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Synthetic studies of furanosesquiterpenoid tetrahydrolinderazulenes. Total synthesis of (±)-echinofuran

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Dedicated to Professor Al Padwa on the occasion of his 65th birthday

Abstract—Echinofuran (**1**) was isolated in 1992 and was reported to inhibit cell division of fertilized sea urchin eggs. The synthesis of **1** was achieved by a Ring A→Ring AC→Ring ABC approach employing 3-methyl-4-(trimethylsilyl)furan (**2**) as a precursor. A Suzuki coupling reaction and a Lewis acid mediated Friedel-Crafts cyclization were the other key steps in the construction of the ring systems. In other preliminary model studies, two furan-containing 5,7,5-fused tricyclic molecules were also realized.

1. Introduction

In recent years, many sesquiterpene metabolites were identified from species of gorgonians.[1] These compounds have been shown to exhibit interesting biological activities including cytotoxicity, antifungal activity, and immunostimulatory activity.[2] Echinofuran (**1**),[3] a kind of furanosesquiterpenoid tetrahydrolinderazulene isolated from the gorgonian *Echinogorgia praelonga*, was found to inhibit cell division of fertilized sea urchin eggs.[4]

Herein, we would like to employ our own organosilicon–organoboron protocol devised towards the synthesis of 3,4-disubstituted furans to achieve the total synthesis of echinofuran (**1**).[5,6] It is noteworthy that similar approaches have been employed by Tanis[7] and Schultz[8] in their quests of pseudoquaianolide sesquiterpenes. In our own synthetic approach, a route involving the sequential construction of Ring A→Ring AC→Ring ABC was designed to construct the target molecule **1** (Fig. 1). The key steps involved are the Suzuki-type cross-coupling reaction,[9,10] which is responsible for the formation of Ring AC and the Lewis acid promoted Friedel-Crafts acylation, which is responsible for the formation of Ring ABC.

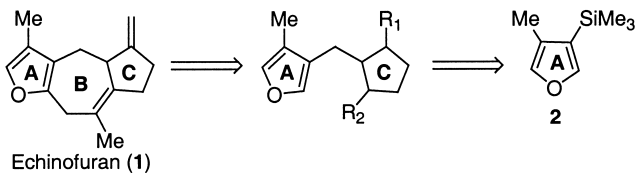

Figure 1.

2. Result and discussion

As depicted in Scheme 1, our strategy makes use of 3-methyl-4-(trimethylsilyl)furan (**2**)[5f,11] as the precursor, which in turn was prepared by a Diels–Alder reaction between 4-phenyloxazole[12] and 1-trimethylsilylpropyne with concomitant extrusion of benzonitrile[5f] under high temperature and pressure. Furan **2** was converted to boroxine **3** upon reaction with boron trichloride.[5f] As expected, **3** smoothly underwent a regiospecific Suzuki cross-coupling reaction with ethyl 4-bromo-3-methoxy-crotonate[13] to give ester **4**. After hydrolysis, β-ketoester **5** was obtained and a route involving alkylation-intramolecular Wittig cyclization was designed by utilizing 3-iodopropyltriphenylphosphonium iodide,[14] leading to ester **6** that provided the basic structure of Ring AC.

In order to construct the central seven-membered ring, one more carbon was required at the ethyl ester side chain of **6**. Acid **9** was eventually obtained from **6** via **7** and **8** by a classical nucleophilic substitution method illustrated in Scheme 2.

Keywords: furan; tricyclic; Lewis acid cyclization.
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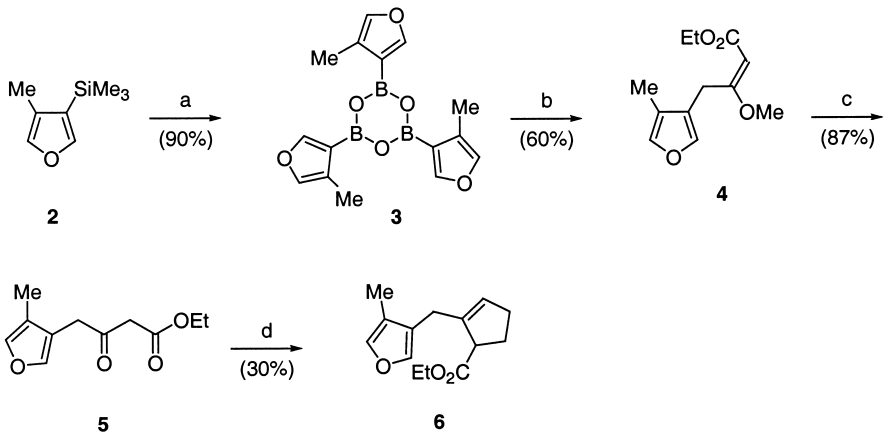
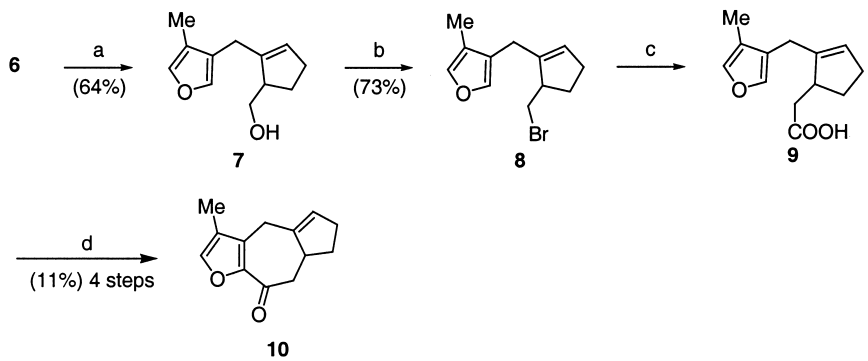


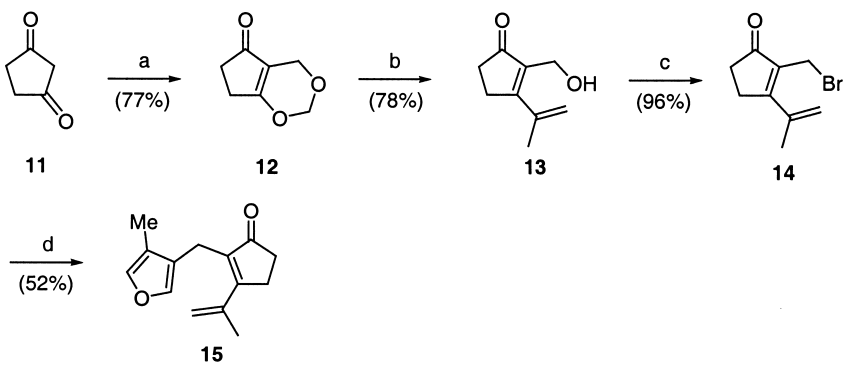
Scheme 1. *Reagents and conditions*. (a) (i) BCl_3, CH_2Cl_2, −78°C, 6 h, (ii) 2 M Na_2CO_3, 2 h. (b) Ethyl 4-bromo-3-methoxycrotonate, $Pd(PPh_3)_4$, 2 M K_3PO_4, THF, reflux. (c) *p*-TsOH, EtOH–H_2O (1:1). (d) 3-Iodopropyltriphenylphosphonium iodide, K_2CO_3, CH_2Cl_2, 18-crown-6, reflux.

Without further purification acid **9** was immediately subjected to an intramolecular Friedel-Crafts acylation. Trifluoroacetic anhydride (TFAA) was found to be the most effective reagent in promoting the cyclization,[15] leading to the formation of the cycloheptenone **10** (Ring ABC). Despite the meager yield of the TFAA-catalyzed cyclization, the synthesis of **10** has nonetheless provided a viable approach towards tetrahydrolinderazulenes. However, the total synthesis of **1** may require more efficient and elaborate synthetic routes. Consequently, we initiated a new program to study alternative cyclization reactions of furans towards the formation of seven-membered rings.

Like other aromatic compounds, furans are able to undergo electrophilic substitutions. However, due to the low stability of furan-containing compounds, low reaction temperatures and mild catalysts are usually required. In our model studies, we placed our attention on improving the efficiency of the cyclization by altering the structure of Ring C in the hope of enhancing the intramolecular cyclization. In this connection, we generated dienone **15** through four steps starting from 1,3-cyclopentanedione (**11**), a commercially available starting material (Scheme 3). According to the literature,[16] 1,3-cyclopentanedione (**11**) was converted to 1,3-dioxin **12** and was followed by an alkylative 1,3-ketone

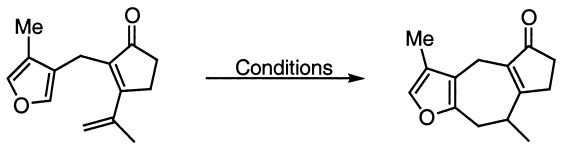


Scheme 2. *Reagents and conditions*. (a) $LiAlH_4$, THF. (b) NBS, PPh_3, DMF. (c) (i) KCN, 18-crown-6, CH_3CN, (ii) NaOH, MeOH, reflux, (iii) 1 M HCl. (d) TFAA, CH_2Cl_2, 0°C.



Scheme 3. *Reagents and conditions*. (a) $(CH_2O)_n$, BF_3–Et_2O, CH_2Cl_2. (b) (i) 2-Bromopropene, ^{t}BuLi, THF, −78°C, (ii) 2N HCl. (c) PBr_3, Et_2O, 0°C. (d) Boroxine **3**, $Pd(PPh_3)_4$, 2 M K_3PO_4, THF, reflux.

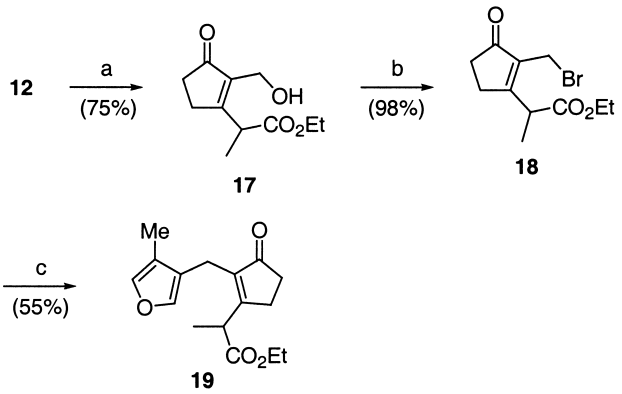
Table 1.



15 16

Reagents	Temperature (°C)	Time (h)	Yield (%)
$FeCl_3$	0, −78	0.1	0[a,b]
$TiCl_4$	0, −78	0.1	0[b]
BF_3–Et_2O	0, −78	0.1	0[b]
$EtAlCl_2$	−20	15	40
Et_2AlCl	0	10	65

[a] 20% of **15** was recovered.
[b] Polymerization.



Scheme 4. *Reagents and conditions*. (a) (i) Ethyl propionate, LDA, THF, −78°C, (ii) 2N HCl. (b) PBr_3, Et_2O, 0°C. (c) Boroxine **3**, $Pd(PPh_3)_4$, 2 M K_3PO_4, THF, reflux.

transposition to afford alcohol **13**. After bromination of **13**, the resulting bromide **14** was allowed to undergo a Suzuki coupling with **3**, affording **15** whose conjugated dienone framework was believed to facilitate the Lewis acid catalyzed cyclization.[17]

Thus, different reaction conditions were attempted to convert **15** to **16** (Table 1). As can be seen, weak Lewis acid and low temperature were both needed to secure a better yield of **16**. With **16** (Ring ABC) in hand, attempts had been made in vain to achieve our target compound **1**, the major difficulty being the position of the C–C double bond. Although **16** did not lead us to **1**, it may still serve as a useful intermediate towards the preparation of tetrahydrolinderazulenes.

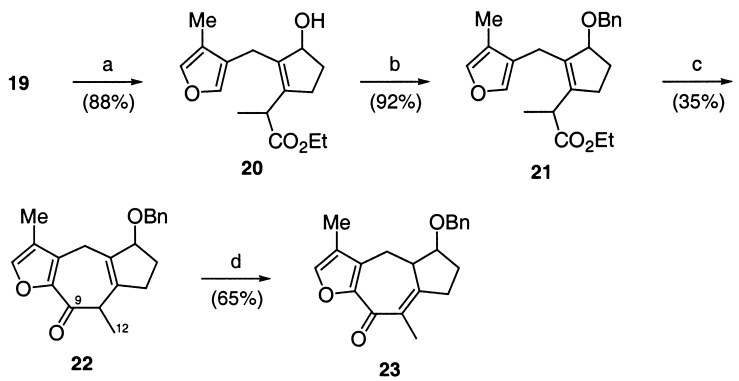
Ester **19** was synthesized in the same way as that for **15** through three steps from 1,3-dioxin **12** (Scheme 4). 1,3-Cyclopentanedione (**11**) was converted to 1,3-dioxin **12** and was followed by an alkylative 1,3-ketone transposition to afford alcohol **17**. After bromination of **17**, the resulting bromide **18** was allowed to undergo a Suzuki coupling with **3**, affording **19**.

To complete our total synthesis of **1**, enone **19** was first reduced to enol **20** by $NaBH_4$ and the resulting hydroxyl group was protected as benzyl ether **21**. Saponification of **21** with NaOH was followed immediately without further purification by a Friedel-Crafts cyclization, leading to **22**, with the desired Ring ABC skeleton very similar to our target molecule. An isomerization reaction was undertaken to convert the β,γ-unsaturated ketone **22** to an α,β-unsaturated ketone **23**. An efficient isomerization procedure was carried out on exposure of **22** to 2.5 mol equiv. of DBU in CH_2Cl_2, affording **23** in 65% yield (Scheme 5).

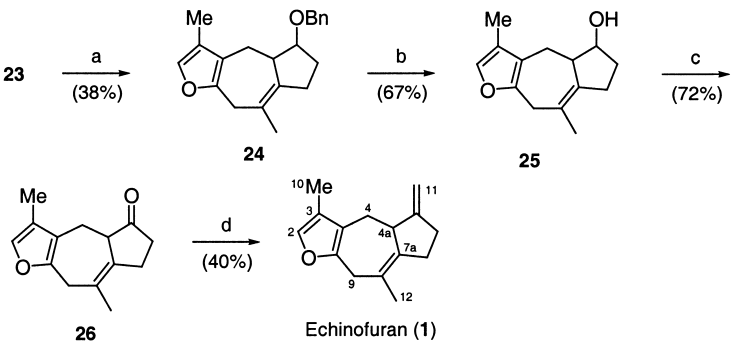
The conversion of **22** to **23** was easily observed by both ^1H and ^{13}C NMR spectroscopic methods. By comparing the ^1H NMR spectrum of **23** with **22**, it was found that the signal of H-12 changed from a doublet to a singlet. In addition, the ^{13}C NMR spectrum of **23** revealed that the formation of an α,β-unsaturated ketone caused an upshield shift of 10 ppm for the carbonyl absorption at C-9.

The final stage of our synthetic route featured three main steps including (i) removal of the carbonyl group at Ring B, (ii) deprotection of the benzyl group at Ring C and (iii) oxidation and methylenation. As depicted in Scheme 6, the carbonyl group at Ring B was removed by reduction to an alcohol and followed by mesylation. The mesylate was reduced further with $LiAlH_4$ to form **24**. The deprotection of benzyl ether **24** led to alcohol **25**, whose hydroxyl group was oxidized to a carbonyl group with IBX,[18] affording the β,γ-unsaturated ketone **26**. The total synthesis of (±)-echinofuran (**1**) was finally achieved by formation of the exomethylene group at Ring C by Peterson olefination.

In conclusion, the first total synthesis of (±)-echinofuran (**1**) was accomplished in 12 steps with a total yield of 0.55%.



Scheme 5. *Reagents and conditions*. (a) $NaBH_4$, $CeCl_3$, MeOH. (b) BnBr, NaH, DMF. (c) (i) NaOH, MeOH, reflux, (ii) TFAA, CH_2Cl_2, 0°C. (d) DBU (2.5 equiv.), CH_2Cl_2, −78°C.



Scheme 6. *Reagents and conditions*. (a) (i) $NaBH_4$, MeOH, 0°C, (ii) MsCl, Et_3N, CH_2Cl_2, (iii) $LiAlH_4$, ether, reflux. (b) (i) BBr_3, CH_2Cl_2, −78°C, (ii) MeOH, 0°C. (c) IBX, CH_2Cl_2. (d) (i) Me_3SiCH_2MgCl, ether, (ii) NaH, THF, reflux.

We are also of the opinion that our study on the formation of the furan-containing 5,7,5-fused tricyclic molecules will be invaluable towards the synthesis of other naturally occurring furanosesquiterpenoid tetrahydrolinder-azulenes.

3. Experimental

3.1. General information

All reagents and solvents were reagent grade. Further purification and drying by standard methods were employed when necessary. All organic solvents were evaporated under reduced pressure with a rotary evaporator. The plates used for thin-layer chromatography (TLC) were E. Merck silica gel $60F_{254}$ (0.25 mm thickness) precoated on aluminum plates, and they were visualized under both long (365 nm) and short (254 nm) UV light. Compounds on TLC plates were visualized with a spray of 5% dodecamolybdophosphoric acid in ethanol and with subsequent heating. Column chromatography was performed using E. Merck silica gel (230–400 mesh).

NMR spectra were recorded on a Bruker DPX-300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C). All NMR measurements were carried out at 300 K in deuterated chloroform solution unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in δ unit in the scale relative to the resonance of $CDCl_3$ (7.26 ppm in the ^1H, 77.00 ppm for the central line of the triplet in the ^{13}C modes, respectively). Coupling constants (J) are reported in Hz. Splitting patterns are described by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^1H NMR data is reported in this order: chemical shift; multiplicity; coupling constant(s), number of proton. Mass spectra (ERMS and HRMS) were obtained with a Thermofinnigan MAT95XL spectrometer and determined at an ionized voltage of 70 eV unless otherwise stated. Relevant data were tabulated as m/z. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences, China.

3.1.1. Ethyl [2-(4-methylfuran-3-yl)methyl]cyclopent-2-ene-1-carboxylate (6). To a mixture of 3-iodopropyltriphenylphosphonium iodide[12] (11 g, 20 mmol), anhydrous potassium carbonate (3.8 g, 27 mmol), 18-crown-6 (34 mg, 0.13 mmol) in CH_2Cl_2 (400 mL) was added **5**[11] (3.5 g, 13 mmol). After refluxing for 3 days, the mixture was filtered. The solvent was removed to give a viscous oil, which was then purified by column chromatography on silica gel (100 g, hexanes/EtOAc, 45:1) to afford **6** (0.8 g, 34%) as a colorless oil: ^1H NMR (C_6D_6) δ 7.27 (d, J=1.2 Hz, 1H), 7.22 (d, J=1.5 Hz, 1H), 5.38 (q, J=1.8 Hz, 1H), 4.00 (dq, J=0.8, 6 Hz, 2H), 3.45 (m, 3H), 2.39 (m, 4H), 1.95 (s, 3H), 0.99 (t, J=6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 148.2, 140.8, 140.7, 129.7, 125.8, 119.2, 60.4, 52.2, 31.4, 28.3, 26.0, 14.2, 8.6. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H 7.14. Found: C, 71.87; H, 7.27.

3.1.2. [2-(4-Methylfuran-3-yl)methyl]cyclopent-2-ene-1-methanol (7). To a solution of **6** (0.4 g, 1.3 mmol) in THF (20 mL) was added lithium aluminum hydride (1 M in THF, 1.5 mL) under N_2. After stirring at room temperature for 3 h, it was cooled to 0°C and quenched with absolute EtOH. Upon removal of solvent, the residue was column chromatographed on silica gel (100 g, hexanes/EtOAc, 20:1) to afford **7** (0.2 g, 64%) as a colorless oil: ^1H NMR (C_6D_6) δ 7.22 (d, J=4 Hz, 1H), 7.20 (d, J=4 Hz, 1H), 5.34 (d, J=1.5 Hz, 1H), 3.43 (dq, J=5, 12 Hz, 2H), 3.29 (d, J=17 Hz, 1H), 3.14 (d, J=17 Hz, 1H), 2.60 (s, 1H), 2.30–2.10 (m, 3H), 1.98 (m, 4H), 1.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 148.3, 142.3, 140.6, 128.8, 126.2, 119.2, 64.6, 49.2, 30.8, 27.3, 25.8, 8.6. Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H 8.39. Found: C, 74.81; H, 8.34.

3.1.3. 3-[1-(5-Bromomethylcyclopent-1-enyl)methyl]-4-methylfuran (8). To a solution of **7** (62 mg, 0.25 mmol) in DMF (5 mL), *N*-bromosuccinimide (90 mg, 0.5 mmol) and triphenylphosphine (135 mg, 0.5 mmol) were added at room temperature. After stirring for 3.5 h, the reaction mixture was quenched with MeOH. The solvent was removed under reduced pressure and the residue was further purified by column chromatography on silica gel (30 g, hexanes/EtOAc, 45:1) to afford **9** (57 mg, 73%) as a colorless oil: ^1H NMR (C_6D_6) δ7.22 (d, J=1.2 Hz, 1H), 7.13 (d, J=1.2 Hz, 1H), 5.37 (q, J=1.8 Hz, 1H), 3.27–3.02 (m, 4H), 2.75 (s, 1H), 2.30–2.00 (m, 2H), 1.96 (m, 4H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 148.4, 142.4, 140.7, 129.4, 125.8, 119.1, 48.5, 37.8, 30.3, 29.3, 25.5, 8.6; HRMS (FAB) calcd for $C_{12}H_{15}OBr$ (M^+) 255.0545. Found: 255.0574.

3.1.4. 4,6,7,7a,8,9-Hexahydro-3-methyl-azulenofuran-9-one (10). To a solution of **8** (16 mg, 0.05 mmol) in CH_3CN (0.5 mL), potassium cyanide (10 mg, 0.15 mmol) and

18-crown-6 (10 mg) were added at room temperature. After stirring for 38 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (10 g, hexanes/EtOAc, 20:1), a colorless oil was obtained, which was mixed with NaOH (2 M, 0.2 mL) in MeOH (0.6 mL) and was heated to 90°C for 10 h. After that H_2O (0.5 mL) was added and the resulting mixture was washed with CH_2Cl_2 (2.0 mL). The aqueous layer was acidified with HCl (2 M) until the pH reached 1. It was then extracted with CH_2Cl_2 (3×5 mL). The combined organic extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue **9** was re-dissolved in anhydrous CH_2Cl_2 (1.0 mL). Trifluoroacetic anhydride (0.01 mL, 0.07 mmol) was slowly added. After stirring for 6 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (10 g, hexanes/EtOAc, 15:1) to give **10** (1.6 mg, 11%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1H), 5.36 (t, J=2 Hz, 1H), 3.50 (m, 3H), 3.08 (m, 2H), 2.25 (m, 2H), 1.99 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 200.6, 147.0, 143.5, 139.0, 131.4, 121.7, 120.7, 60.7, 41.6, 31.7, 28.8, 28.6, 8.8; HRMS (FAB) calcd for $C_{13}H_{14}O_2$ (M^+) 202.1233. Found: 202.1223.

3.1.5. 6,7-Dihydrocyclopenta-1,3-dioxin-5(4*H*)-one (12).[15] A mixture of 1,3-cyclopentanedione (3.24 g, 33.0 mmol), paraformaldehyde (6.00 g, 200 mmol), $BF_3{\cdot}Et_2O$ (12.6 mL, 100 mmol) and CH_2Cl_2 (200 mL) was stirred vigorously at room temperature for 38 h. The mixture was then filtered and the filtrate added to 10% NaOH (130 mL) and ice (50 g). The resulting aqueous layer was extracted with CH_2Cl_2 (3×75 mL), and the combined organic phases were washed with brine and was dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography on silica gel (100 g, hexanes/acetone, 3:1) afforded **12** (3.55 g, 77%) as a white solid; mp 74–76°C (lit. mp 73–75°C). ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 2H), 4.48 (t, J=2.1 Hz, 2H), 2.70 (m, 2H), 2.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 200.6, 181.6, 114.3, 92.2, 62.5, 32.4, 26.2.

3.1.6. 2-(Hydroxymethyl)-3-(2-propenyl)-2-cyclopentenone (13). To a solution of 2-bromopropene (4.1 g, 33.6 mmol) in THF (150 mL) at −78°C was added dropwise *tert*-butyllithium (1.7 M in pentane, 39.5 mL, 67.2 mmol). The solution was allowed to stir for 1 h. To this solution of 2-lithiopropene was added **12** (2.35 g, 16.8 mmol) in THF (25 mL). The reaction mixture was stirred for 1.5 h at −78°C and then quenched with HCl (2 M, 20 mL). After 30 min, the aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic phases were washed with brine and was dried ($MgSO_4$). After removal of solvent, the residue was purified by flash column chromatography on silica gel (100 g, hexanes/EtOAc, 3:1) to afford **13** (2.02 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.30 (t, J=1.2 Hz, 1H), 5.23 (s, 1H), 4.40 (d, J=3.9 Hz, 2H), 3.26 (s, 1H), 2.68 (m, 2H), 2.43 (m, 2H) 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.8, 171.5, 139.9, 137.7, 119.8, 55.6, 33.8, 28.6, 21.2; HRMS (FAB) calcd for $C_9H_{12}O_2$ (M^+) 152.0859. Found: 152.0831.

3.1.7. 2-(Bromomethyl)-3-(2-propenyl)-2-cyclopentenone (14). To a solution of **13** (2.00 g, 13 mmol) in anhydrous Et_2O (30 mL) was added slowly PBr_3 (0.60 mL, 6.5 mmol) at 0°C. After stirring for 30 min, MeOH (5 mL) was added and the resulting mixture was allowed to stir for 10 min. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (60 g, hexanes/EtOAc, 5:1) to afford **14** (2.65 g, 96%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.49 (s, 1H), 5.39 (s, 1H), 4.12 (s, 2H), 2.69 (m, 2H), 2.45 (m, 2H) 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.8, 171.6, 139.8, 135.6, 120.5, 33.5, 28.7, 21.2, 20.8; HRMS (FAB) calcd for $C_9H_{11}OBr$ (M^+) 213.9988. Found: 213.9998.

3.1.8. 2-[(3-Methylfuran-4-yl)methyl]-3-(2-propenyl)-2-cyclopentenone (15). To a refluxing mixture of **14** (2.15 g, 10 mmol), 2 M K_3PO_4 (5 mL) and $Pd(PPh_3)_4$ (0.23 g, 0.20 mmol) in THF (20 mL) was added dropwise a solution of **3** (1.08 g, 3.33 mmol) in THF (25 mL) under nitrogen over 2 h. After addition, the mixture was refluxed for a further 1 h. After filtration, THF was evaporated under reduced pressure. The aqueous residue was extracted with Et_2O (4×50 mL) and was dried ($MgSO_4$). After removal of solvent, the residue was purified by flash column chromatography on silica gel (100 g, hexanes/EtOAc, 5:1) to afford **15** (1.12 g, 52%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.99 (d, J=1.2 Hz, 1H), 6.78 (s, 1H), 5.15 (d, J=3.6 Hz, 1H), 5.13 (d, J=1.2 Hz, 1H), 3.24 (s, 2H), 2.61 (m, 2H), 2.34 (m, 2H), 1.89 (d, J=0.9 Hz, 3H), 1.85 (d, J=0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.5, 168.9, 140.3, 139.1, 138.9, 137.3, 122.7, 119.1, 118.0, 33.2, 28.2, 20.8, 17.9, 7.6; IR: (thin film) 3082, 1705, 1640, 1598 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1145. Found: 216.1144.

3.1.9. 4,6,7,8,9-Pentahydro-3,8-dimethylauzleno[6,5-*b*]furan-5(2*H*)-one (16). To a solution of dienone **15** (1.08 g, 5 mmol) in anhydrous toluene (20 mL) at 0°C was added rapidly diethylaluminum chloride (1.80 M in toluene, 5.55 mL, 10 mmol). The reaction mixture was stirred for 10 h, and then quenched with NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic phases were washed with brine and dried ($MgSO_4$). After removal of solvent, the residue was purified by flash column chromatography on silica gel (100 g, hexanes/EtOAc, 6:1) to afford **16** (0.70 g, 65%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.87 (d, J=1.5 Hz, 1H), 3.48 (d, J=0.9 Hz, 2H), 2.94 (m, 1H), 2.85 (m, 1H), 2.68 (m, 1H), 2.58 (m, 2H), 2.37 (m, 2H), 1.99 (d, J=1.5 Hz, 3H), 1.25 (d, J=12 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.8, 148.6, 140.8, 135.2, 131.7, 118.4, 110.0, 41.4, 33.2, 32.6, 26.6, 21.6, 15.2, 8.2; IR: (thin film) 1679 cm^{-1}. Anal. calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.53. Found: C, 77.45; H, 7.46.

3.1.10. Ethyl 2-(2-hydroxylmethylcyclopent-2-enon-3-yl)propionate (17). To a solution of ethyl propionate (3.50 mL, 30 mmol) in anhydrous THF (20 mL) was added LDA (0.5 M, 70 mL) at −78°C under nitrogen in 10 min. After stirring for 30 min, **16** (3.00 g, 21.4 mmol) in anhydrous THF (120 mL) was added dropwise in a period of 1 h. The reaction mixture was warmed to room temperature and then HCl (2 M, 16 mL) was added. The solution was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), and the combined

organic phase was washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (100 g, hexanes/acetone, 3:1) to afford **17** (3.40 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2H), 4.05 (q, J=7.2 Hz, 2H), 3.91 (q, J=7.2 Hz, 1H), 2.57 (m, 2H), 2.29 (m, 2H), 1.28 (d, J=7.2 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.3, 172.4, 171.6, 139.5, 61.0, 54.1, 40.4, 33.8, 26.2, 14.9, 13.7. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.07; H, 7.74.

3.1.11. Ethyl 2-(2-bromomethylcyclopent-2-enon-3-yl)propionate (18). To a solution of **17** (3.50 g, 16.5 mmol) in anhydrous Et_2O (50 mL) was added PBr_3 (1.00 mL, 10.5 mmol) at 0°C. After stirring for 30 min, MeOH (5 mL) was added. The reaction mixture was stirred for 10 min and then water was added. The aqueous layer was separated and was extracted with Et_2O (3×30 mL). The combined organic phase was washed with brine and dried ($MgSO_4$). After removal of solvent, the residue was purified by flash column chromatography on silica gel (80 g, hexanes/acetone, 4:1) to afford **18** (4.50 g, 98%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.04 (dq, J=2.4, 7.2 Hz, 2H), 3.91 (s, 2H), 3.85 (q, J=7.2 Hz, 1H), 2.52 (m, 2H), 2.29 (m, 2H), 1.29 (d, J=7.2 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.6, 173.7, 170.8, 137.4, 61.0, 40.8, 33.4, 26.2, 18.1, 14.4, 13.6; HRMS (FAB) calcd for $C_{11}H_{15}BrO_3$ $(M+H)^+$ 275.0277. Found: 275.0265.

3.1.12. Ethyl [2-(4-methylfuran-3-yl)methylcyclopent-2-enon-3-yl]propionate (19). To a solution of **18** (500 mg, 1.8 mmol) in anhydrous THF (10 mL) was added K_3PO_4 (2 M, 3 mL) and $Pd(PPh_3)_4$ (100 mg, 0.09 mmol). The mixture was heated to 60°C while **3** (200 mg, 0.7 mmol) in THF (10 mL) was added dropwise in 30 min. The reaction mixture was then refluxed for 2 h. After cooling down, the mixture was filtered through a plug of glass wool and the solids were washed with Et_2O. The aqueous layer was separated and was extracted with Et_2O (3×20 mL). The combined organic phase was washed with brine and dried ($MgSO_4$). After removal of solvent, the residue was purified by flash column chromatography on silica gel (50 g, hexanes/EtOAc, 8:1) to afford **19** (276 mg, 55%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.02 (s, 1H), 6.93 (s, 1H), 4.06 (dq, J=2.4, 7.2 Hz, 2H), 3.83 (q, J=7.2 Hz, 1H), 3.19 (d, J=1.2 Hz, 2H), 2.54 (m, 2H), 2.37 (m, 2H), 1.85 (d, J=0.9 Hz, 3H), 1.25 (d, J=7.2 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.2, 171.7, 170.4, 139.4, 139.3, 139.1, 121.9, 119.5, 60.9, 40.5, 33.6, 25.6, 16.8, 14.8, 13.7, 7.7; IR: (thin film) 1735, 1680 cm^{-1}. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.31; H, 7.40.

3.1.13. Ethyl [1-hydroxy-2-(4-methylfuran-3-yl)methylcyclopent-2-en-3-yl]propionate (20). To a solution of **19** (180 mg, 0.65 mmol) in dry MeOH (10 mL) was added $CeCl_3$ (162 mg, 0.65 mmol). To this solution was added $NaBH_4$ (130 mg, 3.3 mmol). After stirring for 30 min, the reaction mixture was quenched with acetone. The solvent was removed under reduced pressure and the residue was re-dissolved in CH_2Cl_2 (20 mL). Water (5 mL) was added and the aqueous layer was separated and was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phase was dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (30 g, hexanes/EtOAc, 3:1) to afford **20** (160 mg, 88%) as a viscous colorless oil. Compound **20** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 7.06 (a pair of d, J=1.2, 0.9 Hz, 1H), 7.01 (s, 1H), 4.63 (d, J=4.5 Hz, 1H), 4.12 (m, 2H), 3.59 (m, 1H), 3.22 (d, J=4.2 Hz, 2H), 2.51 (m, 3H), 1.93 (a pair of d, J=1.2 Hz, 3H), 1.62 (m, 1H), 1.27 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.7, 140.0, 139.7, 139.6, 139.5, 138.8, 138.6, 137.8, 137.5, 122.6, 122.4, 120.0, 119.9, 78.8, 78.6, 60.6, 60.5, 38.8, 32.1, 29.3, 19.7, 15.5, 15.2, 14.1, 14.0, 7.9; IR: (thin film) 3531, 1724, 1250 cm^{-1}. Anal. calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.11; H, 7.99.

3.1.14. Ethyl[1-benzyloxy-2-(4-methylfuran-3-yl)-methylcyclopent-2-ene-3-yl]propionate (21). To a solution of **20** (100 mg, 0.36 mmol) in anhydrous DMF (5 mL) was added NaH (30 mg, 1.25 mmol). After stirring for 20 min, to the mixture was added slowly benzyl bromide (0.06 mL, 0.54 mmol). The solution was stirred for an additional 2 h at room temperature. The solvent was removed under reduced pressure and the residue was re-dissolved in CH_2Cl_2 (30 mL). The organic phase was washed with water (3×10 mL) and then was separated. After removal of solvent, the residue was purified by flash column chromatography on silica gel (30 g, hexanes/EtOAc, 10:1) to afford **21** (120 mg, 92%) as a pale yellow oil. Compound **21** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 7.14 (d, J=0.9 Hz, 1H), 7.04 (s, 1H), 5.10 (s, 1H), 4.53 (m, 2H), 4.37 (m, 1H), 4.10 (m, 1H), 3.70 (m, 1H), 3.23 (d, J=3.9 Hz, 2H), 2.40 (m, 3H), 1.93 (m, 3H), 1.80 (m, 1H), 1.31 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.8, 173.6, 140.3, 139.8, 139.4, 139.2, 139.1, 138.8, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 127.3, 122.6, 122.4, 119.7, 85.2, 85.1, 70.7, 70.0, 66.2, 60.5, 38.9, 30.0, 29.9, 29.6, 28.4, 28.3, 19.9, 15.7, 15.5, 15.3, 14.1, 8.0; IR: (thin film) 3096, 2982, 1720 cm^{-1}. Anal. calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.72; H, 7.57.

3.1.15. 5-Benzyloxy-4,5,6,7,8-pentahydro-3,8-dimethyl-azuleno[6,5-*b*]furan-9(4*H*)-one (22). To a solution of **21** (368 mg, 1 mmol) in MeOH (15 mL) was added slowly an aqueous solution of NaOH (2 M, 5 mL). The mixture was then refluxed for 10 h. After that water (10 mL) was added and the resulting mixture was washed with CH_2Cl_2 (10 mL). The aqueous layer was acidified with HCl (3N) until the pH reached 1. It was then extracted with CH_2Cl_2 (5×10 mL). The combined organic extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was redissolved in anhydrous CH_2Cl_2 (20 mL). Trifluoroacetic anhydride (0.4 mL, 3.2 mmol) was slowly added. After stirring at 0°C for 6 h, saturated $NaHCO_3$ solution (15 mL) was added. The mixture was allowed to stir for a further 1 h, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel (30 g, hexanes/EtOAc, 8:1) to afford **22** (113 mg, 35%) as a colorless oil. Compound **22** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of

diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 6.96 (s, 1H), 4.53 (d, J=12 Hz, 1H), 4.45 (bs, 1H), 4.37 (d, J=12 Hz, 1H), 3.70 (m, 1H), 3.22 (s, 2H), 2.57 (bs, 1H), 2.28 (m, 1H), 2.14 (m, 1H), 1.93 (s, 3H), 1.86 (m, 1H), 1.30 (a pair of d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 189.1, 147.1, 142.3, 138.7, 138.4, 137.3, 137.2, 137.0, 131.7, 130.4, 128.3, 127.7, 127.5, 122.2, 120.1, 85.2, 70.8, 38.4, 31.4, 29.8, 29.6, 27.3, 27.0, 23.0, 7.9. Anal. calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.13; H, 6.92.

3.1.16. 5-Benzyloxy-4,4a,5,6,7-pentahydro-3,8-dimethylazuleno[6,5-*b*]furan-9(4*H*)-one (23). To a stirred solution of **22** (32 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added DBU (0.04 mL, 0.25 mmol) at −78°C. After being stirred for 30 h at −78°C, the reaction mixture was quenched by the addition of 1N HCl, and Et_2O was then added. The organic layer was separated, washed with brine, and the solvent were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel containing 5% $AgNO_3$ (10 g, hexanes/Et_2O, 15:1) to afford **23** (21 mg, 65%) as a colorless oil. Compound **23** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 7.04 (s, 1H), 4.63 (d, J=12 Hz, 1H), 4.42 (d, J=12 Hz, 1H), 2.72 (m, 2H), 2.47 (m, 2H), 2.04 (m, 2H), 1.95 (s, 3H), 1.86 (m, 2H), 1.74 (a pair of s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.8, 150.8, 147.3, 142.3, 137.8, 137.6, 128.4 127.8, 127.6, 126.4, 126.3, 122.7, 84.4, 73.2, 49.2, 37.7, 29.3, 29.2, 23.0, 22.3, 8.2. Anal. calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.28; H, 6.79.

3.1.17. 5-Benzyloxy-4,4a,5,6,7,9-hexahydro-3,8-dimethylazuleno[6,5-*b*]furan (24). To a solution of **23** (32 mg, 0.1 mmol) in dry MeOH (2 mL) was added $CeCl_3$ (25 mg, 0.1 mmol). To this solution was added $NaBH_4$ (10 mg, 0.2 mmol) at 0°C. After stirring for 30 min, the reaction mixture was quenched with acetone. The solvent was removed under reduced pressure and residue was re-dissolved in CH_2Cl_2 (5 mL), and water (2 mL) was added. The aqueous layer was separated and was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phase was dried ($MgSO_4$). After removal of solvent, the residue was further dried in vacuo. It was then re-dissolved in CH_2Cl_2 (5 mL). To this solution was added Et_3N (0.1 mL) and MsCl (0.01 mL) at 0°C. After being stirred for 12 h, Et_3N and MsCl were removed in vacuo, and the residue was re-dissolved in anhydrous Et_2O (5 mL). To this solution was added lithium aluminum hydride (10 mg) and the reaction mixture was allowed to reflux for 1 day. After that water (2 mL) was added and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic phase was washed with brine (3 mL). After removal of solvent, the residue was purified by flash column chromatography on silica gel (10 g, hexanes/Et_2O, 20:1) to afford **24** (11.6 mg, 38%) as a pale yellow oil. Compound **24** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 6.97 (s, 1H), 4.58 (d, J=12 Hz, 1H), 4.42 (d, J=12 Hz, 1H), 3.70 (m, 1H), 3.13 (m, 1H), 2.86 (m, 2H) 2.54 (m, 2H), 2.24 (m, 2H), 1.92 (a pair of d, J=0.9 Hz, 3H), 1.85 (m, 2H), 1.74 (a pair of s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.6, 140.8, 137.6, 137.2, 137.0, 135.2, 135.0, 128.3, 127.8, 127.6, 121.7, 121.5, 117.2, 84.4, 84.3, 73.9, 73.8, 49.4, 36.4, 36.2, 33.6, 28.3, 25.6, 25.2, 23.0, 8.4; IR: (thin film) 3084, 2950 cm^{-1}. Anal. calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.77; H, 7.75.

3.1.18. 4,4a,5,6,7,9-Hexahydro-5-hydroxy-3,8-dimethylazuleno[6,5-*b*]furan (25). To a solution of **24** (31 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added slowly BBr_3 (1.0 M, 0.15 mL) at −78°C. The reaction mixture was stirred at −78°C for 2 h, then stirred for another 30 min at room temperature. After that, the solution was again cooled to −78°C and was added MeOH (1 mL). The mixture was allowed to stir for a further 1 h. After removal of solvent, the residue was purified by flash column chromatography on silica gel (10 g, hexanes/EtOAc, 5:1) to afford **25** (14.6 mg, 67%) as a viscous colorless oil. Compound **25** showed very complex ^{1}H and ^{13}C NMR spectra due to the presence of a pair of diastereomers in the same ratio. ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 1H), 3.83 (m, 1H), 3.63 (m, 1H), 3.03 (bm, 1H), 2.78 (m, 1H) 2.54 (m, 2H), 2.42 (m, 4H), 1.95 (a pair of d, J=1.2 Hz, 3H), 1.71 (a pair of s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2, 138.5, 138.3, 138.2, 135.2, 135.0, 122.4, 122.1, 117.7, 117.5, 79.9, 51.8, 38.2, 28.5, 28.3, 26.6, 25.6, 25.4, 23.9, 8.2; IR: (thin film) 3497, 1672 cm^{-1}. Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.18; H, 8.03.

3.1.19. 4,4a,6,7,9-Pentahydro-3,8-dimethylazuleno[6,5-*b*]furan-5(4*H*)-one (26). To a solution of **25** (24 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (2 mL) was added IBX[18] (76 mg 0.27 mmol) at room temperature. After being stirred for 2 h, the white solids were filtered and washed with CH_2Cl_2. The solvent was removed under reduced pressure, the residue was purified by flash column chromatography on silica gel (10 g, hexanes/EtOAc, 8:1) to afford **26** (17 mg, 72%) as a viscous colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1H), 3.65 (d, J=18 Hz, 1H), 3.42 (dd, J=13.2, 3.6 Hz, 1H), 2.98 (d, J=18 Hz, 1H), 2.83 (m, 2H), 2.49 (m, 2H), 2.24 (m, 2H), 1.95 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.2, 146.4, 136.2, 135.1, 125.7, 121.7, 116.9, 60.3, 40.8, 33.6, 30.5, 29.3, 19.7, 8.4; HRMS (FAB) calcd for $C_{14}H_{16}O_2$ $(M+H)^+$ 217.1215. Found: 217.1223.

3.1.20. (±)-Echinofuran (1). To a solution of [(trimethylsilyl)methyl]magnesium chloride [prepared from Mg (7.2 mg, 0.296 mmol) and (chloromethyl)trimethylsilane (36.4 mg, 0.3 mmol)] in anhydrous Et_2O (2 mL) was added dropwise a solution of **26** (24.6 mg, 0.1 mmol) in Et_2O (1 mL) at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixuture was poured into saturated NH_4Cl solution, and extracted with Et_2O (3×5 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The residue resulting from the evaporation of the solvent was dissolved in THF (3 mL). To this solution was added NaH (8 mg, 0.33 mmol) under stirring. After refluxing had been continued for 6 h, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with Et_2O (3×5 mL). After removal of solvent, the residue was purified by flash column chromatography on silica gel (5 g, hexanes/EtOAc, 40:1) to afford **1** (9.7 mg, 40%) as a pale yellow oil which darkened on standing. ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H), 4.96 (s, 1H), 4.89 (s, 1H), 3.70 (d, J=18 Hz, 1H), 3.34 (d, J=12 Hz, 1H), 2.98 (d, J=18 Hz, 1H), 2.52 (m, 2H), 2.47 (m, 2H), 2.29 (m, 2H), 1.85 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 157.3, 148.5, 140.8, 135.9, 125.2, 121.3, 118.7, 105.9, 46.3, 34.0, 33.2, 30.6, 30.1, 22.2, 8.6. MS (EI) *m/z* (%) $[M]^+$ 214 (100), 157 (18), 109 (38), 91 (25).

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