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Total Synthesis of (+)-Neomarinone

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Abstract: The first total synthesis of (+)-neomarinone has been achieved by following a concise and convergent route using methyl (*R*)-lactate and (*R*)-3-methylcyclohexanone as chiral building blocks. Key steps of the synthesis are the stereocontrolled formation of the two quaternary stereocenters by diastereoselective 1,4-conjugate addition and enolate alkylation reactions, and the construction of the furanonaphthoquinone skeleton by regioselective Diels–Alder reaction between a 1,3-bis(trimethylsilyloxy)-1,3-diene and a bromoquinone. The synthesis proves the relative and absolute stereochemistry of natural neomarinone.

Keywords: alkylations · asymmetric synthesis · cuprate additions · Diels–Alder reaction · natural products

Introduction

Neomarinone (**1**, Figure 1), a marine natural product isolated from the fermentation broth of actinomycetes (strain #CNH-099), displays in vitro cytotoxicity ($IC_{50}=8\ \mu g\,mL^{-1}$) against HCT-116 colon carcinoma, an interesting value of $IC_{50}=10\ \mu M$ in the NCI-60 panel cell lines of cancer, and moderate antibiotic activity.[1] Neomarinone is a hybrid compound of mixed polyketide–terpenoid origin (meroterpenoid)[2] that belongs to a small group of prenylated naphthoquinones, including the antibiotics furaquinocins[3] and marinone,[4] with a wide range of biological effects.[5] In particular, neomarinone features a dihydroxylated furanonaphthoquinone core linked to a ramified sesquiterpenoid side chain with four stereogenic centers, two of which are quaternary.

The structural determination of neomarinone was made difficult by the presence of five methyl groups with a narrow range of NMR chemical shifts. In fact, the initially proposed structure was revised in 2003 after an elegant study of its biosynthesis, followed by extensive 2D NMR spectroscopic analysis.[6] In this revision, the stereochemistry

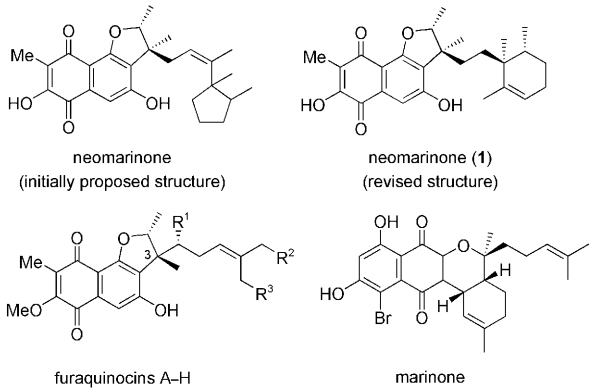

Figure 1. Neomarinone, furaquinocins, and marinone.

of the methyl groups in the cyclohexene unit was assigned as *cis*, based on chemical correlation with the natural products ageline A[7] and subersine,[8] while the relative stereochemistry of the methyl groups at the furan ring was assigned as *cis* by chemical comparison with (−)-furaquinocin C and (+)-3-epifuraquinocin C (Figure 1, $R^1=R^2=R^3=H$).[9] However, the configuration of the cyclohexene ring relative to the furan residue could not be unequivocally determined. Herein, we report the first total synthesis of (+)-neomarinone, which proves the relative and absolute stereochemistry of the natural product.

Results and Discussion

The synthesis of neomarinone was envisaged by construction of the furanonaphthoquinone core by a regioselective Diels–

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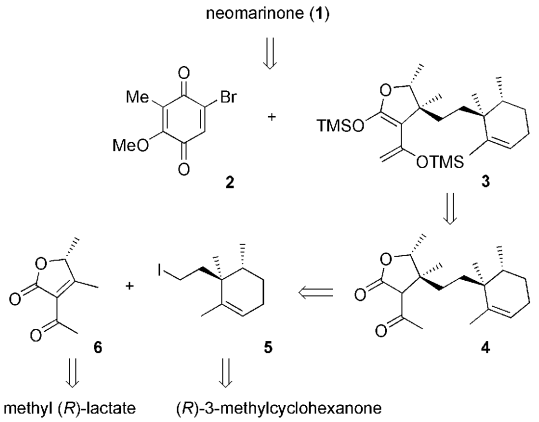
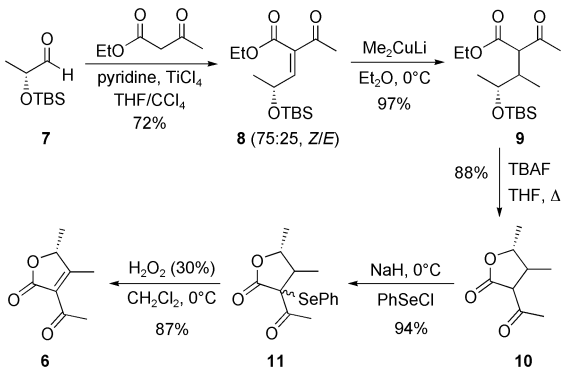
Alder reaction between bromoquinone **2**[10] and the inner-outer ring 1,3-bis(trimethylsilyloxy)-1,3-diene **3**, which contains the furan ring functionalized with the side chain of neomarinone (Scheme 1). Silyloxydienes are highly reactive dienes in Diels–Alder reactions and we have shown that inner-outer ring 1,3-silyloxydienes are particularly useful for the synthesis of a wide variety of polycyclic structures.[11] The synthesis of the 1,3-silyloxydiene was proposed from the 1,3-dicarbonyl compound **4**, prepared by a diastereoselective conjugate addition of an organometallic reagent derived from iodide **5** to the enantiomerically pure α,β-unsaturated lactone **6**. For the enantioselective synthesis of iodide **5**, we devised a sequence starting from commercially available (*R*)-3-methylcyclohexanone with formation of the quaternary stereocenter through stereoselective sequential enolate alkylation reactions.



Scheme 1. Retrosynthetic analysis for neomarinone.

For the synthesis of enantiopure α,β-unsaturated lactone **6**, we planned a short synthetic sequence from commercial methyl (*R*)-lactate. Protection of the hydroxyl group as the TBS ether followed by ester reduction with DIBAL gave the aldehyde **7** in 79% overall yield (Scheme 2).[12] $TiCl_4$-catalyzed Knoevenagel condensation[13] of **7** with ethyl acetoacetate gave the α,β-unsaturated 1,3-carbonyl compound **8** in 72% yield as a mixture of stereoisomers (*Z*/*E* 75:25).[14] Conjugate addition of lithium dimethylcuprate to (*Z*,*E*)-**8** afforded **9** in 97% yield, and cleavage of the TBS ether with TBAF at reflux produced the lactone **10** in excellent yield as a mixture of stereoisomers at C-2 and C-3. The reaction of **10** with NaH and phenylselenyl chloride at 0°C gave the selenide **11** as a diastereomeric mixture in 94% yield. Finally, the reaction of **11** with hydrogen peroxide (30% aq) at 0°C afforded the desired enone **6** in 87% yield (Scheme 2).[15,16]

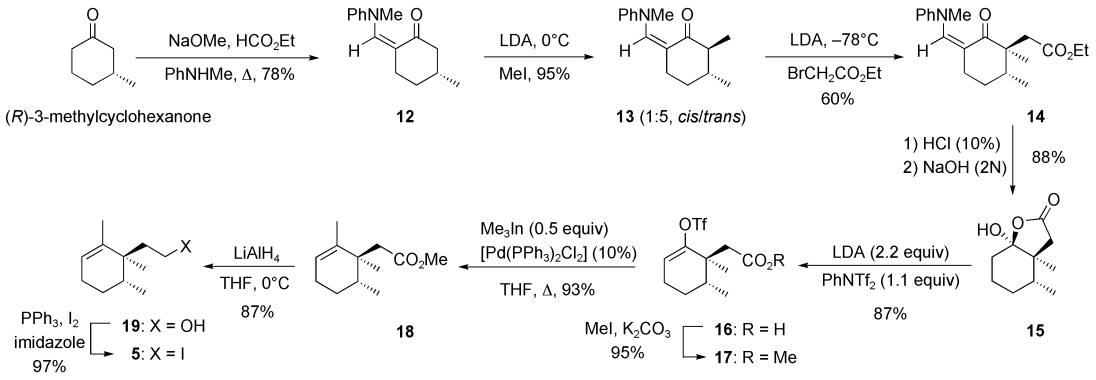
Starting from commercially available (*R*)-methylcyclohexanone, the first step in the enantioselective synthesis of iodide **5** was the preparation of the α-*N*-methylanilinomethylene derivative **12**[17] to perform the enolate alkylation reactions in regio- and stereoselective fashion (Scheme 3). Treatment of **12** with LDA and MeI at 0°C produced the methylated ketone **13**[17] as a 1:5 (*cis*/*trans*) mixture of diastereoisomers. Further reaction of **13** with LDA and ethyl bromoacetate at −78°C afforded stereoselectively the α,α-disubstituted ketone **14** in 60% yield as a single diastereoisomer, as determined by ^{1}H NMR spectroscopy. The acid–base hydrolysis of **14** produced, after purification by recrystallization, the hemiketal **15** in 88% yield. The relative stereochemistry of the methyl groups in **15** was first assigned *cis* by NOESY experiments and confirmed by X-ray analysis.[18] As expected, the enolate alkylation reaction takes place *trans* to the C-3 methyl group. Interestingly, the enantiopure hemiketal **15** was converted to the vinyltriflate **16** by reaction with LDA (2.2 equiv) and $PhNTf_2$ (1.1 equiv),[19] and the carboxylic acid group transformed into the methyl ester **17** by treatment with MeI/K_2CO_3 (83% overall yield). Subsequent palladium-catalyzed reaction of Me_3In (0.5 equiv) with vinyltriflate **17** afforded the cross-coupling product **18** in 93% yield.[20] The reduction of the ester **18** with $LiAlH_4$ (87% yield) and reaction of the resulting alcohol **19** with PPh_3 and I_2 gave the desired iodide **5** in 97% yield. Following this synthetic sequence, the enantiomerically pure iodide **5** was prepared from (*R*)-3-methylcyclohexanone in 25% overall yield (nine steps).[21]



Scheme 2. Enantioselective synthesis of lactone **6**.

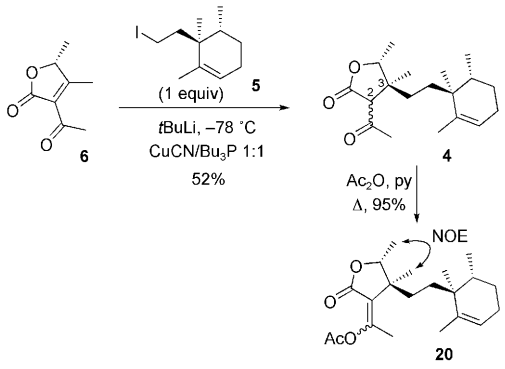
With the enantiomerically pure enone **6** and iodide **5** in hand, we proceeded to assemble both fragments of neomarinone by stereoselective 1,4-cuprate addition. In this endeavor, we first tried the conjugate addition of the Gilman cuprate (R_2CuLi), prepared by halogen-metal exchange of iodide **5** (2 equiv) with *t*BuLi and addition of CuI, to enone **6** at low temperature. Under these conditions, the conjugate addition product **4** was obtained in 56% yield as a mixture of C-2 acetyl epimers and the enol–lactone tautomer. In an effort to improve the atom economy of the reaction, we also tested the possibility of preparing hetero- or mixed cuprates. It was found that the reaction of iodide **5** (1 equiv) with *t*BuLi at −78°C, followed by addition of a solution of copper cyanide (1 equiv) and tri(*n*-butyl)phosphine, and further reaction with **6** at −78°C, afforded **4** in 52% yield (Scheme 4). It is important to note that, although the yields are comparable, the latter procedure consumes half of the starting iodide.

The stereochemistry of the quaternary stereocenter generated in the cuprate addition was studied in the *O*-acetylated



Scheme 3. Enantioselective synthesis of iodide **5**.

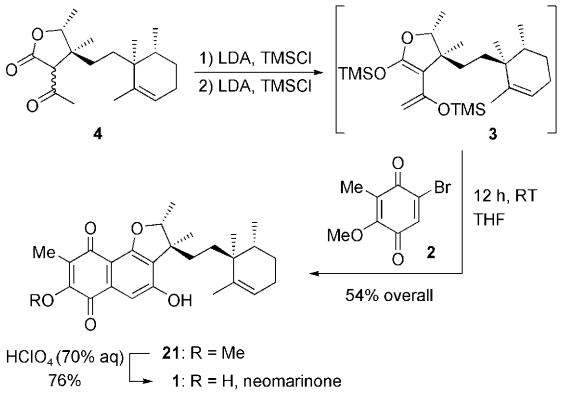
product **20** obtained by reaction of 1,3-dicarbonyl compound **6** with acetic anhydride in pyridine at reflux (95%, Scheme 4). The ^{1}H NMR analysis of the acetylated product showed a single stereoisomer at C-3, and the relative stereochemistry of the β and γ methyl groups at the lactone was assigned as *cis* on the basis of nuclear Overhauser NMR experiments. This result confirms that the stereoselectivity of the cuprate addition reaction takes place *trans* to the γ-methyl group.



Scheme 4. Diastereoselective conjugate addition.

Once the 1,3-dicarbonyl compound **4** had been prepared, the next step was the formation of the corresponding 1,3-bis(silyloxy)-1,3-diene and the Diels–Alder reaction with bromoquinone **2** (Scheme 5). The preparation of the 1,3-bis(trimethylsilyloxy)-1,3-diene **3** was attempted by sequential treatment of **4** with LDA (1.1 equiv) and TMSCl (1.5 equiv). Unfortunately, the diene **3** proved to be very sensitive to hydrolysis and all attempts to isolate this compound failed. For this reason we decided to carry out the diene formation and Diels–Alder reaction in one pot. In this case, addition of bromoquinone **2**[10] at room temperature to a reaction vessel containing the solution of diene **3** led to an exothermic reaction, and the methyl ether of neomarinone **21** was isolated in 54% yield after 12 h. Overall, the conversion of **4** in **21** involves several steps: 1) formation of the silyloxydiene, 2) Diels–Alder reaction, 3) silyl enol ether hydrolysis, 4) trimethylsilyloxy elimination and, 5) aromatization.

The last step in the synthesis was the cleavage of methyl ether in the 1,4-benzoquinone. Initial attempts using Lewis acids,[22] under different reaction conditions, led to decomposition of the starting material. Alternatively, the consideration of the methyl ether in the quinoid system as part of a vinylogous ester prompted us to attempt the hydrolysis. Unfortunately, the reaction of **21** with 1 M NaOH or KOH[23] at RT for 24 h did not afford any reaction product, and heating at 60 °C led to decomposition. Interestingly, acid hydrolysis with HCl (37%)[10b] cleaved the methyl ether in **21**, albeit with isomerization of the double bond at the cyclohexene and epimerization of the methyl group at the furan. Gratifyingly, treatment of **21** with $HClO_4$ (70% aq)[24] at RT for 24 h led to a smooth reaction that afforded neomarinone (**1**) in an excellent 76% yield. Synthetic neomarinone was identical in all respects (^{1}H and ^{13}C NMR, MS, UV, IR, TLC and HPLC) to the natural compound. Additionally, the optical rotation measured ($[\alpha]_D^{20} = +88.3$ ($c = 0.2$ in MeOH)) was coincident in sign and value with that reported in the literature ($[\alpha]_D^{20} = +86$ ($c = 0.5$ in MeOH)).[1]



Scheme 5. Synthesis of neomarinone.

Conclusion

In summary, the first total synthesis of (+)-neomarinone has been developed. The synthesis, which is concise and convergent, is based in the construction of the furanonaphthoquinone skeleton by regioselective Diels–Alder reaction using a 1,3-bis(silyloxy)-1,3-diene. The enantioselective synthesis was performed using methyl (*R*)-lactate and (*R*)-3-methylcyclohexanone as chiral building compounds. The two quaternary stereocenters were formed stereoselectively by 1,4-conjugate addition and enolate alkylation reactions.[25] The total synthesis confirms the relative and absolute stereochemistry of neomarinone.

Experimental Section

General methods: Unless otherwise is stated, all reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. Anhydrous solvents were obtained by distillation from CaH_2 (CH_2Cl_2 and pyridine) or from the sodium/benzophenone (THF and Et_2O). All other commercially available reagents were used as received. Organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by using a rotary evaporator at aspirator pressure (20–30 mmHg). TLC was effected on silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid, or *p*-anisaldehyde reagent followed by heating. Column chromatography was performed on silica gel (230–400 mesh). NMR spectra were performed in a Bruker Avance 300 or Bruker Avance 500 spectrometers in $CDCl_3$ using the residual solvent signal at $\delta =$ 7.26 ppm (^{1}H) or $\delta = 77.0$ ppm (^{13}C) as internal standard. DEPT was used to assign carbon types. The low resolution electron-impact mass spectra were measured on a Thermo Finnigan Trace MS spectrometer at 70 eV. The high resolution mass spectra were measured on a Thermo Finnigan MAT 95XP spectrometer. Infrared spectra were taken with a Bruker Vector 22. Optical rotation values were determined at room temperature in a JASCO DIP-1000 Digital polarimeter. IR spectra were taken with ATR ("attenuated total reflectance"). Melting points are uncorrected.

Ethyl (*R*)-2-acetyl-4-(*tert*-butyldimethylsilyl)oxypent-2-enoate (8): To a cold solution of $TiCl_4$ (4.09 mL, 37.18 mmol) in CCl_4 (5 mL) at −78 °C, a solution of aldehyde **7** (1.75 g, 9.29 mmol) in THF (10 mL), ethyl acetoacetate (2.37 mL, 18.59 mmol) and pyridine (1.46 mL, 27.89 mmol) in THF (5 mL) were successively added via cannula. Alter 12 h, the reaction mixture was poured on ice and extracted with Et_2O (2×150 mL). The combined organic phase was washed with brine (200 mL) and saturated $NaHCO_3$ (200 mL), dried, filtered and concentrated in vacuo, to give an oil which was purified by column chromatography (5% EtOAc/hexanes) to afford **8** (2.01 g, 6.7 mmol, 72%, *E*/*Z* 25:75). (*Z*)-**8**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.30 (d, $J = 6.7$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 4.32 (q, $J =$ 6.7 Hz, 3H), 4.69 (dq, $J = 8.3$, 6.7 Hz, 1H), 6.71 ppm (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = -4.9$ (CH_3), −4.7 (CH_3), 14.1 (CH_3), 18.1 (C), 23.5 (CH_3), 25.7 (3×CH_3), 26.9 (CH_3), 61.3 (CH_2), 66.4 (CH), 133.7 (C), 150.9 (CH), 165.7 (C), 195.4 ppm (C); IR (ATR): $\tilde{\nu} =$ 2955, 2930, 2896, 2857, 1727, 1700, 1629 cm^{-1}; MS (FAB, 3-NBA): *m*/*z* (%): 301 (72) [M^++H], 255 (25) [$M^+ - C_2H_5O$], 243 (100), 169 (29) [$M^+ - C_4H_9SiO$]; HRMS (FAB, 3-NBA): *m*/*z*: calcd for $C_{15}H_{29}O_4Si$: 301.1830 [M^++H]; found: 301.1831. (*E*)-**8**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta =$ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.30 (d, $J = 6.7$ Hz, 3H), 1.32 (t, $J = 7.3$ Hz, 3H), 2.34 (s, 3H), 4.26 (q, $J = 6.7$ Hz, 3H), 4.64 (m, 1H), 6.84 ppm (d, $J = 7.8$ Hz, 1H).

Ethyl (*R*)-2-acetyl-4-(*tert*-butyldimethylsilyl)oxy-3-methylpentanoate (9): To cold suspension of CuI (1.27 g, 6.65 mmol) in Et_2O (15 mL) at 0 °C, a solution of MeLi in Et_2O (10.8 mL, 1.23 M, 13.31 mmol) was added. After 30 min stirring, a solution of **8** (*E*/*Z* 25:75, 1.00 g, 3.33 mmol) in Et_2O (8 mL) was added via cannula dropwise. After 15 minutes, the reaction was quenched at 0 °C by addition of a few drops of saturated NH_4Cl, and extracted with Et_2O (3×25 mL). The combined organic layer was washed with brine (50 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexanes) to give **9** (1.008 g, 3.16 mmol, 97%) as a mixture of stereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.01$ (s, 3H), 0.03+0.06 (2s, 3H), 0.83+1.06 (2d, $J = 6.8$ Hz, 3H), 0.89+0.90 (2s, 9H), 1.12+1.14 (2d, $J = 6.1$ Hz, 3H), 1.26+1.28 (2t, $J = 7.3$ Hz, 3H), 2.22+2.24 (2s, 3H), 2.35 (m, 1H), 3.57 (m, 1H), 3.86 (m, 1H), 4.17 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = -5.2$, −4.9, −4.2, −4.0, 10.0, 11.4, 14.0, 14.1, 18.0, 18.1, 20.5, 21.4, 25.8, 25.9, 29.6, 29.7, 39.7, 40.0, 61.1, 61.2, 62.6, 63.4, 68.4, 69.1, 169.1, 169.3, 203.1, 203.8 ppm; IR (ATR): $\tilde{\nu} =$ 3436, 2972, 2927, 2855, 2001, 1778, 1741 cm^{-1}; MS (FAB, 3-NBA): *m*/*z* (%): 317 (8) [M^+ +H], 316 (17) [M^+], 169 (100); HRMS (FAB, 3-NBA): *m*/*z*: calcd for $C_{16}H_{33}O_4Si$: 317.2148 [M^++H]; found: 317.2157.

(5*R*)-3-Acetyl-4,5-dimethyl-dihydrofuran-2(3*H*)-one (10): To a solution of **9** (820 mg, 2.59 mmol) in THF (15 mL) at RT, TBAF (2.45 g, 7.78 mmol) was added and the mixture was heated at reflux for 2 h. After cooling to RT and evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (30 mL) and the organic layer was washed with saturated NH_4Cl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 20 mL) and the combined organic phase was dried, filtered and concentrated to give an oil which was purified by column chromatography (20% EtOAc/hexanes), affording **10** (355 mg, 88%, 2.26 mmol, *cis*/*trans* 39:61). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.05$ (d, $J =$ 6.8 Hz, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 2.42 (s, 3H), 3.06 (hexaplet, $J =$ 6.8 Hz, 1H), 3.33 (d, $J = 6.8$ Hz, 1H), 4.73 ppm (pentet, $J = 6.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 13.3$ (CH_3), 15.7 (CH_3), 29.7 (CH_3), 34.9 (CH), 61.0 (CH), 78.7 (CH), 171.8 (C), 200.2 ppm (C); IR (ATR): $\tilde{\nu} =$ 2977, 2931, 1760, 1714, 1651 cm^{-1}; MS (FAB, 3-NBA): *m*/*z* (%): 157 (23) [M^++H], 156 (17) [M^+], 154 (100); HRMS (FAB, 3-NBA): *m*/*z*: calcd for $C_8H_{13}O_3$: 157.0865 [M^++H]; found: 157.0858. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.12$ (d, $J = 6.3$ Hz, 3H), 1.43 (d, $J = 6.3$ Hz, 3H), 2.45 (s, 3H), 2.59 (m, 1H), 3.37 (d, $J =$ 6.8 Hz, 1H), 4.11 ppm (m, 1H).

(4*R*,5*R*)-3-Acetyl-dihydro-4,5-dimethyl-3-(phenylselanyl)selenylfuran-2(3*H*)-one (11): To a suspension of NaH (470 mg, 1.92 mmol) in THF (10 mL) at 0 °C, a solution of **10** (200 mg, 1.28 mmol) in THF (4 mL) was added dropwise via cannula, and the resulting mixture was stirred for 10 min at 0 °C and 1 h at RT. The reaction mixture was cooled at −80 °C and a solution of PhSeCl (295 mg, 1.54 mmol) in THF (5 mL) was added via cannula. After 1 h, the reaction was quenched by addition of a few drops of saturated NH_4Cl. The solvent was removed under reduced pressure and the residue dissolved in Et_2O (20 mL). The organic layer was washed with saturated $NaHCO_3$ and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic phase was dried, filtered and concentrated to give an oil which was purified by column chromatography (10% EtOAc/hexanes), to afford the selenide **11** (375 mg, 1.20 mmol, 94%) as a 70:30 mixture of diastereoisomers as yellow oils. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.95$ (d, $J = 7.3$ Hz, 3H), 1.37 (d, $J = 6.3$ Hz, 3H), 2.42 (s, 3H), 3.13 (m, 1H), 5.11 (m, 1H), 7.29–7.48 (m, 3H), 7.52–7.68 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 9.8$, 12.2, 15.2, 16.1, 26.6, 28.9, 39.3, 42.1, 61.5, 75.8, 125.5, 129.4, 129.5, 129.7, 130.7, 136.1, 137.6, 171.1, 172.2, 197.8, 199.6 ppm; IR (ATR): $\tilde{\nu} =$ 3366, 3057, 2976, 2924, 2853, 2042, 1759, 1695 cm^{-1}; MS (FAB, 3-NBA): *m*/*z* (%): 313 (100) [M^++H], 312 (28) [M^+]; HRMS (FAB, 3-NBA): *m*/*z*: calcd for $C_{14}H_{17}O_3Se$: 313.0343 [M^++H]; found: 313.0354. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.25$ (d, $J = 7.3$ Hz, 3H), 1.45 (d, $J = 6.3$ Hz, 3H), 2.39 (s, 3H), 2.52 (m, 1H), 4.54 (m, 1H), 7.34–7.48 (m, 3H), 7.57–7.68 ppm (m, 2H).

(*R*)-3-Acetyl-4,5-dimethylfuran-2(5*H*)-one (6): To a solution of selenide **11** (219 mg, 0.704 mmol) in CH_2Cl_2 (5 mL) at 0 °C, H_2O_2 (200 μL, 30%) was added. After 10 minutes, the reaction mixture was stirred at RT for 40 min. Then, H_2O (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated to give **6** (159 mg, 1.03 mmol, 87%)

as a clear liquid. $[\alpha]_D = -3.4$ ($c = 0.8$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.50$ (d, $J = 7.0$ Hz, 3H), 2.38 (s, 3H), 2.57 (s, 3H), 4.91 ppm (q, $J = 7.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.0$ (CH_3), 17.6 (CH_3), 30.1 (CH_3), 79.3 (CH), 124.7 (C), 170.2 (C), 177.6 (C), 195.1 ppm (C); IR (ATR): $\tilde{\nu} = 2928$, 2255, 1750, 1688, 1632 cm^{-1}; MS (FAB, NPOE): m/z (%): 155 (16) [M^++H], 140 (100), 111 (21) [$M^+ - C_2H_3O$]; HRMS (FAB, NPOE): m/z: calcd for $C_8H_{11}O_3$: 155.0703 [M^++H]; found: 155.0702.

Ethyl 2-[(1*S*,6*R*,*Z*)-1,6-dimethyl-3-[[methyl(phenyl)amino]methylene]-2-oxocyclohexyl]acetate (14): To a cold solution of LDA (0.68 mL, 1.41 mmol) in THF (10 mL) at −78 °C, a solution of **13** (0.312 g, 1.28 mmol) in THF (5 mL) was added dropwise. After 20 min stirring, ethyl bromoacetate (0.50 mL, 4.48 mmol) was added via syringe over a 10 min period and the reaction mixture was slowly allowed to reach RT. The solvent was evaporated under reduced pressure and the residue was partitioned between saturated $NaHCO_3$ (15 mL), H_2O (15 mL) and Et_2O (15 mL). The aqueous phase was extracted and the combined organic extracts were washed with brine (25 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (50% Et_2O/hexanes) to give **14** (251 mg, 0.760 mmol, 60%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.90$ (d, $J = 6.9$ Hz, 3H), 1.02 (s, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.42–1.53 (m, 2H), 2.05–2.25 (m, 3H), 2.40 (d, $J = 16.6$ Hz, 1H), 3.14 (d, $J = 16.6$ Hz, 1H), 3.42 (s, 3H), 4.05–4.17 (m, 2H), 7.03–7.10 (m, 3H), 7.29–7.34 (m, 2H), 7.54 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.2$ (CH_3), 16.3 (CH_3), 19.7 (CH_3), 26.6 (CH_2), 27.6 (CH_2), 34.2 (CH_3), 41.7 (CH_2), 42.3 (CH), 48.1 (C), 59.9 (CH_2), 111.2 (C), 120.9 (CH), 123.6 (CH), 128.8 (CH), 145.4 (CH), 146.1 (C), 172.1 (C), 203.2 ppm (C); IR (ATR): $\tilde{\nu} = 3383$, 2961, 2927, 2324, 1730, 1652, 1598 cm^{-1}; MS (EI): m/z (%): 330 (3) [M^++1], 329 (16) [M^+], 284 (13) [$M^+ - C_2H_5O$], 242 (19) [$M^+ - C_4H_7O_2$]; HRMS (EI): m/z: calcd for $C_{20}H_{27}NO_3$: 329.1985 [M^+]; found: 329.1986.

(3a*S*,4*R*,7a*R*)-Hexahydro-7a-hydroxy-3a,4-dimethylbenzofuran-2(3*H*)-one (15): A solution of **14** (248 mg, 3.34 mmol) in HCl (10 mL, 10%) was heated at reflux for 45 minutes. The mixture was cooled and extracted with Et_2O (3×10 mL). The organic layer was concentrated at reduced volume and treated with a solution of NaOH (10 mL, 2 N) at reflux for 1 h. The mixture was cooled, acidified with HCl (10%) and extracted with Et_2O (3×15 mL). The combined organic phase was washed with brine (20 mL), dried, filtered and concentrated in vacuo. Purification by column chromatography (50% Et_2O/hexanes) afforded **15** (122 mg, 0.66 mmol, 88%) as a white solid. M.p. 107–108 °C; $[\alpha]_D^{25} = -24.8$ ($c = 0.5$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.89$ (d, $J = 6.6$ Hz, 3H), 1.06 (s, 3H), 1.10–1.26 (m, 2H), 1.37–1.57 (m, 2H), 1.64–1.75 (m, 2H), 2.03–2.08 (m, 1H), 2.36 (d, $J = 16.6$ Hz, 1H), 2.66 ppm (d, $J = 16.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 11.6$ (CH_3), 16.4 (CH_3), 21.8 (CH_2), 29.0 (CH_2), 32.4 (CH_2), 37.3 (CH), 41.2 (CH_2), 46.1 (C), 108.2 (C), 176.9 ppm (C); IR (ATR): $\tilde{\nu} = 3333$, 2960, 2948, 2872, 1737, 1724 cm^{-1}; MS (EI): m/z (%): 184 (2) [M^+], 125 (62) [$M^+ - C_2H_3O_2$], 96 (100); HRMS (EI): m/z: calcd for $C_{10}H_{16}O_3$: 184.1094 [M^+]; found: 184.1094.

2-[(1*S*,2*R*)-1,2-Dimethyl-6-oxocyclohexyl]acetic acid (16): To a cold solution of LDA (2.52 mL, 4.20 mmol) in THF (6 mL) at −40 °C, a solution of **15** (352 mg, 1.91 mmol) in THF (8 mL) was added. After 30 min, a solution of $PhNTf_2$ (0.75 g, 2.10 mmol) in THF (5 mL) was added dropwise via syringe and allowed to reach RT in a 6 h period. The reaction was quenched with few drops of MeOH and added over NH_4Cl (20 mL, satd. sol.). The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic extracts were washed with brine (25 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (40% Et_2O/hexanes) to afford **16** (523 mg, 2.03 mmol, 87%) as an oil. $[\alpha]_D^{25} = +36.7$ ($c = 0.45$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.00$ (d, $J = 7.1$ Hz, 3H), 1.12 (s, 3H), 1.47–1.70 (m, 2H), 2.06–2.26 (m, 3H), 2.51 (d, $J = 15.2$ Hz, 1H), 2.66 (d, $J = 15.2$ Hz, 1H), 5.81 ppm (t, $J = 4.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 15.4$ (CH_3), 19.6 (CH_3), 23.1 (CH_2), 25.8 (CH_2), 35.3 (CH), 40.1 (CH_2), 41.0 (C), 117.1 (CH), 120.5 (C), 152.7 (C), 175.8 ppm (C); IR (ATR): $\tilde{\nu} = 3387$, 2931, 2873, 2358, 1756, 1709 cm^{-1}; MS (EI): m/z (%): 257 (12) [$M^+ - C_2H_3O_2$], 96 (100); HRMS (EI): m/z: calcd for $C_9H_{12}O_3F_3S$: 257.0432 [$M^+ - C_2H_3O_2$]; found: 257.0454.

Methyl 2-[(1*S*,6*R*)-1,6-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-2-enyl]-acetate (17): To a solution of **16** (160 mg, 0.506 mmol) in DMF (10 mL), was added MeI (63 μL, 1.01 mmol) and K_2CO_3 (0.140 g, 1.01 mmol). After stirring overnight at RT, water (10 mL) was added and extracted with Et_2O (3×15 mL). The combined organic phase was washed with brine (20 mL), dried, filtered and concentrated to reduced pressure, to give an oil which was purified by column chromatography (20% Et_2O/hexanes) to afford **17** (160 mg, 0.62 mmol, 95%) as a colorless oil. $[\alpha]_D^{20} = +2.1$ ($c = 0.40$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.97$ (d, $J = 6.9$ Hz, 3H), 1.08 (s, 3H), 1.47–1.63 (m, 2H), 2.02–2.14 (m, 1H), 2.17–2.23 (m, 2H), 2.47 (d, $J = 15.1$ Hz, 1H), 2.60 (d, $J = 15.1$ Hz, 1H), 3.66 (s, 3H), 5.79 (t, $J = 4.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 15.5$ (CH_3), 19.6 (CH_3), 23.2 (CH_2), 25.9 (CH_2), 35.3 (CH), 40.2 (CH_2), 41.1 (C), 51.4 (CH_3), 116.7 (CH), 120.4 (C), 153.2 (C), 170.9 (C); IR (ATR): $\tilde{\nu} = 2928$, 2854, 2359, 2208, 2172, 2085, 2018, 1971, 1943 cm^{-1}; MS (EI): m/z (%): 257 (4) [$M^+ - C_3H_5O_2$], 149 (100); HRMS (EI): m/z: calcd for $C_9H_{12}O_3F_3S$: 257.0446 [$M^+ - C_3H_5O_2$]; found: 257.0454.

Methyl 2-[(1*S*,6*R*)-1,2,6-trimethylcyclohex-2-enyl]acetate (18): To a cold solution of $InCl_3$ (44 mg, 0.20 mmol) in THF (5 mL) at −78 °C, a solution of MeLi in Et_2O (0.39 mL, 1.6 M, 0.61 mmol) was slowly added via syringe for a 15 min period. The reaction mixture was allowed to reach RT and a solution of **17** (135 mg, 0.41 mmol) and $[Pd(PPh_3)_2Cl_2]$ (29 mg, 0.04 mmol) in THF (6 mL) was added via cannula. The resulting mixture was heated at reflux overnight, cooled, the solvent removed in the evaporator at reduced pressure. The residue was dissolved in Et_2O (20 mL) and the organic phase successively washed with satd. NH_4Cl (20 mL), satd. $NaHCO_3$ (20 mL) and brine (20 mL), dried, filtered and concentrated to give an oil which was purified by column chromatography (10% Et_2O/hexanes) to afford **18** (74 mg, 0.38 mmol, 93%) as an oil. $[\alpha]_D^{25} = +30$ ($c = 0.5$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.92$ (d, $J = 6.8$ Hz, 3H), 0.97 (s, 3H), 1.36–1.49 (m, 1H), 1.52–1.61 (m, 1H), 1.71 (s, 3H), 1.84–2.02 (m, 3H), 2.43 (d, $J = 14.3$ Hz, 1H), 2.52 (d, $J = 14.3$ Hz, 1H), 3.64 (s, 3H), 5.42 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 15.9$ (CH_3), 19.4 (CH_3), 20.9 (CH_3), 24.5 (CH_2), 26.8 (CH_2), 34.5 (CH), 40.5 (C), 41.7 (CH_2), 51.1 (CH_3), 123.5 (CH), 138.3 (C), 172.4 ppm (C); IR (ATR): $\tilde{\nu} = 2923$, 1734, 1435, 1377, 1316, 1281 cm^{-1}; MS (EI): m/z (%): 196 (8) [M^+], 123 (55) [$M^+ - C_3H_5O_2$], 122 (100); HRMS (EI): m/z: calcd for $C_{12}H_{20}O_2$: 196.1458 [M^+]; found: 196.1450.

2-[(1*S*,6*R*)-1,2,6-Trimethylcyclohex-2-enyl]ethanol (19): To a solution of **18** (216 mg, 1.10 mmol) in THF (12 mL) at 0 °C, a solution of $LiAlH_4$ in THF (3.3 mL, 1 M, 3.30 mmol) was added via syringe. After 3 h, the solvent was removed and the residue was dissolved in Et_2O (15 mL) and the resulting organic phase was washed with HCl (10 mL, 5%), and brine (20 mL), dried, filtered and concentrated. The residue was purified by column chromatography (40% Et_2O/hexanes) to afford **19** (161 mg, 0.96 mmol, 87%) as an oil. $[\alpha]_D^{25} = +36.3$ ($c = 0.44$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.89$ (s, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 1.26–1.30 (m, 1H), 1.38–1.47 (m, 2H), 1.67 (broad s, 3H), 1.75 (t, $J = 7.6$ Hz, 2H), 1.91–1.98 (m, 2H), 3.45–3.55 (m, 1H), 3.60–3.68 (m, 1H), 5.43 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 16.0$ (CH_3), 19.3 (CH_3), 21.0 (CH_3), 25.4 (CH_2), 26.9 (CH_2), 34.2 (CH), 39.1 (CH_2), 39.6 (C), 59.9 (CH_2), 124.2 (CH), 139.4 ppm (C); IR (ATR): $\tilde{\nu} = 3312$, 2960, 2920, 2876, 2857, 2837, 1453, 1437, 1377 cm^{-1}; MS (EI): m/z (%): 169 (4) [M^++1], 168 (4) [M^+], 123 (100) [$M^+ - C_2H_5O$]; HRMS (EI): m/z: calcd for $C_{11}H_{20}O$: 168.1509 [M^+]; found: 168.1505.

(5*R*,6*S*)-6-(2-Iodoethyl)-1,5,6-trimethylcyclohex-1-ene (5): To a solution of **19** (154 mg, 0.915 mmol) in dry THF (15 mL) at RT, PPh_3 (288 mg, 1.10 mmol), imidazole (125 mg, 1.83 mmol) and I_2 (279 mg, 1.10 mmol) were successively added. After 45 min, the reaction mixture was poured in a separating funnel with $Na_2S_2O_3$ (10 mL, satd. sol.). The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic phase was washed with brine (20 mL), dried, filtered and concentrated to give a residue which was purified by column chromatography (hexanes), to afford **5** (247 mg, 0.89 mmol, 97%) as a colorless oil. $[\alpha]_D = -3.4$ ($c = 0.8$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.87$ (s, 3H), 0.89

(d, $J=6.9$ Hz, 3H), 1.40–1.51 (m, 2H), 1.58–1.72 (m, 4H), 1.91–1.96 (m, 2H), 2.09 (dd, $J=8.5$, 6.0 Hz, 2H), 2.83–2.92 (m, 1H), 3.07–3.16 (m, 1H), 5.48 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=1.2$ (CH_2), 15.9 (CH_3), 19.1 (CH), 20.5 (CH_3), 25.4 (CH_2), 26.7 (CH_2), 33.0 (CH_3), 41.9 (CH_2), 43.5 (C), 125.2 (CH), 138.0 ppm (C); IR (ATR): $\tilde{\nu}=3020$, 2961, 2920, 2874, 2855, 2836 cm^{-1}; MS (EI): m/z (%): 278 (49) [M^+], 123 (100) [$M^+-C_2H_4I$]; HRMS (EI): m/z: calcd for $C_{11}H_{19}I$: 278.0526 [M^+]; found: 278.0516.

(4*S*,5*R*)-3-Acetyl-4,5-dimethyl-4-{2-[(1*S*,6*R*)-1,2,6-trimethylcyclohex-2-enyl]ethyl}-dihydrofuran-2(3*H*)-one (4): To a solution of *t*BuLi (690 μL, 1.7 M in pentane, 1.173 mmol) in Et_2O (5 mL) at −78 °C, a solution of iodide **5** (163 mg, 0.586 mmol) in Et_2O (3 mL) was added dropwise via cannula for 10 min. After 30 min, a clear solution of CuCN (58 mg, 0.65 mmol) and Bu_3P (240 μL, 0.973 mmol) in Et_2O (3 mL) was added via cannula. The mixture was left for 1 h at −78 °C and slowly warmed up to −40 °C during 1 h. Then, the reaction mixture was cooled to −78 °C and a solution of **6** (110 mg, 0.704 mmol) in Et_2O (4 mL) was added via cannula. After 1 h, the reaction was quenched with few drops of methanol and poured into a separating funnel with satd. NH_4Cl (25 mL). The mixture was extracted with Et_2O (30 mL) and the organic phase was washed with brine (25 mL), dried, filtered and concentrated, to give a residue which was purified by column chromatography (20% EtOAc/hexanes) to afford **4** (94 mg, 0.31 mmol, 52%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.85$–0.89 (m, 6H), 1.01–1.14 (m, 3H), 1.25–1.31 (m, 5H), 1.35–1.48 (m, 4H), 1.52–1.70 (m, 4H), 1.92–2.02 (m, 2H), 2.37 (s, 3H), 3.40+3.43 (2s, 1H), 4.31+4.39+4.73 (3q, $J=6.5$ Hz, 1H), 5.43 ppm (brs, 1H); IR (ATR): $\tilde{\nu}=3413$, 2965, 1776, 1711, 1453 cm^{-1}; MS (FAB, thioglycerol): m/z (%): 307 (22) [M^++H], 123 (100); HRMS (FAB, thioglycerol): m/z: calcd for $C_{19}H_{31}O_3$: 307.2268 [M^++H]; found: 307.2253.

1-[(4*S*,5*R*)-4,5-Dimethyl-2-oxo-4-{2-[(1*S*,6*R*)-1,2,6-trimethylcyclohex-2-enyl]ethyl}-dihydrofuran-3(2*H*)-ylidene]ethyl acetate (20): To a solution of **4** (17 mg, 0.055 mmol) in CH_2Cl_2 (3 mL), pyridine (90 μL, 1.108 mmol) and Ac_2O (40 μL, 0.440 mmol) were added via syringe and the resulting solution was heated at reflux for 12 h. The reaction mixture was cooled and washed with satd. NH_4Cl (5 mL) and brine (10 mL). The organic phase was dried, filtered and concentrated to give a residue which was purified by column chromatography (20% EtOAc/hexanes) to afford **20** (18 mg, 0.05 mmol, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta=0.87$ (d, $J=7.0$ Hz, 3H), 0.88 (s, 3H), 1.14 (s, 3H), 1.28 (d, $J=6.5$ Hz, 3H), 1.28–1.36 (m, 3H), 1.39–1.46 (m, 2H), 1.59 (s, 3H), 1.61–1.70 (m, 2H), 1.96–2.00 (m, 2H), 2.22 (s, 3H), 2.46 (s, 3H), 4.30 (q, $J=6.5$ Hz, 1H), 5.46 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta=15.9$ (CH_3), 16.4 (CH_3), 18.1 (CH_3), 19.0 (CH_3), 19.6 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 25.5 (CH_2), 26.9 (CH_2), 30.4 (CH_2), 32.9 (CH_2), 33.2 (CH), 40.3 (C), 45.7 (C), 80.1 (CH), 122.0 (C), 124.9 (CH), 138.8 (C), 159.9 (C), 167.8 (C), 170.0 ppm (C); IR (ATR): $\tilde{\nu}=2922$, 1763, 1749, 1672, 1446, 1372 cm^{-1}; MS (FAB, 3-NBA): m/z (%): 349 (22) [M^++H], 307 (75) [$M^+-C_2H_3O$], 123 (100); HRMS (FAB, 3-NBA): m/z: calcd for $C_{21}H_{33}O_4$: 349.2373 [M^++H]; found: 349.2375.

(2*R*,3*S*)-4-Hydroxy-7-methoxy-2,3,8-trimethyl-3-{2-[(1*S*,6*R*)-1,2,6-trimethylcyclohex-2-enyl]ethyl}-2,3-dihydronaphtho[1,2-*b*]furan-6,9-dione (21): To a cold solution of **4** (130 mg, 0.424 mmol) in THF (3 mL) at −78 °C, a solution of LDA in THF (880 μL, 0.483 M, 0.424 mmol) was added dropwise via syringe. After 20 minutes, freshly distilled TMSCl (80 μL, 0.636 mmol) was added and the reaction warmed at RT for 30 min. Then, the reaction mixture was cooled at −78 °C and a solution of LDA (880 μL, 0.483 M in THF, 0.424 mmol) added via syringe over a 5 minutes period. After 20 minutes, freshly distilled TMSCl (80 μL, 0.636 mmol) was added via syringe, and the reaction mixture was allowed to reach RT for 1 h. Then, a solution of the bromoquinone **2** (117 g, 0.509 mmol) in THF (3 mL) was added to the previously prepared 1,3-bis(trimethylsilyloxy)-1,3-diene, dropwise via cannula. After 15 h, a catalytic amount of TsOH was added, and the mixture stirred for 30 minutes. The solvent was removed and the residue was dissolved in Et_2O (10 mL). The organic phase was washed with HCl (5%, 20 mL) and brine (20 mL), dried, filtered and concentrated, to give a residue which was purified by column chromatography (30% to 50% EtOAc/hexanes) to afford **21** (100 mg, 0.23 mmol, 54%) as a brilliant yellow solid. M.p. > 200 °C; $[\alpha]_D=+49.1$ ($c=0.25$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta=0.80$ (s, 3H), 0.81 (d, $J=6.9$ Hz, 3H), 1.25 (s, 3H), 1.27–1.43 (m, 4H), 1.45 (d, $J=6.5$ Hz, 3H), 1.55 (s, 3H), 1.62–1.78 (m, 3H), 1.91–1.99 (m, 2H), 2.07 (s, 3H), 4.00 (s, 3H), 4.85 (q, $J=6.5$ Hz, 1H), 5.41 (brs, 1H), 6.73 (brs, 1H), 7.19 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta=9.4$ (CH_3), 15.3 (CH_3), 15.9 (CH_3), 19.1 (CH_3), 20.2 (CH_3), 21.2 (CH_3), 25.6 (CH_2), 27.0 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 33.3 (CH), 40.3 (C), 46.7 (C), 60.7 (CH_3), 87.8 (CH), 108.9 (CH), 109.6 (C), 124.6 (CH), 128.0 (C), 133.3 (C), 134.0 (C), 139.1 (C), 156.7 (C), 156.8 (C), 161.2 (C), 181.2 (C), 184.0 ppm (C); IR (ATR): $\tilde{\nu}=3310$, 2922, 2852, 2359, 2325, 2051, 1981, 1666, 1627, 1572, 1291 cm^{-1}; MS (FAB, 3-NBA): m/z (%): 439 (50) [M^++H], 438 (10) [M^+], 154 (100); HRMS (FAB, 3-NBA): m/z: calcd for $C_{27}H_{35}O_5$: 439.2479 [M^++H]; found: 439.2490.

(2*R*,3*S*)-4,7-Dihydroxy-2,3,8-trimethyl-3-{2-[(1*S*,6*R*)-1,2,6-trimethylcyclohex-2-enyl]ethyl}-2,3-dihydronaphtho[1,2-*b*]furan-6,9-dione (1): To a solution of **21** (10.9 mg, 0.031 mmol) in THF (3 mL) at RT, $HClO_4$ (1.2 mL, 70% aq) was added. After 16 h, the solvent was removed, and the residue dissolved in EtOAc (15 mL). The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried, filtered and concentrated to give a residue which was purified by column chromatography (30% EtOAc/hexanes) to afford **1** (8 mg, 0.02 mmol, 76%) as a fine yellow solid. M.p. > 200 °C; $[\alpha]_D^{20}=+88.3$ ($c=0.2$, MeOH); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta=0.74$ (s, 3H), 0.78 (d, $J=6.8$ Hz, 3H), 1.14 (s, 3H), 1.15–1.26 (m, 2H), 1.30 (d, $J=6.5$ Hz, 3H), 1.32–1.40 (m, 3H), 1.52 (s, 3H), 1.66–1.73 (m, 1H), 1.82 (s, 3H), 1.84–1.96 (m, 3H), 4.65 (q, $J=6.5$ Hz, 1H), 5.36 (brs, 1H), 7.04 (s, 1H), 10.28 (brs, 1H), 10.71 ppm (brs, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 25 °C): $\delta=8.6$ (CH_3), 15.1 (CH_3), 15.7 (CH_3), 18.8 (CH_3), 19.7 (CH_3), 20.9 (CH_3), 25.1 (CH_2), 26.6 (CH_2), 30.5 (CH_2), 31.0 (CH_2), 32.8 (CH), 39.7 (C), 46.0 (C), 86.3 (CH), 107.9 (C), 107.9 (CH), 120.3 (C), 123.9 (CH), 127.3 (C), 131.6 (C), 138.9 (C), 153.7 (C), 157.7 (C), 159.9 (C), 180.4 (C), 182.7 ppm (C); IR (ATR): $\tilde{\nu}=3295$, 2923, 2853, 2360, 2324, 2164, 2050, 1981, 1655, 1629, 1566, 1297 cm^{-1}; UV (MeOH) $\lambda_{max}=398$, 318, 266, 216 nm; MS (FAB, 3-NBA): m/z (%): 425 (20) [M^++H], 424 (5) [M^+], 137 (100); HRMS (FAB, 3-NBA): m/z: calcd for $C_{26}H_{33}O_5$: 425.2323 [M^++H]; found: 425.2320.

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