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Diels−Alder Cycloaddition Approach to Puupehenone-Related Metabolites: Synthesis of the Potent Angiogenesis Inhibitor 8-Epipuupehedione

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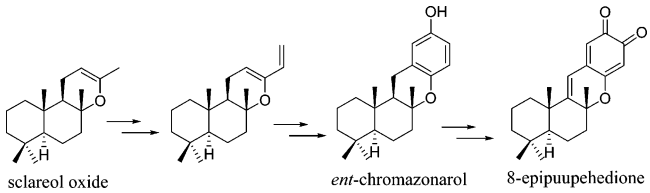
Received December 28, 2006



A new synthetic strategy toward puupehenone-related bioactive metabolites from sclareol oxide, based on a Diels−Alder cycloaddition approach, is described. Utilizing this, marine *ent*-chromazonarol and the potent angiogenesis inhibitor 8-epipuupehedione have been synthesized.

Introduction

Puupehenones belong to an important group of marine metabolites of mixed biosynthesis, which are constructed of drimane and polyphenolic moieties.[1] These compounds have become of great interest mainly due to the wide variety of biological activities they exhibit.[2] Some of them have more recently been described as potent angiogenesis[3] and lipoxygenase inhibitors,[3b] which greatly increases their pharmaceutical potential.

Representative examples of this type of compounds are puupehenone (**1a**)[4] and some derivatives bearing different substituents on C-4, C-9, C-15, or C-21, such as hydroxyl,[5] cyano,[4b] halogen[4a,c] or acyl groups,[5] puupehedione (**2a**),[4b] 15-cyanopuupehenol (**3**),[6] and 15-oxopuupehenol (**4a**).[2h,7] Other structurally related compounds are the marine *ent*-chromazonarol (**5**),[8] the antibacterial antibiotic hongoquercin A (**6**),[9] isolated from a terrestrial fungus, and the marine drimenyl hydroquinones

† In memory of my father.

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10.1021/jo0626663 CCC: $37.00
Published on Web 03/28/2007

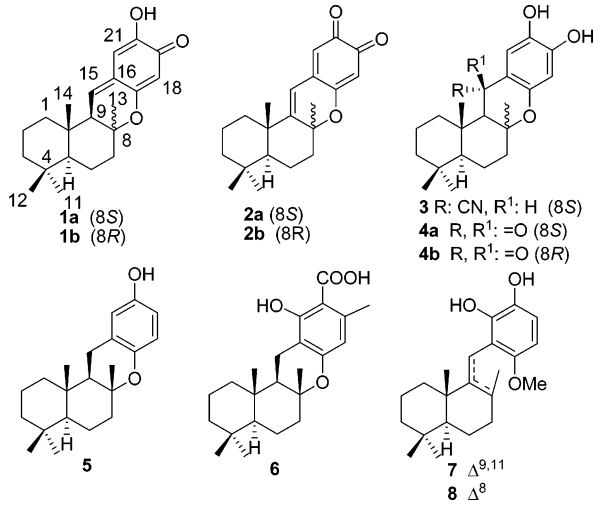


FIGURE 1. Examples of puupehenone (**1a**)-related metabolites.

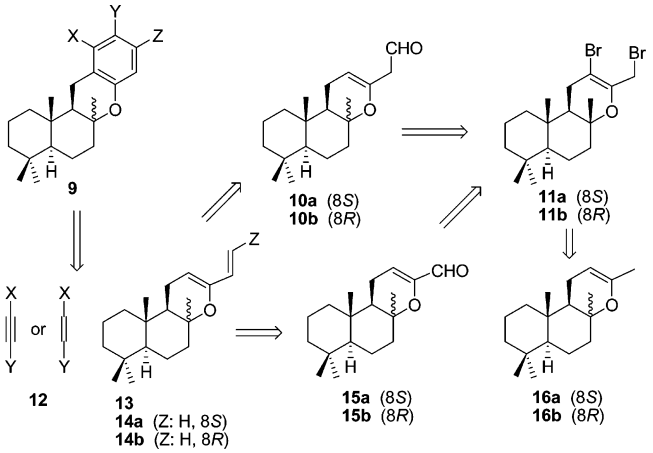
wiedendiol A (**7**) and wiedendiol B (**8**), which are potential antiatherosclerosis agents as these inhibit cholesteryl ester transfer protein (Figure 1).[10]

The important properties of these compounds have encouraged chemists to study their synthesis. In all reported approaches, the strategy involves the initial formation of a suitably functionalized bicyclic terpenoid unit and the subsequent construction of a pyran ring. The carbon skeleton of these compounds has been elaborated through the reaction of an aryllithium derived from a suitably protected polyphenol with an acyclic (farnesane derivative)[11] or bicyclic (drimane derivative)[5,11b,12] electrophile, or alternatively by the reaction of a nordrimane anion with a protected polyhydroxybenzaldehyde.[13]

A variety of procedures, the stereoselectivity of which determines the C-8 stereochemistry, have been utilized to accomplish the further C pyran ring construction. Electrophilic acid,[8b,c,11a,12c] selenium induced[12a] or palladium(II)[7] promoted cyclizations of a drimenyl phenol have been used for this purpose. Electrocyclization of a conjugated tetraenone also enables generation of the pyran ring.[12c,13] An alternative procedure involves the oxygen attack of an 8-hydroxydrimane on the adjacent aromatic ring.[12d]

Very recently, a new strategy to synthesize hongoquercin A (**6**) has been reported. The sequence involves the simultaneous construction of the pyran and aromatic rings via the formal oxa-[3+3] cycloaddition of an α,β-unsaturated drimane aldehyde and a substituted 1,3-cyclohexanedione.[9c]

SCHEME 1. Retrosynthetic Analysis of Target Compounds



Results and Discussion

Continuing our research into the synthesis of this type of bioactive compound from abundant natural diterpenes, we have planned a new strategy to elaborate the merosesquiterpene tetracyclic skeleton based on a Diels−Alder cycloaddition approach (Scheme 1). The target compound **9** should be obtained after aromatization of the adduct, resulting from the reaction of a diene **14**, containing the tricyclic pyran unit, with the appropriate dienophile **12**.

In the first approach we have undertaken the synthesis of the marine metabolite *ent*-chromazonarol (**5**), which could also be a suitable intermediate to access 8-epipuupehenone-related compounds, such as the potent angiogenesis inhibitor 8-epipuupehedione (**2b**).[3a] Compound **5** could be obtained after the reaction of methyl propiolate with diene **14b**, which will be synthesized from aldehydes **10b** or **15b**, via dibromide **11b**, starting from sclareol oxide (**16b**), whose efficient synthesis from sclareol we have reported previously.[14]

Treatment of enol ether **16b** with NBS (2.2 equiv) in dry MeOH at 0 °C and further reaction at 25 °C for 3 h gave the dibromoketal **17** in 80% yield, which after treatment with *p*-toluenesulphonic acid in $CHCl_3$ led to the dibromide **11b** in 95% yield (Scheme 2). Sclareol oxide (**16b**) can be directly converted into compound **11b**, utilizing a modification of Vlad's procedure.[15] The transformation of dibromide **11b** into aldehyde **10b** was then addressed; this was sought to be achieved by reduction of the corresponding bromonitrile resulting from the cyanation of allyl bromide. However, all attempts to substitute the allylic bromine by cyanide were unsuccessful. Therefore, the alternative route toward diene **14b**, involving aldehyde **15b**,[16] was investigated. Two procedures were developed to elaborate the precursor alcohol **19**. The first involves the preparation of the acetate **18** by treating the dibromide **11b** with NaOAc and its further saponification with K_2CO_3 in MeOH. The second method is based on the treatment of compound **11b** with K_2CO_3 in DMSO at 120 °C. In all cases, the obtained allyl alcohol

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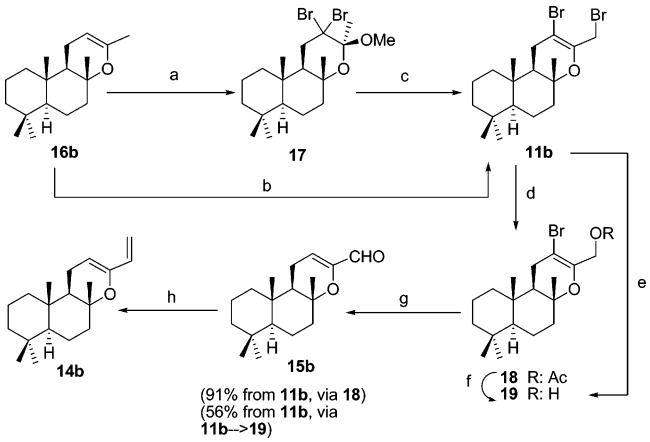
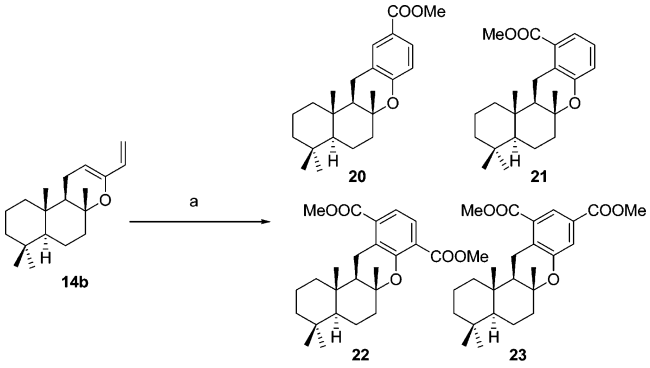
SCHEME 2. Synthesis of Diene 14b from Sclareol Oxide (16b)[a]



[a] Reagents and conditions: (a) NBS (2.2 equiv), MeOH, 0 °C to rt, 3 h, 80%; (b) NBS (2.2 equiv), AcOH (4 equiv), $CHCl_3$, 0 °C, 15 h, 93%; (c) TsOH, $CHCl_3$, rt, 15 min, 95%; (d) AcONa (3 equiv), DMF, 70 °C, 15 h, 97%; (e) K_2CO_3 (5 equiv), DMSO, 120 °C, 15 h; (f) K_2CO_3, MeOH, rt, 1 h; (g) TsOH, CH_2Cl_2, rt, 5 min; (h) $MePPh_3^+$ Br^-, BuLi, THF, 0 °C, 15 min, 94%.

SCHEME 3. Diels−Alder Cycloaddition of Diene 14b with Methyl Propiolate[a]



[a] Reagents and conditions: (a) methyl propiolate (2.5 equiv), Δ, DDQ, dioxane, rt, 5 min.

was found to be very unstable, quickly undergoing partial decomposition and transformation into aldehyde **15b**, which was obtained in low yields (20−40%) after column chromatography of the dark crude mixture reaction. This difficulty was circumvented by treating the partially evaporated ethereal solution of the crude alcohol with *p*-toluenesulphonic acid in CH_2Cl_2; in this way, aldehyde **15b** was obtained in 91% yield from **11b** via acetate **18**. During the course of this research, Snider et al., have reported the synthesis of aldehyde **15b** from sclareol oxide (**16b**); these authors describe the instability of alcohol **19**, resulting from the saponification of acetate **18** and its spontaneous conversion into aldehyde **15b**;[16] and the mechanism these authors proposed for this transformation, based on the protonation of the double bond of **19** and subsequent deprotonation of the CH_2OH group to give a bromo enol, which loses HBr affording compound **15b**, is corroborated by our results.

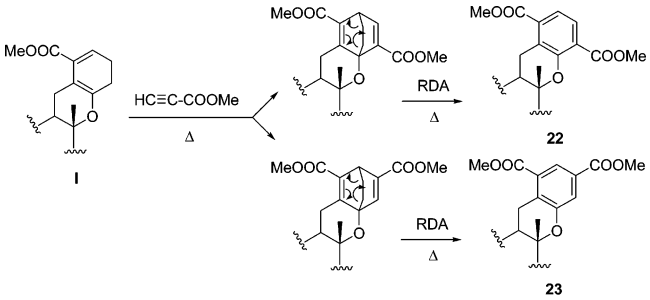
We then tackled the construction of the aromatic ring of the target molecules through the Diels−Alder reaction. The reaction of methyl propiolate with diene **14b** under different experimental conditions was studied; the crude material resulting from cycloaddition was treated with DDQ in dioxane for 15 min before isolation. In all cases, the desired ester **20** was obtained,

TABLE 1. Diels−Alder Cycloadditions of Diene 14b with Methyl Propiolate

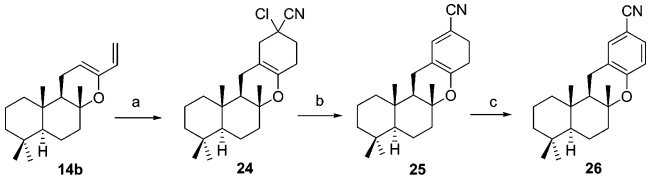
entry	solvent	*T* °C	reaction time (d)	**20**:**21**:**22**:**23**[a]
1	benzene	reflux	3	no reaction
2	toluene	100	2.5	13:2:4:1
3	toluene	reflux	2	7.5:1:2.5:1.5
4	toluene	100	5	9:1:2.8:1.4
5	toluene	reflux	5	6:0:3:1

[a] Relative proportion deduced from the ^1H NMR spectrum of crude reaction after treatment with DDQ.

SCHEME 4. Mechanism for the Formation of Diesters 22 and 23



SCHEME 5. Synthesis of Nitrile 26 from Diene 14b[a]



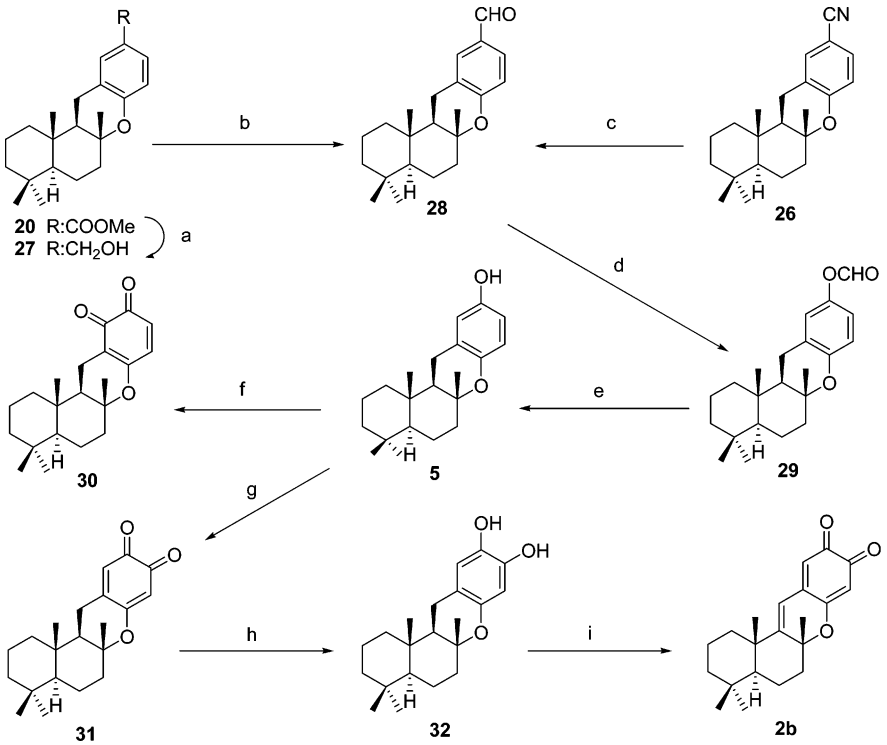
[a] Reagents and conditions: (a) α-chloroacrylonitrile, toluene, reflux, 4 days, 70%; (b) DBU, benzene, reflux, 2 h, 85%; (c) DDQ, dioxane, rt, 1 h, 93%.

together with variable amounts of its regioisomer **21** and diesters **22** and **23** (Scheme 3; Table 1). When the temperature is increased or the reaction time is longer, the proportion of ester **21** decreases and that of diesters **22** and **23** becomes higher. The best results were obtained with toluene at 100 °C for 2.5 days (65% yield of compound **20** from diene **14b**; entry 2).

Diesters **22** and **23** should be formed after a second Diels−Alder cycloaddition on diene **I**, resulting from the isomerization of the adduct precursor of compound **21**, followed by a retro Diels−Alder process with extrusion of ethylene (Scheme 4). Diene **I**, less stable and more accessible to the dienophile attack than the corresponding diene precursor of ester **20**, undergoes the DA-RDA sequence leading to the diesters **22** and **23**, before the aromatization that produces the monoester **21**. Experimental data seem to support the proposed mechanism. The aromatic ester **21**, which is formed from diene **I**, was not obtained after long-term reaction under reflux, while the proportion of diester **22**, resulting from the RDA reaction, was increased (Table 1, entry 5).

An alternative process to the above Diels−Alder cycloaddition, utilizing α-chloroacrylonitrile as dienophile, has also been investigated. The reaction of this nitrile with diene **14b** in toluene under reflux for 4 days took place with complete regioselectivity, affording adduct **24** in 70% yield. Diene nitrile **25** was obtained when compound **24** was refluxed with DBU in benzene. Treatment of nitrile **25** with DDQ in dioxane at room temperature led to aromatic nitrile **26** (Scheme 5).

SCHEME 6. Synthesis of *ent*-Chromazonarol (5) and 8-Epipuupehedione (2b) from Ester 20[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 10 min, 96%; (b) PDC, CH_2Cl_2, rt, 3 h, 93%; (c) DIBAH, THF, −78 °C, 2 h, 71%; (d) MCPBA (1.2 equiv), CH_2Cl_2, rt, 12 h, 91%; (e) K_2CO_3, MeOH, rt, 15 min, aq HCl, 97%; (f) $(PhSeO)_2O$, THF, reflux, 15 min, 82%; (g) $(KSO_3)_2NO$, acetone, H_2O, rt, 15 h, 85%; (h) $NaBH_4$, EtOH, rt, 5 min, 98%; (i) DDQ, dioxane, 60 °C, 6 h, 81%.

Finally, the synthesis of 8-epipuupehedione (**2b**), via *ent*-chromazonarol (**5**), was undertaken (Scheme 6). The key intermediate is the aldehyde **28**, which was easily obtained from ester **20** or nitrile **26**. Compound **5** was obtained by saponification of formate **29**, resulting from the Baeyer−Villiger oxidation of aldehyde **28**. The oxidation of phenol **5** to the appropriate ortho-quinone precursor of target compound **2b** was then addressed. A mixture of quinones and degradation products resulted under different oxidizing conditions, but the reaction with Fremy's salt and benzeneseleninic anhydride took place with complete regioselectivity. Thus, the oxidation of compound **5** with $(KSO_3)_2NO$ in acetone−H_2O at room temperature gave 8-epi-9,11-dihydropuupehedione (**31**); the preference for the C-19 oxidation is in accordance with the results previously reported for 3,4-disubstituted phenols and has been attributed to steric effects.[17] However, the treatment of *ent*-chromazonarol (**5**) with $(PhSeO)_2O$ in THF under reflux led to quinone **30**. Only one example of regioselective oxidation with this oxidizing reagent, involving the transformation of β-naphthol into 1,2-naphthoquinone, has been found in the literature;[18] this result could be expected considering both the stability of the resulting quinone and the preferent electrophilic attack on the C-1.[19] However, the justification of the ortho versus ortho' regioselectivity reported now seems rather less clear-cut and will require further studies. Finally, the reduction of quinone **31** with $NaBH_4$ yielded 8-epipuupehenol (**32**), which after treatment with DDQ in dioxane under reflux afforded 8-epipuupehedione (**2b**), whose spectroscopic properties were identical to those previously reported.[12c]

In summary, a new strategy for puupehenone-related metabolites, based on a Diels−Alder cycloaddition approach, has been developed. When this was utilized, the potent angiogenesis inhibitor 8-epipuupehedione (**2b**) was synthesized from sclareol oxide (**16b**); in this case, the methodology reported here prevents the obtention of the 8-epimer **2a**, which is also formed in some cases when the electrophilic cyclization methodology is utilized.[12c] The scope of this new methodology, using different dienes and dienophiles, is under study. The use of quinone **30** for synthesizing wiedendiol-type metabolites, after pyran ring opening, is being investigated.

Experimental Section

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2,2-Dibromo-3-methoxy-3,4a,7,7,10a-pentamethyl-2,3,4a,5,6,6a,7,8,9,10,10a,10b-dodecahydro-1*H*-benzo[*f*]chromene (17). *N*-Bromosuccinimide (5.95 g, 33.44 mmol) was added to a stirred solution of **16b** (4 g, 15.2 mmol) in dry methanol (40 mL) at 0 °C, and the yellow solution was stirred at this temperature for 3 h. Then the precipitated solid was filtered, washing with water. After drying in vacuo over P_2O_5, pure **17** (5 g, 73%) was obtained. From the filtrate a second crop (0.5 g, 7%) was obtained after standing overnight: $[\alpha]_D^{25} = +106.5$ (*c* 1.1, $CHCl_3$); mp 120−121 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.30 (s, 3H), 2.76 (dd, $J = 13.8$, 12.5 Hz, 1H), 2.46 (dd, $J = 13.8$ and 1.9 Hz, 1H), 2.10 (dd, $J = 12.5$, 1.9 Hz, 1H), 1.65−180 (m, 3H), 1.64

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(19) For studies on the mechanism of the benzeneseleninic anhydride oxidation, see: (a) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473−1476. (b) Barton, D. H. R.; Finet, J.- P.; Thomas, M. *Tetrahedron* **1988**, *44*, 6397−6406.

(s, 3H), 150−163 (m, 2H), 1.45 (m, 1H), 1.40 (m, 2H), 1.31 (m, 1H), 1.8 (m, 1H), 1.37 (s, 3H), 0.99 (dd, J = 12.4 and 2.3 Hz, 1H), 0.85 (s, 3H), 0.81 (s, 3H), 0.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.5 (C-1), 18.4 (C-2), 41.9 (C-3), 33.4 (C-4), 56.4 (C-5), 19.8(C-6), 42.0 (C-7), 78.3 (C-8), 51.6 (C-9), 36.9 (C-10), 39.1 (C-11), 77.7 (C-12), 102.1 (C-13), 21.2 (C-14), 33.3 (C-15), 21.8 (C-16), 17.1 (C-17), 23.5 (C-18), 56.4 (C−OMe); IR (KBr) 1459, 1378, 1313, 1246, 1221, 1173, 1108, 1051, 957, 933, 879, 840, 716 cm^{-1}; MS-EI *m*/*z* (relative intensity) 422 (22), 340 (19), 259 (8), 201(6), 191(100), 177 (39), 149 (7).

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-3-(bromomethyl)-4a,7,7,-10a-tetramethyl 4a,5,6,6a,7,8,9,10,10a,10b-Decahydro(1*H*)benzo-[*f*]chromene (11b) from 17. To a solution of **17** (1 g, 2.21 mmol) in $CHCl_3$ (20 mL) was added *p*-toluenesulphonic acid (0.25 g, 1.31 mmol) and the solution immediately darkened. After stirring for 15 min at room temperature, TLC indicated no remaining starting material. The solvent was evaporated under vacuum to give a crude product that was dissolved in ether (30 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), water, and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give pure **11b** (0.88 g, 95%) as a colorless syrup.

(3S,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-3-(bromomethyl)-4a,7,7,-10a-tetramethyl 4a,5,6,6a,7,8,9,10,10a,10b-Decahydro(1*H*)benzo-[*f*]chromene (11b) from 16b. NBS (17.8 g, mmol) was added slowly to a stirred solution of **16b** (8 g, 30.53 mmol) and acetic acid (7.13 g, mmol) in $CHCl_3$ (125 mL) at 0 °C. After stirring for 15 h at room temperature, TLC indicated no remaining starting material. The solvent was removed to give a crude product that was dissolved in ether (100 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 20 mL), water, and brine. The organic phase was dried over Na_2SO_4 and concentrated to give pure **11b** (11.86 g, 93%)

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-4a,7,7,10a-tetramethyl 4a,5,6,-6a,7,8,9,10,10a,10b-Decahydro(1*H*)benzo[*f*]chromene-3-carbox-aldehyde (15b) from 11b. K_2CO_3 (6.9 g, 49.9 mmol) was added to a stirred solution of **11b** (5 g, 12.6 mmol) in DMSO (50 mL), and the reaction mixture was heated at 100 °C for 15 h. Then it was extracted with ether (2 × 50 mL), the organic phase was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated. After this, *p*-toluenesulphonic acid (1 g, 5.25 mmol) was added to a solution of crude product in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature for 15 min. Then it was diluted with ether (40 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product that was purified by flash chromatography on silica gel (H/E, 9:1) to give **15b** (1.95 g, 56%) as a yellow syrup.

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-3-(methylacetate)-4a,7,7,-10a-tetramethyl 4a,5,6,6a,7,8,9,10,10a,10b-Decahydro(1*H*)benzo-[*f*]chromene (18). To a solution of **11b** (4 g, 9.57 mmol) in anhydrous DMF (35 mL) was added AcONa (2.35 g, 28.6 mmol), and the mixture was stirred at 70 °C for 15 h. Then the mixture was extracted with ether (2 × 60 mL), the organic phase was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give pure **18** (3.69 g, 97%) as a colorless syrup.

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-4a,7,7,10a-tetramethyl4a,5,6,-6a,7,8,9,10,10a,10b-Decahydro(1*H*)benzo[*f*]chromene-3-carbox-aldehyde (15b) from 18. K_2CO_3 (2 g, 14.49 mmol) was added to a stirred solution of **18** (3.69 g, 9.28 mmol) in MeOH (15 mL), and the mixture was kept stirring at room temperature for 1 h. Then the solvent was removed under reduced pressure and the crude product was fractionated in water/ether (70 mL, 1:3). The organic phase was washed with water and brine, dried over Na_2SO_4, and after removing approximately four-fifth of the solvent, it was diluted with CH_2Cl_2 (15 mL), *p*-toluenesulphonic acid (0.5 g, 2.625 mmol) was added, and the mixture was stirred at room temperature for 15 min. Then it was diluted with ether (40 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give pure **15b** (2.4 g, 94%).

(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-2-Bromo-4a,5,6,6a,7,8,9,10,10a,10b-decahydro(1*H*)-4a,7,7,10a-tetramethyl-3-vinyl-benzo[*f*]-chromene (14b). A 2 M solution of *n*-butyllithium in cyclohexane (12 mL) was added slowly under an argon atmosphere to a stirred suspension of methyltriphenylphosphonium bromide (7.76 g, 21.7 mmol) in dry THF (30 mL) at 0 °C. The mixture was allowed to warm to room temperature after stirring for 20 min, a solution of **15b** (3 g, 10.86 mmol) in dry THF (20 mL) was added dropwise at 0 °C, and the reaction mixture was further stirred for 15 min. Then water (1 mL) was added to quench the reaction and the solvent was removed under vacuum. The crude product was fractionated in water/ether (30 mL) and extracted with ether (2 × 20 mL). The dried organic layers were evaporated, and the residue was directly purified by flash chromatography (H/E, 95:5) to yield diene **14b** (2.8 g, 94%) as a colorless syrup: $[\alpha]_D^{25}$ = +3.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.04 (dd, J = 17.1, 10.7 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 4.92 (d, J = 10.7 Hz, 1H), 4.76 (dd, J = 4.8, 2.6 Hz, 1H), 2.10−1.8 (m, 3H), 1.78−1.53 (m, 4H), 1.51−1.20 (m, 4H), 1.16 (m, 1H), 1.15 (s, 3H), 0.99 (dd, J = 12.5, 2.2 Hz, 1H), 0.92 (m, 1H), 0.91 (s, 3H), 0.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4 (C-1), 18.6 (C-2), 41.1 (C-3), 33.2 (C-4), 56.3 (C-5), 19.0 (C-6), 39.4 (C-7), 76.1 (C-8), 52.6 (C-9), 36.8 (C-10), 19.8 (C-11), 101.9 (C-12), 148.5 (C-13), 20.0 (C-14), 33.5 (C-15), 21.6 (C-16), 15.0 (C-17), 133.3 (C-18), 11.4 (C-19); IR (film) 1655, 1601, 1459, 1156, 1126, 1047, 905, 781, 700 cm^{-1}; MS-EI *m*/*z* (relative intensity) 191(41), 177 (45), 149 (17), 137 (51), 123 (43), 69 (100), 55 (95); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{30}ONa$, 297.2194; found, 297.2200.

Diels−Alder Reaction of 14b and Methyl Propiolate. Methyl propiolate (0.65 g, 7.73 mmol) was added to a solution of diene **14b** (1 g, 3.64 mmol) in toluene (20 mL), and the mixture was heated at 100 °C for 2.5 days. At this time, TLC showed no remaining starting material. The reaction was allowed to cool to room temperature and then concentrated in vacuo to give an unresolvable mixture of adducts (1.3 g). To a solution of this crude product in 1,4-dioxane (15 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.5 g, 6.63 mmol), and the reaction mixture was stirred at room temperature for 15 min. The solvent was evaporated in vacuo, and the residue was dissolved in ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (5 × 15 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product with quantitative mass recovery. The ^{1}H NMR spectrum of the crude product indicated a 13:2:4:1 mixture of **20**:**21**:**22**:**23**, respectively. After column chromatography (H/E, 9:1) 0.84 g of **20** (65%), 128 mg of **21** (10%), 0.3 g of **22** (20%), and 75 mg of **23** (5%), as colorless syrups, were obtained.

Methyl-[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,-12b-decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-10-carboxylate (20). $[\alpha]_D^{25}$ = +11.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 8.5, 1.8 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 2.65 (m, 2H), 2.08 (dt, J = 12.2, 2.1 1H), 1.84−1.55 (m, 4H), 1.52−1.24 (m, 3H), 1.20 (s, 3H), 1.18 (m, 2H), 1.02 (dd, J = 12.3, 1.8 Hz, 1H), 0.95 (m, 1H), 0.90 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1 (C-1), 18.5 (C-2), 40.9 (C-3), 33.2 (C-4), 56.0 (C-5), 19.7 (C-6), 41.7 (C-7), 78.2 (C-8), 51.8 (C-9), 36.8 (C-10), 20.9 (C-11), 33.4 (C-12), 21.5 (C-13), 14.9 (C-14), 22.1 (C-15), 121.3 (C-16), 128.9 (C-17), 122.1 (C-18), 131.9 (C-19), 116.8 (C-20), 157.5 (C-21), 167.1 (*C*OOMe), 51.8 (COO*Me*); IR (film) 1718, 1582, 1601, 1497, 1436, 1388, 1263, 1192, 1126, 938, 804, 757 cm^{-1}; MS-EI *m*/*z* (relative intensity) 356 (18), 341 (9), 271 (5), 245 (13), 217(10), 203 (17), 191 (82), 165 (43), 121 (40), 95 (75), 69 (93), 55 (100); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{32}O_3Na$, 379.2249; found, 379.2249.

**Methyl-[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,-12b-decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-11-

carboxylate (21). $[\alpha]_D^{25} = +12.2$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (dd, $J = 5.7$, 0.9 Hz, 1H), 7.11 (t, $J = 6.0$ Hz, 1H), 6.93 (dd, $J = 6.0$, 0.9 Hz, 1H), 3.87 (s, 3H), 3.06 (dd, $J = 13.5$, 3.6 Hz, 1H), 2.82 (dd, $J = 13.5$, 9.9 Hz, 1H), 2.06 (dt, $J = 12.3$, 2.0 Hz, 1H), 1.85−1.70 (m, 2H), 1.70−1.50 (m, 4H), 1.50−1.30 (m, 2H), 1.27−1.10 (m, 2H), 1.18 (s, 3H), 1.02 (dd, $J = 12.1$, 2.1 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1 (C-1), 18.4 (C-2), 41.0 (C-3), 33.2 (C-4), 56.2 (C-5), 19.7 (C-6), 41.9 (C-7), 72.8 (C-8), 51.7 (C-9), 36.9 (C-10), 20.6 (C-11), 33.4 (C-12), 21.6 (C-13), 14.8 (C-14), 25.6 (C-15), 124.9 (C-16), 130.1 (C-17), 126.6 (C-18), 121.6 (C-19), 122.6 (C-20), 153.7 (C-21), 167.9 (*C*OOMe), 51.8 (COO*Me*); IR (film) 1723, 1582, 1457, 1379, 1272, 1192, 1128, 1082, 1022, 942, 756 cm^{-1}; MS-EI *m/z* (relative intensity) 356 (17), 341 (4), 277 (7), 218 (8), 203 (15), 191 (46), 177, 165 (43), 159 (27), 149 (12), 137 (21), 123 (22), 121 (40), 109 (25), 95 (31), 81 (38), 69 (64), 55 (100); HRMS (FAB) *m/z* calcd for $C_{23}H_{32}O_3Na$, 379.2249; found, 379.2245.

Dimethyl-[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2H)-1,3,4,4a,5,6,6a,12,12a,-12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene-8,11-dicarboxylate (22). $[\alpha]_D^{25} = +22.4$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, $J = 8.1$ Hz, 1H), 7.41 (d, $J = 8.1$, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.05 (dd, $J = 15.5$, 5.2 Hz, 1H), 2.85 (dd, $J = 15.5$, 13.3 Hz, 1H), 2.10 (m, 1H), 1.85−1.70 (m, 2H), 1.68−1.53 (m, 2H), 1.50−1.35 (m, 4H), 1.30−1.10 (m, 2H), 1.22 (s, 3H), 1.04 (dd, $J = 12.4$, 1.8 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (C-1), 18.6 (C-2), 40.8 (C-3), 33.4 (C-4), 56.3 (C-5), 19.9 (C-6), 42.0 (C-7), 77.5 (C-8), 51.1 (C-9), 36.8 (C-10), 20.8 (C-11), 33.6 (C-12), 21.8 (C-13), 14.9 (C-14), 22.0 (C-15), 123.6 (C-16), 133.0 (C-17), 125.9 (C-18), 127.8 (C-19), 120.9 (C-20), 153.2 (C-21), 167.3 (*C*OOMe), 166.8 (*C*OOMe), 52.2 (COO*Me*), 52.2 (COO*Me*); IR (film) 1724, 1602, 1571, 1434, 1411, 1388, 1290, 1193, 1139, 1081, 1026, 941, 807, 756 cm^{-1}; MS-EI *m/z* (relative intensity) 414 (3), 399 (12), 203 (5), 191 (54), 177 (6), 163 (13),149 (18), 137 (21), 123 (45), 121 (37), 109 (38), 95 (59), 69 (81), 55 (100); HRMS (FAB**)** *m/z* calcd for $C_{25}H_{34}O_5Na$, 437.2304; found, 437.2307.

Dimethyl-[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,-12b-decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-9,11-dicarboxylate (23). $[\alpha]_D^{25} = +10.7$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, $J = 2.3$ Hz, 1H), 7.87 (d, $J = 2.3$ Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.67 (m, 2H), 2.10 (dt, $J = 12.3$, 2.9 Hz, 1H), 1.90−1.1.30 (m, 8H), 1.21 (s, 3H), 1.18 (m, 2H), 1.04 (dd, $J = 12.3$, 1.8 Hz, 1H), 0.89 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0 (C-1), 18.5 (C-2), 40.6 (C-3), 33.4 (C-4), 56.0 (C-5), 19.7 (C-6), 41.8 (C-7), 79.3 (C-8), 51.2 (C-9), 36.9 (C-10), 21.0 (C-11), 33.2 (C-12), 21.5 (C-13), 14.9 (C-14), 22.5 (C-15), 119.6 (C-16), 135.0 (C-17), 123.9 (C-18), 131.2 (C-19), 120.6 (C-20), 157.4 (C-21), 166.1 (*C*OOMe), 166.5 (*C*OOMe), 51.9 (COO*Me*), 51.9 (COO*Me*); IR (film) 1722, 1606, 1435, 1411, 1388, 1312, 1157, 1125, 1080, 1008, 931, 802, 757 cm^{-1}; MS-EI *m/z* (relative intensity) 414 (7), 399 (5), 383 (5), 367 (4), 277(7), 245 (6), 223 (9), 203 (5), 191 (75), 177 (12), 163 (17), 149 (22), 137 (28), 123 (39), 121 (40), 109 (44), 95 (52), 69 (84), 55 (100); HRMS (FAB) *m/z* calcd for $C_{25}H_{34}O_5Na$, 437.2304; found, 437.2299.

Diels−Alder Reaction of 14b Utilizing the Experimental Conditions of Entry 1 (Table 1). Reaction of **14b** (0.5 g, 1.82 mmol) with methyl propiolate (0.325 g, 3.86 mmol) utilizing the experimental conditions shown in Table 1 (Entry 1) gave the unreacted starting material.

Diels−Alder Reaction of 14b Utilizing the Experimental Conditions of Entry 3 (Table 1). Reaction of **14b** (0.5 g, 1.82 mmol) with methyl propiolate (0.325 g, 3.86 mmol) under the experimental conditions shown in Table 1 (entry 3) and the further treatment with DDQ (0.75 g, 3.31 mmol) in 1,4-dioxane (12 mL) gave 660 mg of a mixture of compounds **20**−**23** (relative proportion 7.5:1:2.5:1.5).

Diels−Alder Reaction of 14b Utilizing the Experimental Conditions of Entry 4 (Table 1). Reaction of **14b** (0.5 g, 1.82 mmol) with methyl propiolate (0.325 g, 3.86 mmol) utilizing the experimental conditions shown in Table 1 (entry 4) and the further treatment with DDQ (0.75 g, 3.31 mmol) in 1,4-dioxane (10 mL) gave 0.62 g of a mixture of compounds **20**−**23** (relative proportion 9:1:2.8:1.4).

Diels−Alder Reaction of 14b Utilizing the Experimental Conditions of Entry 5 (Table 1). Reaction of **14b** (0.5 g, 1.82 mmol) with methyl propiolate (0.325 g, 3.86 mmol) utilizing the experimental conditions show in Table 1 (entry 5) and the further treatment with DDQ (0.75 g, 3.31 mmol) in 1,4-dioxane (10 mL) gave 0.63 g of a mixture of compounds **20**−**23** (relative proportion 6:0:3:1).

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b,17,18,-19,20-Tetradecahydro-10-chloro-4,4,6a,12b-tetramethyl-benzo-[*a*]xanthen-10-carbonitrile (24). Methyl 2-chloro-acrylonitrile (0.875 g, 10 mmol) was added to a solution of diene **14b** (1 g, 3.64 mmol) in toluene (20 mL), and the mixture was refluxed (oil bath) for 4 days, at which time TLC showed no **14b**. After evaporating the solvent in vacuo, 1.4 g of a crude product was obtained. Flash chromatography on silica gel (hexane/ether, 95:5) gave 0.92 mg of **24** (70%) as a yellow syrup: $[\alpha]_D^{25} = +10.4$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.89 (br s, 1H), 2.76 (dd, $J = 18.9$, 4.9 Hz, 1H), 2.65 (dd, J =13.9, 1.9 Hz, 1H), 2.45 (dd, $J = 18.9$, 13.9 Hz, 1H), 2.35 (dt, $J = 12.9$, 3.4 Hz, 1H), 2.15 (m, 1H), 2.10−1.85 (m, 2H), 1.84−1.35 (m, 8H), 1.32 (m, 2H), 1.23 (s, 3H), 1.04 (dd, $J = 12.3$, 2.1 Hz, 1H), 0.97 (m,1H), 0.90 (s, 3H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.9 (C-1), 18.3 (C-2), 41.4 (C-3), 33.2 (C-4), 56.0 (C-5), 19.4 (C-6), 41.7 (C-7), 78.7 (C-8), 49.9 (C-9), 36.5 (C-10), 21.4 (C-11), 33.3 (C-12), 22.6 (C-13), 14.9 (C-14), 22.7 (C-15), 110.6 (C-16), 45.4 (C-17), 72,8 (C-18), 30.1 (C-19), 25.1 (C-20), 156.6 (C-21), 118.3 (*C*N); IR (film) 2214, 1720, 1683, 1619, 1459, 1389, 1313, 1216, 1173, 1157, 1126, 1109, 1082, 1032, 976, 936, 756. cm^{-1}; MS-EI *m/z* (relative intensity) 361 (5), 325 (31), 253 (17), 192 (33), 191 (100), 177 (13), 172 (23), 137 (48); HRMS (FAB) *m/z* calcd for $C_{22}H_{32}ONClNa$, 384.2070; found, 384.2073.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b,19,20-Dodecahydro-10-cyano-4,4,6a,12b-tetramethyl-benzo[*a*]xanthen (25). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 2 equiv) was added to a stirred solution of **24** (0.5 g, 1.38 mmol) in benzene (15 mL), and the mixture was stirred under reflux for 2 h, at which time TLC showed no **24**. Then it was diluted with ether (30 mL) and washed with 1 M aqueous HCl and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield 0.38 g of pure **25** (85%) as a yellow syrup: $[\alpha]_D^{25} = +10.5$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.54 (s, 1H), 2.43 (t, $J = 9.6$ Hz, 2H), 2.38−2.17 (m, 2H), 1.95 (dt, $J = 12.4$, 2.2 Hz, 1H), 1.92 (m, 1H), 1.73 (m, 1H), 1.64−1.50 (m, 3H), 1.48−1.37 (m, 3H), 2.32 (m, 1H), 1.18 (m, 2H), 1.16 (s, 3H), 0.97 (dd, $J = 12.4$, 2.0 Hz, 1H), 0.90 (m, 1H), 0.89 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.5 (C-1), 18.7 (C-2), 40.8 (C-3), 33.6 (C-4), 56.3 (C-5), 19.9 (C-6), 42.0 (C-7), 79.4 (C-8), 52.8 (C-9), 37.1 (C-10), 20.9 (C-11), 33.4 (C-12), 21.7 (C-13), 15.3 (C-14), 20.8 (C-15), 103.5 (C-16), 144.2 (C-17), 96.9 (C-18), 24.9 (C-19), 26.7 (C-20), 154.5 (C-21), 121.2 (*C*N); IR (film) 2200, 1652, 1565, 1459, 1381, 1342, 1262, 1193, 1155, 1124 1079, 1042, 972, 757 cm^{-1}; MS-EI *m/z* (relative intensity) 325 (7), 212 (3), 191 (77), 177 (14), 172 (25), 137 (22), 69 (100); HRMS (FAB) *m/z* calcd for $C_{22}H_{31}ONNa$, 348.2303; found, 348.2299.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-10-cyano-4,4,6a,12b-tetramethyl-benzo[*a*]xanthen (26). A solution of **25** (0.3 g, 0.923 mmol) in 1,4-dioxane (10 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 313 mg, 1.38 mmol) were kept stirring at room temperature for 1 h. The solvent was evaporated in vacuo, and the residue was dissolved in ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (5 × 15 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4

and concentrated to give 277 mg of pure **26** (93%) as a yellow syrup: $[\alpha]_D^{25} = +21.0$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (br s,1H), 7.36 (br d, $J = 8.1$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 2.62 (m, 2H), 2.08 (dt, $J = 12.3$, 3.1 Hz, 1H), 1.80−1.50 (m, 5H), 1.42−1.22 (m, 3H), 1.20 (s, 3H), 1.19−1.10 (m, 2H), 1.02 (dd, $J = 12.3$, 2.1 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (C-1), 18.5 (C-2), 40.9 (C-3), 33.2 (C-4), 56.1 (C-5), 19.7 (C-6), 41.8 (C-7), 78.9 (C-8), 51.6 (C-9), 37.0 (C-10), 21.0 (C-11), 33.4 (C-12), 21.6 (C-13), 15.0 (C-14), 22.1 (C-15), 123.4 (C-16), 134.0 (C-17), 102.4 (C-18), 131.1 (C-19), 117.8 (C-20), 157.0 (C-21), 119.5 (*C*N); IR (film) 2223, 1609, 1577, 1493, 1460, 1388, 1310, 1263, 1193, 1156, 1125, 1080, 1042, 937, 823, 756 cm^{-1}; MS-EI *m*/*z* (relative intensity) 323 (12), 308 (11), 238 (5), 212 (9), 191 (54), 170 (29), 156 (13), 137 (19), 132 (28), 69 (100); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{29}ONNa$, 346.2147; found, 346.2150.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-10-carboxaldehyde (28) from 26. A 1 M solution of DIBAL-H in hexane (1.5 mL, 1.5 mmol) was added slowly to a stirred solution of **26** (0.2 g, 0.619 mmol) in THF (10 mL) at 0 °C. After stirring for 30 min, TLC indicated no starting nitrile **26** remained. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the cooling bath was removed. After stirring for 2 h, the mixture was poured into water (5 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (hexane/ether, 9:1) to give 143 mg (71%) of **28** as a colorless syrup: $[\alpha]_D^{25} = +57.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (s, 1H), 7.61 (s, 1H), 7.60 (br d, $J = 8.9$ Hz, 1H), 6.85 (d, $J = 8.9$ Hz, 1H), 2.68 (m, 2H), 2.10 (dt, $J = 12.3$, 2.9 Hz, 1H), 1.90−1.58 (m, 5H), 1.56−1.30 (m, 2H), 1.28−1.10 (m, 2H), 1.22 (s, 3H), 1.01 (dd, $J = 12.3$, 2.1 Hz, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (C-1), 18.5 (C-2), 40.9 (C-3), 33.2 (C-4), 56.1 (C-5), 19.7 (C-6), 41.8 (C-7), 78.7 (C-8), 51.8 (C-9), 36.9 (C-10), 21.0 (C-11), 33.4 (C-12), 21.6 (C-13), 14.8 (C-14), 22.1 (C-15), 122.9 (C-16), 129.5 (C-17), 129.1 (C-18), 132.4 (C-19), 117.7 (C-20), 159.1 (C-21), 190.9 (*C*HO); IR (film) 1689, 1602, 1578, 1494, 1387, 1324, 1260, 937, 825, 756 cm^{-1}; MS-EI *m*/*z* (relative intensity) 326 (20), 311 (13), 241 (9), 215 (14), 191 (66), 187 (12), 173 (31), 159 (25), 135 (93), 123 (34), 121 (41), 109 (41), 95 (46), 81 (36), 69 (66), 55 (100); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{30}O_2$-Na, 349.2143; found, 349.2141.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-10-hydroxymethyl-4,4,6a,12b-tetramethyl-benzo[*a*]xanthen (27). $LiAlH_4$ (0.3 g, 7.9 mmol) was added to a stirred solution of **20** (0.75 g, 2.10 mmol) in dry THF (10 mL) cooled to 0 °C (ice/water), and the reaction mixture was kept stirred in an argon atmosphere for 10 min, at which time TLC showed no remaining starting material. Then 2 N HCl (0.5 mL) was added slowly, and it was extracted with ether (2 × 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 0.66 g of pure **27** (96%) as a colorless syrup: $[\alpha]_D^{25} = +23.1$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (s, 1H), 7.04 (d, $J = 7.9$, 1H), 6.72 (d, $J = 7.9$ Hz, 1H), 4.54 (s, 2H), 2.61 (m, 2H), 2.18 (s, 1H), 2.05 (dt, $J = 12.4$, 2.1 Hz, 1H), 1.90−1.55 (m, 5H), 1.52−1.35 (m, 3H), 1.30−1.10 (m, 2H), 1.20 (s, 3H), 1.01 (dd, $J = 12.4$, 1.9 Hz, 1H), 0.93 (m, 1H), 0.92 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (C-1), 18.5 (C-2), 41.1 (C-3), 33.2 (C-4), 56.1 (C-5), 19.7 (C-6), 41.8 (C-7), 77.0 (C-8), 52.0 (C-9), 36.9 (C-10), 20.8 (C-11), 33.4 (C-12), 21.6 (C-13), 14.9 (C-14), 22.3 (C-15), 122.4 (C-16), 129.1 (C-17), 132.1 (C-18), 126.4 (C-19), 117.0 (C-20), 152.9 (C-21), 65.2 (*C*H_2OH); IR (film) 3404, 1615, 1587, 1498, 1459, 1378, 1309, 1255, 1193, 1126, 1080, 938, 822, 756 cm^{-1}; MS-EI *m*/*z* (relative intensity) 328 (26), 311 (9), 243 (2), 191 (63), 175 (31), 159 (23), 137 (64), 121 (45), 123 (34), 121 (41), 69 (90), 55 (100); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{32}O_2Na$, 351.2300; found, 351.2297.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-10-carboxaldehyde (28) from 27. Pyridinium dichromate (PDC; 0.86 g, 2.28 mmol) was added to a stirred solution of **27** (0.5 g, 1.52 mmol) in dry CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature in an argon atmosphere for 3 h, at which time TLC showed no remaining starting material. Then the reaction was worked up by the addition of CH_2Cl_2 (10 mL), and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether/CH_2Cl_2 (10:30 mL). The solvent was evaporated to yield 460 mg of pure **28** (93%) as a colorless syrup.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthen-10-yl formate (29). *m*-Chloroperbenzoic acid (MCPBA, 75%; 0.365 g, 1.58 mmol) was added at room temperature to a stirred solution of **28** (0.4 g, 1.22 mmol) in CH_2Cl_2 (15 mL). After stirring for 14 h, TLC indicated no starting aldehyde **28** remaining. The reaction was quenched with saturated aqueous Na_2SO_3 (1 mL), and the reaction mixture was stirred for an additional 45 min. Then the mixture was poured into ether/water (30:10 mL), the organic phase was washed with saturated aqueous $NaHCO_3$ (6 × 10 mL) and brine, and dried over anhydrous Na_2SO_4. After evaporating the solvent in vacuo, 379 mg of pure **29** (91%) was obtained as a colorless syrup: $[\alpha]_D^{25} = +4.2$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (s, 1H), 6.82 (s, 1H), 6.80 (br d, $J = 7.4$ Hz, 1H), 6.73 (d, $J = 7.4$ Hz, 1H), 2.61 (d, $J = 9.0$ Hz, 2H), 2.05 (dt, $J = 12.5$, 2.3 Hz, 1H), 1.90−1.52 (m, 5H), 1.50−1.30 (m, 3H), 1.15 (m, 1H), 1.20 (s, 3H), 1.01 (dd, J= 12.5, 1.9 Hz, 1H), 0.91 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.3 (C-1), 18.7 (C-2), 41.2 (C-3), 33.4 (C-4), 56.3 (C-5), 19.9 (C-6), 42.0 (C-7), 77.1 (C-8), 51.9 (C-9), 36.8 (C-10), 21.0 (C-11), 33.6 (C-12), 21.8 (C-13), 15.1 (C-14), 22.6 (C-15), 123.5 (C-16), 119.8 (C-17), 142.7 (C-18), 122.0 (C-19), 117.9 (C-20), 151.1 (C-21), 160.2 (O*C*HO); IR (film) 1738, 1490, 1387, 1260, 1125, 754, 668 cm^{-1}; MS-EI *m*/*z* (relative intensity) 342 (15), 327 (4), 297 (2), 257 (3), 231 (5), 217(3), 203 (6), 191 (68), 177 (19), 161 (27), 151 (18), 137 (27), 123 (49), 109 (43), 95 (49), 81 (85), 55 (75), 46 (100); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{30}O_3Na$, 365.2093; found, 365.2096.

Synthesis of *ent*-Chromazonarol (5). K_2CO_3 (0.5 g, 3.61 mmol) was added to a cooled (0 °C) solution of **29** (0.35 g, 1.02 mmol) in MeOH (5 mL), and the reaction mixture was stirred for 15 min, at which time TLC showed no **29**. The reaction was quenched with 2 N HCl (2 mL) and the cooling bath was removed. The mixture was poured into ether/water (30:10 mL), and it was extracted with ether (2 × 15 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 310 mg of **5** (97%) as a colorless syrup.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-10,11-dione (30). Benzeneseleninic anhydride (0.36 g, 1 mmol) was added to a stirred solution of **5** (50 mg, 0.159 mmol) in dry THF (7 mL) in an argon atmosphere. The reaction mixture was heated under reflux (oil bath) for 15 min, at which time TLC showed no **5**. The reaction was allowed to cool to room temperature and then concentrated in vacuo to give a crude product, which was purified by flash chromatography on florisil (100−200 Mesh; H/E, 3:2), affording 43 mg of **30** (82%) as a red syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (d, $J = 7.8$ Hz, 1H), 6.27 (d, $J = 7.8$ Hz, 1H), 2.60 (dd, $J = 9.6$, 5.2 Hz, 1H), 2.10 (dt, $J = 12.4$, 2.4 Hz, 1H), 2.05 (dd, $J = 13.2$, 9.6 Hz, 1H), 1.90−1.55 (m, 4H), 2.42−2.35 (m, 3H), 2.32−1.05 (m, 2H), 1.23 (s, 3H), 0.92 (m, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4 (C-1), 18.6 (C-2), 40.5 (C-3), 33.4 (C-4), 56.1 (C-5), 19.9 (C-6), 41.9 (C-7), 82.9 (C-8), 51.5 (C-9), 37.4 (C-10), 21.1 (C-11), 33.6 (C-12), 21.7 (C-13), 15.3 (C-14), 16.1 (C-15), 114.1 (C-16), 181.2 (C-17), 177,3 (C-18), 139.7 (C-19), 129.2 (C-20), 161.7 (C-21); IR (film) 1689, 1602, 1578,

1494, 1387, 1324, 1260, 937, 825, 756 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{21}H_{28}O_3Na$, 351.1936; found, 351.1935.

[(4a*S*,6a*R*,12a*R*,12b*S*)]-(2*H*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-4,4,6a,12b-tetramethyl Benzo[*a*]xanthene-9,10-dione (31). Potassium nitrosodisulfonate (0.5 g, 1.86 mmol) and disodium hydrogen phosphate (0.5 g, 2.8 mmol) were added to a stirred solution of **5** (0.25 g, 0.796 mmol) in acetone (15 mL) and water (1 mL). After stirring for 16 h, TLC indicated no **5**, the solvent was evaporated, and the crude product was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 222 mg of **31** (85%) as a red syrup.

Synthesis of 8-Epipuupehenol (32). Sodium borohydride (70 mg, 1.84 mmol) was added to a stirred solution of **31** (0.2 g, 0.613 mmol) in EtOH (7 mL), and the reaction mixture was stirred at room temperature for 10 min at which time TLC showed no **31**. The reaction mixture was quenched at 0 °C with 2 N HCl (1 mL), the solvent was evaporated, and the crude product was diluted with ether (20 mL) and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give 197 mg of **32** (98%) as a colorless syrup.

Synthesis of 8-Epipuupehedione (2b). A solution of **32** (100 mg, 0.305 mmol) in 1,4-dioxane (10 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 275 g, 1.216 mmol) was stirred at 60 °C for 6 h, at which time TLC showed no **32**. Following the same workup used for **25**, 80 mg of **2b** was obtained (81%), as a red solid.

Acknowledgment. The authors thank the Spanish Ministry of Science and Technology (Project CTQ2006-12697) and the "Junta de Andalucia" (PAI group FQM-348) for their financial support.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **2b**, **14b**, **17**, and **20**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0626663