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An approach toward the synthesis of PPAP natural product garsubellin A: construction of the tricyclic core

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ABSTRACT

In a study directed toward the bioactive natural product garsubellin A, an expedient route to the bicyclo [3.3.1]nonan-9-one bearing tricyclic core, with a bridgehead anchored tetrahydrofuran ring, is delineated. The approach emanating from commercially available dimedone involved a DIBAL-H mediated retro aldol/re-aldol cyclization cascade and a PCC mediated oxidative cyclization as the key steps.

1. Introduction

In recent years, particularly during the past decade, natural products based on **P**olycyclic **P**olyprenylated **A**cyl **P**hloroglucin (PPAP) framework have been encountered with increasing frequency among diverse terrestrial plant species and their number has now crossed a century mark. The diversity among PPAP natural products manifests through a myriad of structural, functional group and stereochemical variations. Thus, PPAPs may embody one or more prenyl/geranyl groups at various biosynthetically ordained locations on their bicyclo[3.3.1]nona-9-one framework embellished with dense functionalization pattern.[1,2] Among the more prominent examples of the growing PPAP family with a generous complement of prenyl groups are hyperforin **1**,[2a,b] papuaforin A **2**,[2e] garcinielliptone L **3**[2c] and nemorosone **4**[2a,f,g] to name a few (Fig. 1). Apart from their structural complexity and varied functionalization patterns, PPAP's display wide range of biological activities that range from enhancement of choline acetyltransferase (ChAT) activity,[3e] cytotoxicity,[3b] antidepressant activity,[3c] antibacterial,[3d] antimalarial[3a] and even anti-HIV activity.[2b] Among these bioactivity attributes, the ability to upregulate choline acetyltransferase (ChAT) activity has implications in neurodegenerative disorders like Alzheimers', a disease condition that according to the cholinergic hypothesis can be traced to the reduced synthesis of the neurotransmitter acetylcholine (ACh).[3e] Thus, the inducers of the enzyme choline acetyltransferase (ChAT), an enzyme responsible for the biosynthesis of acetylcholine (ACh) can be regarded as possible therapeutic lead compounds against Alzheimers' disease. In this context, garsubellin A **5**,[2h] a complex PPAP natural product reported by the group of Fukuyama in 1997 from the wood of *Garcinia subelliptica* has received wide spread attention. It has been reported by these authors through in vitro experiments that garsubellin A **5**, enhanced the choline acetyltransferase (ChAT) activity in P 10 rat septal neurons by 154% at 10 μM concentration.[2h] This was a significant observation and indicated a possible role for garsubellin A **5** in Alzheimers' therapeutics and this in turn triggered a flurry of activity toward its synthesis. During the past decade several total syntheses of garsubellin A **5** along with model studies aimed at accessing its framework and analogs have surfaced in the literature.[4,5]

As part of our continuing program[5,6] toward the total synthesis of PPAP natural products and convenient access to the diverse frameworks present in them, we have explored the synthetic potential and generality of a reconstructive aldol cyclization strategy to gain facile entry into the bicyclo[3.3.1]nonanone framework from a conveniently accessible precursor as indicated in Scheme 1. The corner stone of this strategy was the rapid construction of a bicyclic enol-lactone moiety **6** and its rearrangement through retro-aldol, re-aldol steps to a bridged ketone **7** under thermodynamically controlled

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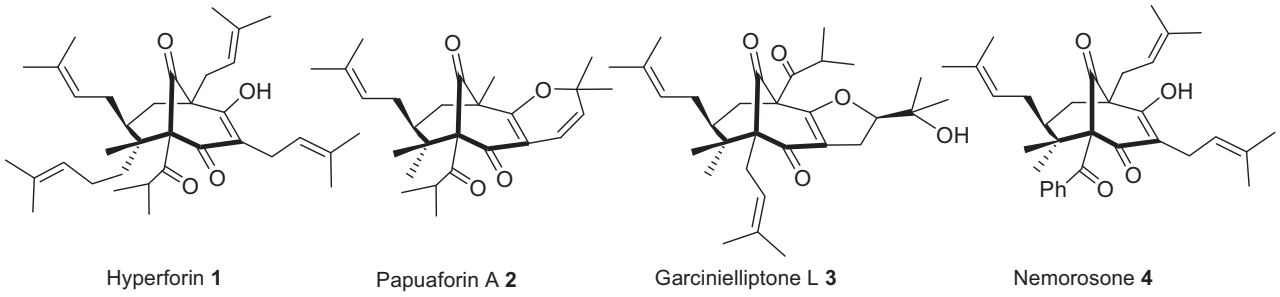
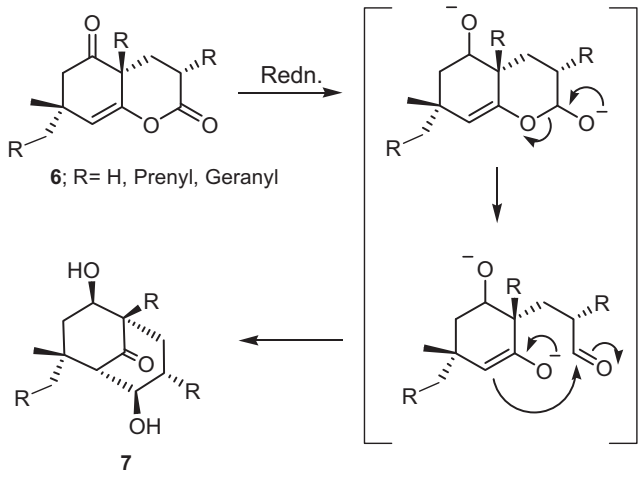


Fig. 1. Representative PPAP natural products.

reaction regime, Scheme 1. Herein, we outline an extension of the reconstructive aldol protocol toward construction of the tricyclic framework present in garsubellin A **5**.

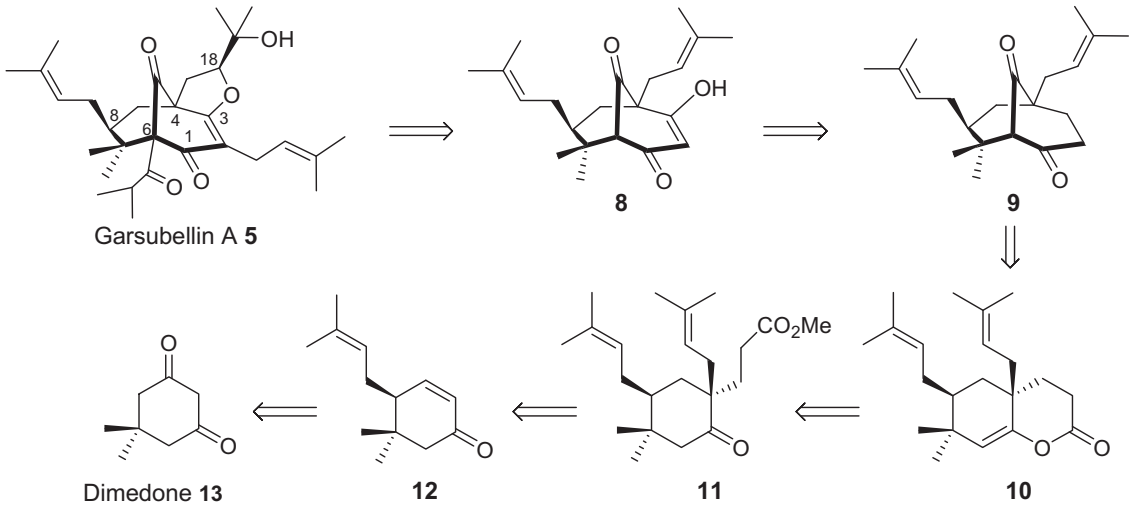


Scheme 1. General strategy to access PPAP framework.

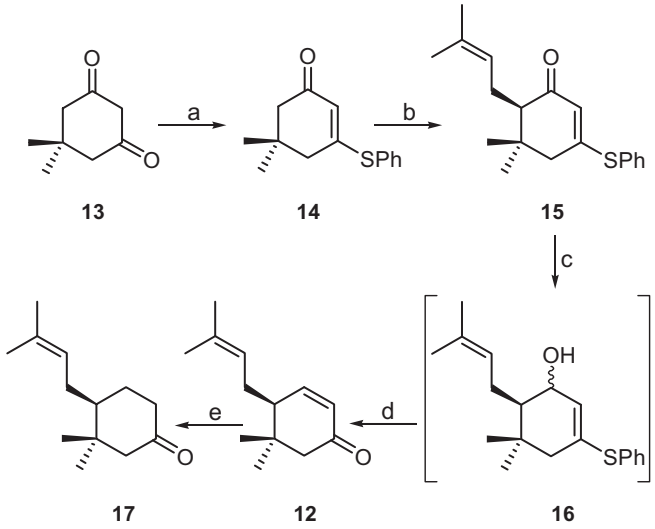
2. Results and discussion

In retrosynthetic terms, garsubellin A **5** framework, particularly its bridgehead anchored tetrahydrofuran moiety, was sought to be obtained from an advanced bicyclic β-hydroxyenone **8** through oxidative tetrahydrofuran generating cyclization of its enolic hydroxyl group on the neighboring prenyl group, Scheme 2. β-Hydroxyenone **8** embodies a versatile functional motif ubiquitous[1,2] among PPAPs and could be accessed through functional group modifications in the bridged bicyclic precursor **9.** Bicyclic **9** in turn was resourced through our previously tested reconstructive aldol strategy from bicyclic enol lactone **10**.[5b] The enol lactone **10** could be prepared from precursor **11**, which harbored the quaternary center and the two prenyl arms in requisite relative stereochemistry. Intermediate **11** was to be obtained from the prenylated cyclohexenone **12**, whose possible origin could be traced to a versatile and readily available dimedone **13**, Scheme 2.

To implement the synthetic strategy unraveled through the retrosynthetic analysis, commercially sourced dimedone **13** was transformed to 5,5-dimethyl-3-phenylthio-2-cyclohexenone **14** following a reported two step procedure.[7] LDA mediated deprotonation in **14**, under kinetically controlled conditions, and addition of prenyl bromide led smoothly to the mono-prenylated product **15**. The vinylogous thioether derivative **15** was reduced with LAH to furnish epimeric allylic alcohols **16** and the mixture was used as such for the next step involving $HgCl_2$ mediated eliminative unmasking of the carbonyl group[8] to deliver the key cyclohexenone building block **12**, Scheme 3. The next objective was to regioselectively reduce the enone double bond in **12** to obtain **17** and setup the key quaternary center through stereo- and regiocontrolled tandem prenylation-Michael addition sequence. After some exploratory experiments using various conjugate enone reduction protocols, chemoselective reduction of the enone double bond in **12** was successfully executed in the presence of nickelboride,[9] generated in situ from $NiCl_2.6H_2O$ and $NaBH_4$, to afford the saturated cyclohexanone derivative **17**, Scheme 3.



Scheme 2. Retrosynthetic consideration enroute garsubellin A **5**.

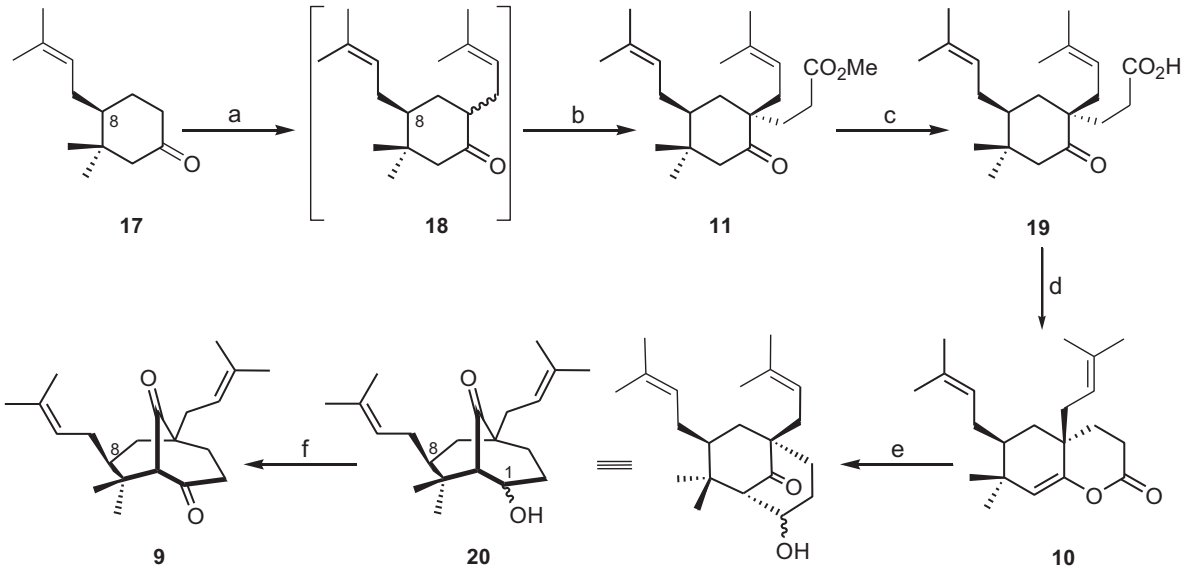


Scheme 3. Reagents and conditions: a) i) $(COCl)_2$, DMF, 0 °C → rt, 1 h, 97%; ii) PhSH, NaOH, MeOH, rt, 6 h, 86%; b) LDA, prenyl bromide, THF, −78 °C → 0 °C, 12 h, 95%; c) LAH, THF, 0 °C → rt, 1 h; d) $HgCl_2$, CH_3CN–H_2O (5:1), 60 °C, 1 h, 64% (over two steps); e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C → rt, 1 h, 94%.

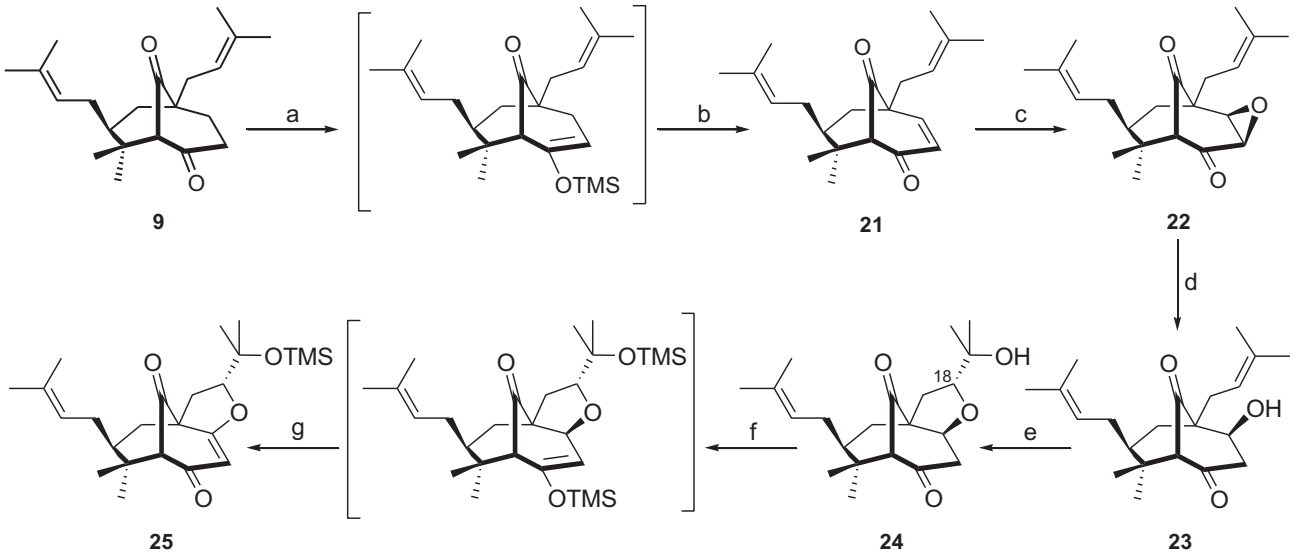
LDA promoted prenylation on **17** was first implemented and this proceeded smoothly and regioselectively to deliver the mono-prenylated product **18**. Michael addition of methyl acrylate to mono prenylated product **18** was effected in the presence of potassium *tert*-butoxide to stereoselectively afford **11** as a single diastereomer, Scheme 4. Stereoselectivity during the Michael addition step could be attributed to the 1,3-stereoinductive effect of the bystander prenyl group at C-8 (garsubellin A **5** numbering). Generation of the quaternary center in **11** through tandem prenylation-Michael addition sequence resulted in the *cis*-disposition of the two prenyl groups, necessary for further evolution toward the target. This also ensured the *exo* disposition of the C-8 prenyl arm on the bicyclo[3.3.1]nonanone framework of the natural product. Ester group in **11** was routinely hydrolyzed to deliver the carboxylic acid **19** and was transformed to the enol-lactone **10** following well established protocols, Scheme 4. Arrival of enol lactone **10** set the stage for executing the reconstructive aldol strategy. This was sought to be implemented through DIBAL-H promoted retro-aldol/re-aldol reaction cascade. Toward this end, enol-lactone **10** was reduced with DIBAL-[10] to trigger the desired structural reorganization and furnished the bicyclo[3.3.1]nonanone derivative **20** as a mixture of C-1 hydroxy epimers. PCC oxidation in **20** readily furnished a single bicyclo[3.3.1]nonane based dione **9** embodying the bicyclic core of garsubellin A **5**, Scheme 4.

Arrival at the bicyclo[3.3.1]nonanone derivative **9**, with appropriate positioning of requisite substituents/functionalities at C-4 and C-8 paved the way for further elaboration toward β-hydroxyenone **8** as delineated in the retrosynthetic perspective (Scheme 2). This required installation of a 1,3-dicarbonyl moiety on to the bicyclic framework to access **8**. For this purpose, bicyclic dione **9** needed to be first transformed to the corresponding enone **21** and this was accomplished following the Saegusa protocol[11] involving Pd-mediated eliminative dehydrosilylation. Thus, bicyclic ketone **9** was smoothly transformed to its TMS enol ether and Pd^{+2} mediated desilylation delivered the bicyclic enone **21**, Scheme 5.

Nucleophilic epoxidation in enone **21** in the presence of H_2O_2–NaOH was straight forward and stereoselectively afforded α,β-epoxy ketone **22** in good yield. After a few trials, it was found that the epoxide moiety in α,β-epoxy ketone **22** could be reductively cleaved in a regioselective manner employing the PhSeSePh-$NaBH_4$-EtOH milieu[12] to furnish the β-hydroxy ketone **23**, Scheme 5. It was expected that oxidation of **23** would generate the desired 1,3-dicarbonyl precursor **8** for implementing the oxy-functionalization of the bridgehead C-4 prenyl side arm as envisaged in Scheme 2. However, this seemingly innocuous oxidation of **23** to **8** proved difficult despite recourse to a variety of reagents. In the case of PCC-silica gel as the oxidant the outcome from **23** was unexpected but *prima facie* interesting. Indeed, PCC oxidation of **23** delivered tricyclic compound **24**, embodying a properly positioned tetrahydrofuran ring, and this seemed to be a great bonus at first sight and a fortuitous outcome as we were seeking the 1,3-dicarbonyl compound **8** as a prelude to the generation of the tetrahydrofuran ring present in our target molecule. Although the structure of **24** was clearly dictated from its spectral characteristics, the data was not incisive enough to delineate the stereochemical signature at the newly generated C-18 stereogenic center. Therefore recourse was taken to single crystal X-ray structure determination[13] and an ORTEP representation is displayed in Fig. 2.



Scheme 4. Reagents and conditions: a) LDA, prenyl bromide, THF, −78 °C, 6 h, 72%; b) KO^{t}Bu, methyl acrylate, benzene, rt, 30 min, 71%; c) KOH, MeOH, H_2O, 65 °C, 2 h, 93%; d) NaOAc, Ac_2O, 140 °C, 1 h, 79%; e) DIBAL-H, DCM, 0 °C, 2 h, 67%; f) PCC, DCM, rt, 1 h, 95%.



Scheme 5. Reagents and conditions: a) Et_3N, DMAP, TMSOTf, DCM, 0 °C, 1 h; b) $Pd(OAc)_2$, CH_3CN, 55 °C, 6 h, 59% (over two steps); c) H_2O_2, NaOH, MeOH, 0 °C, 1 h, 85%; d) PhSeSePh, $NaBH_4$, AcOH, EtOH, 0 °C, 1 h, 71%; e) PCC, DCM, rt 1 h, 76%; f) Et_3N, DMAP, TMSOTf, DCM, 0 °C, 1 h; g) $Pd(OAc)_2$, CH_3CN, 55 °C, 6h, 55% (over two steps).

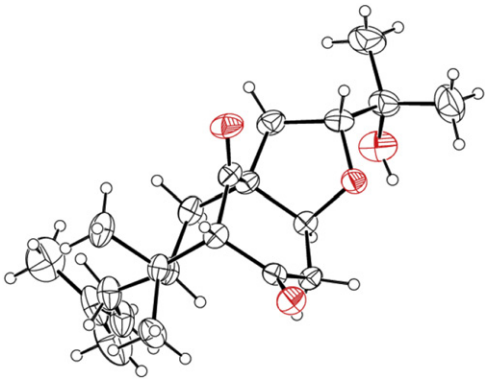
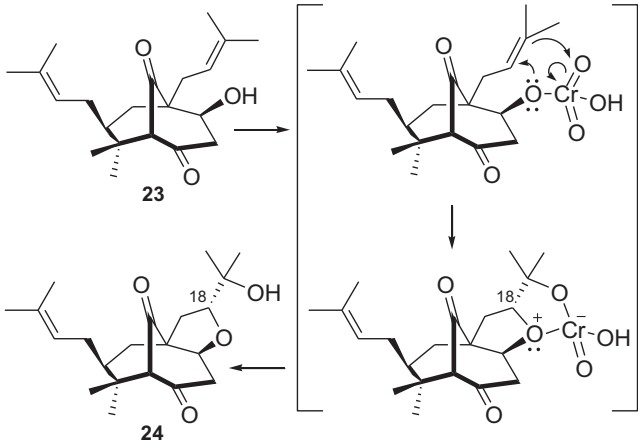


Fig. 2. ORTEP diagram of compound **24.**

While X-ray determination confirmed our assignment of gross structure to **24**, its stereochemistry at C-18 subdued our excitement as it turned out to be epimeric with respect to that present in the natural product, Scheme 5. Smooth formation of **24** during oxidation with PCC indicated that the C-3 hydroxyl group is refractory to oxidation and the oxidant PCC seem to induce a chromate ester mediated stereoselective cyclization of **23** with the neighboring prenyl participation to furnish **24**, Scheme 6. A possible mechanism



Scheme 6. Plausible mechanism for formation of **24**.

and the stereochemical outcome for the formation of **24** is indicated in Scheme 6 and has some precedence.[14]

Undeterred by the stereochemical truancy displayed by **23** during the oxidative cyclization, we decided to proceed further and reinstall the C-2, C-3 double bond necessary for further progress toward the natural product. Consequently, tricyclic ketone **24** was subjected to Saegusa protocol[11] via TMS enol ether formation and palladium mediated eliminative dehydrosilylation to furnish enone **25** with concomitant protection of the tertiary hydroxyl group as TMS-ether, Scheme 5.

Arrival at **25** signaled significant progress toward the synthesis of garsubellin A as intermediates similar to it have been previously subjected to a straight forward end game[4] to deliver the natural product. However, in our case the epimeric nature of the C-18 center prevented further march from **24** or **25** toward the target. Nonetheless, the efficacy of our concise approach toward garsubellin A core has been demonstrated and efforts are underway to adapt its strategic elements to devise a synthesis of the natural product.

3. Conclusion

In summary, we have demonstrated a concise and efficient strategy to construct polyprenylated tricyclic core present in garsubellin A **5** from commercially available dimedone. A reconstructive aldol cyclization step and a fortuitous tetrahydrofuran formation through oxidative prenyl cyclization were pivotal to the success of our construction enroute garsubellin A. We believe that a sound ground work has been laid in this effort to craft a synthesis of this complex PPAP natural product.

4. Experimental section

4.1. General information

All reagents employed were purchased from commercial sources and used without further purification. Commercially available Sisco Research Laboratories (SRL) silica gel (100–200 mesh particle size) was used for column chromatography. The column was usually eluted with various combinations of ethyl acetate–petroleum ether mixtures. Visualization of the spots on TLC plates was achieved under UV light or by exposure to iodine vapor or by

employing ethanolic vanillin stain. Unless otherwise stated, all dry and air sensitive reactions were performed in oven dried glassware under argon/nitrogen atmosphere using standard syringe and septum technique. Solvent, such as THF, was freshly distilled from sodium benzophenone radical anion. Removal of solvents was performed under reduced pressure using a rotary evaporator. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-LA 300 or Bruker AMX 400 instruments. ^{1}H and ^{13}C samples were generally made in $CDCl_3$ as solvent and TMS and $CDCl_3$ were employed as an internal reference for ^{1}H and ^{13}C NMR, respectively unless otherwise mentioned.

*4.1.1. 5,5-Dimethyl-6-(3-methyl-2-butenyl)-3-(phenylsulfanyl)-2-cyclohexen-1-one (**15**).* To a THF solution of LDA (55 mL, 1.0 M, freshly prepared from equimolar amount of DIPA and *n*-BuLi), kept at −78 °C, was added a THF (20 mL) solution of enone **14** (6.90 g, 29.7 mmol) over a period of 10 min. The resulting solution was stirred for 1 h and then prenyl bromide (10.3 mL, 89.2 mmol) was added to it. After additional 1 h at −78 °C, the reaction mixture was allowed to warm up to 0 °C and stirred for 12 h at the same temperature. Reaction was quenched by adding 20 mL of satd NH_4Cl solution and the product was extracted with ether (3×100 mL). The combined ether extracts were washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the resulting crude material was purified on a silica gel column (eluent 10–20% ethyl acetate in petroleum ether) to obtain **15** (8.47 g, 95%) as a light yellow oil. IR (Neat) ν 1660, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.40 (m, 5H), 5.42 (s, 1H), 5.16–5.11 (m, 1H), 2.49–2.30 (m, 2H), 2.24–2.19 (m, 2H), 2.06–2.02 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.08 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 162.2, 135.4 (2C), 131.9, 130.0, 129.8 (2C), 128.3, 122.8, 119.5, 57.9, 42.9, 36.9, 28.4, 25.7, 24.7, 24.3, 17.7; HRMS (ESI) (*m*/*z*): found 301.1614 $[M+H]^+$; calcd for $C_{19}H_{24}OS$ 301.1626.

*4.1.2. 5,5-Dimethyl-4-(3-methyl-2-butenyl)-2-cyclohexen-1-one (**12**).* To a solution of the enone **15** (8.47 g, 28.2 mmol) in dry THF (30 mL) was added LAH (1.07 g, 28.2 mmol) portion wise at 0 °C and the reaction mixture was stirred for 1 h at room temperature. Excess LAH was quenched with ethyl acetate and the reaction mixture was then diluted with water (20 mL). The product was extracted with ethyl acetate (3×100 mL) and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude allylic alcohol **16** was used for next reaction without further purification.

$HgCl_2$ (15.33 g, 56.5 mmol) was added to a solution of crude allylic alcohol **16** in 25 mL of acetonitrile–water (5:1) and the resulting mixture was heated at 60 °C for 1 h. Mercury salts were filtered off and the organic solvent was removed under reduced pressure. The product was extracted from the aqueous residue with ether (3×50 mL). The crude product was purified on a short silica gel column (eluent 10% ethyl acetate in petroleum ether) to afford the corresponding enone **12** (3.47 g, 64%) as a light yellow oil. IR (Neat) ν 1682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, *J*=10.2, 2.7 Hz, 1H), 5.98 (dd, *J*=10.2, 2.7 Hz, 1H), 5.17–5.14 (m, 1H), 2.28–2.19 (m, 4H), 1.99–1.84 (m, 1H), 1.74 (s, 3H), 1.63 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 152.6, 134.1, 128.2, 122.0, 52.4, 47.3, 37.02, 28.9, 27.2, 25.8, 21.5, 17.9; HRMS (ESI) (*m*/*z*): found 193.1591 $[M+H]^+$; calcd for $C_{13}H_{20}O$ 193.1592.

*4.1.3. 3,3-Dimethyl-4-(3-methyl-2-butenyl)cyclohexan-1-one (**17**).* $NiCl_2.6H_2O$ (21.5 g, 90.4 mmol) was dissolved in 25 mL of dry methanol. The resulting green colored solution was cooled to 0 °C and $NaBH_4$ (3.43 g, 90.4 mmol) was added to it over a period of 5 min with concurrent gas evolution. The resulting black suspension was stirred at the same temperature for an additional 15 min and then a methanolic solution of enone **12** (3.47 g, 18.1 mmol) was transferred to it using a cannula. The cooling bath was removed immediately after the addition and the reaction mixture was allowed to stir at room temperature for 1 h. Reaction mixture was diluted with ether (50 mL), the black mass was filtered off and the crude product was purified on a silica gel column (eluent 5–10% ethyl acetate in petroleum ether) to produce cyclohexanone **17** (3.30 g, 94%) as a colorless oil. IR (Neat) ν 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (m, 1H), 2.36–2.21 (m, 5H), 2.11–1.99 (m, 3H), 1.71 (s, 3H), 1.61 (s, 3H), 1.54–1.42 (m, 1H), 1.05 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 132.6, 123.5, 55.9, 46.1, 41.0, 38.6, 29.9, 27.9, 27.7, 25.8, 20.8, 17.8; HRMS (ESI) (*m*/*z*): found 217.1559 $[M+Na]^+$; calcd for $C_{13}H_{22}ONa$ 217.1568.

4.1.4. Methyl 3-[(1R,5S*)-4,4-dimethyl-1,5-di(3-methyl-2-butenyl)-2-oxocyclohexyl] propanoate (**11**).* To a THF solution of LDA (35 mL, 1.0 M, freshly prepared from equimolar amount of DIPA and *n*-BuLi), kept at −78 °C, was added a THF (10 mL) solution of cyclohexanone derivative **17** (3.3 g, 17.0 mmol) over a period of 10 min. The resulting solution was stirred for 1 h at the same temperature and then prenyl bromide (3.93 mL, 34.0 mmol) was added to it and the resulting mixture was stirred for 6 h at the same temperature. Reaction was quenched by adding 15 mL of satd NH_4Cl solution and the product was extracted with ether (3×50 mL). The combined ether layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. After evaporation of solvent, the crude material was purified on a short silica gel column (eluent 5–15% ethyl acetate in petroleum ether) to obtain di-prenylated cyclohexanone derivative **18** (3.2 g, 72%) as a light yellow oil, which was used directly for the next reaction.

Methyl acrylate (1.30 mL, 14.6 mmol) and KO^{t}Bu (1.59 g, 14.2 mmol) were added to a stirred solution of di-prenylated cyclohexane derivative **18** (3.2 g, 12.2 mmol) in dry benzene (30 mL) at room temperature. After 30 min, the reaction mixture was diluted with ether (30 mL) and quenched with water (20 mL). The organic phase was separated and the aqueous part was extracted with ether (2×50 mL). The combined ether extract was washed with water, brine and dried over Na_2SO_4. Removal of solvent produced a crude brown mass, which was purified by silica gel column chromatography (10–20% ethyl acetate in petroleum ether) to obtain **11** (3.0 g, 71%) as a colorless oil. IR (Neat) ν 1741, 1704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11–5.02 (m, 2H), 3.65 (s, 3H), 2.47–2.09 (m, 8H), 1.98–1.88 (m, 2H), 1.79–1.65 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.59 (s, 6H), 1.42–1.33 (m, 1H), 1.04 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 173.9, 134.3, 132.5, 123.3, 119.3, 53.7, 51.7, 51.1, 42.0, 38.7(2C), 32.1, 31.0, 29.6, 28.7, 28.3, 26.0, 25.8, 19.9, 18.0, 17.9; HRMS (ESI) (*m*/*z*): found 371.3563 $[M+Na]^+$; calcd for $C_{22}H_{36}O_3Na$ 371.3562.

4.1.5. 3-[(1R,5S*)-4,4-Dimethyl-1,5-di(3-methyl-2-butenyl)-2-oxocyclohexyl]propanoic acid (**19**).* To a solution of ester **11** (3 g, 8.62 mmol) in 11 mL of methanol–water (10:1) was added KOH (965 mg, 17.3 mmol) and the resulting mixture was heated at 65 °C (oil bath temperature) for 2 h. After completion of the reaction, methanol was evaporated and the resulting residue was diluted with 25 mL of ether and 25 mL of water. Both layers were separated. The aqueous layer was carefully acidified to pH 1 (as indicated by Litmus paper) with 6 N HCl and extracted with ethyl acetate (3×50 mL). Combined ethyl acetate extract was washed with brine and dried over Na_2SO_4. Removal of solvent in vacuo afforded carboxylic acid **19** (2.67 g, 93%) as colorless liquid. IR (Neat) ν 3189, 1707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11–5.02 (m, 2H), 2.46–2.41 (m, 1H), 2.37–2.05 (m, 5H), 2.02–1.87 (m, 2H), 1.75–1.64 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.59 (s, 6H), 1.44–1.22 (m, 3H), 1.04 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 178.8, 134.5, 132.6, 123.3, 119.2, 53.7, 51.1, 42.1, 38.7, 38.6, 32.1, 30.7, 29.6, 28.7,

28.3, 26.1, 25.9, 19.9, 18.0, 17.9; HRMS (ESI) (*m*/*z*): found 357.2406 $[M+Na]^+$; calcd for $C_{21}H_{34}O_3Na$ 357.2406.

4.1.6. (4aR,6S*)-7,7-Dimethyl-4a,6-di(3-methyl-2-butenyl)-3,4,4a,5,6,7-hexahydro-2H-2-chromenone (**10**).* To a stirred solution of carboxylic acid **19** (1.0 g, 2.99 mmol) in Ac_2O (5 mL) was added NaOAc (1.23 g, 14.9 mmol) and the resulting mixture was refluxed at 140 °C for 1 h under N_2. Upon completion of the reaction, the reaction mixture was cooled to 0 °C and diluted with 15 mL of water and 15 mL of ether. The acetic acid generated from Ac_2O was quenched by slowly adding solid $NaHCO_3$. Layers were separated and the aqueous phase was extracted with ether (2×50 mL) and followed by usual work up. Ether was evaporated to give a residue, which was purified on a silica gel column (eluent 5–10% ethyl acetate in petroleum ether) to obtain **10** (747 mg, 79%) as a colorless oil. IR (Neat) ν 1765, 1683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 5.07–5.04 (m, 2H), 2.68–2.55 (m, 3H), 2.17–2.05 (m, 4H), 1.92–1.78 (m, 1H), 1.71 (s, 6H), 1.60 (s, 6H), 1.54–1.43 (m, 2H), 1.30–1.24 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 150.0, 134.8, 132.6, 123.4, 120.7, 119.3, 41.4, 37.6, 35.2, 35.1, 34.8, 29.7, 29.1, 28.1, 28.0, 25.9, 25.8, 22.0, 18.1, 17.9; HRMS (ESI) (*m*/*z*): found 317.2484 $[M+H]^+$; calcd for $C_{21}H_{33}O_2$ 317.2480.

4.1.7. (1S,5R*,7S*)-8,8-Dimethyl-5,7-di(3-methyl-2-butenyl) bicyclo [3.3.1]nonane-2,9-dione (**9**).* DIBAL-H (20% solution in toluene, 4.2 mL, 5.91 mmol) was added to a dichloromethane (20 mL) solution of enol lactone **10** (747 mg, 2.36 mmol) at 0 °C under N_2 and stirred for 2 h at the same temperature. Reaction was quenched by adding 5% HCl solution (10 mL) and the product was extracted with dichloromethane (3×50 mL). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in rotary evaporator and the crude product was purified on a silica gel column (eluent 30–50% ethyl acetate in petroleum ether) to furnish **20** (503 mg, 67%) as a colorless oil.

To a dichloromethane (25 mL) solution of alcohol **20** (503 mg, 1.58 mmol), kept at room temperature, was added pre-dried PCC (680 mg, 3.16 mmol) and silica gel (680 mg, 100–200 mesh) at a time. The resulting orange colored suspension was stirred at the same temperature for 1 h and then passed through a short silica gel column (eluent 10% ethyl acetate in petroleum ether) to obtain bicyclic diketone **9** (475 mg, 95%) as colorless oil. IR (Neat) ν 1724, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23–5.18 (m, 1H), 5.11–5.06 (m, 1H), 2.88 (s, 1H), 2.78–2.51 (m, 3H), 2.23–1.80 (m, 6H), 1.73 (s, 6H), 1.68–1.52 (m, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 208.3, 134.5, 133.1, 122.7, 119.3, 79.4, 49.3, 45.6, 42.7, 42.4, 39.5, 35.3, 29.6, 29.5, 26.7, 26.1, 25.9, 21.2, 17.9(2C); HRMS (ESI) (*m*/*z*): found 339.2308 $[M+Na]^+$; calcd for $C_{21}H_{32}O_2Na$ 339.2300.

4.1.8. (1S,5R*,7S*)-8,8-Dimethyl-5,7-di(3-methyl-2-butenyl) bicyclo [3.3.1]non-3-ene-2,9-dione (**21**).* To a dichloromethane (10 mL) solution of diketone **9** (475 mg, 1.50 mmol), kept at 0 °C, was added Et_3N (525 μL, 3.76 mmol), DMAP (18 mg, 10 mol %) and TMSOTf (545 μL, 3.01 mmol) sequentially. After 1 h, reaction was quenched by adding 10 mL of water. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×30 mL). Combined organic extract was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent gave a crude TMS enol ether (524 mg), which was thoroughly dried and directly used for next reaction.

To a solution of TMS enol ether (524 mg, 1.35 mmol) in freshly distilled acetonitrile (10 mL) was added $Pd(OAc)_2$ (364 mg, 1.60 mmol) and the resulting mixture was heated at 55 °C (oil bath temperature) under N_2 for 6 h. After completion of reaction, acetonitrile was removed under reduced pressure and the black residue was charged to a silica gel column (5–10% ethyl acetate in petroleum ether) to obtain the pure enone **21** (278 mg, 59% over two steps) as colorless liquid. IR (Neat) ν 1732, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J*=9.7 Hz, 1H), 6.34 (d, *J*=9.7 Hz, 1H), 5.15–5.10 (m, 1H), 5.01–4.96 (m, 1H), 2.91 (s, 1H), 2.56–2.46 (m, 1H), 2.27–2.11 (m, 2H), 1.87–1.81 (m, 1H), 1.79–1.62 (m, 2H), 1.72 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H), 1.49–1.36 (m, 1H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 197.8, 152.2, 135.3, 133.2, 131.6, 122.4, 118.4, 76.2, 53.4, 43.6, 40.1, 38.4, 32.1, 27.4, 26.6, 25.9, 25.8, 20.6, 18.0, 17.8; HRMS (ESI) (*m*/*z*): found 337.2139 $[M+Na]^+$; calcd for $C_{21}H_{30}O_2Na$ 337.2144.

4.1.9. (1R,2R*,4R*,6R*,8S*)-7,7-Dimethyl-1,8-di(3-methyl-2-butenyl)-3-oxatricyclo[4.3.1.0^{2,4}]decane-5,10-dione (**22**).* To a methanolic solution (10 mL) of the enone **21** (278 mg, 0.89 mmol), kept at 0 °C, was added 50% aqueous solution of H_2O_2 (200 μL, 2.66 mmol) and an aqueous solution of NaOH (35 mg, 0.89 mmol). After stirring for 1 h, methanol was evaporated and the product was extracted with ether (3×20 mL). Combined organic extract was washed by water, brine and dried over anhydrous Na_2SO_4. After removal of solvent, the crude residue was purified on a silica gel column (eluent 10–20% ethyl acetate in petroleum ether) to obtain epoxy ketone **22** (248 mg, 85%) as colorless oil. IR (Neat) ν 1736, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.28–5.23 (m, 1H), 5.10–5.00 (m, 1H), 3.49–3.47 (m, 1H), 3.43–3.42 (m, 1H), 2.67 (s, 1H), 2.63–2.55 (m, 1H), 2.39–2.32 (m, 1H), 2.21–2.15 (m, 2H), 1.84–1.69 (m, 2H), 1.77 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H), 1.43–1.26 (m, 1H), 1.11 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 202.2, 136.3, 134.0, 122.6, 118.2, 72.9, 58.7, 55.9, 51.0, 46.7, 41.8, 37.4, 31.7, 28.5, 27.0, 26.5, 26.3, 21.2, 18.4, 18.3; HRMS (ESI) (*m*/*z*): found 353.1636 $[M+Na]^+$; calcd for $C_{21}H_{30}O_3Na$ 353.1626.

4.1.10. (1S,4S*,5R*,7S*)-4-Hydroxy-8,8-dimethyl-5,7-di(3-methyl-2-butenyl)bicyclo[3.3.1]nonane-2,9-dione (**23**).* Acetic acid (30 μL, 0.25 mmol) was added to an ethanolic solution of PhSeNa, prepared by the reduction of PhSeSePh (470 mg, 1.50 mmol) with $NaBH_4$ (114 mg, 3.01 mmol) in ethanol (6 mL), and the mixture was stirred for 10 min at room temperature. The resulting solution was added at once to a solution of epoxy ketone **22** (248 mg, 0.75 mmol) in ethanol (4 mL) under N_2 at ice cold condition. After being stirred for 1 h at the same temperature, the reaction mixture was diluted with ethyl acetate and washed with brine. Removal of the solvent left the residue, which was purified by silica gel column chromatography (eluent 30% ethyl acetate in petroleum ether) to give pure β-hydroxy ketone **23** (177 mg, 71%) as an amorphous solid. IR (Thin film) ν 3420, 1726, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27–5.22 (m, 1H), 5.07–5.04 (m, 1H), 4.09 (br s, 1H), 3.02–2.57 (m, 4H), 2.89 (s, 1H), 2.25–2.13 (m, 5H), 1.74 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.51–1.34 (m, 1H), 1.04 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 206.8, 135.8, 133.3, 122.3, 118.4, 79.1, 70.2, 54.3, 48.8, 45.3, 42.4, 39.4, 31.4, 30.0, 26.9, 26.1, 25.9, 21.3, 18.0, 17.9; HRMS (ESI) (*m*/*z*): found 355.2249 $[M+Na]^+$; calcd for $C_{21}H_{32}O_3Na$ 355.2249.

4.1.11. (1S,3R*,5S*,8S*,10S*)-3-(1-Hydroxy-1-methylethyl)-9,9-dimethyl-10-(3-methyl-2-butenyl)-4-oxatricyclo [6.3.1.0^{1,5}] dodecane-7,12-dione (**24**).* A mixture of pre-dried PCC (230 mg, 1.07 mmol) and silica gel (230 mg, 100–200 mesh) was added, at a time, to a solution of β-hydroxy ketone **23** (177 mg, 0.53 mmol) in dry dichloromethane (5 mL) at room temperature. After stirring for 1 h at the same temperature, the orange colored mixture was filtered through a small silica gel column (eluent 30–40% ethyl acetate in petroleum ether) to obtain **24** (141 mg, 76%) as a white solid. Mp. 113–115 °C; IR (Thin film) ν 3516, 1727, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04–5.01 (m, 1H), 4.22–4.19 (m, 1H), 3.79–3.75 (m, 1H), 2.92 (s, 1H), 2.84–2.82 (m, 2H), 2.66–2.59 (m, 1H), 2.17–2.05 (m, 3H), 1.78–1.64 (m, 4H), 1.72 (s, 3H), 1.58 (s, 3H), 1.22 (s,

3H), 1.12 (s, 3H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 205.8, 133.7, 122.2, 83.7, 79.9, 77.7, 71.8, 58.0, 46.0, 45.4, 42.8, 38.7, 33.3, 28.6, 27.4, 26.5, 25.9, 24.1, 21.3, 17.9; HRMS (ESI) (*m*/*z*): found 371.2191 $[M+Na]^+$; calcd for $C_{21}H_{32}O_4Na$ 371.2198.

4.1.12. (1S,3R*,8S*,10S*)-9,9-Dimethyl-10-(3-methyl-2-butenyl)-3-1-methyl-1-[(1,1,1-trimethylsilyl)oxy]ethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (**25**).* To a dichloromethane (5 mL) solution of diketone **24** (141 mg, 0.41 mmol), kept at 0 °C, were added Et_3N (170 μL, 1.22 mmol), DMAP (5 mg, 10 mol %) and TMSOTf (145 μL, 0.81 mmol) sequentially and stirred for 1 h at the same temperature. Upon completion, the reaction was quenched by adding 5 mL of water. Organic phase was separated and the aqueous phase was extracted with dichloromethane (2×20 mL) followed by usual work up. Removal of solvent gave a crude TMS enol ether (175 mg), which was thoroughly dried and directly used for next reaction.

To a solution of TMS enol ether (175 mg, 0.36 mmol) in freshly distilled acetonitrile (5 mL) was added $Pd(OAc)_2$ (120 mg, 0.54 mmol) and the resulting mixture was heated at 55 °C (oil bath temperature) under N_2 for 6 h. After completion of the reaction, acetonitrile was removed under reduced pressure and the black residue was charged on a silica gel column (eluent 5–10% ethyl acetate in petroleum ether) to obtain the enone **25** (93 mg, 55% over two steps) as colorless liquid. IR (Neat) ν 1735, 1654, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.05–5.01 (m, 1H), 4.19–4.14 (m, 1H), 2.97–2.89 (m, 1H), 2.80 (s, 1H), 2.34–2.17 (m, 2H), 1.82–1.69 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.52–1.42 (m, 2H), 1.39 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 0.88 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 194.5, 179.4, 133.0, 122.7, 105.4, 93.1, 73.4, 72.9, 59.7, 42.0, 41.3, 41.0, 27.5, 27.3, 27.0, 26.8, 26.3, 25.8, 20.4, 17.9, 2.5 (3C); HRMS (ESI) (*m*/*z*): found 419.2609 $[M+Na]^+$; calcd for $C_{24}H_{38}O_4SiNa$ 419.2617.

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13. Single crystal X-ray diffraction data of **24** was collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K. The X-ray generator was operated at 50 kV and 35 mA using MoK_α radiation. The data was collected with a ω scan width of 0.3°. A total of 606 frames per set were collected using SMART in three different settings of φ (0°, 90° and 180°) keeping the sample at a detector distance of 6.062 cm and the 2θ value fixed at −25°. The data was reduced by SAINTPLUS; an empirical absorption correction was applied using the package SADABS, and XPREP was used to determine the space group. The structure was solved using SIR92 and refined using SHELXL97.Crystallographic data have been deposited with the Cambridge Crystallographic data Centre, CCDC 846775. Crystal data for compound **24**: $C_{21}H_{32}O_4$, M = 348.48, triclinic, space group $P\bar{1}$, a=6.681(6) Å, b=11.084(9) Å, c=14.952(13) Å, α=71.602(14)°, β=82.291(14)°, γ=73.374(14)°, V=1005.6(15) Å^3. Z=2, ρ_{calcd}=1.151 g cm^{-3}, $F(000)$=380, μ=0.078 mm^{-1}, T=291 K, number of l.s parameters=298, R=0.0543, R_w=0.1260. GOF=1.039.
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