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# Synthetic Studies Towards Bridgehead Diprenyl-Substituted Bicyclo[3.3.1]nonane-2,9-diones as Models for Polyprenylated Acylphloroglucinol Construction

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The synthesis of bridgehead diprenylated bicyclo[3.3.1]-nonane-2,9-dione, based on a reductive rearrangement of an enol lactone, is presented. The same target could be reached by a one-step sequence involving Michael addition of 2,6-diprenylcyclohexanone onto acrolein and intramolecular aldol reaction. The first method could be extended to the formation of a compound with *gem*-dimethyl substituents adjacent to the bridgehead position, but the construction of a suitably substituted enol lactone, with a view to polyprenylated acylphloroglucinol elaboration, could not be achieved.


## Introduction

A number of polyprenylated acylphloroglucinols (PPAPs) with a bicyclo[3.3.1]nonane-2,4,9-trione core skeleton have been isolated from plants and trees of the family Clusiaceae (Guttiferae), some of them presenting interesting biological activities.[1] These compounds can be divided principally into two classes: whereas type A PPAPs have a bridgehead acyl group adjacent to a quaternary center, those of type B have two bridgehead isoprenyl chains and a C-3 acyl group (Figure 1).[2] The first total syntheses of a compound of this class, garsubellin A (type A PPAP), have been reported recently.[3]

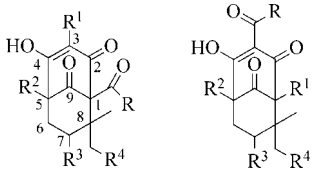


Figure 1. Main types A and B polyprenylated acylphloroglucinols (PPAPs).

Our interest in this field arose from the observation[4] that xanthochymol (**1**) (Figure 2) was active in a tubulin disassembly inhibition test and from the recent isolation of the analogues oblongifolins A–D.[5] We also undertook synthetic studies on these type B PPAPs, leading to the synthesis of (±)-clusianone (**2**)[6] based on a Lewis acid catalyzed Effenberger α,α′-annulation[7] of a suitably substituted cyclohexanone silyl enol ether with malonyl chloride.

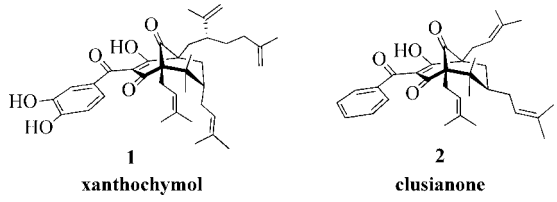


Figure 2. Some examples of type B polyprenylated benzoylphloroglucinols.

Simpkins and co-workers published the synthesis of (±)-clusianone (**2**) using a similar approach with a less-substituted cyclohexanone derivative and by bridgehead deprotonation and prenylation of a bicyclo[3.3.1]nonane-2,4,9-trione enol methyl ether.[8]

The most direct route to the bicyclic core of type B polyprenylated benzoylphloroglucinols, starting from a substituted cyclohexanone, is the Effenberger α,α′-annulation,[7] but it is limited to compounds with a prenyl at C-7 in an equatorial configuration (*exo*), such as **2**, owing to the axial attack of malonyl chloride on the enol derivative.[6,8] Thus, we became interested in other methods for the construction of the bridged bicyclic system of these natural products. As we had already shown that *C*-benzoylation of the enolic β-dicarbonyl moiety of a compound such as **4** can be achieved using acyl cyanide,[6] we chose a potential precursor of **4** as a target (Scheme 1). With this aim, bicyclo[3.3.1]nonane-2,9-diones **3**, with two isoprenyl chains at bridgehead positions, could be an interesting choice if the functionalization

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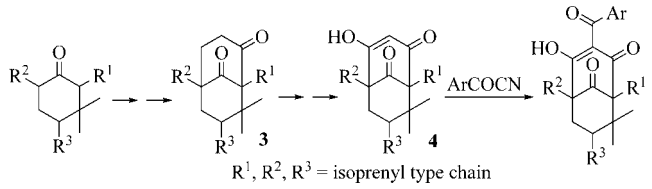
at C-4 by further oxidation is easy. We also wanted to reach this goal directly starting from cyclohexanones substituted by prenyls, without protection of these groups[3a] and avoiding olefin metathesis for their introduction.[3]




Scheme 1. Synthetic plan towards type B polyprenylated benzoylphloroglucinols.

There are only a few methods for the synthesis of bicyclo[3.3.1]nonane-2,9-diones with alkyl groups at bridgehead positions starting from the corresponding cyclohexanones. When one of these positions is substituted by an acyl or alkoxycarbonyl group, Michael addition onto α,β-unsaturated aldehydes followed by intramolecular aldol reaction can be used.[9] In the case of a 2,6-dialkylcyclohexanone, indirect methods for the same type of cyclization have been published,[10] but which are more difficult to apply with acid-sensitive prenyl groups.

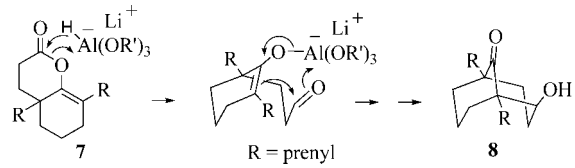
An interesting way to reach the same target is the efficient reductive rearrangement of a enol δ-lactone, which also implies intramolecular aldol reaction.[11] It should be noted that this method has been recently applied to the synthesis of a bicyclo[3.3.1]nonan-9-one derivative with only one bridgehead prenyl group.[12]

Here, we report explorative work in this area and, in particular, our results concerning the evaluation of methods for the synthesis of bridgehead diprenylated bicyclo[3.3.1]-nonane-2,9-diones.

## Results and Discussion

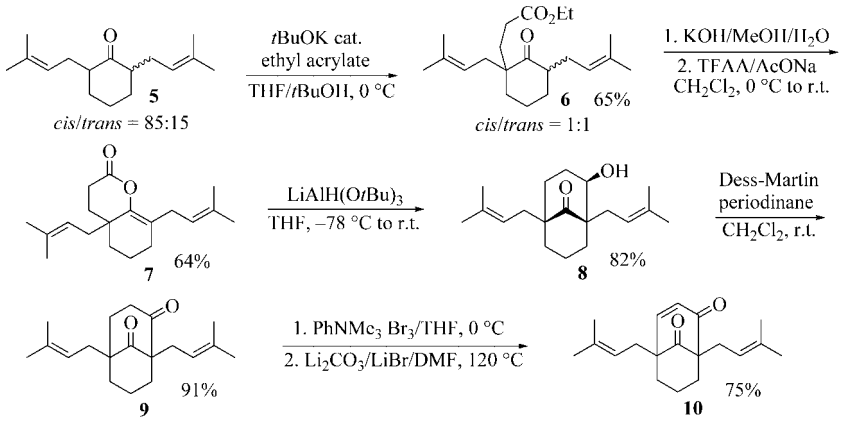
We first investigated the Martin reductive rearrangement[11] starting from the enol lactone **7** to evaluate this methodology for reaching the bicyclic structure with two prenyl groups at bridgehead positions (Scheme 1).

Starting from 2,6-diprenylcyclohexanone (**5**), as a mixture of isomers,[6] addition of ethyl acrylate followed by saponification and treatment of the intermediate acid with trifluoroacetic anhydride[13] gave enol lactone **7**. Reduction of **7**, under the conditions described by Martin and coworkers,[11] gave the bicyclic aldol product **8** in 82% yield, essentially as a single *exo* isomer with the hydroxy group in an axial position (Scheme 2). The efficiency and stereochemistry of this aldol reaction could be attributed to the generation of the ketone enolate close to the aldehyde according to a mechanism illustrated in Scheme 3, as suggested by Martin et al.[11b] Oxidation of alcohol **8** led to 1,5-diprenylbicyclo[3.3.1]nonane-2,9-dione (**9**) which could be transformed into enone **10** by a bromination/dehydrobromination sequence.[10]



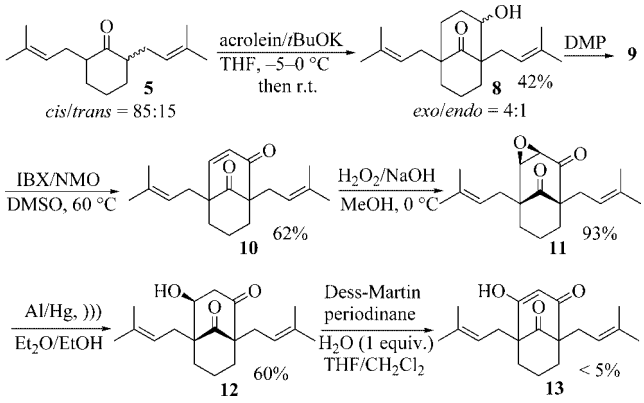

Scheme 3. Possible mechanism for the formation of the axial *exo* alcohol **8**.

Surprisingly, we found that a mixture of **8** (major compound) and its epimer could be directly obtained in 42% yield from cyclohexanone **5** by a one-step sequence involving Michael addition onto acrolein in the presence of *t*BuOK followed by intramolecular aldol reaction (Scheme 4). It is worth noting that, to the best of our knowledge, such a reaction has no precedent in the literature, acrolein leading usually, with ketone enolates, to compounds resulting from addition onto a carbonyl rather than from conjugate addition. A series of equilibria involving aldol and retroaldol reactions and proton transfers between the different carbonyl derivatives and their enolates could explain this intriguing result. Moreover, direct oxidation of ketone **9** to enone **10** could be achieved by the method of Nicolaou et al. using 2-iodoxybenzoic acid (IBX) in the presence of NMO.[14]




Scheme 2. Formation of bicyclic aldol compound **8** by reductive rearrangement of **7**.



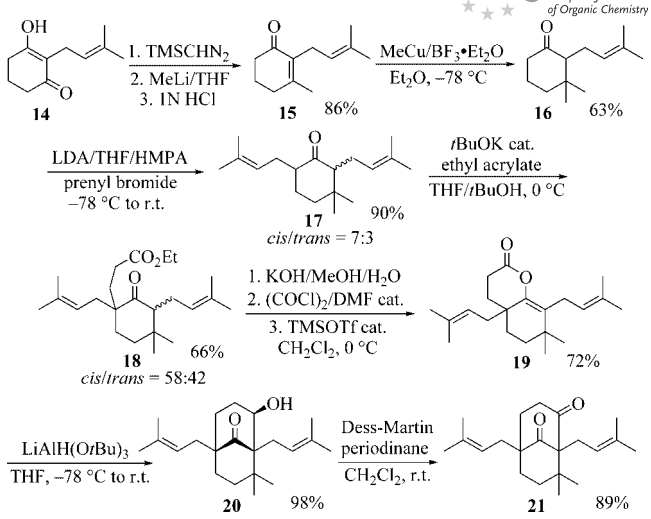

Scheme 4. α,α′-Annulation of 2,6-diprenylcyclohexanone with acrolein and further oxidation.

Epoxidation of enone **10** with basic hydrogen peroxide gave, as anticipated and without retroaldol reaction, the *exo* derivative **11** in good yield, but its reduction to β-hydroxy ketone **12** was more problematic. Miyashita conditions with sodium phenylseleno(triethoxyborate) in the presence of acetic acid[15] gave a disappointing 15% yield of **12** accompanied by 50% of enone **10**. With $SmI_2$ at a low temperature,[16] **10** was the very major product (90%) and **12** was isolated in trace amounts. Aluminium amalgam gave the best results (60% of **12**), but only under sonication conditions.[17] This result is of significance since this type of reduction proved to be very difficult in an approach to nemorosone by Ciochina.[18] We ascribe the easy elimination, leading to enone **10**, to the axial position of the *exo* hydroxy group in **12**.

Unfortunately, we have not yet been able to oxidize the β-hydroxy ketone **12** to the desired β-dicarbonyl derivative under classical conditions (PDC, TPAP/NMO, Jones, Collins, Swern and Dess–Martin reagents). Only Dess–Martin periodinane, in the presence of 1 equivalent of water,[19] gave minute amounts of the desired bicyclo[3.3.1]nonane-2,4,9-trione **13**.[6] This problem is not so trivial owing to the axial position of the hydroxy group and it has already been encountered in similar situations, but not with substituents at the bridgehead positions.[20]

We then examined if the reductive rearrangement of an enol lactone could be applied to a compound with *gem*-dimethyl substituents adjacent to a prenyl group to see if it could be possible to reach, by this method, a bicyclic derivative with two contiguous quaternary carbons, as is required for the synthesis of PPAPs.

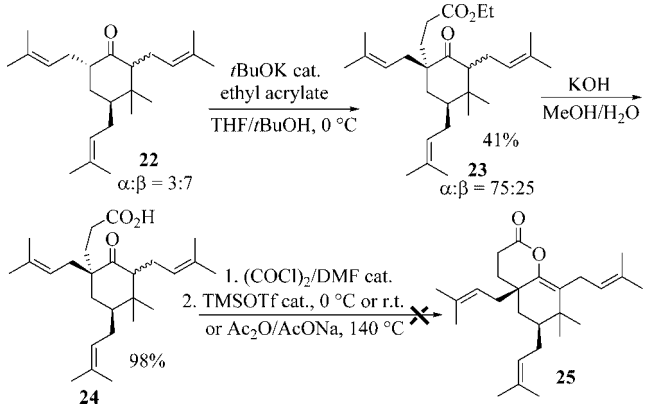
Enone **15**[21] was obtained from 2-prenylcyclohexane-1,3-dione (**14**)[6] via the vinylogous methyl ester[22] and conjugate addition of methyl copper onto enone **15**, in the presence of $BF_3$ etherate, followed by regioselective alkylation of ketone **16**[23] with prenyl bromide led to the tetrasubstituted cyclohexanone **17** as a mixture of isomers (Scheme 5). After carboxyethylation of **17**, lactonization could not be achieved using the trifluoroacetic-carboxylic mixed anhydride shown in Scheme 2 for the lactonization of **6**; the best conditions were found starting from the acid chloride and by activation with TMSOTf.




Scheme 5. Access to the 8,8-dimethyl-1,5-diprenyl bicyclic system.

Reduction of the lactone **19** was accompanied by an efficient aldol reaction, giving bicyclic compound **20** in an excellent yield and as a single *exo* isomer which could be oxidized with Dess–Martin periodinane to the bicyclo-[3.3.1]nonane-2,9-dione **21** in 89% yield.

Finally, enol lactonization was attempted starting from the cyclohexanone **22**,[6] with the substitution pattern required for the synthesis of clusianone (**2**), according to Scheme 6. Regio- and stereoselective introduction of the ethoxycarbonylethyl chain (*anti* to the γ prenyl group)[3a,6] by Michael addition onto ethyl acrylate gave **23** as a mixture of isomers which could be separated. Formation of the corresponding acids **24** by basic hydrolysis and conversion into the acid chlorides proceeded in good yields.




Scheme 6. Failure of enol lactone **25** formation.

Unfortunately we could not obtain enol lactone **25** under the conditions described in Scheme 6 at 0 °C or at room temperature or even under more classic conditions starting from the acids **24** with acetic anhydride in the presence of sodium acetate at 140 °C.[11] We ascribe this failure to the difficulty in obtaining the reactive conformation, that is,

with the π bond of the chlorocarbonyl function in the direction of the lone pair of the ketone oxygen. Torsional strain between the prenyl group adjacent to the carbonyl and the *gem*-dimethyl substituents and the latter could disfavor ring-conformation change.

A slightly different problem, relating to the aldol reaction in the case of a compound with a prenyl at C-4, was encountered by Shibasaki and co-workers[3a] in their synthesis of garsubellin A.

Thus, the enol lactone reductive rearrangement methodology could not be applied, in this case, to the preparation of bicyclo[3.3.1]nonane-2,9-diones suitably substituted for the synthesis of type B PPAPs. It should be also noted that annulation of the pentasubstituted ketone **22** with acrolein in the presence of *t*BuOK did not proceed.

## Conclusions

We have shown that we can obtain bicyclo[3.3.1]nonane-2,9-dione with two prenyl groups at bridgehead positions starting from the corresponding 2,6-disubstituted cyclohexanone and without protecting the olefinic double bonds. This was achieved by either a reductive rearrangement of an enol lactone or a one-step sequence involving Michael addition onto acrolein and intramolecular aldol reaction. Enol lactonization succeeded also with a *gem*-dimethyl derivative, allowing, by reduction, the formation of a compound with two contiguous quaternary carbon atoms in good yield. The reaction failed with the suitably triprenyl-substituted cyclohexanone that is necessary for the synthesis of PPAPs such as clusianone. Oxidation of 1,5-diprenylbicyclo[3.3.1]nonane-2,9-dione to a β-hydroxy ketone could be achieved, but the major problem remaining to reach PPAPs is the subsequent transformation into the enolic β-dicarbonyl derivative. Investigations for finding prenyl-compatible oxidative conditions are currently underway and will be reported in due course.

## Experimental Section

**General Remarks:** NMR spectra were recorded with the following Bruker spectrometers: AC250 (250 MHz), AC300 (300 MHz), Avance 300 (300 MHz), DPX 400 (400 MHz), and Avance 500 (500 MHz). FTIR spectra were recorded as a film on NaCl or diamond (SensIR Durasamp*IRII*) cell with a Perkin–Elmer Spectrum BX FT-IR spectrometer. Mass spectra were recorded by electrospray ionization with a Micromass LCT (ESI-TOF) spectrometer.

**Ethyl 3-[1,3-Bis(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoate (6):** A solution of 1.66 M *t*BuOK in THF (120 μL, 0.2 mmol) and, after 15 min at 0 °C, ethyl acrylate (113 μL, 1.04 mmol) were added dropwise to a solution of a 85:15 *cis*/*trans* mixture of 2,6-diprenylcyclohexanone[6] (243 mg, 1.04 mmol) in THF/dry *t*BuOH (1:1, 1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h 30 min and quenched at that temperature with saturated $NH_4Cl$. The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic phases were washed with water (3 mL), brine (3 mL), dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure. Column chromatography on silica gel (heptane/ethyl acetate, 98:2) afforded **6** as a 1:1 mixture of the two diastereoisomers (227.2 mg, 65%) as a colorless oil. An analytical sample of each epimer was obtained.

**Less Polar Epimer:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.22 (m, 2 H), 1.22 (t, $J$ = 7.2 Hz, 3 H), 1.52 (m, 1 H), 1.58 (s, 3 H), 1.58 (s, 3 H), 1.60 (m, 1 H), 1.66 (s, 3 H), 1.68 (s, 3 H), 1.70 (m, 1 H), 1.82 (m, 1 H), 1.85 (m, 1 H), 1.87 (m, 1 H), 1.90 (m, 1 H), 2.10 (m, 1 H), 2.20 (m, 1 H), 2.21 (m, 2 H), 2.36 (m, 1 H), 2.45 (m, 1 H), 4.08 (q, $J$ = 7.2 Hz, 2 H), 5.03 (br. t, $J$ = 7.6 Hz, 1 H), 5.06 (br. t, $J$ = 7.6 Hz 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.1, 17.7, 17.9, 20.9, 25.7, 26.1, 28.0, 28.9, 29.8, 32.3, 33.5, 37.6, 47.5, 51.5, 60.4, 119.6, 122.3, 132.8, 134.0, 173.3, 215.5 ppm. IR: $\tilde{\nu}$ = 2927, 1732, 1702, 1450, 1375, 1182 cm$^{-1}$.

**More Polar Epimer:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.21 (m, 2 H), 1.22 (t, $J$ = 7.2 Hz, 3 H), 1.49 (m, 1 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.66 (s, 3 H); 1.68 (m, 1 H), 1.70 (m, 1 H), 1.80 (m, 1 H), 1.86 (m, 1 H), 1.87 (m, 1 H), 1.90 (m, 1 H), 2.12 (m, 1 H), 2.25 (m, 2 H), 2.36 (m, 1 H), 2.42 (m, 1 H), 2.47 (m, 1 H), 4.10 (q, $J$ = 7.2 Hz, 2 H), 4.87 (br. t, $J$ = 7.0 Hz, 1 H), 5.04 (br. t, $J$ = 6.7 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.1, 17.7, 18.0, 21.0, 25.7, 25.9, 27.9, 29.3, 29.9, 33.5, 33.6, 36.3, 47.4, 51.5, 60.1, 118.0, 122.4, 132.6, 134.6, 174.1, 215.1 ppm. IR: $\tilde{\nu}$ = 2928, 1732, 1702, 1445, 1376, 1176 cm$^{-1}$.

**3-[1,3-Bis(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoic Acid:** A mixture of esters **6** (1.134 g, 3.39 mmol) was solubilized in a solution of 85% KOH (291 mg, 4.41 mmol) in MeOH/$H_2O$ (2:1, 7 mL) and stirred at room temperature for 24 h. Acetic acid (240 μL, 4.2 mmol) was added to the mixture and extraction was carried out with dichloromethane (3 × 5 mL). The organic layer was dried with $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure to give acids as a colorless oil (1005 mg, 97%) and as a mixture of epimers which could not be separated. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.20–1.22 (m, 1 H), 1.45–1.56 (m, 1 H), 1.58, 1.59, 1.60 (3 × br. s, 6 H), 1.67, 1.69 (2 × br. s, 6.5 H), 1.72–1.99 (m, 5 H), 2.04–2.53 (m, 7.5 H), 4.87 (br. t, $J$ = 7.4 Hz, 0.5 H), 5.04 (m, 1 H), 5.06 (br. t, $J$ = 7.4 Hz, 0.5 H), 10.16 (br. s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7, 17.7, 17.9, 18.0, 20.8, 21.1, 25.7, 25.9, 26.0, 27.9, 28.0, 28.7, 29.1, 29.5, 29.7, 32.3, 33.5, 33.6, 33.7, 36.4, 37.5, 47.4, 47.5, 51.4, 51.5, 117.8, 119.3, 122.2, 122.3, 132.7, 132.9, 134.2, 134.8, 179.4, 180.4, 215.2, 215.5 ppm. IR: $\tilde{\nu}$ = 3400–2400, 2926, 1702, 1445, 1376, 1221, 1113 cm$^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{30}NaO_3$ 329.2093; found 329.2101.

**4a,8-Bis(3-methylbut-2-enyl)-3,4,4a,5,6,7-hexahydro-2*H*-chromen-2-one (7):** TFAA (1.43 mL, 10.1 mmol) was added dropwise during 10 min to a solution of a mixture of the above acids (2.613 g, 8.53 mmol) in dichloromethane at 0 °C (41 mL) containing dry AcONa (704 mg, 8.58 mmol). The reaction mixture was vigorously stirred at 0 °C for 2 h and at room temperature for 1 h. TEA (3.3 mL, 23.7 mmol) was added and, after dilution with diethyl ether (50 mL) and water (25 mL), the phases were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The organic extracts were combined and dried with $Na_2SO_4$. Concentration and purification by silica gel chromatography (heptane/ethyl acetate/TEA, 90:10:1) provided enol lactone **7** (1.637 g, 66%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.30 (m, 1 H), 1.53 (m, 1 H), 1.57 (m, 1 H), 1.63 (s, 3 H), 1.65 (s, 3 H), 1.67 (m, 1 H), 1.69 (s, 3 H), 1.73 (s, 3 H), 1.80 (m, 1 H), 1.83 (m, 1 H), 2.03 (dd, $J$ = 7.1, 6.5 Hz, 2 H), 2.21 (br. d, $J$ = 7.3 Hz, 2 H), 2.55 (dd, $J$ = 8.5, 5.9 Hz, 2 H), 2.82 (m, 2 H), 5.04 (br. t, $J$ = 7.3 Hz, 1 H), 5.06 (br. t, $J$ = 7.3 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 18.1, 18.5, 25.7, 26.1, 27.8, 28.0, 28.3, 30.0, 32.8, 33.9, 36.0,

118.5, 118.6, 121.4, 132.7, 134.9, 147.1, 169.9 ppm. IR: $\tilde{\nu}$ = 2926, 1750, 1686, 1451, 1247, 1146, 1115 $cm^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{28}NaO_2$ 311.1987; found 311.1992.

**(1*R**,2*R**,5*R**)-2-Hydroxy-1,5-bis(3-methylbut-2-enyl)bicyclo-[3.3.1]nonan-9-one (8):** A 1 M $LiAlH(OtBu)_3$ solution in THF (2.75 mL, 2.75 mmol) was slowly added to a solution of lactone **7** (582.5 mg, 2.02 mmol) in dry THF (1.2 mL) at –78 °C. The mixture was stirred for 30 min at –78 °C, warmed up to room temperature for 1 h, quenched by the addition of brine (6 mL), and filtered through Celite. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL), dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure. Column chromatography on silica gel (heptane/ethyl acetate, 95:5) furnished **8** (480 mg, 82%) as a viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.52 (m, 1 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.68 (m, 1 H), 1.70 (m, 1 H), 1.70 (s, 3 H), 1.71 (s, 3 H), 1.74 (m, 1 H), 1.84 (m, 1 H), 1.99 (m, 1 H), 2.00 (m, 1 H), 2.01 (m, 1 H), 2.03 (m, 1 H), 2.11 (m, 1 H), 2.13 (br. d, *J* = 7.5 Hz, 2 H), 2.42 (m, 1 H), 2.52 (m, 1 H), 4.10 (br. s, 1 H), 5.16 (br. t, *J* = 7.4 Hz, 1 H), 5.18 (br. t, *J* = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 17.9, 21.1, 26.0, 26.1, 28.9, 31.8, 34.1, 35.8, 35.9, 39.1, 49.5, 54.4, 78.1, 119.4, 120.2, 133.5, 134.6, 219.1 ppm. IR: $\tilde{\nu}$ = 3494, 2915, 1703, 1448, 1375, 1103 $cm^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{30}NaO_2$ 313.2144; found 313.2101.

**Annulation of 5 with Acrolein:** A 20% *t*BuOK solution in THF (11 mL, 18.7 mmol) was added dropwise to a solution of an 85:15 *cis*/*trans* mixture of 2,6-diprenylcyclohexanone (**5**)[6] (4 g, 17 mmol) in THF (57 mL) at room temperature and, after 30 min, the mixture was cooled to –10 °C. A solution of acrolein (1.6 mL, 23.9 mmol) in THF (30 mL) was then added at that temperature during 2 h through a syringe-drive. The reaction mixture was stirred for 30 min between –5 °C and 0 °C and at room temperature for 3 h and was then quenched with a pH 7 buffer. Extraction with diethyl ether (3 × 5 mL), followed by washing with brine, drying with $Na_2SO_4$, and solvent removal under reduced pressure gave a brown oil. Column chromatography on silica gel (heptane/ethyl acetate, 9:1) afforded a 4:1 mixture of *exo* and *endo* alcohols **8** as a colorless oil (2.05 g, 42%). An analytical sample of the minor *endo* epimer (colorless oil) was obtained by column chromatography on silica gel using the same eluent. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.25 (m, 1 H), 1.44 (m, 2 H), 1.50 (m, 1 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.69 (m, 1 H), 1.70 (s, 3 H), 1.71 (s, 3 H), 1.72 (m, 1 H), 1.90 (m, 2 H), 1.93 (m, 1 H), 2.01 (m, 1 H), 2.09 (m, 2 H), 2.14 (m, 1 H), 2.43 (m, 1 H), 3.80 (dd, *J* = 11.2, 6.8 Hz, 1 H), 5.14 (br. t, *J* = 7.6 Hz, 1 H), 5.33 (br. t, *J* = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 17.9, 21.2, 26.1 (2 C), 29.6, 32.8, 33.1, 33.8, 35.9, 38.8, 48.8, 56.0, 77.0, 120.1, 121.4, 133.7, 134.2, 218.1 ppm. MS (EI): *m*/*z* = 313.2 $[M + Na]^+$.

**1,5-Bis(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-2,9-dione (9):** A 0.5 M Dess–Martin periodinane solution in dichloromethane (4.95 mL, 2.48 mmol) was added to a solution of alcohol **8** (480 mg, 1.65 mmol) in dry dichloromethane (3.75 mL) under argon at room temperature. The mixture was stirred for 3 h at room temperature, quenched by the addition of a solution of saturated $NaHCO_3$ (75 mL) containing $Na_2S_2O_3$ (15 g), and diluted with diethyl ether (30 mL). The mixture was stirred under a normal atmosphere until two limpid phases were obtained which were separated. The organic layer was washed with water (2 × 10 mL) and the aqueous phase extracted with diethyl ether (2 × 10 mL) and, finally, the combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated. Purification on silica gel (heptane/ethyl acetate, 95:5) afforded dione **9** (433 mg, 91%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.56 (m, 2 H), 1.60 (s, 3 H), 1.62 (m, 1 H), 1.63 (s, 3 H), 1.63 (s, 3 H), 1.73 (s, 3 H), 1.74 (m, 1 H), 1.90 (m, 1 H), 1.95 (m, 1 H), 2.04 (m, 1 H), 2.06 (m, 1 H), 2.24 (m, 1 H), 2.27 (m, 1 H), 2.32 (m, 1 H), 2.36 (m, 2 H), 2.55 (ddd, *J* = 14.5, 6.5, 2.7 Hz, 1 H), 5.07 (br. t, *J* = 7.1 Hz, 1 H), 5.18 (br. t, *J* = 6.9 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 18.0, 19.7, 25.9, 26.1, 26.5, 31.4, 35.7, 41.3, 42.0, 42.6, 49.2, 66.2, 119.0, 119.4, 134.3, 134.6, 212.9, 214.0 ppm. IR: $\tilde{\nu}$ = 2925, 1699, 1448 $cm^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{28}NaO_2$ 311.1987; found 311.1963.

**(1*S**,3*S**,5*S**)-3-Bromo-1,5-bis(3-methylbut-2-enyl)bicyclo-[3.3.1]nonane-2,9-dione:** A solution of ketone **9** (266.7 mg, 0.92 mmol) in THF (750 μL) was added dropwise to a suspension of $PhNMe_3Br_3$ (346 mg, 0.92 mmol) in THF (7.5 mL) at 0 °C under argon. The orange mixture was stirred for 30 min at 0 °C until complete discoloration, and the resultant suspension was added to a saturated brine/0.1 N $Na_2S_2O_3$ (1:1, 4 mL) mixture. The mixture was filtered through Celite and extracted with dichloromethane (3 × 10 mL). The organic phases were washed with brine, dried with $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure to yield the bromo ketone (338 mg, 100%) as a crude oil which was used directly in the next step without any further purification. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.60 (m, 2 H), 1.62 (s, 3 H), 1.64 (s, 3 H), 1.68 (s, 3 H), 1.70 (m, 1 H), 1.74 (s, 3 H), 1.78 (m, 1 H), 1.96 (m, 1 H), 2.28 (m, 1 H), 2.29 (m, 1 H), 2.39 (m, 1 H), 2.43 (m, 2 H), 2.50 (m, 1 H), 2.58 (m, 1 H), 4.48 (dd, *J* = 4.6, 2.6 Hz, 1 H), 5.21 (br. t, *J* = 7.7 Hz 1 H), 5.32 (br. t, *J* = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7, 18.0, 19.4, 25.9, 26.1, 32.9, 35.7, 35.8, 43.4, 44.6, 47.9, 48.8, 64.6, 119.1, 119.6, 133.9, 135.0, 204.6, 212.0 ppm. IR: $\tilde{\nu}$ = 2924, 1702, 1440, 1375, 1093 $cm^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{27}BrNaO_2$ 389.1092; found 389.1107.

**1,5-Bis(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (10):** A solution of the above bromo ketone (326.9 mg, 0.89 mmol) in dry DMF (500 μL) was added to a stirred suspension of dry LiBr (309 mg, 3.56 mmol) and $LiCO_3$ (255 mg, 3.45 mmol) in dry DMF (2.9 mL) at 120 °C under argon. The reaction was stirred at 120 °C for 75 min and the mixture was cooled to room temperature and diluted with saturated brine. Then the aqueous solution was extracted with diethyl ether (2 × 20 mL) and dichloromethane (3 × 10 mL). The organic layers were combined, washed with brine, water, and brine, dried with $Na_2SO_4$, filtered, concentrated, and purified by chromatography on silica gel (heptane/ethyl acetate, 95:5) to give enone **10** (192 mg, 75%) as a slightly yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.60 (m, 2 H), 1.61 (s, 3 H), 1.63 (s, 3 H), 1.63 (s, 3 H), 1.66 (m, 1 H), 1.66 (m, 1 H), 1.71 (s, 3 H), 1.86 (m, 1 H), 1.92 (m, 1 H), 2.30 (m, 1 H), 2.46 (m, 2 H), 2.51 (m, 1 H), 4.97 (br. t, *J* = 7.0 Hz, 1 H), 5.13 (br. t, *J* = 7.4 Hz, 1 H), 6.42 (d, *J* = 10.0 Hz, 1 H), 6.80 (d, *J* = 10.0 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.9, 18.0, 18.5, 25.9, 26.0, 29.5, 32.3, 36.5, 40.5, 53.3, 66.4, 118.5, 119.9, 132.3, 133.6, 135.3, 150.3, 200.9, 209.9 ppm. IR: $\tilde{\nu}$ = 2923, 1726, 1672, 1445, 1375, 1109 $cm^{-1}$. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{26}NaO_2$ 309.1831; found 309.1847.

**Oxidation of Ketone 9 to Enone 10 with IBX and NMO:** A 60% NMO solution in water (2.13 mL, 12.4 mmol) was added to a suspension of IBX (3.45 g, 12.4 mmol) in DMSO (62 mL), protected from the light and under argon, and the mixture was vigorously stirred until dissolution. A solution of ketone **9** (1.19 g, 4.12 mmol) in DMSO (4 mL) was added and the mixture was heated at 60–70 °C for 60–72 h. After cooling to room temperature, aqueous 5% $NaHCO_3$ (50 mL) was added and the mixture was extracted with diethyl ether. The organic phase was washed with saturated aque-

ous $NaHCO_3$, water, and brine, dried with $Na_2SO_4$, and the solvent removed under reduced pressure. Column chromatography on silica gel (heptane/ethyl acetate, 97:3) gave enone **10** (730 mg, 62%) as a nearly colorless oil.

**(1*S**,2*R**,4*R**,6*S**)-1,6-Bis(3-methylbut-2-enyl)-3-oxatricyclo[4.3.1-.0$^{2,4}$]decane-5,10-dione (11):** Solutions of 35% $H_2O_2$ (270 μL, 2.81 mmol) and 1.5 M NaOH (120 μL, 0.18 mmol) were slowly added to a solution of enone **10** (192 mg, 0.67 mmol) in MeOH (2 mL) at 0 °C under argon . The mixture was stirred at 0 °C for 5 h and then ice (3 g) and cold saturated brine (4 mL) were added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic phases were washed with brine, dried with $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure to furnish epoxy ketone **11** (187.9 mg, 93%) as a pure compound. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.57 (s, 3 H), 1.58 (m, 1 H), 1.59 (m, 2 H), 1.59 (m, 1 H), 1.59 (s, 3 H), 1.63 (s, 3 H), 1.72 (s, 3 H), 2.09 (m, 1 H), 2.19 (m, 1 H), 2.33 (br. d, $J$ = 6.9 Hz, 2 H), 2.37 (dd, $J$ = 14.9, 8.6 Hz, 1 H), 2.59 (dd, $J$ = 14.9, 7.2 Hz, 1 H), 3.40 (d, $J$ = 3.9 Hz, 1 H), 3.44 (d, $J$ = 3.9 Hz, 1 H), 4.87 (br. t, $J$ = 7.1 Hz, 1 H), 5.22 (br. t, $J$ = 7.7 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7, 17.8, 19.3, 25.6, 26.0, 30.3, 31.7, 35.2, 43.8, 50.8, 56.7, 56.9, 64.0, 117.8, 119.1, 133.7, 135.8, 207.1, 207.5 ppm. IR: $\tilde{\nu}$ = 2927, 1701, 1447, 1256, 1147, 1037 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{19}H_{26}NaO_3$ 325.1780; found 325.1771.

**(1*R**,4*S**,5*S**)-4-Hydroxy-1,5-bis(3-methylbut-2-enyl)bicyclo-[3.3.1]nonane-2,9-dione (12):** Aluminium amalgam, prepared from aluminium foils (1.56 g, 57.8 mmol) and a 0.19 M aqueous solution of mercuric chloride, was added to a solution of epoxy ketone **11** (350 mg, 1.16 mmol) in EtOH/$H_2O$/THF/saturated $NaHCO_3$ (87:48:30:3 v/v, 25 mL) under argon. The reaction mixture was sonicated (TI-H-15Transsonic ultrasonic cleaning unit, 1250 W, max. vol. 14.4/12.2 L) at 35 kHz and 80% of the power for 1 h 30 min at room temperature. After decantation, the mixture was filtered through a pad of Celite and the organic layer was washed with brine, dried with $Na_2SO_4$, filtered, and concentrated. Column chromatography on silica gel (heptane/ethyl acetate, 95:5) furnished β-hydroxy ketone **12** (211.3 mg, 60%) as a pure compound. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.64 (s, 6 H), 1.68 (s, 3 H), 1.72 (m, 2 H), 1.74 (s, 3 H), 1.83 (m, 1 H), 1.85 (m, 1 H), 2.04 (m, 1 H), 2.18 (m, 1 H), 2.25 (m, 1 H), 2.44 (br. d, $J$ = 6.8 Hz, 2 H), 2.66 (m, 1 H), 2.74 (dd, $J$ = 18.4, 2.5 Hz, 1 H), 3.02 (dd, $J$ = 18.5, 4.9 Hz, 1 H), 4.13 (dd, $J$ = 4.6, 2.8 Hz, 1 H), 5.00 (br. t, $J$ = 6.9 Hz, 1 H), 5.26 (br. t, $J$ = 7.7 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.9, 18.0, 20.4, 25.9, 26.2, 29.8, 31.7, 36.7, 41.6, 48.4, 54.2, 68.0, 69.8, 118.7, 120.2, 133.3, 135.8, 210.0, 211.5 ppm. IR: $\tilde{\nu}$ = 3506, 2916, 1727, 1691, 1442, 1376, 1032 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{19}H_{28}NaO_3$ 327.1936; found 327.1960.

**3-Methoxy-2-(3-methylbut-2-enyl)cyclohex-2-enone:** First DIPEA (2.96 mL, 17.0 mmol) and, 5 min later, a solution of 2 M TMS diazomethane in hexanes (8.96 mL, 17.9 mmol) were added to a solution of 2-prenylcyclohexane-1,3-dione (**14**)[6] (2.31 g, 12.8 mmol) in MeOH (5 mL) and $CH_3CN$ (45 mL) under argon at room temperature. The solution was stirred overnight at room temperature and the solvent was removed under reduced pressure to provide a brown oil (2.66 g). Purification on silica gel (heptane/ethyl acetate, 6:4 + 0.5% of TEA) afforded the methyl vinylogous ester (2.30 g, 92%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.57 (s, 3 H), 1.63 (s, 3 H), 1.91 (quint., $J$ = 6.5 Hz, 2 H), 2.26 (br. t, $J$ = 6.4 Hz, 2 H), 2.50 (t, $J$ = 6.2 Hz, 2 H), 2.88 (d, $J$ = 7.2 Hz, 2 H), 3.74 (s, 3 H), 4.98 (br. t, $J$ = 7.2 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.3, 20.5, 20.9, 24.5, 25.4, 36.0, 54.8, 118.7, 122.5, 130.6, 171.3, 197.6 ppm. IR: $\tilde{\nu}$ = 2939, 1718, 1596, 1374, 1168 cm$^{-1}$. HRMS (ESI): $m/z$ calcd. for $C_{12}H_{18}NaO_2$ 217.1204; found 217.1212.

**3-Methyl-2-(3-methylbut-2-enyl)cyclohex-2-enone (15):** A 1.6 M MeLi solution in diethyl ether (10.75 mL, 17.2 mmol) was added to a solution of the above vinylogous ester (2.30 g, 11.84 mmol) in dry THF (41 mL) at 0 °C. After stirring for 30 min at room temperature, the reaction mixture was cooled to 0 °C and treated slowly with 1 N HCl (29 mL, 29 mmol). After stirring for another 30 min at room temperature, the layers were separated and the aqueous layer extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried with $Na_2SO_4$ and the solvent was removed under reduced pressure to give enone **15** (1.97 g, 93%) as a pale yellow oil which was used without any further purification. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.64 (s, 3 H), 1.68 (s, 3 H), 1.91 (quint., $J$ = 6.3 Hz, 2 H), 1.91 (s, 3 H), 2.32 (t, $J$ = 6.1 Hz, 2 H), 2.36 (t, $J$ = 6.4 Hz, 2 H), 2.98 (d, $J$ = 7.0 Hz, 2 H), 4.91 (br. t, $J$ = 6.9 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7, 21.2, 22.2, 24.2, 25.6, 32.8, 37.7, 122.1, 131.2, 134.9, 155.6, 198.5 ppm. IR: $\tilde{\nu}$ = 2926, 1714, 1659, 1429, 1377, 1180, 1120 cm$^{-1}$. HRMS (ESI): $m/z$ calcd. for $C_{12}H_{18}NaO$ 201.1255; found 201.1277.

**3,3-Dimethyl-2-(3-methylbut-2-enyl)cyclohexanone (16):** A 1.55 M MeLi solution in diethyl ether (19.35 mL, 30.0 mmol) was added dropwise to a suspension of CuI (6.0 g, 31.5 mmol) in diethyl ether (56 mL) at 0 °C. After cooling to –78 °C, freshly distilled $BF_3{\cdot}Et_2O$ (3.8 mL, 30.0 mmol) was added dropwise and, after 10 min at that temperature, a solution of enone **15** (534.8 mg, 3.0 mmol) in THF (8 mL) was added. The reaction was stirred for 3 h 30 min at –78 °C and quenched by the addition of saturated aqueous $NH_4Cl$/20% $NH_4OH$ (9:1, 80 mL). The mixture was brought to room temperature and stirring continued under a normal atmosphere until the mixture turned deep blue. The suspension was filtered through Celite, the organic layer separated, and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried with $Na_2SO_4$, filtered, and the solvents evaporated. Column chromatography on silica gel (heptane/ethyl acetate, 97:3) afforded ketone **16** (367.2 mg, 63%) as a colorless oil and starting enone **15** (101.3 mg, 19%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.77 (s, 3 H), 1.04 (s, 3 H), 1.59 (s, 3 H), 1.61 (s, 3 H), 1.72 (m, 2 H), 1.81 (m, 2 H), 2.00 (m, 1 H), 2.12 (dd, $J$ = 7.2, 3.0 Hz, 1 H), 2.25 (m, 1 H), 2.28 (m, 2 H), 5.00 (br. t, $J$ = 7.1 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.6, 22.0, 22.9, 23.1, 25.6, 29.4, 39.0, 39.6, 41.1, 61.6, 123.4, 131.6, 213.0 ppm. IR: $\tilde{\nu}$ = 2962, 2921, 1711, 1460, 1374, 1265 cm$^{-1}$. HRMS (ESI): $m/z$ calcd. for $C_{13}H_{22}NaO$ 217.1568; found 217.1583.

**3,3-Dimethyl-2,6-bis(3-methylbut-2-enyl)cyclohexanone (17):** A 1.1 M BuLi solution in hexanes (1.89 mL, 2.08 mmol) was added to a solution of DIPA (325 μL 2.32 mmol) in THF (4.2 mL) at 0 °C under argon, and stirring was continued for 30 min at the same temperature. At –78 °C a solution of ketone **16** (367.2 mg, 1.89 mmol) in THF (1.9 mL) was added dropwise and stirring was continued for 1 h at the same temperature. Then a solution of 90% prenyl bromide (224 μL, 1.75 mmol) in distilled HMPA (1.3 mL, 7.5 mmol) was added dropwise and the mixture was warmed up slowly to room temperature overnight. A saturated solution of $NH_4Cl$ and ether were added and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were dried with $Na_2SO_4$, filtered, and the solvents evaporated. Column chromatography on silica gel (heptane/ethyl acetate, 98:2) afforded ketone **17** (446.4 mg, 90%) as a colorless oil and as a 73:27 *cis*/*trans* mixture. Only the less polar *cis* epimer was obtained as a pure compound.

***cis* Epimer:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.70 (s, 3 H), 1.10 (s, 3 H), 1.37 (m, 1 H), 1.52 (td, $J$ = 13.6, 4.1 Hz, 1 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.64 (s, 3 H), 1.68 (s, 3 H), 1.74 (dt, $J$ = 13.7, 3.7 Hz, 1 H), 1.94 (m, 1 H), 1.95 (m, 1 H), 2.03 (m, 1 H), 2.18 (m, 1 H), 2.22 (m, 1 H), 2.37 (m, 1 H), 2.38 (m, 1 H), 5.05 (br. t, $J$ = 7.3 Hz, 1 H), 5.07 (br. t, $J$ = 7.5 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.6, 17.8, 20.5, 22.0, 25.7, 25.8, 27.7, 29.9, 30.1, 31.9, 40.8, 51.0, 61.6, 122.2, 124.2, 131.3, 132.7, 212.8 ppm. IR: $\tilde{\nu}$ = 2923, 1710, 1455, 1368 cm$^{-1}$. HRMS (ESI): $m/z$ calcd. for $C_{18}H_{30}NaO$ 285.2194; found 285.2171.

**Ethyl 3-[4,4-Dimethyl-1,3-bis(3-methylbut-2-enyl)-2-oxocyclohexyl]-propanoate (18):** A 1.66 M *t*BuOK solution in THF (560 μL, 0.93 mmol) and, after 15 min at 0 °C, ethyl acrylate (500 μL, 4.6 mmol) were added dropwise to a solution of ketone **17** (1214.2 mg, 4.63 mmol) in THF/dry *t*BuOH (1:1, 5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h 30 min and quenched at that temperature with saturated $NH_4Cl$. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with water, brine, dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure to yield esters **18** which were purified by column chromatography on silica gel (heptane/ethyl acetate, 98:2) to afford, first, the major epimer (637.6 mg, 38%) and then the minor one (462.0 mg, 28%) as colorless oils. HRMS (mixture of epimers) (ESI): $m/z$ calcd. for $C_{23}H_{38}NaO_3$ 385.2719; found 385.2707.

**Less Polar Epimer:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.67 (s, 3 H), 1.09 (s, 3 H), 1.22 (t, $J$ = 7.0 Hz, 3 H), 1.35 (m, 1 H), 1.58 (s, 3 H), 1.60 (br. s, 3 H), 1.61 (br. s, 3 H), 1.64 (m, 2 H), 1.68 (s, 3 H), 1.70 (m, 1 H), 1.77 (m, 1 H), 1.91 (m, 1 H), 1.93 (m, 1 H), 2.07 (m, 1 H), 2.18 (m, 1 H), 2.19 (m, 1 H), 2.20 (m, 1 H), 2.31 (m, 1 H), 2.37 (m, 1 H), 4.09 (q, $J$ = 7.2 Hz, 2 H), 5.05 (m, 1 H), 5.06 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.1, 17.6, 17.9, 20.5, 21.8, 25.5, 26.1, 28.7, 29.7, 30.0, 32.1, 33.0, 36.4, 40.2, 50.5, 57.8, 60.3, 119.5, 124.0, 131.6, 134.1, 173.4, 215.1 ppm.

**More Polar Epimer:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.68 (s, 3 H), 1.08 (s, 3 H), 1.23 (t, $J$ = 7.2 Hz, 3 H), 1.38 (m, 1 H), 1.59 (br. s, 3 H), 1.60 (br. s, 3 H), 1.62 (br. s, 3 H), 1.63 (m, 2 H), 1.64 (br. s, 3 H), 1.68 (m, 1 H), 1.92 (m, 1 H), 1.94 (m, 1 H), 1.94 (m, 1 H), 1.96 (m, 1 H), 2.07 (m, 1 H), 2.27 (m, 1 H), 2.34 (m, 1 H), 2.34 (m, 1 H), 2.59 (m, 1 H), 4.10 (q, $J$ = 6.9 Hz, 2 H), 4.81 (br. t, $J$ = 7.3 Hz, 1 H), 4.98 (br. t, $J$ = 7.4 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.2, 17.6, 18.0, 20.5, 21.9, 25.6, 25.9, 29.2, 30.0, 30.1, 32.0, 33.8, 36.5, 40.1, 50.3, 57.5, 60.2, 118.2, 124.1, 131.0, 134.4, 174.1, 214.5 ppm.

**3-[4,4-Dimethyl-1,3-bis(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoic Acid**

**Major Epimer:** The major ester **18** (500.6 mg, 1.38 mmol) was solubilized in a solution of 85% KOH (110 mg, 1.66 mmol) in MeOH/$H_2O$ (2:1, 5.5 mL) and stirred at room temperature for 24 h. Acetic acid (110 μL, 1.9 mmol) was added to the mixture and an extraction was carried out with dichloromethane. The organic layer was dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure to give the acid (452.4 mg, 98%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.68 (s, 3 H), 1.10 (s, 3 H), 1.37 (m, 1 H), 1.59 (s, 3 H), 1.62 (s, 6 H), 1.69 (m, 2 H), 1.70 (s, 3 H), 1.70 (m, 1 H), 1.87 (m, 1 H), 1.92 (m, 1 H), 1.97 (m, 1 H), 2.03 (m, 1 H), 2.20 (m, 1 H), 2.23 (m, 1 H), 2.30 (m, 1 H), 2.36 (m, 1 H), 2.37 (m, 1 H), 5.05 (m, 1 H), 5.05 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.6, 17.9, 20.5, 21.8, 25.5, 26.0, 28.5, 29.4, 29.9, 32.1, 33.0, 36.3, 40.2, 50.4, 57.9, 119.3, 123.8, 131.9, 134.3, 179.5, 215.1 ppm. IR: $\tilde{\nu}$ = 3400–2400, 2917, 1697, 1438, 1250, 1108 cm$^{-1}$.

**Minor Epimer:** The minor ester **18** was saponified under the same conditions as above and with the same yield. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.69 (s, 3 H), 1.10 (s, 3 H), 1.40 (m, 1 H), 1.60 (s, 3 H), 1.62 (s, 3 H), 1.63 (s, 3 H), 1.65 (m, 2 H), 1.66 (s, 3 H), 1.75 (m, 1 H), 1.90 (m, 1 H), 1.95 (m, 1 H), 1.97 (m, 1 H), 2.09 (m, 1 H), 2.29 (m, 1 H), 2.31 (m, 1 H), 2.32 (m, 1 H), 2.35 (m, 1 H), 2.59 (m, 1 H), 4.82 (br. t, $J$ = 7.3 Hz, 1 H), 4.99 (br. t, $J$ = 7.3 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.6, 18.0, 20.5, 21.9, 25.7, 25.9, 29.0, 29.8, 30.1, 32.0, 33.9, 36.5, 40.2, 50.4, 57.5, 118.0, 124.0, 131.2, 134.6, 179.9, 214.7 ppm.

**7,7-Dimethyl-4a,8-bis(3-methylbut-2-enyl)-3,4,4a,5,6,7-hexahydro-2*H*-chromen-2-one (19):** Oxalyl chloride (51 μL, 0.58 mmol) was added dropwise to a solution of the major above acid (163.0 mg, 0.49 mmol) in dichloromethane (5.3 mL) containing one drop of dry DMF at room temperature. The reaction was stirred overnight and the solvent and excess reagents were removed under reduced pressure to yield the acid chloride (172.0 mg, quant.). IR: $\tilde{\nu}$ = 2926, 1798, 1702, 1451, 1368, 1120 cm$^{-1}$. TMSOTf (20 μL, 0.11 mmol) was added to a solution of the acid chloride (100.0 mg, 0.28 mmol) in dry dichloromethane (2 mL) at 0 °C and the mixture was stirred for 3 h 30 min at 0 °C. TEA (70 μL, 0.5 mmol) was added to the reaction and, after dilution with diethyl ether (4 mL) and water (4 mL), the phases were separated and the aqueous layer was extracted with diethyl ether (2 × 5 mL). The organic extracts were combined and dried with $Na_2SO_4$. Concentration and purification by silica gel chromatography (dichloromethane) provided the enol lactone **19** (64.7 mg, 73%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.76 (s, 3 H), 1.06 (s, 3 H), 1.36 (m, 1 H), 1.54 (m, 2 H), 1.60 (m, 1 H), 1.62 (s, 3 H), 1.65 (s, 3 H), 1.67 (s, 3 H), 1.72 (s, 3 H), 1.75 (m, 1 H), 1.77 (m, 1 H), 2.17 (m, 2 H), 2.51 (m, 2 H), 2.77 (d, $J$ = 6.6 Hz, 2 H), 4.97 (br. t, $J$ = 6.8 Hz, 1 H), 5.06 (br. t, $J$ = 7.4 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 18.1, 21.8, 24.5, 25.7, 26.0, 26.6, 27.9, 29.9, 30.3, 33.1, 34.9, 36.6, 43.3, 118.9, 123.6, 126.4, 130.4, 134.8, 148.1, 170.1 ppm.

**(1*S**,5*R**,8*R**)-8-Hydroxy-2,2-dimethyl-1,5-bis(3-methylbut-2-enyl)bicyclo[3.3.1]nonan-9-one (20):** A 1 M $LiAlH(OtBu)_3$ solution in dry THF (0.15 mL, 150 μL) was slowly added to a solution of lactone **19** (38.1 mg, 0.12 mmol) in dry THF (120 μL) at –78 °C. The mixture was stirred for 30 min at –78 °C, warmed up to room temperature for 1 h, quenched by the addition of cold brine (2 mL), and filtered through Celite. The aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL), dried with $Na_2SO_4$, filtered, and concentrated. Column chromatography on silica gel (heptane/ethyl acetate, 95:5) furnished alcohol **20** (37.6 mg, 98%) as a very viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.87 (s, 3 H), 1.11 (s, 3 H), 1.23 (m, 1 H), 1.47 (m, 1 H), 1.61 (s, 3 H), 1.62 (m, 1 H), 1.71 (br. s, 3 H), 1.718 (br. s, 3 H), 1.720 (br. s, 3 H), 1.78 (m, 1 H), 1.79 (m, 2 H), 1.96 (m, 1 H), 2.14 (m, 2 H), 2.26 (m, 1 H), 2.37 (dd, $J$ = 15.6, 9.0 Hz, 1 H), 2.56 (br. d, $J$ = 16.4 Hz, 1 H), 4.38 (br. s, 1 H), 5.16 (br. t, $J$ = 7.0 Hz, 1 H), 5.41 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 17.9, 25.2, 25.3, 26.07, 26.12, 26.5, 31.6, 31.9, 36.1, 36.1, 36.6, 43.5, 48.0, 61.6, 74.8, 120.2, 122.6, 133.7, 134.1, 218.1 ppm. IR: $\tilde{\nu}$ = 3510, 2922, 1705, 1451, 1376 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{21}H_{34}NaO_2$ 341.2457; found 341.2447.

**8,8-Dimethyl-1,5-bis(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-2,9-dione (21):** Starting from alcohol **20**, the procedure described for the synthesis of **9** gave ketone **21** (89%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.83 (s, 3 H), 1.10 (s, 3 H), 1.33 (m, 1 H), 1.60 (s, 3 H), 1.63 (s, 6 H), 1.73 (s, 3 H), 1.74 (m, 1 H), 1.81 (m, 2

H), 1.82 (m, 2 H), 2.14 (m, 1 H), 2.26 (m, 2 H), 2.34 (m, 1 H), 2.51 (m, 1 H), 2.59 (m, 1 H), 4.84 (br. t, $J$ = 7.1 Hz, 1 H), 5.20 (br. t, $J$ = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.8, 18.0, 23.0, 25.3, 25.7, 25.9, 26.1, 28.2, 35.8, 36.0, 36.5, 41.3, 45.6, 47.9, 73.1, 119.4, 119.8, 133.8, 134.5, 211.6, 213.2 ppm. IR: $\tilde{\nu}$ = 2967, 2926, 1694, 1453, 1373, 1264, 1152 cm$^{-1}$. HRMS (ESI): $m/z$ calcd. for $C_{21}H_{32}NaO_2$ 339.2300; found 339.2292.

**Ethyl 3-[(1*R**,5*S**)-4,4-Dimethyl-1,3,5-tris(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoate (23):** A 1.66 M *t*BuOK solution in THF (464 μL, 0.77 mmol) and, after 15 min at 0 °C, ethyl acrylate (425 μL, 3.9 mmol) were added dropwise to a solution of a 70:30 mixture of *trans*- and *cis*-**22**[6] (1267.2 mg, 3.83 mmol) in THF/dry *t*BuOH (1:1, 4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and quenched at that temperature with saturated $NH_4Cl$. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with water, brine, dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure. The two epimers could barely be separated by column chromatography on silica gel (heptane/ethyl acetate, 99:1) to afford *cis*-**23** (179.4 mg, 11%) and *trans*-**23** (501.1 mg, 30%) as colorless oils (and 646.7 mg of a mixture of *cis*-**23** + starting ketone). For the mixture of epimers: IR: $\tilde{\nu}$ = 2917, 1729, 1446, 1318, 1189 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{28}H_{46}NaO_3$ 453.3345; found 453.3338.

**Ethyl 3-[(1*R**,3*S**,5*S**)-4,4-Dimethyl-1,3,5-tris(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoate (*cis*-23):** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.56 (s, 3 H), 1.12 (s, 3 H), 1.23 (t, $J$ = 7.2 Hz, 3 H), 1.25 (m, 1 H), 1.58 (s, 6 H), 1.61 (s, 6 H), 1.69 (s, 3 H), 1.71 (s, 3 H), 1.72 (m, 2 H), 1.78 (m, 1 H), 1.79 (m, 1 H), 1.80 (m, 1 H), 2.00 (m, 1 H), 2.06 (m, 1 H), 2.18 (m, 1 H), 2.18 (m, 2 H), 2.22 (m, 1 H), 2.39 (m, 1 H), 2.40 (m, 1 H), 4.09 (q, $J$ = 7.2 Hz, 2 H), 5.06 (m, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.2, 15.1, 17.6, 17.8, 17.9, 21.7, 25.5, 25.8, 26.1, 26.6, 28.7, 28.7, 30.5, 32.3, 39.8, 43.3, 43.4, 50.8, 58.3, 60.4, 119.5, 123.5, 124.1, 131.7, 132.4, 134.1, 173.5, 215.1 ppm.

**Ethyl 3-[(1*R**,3*R**,5*S**)-4,4-Dimethyl-1,3,5-tris(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoate (*trans*-23):** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.79 (s, 3 H), 0.94 (s, 3 H), 1.12 (m, 1 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 1.54 (m, 2 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 1.62 (s, 6 H), 1.66 (s, 3 H), 1.68 (m, 1 H), 1.69 (s, 3 H), 1.94 (m, 1 H), 1.94 (m, 1 H), 2.03 (m, 1 H), 2.08 (m, 2 H), 2.09 (m, 1 H), 2.19 (m, 2 H), 2.31 (m, 1 H), 2.36 (m, 1 H), 4.09 (q, $J$ = 7.2 Hz, 2 H), 4.92 (m, 1 H), 4.94 (m, 1 H), 5.07 (br. t, $J$ = 7.3 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.2, 17.6, 17.82, 17.85, 22.4, 22.9, 23.8, 25.66, 25.69, 25.9, 28.2, 28.2, 29.3, 34.2, 35.7, 40.3, 43.3, 51.2, 56.9, 60.2, 118.9, 123.3, 123.4, 131.8, 132.9, 134.0, 173.8, 217.0 ppm.

**3-[(1*R**,3*R**,5*S**)-4,4-Dimethyl-1,3,5-tris(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoic Acid (*trans* 24):** The *trans* ester **23** (267.0 mg, 0.62 mmol) was solubilized in a solution of 85% KOH (54 mg, 0.8 mmol) in MeOH/$H_2O$ (2:1, 1.2 mL) and stirred at room temperature for 24 h. Acetic acid (50 μL, 0.87 mmol) was added to the mixture and an extraction was carried out with dichloromethane. The organic layer was dried with $Na_2SO_4$, filtered, and the solvent removed under reduced pressure to give the *trans* acid **24** (243.9 mg, 98%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.80 (s, 3 H), 0.95 (s, 3 H), 1.11 (m, 1 H), 1.57 (m, 2 H), 1.57 (s, 3 H), 1.60 (s, 3 H), 1.62 (br. s, 3 H), 1.63 (br. s, 3 H), 1.67 (s, 3 H), 1.70 (s, 3 H), 1.72 (m, 1 H), 1.76 (m, 1 H), 1.91 (m, 1 H), 1.93 (m, 1 H), 2.05 (m, 1 H), 2.10 (m, 2 H), 2.26 (m, 2 H), 2.32 (m, 1 H), 2.38 (m, 1 H), 4.92 (m, 1 H), 4.93 (m, 1 H), 5.07 (br. t, $J$ = 7.2 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7, 17.8, 17.9, 22.4, 22.8, 23.7, 25.7 (2 C), 25.9, 28.0, 28.1, 29.0, 34.3, 35.7, 40.4, 43.4, 51.2, 56.8, 118.7, 123.2, 123.3, 131.9, 133.1, 134.2, 180.0, 217.0 ppm. IR: $\tilde{\nu}$ = 3400–2400, 2913, 1700, 1445, 1308, 1112 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for $C_{26}H_{42}NaO_3$ 425.3032; found 425.3030.

**3-[(1*R**,3*S**,5*S**)-4,4-Dimethyl-1,3,5-tris(3-methylbut-2-enyl)-2-oxocyclohexyl]propanoic Acid (*cis*-24):** Starting from the *cis* ester **23**, the above procedure gave, with the same yield, the *cis* acid **24** as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.57 (s, 3 H), 1.14 (s, 3 H), 1.26 (m, 1 H), 1.29 (m, 1 H), 1.59 (s, 6 H), 1.62 (m, 2 H), 1.63 (s, 6 H), 1.70 (m, 1 H), 1.71 (s, 3 H), 1.72 (s, 3 H), 1.79 (m, 1 H), 1.82 (m, 1 H), 2.00 (m, 1 H), 2.10 (m, 1 H), 2.20 (m, 1 H), 2.23 (m, 2 H), 2.38 (m, 1 H), 2.39 (m, 1 H), 5.05 (m, 1 H), 5.06 (m, 1 H), 5.10 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 15.1, 17.6, 17.9 (2 C), 21.7, 25.5, 25.8, 26.1, 26.6, 28.4, 28.7, 30.2, 32.3, 39.8, 43.4, 43.5, 50.7, 58.4, 119.3, 123.5, 124.0, 132.0, 132.5, 134.3, 179.5, 215.0 ppm.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