiHMDS and MeI afforded ketone **17** in 87% yield. The latter was then subjected to LDA and proparyl bromide to give **18** in 62% yield as a 3:1 mixture of diastereomers. Treatment of enone **18** with a catalytic amount of CuI, dimethyl sulfide and MeMgBr provided ketone **19** in 53% yield which was converted to the corresponding silylenol ether **20** in 46%. Pleasingly, the exposure of **20** to the phosphino gold catalyst **8** (2 mol%) in dichloromethane afforded the desired bicyclic ketone **21** in 88% yield. Encouraged by these results, we turned our attention toward the functionalization of carbon centers C1, C2 and C4. After analyzing various scenarios, we opted to install the ketone at C4 prior to Au(I)-cyclization and the acyl group at C1 via a direct acylation on the bicyclo[3.3.1]nonane core. This modular approach would allow the synthesis of hyperforin (**1**), papuaforin A-C (**2**-**4**) and other PPAPs from common intermediates.

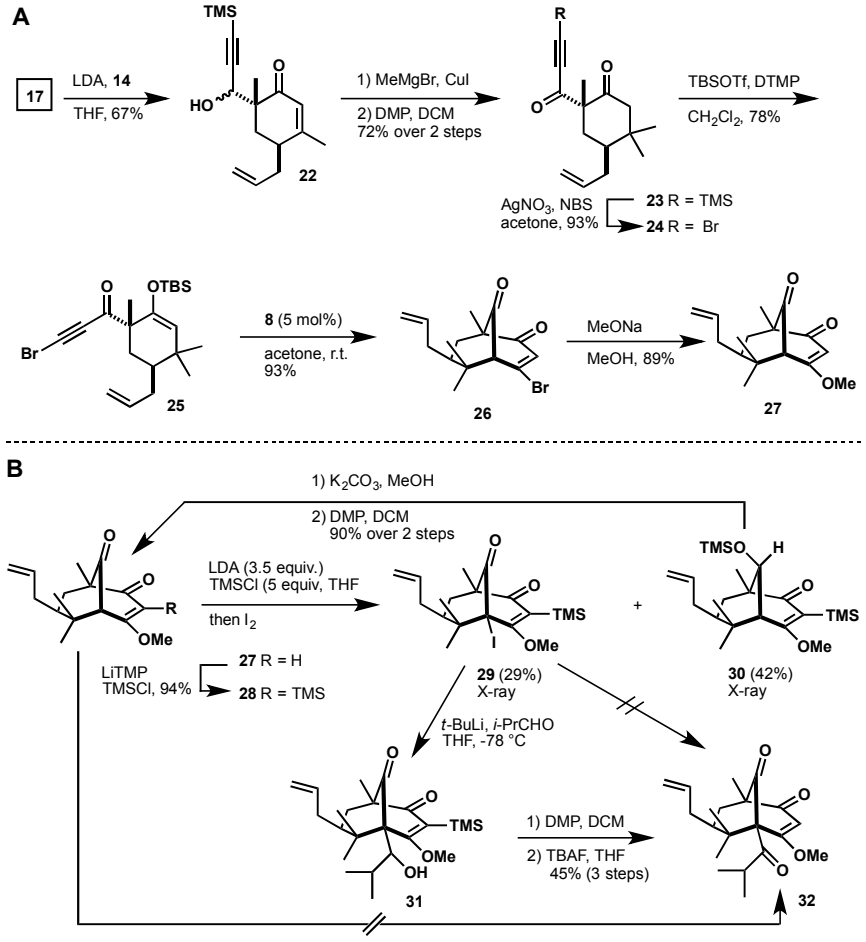


Scheme 2. Preliminary study

As shown in Scheme 3A, enone **17** was converted to the aldol product **22** in 67% yield which underwent a organocuprate addition followed by an oxidation to give ketone **23** in 72% yield over two steps. The replacement of the TMS group by a bromide using $AgNO_3$ and NBS delivered the bromoethynyl **24** in 93% yield. The latter was then transformed to the corresponding TBS-enol **25** using TBSOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTMP) in 78% yield. Using 5 mol% of [(JohnPhos)Au(NCMe)][SbF_6] (**8**) in acetone, the enol ether **25** was directly converted into the desired bicyclic ketone **26** in 93% yield. It is important to notice that the gold(I)-carbocyclization operated in a sterically crowded environment and the reaction can be performed on a multi-gram scale (>10g). Finally, the treatment of **26** with a solution of sodium methoxide in methanol led to the formation of enone **27** in 89% yield having the proper functional groups at C2 and C4.

Drawing inspiration from the work of Danishefsky[9b] and Simpkins,[8b,9c] we envisaged the introduction of the acyl group C1 through a deprotonation/acylation process (Scheme 3B). First, treatment of **27** with LiTMP and freshly distilled TMSCl gave the C3-TMS enone **28** in 94% yield. Preliminary efforts at direct acylation at C1 using *n*-BuLi, *t*-BuLi and amide lithium bases and various acylating agents were fruitless. After substantial experimentation, we found that deprotonation using LDA (3.5 equivalents) in the presence of TMSCl (5 equivalents) at -78 °C in THF followed by the addition of molecular iodine gave the desired iodoketone **29** in 29% yield along with a significant quantity of by-product **30** (42% yield). The relative stereochemistry of both structures was confirmed by X-ray

analysis. In an effort to prevent the formation of **30**, various conditions for the deprotonation using other hindered bases such as LiTMP and lithium isopropyl-*tert*-butyl amide were examined. Unfortunately, lower yields ranging from <5% to 15% for the formation of **29** were observed in all cases. Although a competitive LDA-mediated reduction was operative,[14,8c] we took some solace in the fact that the formation of iodoketone **29** proved to be reproducible and amenable to gram-scale synthesis. In addition, the reduced product **30** can be easily recycled to **28** in high yields by a selective TMS-deprotection using K_2CO_3/MeOH followed by an oxidation. Next, we investigated the metalation through an iodo-lithium exchange followed electrophile addition. A rapid survey of various conditions rapidly identified *tert*-BuLi as the base of choice. Surprisingly, direct acylation using various acyl chlorides or cyanides did not lead to the desired product, only deiodonated product **28** was recovered. However, iodo-lithium exchange followed by the addition of isobutyraldehyde led to alcohol **31**, which was oxidized to the corresponding ketone. Finally, the latter was treated with TBAF to deliver **32** in 45% yield over three steps.

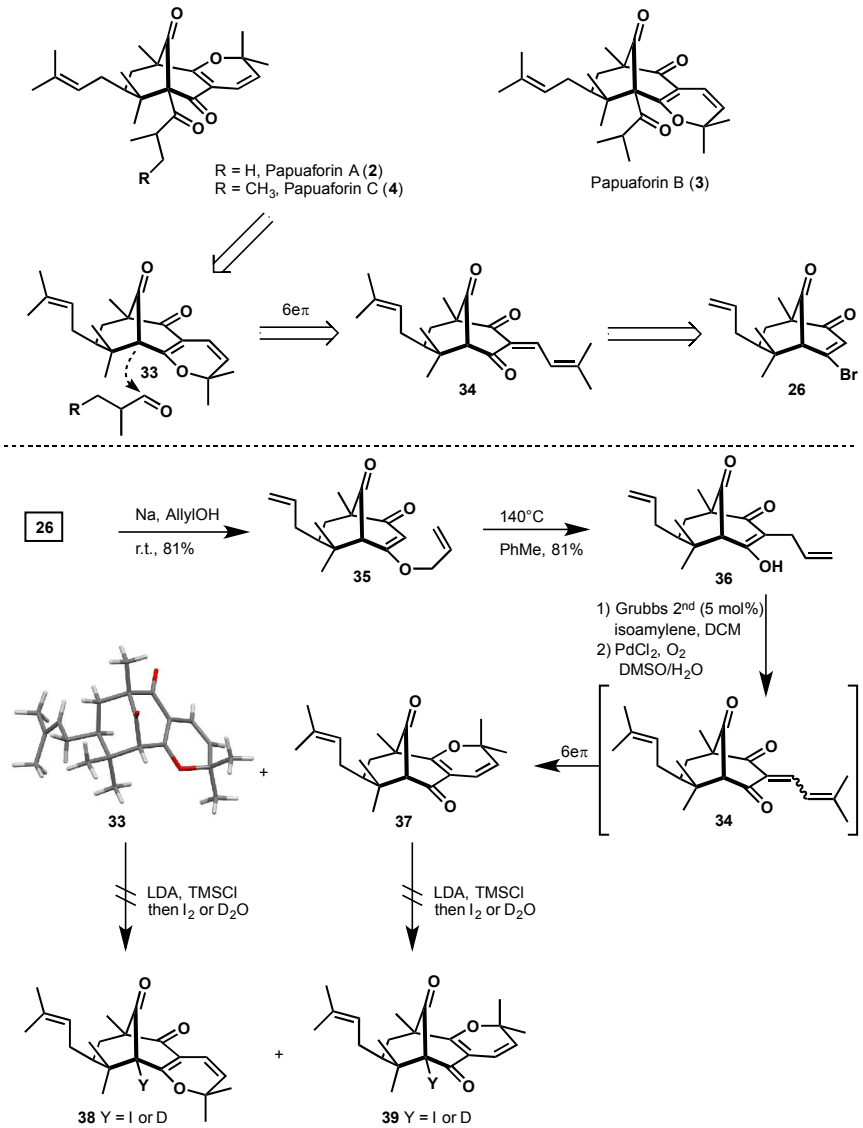


Scheme 3. Synthesis of PPAPs core via gold(I)-carbocyclization and functionalization at C1

Total Synthesis of Papuaforins A (2), B (3) and C (4)

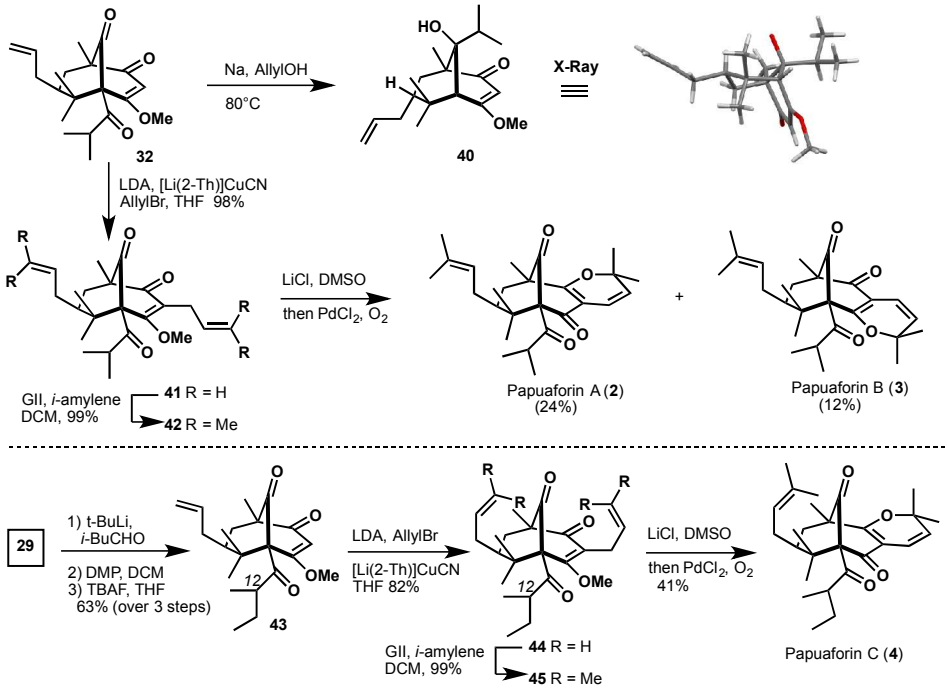
With conditions to functionalize at C1 in hand, we envisioned the completion of papuaforins A-C (**2-4**) by constructing first the pyran moiety and then installing the acyl unit at C1 (Scheme 4). Upon a cursory inspection of the papuaforin core, one can propose that the pyran ring system could originate from a 6□-electrocyclization of dienone **34**. Although a Knoevenagel condensation was originally considered, an approach involving oxidation of the prenyl unit to generate intermediate **34** was the privileged option. To test this idea, bromoenone **26** was converted to the corresponding allyl ether **35** in 81% yield by treatment with a solution of NaOallyl/allylOH at 50 °C. The latter was then converted to **36** through a Claisen rearrangement in 84% yield. A cross-metathesis followed by oxidation of the prenyl unit at C3 using $PdCl_2$ and O_2 in wet DMSO/H_2O (9:1) produced the corresponding dienone **34**

which underwent a spontaneous 6π-electrocyclization to provide pyrans **33** and **37** as a separable mixture of 2:1 in 33% overall yields.[15] To complete the synthesis of **2**-**4**, installation of the acyl group at C1 was attempted using the LDA deprotonation/iodination protocol. To our dismay, no desired products **38** and **39** were detected; starting materials **33** and **37** were mostly recovered along with a small quantity of the corresponding reduced products. In addition, deuterium-labelling experiments confirmed that no deprotonation reaction operated at C1 suggesting that pyran ring might be detrimental to reaction.[16]



Scheme 4. Formation of the pyran ring of the papuaforins

Taking into consideration these results, we revised our strategy to include the oxidation/electrocyclization as the last synthetic step. Surprisingly, the installation of the allyl chain at C3 via a Claisen strategy did not follow previous findings (*e.g.* **35→36**). The rearranged product **40** along with a minor isomer was isolated after treatment of **32** with a solution of NaOallyl in allylic alcohol at 80 °C. One can explain the formation of compounds **40** through retro-Dieckman/decarboxylation process followed by an aldol reaction. The structure of **41** was determined by single-crystal X-ray analysis. To connect the prenyl group at C3, enone **32** was exposed to LDA in the presence of Li(2-Th)CuCN and allyl bromide to produce the allyl **41** in 98% yield followed by global cross-metathesis to afford **42** in 99% yield. The latter was subjected to a one pot-demethylation/oxidation/electrocyclization with LiCl in DMSO followed by the Pd-mediated oxidation to generate papuaforin A (**2**) in 24% yield and papuaforin B (**3**) in 12% yield. Papuaforin C (**4**) was prepared using a similar synthetic approach. Intermediate **43** was readily obtained from following the three steps sequence illustrated in Scheme 5. It is important to outline that only one diastereoisomer was observed at C12 but the relative stereochemistry was not established. Nevertheless, prenyl **45** was carried through the final sequence to give papuaforin C (**4**) in 41% yield which was spectroscopically identical to the natural product.

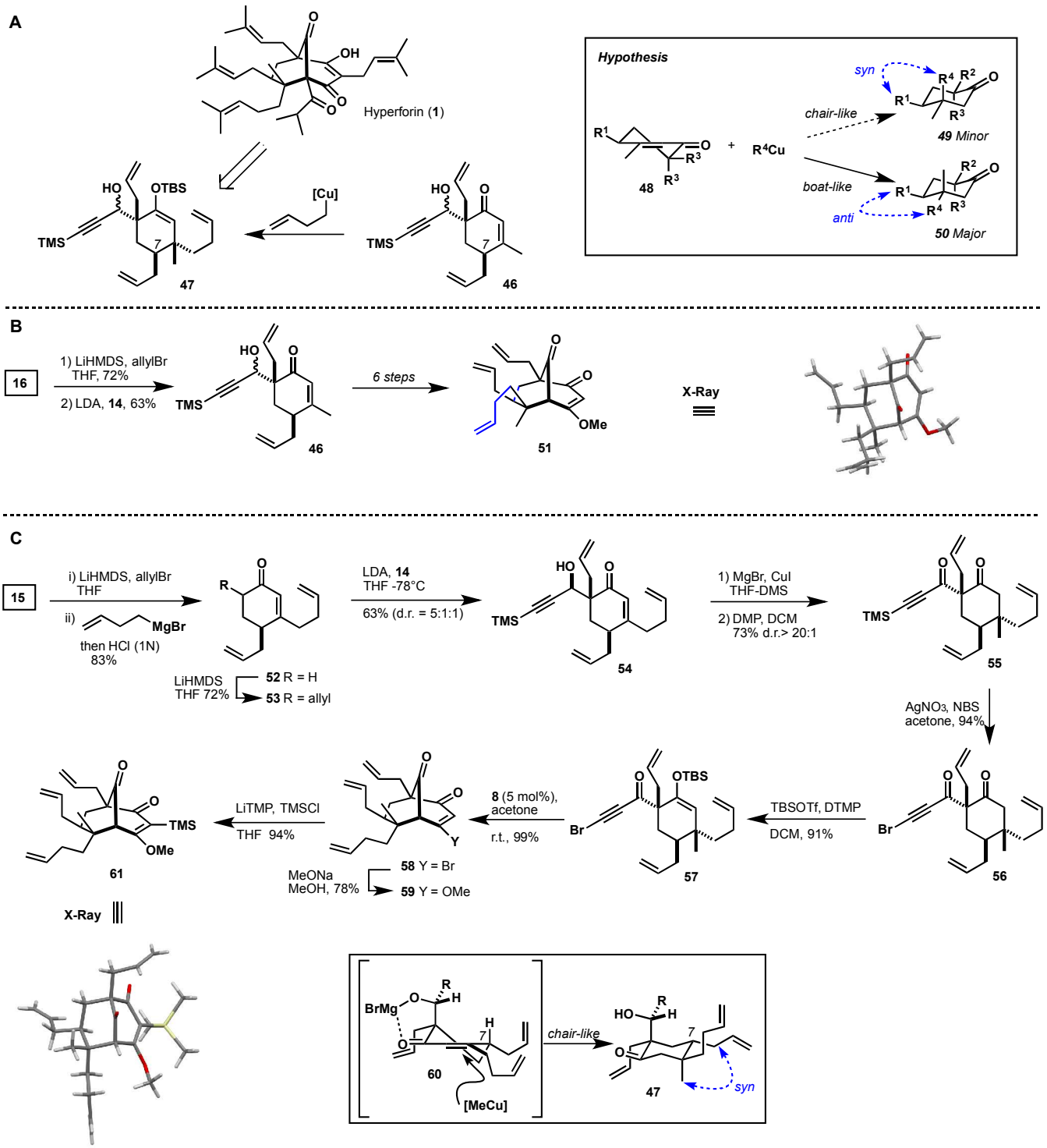


Scheme 5. Total synthesis of papuaforins A (**2**), B (**3**) and C (**4**)

Total Synthesis of Hyperforin (1)

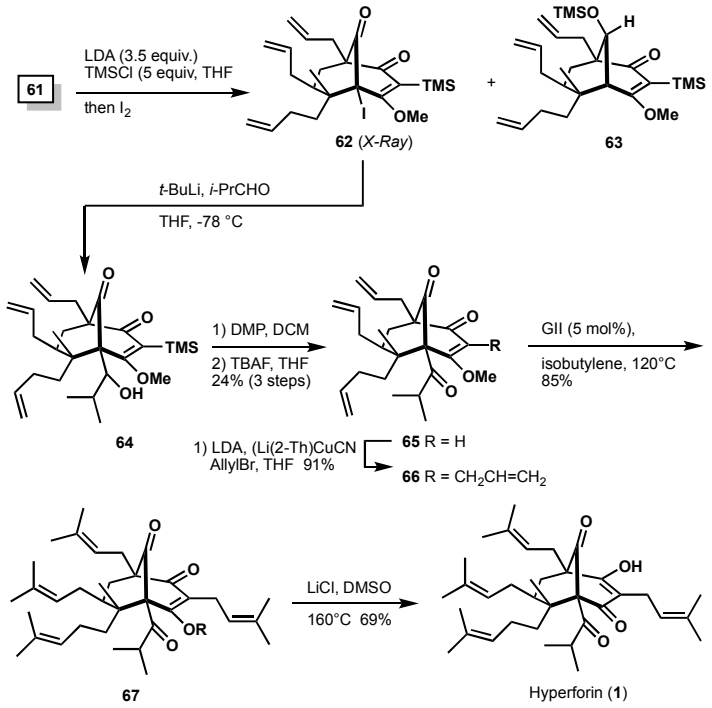
Having secured the synthesis of **2-4**, we turned our attention to completing the synthesis of hyperforin (**1**). At the outset of our retrosynthetic analysis, we imagined that the conjugate addition of the homoallylic chain on **46** would proceed *anti* to the allylic chain at C7 to give alcohol **47** (Scheme 6A). This hypothesis was based on the work of Tostain and Riviere showing that the addition alkyl cuprates to γ-substituted cyclohex-2-enones **48** gives mainly the *anti* product **47** presumably through a boat like transition state (**48**→**50**).[17] Alcohol **46** was readily prepared from compound **16** following the same synthetic route previously described in Scheme 3. The cuprate addition of homoallyl unit to **46** followed by oxidation with the Dess-Martin periodinane provided the corresponding ketone with the correct stereochemistry at C8 (**46**→**47**). Although the relative configuration of the major product was not determined, we continued the synthesis of the hyperforin core following the previous protocols (Scheme 6B). To our surprise, single crystal X-ray analysis of the major product **51** revealed that the homoallylic chain was *syn* to allyl group which indicated that the cuprate addition did not correlate with Tostain and Riviere' findings. These results suggest that the cuprate reaction on enone **46** proceeds via chair-like transition state (**48**→**49**) favoring the *syn-addition* product. In order to obtain the correct stereochemistry at C8, the homoallyl chain must be installed first on the cyclohexenone framework. Starting from **15**, enone **52** was readily prepared in 83% yield via one-pot allylation/alkylation using homoallyl magnesium bromide (Scheme 6C). A second allylation followed (**52**→**53**) by an aldol reaction using LDA and aldehyde **14** afforded the desired alcohol **54** as the major diastereomers in 63% yield (d.r. 5:1:1). The relative stereochemistry of **54** was subsequently established by X-ray analysis (see supporting info for details). Gratifyingly, the addition of dimethyl cuprate addition followed by an oxidation gave ketone **55** in 73% yield over two steps as the sole diastereomer (d.r. > 20:1). The high diastereoselectivity of the reaction could be rationalized via the formation of a Mg-chelated intermediate **60** in which the axial substituent blocks the top face. Consequently, one can imagine that this

conformation favors the *syn* addition of the organocuprate leading to the formation of **47**.[18,61] Following the previous established sequence, ketone **55** was efficiently converted the desired bicyclic ketone **59** in high yields. Silyation at C3 using LiTMP and TMSCl provided the key intermediate **61** in 94% yield. The relative stereochemistry of **61** was confirmed without ambiguity by single crystal X-ray analysis.



Scheme 6. Synthesis of intermediate **61**

Ketone **61** was subjected to the deprotonation/iodination conditions to provide **62** in 18% yield along with 41% yield of reduced product **63** and starting material **61** (35%) (Scheme 7). Iodo-lithium/alkylation of **63** with isobutyraldehyde to furnish alcohol **64** which was oxidized and then treated with TBAF to give the desired ketone **65** in 24% overall yield in three steps. Allylation and cross-metathesis with isobutylene in the presence of Grubbs II (5 mol%) led to tetraprenylated intermediate **67** in 85% yield.[7c] Finally, demethylation in hot solution of LiCl in DMSO unveiled hyperforin (**1**) in 69% yield concluding this synthetic journey.



Scheme 7. Total synthesis of hyperforin (**1**)

CONCLUSION

The main objective of this study was to establish a short and modular approach allowing the synthesis of papuaforins A-C (**2**-**4**) and hyperforin (**1**) from common intermediates. Some of the significant features of the synthesis include: (1) a short synthesis and multigram-scale of the bicyclo[3.3.1]nonanones **11** via an effective gold(I)-catalyzed carbocyclization; (2) stereoselective additions and late-stage functionalization of **11** allowing access to a wide variety of PPAPs. This

modular approach can be utilized to rapidly build PPAPs and its derivatives for further biological investigations.

EXPERIMENTAL SECTION

All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were freshly distilled prior to use; diethyl ether and THF over sodium and benzophenone; toluene, triethylamine, and DCM over calcium hydride. All other commercial reagents were used without purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F254. Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or p-anisaldehyde staining solution. Flash chromatography was carried out with silica gel 60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H: 7.26; ^{13}C: 77.1). Assignments of ^{13}C signal were made by DEPT experiments. IR spectra were recorded with a FTIR spectrometer. HRMS were conducted by the John L. Holmes Mass Spectrometry Facility at the University of Ottawa using a Kratos Concept instrument equipped with magnetic sector electron and electron multiplier detector. Melting points were measured in capillary tubes and were uncorrected.

***rac*-4-Allyl-3-methylcyclohex-2-enone (16).** A solution of *n*-BuLi (2.4 M in hexanes, 0.233 mL, 8.72 mmol) was added slowly to freshly distilled diisopropylamine (1.30 mL, 9.12 mmol) in THF (30 mL) at −78 °C and the solution was stirred for 30 min at -78 °C and 15 min at 0 °C before being cooled to -78 °C. A solution of 3-methoxycyclohex-2-enone (**15**) (1 g, 7.93 mmol) in THF (3 mL) was cannulated at −78°C and the solution was stirred for 60 min to obtain a slurry. Allyl bromide (0.857 mL, 9.91 mmol) was added in one portion, the mixture was stirred 60 min at -78 °C and 3 h at r.t. The solution was then cooled to -78 °C and MeLi (1.5 M in Et_2O, 13.2 mL, 19.8 mmol) was added in one portion. The resulting mixture was stirred for 30 min at -78 °C. It was then warmed to r.t. and stirred for one more

hour. A solution of 1 M of HCl (30.0 mL) was then added and stirred vigorously for 1 h. Water (30.0 ml) was then added with brine (30.0 mL) and Et_2O (30.0 mL), the phases were separated and the aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (7-15% EtOAc:hexanes) to give **16** (0.785 g, 66%) as a clear yellow oil. Spectral data was in accordance with reported data and full characterization is available through the literature.[19]

***rac*-4-allyl-3,6-dimethylcyclohex-2-enone (17).** LiHMDS (19.5 g, 113 mmol) was charged to 1 L flame dried flask. THF (500 mL) was added at r.t. and stirred, once all LiHMDS was dissolved the solution was cooled to −78 °C and **16** (15.5 g, 103 mmol) in THF (30.0 mL) was added via cannula to the solution. The solution was stirred 1h at -78 °C, 1h at -43 °C and iodomethane (7.68 mL, 123 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 3-4 h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ether (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-7% EtOAc:hexanes) to give **17** (14.8 g, 87%) as a lightly yellow oil. IR (neat film NaCl) 3077, 2964, 2930, 2872, 1673, 1639, 1443, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, J = 6.9 Hz, 3H), 1.71-1.80 (m, 1H), 1.95 (s, 3H), 1.99 (ddd, J = 13.5, 4.8, 2.8 Hz, 1H), 2.18-2.33 (m, 2H), 2.37-2.48 (m, 2H), 5.07-5.12 (m, 2H), 5.79 (s, 1H), 5.74-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.4 (CH_3), 22.9 (CH_3), 34.5 (CH_2), 35.6 (CH_2), 35.9 (CH), 39.2 (CH), 117.1 (CH_2), 126.4 (CH), 136.5 (CH), 164.0 (C), 201.9 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{11}H_{16}O$ 164.1201; Found: 164.1205.

***rac*-4-allyl-3,6-dimethyl-6-(prop-2-ynyl)cyclohex-2-enone (18).** A solution of *n*-BuLi (1.60 M in hexanes, 21.8 mL, 35.0 mmol) was added slowly to diisopropylamine (5.17 mL, 36.6 mmol) in THF (150 mL) at −78 °C for 45 min. **17** (5.00 g, 33.3 mmol) was added at −78 °C for 60 min and then propargyl bromide (2.49 mL, 39.9 mmol) was added. The mixture was stirred at r.t. for 3 h. An aqueous saturated solution of NH_4Cl was added and the aqueous layers were extracted with ethyl acetate (3x). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give

enone **18** (4.92 g, 90%) as a mixture of diastereomer (d.r. = 3:1). **Major isomer**: IR (neat NaCl): 3305(br.) 3305, 3077, 2976, 2930, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.69 (m, 1H), 5.10 (m, 2H), 2.49 (m, 2H), 2.35 (m, 1H), 2.15 (m, 3H), 2.01 (t, J = 2.6 Hz, 1H), 1.93 (s, 3H), 1.57 (dd, J = 13.8, 10.3 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.6 (C), 163.0 (C), 135.3(CH), 126.5 (CH), 118.1 (CH_2), 80.5 (C), 71.4 (CH), 44.0 (C), 38.5 (CH_2), 36.9 (CH), 36.7 (CH_2), 26.8 (CH_2), 22.3 (2 x CH_3); HRMS (EI) *m/z*: [M^+] Calcd for $C_{14}H_{18}O$ 202.1358; Found 202.1379.

***rac*-4-Allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone (19)**. To a solution of CuI (63.0 mg, 0.33 mmol) and enone **18** (306 mg, 1.52 mmol) in THF (15.0 mL) and Me_2S (1.50 mL) at 0 °C was slowly added MeMgBr (1.11 mL, 3.0 M in Et_2O, 3.33 mmol) over 1 hour. The mixture was then stirred 1 h at 0 °C, then the reaction was stopped by adding NH_4Cl aqueous solution, and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography to provide **19** (176 mg, 53%) a dark orange oil. IR (neat NaCl) 3310, 3076, 2965, 2931, 2871, 2124, 1716, 1640, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.02 (m, 2H), 2.49 (m, 0.5H), 2.45 (m, 1H), 2.37 (m, 2H), 2.33 (m, 0.5H), 2.00 (m, 2.5H), 1.70 (m, 2.5H), 1.26 (t, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 0.96 (m, 1H), 0.73 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.2 (C), 137.6 (CH), 116.3 (CH_2), 79.5 (C), 71.5 (CH), 52.9 (CH_2), 48.0 (C), 41.5 (CH), 40.0 (CH_2), 39.3 (C), 34.2 (CH_2), 29.8 (CH_3), 27.8 (CH_2), 22.2 (CH_3), 20.1 (CH_3); HRMS (EI) *m/z*: [M^+] Calcd for $C_{15}H_{22}O$ 218.1671; Found 218.1659.

***rac*-4-Allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone (20).** Ketone **19** (300 mg, 1.37 mmol) was dissolved in acetonitrile (30.0 mL), and Et_3N (0.383 mL, 2.74 mmol) was added. Then flame-dried NaI (0.309 g, 2.04 mmol) and TBSCl (310 mg, 2.04 mmol) were added. The reaction mixture was allowed to reflux overnight and was then quenched with $NaHCO_3$ saturated solution, and the aqueous phase was extracted with DCM (3x). The organic phases were then combined, dried and concentrated. The resulting mixture was filtered through a small silica pad and washed with solution of 7% EtOAc in hexanes and concentrated again. The crude enol ether **20** (209 mg, 46%) was then directly used for the next reaction without further purification.

***rac*-7-Allyl-5,8,8-trimethylbicyclo[3.3.1]non-2-en-9-one (21).** A solution of silyl enol ether **20** (20.0 mg, 0.060 mmol) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) (0.92 mg, 0.0012 mmol) in DCM (1 mL) was stirred for 6 h at r.t. The solvent was evaporated and the residue was purified by flash column chromatography on silica (10% EtOAc:hexanes) to give **21** (11.2 mg, 88%) as a white solid. IR (neat NaCl) 3081, 3039, 2967, 2921, 1709, 1449, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.76 (m, 1H), 5.63 (dddd, J = 9.5 Hz, 6.0 Hz, 1.9 Hz, 1.9 Hz, 1H), 5.03 (m, 1H), 2.41 (m, 3H), 2.25 (m, 1H), 2.03 (m, 1H), 1.82 (dd, J = 13.9 Hz, 4.5 Hz, 1H), 1.59 (ddd, J = 13.7 Hz, 10.8 Hz, 8.6 Hz, 2H), 1.28 (m, 4H), 1.02 (s, 3H), 0.99 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 216.5 (C), 138.0 (CH), 129.8 (CH), 126.6 (CH), 116.0 (CH_2), 60.3 (CH), 46.0 (CH_2), 45.6 (CH_2), 42.4 (C), 38.1 (CH), 34.1 (C), 29.7 (CH_2), 26.1 (CH_3), 23.5 (CH_3), 20.8 (CH_3); HRMS (EI) *m/z*: [M^+] Calcd for $C_{15}H_{22}O$ 218.1671; Found 218.1652.

***rac*-4-Allyl-6-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)-3,6-dimethylcyclohex-2-enone (22).** A solution of *n*-BuLi (9.8 M in hexanes, 5.18 mL, 50 mmol) was added slowly to freshly distilled diisopropylamine (7.57 mL, 53.1 mmol) in THF (250 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. 4-Allyl-3,6-dimethylcyclohex-2-enone (**17**) (7.93 g, 48.3 mmol) was added via cannula to the solution at -78 °C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**7**) (7.32 g, 58 mmol) was added and the mixture was stirred at -78 °C for 10 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78 °C. Distilled water was added and the aqueous layer was extracted with EtOAc:Et_2O 1:3 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (5-15% EtOAc:hexanes) to give alcohol enone (**22**) (9.39 g, 67%) as a mixture of two diastereomer at C4. **Major diastereomer at C4:** M.p. 53-54 °C; IR (neat NaCl) 3421, 2928, 2856, 1657, 1471, 1249, 1060, 838, 811, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.20 (s, 3H), 1.71 (dd, J = 14.3, 8.6 Hz, 1H), 1.96 (s, 3H), 2.13 (m, 2H), 2.51-2.56 (m, 2H), 2.69 (s, 1H), 4.54 (s, 1 H), 5.10-5.14 (m, 2H), 5.66-5.76 (m, 1H), 5.83 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (3x CH_3), 17.2 (CH_3), 22.1 (CH_3), 36.7 (CH), 36.9 (CH_2), 37.4 (CH_2), 48.2 (C), 66.8 (CH), 91.2 (C), 102.5 (C), 117.8 (CH_2), 126.0 (CH), 135.2 (CH), 163.5 (C),

202.8 (C); HRMS (EI) *m/z*: [M^+ -Me] Calcd for $C_{16}H_{23}O_2Si$ 275.1467; Found: 275.1461. **Minor diastereomer at C4:** mp. 68-70 °C; IR (neat NaCl) 3427, 2962, 1647, 1247, 1053, 1000, 837, 759 cm^{-1}; ^1H NMR, (400 MHz, $CDCl_3$) δ 0.14 (s, 9 H) 1.17 (s, 3H) 1.73 (dd, J = 14.3, 6.5 Hz, 1H) 1.97 (s, 3H) 2.16 (dt, J = 14.2, 9.0 Hz, 1H), 2.35 (dd, J =14.3, 5.9 Hz, 1H), 2.48-2.55 (m, 1H), 2.64 (d, J=6.3 Hz, 1H), 2.65-2.72 (m, 1H), 4.47 (d, J = 6.3 Hz, 1H), 5.08-5.13 (m, 2H), 5.77 (dddd, J = 15.7, 11.4, 7.8, 6.2 Hz, 1H), 5.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (3x CH_3), 22.2 (CH_3), 22.6 (CH_3), 33.5 (CH_2), 37.3 (CH_2), 37.8 (CH), 48.4 (C), 68.6 (CH), 91.5 (C), 103.8 (C), 117.5 (CH_2), 127.0 (CH), 135.9 (CH), 164.4 (C), 202.2 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{17}H_{26}O_2Si$ 290.1702; Found: 290.1656.

***rac*-4-Allyl-2,5,5-trimethyl-2-(3-(trimethylsilyl)propioloyl)cyclohexanone) (23).** To a solution of purified CuI (9.47 g, 49.7 mmol) and enone (**22**) (7.83 g, 27 mmol,) in THF (250 mL), Me_2S (25 mL) was added at 0°C and the solution was stirred until the solution becomes homogenous. MeMgBr (41.4 mL, 3.0 M in Et_2O, 124 mmol) was added over 90 min with a syringe pump under heavy stirring. After the addition was completed, the reaction becomes a very dense dark green solution and the solution was allowed to warm to rt and stirred for 5 h. A saturated solution of NH_4Cl was added with equal amount of distilled water. The mixture was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$ and filtered over a short pad of celite. The crude was concentrated and filtered over celite one more time using ether to wash the celite pad and concentrated again. The residue was not purified any further and is use for the next step.

To a solution of crude alcohol in wet DCM (150 mL) was added Dess-Martin periodinane (13.71 g, 32.3 mmol). The reaction was stirred for 1 h and quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase is extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5% EtOAc:hexane) to provide diketone (**23**) (5.90 g, 72 %) as a white solid over 2 steps. M.p. 51-55 °C; IR (neat NaCl) 3074, 2961, 2931, 2855, 1722, 1668, 1454, 1252, 1252, 1047, 848, 762 cm^{-1}; ^1H NMR, (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 0.74 (s, 3H), 1.01 (s, 3H), 1.25 (s, 3H), 1.29 (dd, J = 14.70, 12.5 Hz, 1H), 1.59-

1.71 (m, 2H), 2.13 (d, J = 13.5 Hz, 1H), 2.36-2.41 (m, 1H), 2.44 (d, J = 13.5 Hz, 1H), 2.67 (dd, J = 14.6, 3.2 Hz, 1H), 5.03-5.10 (m, 2H), 5.79 (dddd, J = 17.1, 10.0, 8.2, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.9 (3x CH_3), 19.9 (CH_3), 20.4 (CH_3), 29.6 (CH_3), 34.1 (CH_2), 38.7 (CH_2), 39.3 (C), 42.7 (CH), 55.5 (CH_2), 63.4 (C), 98.8 (C), 101.6 (C), 116.4 (CH_2), 137.3 (CH), 188.6 (C), 207.7 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{18}H_{28}O_2Si$ 304.1859; Found: 304.1848.

***rac*-4-Allyl-2-(3-bromopropioloyl)-2,5,5-trimethylcyclohexanone (24).** To a solution of diketone (**23**) (1.49 g, 6.41 mmol) in dry acetone (30 mL), was added $AgNO_3$ (0.545 g, 3.21 mmol). The mixture was stirred for 5 min before the addition of recrystallized NBS (1.25 g, 7.05 mmol). The reaction was stirred 2h at r.t. then filtered over celite and washed with acetone. The filtrate was concentrated and purified by flash chromatography (5% EtOAc:hexanes) to afford the corresponding bromide **24** (1.87 g, 93 %) as a white solid. M.p.88-89 °C; IR (neat NaCl) 2967, 2937, 2864, 1772, 1669, 1447, 1369, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.02 (s, 3H), 1.26 (s, 3H), 1.31 (dd, 1H), 1.59-1.73 (m, 2H), 2.15 (d, J = 13.5 Hz, 1H), 2.36-2.41 (m, 2H), 2.63 (dd, J = 14.6, 3.2 Hz, 1H), 5.06-5.10 (m, 2H), 5.75-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 20.2 (CH_3), 29.6 (CH_3), 34.0 (CH_2), 38.3 (CH_2), 39.3 (C), 42.8 (CH), 55.6 (CH_2), 60.3 (C), 63.7 (C), 77.2 (C), 116.5 (CH_2), 137.2 (CH), 186.9 (C), 207.0 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{15}H_{19}BrO_2$ 310.0568; Found: 310.0540.

***rac*-1-(5-Allyl-2-((tert-butyldimethylsilyl)oxy)-1,4,4-trimethylcyclohex-2-en-1-yl)-3-bromoprop-2-yn-1-one (25).** 2,6-Di-tert-butyl-4-methylpyridine (12.64 g, 61.5 mmol) was charged to a flame dried flask under argon atmosphere. DCM (30 mL) was added followed by the addition of diketone (**24**) (3.83 g, 12.31 mmol) and the addition of TBSOTf (11.31 mL, 49.2 mmol). The solution was stirred 3 days at 40°C in an oil bath (lower temperature provide lower yields and higher temperature degrades starting material). The brown solution was quenched slowly with a solution of 5% $NaHCO_3$ and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The mixture was purified immediately by flash chromatography (pure hexane to recuperate 2,6-Di-tert-butyl-4-methylpyridine, 30% benzene/hexanes to recuperate the desired silane enol ether **25** (4.09 g, 78%) a pale yellow oil which becomes a white solid after recrystallization in 5%

EtOAC:hexanes. M.p. 68-69 °C; IR (neat NaCl) 2962, 2929, 2856, 2358, 2175, 1670, 1463, 1251, 1155, 1054, 871, 827, 777 cm^{-1}; ^1H NMR, (400 MHz, $CDCl_3$) δ 0.17 (d, J = 1.8 Hz, 6H), 0.82 (s, 3H), 0.87 (s, 9H), 1.02 (s, 3H), 1.29 (s, 3H), 1.31-1.34 (m, 1H), 1.45-1.68 (m, 2H), 2.03 (dd, J = 14.0, 2.6 Hz, 1H), 2.24-2.30 (m, 1H), 4.65 (s, 1H), 4.97-5.02 (m, 2H), 5.64-5.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0 (CH_3), -4.3 (CH_3), 18.2 (C), 22.3 (CH_3), 23.1 (CH_3), 25.7 (3xCH_3), 29.3 (CH_3), 34.2 (CH_2), 35.1 (C), 36.5 (CH_2), 40.1 (CH), 54.0 (C), 57.9 (C), 79.2 (C), 116.0 (CH_2), 117.6 (CH), 137.8 (CH), 148.4 (C), 190.0 (C); HRMS (EI) *m/z*: [M^+-*t*-Bu] Calcd for $C_{21}H_{33}BrO_2Si$ 367.0729; Found: 367.0727.

***rac*-7-allyl-4-bromo-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (26).** To a solution of silane enol ether **25** (3.31 mmol) in dry acetone (10 mL) was added [JohnPhosAuNCMe][SbF_6] (**8**) (0.128 g, 0.166 mmol). The resulting mixture was left open to air at rt and monitored by TLC until consumption all the starting material (30 min). The mixture was concentrated and purified by flash chromatography (3-5% EtOAc:hexanes) to afford the desired bicyclic ketone **26** (0.98 g, 96%) as a white solid. M.p. 94-96 °C; IR (neat NaCl) 3078, 2973, 2937, 1738, 1675, 1594, 1374, 1275, 1143, 993 cm^{-1}; ^1H NMR, (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.18 (s, 3H), 1.27 (s, 3H), 1.32 (t, J = 13.4 Hz, 1H), 1.56-1.66 (m, 1H), 1.72-1.79 (m, 1H), 1.99 (dd, J = 13.7, 4.3 Hz, 1H), 2.25-2.30 (m, 1H), 3.28 (s, 1H), 4.96-5.01 (m, 2H), 5.56-5.67 (m, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (CH_3), 20.6 (CH_3), 27.5 (CH_3), 33.9 (CH_2), 37.8 (CH), 41.9 (C), 42.2 (CH_2), 60.6 (C), 70.6 (CH), 117.1 (CH_2), 135.6 (CH), 136.1 (CH), 145.8 (C), 197.4 (C), 205.5 (C); HRMS (ESI) *m/z*: [M^+ H-Me] Calcd for $C_{14}H_{17}BrO_2$ 296.0412; Found: 296.0351.

***rac*-7-allyl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (27).** Sodium methoxide (1.17g, 21.69 mmol) was charged to flame-dried flask. Methanol (20 mL) was then added slowly. Once the solution was homogenous, compound **26** (7.23 mmol) was added in one portion. Then the solution was heated to 45˚C in an oil bath. After 3h, the solvent was evaporated and the crude was purified directly by flash chromatography (15-20% EtOAc:hexane) to afford the desired compound **27** (1.68 g, 89%) as a white solid. M.p. 160-162 °C; IR (neat NaCl) 3085, 2965, 2936, 1730, 1656, 1603, 1443, 1374, 1194, 998 cm^{-1}; ^1H NMR, (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.03 (s, 3H), 1.18 (s, 3H), 1.24-1.31

(m, 1H), 1.58-1.66 (m, 1H), 1.72-1.79 (m, 1H), 2.00 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.21-2.27 (m, 1H), 2.85 (s, 1H), 3.74 (s, 3H), 4.95-4.99 (m, 2H), 5.57-5.67 (m, 1H), 5.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 20.4 (CH_3), 27.0 (CH_3), 34.0 (CH_2), 38.7 (CH), 41.3 (C), 42.0 (CH_2), 56.5 (CH_3), 60.1 (C), 65.5 (CH), 105.4 (CH), 116.8 (CH_2), 136.5 (CH), 174.6 (C), 197.6 (C), 207.8 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{16}H_{22}O_3$ 262.1569; Found: 262.1579.

***rac*-7-allyl-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione (28).** To a solution of **27** (4.76 mmol) in THF (24 mL) at -78 °C was added a freshly prepared solution of LiTMP (10.48 mL, 1M in THF, 10.48 mmol). The reaction mixture was stirred for 5 min before the addition of freshly distilled TMSCl (2.56 mL, 20.0 mmol). The reaction mixture was stirred and allowed to warm to -40 °C over 2 h. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude is purified by flash chromatography (5-10% EtOAc:hexanes) to afford **28** (1.49 g, 94%) as a white solid. M.p. 93-96 °C; IR (neat NaCl) 3077, 2973, 2897, 1732, 1644, 1558, 1333, 1214 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 0.92 (s, 3H), 1.09 (s, 3H), 1.14 (s, 3H), 1.24 (t, *J* = 13.0 Hz, 1H), 1.56-1.71 (m, 2H), 1.98 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.21-2.26 (m, 1H), 3.27 (s, 1H), 3.74 (s, 3H), 4.95-5.00 (m, 2H), 5.56-5.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5 (3x CH_3), 15.8 (CH_3), 20.8 (CH_3), 25.8 (CH_3), 33.7 (CH_2), 38.2 (CH), 42.1 (C), 42.2 (CH_2), 56.1 (CH_3), 60.2 (C), 60.8 (CH), 116.7 (CH_2), 123.1 (C), 136.5 (CH), 178.9 (C), 201.5 (C), 208.8 (C); HRMS (ESI) *m/z*: [M^+H -Me] Calcd for $C_{18}H_{28}O_3Si$ 320.1808; Found 320.1749.

***rac*-7-allyl-5-iodo-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione (29) and *rac*-7-allyl-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)-9-(trimethylsilyloxy)bicyclo [3.3.1]non-3-en-2-one (30).** To a solution of **28** (5 mmol) in THF (5 mL) was added freshly distilled TMSCl (25 mmol) (distilled over CaH_2) (mmol) at room temperature and then the solution was transfer via cannula to a freshly prepared LDA solution (0.58 M in THF, 30 mL, 17.49 mmol) at -78 °C. After stirring for 10 min at -78 °C, the reaction mixture was warmed to 0°C in an ice bath. After stirring for 30 sec at 0 °C, a solution of iodine (3.81g, 15 mmol) in THF (5 mL) was added to mixture via cannula.

The resulting solution was stirred for 15 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and extracted 3x with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40-60% benzene:hexanes then 5% EtOAc:hexanes) to afford iodide **29** (0.666 g, 29%) as a crystalline pale yellow solid along with compound **30** (0.857 g, 42%) as white solid. **Compound 29:** M.p. 75-80 °C; IR (neat NaCl) 2985, 2939, 2358, 1733, 1651, 1650, 1544, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.92 (s, 3H), 1.24 (s, 3H), 1.27 (s, 3H), 1.30-1.38 (m, 1H), 1.65-1.74 (m, 1H), 1.90-1.99 (m, 2H), 2.36-2.41 (m, 1H), 3.93 (s, 3H), 4.98-5.03 (m, 2H), 5.60 (dddd, J = 16.7, 10.3, 8.6, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5 (3xCH_3), 17.5 (CH_3), 20.7 (CH_3), 29.0 (CH_3), 36.3 (CH_2), 39.6 (CH), 41.3 (CH_2), 48.0 (C), 62.7 (C), 66.3 (CH_3), 85.9 (C), 117.1 (CH_2), 125.6 (C), 136.4 (CH), 178.9 (C), 200.2 (C), 200.4 (C); HRMS (EI) *m/z*: [M^+-Me] Calcd for $C_{18}H_{26}IO_3Si$ 445.0696; Found 445.0695. **Compound 30:** M.p. 90-94 °C; IR (neat NaCl) 2985, 2939, 2358, 1733, 1650, 1544, 1255, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (m, 9H), 0.16 (s, 9H), 0.91 (s, 3H), 0.97 (s, 3H), 1.11 (s, 3H), 1.29 (m, 3H), 1.61 (m, 1H), 2.19 (m, 1H), 2.61 (d, J = 3.1 Hz, 1H), 3.69 (s, 3H), 3.73 (d, J = 3.1 Hz, 1H), 4.94 (m, 2H), 5.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0 (3x CH_3), 0.7 (3x CH_3), 20.4 (CH_3), 24.0 (CH_3), 27.4 (CH_3), 32.5 (CH_2), 34.4 (C), 34.8 (CH_2), 38.6 (CH), 48.7 (C), 49.8 (CH), 55.3 (CH_3), 74.4 (CH), 115.8 (CH_2), 120.4 (C), 138.0 (CH), 183.0 (C), 206.9 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{22}H_{40}O_3Si_2$ 408.2516; Found: 408.2522.

***rac*-(7-allyl-5-isobutyryl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (32)**. Iodide **29** (0.880 mmol) was charged to a flame-dried flask and THF (7 mL) was added. The resulting mixture was cooled to -78 °C and *t*-BuLi (1.6M solution in pentane, 1.26 mL, 2.02 mmol) was added dropwisely to obtain a bright yellow solution. After stirring the solution for 5 min at -78 °C, freshly distilled isobutyraldehyde (0.16 mL, 1.75 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 °C. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The organic layers are combined, dried over $MgSO_4$ and concentrated.

The crude **31** was used as is and dissolved in wet DCM (7 mL) and DMP (1.87 g, 4.40 mmol) was added in one portion. After stirring for 3 days, a 1:1 solution of 5% $NaHCO_3$ and saturated solution of $Na_2S_2O_3$ was added under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was rapidly purified over a pad of silica (5% EtOAc:hexanes).

The crude mixture was put under an atmosphere of argon and THF (7 mL) was added. The solution was cooled to 0 °C before adding TBAF (1M solution in THF, 1.05 mL, 1.056 mmol) dropwise. The mixture was stirred at 0˚C for 1h before adding a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with Et_2O and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (15-30% EtOAc:hexanes) to afford ketone **32** (0.133 g, 45% over 3 steps) as a white solid. M.p. 82-84 °C; IR (neat NaCl) 2975, 2933, 2360, 1720, 1654, 1601, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.00 (d, J = 6.5 Hz, 3H), 1.03 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H), 1.22 (br s, 6H), 1.32 (dd, J = 13.6, 12.8 Hz, 1H), 1.59-1.64 (m, 1H), 1.68-1.76 (m, 1H), 1.96 (dd, J = 13.7, 4.5 Hz, 1H), 2.24-2.35 (m, 2H), 3.81 (s, 3H), 4.95-4.99 (m, 2H), 5.54-5.64 (m, 1H), 5.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6 (CH_3), 15.9 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 24.0 (CH_3), 33.6 (CH_2), 40.7 (CH), 41.9 (CH), 42.6 (CH_2), 45.2 (C), 56.3 (CH_3), 61.0 (C), 75.8 (C), 107.1 (CH), 116.9 (CH_2), 136.6 (CH), 173.1 (C), 195.7 (C), 207.4 (C), 208.5 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{20}H_{28}O_4$ 332.1988; Found: 332.2006.

***rac*-7-Allyl-4-(allyloxy)-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (35).** Sodium (0.022 g, 0.961 mmol) was added to allyl alcohol (3.00 mL) and stirred until all sodium is consumed. Compound **26** (0.23 g, 0.739 mmol) was diluted in a minimum of allyl alcohol and added to the solution of sodium allyl alkoxide. After stirring at 50 °C, the resulting mixture was concentrated and the residue was purified by flash chromatography (2% EtOAc:hexanes) to provide **35** (0.602 g, 81%). M.p. 72-74 °C; IR (neat NaCl) 3081, 2971, 2934, 1733, 1652, 1601, 1340, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.05 (s, 3H), 1.17 (s, 3H), 1.27 (m, 1H), 1.61 (m, 1H), 1.76 (m, 1H), 2.00 (m, 1H), 2.24 (m, 1H), 2.87 (s, 1H), 4.42 (m, 2H), 4.96 (m, 2H), 5.32 (dd, J = 10.5, 1.1 Hz, 1H), 5.38 (dd, J = 17.3, 1.3 Hz, 1H), 5.67 (m, 1H), 5.67 (s,

1H), 5.94 (dddd, J = 16.9, 11.0, 5.7, 5.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.5 (CH_3), 20.5 (CH_3), 27.1 (CH_3), 34.0 (CH_2), 38.7 (CH), 41.3 (C), 42.0 (CH_2), 60.1 (C), 65.5 (CH), 70.2 (CH_2), 106.2 (CH), 116.8 (CH_2), 119.5 (CH_2), 130.7 (CH), 136.6 (CH), 173.3 (C), 197.7 (C), 207.8 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{18}H_{24}O_3$ 288.1725; Found: 288.1734.

***rac*-3,7-Diallyl-4-hydroxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (36).** A solution of allyl enol ether **35** (0.100 g, 0.347 mmol) in toluene was placed in a sealed tube and heated at 140 °C for 7 hours. The mixture was cooled down to r.t. and was concentrated. The residue was purified by flash chromatography (50 % EtOAc:hexanes) to give **36** (0.084 g, 84%) as a lightly yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.14 (t, J = 7.3 Hz, 1H), 1.21 (t, J = 12.9 Hz, 2H), 1.61 (m, 2H), 1.77 (dd, J = 13.5, 4.3 Hz, 1H), 2.20 (m, 1H), 2.93 (m, 3H), 4.82 (dd, J = 10.1, 2.3 Hz, 1H), 4.88 (dd, J = 17.2, 2.2 Hz, 1H), 4.94 (s, 1H), 4.98 (d, J = 4.7 Hz, 1H), 5.68 (m, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 16.4 (CH_3), 20.4 (CH_3), 26.2 (CH_3), 26.9 (CH_2), 33.3 (CH_2), 38.3 (CH), 40.6 (C), 40.7 (C), 41.23 (CH_2), 41.84 (CH_2), 58.0 (C), 113.8 (C), 115.2 (CH_2), 116.3 (CH_2), 136.6 (CH), 137.4 (CH), 208.1 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{18}H_{24}O_3$ 288.1725; Found: 288.1707.

***rac*-2,2,6,9,9-Pentamethyl-8-(3-methylbut-2-en-1-yl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione (33) and *rac*-2,2,7,7,10-pentamethyl-8-(3-methylbut-2-en-1-yl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione (37).** Grubb's 2nd generation (0.106 g, 0.125 mmol, 15% loading) was added to a solution of **36** (0.24 g, 0.832 mmol) in DCM (3.00 mL) and the solution was heated at 40 °C for 24h. The solution was thereafter concentrated and diluted in DMSO: H_2O 9:1 (2 mL). $PdCl_2$ (0.166 g, 0.941 mmol) was added and O_2 was bubbled through the solution by means of a balloon for 1h. The crude residue was purified by flash chromatography (20% EtOAc:hexanes) to give a separable mixture of **33** (62 mg, 22%) and **37** (31 mg, 11%) as crystalline solids. **Compound 33:** IR (neat NaCl) 2979, 2366, 1731, 1654, 1587 cm^{-1}; ^{1}H NMR, (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.12 (s, 3H), 1.20 (s, 3H), 1.22-1.29 (m, 1H), 1.40 (s, 3H), 1.47 (s, 3H), 1.54 (s, 3H), 1.63-1.65 (m, 2H), 1.65 (s, 3H), 2.01 (dd, J = 13.7, 4.1 Hz, 1H), 2.05-2.09 (m, 1H), 2.83 (s, 1H), 4.95-4.98 (m, 1H), 5.29 (d, J = 10.2 Hz, 1H), 6.39 (d, J = 10.0 Hz, 1H); ^{13}C NMR

(400 MHz, $CDCl_3$) δ 16.0 (CH_3), 17.9 (CH_3), 20.6 (CH_3), 25.8 (CH_3), 27.3 (CH_3), 28.0 (CH_2), 28.8 (CH_3), 29.4 (CH_3), 40.2 (CH), 42.1 (CH_2), 42.2 (C), 60.1 (C), 65.3 (CH), 82.4 (C), 112.7 (C), 115.3 (CH), 122.3 (CH), 123.7 (CH), 133.2 (C), 168.2 (C), 193.7 (C), 207.3 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{22}H_{30}O_3$ 342.2195; Found: 342.2182. **Compound 37:** IR (neat NaCl) 2974, 2356, 1733, 1647, 1575, 1326, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.09 (s, 3H), 1.23 (s, 3H), 1.29-1.35 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.55 (s, 3H), 1.65 (s, 5H), 1.99 (dd, J = 13.8, 3.8 Hz, 1H), 2.07-2.14 (m, 1H), 2.90 (s, 1H), 4.98-5.01 (m, 1H), 5.30 (d, J = 10.0 Hz, 1H), 6.40 (d, J = 10.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.1 (CH_3), 17.8 (CH_3), 20.5 (CH_3), 25.7 (CH_3), 26.5 (CH_3), 27.2 (CH_2), 27.9 (CH_3), 28.2 (CH_3), 39.8 (CH_2), 41.3 (CH), 42.3 (C), 52.5 (C), 74.3 (CH), 81.4 (C), 113.5 (C), 115.9 (CH), 122.6 (CH), 123.5 (CH), 133.2 (C), 171.4 (C), 189.7 (C), 206.6 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{22}H_{30}O_3$ 342.2195; Found: 342.2182.

***rac*-7-Allyl-9-hydroxy-9-isopropyl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-en-2-one (40)** Sodium (4.15 mg, 0.180 mmol) was added to allyl alcohol (1.00 mL) in a r.b.f. and stirred until all sodium has been consumed. Compound **32** (1.2 mg, 0.036 mmol) was diluted in a minimum of allyl alcohol and added to the solution of sodium allyl alkoxide. The mixture was heated at 80 °C. After stirring for 18h, the resulting mixture was concentrated and purified by flash chromatography (10% EtOAc:hexanes) to provide **40** (1 mg, > 90%). **Major diastereomer:** IR (neat NaCl) 3475, 2948, 2347, 1645, 1610, 1365, 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J = 6.9 Hz, 3H), 0.87 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.15 (s, 3H), 1.27 (s, 3H), 1.47 (dd, J = 14.7, 8.0 Hz, 1H), 1.73 (m, 1H), 1.78 (dd, J = 14.7, 6.1 Hz, 1H), 1.91 (dt, J = 13.6, 6.7 Hz, 1H), 2.10 (s, 1H), 2.19 (s, 1H), 2.32 (s, 1H), 3.64 (s, 3H), 4.91 (m, 2H), 5.24 (s, 1H), 5.61 (dddd, J = 16.9, 10.2, 8.4, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 18.7 (CH_3), 19.2 (CH_3), 20.0 (CH_3), 24.1 (CH_3), 33.9 (CH_3), 35.7 (CH), 35.8 (CH), 36.2 (CH_2), 36.8 (CH_2), 40.5 (CH), 54.4 (CH_3), 55.3 (CH), 79.3 (C), 102.7 (CH), 115.9 (CH_2), 138.8 (CH), 178.1 (C), 203.5 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{19}H_{30}O_3$ 306.2195; Found: 306.2217.

***rac*-3,7-Diallyl-5-isobutyryl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione (41).** A solution of *n*-BuLi (2.4 M in hexanes, 0.474 mL, 1.138 mmol) was added slowly to freshly distilled

diisopropylamine (0.165 mL, 1.156 mmol) in THF (2 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0 °C. A solution of compound **32** (0.373 mmol) in THF (0.5 mL) was added via cannula at -78 °C. The solution was stirred for 10 min and a solution of lithium 2-thienylcyanocuprate (0.25M in THF, 2.98 mL, 0.746 mmol) was added at -78 °C. After stirring for 20 min, allyl bromide (0.484 mL, 5.60 mmol) was added dropwisely to the solution and the mixture was stirred another 20 min. The reaction mixture was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to afford the desired allyl **41** (138 mg, 0.365 mmol, 98%) as a colorless oil. IR (neat NaCl) 2933, 2362, 1724, 1658, 1598, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.21 (s, 3H), 1.26 (s, 3H), 1.28-1.31 (m, 1H), 1.57-1.65 (m, 1H), 1.75 (dddd, J = 12.8, 10.5, 4.6, 2.6 Hz, 1H), 1.94 (dd, J = 13.72, 4.51 Hz, 1H), 2.26-2.32 (m, 1H), 2.37 (sept, J = 6.5 Hz, 1H), 3.40 (m, 2H), 4.10 (s, 3H), 4.95-5.03 (m, 3H), 5.12 (dq, J = 10.3, 1.60 Hz, 1H), 5.54-5.64 (m, 1H), 5.87-5.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (2xCH_3), 21.3 (CH_3), 21.5 (CH_3), 24.3 (CH_3), 28.5 (CH_2), 33.5 (CH_2), 40.5 (CH), 42.6 (CH_2), 42.7 (CH), 45.2 (C), 60.5 (CH_3), 60.6 (C), 77.2 (C), 115.7 (CH_2), 116.9 (CH_2), 120.4 (C), 136.5 (CH), 136.6 (CH), 170.3 (C), 196.3 (C), 208.0 (C), 208.9 (C). HRMS (EI) *m/z*: [M^+] Calcd for $C_{23}H_{32}O_4$ 372.2301; Found: 372.2290.

***rac*-5-isobutyryl-4-methoxy-1,6,6-trimethyl-3,7-bis(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (42).** The bis-allyl compound **41** (81 mg, 0.217 mmol) was dissolved in DCM (0.75 mL), to which 2-methyl-2-butene (4.95 mL, 46.8 mmol) was then added. The resulting mixture was added to a dried seal tube under argon atmosphere containing Grubbs 2nd generation catalyst (18 mg, 0.022 mmol). The resulting red mixture was heated at 40 °C for 2 hours and the solution was cooled to r.t. Ethyl vinyl ether (0.2 mL) was added to the mixture and the solution was stirred for 2 min then concentrated. The residue was purified by flash chromatography (3-5% EtOAc:hexanes) to afford **42** (92 mg, 0.215 mmol, 99%) as a colorless oil. IR (neat NaCl) 2979, 2933, 1722, 1658, 1596, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.03 (d, J = 6.5 Hz, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.20 (s,

3H), 1.26 (s, 3H), 1.28 (dd, *J* = 13.5, 12.5 Hz, 1H), 1.54 (s, 3H), 1.57-1.62 (m, 2H), 1.65 (s, 3H) 1.67-1.68 (m, 6H), 1.91 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.08-2.12 (m, 1H), 2.36 (sept, *J* = 6.5 Hz, 1H), 3.19-3.24 (m, 1H), 3.36-3.42 (m, 1H), 4.05 (s, 3H), 4.91-4.94 (m, 1H), 4.97-5.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 16.5 (CH_3), 17.8 (CH_3), 18.1 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 23.5 (CH_2), 24.3 (CH_3), 25.6 (CH_3), 25.8 (CH_3), 27.3 (CH_2), 40.4 (CH), 42.8 (CH_2), 43.7 (CH), 45.2 (C), 60.4 (CH_3), 60.6 (C), 77.3 (C), 122.4 (2xCH) ,123.0 (C), 132.9 (C), 133.3 (C), 169.9 (C), 196.6 (C), 208.2 (C), 209.2 (C). HRMS (EI) *m/z*: [M^+] Calcd for $C_{27}H_{40}O_4$ 428.2927; Found: 428.2924.

***rac*-Papuaforin A (2) and *rac*-papuaforin B (3).** Compound (**42**) (38 mg, 0.089 mmol) was dissolved in dry DMSO (1.1 mL) and LiCl (30 mg, 0.709 mmol) was added in one portion. The resulting mixture was degassed for 10 min and was heated at 120 °C for 120 min. The resulting dark solution was cooled to r.t. $PdCl_2$ (21 mg, 0.120 mmol) and distilled water (0.11 mL) were added and oxygen was bubbled through the stirred solution for 90 seconds. Water was added and extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was first purified by flash chromatography (15% EtOAc:hexanes). The resulting mixture of **2** and **3** was then purified again by a preparative flash chromatography (5% EtOAc:hexanes) to afford papuaforin A (**2**) (8.6 mg, 0.021 mmol, 24%) and papuaforin B (**3**) (4.3 mg, 0.010 mmol, 12%). **Papuaforin A (2):** IR (neat NaCl) 2954, 2362, 1731, 1641, 1579, 1456, 1411, 1328, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.38-1.41 (m, 1H), 1.39 (s, 3H), 1.51-1.54 (m, 1H), 1.49 (s, 3H), 1.55 (s, 3H), 1.65 (s, 3H), 1.62-1.72 (m, 1H), 1.95 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.04-2.14 (m, 2H), 4.94-4.98 (m, 1H), 5.37 (d, *J* = 10.0 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3 (CH_3), 15.8 (CH_3), 17.8 (CH_3), 20.5 (CH_3), 21.6 (CH_3), 22.8 (CH_3), 25.7 (CH_3), 26.4 (CH_2), 28.1 (CH_3), 28.3 (CH_3), 40.3 (CH_2), 42.3 (CH), 43.2 (CH), 46.3 (C), 52.6 (C), 81.9 (C), 83.4 (C), 113.9 (C), 115.7 (CH), 122.6 (CH), 123.9 (CH), 133.3 (C), 170.8 (C), 188.6 (C), 207.0 (C), 209.2 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{26}H_{36}O_4$ 412.2614; Found: 412.2605. **Papuaforin B (3):** IR (neat NaCl) 2954, 2352, 1731, 1654 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.24 (s, 3H), 1.32-1.35 (m, 1H), 1.35

(s, 3H), 1.50 (s, 3H), 1.54 (s, 6H), 1.63-1.66 (m, 1H), 1.66 (s, 3H), 1.67-1.68 (m, 1H), 1.97 (dd, J = 13.8, 4.3 Hz, 1H), 2.10-2.15 (m, 1H), 2.40 (sept, J = 6.6 Hz, 1H), 4.93-4.96 (m, 1H), 5.39 (d, J = 10.1 Hz, 1H), 6.51 (d, J = 10.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2 (CH_3), 16.8 (CH_3), 17.8 (CH_3), 21.3 (CH_3), 21.5 (CH_3), 24.0 (CH_3), 25.8 (CH_3), 27.4 (CH_2), 29.0 (CH_3), 29.4 (CH_3), 40.7 (CH), 42.5 (CH_2), 43.7 (CH), 46.2 (C), 61.0 (C), 75.6 (C), 83.8 (C), 115.1 (C), 115.9 (CH), 122.3 (CH), 124.1 (CH), 133.4 (C), 167.3 (C), 191.9 (C), 206.7 (C), 208.9 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{26}H_{36}O_4$ 412.2614; Found: 412.2539.

***rac*-7-Allyl-4-methoxy-1,6,6-trimethyl-5-(2-methylbutanoyl)bicyclo[3.3.1]non-3-ene-2,9-dione (43).** Iodide (**29**) (0.25 g, 0.543 mmol) was charged to a flame dried flask and THF (4 mL) was added. The resulting mixture is cooled to -78 °C and *t*-BuLi (1.6 M solution in pentane, 0.78 mL, 1.25 mmol) was added dropwise to obtain a bright yellow solution. After stirring the solution for 5 min at -78˚C, 2-methylbutanal (0.116 mL, 1.09 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 °C before quenching with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The organic layers are combined, dried over $MgSO_4$ and concentrated.

The crude was dissolved in wet DCM (6 mL) and DMP (0.95 g, 2.24 mmol) was added in one portion. The solution was stirred 3 days at r.t. The resulting reaction mixture was quenched with a 1:1 mixture of 5% $NaHCO_3$ and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was extracted 3x with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was rapidly purified over a pad of silica (5% EtOAc:hexanes).

The resulting residue was put under an atmosphere of argon and THF (6 mL) was added. The solution was cooled to 0˚C before adding a TBAF (1M solution in THF, 0.537 mL, 0.537 mmol) dropwise. The mixture was stirred at 0 °C for 1h before quenching the solution with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10-30% EtOAc:hexanes) to afford compound **43** (0.115 g, 0.309 mmol, 63% over 3 steps) as a clear oil. IR (neat NaCl) 2958, 1722, 1658, 1598, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 1.03 (s, 3H), 1.15 (d, J = 6.5

Hz, 3H), 1.21 (s, 6H), 1.27-1.36 (m, 2H), 1.46-1.53 (m, 1H), 1.55-1.63 (m, 1H), 1.68-1.75 (m, 1H), 1.95 (dd, J = 13.6, 4.6 Hz, 1H), 1.99-2.07 (m, 1H), 2.24-2.29 (m, 1H), 3.79 (s, 3H), 4.94-4.98 (m, 2H), 5.53-5.64 (m, 1H), 5.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 15.6 (CH_3), 16.0 (CH_3), 17.4 (CH_3), 24.0 (CH_3), 27.5 (CH_2), 33.5 (CH_2), 42.0 (CH), 42.6 (CH_2), 45.2 (C), 47.5 (CH), 56.3 (CH_3), 61.0 (C), 75.9 (C), 107.1 (CH), 116.9 (CH_2), 136.5 (CH), 173.2 (C), 195.7 (C), 207.2 (C), 208.1 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{21}H_{30}O_4$ 346.2144; found: 346.2148.

***rac*-3,7-Diallyl-4-methoxy-1,6,6-trimethyl-5-(2-methylbutanoyl)bicyclo[3.3.1]non-3-ene-2,9-dione (44).** A solution of *n*-BuLi (2.4 M in hexanes, 0.474 mL, 1.138 mmol) was added slowly to freshly distilled diisopropylamine (0.165 mL, 1.156 mmol) in THF (2 mL) at −78 °C and the solution was stirred for 30 min at -78 °C and 15 min at 0°C. A solution of **43** (129 mg, 0.373 mmol) in THF (0.5 mL) was added via cannula at -78 °C. The solution was stirred for 10 min and a solution of lithium 2-thienylcyanocuprate (0.25M in THF, 2.98 mL, 0.746 mmol) was added at -78 °C. After stirring for 20 min, allyl bromide (0.484 mL, 5.60 mmol) was added dropwisely to the solution and the mixture was stirred another 20 min. The reaction mixture was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to afford **44** (124 mg, 82%) as a colorless oil. IR (neat,) 2958, 2356, 1722, 1658, 1596, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 1.01 (s, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.21 (s, 3H), 1.25 (s, 3H), 1.27-1.36 (m, 2H), 1.54-1.65 (m, 2H), 1.70-1.78 (m, 1H), 1.93 (dd, J = 13.7, 4.7 Hz, 1H), 2.06-2.14 (m, 1H), 2.26-2.31 (m, 1H), 3.32-3.48 (m, 2H), 4.09 (s, 3H), 4.95-5.03 (m, 3H), 5.09 (dq, J = 10.2, 1.7 Hz, 1H), 5.53-5.64 (m, 1H), 5.85-5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 16.4 (CH_3), 16.5 (CH_3), 17.5 (CH_3), 24.4 (CH_3), 27.7 (CH_2), 28.4 (CH_2), 33.5 (CH_2), 42.6 (CH_2), 42.7 (C) 45.2 (CH), 47.4 (CH), 60.5 (CH_3), 60.6 (C), 77.4 (C), 115.7 (CH_2), 116.8 (CH_2), 120.4 (C), 136.4 (CH), 136.6 (CH), 170.5 (C), 196.2 (C), 207.9 (C), 208.5 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{24}H_{34}O_4$ 386.2457; Found: 386.2472.

***rac*-4-Methoxy-1,6,6-trimethyl-3,7-bis(3-methylbut-2-en-1-yl)-5-(2-methylbutanoyl) bicyclo[3.3.1] non-3-ene-2,9-dione (45).** Compound **44** (113 mg, 0.293 mmol) was dissolved in DCM (0.75 mL), to which 2-methyl-2-butene (4.95 mL, 46.8 mmol) was then added. The resulting mixture was added to a pre-dried seal tube under argon atmosphere containing Grubbs 2nd generation catalyst (24 mg, 0.029 mmol). The resulting red mixture was heated at 40 °C for 2 hours and the solution was cooled to to r.t. Ethyl vinyl ether (0.2 mL) was added to the mixture and the solution was stirred for 2 min then concentrated. The residue was purified by flash chromatography (3-5% EtOAc:hexanes) to afford compound the desired prenyl compound **45** (129 mg, 99%) as a colorless oil. IR (neat NaCl) 2933, 2347, 1726, 1660, 1593, 1452, 1245 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 1.02 (m, 3H), 1.14 (d, J = 6.5 Hz, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 1.28-1.36 (m, 2H), 1.53 (s, 3H), 1.57-1.62 (m, 3H), 1.65 (s, 3H), 1.68 (m, 6H), 1.90 (dd, J = 13.5, 4.1 Hz, 1H), 2.07-2.15 (m, 2H), 3.17-3.23 (m, 1H), 3.41-3.48 (m, 1H), 4.04 (s, 3H), 4.90-4.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (CH_3), 16.5 (CH_3), 16.6 (CH_3), 17.5 (CH_3), 17.8 (CH_3), 18.1 (CH_3), 23.3 (CH_2), 24.4 (CH_3), 25.6 (CH_3), 25.8 (CH_3), 27.3 (CH_2), 27.6 (CH_2), 42.8 (CH_2), 43.8 (CH), 45.3 (C), 47.3 (CH), 60.3 (CH_3), 60.6 (C), 77.4 (C), 122.3 (CH), 122.4 (CH), 123.0 (C), 132.9 (C), 133.3 (C), 170.1 (C), 196.5 (C), 208.2 (C), 208.8 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{28}H_{42}O_4$ 442.3083; Found: 442.3083.

***rac*-Papuaforin C (4).** Compound (**29**) (120 mg, 0.271 mmol) was dissolved in dry DMSO (3.61 mL) and LiCl (92mg, 2.169 mmol) was added in one portion. The resulting mixture was degassed for 10 min before heating at 120 °C for 120 min. The resulting dark solution is then allowed to cool down to r.t. To this mixture was added $PdCl_2$ (65 mg, 0.366 mmol) and distilled water (0.5 mL). Oxygen was then bubbled through the stirred solution for 90 seconds. Water was added and extracted with EtOAc (3x). The organic phases are combined, dried over $MgSO_4$ and concentrated. The residue was purified in a first time by flash chromatography (15% EtOAc:hexanes) to eliminate most impurities. The resulting residue was then purified again by preparatory chromatography (1-5% EtOAc:hexanes) to afford papuaforin C (**4**) (48 mg, 0.113 mmol, 41%) along with other isomer (10 mg, 0.023 mmol, 8%). IR (neat NaCl) 2954, 2356, 1730, 1637, 1587, 1328 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, J = 7.5

Hz, 3H), 1.02 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.30-1.34 (m, 1H), 1.38-1.43 (m, 1H), 1.39 (s, 3H), 1.46-1.53 (m, 1H), 1.50 (s, 3H), 1.55 (s, 3H), 1.65 (s, 3H), 1.65-1.74 (m, 2H), 1.80-1.88 (m, 1H) 1.94 (dd, J = 13.5, 3.9 Hz, 1H), 2.10-2.15 (m, 1H), 4.94-4.98 (m, 1H), 5.37 (d, J = 10.0 Hz, 1H), 6.48 (d, J = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 15.3 (CH_3), 15.8 (CH_3), 16.7 (CH_3), 17.8 (CH_3), 22.8 (CH_3), 25.7 (CH_3), 26.4 (CH_2), 27.5 (CH_2), 28.2 (CH_3), 28.2 (CH_3), 40.3 (CH_2), 43.3 (CH), 46.4 (C), 49.0 (CH), 52.6 (C), 81.8 (C), 83.4 (C), 114.0 (C), 115.8 (CH), 122.6 (CH), 124.0 (CH), 133.3 (C), 170.7 (C), 188.7 (C), 207.0 (C), 208.7 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{27}H_{38}O_4$ 426.2770; Found: 426.2750.

***rac*-4,6-Diallyl-6-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)-3-methylcyclohex-2-enone (46).** A solution of *n*-BuLi (9.8 M in hexanes, 5.48 mL, 53.7 mmol) was added slowly to freshly distilled diisopropylamine (8.02 mL, 56.3 mmol) in THF (250 mL) at −78 °C and the solution was stirred for 30 min at -78 °C and then 15 min at 0 °C. Compound **16** (9.74 g, 51.2 mmol) was dissolved in THF (30mL) and add via cannula to the solution at −78 °C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**14**) (7.75g, 61.4 mmol) was added and the mixture was stirred at -78 °C for 10 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78 °C. Distilled water was added and the aqueous layer was extracted with EtOAc:Et_2O 1:3 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (5-15% EtOAc:hexanes) to give alcohol enone **46** (10.25 g, 63%) as a mixture of diastereoisomere at C4. **Major diastereomer at C4:** M.p. 55-58 °C; IR (neat NaCl) 3439, 3076, 2958, 2858, 2172, 1652, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.77 (dd, J = 14.4, 11.1 Hz, 1H), 1.95 (s, 3H), 2.07-2.19 (m, 3H), 2.39-2.40 (m, 1H), 2.50-2.61 (m, 2H), 2.84 (dd, J = 13.9, 6.3 Hz, 1H), 4.59 (s, 1H), 5.03-5.13 (m, 4H), 5.64-5.80 (m, 2H), 5.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.3 (3x CH_3), 22.0 (CH_3), 34.7 (CH_2), 35.4 (CH_2), 35.9 (CH), 36.7 (CH_2), 51.9 (C), 66.0 (CH), 92.1 (C), 102.4 (C), 117.8 (CH_2), 118.6 (CH_2), 127.0 (CH), 134.5 (CH), 134.9 (CH), 163.6 (C), 200.9 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{19}H_{28}O_2Si$ 316.1859; Found: 316.1851. **Minor diastereomer at C4:** M.p. 63-65 °C; IR (neat NaCl) 2956, 2360, 1647, 1249 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 0.15 (s, 9H), 1.82 (dd, J = 14.5, 8.6 Hz, 1H), 1.97 (s, 3H), 2.17-2.22 (m, 2H), 2.37 (dd, J = 13.9, 8.0 Hz, 1H), 2.46-2.57 (m, 3H), 2.78-2.85 (m, 1H), 4.44 (d, J = 7.1 Hz, 1H), 5.07-5.15 (m, 4H), 5.63-5.82 (m, 2H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (3x CH_3), 22.5 (CH_3), 32.1 (CH_2), 37.1 (CH_2), 37.15 (CH), 39.2 (CH_2), 51.5 (C), 67.7 (CH), 92.0 (C), 103.9 (C), 117.5 (CH_2), 119.1 (CH_2), 127.9 (CH), 133.4 (CH), 135.7 (CH), 164.5 (C), 201.1 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{19}H_{28}O_2Si$ 316.1859; Found: 316.1842.

***rac*-1,7-Diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione (51).** IR (neat NaCl) 2939, 2362, 1731, 1658, 1604, 1217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.21 (ddd, J = 13.8, 12.1, 4.4 Hz, 1H), 1.33 (td, J = 12.9, 4.9 Hz, 1H), 1.44 (t, J = 13.2 Hz, 1H), 1.66 (ddd, J = 13.6, 10.7, 8.4 Hz, 1H), 293 1.76-1.83 (m, 1H), 1.92 (dd, J = 13.5, 4.5 Hz, 1H), 1.95-2.03 (m, 1H), 2.19-2.29 (m, 2H), 2.41-2.53 (m, 2H,) 3.2 (s, 1H), 3.7 (s, 3H), 4.94-5.00 (m, 4H), 5.04 (ddd, J = 10.5, 3.4, 1.4 Hz, 1H), 5.08 (ddd, J = 10.4, 1.7, 1.5 Hz, 1H), 5.60 (dddd, J = 16.3, 10.7, 8.3, 5.5 Hz, 1H), 5.68-5.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_3), 27.2 (CH_2), 31.4 (CH_2), 33.6 (CH_2), 34.6 (CH_2), 40.0 (CH_2), 40.3 (CH), 43.8 (C), 56.5 (CH_3), 60.6 (CH), 63.2 (C), 106.2 (CH), 115.0 (CH_2), 116.9 (CH_2), 118.1 (CH_2), 134.0 (CH), 136.6 (CH), 138.2 (CH), 174.6 (C), 197.0 (C), 207.2 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{21}H_{28}O_3$ 328.2038; Found: 328.2088.

***rac*-4-Allyl-3-(but-3-en-1-yl)cyclohex-2-enone (52).** A solution of *n*-BuLi (9.5 M in hexanes, 8.54 mL, 81 mmol) was added slowly to freshly distilled diisopropylamine (12.08 mL, 85 mmol) in THF (250 mL) at −78 °C and the solution was stirred for 30 min at -78 °C and 15 min at 0 °C and then cooled to -78 °C. A solution of 3-methoxycyclohex-2-enone (**15**) (9.3 g, 73.7 mmol) in THF (35 mL) was added via cannula at −78 °C and the solution was stirred for 60 min to obtain a slurry. Allyl bromide (7.97 mL, 92 mmol) was added in one portion, the mixture was stirred for 1h at -78 °C and 3h at r.t. The solution was cooled to -78 °C and a freshly prepared solution of but-3-en-1-ylmagnesium bromide (0.15 M in Et_2O, 1005 mL, 158 mmol) was added in one portion. The resulting mixture was stirred for 30 min at -78 °C and 1h at rt. A solution of HCl (2M, 250 mL) was added and the mixture was stirred vigorously for 1h. Water (100 mL) was added with brine (100 mL) and Et_2O (250 mL), the organic

phase was separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (5-10% EtOAc:hexanes) to give 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone (**52**) (11.6 g, 83%) as a clear yellow oil. IR (neat NaCl) 2933, 2356, 1674, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89-2.03 (m, 2H), 2.13-2.47 (m, 9H), 4.96-5.11 (m, 4H), 5.70-5.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9 (CH_2), 31.2 (CH_2), 33.4 (CH_2), 34.9 (CH_2), 35.6 (CH_2), 37.8 (CH), 115.6 (CH_2), 117.2 (CH_2), 125.8 (CH), 136.0 (CH), 136.9 (CH), 167.9 (C), 199.3 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{13}H_{18}O$ 190.1350; Found: 190.1392.

***rac*-4,6-Diallyl-3-(but-3-en-1-yl)cyclohex-2-enone (53).** LiHMDS (11.5 g, 68.6 mmol) was charged to 1L flame dried flask. THF (150 mL) was added at rt and the mixture was stirred. After all LiHMDS was dissolved, the solution was cooled to −78 °C and 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone (**52**) (10.88 g, 57.2 mmol) in THF (30 mL) was added via cannula −78 °C. The solution was stirred for 1h at -78°C and then 1h at -40°C before cooling it again at -78°C and allyl bromide (6.43 mL, 74.3 mmol) was added. The mixture was allowed to warm to rt and stirred for 3h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (2-5% EtOAc:hexanes) to give compound **53** (12.5 g, 95%) as a lightly yellow oil. **Major diastereomer:** IR (neat NaCl) 2974, 2362, 1668, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (td, J = 13.0, 5.4 Hz, 1H), 2.00-2.10 (m, 2H) 2.17-2.46 (m, 8 H) 2.60-2.67 (m, 1H), 4.97-5.10 (m, 6H), 5.66-5.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0 (CH_2), 31.2 (CH_2), 34.0 (CH_2), 34.8 (CH_2), 35.7 (CH_2), 37.8 (CH), 40.6 (CH), 115.6 (CH_2), 116.6 (CH_2), 117.2 (CH_2), 125.5 (CH), 136.1 (CH), 136.2 (CH), 136.9 (CH), 167.0 (C), 200.3 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{16}H_{22}O$ 230.1671; Found: 230.1641.

***rac*-4,6-Diallyl-3-(but-3-en-1-yl)-6-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)cyclohex-2-en-1-one (54).** A solution of *n*-BuLi (2.4 M in hexanes, 1.90 mL, 4.56 mmol) was added slowly to freshly distilled diisopropylamine (0.681 mL, 4.78 mmol) in THF (22 mL) at −78 °C and the solution was

stirred for 30 min at -78 °C and 15 min at 0 °C. Compound **53** (1 g, 4.34 mmol) was dissolved in a minimum of THF and the solution was added to the mixture via cannula at −78 °C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**14**) (0.770 mL, 5.21 mmol) was added and the mixture was stirred at -78 °C for 15 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78 °C. Distilled water was added and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (3-15% EtOAc:hexanes) to give alcohol enone **54** (1.03 g, 66%). IR (neat NaCl) 2964, 2356, 1660, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.79 (dd, J = 14.3, 10.8 Hz, 1H), 2.07-2.43 (m, 8H), 2.51-2.62 (m, 2H), 2.83-2.88 (m, 1H), 4.57 (d, J = 4.5 Hz, 1H), 4.99-5.14 (m, 6H), 5.64-5.82 (m, 3H), 5.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (3x CH_3), 31.4 (CH_2), 33.9 (CH_2), 34.7 (CH), 34.8 (CH_2), 35.1 (CH_2), 36.7 (CH_2), 51.7 (C), 66.1 (CH), 92.2 (C), 102.4 (C), 115.8 (CH_2), 117.8 (CH_2), 118.6 (CH_2), 125.9 (CH), 134.5 (CH), 134.9 (CH), 136.8 (CH), 165.9 (C), 201.1 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{22}H_{32}O_2Si$ 356.2172; Found: 356.2102.

***rac*-2,4-Diallyl-5-(but-3-en-1-yl)-5-methyl-2-(3-(trimethylsilyl)propioloyl)cyclohexanone (55).** To a solution of purified CuI (9.29 g, 48.8 mmol) and enone **54** (8.70 g, 24.40 mmol,) in THF (244 mL), Me_2S (25 mL) was added at 0 °C and the solution was stirred until the solution becomes homogenous. MeMgBr (40.7 mL, 3.0 M in Et_2O, 122 mmol) was added over 90 min with a syringe pump under heavy stirring. The dark green solution was warm rt and stirred for 12 h. A large quantity of saturated solution of NH_4Cl was added with equal amount of distilled water. The mixture was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$ and filtered over a short pad of celite. The crude was concentrated and filtered over celite one more time using ether to wash the celite pad and concentrated again. The residue was not purified and was used for the next step.

To a solution of the crude alcohol in wet DCM (200 mL) was added Dess-Martin periodinane (13.46 g, 31.7 mmol). The reaction was stirred for 1 h and quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase is extracted 3x with DCM. The organic phases are combined,

dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (1.5-3% EtOAc:hexanes) to provide diketone **54** (8.7015 g, 78 %) as a pale yellow oil over 2 steps. IR (neat NaCl) 2964, 2352, 1720, 1668, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 0.73 (s, 3H), 1.30-1.50 (m, 3H), 1.59-1.67 (m, 1H), 1.76-1.83 (m, 1H), 1.92-2.00 (m, 2H), 2.09 (d, J = 13.3 Hz, 1H), 2.31-2.36 (m, 1H), 2.40-2.49 (m, 2H), 2.52-2.61 (m, 2H), 4.95 (t, J = 11.4 Hz, 1H), 5.02-5.10 (m, 5H), 5.66-5.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.9 (3x CH_3), 19.3 (CH_3), 27.6 (CH_2), 33.7 (CH_2), 35.5 (CH_2), 38.7 (CH_2), 39.5 (CH), 40.4 (C), 41.4 (C), 52.2 (CH_2), 66.8 (C), 99.3 (C), 102.1 (C), 114.7 (CH_2), 116.5 (CH_2), 119.0 (CH_2), 132.6 (CH), 137.0 (CH), 138.4 (CH), 187.4 (C), 207.3 (C); HRMS (EI) *m/z*: [M^+ - H] Calcd for $C_{22}H_{31}O_2Si$ 355.2093; Found: 355.2089.

***rac*-2,4-Diallyl-2-(3-bromopropioloyl)-5-(but-3-en-1-yl)-5-methylcyclohexan-1-one (56).** To a solution of diketone **55** (1.94 g, 5.25 mmol) in dry acetone (45 mL), was added $AgNO_3$ (0.446 g, 2.63 mmol). The mixture was stirred for 5 min before the addition of NBS (1.029 g, 5.78 mmol). The reaction was stirred 2h at r.t. before it was filtered over celite and washed with acetone. The filtrate was concentrated and purified by flash chromatography (2-4% EtOAc:hexanes) to afford diketone **56** (1.86 g, 4.93 mmol, 94 %) as a white solid. IR (neat NaCl) 2939, 2179, 1716, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3H), 1.30-1.50 (m, 3H), 1.57-1.66 (m, 1H), 1.75-1.83 (m, 1H), 1.89-1.99 (m, 2H), 2.11 (d, J = 13.3 Hz, 1H), 2.31-2.35 (m, 1H), 2.39-2.47 (m, 2H), 2.54-2.58 (m, 2H), 4.92-5.10 (m, 6H), 5.62-5.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (CH_3), 27.6 (CH_2), 33.5 (CH_2), 35.0 (CH_2), 38.5 (CH_2), 39.6 (CH), 40.3 (CH_2), 41.4 (C), 52.2 (CH_2), 60.8 (C), 67.1 (C), 77.7 (C), 114.7 (CH_2), 116.6 (CH_2), 119.3 (CH_2), 132.1 (CH), 136.9 (CH), 138.3 (CH), 185.7 (C), 206.7 (C); HRMS (EI) *m/z*: [M^+ - allyl] Calcd for $C_{20}H_{25}O_2Br$ 335.0647; Found: 335.0792.

***rac*-3-Bromo-1-(1,5-diallyl-4-(but-3-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)-4-methylcyclohex-2-en-1-yl)prop-2-yn-1-one (57).** 2,6-Di-tert-butyl-4-methylpyridine (6.53 g, 31.8 mmol) was charged to a flame-dried flask under argon atmosphere. DCM (50 mL) was then added. To the stirred solution, diketone **56** (2.4 g, 6.36 mmol) was added in one portion, followed by dropwise addition of TBSOTf (5.84 mL, 25.4 mmol) and the solution was stirred 3 days at 40 °C in an oil bath. The aged brown

solution is quenched slowly with a solution of 5% $NaHCO_3$ and the aqueous phase is extracted 3x with DCM. The organic phases are combined, dried over $MgSO_4$ and concentrated. The mixture is purified immediately by flash chromatography (pure hexane to recuperate 2,6-Di-tert-butyl-4-methylpyridine, 30% benzene:hexanes to recuperate desired silane enol ether **57** (2.83 g, 91 %) as a pale yellow oil. IR (neat NaCl) 2939, 2362, 2179, 1668, 1249, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.19 (m, 6H), 0.79 (s, 3H), 0.88 (s, 9H), 1.20-1.28 (m, 1H), 1.51-1.62 (m, 3H), 1.71-1.79 (m, 2H), 1.98-2.04 (m, 2H), 2.19-2.28 (m, 2H), 2.62-2.67 (m, 1H), 4.68 (s, 1H), 4.90-5.12 (m, 6H), 5.57-5.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9 (CH_3), -4.4 (CH_3), 18.1 (C), 23.3 (CH_3), 25.6 (3xCH_3), 29.1 (CH_2), 31.8 (CH_2), 33.7 (CH_2), 35.0 (CH), 37.9 (CH_2), 38.2 (C), 39.9 (CH_2), 57.0 (C), 58.3 (C), 79.6 (C), 114.0 (CH_2), 116.1 (CH_2), 117.2 (CH), 118.6 (CH_2), 133.9 (CH), 137.5 (CH), 139.4 (CH), 147.6 (C), 189.9 (C); HRMS (EI) *m/z*: [M^+ -C_4H_9] Calcd for $C_{22}H_{30}O_2BrSi$ 433.1198; Found: 433.1196.

***rac*-1,7-Diallyl-4-bromo-6-(but-3-en-1-yl)-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione (58).** To a solution of silane enol ether **57** (2.18 g, 4.45 mmol) in dry acetone (15 mL) was added [JohnPhosAuNCMe][SbF_6] (**8**) (0.171 g, 0.222 mmol). The resulting mixture was left open to air at rt and monitored by TLC until cunsmption all the starting material (30 min). The mixture was concentrated and purified by flash chromatography (3-5% EtOAc:hexanes) to afford the desired bicyclic ketone **58** (1.68 g, 4.45 mmol, 99%) as a colorless oil. IR (neat NaCl) 2943, 1731, 1668, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3 H) 1.46 (t, J = 13.2 Hz, 1H), 1.51-1.59 (m, 2H), 1.62-1.74 (m, 2H), 1.92 (dd, J = 13.7, 4.5 Hz, 1H), 2.00-2.09 (m, 1H), 2.31-2.35 (m, 2H), 2.41-2.52 (m, 2H), 3.46 (s, 1H), 4.95-5.04 (m, 5H), 5.08 (d, J = 1.4 Hz, 1H), 5.54-5.84 (m, 3H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (CH_3), 27.7 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 36.1 (CH_2), 37.4 (CH), 40.4 (CH_2), 44.9 (C), 63.6 (C), 66.4 (CH), 115.1 (CH_2), 117.2 (CH_2), 118.8 (CH_2), 133.2 (CH), 136.0 (CH), 136.4 (CH), 137.5 (CH), 145.3 (C), 196.5 (C), 204.6 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{20}H_{25}O_2Br$ 376.1038; Found: 376.1015.

***rac*-1,7-Diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione (59).** Sodium methoxide (1.17 g, 21.7 mmol) was charged to flame-dried flask. Methanol (20 mL) was then

added slowly. Once the solution was homogenous, compound **58** (1.72 g, 4.57 mmol) was added in one portion. Then the solution was heated to 45˚C in an oil bath. After 3h, the solvent was evaporated and the crude was purified directly by flash chromatography (15-20% EtOAc:hexanes) to afford the desired compound **59** (1.17 g, 78%) as a colorless oil. IR (neat NaCl) 2948, 1730, 1652, 1602, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.13 (dt, J = 13.1, 3.8 Hz, 1H), 1.37 (dd, J = 13.0,13.4 Hz, 1H), 1.53-1.74 (m, 3H), 1.88-1.97 (m, 2H), 2.17-2.29 (m, 2H), 2.39-2.51 (m, 2H), 3.08 (s, 1H), 3.71 (s, 3H), 4.91-5.01 (m, 5H), 5.02-2.08 (m, 1H), 5.53-5.63 (m, 1H), 5.66-5.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (CH_3), 27.4 (CH_2), 34.1 (CH_2), 34.6 (CH_2), 37.7 (CH_2), 38.4 (CH), 40.2 (C), 44.3 (CH_2), 56.4 (CH_3), 61.6 (CH), 63.0 (C), 106.0 (CH), 114.5 (CH_2), 116.8 (CH_2), 118.1 (CH_2), 133.9 (CH), 136.3 (CH), 138.3 (CH), 174.2 (C), 196.8 (C), 207.0 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{21}H_{28}O_3$ 328.2038; Found: 328.2048.

***rac*-1,7-Diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione (61).** To a solution of **59** (1.0 g, 3.04 mmol) in THF (24 mL) at -78 °C was added a freshly prepared solution of LiTMP (6.69 mL, 1M in THF, 6.69 mmol). The reaction mixture was stirred for 5 min before the addition of freshly distilled TMSCl (1.63 mL, 12.8 mmol). The reaction mixture was stirred and allowed to warm to -40 °C over 2 h. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with Et_2O. The combined organic extracts were dried over MgSO4, and the solvent was removed under reduced pressure. The crude is purified by flash chromatography (5-10% EtOAc:hexanes) to afford **61** (1.15 g, 94%) as a white solid. IR (neat NaCl) 2943, 2341, 1730, 1645, 1558, 1242, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 0.88 (s, 3H), 1.32 (t, J = 13.0 Hz, 1H), 1.49 (dd, J = 9.3, 7.7 Hz, 2H), 1.53-1.64 (m, 1H), 1.68-1.75 (m, 1H), 1.94-2.09 (m, 3H), 2.17-2.21 (m, 1H), 2.37-2.48 (m, 2H), 3.24 (s, 1H), 3.72 (s, 3H), 4.92-5.03 (m, 6H), 5.56-5.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3 (3xCH_3), 19.9 (CH_3), 27.7 (CH_2), 33.8 (CH_2), 34.9 (CH_2), 35.9 (CH), 38.0 (CH_2), 40.3 (CH_2), 45.2 (C), 57.0 (CH_3), 59.9 (CH), 62.9 (C), 114.8 (CH_2), 116.7 (CH_2), 118.0 (CH_2), 125.7 (C), 133.7 (CH), 136.1 (CH), 138.0 (CH), 178.6 (C), 201.7 (C), 207.8 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{24}H_{36}O_3Si$ 400.2434; Found: 400.2413.

***rac*-1,7-Diallyl-6-(but-3-en-1-yl)-5-iodo-4-methoxy-6-methyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione (62) and *rac*-1,7-diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methyl-3-(trimethylsilyl)-9-((trimethylsilyl)oxy)bicyclo[3.3.1]non-3-en-2-one (63).** To a solution of **61** (2.02 g, 5.06 mmol) in THF (5 mL) was added freshly distilled TMSCl (3.22 mL, 25.3 mmol) (distilled over CaH_2) at room temperature and then the solution was transfer via cannula to a freshly prepared LDA solution (0.58 M in THF, 30.5 mL, 17.71 mmol) at -78 °C. After stirring for 10 min at -78 °C, the reaction mixture was warmed to 0°C in an ice bath. After stirring for 30 sec at 0 °C, a solution of iodine (3.85 g, 15 mmol) in THF (5 mL) was added to mixture via cannula. The resulting solution was stirred for 15 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and extracted 3x with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40-60% benzene:hexanes then 5% EtOAc:hexanes) to afford iodide **62** (0.48 g, 0.911 mmol, 18%), compound **63** (0.99 g, 41%) and recovered starting material **61** (0.72 g, 35%). **Compound 62:** IR (neat NaCl) 2954, 2352, 1733, 1654, 1546, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.91 (s, 3H), 1.45 (t, J = 13.5 Hz, 1H), 1.67-2.00 (m, 5H), 2.05-2.22 (m, 2H), 2.28-2.33 (m, 1H), 2.46-2.51 (m, 1H), 2.56-2.62 (m, 1H), 3.91 (s, 3H), 4.94-5.12 (m, 6H), 5.57-5.67 (m, 1H), 5.70-5.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5 (3xCH_3), 21.4 (CH_3), 28.2 (CH_2), 35.9 (CH_2), 36.1 (CH_2), 36.5 (CH), 38.0 (CH_2), 40.6 (CH_2), 50.0 (C), 64.5 (C), 66.8 (CH_3), 88.4 (C), 114.7 (CH), 117.2 (CH), 118.7 (CH), 126.9 (C), 133.9 (CH), 136.0 (CH), 138.2 (CH), 178.8 (C), 199.4 (C), 199.9 (C HRMS (EI) *m/z*: [M^+ -CH_3] Calcd for $C_{23}H_{32}IO_3Si$ 511.1165; Found: 511.1174. **Compound 63:** M.p. 75-78 °C; IR (neat NaCl) 2948, 2362, 1650, 1573, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 18H), 1.07 (s, 3H), 1.11-1.19 (m, 1H), 1.26-1.35 (m, 2H), 1.39-1.48 (m, 2H), 1.54-1.62 (m, 1H), 1.87-2.02 (m, 2H), 2.10 (dd, J = 14.1, 7.8 Hz, 1H), 2.15-2.20 (m, 1H), 2.46-2.51 (m, 1H), 2.67 (d, J = 3.1 Hz, 1H), 3.67 (s, 3H), 3.94 (d, J = 2.9 Hz, 1H), 4.89-4.99 (m, 6H), 5.44-5.62 (m, 2H), 5.68-5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5 (3xCH_3), 0.6 (3xCH_3), 22.4 (CH_3), 28.2 (CH_2), 32.1 (CH_2), 34.9 (CH_2), 37.14 (CH_2), 37.16 (CH), 37.9 (C), 39.4 (CH_2), 47.8 (CH), 52.3 (C), 56.5 (CH_3), 71.3 (CH), 114.1 (CH_2), 115.8

(CH_2), 117.8 (CH_2), 124.5 (C), 134.0 (CH), 137.5 (CH), 139.0 (CH), 183.3 (C), 206.9 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{27}H_{46}O_3Si_2$ 474.2985, Found: 474.2966.

***rac*-1,7-Diallyl-6-(but-3-en-1-yl)-5-isobutyryl-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione (65)**. Iodide (**62**) (1.44 g, 2.62 mmol) was charged to a flame dried flask and THF (20 mL) was added. The resulting mixture was cooled to -78 °C and *t*-BuLi (1.6 M solution in pentane, 3.76 mL, 6.03 mmol) was added dropwisely to obtain a bright yellow solution. After stirring the solution for 5 min at -78 °C, freshly distilled isobutyraldehyde (0.48 mL, 5.24 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 °C. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc and the organic layers were combined, dried over $MgSO_4$ and concentrated.

The crude alcohol **64** was dissolved in DCM (20 mL) and DMP (5.56 g, 13.1 mmol) was added in one portion. After stirring for 3 days, a 1:1 solution of 5% $NaHCO_3$ and saturated solution of $Na_2S_2O_3$ was added under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was rapidly purified over a pad of silica (5% EtOAc:hexanes).

The crude ketone was put under an atmosphere of argon and THF (20 mL) was added. The solution was cooled to 0˚C before adding TBAF (1 M solution in THF, 3.14 mL, 3.14 mmol) dropwisely. The mixture was stirred at 0 °C. After stirring for 1h, a saturated solution of NH_4Cl was added. The aqueous phase was extracted 3x with Et_2O and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10-15-30% EtOAc:hexanes) to afford **66** (250 mg, 24% over 3 steps) as transparent oil. IR (neat NaCl) 2943, 2362, 1733, 1652, 1604, 1224 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, J = 6.7 Hz, 3H), 1.05 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H), 1.38 (t, J = 13.0 Hz, 1H), 1.61-1.74 (m, 2H), 1.79-1.87 (m, 3H), 1.92 (dd, J = 13.5, 4.5 Hz, 1H), 2.01-2.12 (m, 1H), 2.18-2.24 (m, 1H), 2.24-2.31 (m, 1H), 2.46-5.58 (m, 2H), 3.77 (s, 3H), 4.90-5.11 (m, 6H), 5.56-5.77 (m, 3H), 5.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 29.8 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 36.2 (CH_2), 39.6 (CH), 40.6 (CH_2), 41.1 (CH), 47.7 (C) 56.2 (CH_3),

63.9 (C), 76.1 (C), 107.5 (CH), 114.4 (CH_2), 117.1 (CH_2), 118.5 (CH_2), 133.5 (CH), 136.1 (CH), 138.6 (CH), 172.4 (C), 195.3 (C), 206.6 (C), 208.6 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{25}H_{34}O_4$ 398.2457; Found: 398.2446.

***rac*-1,3,7-Triallyl-6-(but-3-en-1-yl)-5-isobutyryl-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione (66).** A solution of *n*-BuLi (2.4 M in hexanes, 0.032 mL, 0.077 mmol) was added slowly to freshly distilled diisopropylamine (3.62 μL, 0.025 mmol) in THF (1 mL) at −78 °C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. A solution of **65** (9.95 mg, 0.025 mmol) in THF (0.5 mL) was added via cannula at -78˚C. The solution was stirred for 10 min and a solution of lithium 2-thienylcyanocuprate (0.25 M in THF, 0.2 mL, 0.05 mmol) was added at -78 °C. After stirring for 20 min, allyl bromide (0.032 mL, 0.375 mmol) was added dropwisely to the solution and the mixture was stirred another 20 min. The reaction mixture was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to afford the desired allyl **66** (10 mg, 91%) as a colorless oil. IR (neat NaCl) 2927, 2362, 1724, 1658, 1595, 1245 cm^{-1}; ^1H NMR, (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.04 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.39 (t, J = 13.1 Hz, 1H), 1.60-1.70 (m, 2H), 1.74-1.80 (m, 1H), 1.84-1.91 (m, 2H), 1.95-2.01 (m, 1H), 2.13-2.20 (m, 1H), 2.23-2.28 (m, 1H), 2.4 (sept, J = 6.4 Hz, 1H), 2.45-2.50 (m, 1H), 2.52-2.56 (m, 1H), 3.34-3.39 (m, 1H), 3.44-3.50 (m, 1H), 4.08 (s, 3H), 4.90-4.93 (m, 1H), 4.96-5.00 (m, 5H), 5.03-5.07 (m, 1H), 5.08-5.11 (m, 1H), 5.55-5.63 (m, 1H), 5.66-5.78 (m, 2H), 5.88-5.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (CH_3), 21.4 (CH_3), 21.4 (CH_3), 28.4 (CH_2), 30.5 (CH_2), 34.0 (CH_2), 34.9 (CH_2), 36.6 (CH_2), 40.6 (CH_2), 40.8 (CH), 41.6 (CH), 47.8 (C), 60.4 (CH_3), 63.3 (C), 77.9 (C), 114.3 (CH_2), 115.8 (CH_2), 117.0 (CH_2), 118.5 (CH_2), 120.4 (C), 133.7 (CH), 136.3 (CH), 136.6 (CH), 138.8 (CH), 169.2 (C), 195.9 (C), 207.0 (C), 209.1 (C); HRMS (EI) *m/z*: [M^+] Calcd for $C_{28}H_{38}O_4$ 438.2770; found: 438.2744.

***rac*-O-Methylated hyperforin (67).** Compound **66** (7.5 mg, 0.017 mmol) and Grubbs II catalyst (1.45 mg, 1.710 μmol, 10 mol %) was added to a sealed tube. Isobutene (2 mL) was condensed in a

separate round bottom flasked cooled to -78 °C and added to the sealed tube via cannula in the sealed tube cooled at -78 °C. The closed sealed tube was slowly warm up to 120 °C. After stirring for 4 h, the sealed tube was cooled to -78 °C and opened. The mixture tube was warmed up to room temperature to vent off the excess isobutene. The residue was purified by flash chromatography (2-4% EtOAc:hexanes) to afford the desired prenylated compound **67** (8 mg, 85%) as a transparent oil. IR (neat NaCl) 2927, 2362, 1722, 1660, 1592, 1446, 1375, 1240 cm^{-1}; ^1H NMR, (500 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.05 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 1.37 (t, J = 12.9 Hz, 1H), 1.41-1.47 (m, 1H), 1.53 (s, 3H), 1.59 (s, 3H), 1.60-1.72 (m, 2H), 1.62 (s, 3H), 1.64 (s, 3H), 1.66 (m, 9H), 1.68 (s, 3H), 1.79 (dd, J = 13.4, 4.4 Hz, 1H), 1.85 (dt, J = 13.5, 4.9 Hz, 1H), 1.89-196 (m, 1H), 2.08-2.16 (m, 2H), 2.36 (sept, J = 6.5 Hz, 1H), 2.42 (dd, J = 6.4 Hz, 2H), 3.23 (dd, J = 15.7, 5.9 Hz, 1H), 3.36 (dd, J = 16.2, 6.2 Hz, 1H), 4.01 (s, 3H), 4.90-4.96 (m, 2H), 4.99-5.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 (CH_3), 17.8 (CH_3), 17.9 (CH_3), 18.1 (CH_3), 21.3 (CH_3), 21.3 (CH_3), 23.7 (CH_3), 25.1 (CH_3), 25.6 (CH_2), 25.7 (CH_3), 25.9 (CH_3), 25.9 (CH_3), 28.0 (CH_2), 29.6 (CH_2), 29.7 (C), 37.6 (CH_2), 40.3 (CH_2), 40.6 (CH), 43.4 (CH_2), 47.7 (C), 60.6 (CH), 63.9 (CH_3), 78.1 (C), 119.7 (C), 122.4 (C), 122.5 (C), 123.5 (C), 124.7 (C), 131.3 (CH), 132.8 (CH), 133.3 (CH), 134.1 (CH), 169.2 (C), 196.7 (C), 207.6 (C), 209.5 (C); HRMS (EI) *m/z*: [M^+ - C_5H_9] Calcd for $C_{31}H_{45}O_4$ 481.3318; found: 481.3328.

***rac*-Hyperforin (1).** O-methylated hyperforin **67** (15 mg, 0.027 mmol) was dissolved in dry DMSO (1 mL) and LiCl (0.017 mg, 0.408 mmol) was added in one portion. The resulting mixture was degassed for 10 min and then heated at 120˚C for 1h. The resulting dark solution was cooled to r.t. Water (10 mL) and brine (2 mL) were added and the mixture was extracted with Et_2O (without stabilizers) (3x) and once with EtOAc. The organic phases are combined, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (5-10% EtOAc:hexane) to afford hyperforin (**1**) (10.1 mg, 0.019 mmol, 69%). IR (neat NaCl) 2927, 1718, 1601, 1571, 1211 cm^{-1}; ^1H NMR, (500 MHz, MeOD) δ 0.97 (s, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.39 (dd, J = 13.3, 12.2 Hz, 1H), 1.58 (s, 3H), 1.59 (s, 3H), 1.62 (d, J = 0.8 Hz, 3H), 1.64 (d, J = 0.8 Hz, 3H), 1.65 (s, 3H), 1.63-1.68 (m, 1H), 1.68 (s, 6H), 1.70 (m, 3H), 1.70-1.77 (m, 3H), 1.86-2.01 (m, 3H), 2.02-2.11 (m, 2H), 2.41 (dd, J = 14.6,

7.1 Hz, 1H), 2.50 (dd, J = 14.6, 6.9 Hz, 1H), 3.07 (dd, J = 14.9, 6.9 Hz, 1H), 3.13 (dd, J = 14.9, 6.9 Hz, 1H), 4.94-5.03 (m, 3H), 5.09 (tt, J = 7.1, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, MeOD) δ 15.3 (CH_3), 17.9 (CH_3), 18.1 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 21.2 (CH_3), 22.0 (CH_3), 22.6 (CH_2), 25.5 (CH_2), 25.9 (CH_3), 26.0 (C), 26.1 (CH_3), 26.2 (CH_3), 28.7 (CH_2), 30.7 (CH_2), 37.9 (CH_2), 40.8 (CH_2), 43.0 (CH), 43.1 (CH), 49.5 (C), 120.9 (CH), 122.1 (C), 122.6 (CH), 123.9 (CH), 126.1 (CH), 131.9 (C), 133.6 (C), 134.3 (C), 134.7 (C), 208.9 (C), 211.8 (C); HRMS (ESI-MS) *m/z*: [M^+ -H] calcd for $C_{35}H_{51}O_4$ 535.3787; Found: 535.378.

SUPPORTING INFORMATION

High-resolution ^{1}H and ^{13}C NMR spectra for compounds **1-4**, **17-30**, **32**, **33**, **35**, **37**, **40-46**, **51-67**, NMR comparison of synthetic and natural hyperforin (**1**), papuaforins A (**2**), B (**3**) and C (**4**) and crystallographic data (CIF) for compounds **29**, **30**, **33**, **40**, **51** and **61**. This material is available free of charge on the ACS Publication website.

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Present address: IntelliSyn R&D, 7171 rue Frederick Banting, Saint-Laurent, QC, Canada H4S1Z9

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