A Regioselective Tsuji–Trost Pentadienylation of 3-Allyltetronic Acid

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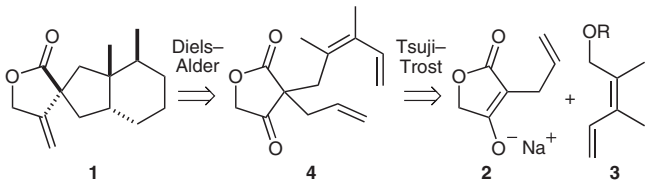
Abstract: A regioselective Tsuji–Trost reaction of sodium 3-allyltetronate with methyl 5-trimethylsilylpenta-2,4-dienyl carbonate was developed. Carbon–carbon bond formation at the more highly substituted terminus of the pentadienyl residue was possible by introduction of an easy to remove $SiMe_3$ shielding group at the remote end of the π-system. This carbonate reacted fast enough to avoid scrambling and formation of symmetric bisallyl tetronic acids. The 3-allyl-3-penta-2,4-dienyltetronic acid thus obtained is a key intermediate en route to the natural spirolactone bakkenolide A.

Key words: allylation, regioselectivity, palladium, tetronic acid, Schlosser–Wittig reaction

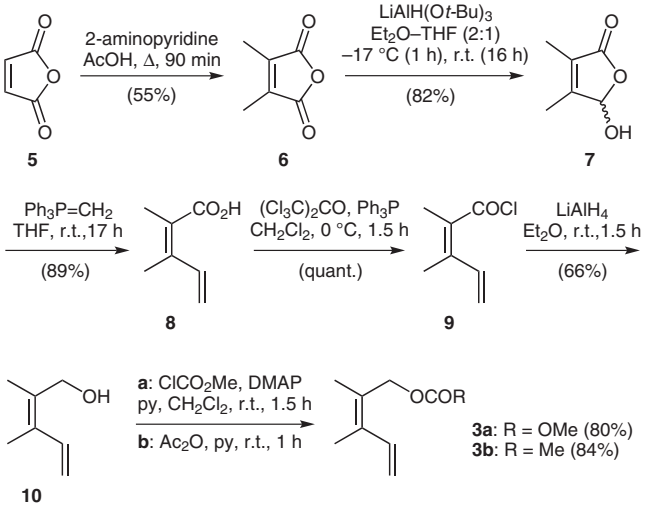
We had previously reported that sodium 3-allyltetronates are amenable to a Tsuji–Trost reaction[1] with allyl acetates to yield 3,3-bisallyltetronic acids without scrambling of residues.[2] For a synthesis[3–6] of the natural spirolactone bakkenolide A (**1**)[7–11] we now wanted to introduce pentadienyl rather than allyl residues under similar conditions. This would enable us to eventually generate the carbocycle **1** by a Diels–Alder reaction. Hence, we considered a Tsuji–Trost pentadienylation of the sodium salt **2** of 3-allyltetronic acid, which is readily accessible by Claisen rearrangement of 4-*O*-allyl tetronate[12] (Scheme 1).



Scheme 1 Retrosynthesis of bakkenolide A (**1**)

Tsuji–Trost allylations are mechanistically well understood.[13] They have been widely used in natural product synthesis due to their regio- and stereoselectivity.[14] The intermediate (η^3-allyl)palladium complexes can react with nucleophiles at either end, but directing methods were developed. For instance, the so-called memory effect,[15–18] that is, the nucleophilic attack at the C-atom that originally bore the leaving group, is observed with bulky chiral ligands on palladium such as MeOMOP,[19] PHOX,[20] and PCy_3.[16] With penta-2,4-dienyl acetates or carbonates in Tsuji–Trost reactions there are two inter-mediate (η^3-pentadienyl)-palladium complexes in equili-brium, affording up to three regioisomeric product dienes upon reaction with nucleophiles. The factors influencing this equilibrium and the site of nucleophilic attack have been intensively studied, including the substituents on the diene,[13b,21–24] the nature of the nucleophile,[25] and the ligands on palladium.[26]

For the Tsuji–Trost synthesis of bakkenolide A precursor **4** from tetronate **2** we prepared methyl 2,3-dimethylpenta-2,4-dienyl methyl carbonate (**3a**) and 2,3-dimethylpenta-2,4-dienyl acetate (**3b**) (Scheme 2). Maleic anhydride (**5**) was dimethylated in the presence of 2-aminopyridine.[27] Deviating from the literature procedure, the crude product was purified by sublimation to leave anhydride **6** in 55% yield.



Scheme 2 Synthesis of 1-acyloxy-2,3-dimethylpenta-2,4-dienes **3**

The anhydride **6** was reduced to the lactol **7** with $LiAlH(Ot\text{-}Bu)_3$ in diethyl ether–tetrahydrofuran at –17 °C.[28] Wittig methylenation of **7** afforded (2*Z*)-2,3-dimethylpenta-2,4-dienoic acid (**8**) in ca. 90% yield.[29] Not many alkenations of 5-hydroxybutenolides by an unstabilized phosphorus ylide have been reported, so far.[29–31] Acid chloride **9** was obtained almost quantitatively according to the general protocol by Villeneuve et al.[32] while procedures using thionyl chloride or oxalyl chloride led to an isomerization of the 2*Z*-double bond. Reduction of crude chloride **9** with $LiAlH_4$ furnished alcohol **10** in 66% over two steps. Its acylation gave the carbonate **3a** and the acetate **3b**, respectively, which were submitted as the allylic component to the Tsuji–Trost reaction with sodium tetronate (**2**)[2] (Scheme 3). In either case we obtained a

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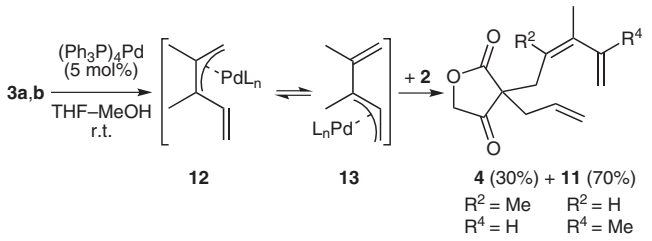
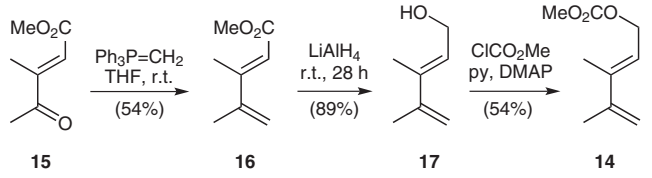
30:70 mixture (determined by ^{1}H NMR spectra) of the regioisomers **4** and **11**, the former originating from an attack of the 3-allyltetronate at the vinyl(π-allyl) complex **12**, the latter from the preferred reaction of complex **13**. 3,3-Diallylfuran-(2*H*)-2,4-dione was also formed as a byproduct via self reaction of tetronate **2**, especially when **3b** with the poor leaving group acetate was used.



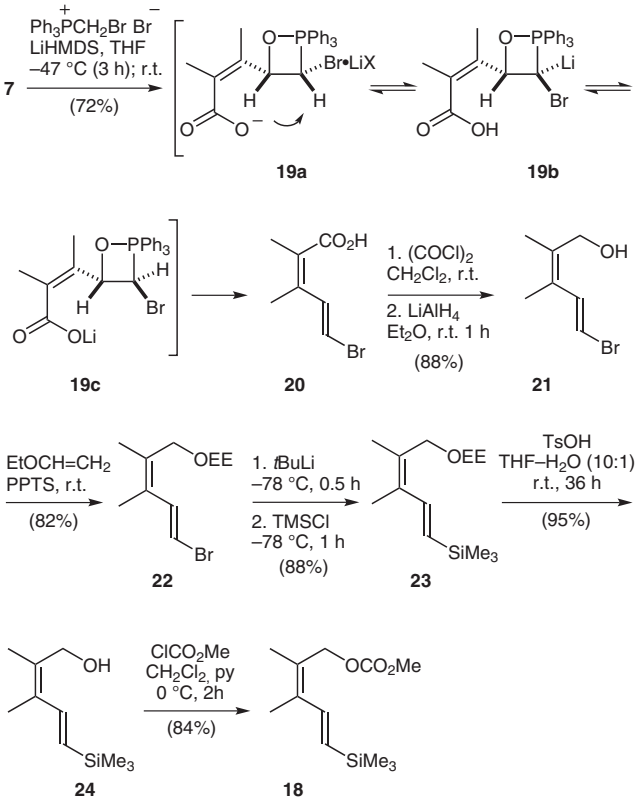
Scheme 3 Unselective Tsuji–Trost pentadienylation of sodium 3-allyltetronate (**2**) with either compound **3a** or **3b**

In line with the mechanistic rationale of an equilibrium of two isomeric (η^3-pentadienyl)palladium complexes **12** and **13**, the pentadienyl carbonate **14** gave virtually the same product mixture of **4** (32%) and **11** (68%) upon reaction with tetronate **2** as evidenced by ^{1}H NMR spectrum. Compound **14** was prepared from γ-keto ester **15**[33] in three steps, a Wittig reaction leading to pentadienoate **16**, followed by a reduction to alcohol **17**, which was finally converted into carbonate **14** with methyl chloroformate (Scheme 4).



Scheme 4 Synthesis of 3,4-dimethylpenta-2,4-dienyl methyl carbonate (**14**)

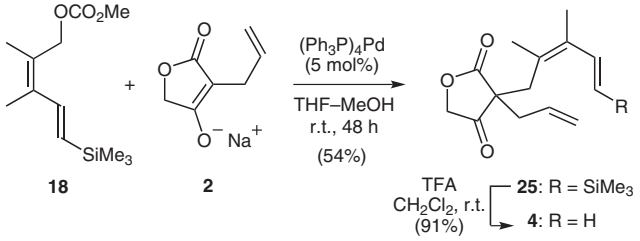
Replacement of Ph_3P by the MeOMOP ligand[19] in Tsuji–Trost reactions of **3a** and **2** in order to exploit the above mentioned memory effect merely led to mixtures of **4** and **11** with ratios no better than 28:72. In addition, heating to 50 °C was necessary for the reaction to take place. Apparently, regioselectivity in Tsuji–Trost pentadienylations of tetronates mainly arises from differences in the sterical accessibility of the two possible allyl ligands, for example, **12** and **13**. Reaction of the former will predominate when a bulky electron-releasing group such as $SiMe_3$ is attached at the methylene terminus C-5 of **3a** or **3b**. The finding that vinylic $SiMe_3$ groups facilitate nucleophilic attack on the remote end of π-allyl palladium complexes even if other sterically demanding residues are present came to be known as the silicon effect.[34–36] 2,3-Dimethyl-5-(trimethylsilyl)penta-2,4-dienyl methyl carbonate (**18**) was thus prepared as depicted in Scheme 5. Lactol **7** was alkenated by Ph_3P=CHBr, generated from $[Ph_3PCH_2Br]Br$[37,38] and LiHMDS as the base, to give pure (2*Z*,4*E*)-2,3-dimethyl-5-bromopenta-2,4-dienoic acid (**20**). It is worthy of note that olefination of **7** by the same ylide prepared with NaHMDS as the base proceeded with only moderate 4*E*-selectivity (*E*/*Z* = 75:25). The high selectivity in the case of LiHMDS is untypical of semi-stabilized ylides. It can be rationalized by assuming an intramolecular Schlosser-type mechanism.[39,40]



Scheme 5 Synthesis of (2*Z*,4*E*)-2,3-dimethyl-5-(trimethylsilyl)penta-2,4-dienyl methyl carbonate (**18**)

In the presence of Li salts the initial mixture of *erythro*-**19a** and *threo*-oxaphosphetanes is deprotonated/lithiated to give predominantly the lithiated *threo*-oxaphos-phetane **19b**. This gets reprotonated with retention by the adjacent carboxylic acid thus leaving the *threo*-oxaphosphetane **19c** that collapses to the corresponding (2*Z*,4*E*)-5-bromo-2,3-dimethylpenta-2,4-dienoic acid (**20**). It was converted to the acid chloride and immediately reduced with $LiAlH_4$ to the alcohol **21**, which was protected with a 1-ethoxyethyl (EE) group to give **22**.[41] Other protective groups such as THP and MOM were unsuitable. With THP the Li–Br exchange[42] failed, while MOM could not be cleaved without removal of the $SiMe_3$ group. Vinyl bromide **22** was converted with retention to the vinyl silane **23** under carefully optimized conditions. Treatment first with *t*-BuLi at –78 °C for 30 minutes and then with Me_3SiCl at this temperature furnished the product diene **23** in 88% yield. High-yielding acid-catalyzed deprotection of acetal **23** afforded the alcohol **24**, which was converted to the target carbonate **18** using methyl chloroformate.

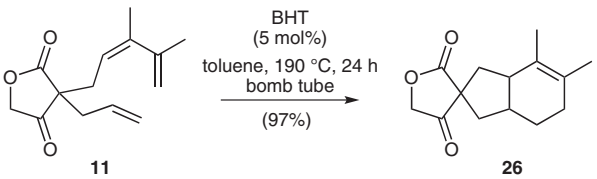
Gratifyingly, the Tsuji–Trost reaction of carbonate **18** with sodium 3-allyltetronate (**2**) under standard conditions afforded the 3-allyl-3-(penta-2,4-dienyl)furan-(2*H*)-2,4-dione (**25**) in over 50% yield as the sole product. Neither symmetric bisallyl derivatives from self reaction of **2** nor regioisomers stemming from attack at C-5 of **18** were found (Scheme 6). It should be noted that acetates and carbonates derived from vinyl bromide **21** did not react with **2**. The silyl group of **25** was removed almost quantitatively with TFA to give compound **4**.



Scheme 6 Regioselective Tsuji–Trost pentadienylation of tetronate **2** with 5-silylated pentadienyl carbonate **18**

In summary, we have developed a regioselective Pd-catalyzed 3-pentadienylation of sodium 3-allyltetronate **2**, which should be also applicable to tetronic acids with other patterns of substitution and to tetramic acids as well. The nucleophilic attack by the tetronate was directed exclusively to the more hindered terminus of the pentadienyl electrophile by attaching a $SiMe_3$ group to the methylene terminus of the starting pentadienyl carbonate **3a**. This $SiMe_3$ group tolerates the conditions of the Tsuji–Trost reaction, but can be easily removed afterwards with TFA.

We are currently investigating asymmetric[2,14] variants of this Tsuji–Trost reaction. First experiments with chiral ligands such as BINAP, phenyl Trost ligand, MeOMOP, and PhBOX were unsuccessful. No reaction took place, except with BINAP, which led to tetronate **2** being consumed by self reaction to yield 3,3-diallyltetronate. We have also begun to explore the planned Diels–Alder step. While 3-allyl-3-penta-2,4-dienyl derivatives with R^2 = H such as **11** reacted readily under Back's conditions[6] to afford the corresponding tricyclic products such as **26** (inseparable unassigned 6:6:1:1 mixture of stereoisomers according to GC) no conversion was yet obtained under these conditions with the analogues **4** or **25** (Scheme 7).



Scheme 7 Preliminary test reaction towards the intramolecular Diels–Alder reaction of 3-allyl-3-penta-2,4-dienylfuran(2*H*)-2,4-diones

Melting points were recorded on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer equipped with an ATR sampling unit. NMR spectra were recorded under conditions as indicated on a Bruker Avance 300 spectrometer. Chemical shifts are given in parts per million (δ) downfield from TMS as internal standard. Analytical gas chromatography was conducted on a DB-5 silica column (l = 30 m; ∅ = 0.32 mm; J & W Scientific). Mass spectra were recorded using a Varian MAT 311A spectrometer (EI, 70 eV). Microanalyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer. For chromatography Merck silica gel 60 (230–400 mesh) was used.

3,4-Dimethylmaleic Anhydride (6)[27]

A solution of maleic anhydride (**5**; 196.2 g, 2.0 mol) in AcOH (300 mL) was added within 1 h to a refluxing solution of 2-aminopyridine (94.1 g, 1.0 mol) in AcOH (200 mL). After refluxing for 2.5 h, the solvent was removed, aq 2 M H_2SO_4 (600 mL) was added, and the mixture was refluxed for another 2 h. Cooling to r.t. resulted in the formation of a brown precipitate, which was collected by filtration, washed with aq 2 M H_2SO_4 (50 mL) and H_2O (2 × 50 mL), and finally dried over P_2O_5. Sublimation at 60 °C/0.02 mbar yielded **6** as colorless crystals (68.0 g, 54%); mp 92 °C (Lit.[27] mp 95 °C); R_f = 0.46 (cyclohexane–EtOAc, 1:1).

IR (ATR): 1815, 1791, 1734, 1687, 1278, 1123 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.02 (s, 6 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.2, 140.7, 166.0.

MS: *m*/*z* (%) = 126 (15, [M^+]), 82 (38), 54 (91), 50 (30), 39 (100).

HRMS (EI): *m*/*z* calcd for $C_6H_6O_3$: 126.0317; found: 126.0317.

5-Hydroxy-3,4-dimethylfuran-(5*H*)-2-one (7)[28]

A solution of $LiAlH(Ot\text{-}Bu)_3$ (22.38 g, 88 mmol) in THF–Et_2O (2:1, 240 mL), freshly prepared from $LiAlH_4$ (3.34 g, 88 mmol) and *t*-BuOH (25.1 mL, 264 mmol), was added within 20 min to a solution of **6** (10.09 g, 80 mmol) in Et_2O (300 mL) at –17 °C. After stirring at –17 °C for another hour, the reaction was allowed to warm to r.t. and stirred for a further 16 h. Aq 2 M H_2SO_4 (300 mL) was added and the aqueous layer was extracted with Et_2O (2 × 80 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was dissolved in a minimum amount of $CHCl_3$, precipitated by the addition of pentane, filtered off after 18 h at –20 °C and washed with pentane (2 × 10 mL) to yield **7** as colorless crystals (8.29 g, 81%); mp 80 °C (Lit.[28] mp 81–82 °C); R_f = 0.41 (Et_2O).

IR (ATR): 3350, 1729, 1694, 1439, 1338, 1079 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.75 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3), 5.80 (s, 1 H, OH), 5.86 (s, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.1, 11.3, 98.7, 125.5, 156.6, 173.6.

MS: *m*/*z* (%) = 128 (1, [M^+]), 100 (100), 83 (41), 55 (67).

HRMS (EI): *m*/*z* calcd for $C_6H_8O_3$: 128.0473; found: 128.0473.

(*Z*)-2,3-Dimethylpenta-2,4-dienoic Acid (8)[29]

A solution of methylidenetriphenylphosphorane (16.71 g, 60.5 mmol) in THF (300 mL) was treated with **7** (3.68 g, 28.7 mmol) and stirred at r.t. for 17 h. The solvent was removed and the residue was taken up with aq $NaHCO_3$ (200 mL, 10% w/w) and washed with EtOAc (3 × 50 mL). The aqueous layer was acidified with concd HCl and then extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were dried (Na_2SO_4) and concentrated to leave **8** as colorless crystals (3.21 g, 89%); mp 47 °C; R_f = 0.58 (Et_2O).

IR (ATR): 2927, 2612, 1673, 1578, 1404, 1292 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.96 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 5.27 (d, *J* = 11.1 Hz, 1 H, H-5), 5.46 (d, *J* = 17.4 Hz, 1 H, H-5), 7.37 (dd, *J* = 17.4, 11.1 Hz, 1 H, H-4), 11.29 (s, 1 H, CO_2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 16.6, 117.3, 125.2, 136.0, 143.3, 174.0.

MS: *m*/*z* (%) = 126 (100, [M$^+$]), 125 (62), 111 (75), 96 (33), 83 (43), 81 (38), 79 (64).

HRMS (EI): *m*/*z* calcd for $C_7H_{10}O_2$: 126.0681; found: 126.0681.

(*Z*)-2,3-Dimethylpenta-2,4-dienoyl Chloride (9)[32]

A mixture of **8** (2.92 g, 23.1 mmol), hexachloroacetone (1.75 mL, 11.6 mmol), and CH_2Cl_2 (120 mL) was cooled to 0 °C, treated with PPh_3 (6.06 g, 23.1 mmol) and stirred for 1.5 h. The solvent was removed under reduced pressure to yield **9** as a colorless liquid (3.34 g, 100%), which was used in the next step; bp 94 °C/11 mbar.

IR (ATR): 2926, 1764, 1569, 1171, 984, 907 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 5.35 (d, *J* = 11.0 Hz, 1 H, H-5), 5.54 (d, *J* = 17.1 Hz, 1 H, H-5), 6.92 (dd, *J* = 17.1, 11.0 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 17.0, 119.5, 130.2, 134.7, 142.3, 168.5.

(*Z*)-2,3-Dimethylpenta-2,4-dien-1-ol (10)

A solution of crude **9** (640 mg, 4.75 mmol) in Et_2O (80 mL) was treated with $LiAlH_4$ (210 mg, 5.54 mmol) and the resulting mixture was stirred at r.t. for 1.5 h. After cooling to 0 °C, it was treated with aq 2 M H_2SO_4 (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give **10** as a colorless oil (350 mg, 66%); R_f = 0.23 (cyclohexane–Et_2O, 2:1); bp 110 °C/19 mbar.

IR (ATR): 3348, 2925, 1380, 1000, 897 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 2.89 (s, 1 H, OH), 4.28 (s, 2 H, H-1), 5.07 (d, *J* = 10.9 Hz, 1 H, H-5), 5.23 (d, *J* = 17.1 Hz, 1 H, H-5), 6.88 (dd, *J* = 17.1, 10.9 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 17.9, 62.9, 113.4, 131.0, 133.5, 134.3.

MS: *m*/*z* (%) = 112 (39, [M$^+$]), 97 (71), 94 (42), 83 (56), 79 (60), 77 (40), 69 (28), 67 (27), 55 (74), 53 (36), 43 (90), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_7H_{12}O$: 112.0888; found: 112.0888.

(*Z*)-2,3-Dimethylpenta-2,4-dienyl Methyl Carbonate (3a)

A mixture of **10** (561 mg, 5.0 mmol), CH_2Cl_2 (5 mL), and pyridine (2.0 mL, 25.0 mmol) was cooled to 0 °C, treated with methyl chloroformate (0.96 mL, 12.5 mmol), and stirred at for 2 h. MeOH (2 mL) and then aq 1 M HCl (30 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with aq 1 M HCl (30 mL), brine (30 mL), and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography on silica gel to yield **3a** as a colorless liquid (682 mg, 80%); R_f = 0.30 (cyclohexane–Et_2O, 9:1).

IR (ATR): 2960, 1746, 1442, 1253, 983 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.79 (s, 2 H, H-1), 5.11 (d, *J* = 10.9 Hz, 1 H, H-5), 5.24 (d, *J* = 17.1 Hz, 1 H, H-5), 6.86 (dd, *J* = 17.1, 10.9 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.8, 54.7, 67.8, 114.4, 127.8, 133.7, 134.2, 155.9.

MS: *m*/*z* (%) = 170 (20, [M$^+$]), 111 (15), 95 (42), 94 (53), 79 (100).

(*Z*)-2,3-Dimethylpenta-2,4-dienyl Acetate (3b)

A solution of **10** (1.92 g, 17.1 mmol) in pyridine (40 mL) was treated with Ac_2O (6.80 mL, 68.4 mmol) and the mixture was stirred at r.t. for 30 min. MeOH (20 mL) was added and stirring was continued for 30 min. The volatiles were removed under reduced pressure and H_2O (40 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were washed with aq 2 M HCl (5 × 50 mL), dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by column chromatography on silica gel to leave **3b** as a colorless liquid (2.22 g, 84%); R_f = 0.40 (cyclohexane–EtOAc, 9:1).

IR (ATR): 2926, 1736, 1375, 1224, 1021, 986 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 4.68 (s, 2 H, H-1), 5.04 (d, *J* = 11.0 Hz, 1 H, H-5), 5.19 (d, *J* = 17.0 Hz, 1 H, H-5), 6.79 (dd, *J* = 17.0, 11.0 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 18.3, 21.2, 64.6, 114.3, 128.7, 133.4, 134.6, 171.4.

MS: *m*/*z* (%) = 154 (7, [M$^+$]), 112 (15), 97 (8), 94 (31), 79 (100).

HRMS (EI): *m*/*z* calcd for 154.0993: $C_9H_{14}O_2$; found: 154.0988.

(*E*)-Methyl 3,4-Dimethylpenta-2,4-dienoate (16)

A solution of **15** (3.30 g, 23.2 mmol, *E*/*Z* = 69:31) in THF (30 mL) was added to a solution of $Ph_3P{=}CH_2$ (7.04 g, 25.5 mmol) in THF (100 mL) at r.t. The mixture was stirred for 28 h, the solvent evaporated, and the crude product purified by column chromatography on silica gel to yield **16** as a yellowish liquid (1.67 g, 51%); R_f = 0.57 (cyclohexane–Et_2O, 2:1).

IR (ATR): 2950, 1717, 1625, 1606, 1294, 1177 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 2.32 (d, *J* = 1.1 Hz, 3 H, CH_3), 3.71 (s, 3 H, OCH_3), 5.23 (s, 1 H, H-5), 5.42 (s, 1 H, H-5), 5.90 (q, *J* = 1.1 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 20.6, 51.0, 115.7, 118.1, 144.1, 154.2, 167.7.

MS: *m*/*z* (%) = 140 (94, [M$^+$]), 139 (90), 125 (100), 109 (77), 81 (92), 79 (67).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.74; H, 8.56.

(*E*)-3,4-Dimethylpenta-2,4-dien-1-ol (17)

A mixture of **16** (701 mg, 5.0 mmol), Et_2O (30 mL), and $LiAlH_4$ (216 mg, 5.70 mmol) was stirred at r.t. for 1 h, then cooled to 0 °C, and treated with aq 2 M H_2SO_4 (50 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL), the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was filtered over a column of silica gel to leave **17** as a colorless liquid (315 mg, 56%), which was used without further purification; R_f = 0.32 (cyclohexane–Et_2O, 1:1).

IR (ATR): 3326, 2949, 1609, 1441, 1375, 1089 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.79 (s, 3 H, CH_3), 1.89 (s, 3 H, CH_3), 2.52 (s, 1 H, OH), 4.26 (d, *J* = 6.5 Hz, 2 H, H-1), 4.94 (s, 1 H, H-5), 5.05 (s, 1 H, H-5), 5.72 (t, *J* = 6.5 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 20.6, 59.7, 112.6, 126.2, 136.8, 143.9.

MS: *m*/*z* (%) = 112 (18, [M$^+$]), 97 (43), 94 (56), 91 (25), 83 (76), 79 (100).

(*E*)-3,4-Dimethylpenta-2,4-dienyl Methyl Carbonate (14)

A mixture of **17** (112 mg, 1.0 mmol), CH_2Cl_2 (10 mL), pyridine (0.32 mL, 4.0 mmol), and DMAP (25 mg, 0.2 mmol) was cooled to 0 °C and treated with methyl chloroformate (1.24 mL, 16.0 mmol). The mixture was stirred at r.t. for 2 h, quenched with MeOH (2 mL),

and treated with aq 1 M HCl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), the combined organic phases were washed with aq 1 M HCl (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. Column chromatography (silica gel, cyclohexane–Et_2O, 9:1) gave **14** as a colorless liquid (92 mg, 54%); R_f = 0.40 (cyclohexane–Et_2O, 2:1).

IR (ATR): 2956, 1744, 1611, 1442, 1373, 1248 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.87 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.80 (d, *J* = 6.8 Hz, 2 H, H-1), 5.00 (s, 1 H, H-5), 5.12 (s, 1 H, H-5), 5.70 (t, *J* = 6.8 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.6, 54.7, 65.2, 113.7, 120.2, 140.1, 143.7, 155.8.

MS: *m*/*z* (%) = 170 (21, [M^+]), 111 (33), 95 (53), 94 (63), 91 (23), 79 (100), 77 (47).

(2*Z*,4*E*)-5-Bromo-2,3-dimethylpenta-2,4-dienoic Acid (20)

BuLi (2.4 M in hexane, 11.77 mL, 28.0 mmol) was added at 0 °C to a solution of hexamethyldisilazane (6.50 mL, 29.4 mmol) in THF (120 mL). After stirring at r.t. for 1 h, the mixture was cooled to –47 °C and [Ph_3PCH_2Br]Br (6.72 g, 15.4 mmol) was added. The resulting bright yellow suspension was stirred at –47 °C for 1 h, **7** (1.78 g, 13.89 mmol) was added, and stirring was continued at –47 °C for 4 h and finally at r.t. for 16 h. Aq $KHCO_3$ (100 mL, 10% w/w) was added, the volatiles were removed under reduced pressure, and the aqueous layer was washed with EtOAc (3 × 100 mL). The combined organic layers were extracted with aq $KHCO_3$ (2 × 50 mL, 10%) and the combined aqueous layers were acidified with concd HCl. The product was extracted with Et_2O (3 × 100 mL), the combined Et_2O layers were dried (Na_2SO_4), and evaporated to dryness. The crude product was dissolved in a minimum amount of EtOAc, precipitated by the addition of pentane, filtered off after 3 d at –20 °C, and washed with pentane (2 × 10 mL) to leave **20** as colorless crystals (2.05 g, 72%); mp 82 °C; R_f = 0.49 [cyclohexane–Et_2O (1:1) + 0.5% AcOH].

IR (ATR): 2870, 1676, 1627, 1576, 1410, 1292 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3), 6.63 (d, *J* = 13.8 Hz, 1 H, H-5), 7.89 (d, *J* = 13.8 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 16.3, 111.4, 125.7, 136.6, 141.0, 173.0.

MS: *m*/*z* (%) = 205 (6, [M^+]), 189 (9), 125 (100), 80 (17), 79 (16), 77 (19), 53 (13), 43 (34), 41(42).

HRMS (EI): *m*/*z* calcd for $C_7H_9BrO_2$: 205.9765; found: 205.9776.

(2*Z*,4*E*)-5-Bromo-2,3-dimethylpenta-2,4-dien-1-ol (21)

A solution of **20** (1.95 g, 9.50 mmol) in CH_2Cl_2 (50 mL) was treated with oxalyl chloride (2.01 mL, 23.75 mmol) and the mixture was stirred at r.t. for 1 h. All volatiles were removed under reduced pressure and the oily residue was redissolved in Et_2O (75 mL). After addition of $LiAlH_4$ (378 mg, 9.98 mmol), the mixture was stirred at r.t. for another hour and finally quenched by the addition of aq 1 M H_2SO_4 (40 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic phases were washed with brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (silica gel, cyclohexane–EtOAc, 3:1) gave alcohol **21** (1.59 g, 88%) as a yellowish liquid; R_f = 0.24 (cyclohexane–EtOAc, 3:1).

IR (ATR): 3310, 2921, 1579, 1439, 1382, 1211 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.75 (s, 3 H, CH_3), 1.81 (s, 3 H, CH_3), 2.54 (s, 1 H, OH), 4.16 (s, 2 H, H-1), 6.26 (d, *J* = 13.6 Hz, 1 H, H-5), 7.18 (d, *J* = 13.6 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 17.7, 62.5, 106.3, 128.8, 134.7, 135.5.

MS: *m*/*z* (%) = 192 (3, [M^+]), 190 (3, [M^+]), 174 (5), 172 (5), 111 (27), 93 (33), 91 (48), 77 (25), 36 (100).

Anal. Calcd for $C_7H_{11}BrO$: C, 44.00; H, 5.80. Found: C, 43.76; H, 5.55.

(1*E*,3*Z*)-1-Bromo-5-(1′-ethoxyethoxy)-3,4-dimethylpenta-1,3-diene (22)[41]

A mixture of **21** (1.60 g, 8.35 mmol), ethyl vinyl ether (16 mL) and PPTS (50 mg, 0.20 mmol) was stirred at r.t. for 2 h, then filtered over a short plug of silica gel, which was washed with CH_2Cl_2 (180 mL). Concentration of the combined filtrates and Kugelrohr distillation of the residue (160 °C/0.13 mbar) yielded **22** as a yellow liquid (1.80 g, 82%); R_f = 0.63 (cyclohexane–EtOAc, 1:1).

IR (ATR): 2979, 2924, 1583, 1448, 1383, 1337, 1212, 1128, 1094, 1084 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.21 (dd, *J* = 7.1, 7.1 Hz, 3 H, H-4′), 1.30 (d, *J* = 5.4 Hz, 3 H, H-2′), 1.76 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 3.48 (dq, *J* = 9.3, 7.1 Hz, 1 H, H-3′a), 3.62 (dq, *J* = 9.3, 7.1 Hz, 1 H, H-3′b), 4.09 (s, 2 H, H-1), 4.67 (q, *J* = 5.4 Hz, 1 H, H-1′), 6.26 (d, *J* = 13.5 Hz, 1 H, H-5), 7.19 (d, *J* = 13.5 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 15.3, 18.2, 19.7, 60.5, 64.8, 98.9, 106.2, 129.9, 132.3, 135.8.

MS: *m*/*z* (%) = 191 (3), 189 (3), 175 (16), 173 (16), 149 (8), 111 (22), 110 (19), 109 (23), 94 (42), 73 (100).

Anal. Calcd for $C_{11}H_{19}BrO_2$: C, 50.20; H, 7.28. Found: C, 50.36; H, 7.18.

(1*E*,3*Z*)-5-(1′-Ethoxyethoxy)-3,4-dimethyl-1-(trimethylsilyl)penta-1,3-diene (23)[42]

A solution of vinyl bromide **22** (1.74 g, 6.61 mmol) in THF (50 mL) was cooled to –78 °C and slowly treated with *t*-BuLi (7.0 mL, 1.9 M, 13.3 mmol) via syringe/septa technique. The pink solution was stirred at this temperature for 30 min and then treated with Me_3SiCl (2.10 mL, 16.53 mmol), freshly distilled from CaH_2. The solution immediately turned colorless and was stirred for another hour before it was quenched with aq $KHCO_3$ (30 mL, 10% w/w) and allowed to reach r.t. The aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to yield **23** (1.49 g, 88%) as a yellow liquid, which was used in the next step without purification; R_f = 0.61 (cyclohexane–EtOAc, 4:1).

IR (ATR): 2955, 2896, 1570, 1443, 1379, 1247, 1127, 1083, 1057, 1029, 979, 865, 835, 731 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.08 [s, 9 H, $Si(CH_3)_3$], 1.21 (dd, *J* = 7.1, 7.1 Hz, 3 H, H-4′), 1.32 (d, *J* = 5.3 Hz, 3 H, H-2′), 1.80 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3), 3.50 (dq, *J* = 9.4, 7.1 Hz, 1 H, H-3′a), 3.65 (dq, *J* = 9.4, 7.1 Hz, 1 H, H-3′b), 4.20 (s, 2 H, H-1), 4.70 (q, *J* = 5.3 Hz, 1 H, H-1′), 5.85 (d, *J* = 18.9 Hz, 1 H, H-5), 7.06 (d, *J* = 18.9 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.2, 14.3, 15.3, 18.6, 19.7, 60.3, 64.7, 98.7, 128.4, 131.4, 133.0, 141.4.

MS: *m*/*z* (%) = 183 (4), 167 (4), 147 (3), 137 (4), 109 (5), 95 (7), 75 (6), 73 (100).

(2*Z*,4*E*)-2,3-Dimethyl-5-(trimethylsilyl)penta-2,4-dien-1-ol (24)

A mixture of **23** (1.49 g, 5.83 mmol) and $TsOH·H_2O$ (100 mg, 0.53 mmol) in THF–H_2O (10:1, 22 mL) was stirred at r.t. for 40 h. Aq $KHCO_3$ (30 mL, 10% w/w) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried, concentrated, and the residue purified by column chromatography on silica gel to leave **24** (1.02 g, 95%) as a yellow liquid; R_f = 0.40 (cyclohexane–EtOAc, 4:1).

IR (ATR): 3364, 2954, 1738, 1365, 1247, 1217, 1162, 1056, 1014, 979, 864, 834, 743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.09 [s, 9 H, $Si(CH_3)_3$], 1.81 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 2.34 (s, 1 H, OH), 4.32 (s, 2 H, H-1), 5.88 (d, *J* = 18.8 Hz, 1 H, H-5), 7.06 (d, *J* = 18.8 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.1, 14.3, 18.2, 62.7, 128.9, 132.1, 134.0, 140.9.

MS: *m*/*z* (%) = 184 (25, [M^+]), 169 (33), 111 (11), 94 (8), 75 (90), 73 (100).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{20}OSi$: 184.1283; found: 184.1322.

(2*Z*,4*E*)-2,3-Dimethyl-5-(trimethylsilyl)penta-2,4-dienyl Methyl Carbonate (18)

Analogous to the synthesis of carbonate **3a**, compound **18** (1.13 g, 84%) was obtained from **24** (1.02 g, 5.53 mmol) as a yellow oil; R_f = 0.51 (cyclohexane–EtOAc, 4:1).

IR (ATR): 2956, 1748, 1442, 1373, 1247, 977 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.08 [s, 9 H, $Si(CH_3)_3$], 1.80 (s, 3 H, CH_3), 1.84 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.83 (s, 2 H, H-1), 5.91 (d, *J* = 18.7 Hz, 1 H, H-5), 7.02 (d, *J* = 18.7 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.2, 14.5, 18.1, 54.7, 67.7, 128.1, 130.1, 134.8, 140.8, 155.9.

MS: *m*/*z* (%) = 242 (29, [M^+]), 153 (7), 146 (16), 94 (100), 91 (94), 77 (38).

Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.33; H, 8.98.

3-Allyl-3-[(2′*Z*,4′*E*)-2′,3′-dimethyl-5′-(trimethylsilyl)penta-2′,4′-dienyl]furan(5*H*)-2,4-dione (25)[2]

A suspension of sodium allyltetronate (**2**; 163 mg, 1.0 mmol) in THF (10 mL) was treated with MeOH until a clear solution was obtained (ca. 3 mL). Carbonate **18** (271 mg, 1.06 mmol) dissolved in THF (4 mL) and $Pd(Ph_3)_4$ (58 mg, 5 mol%) were added and the mixture was stirred at r.t. until complete consumption of **18** (GC control). Filtration over a plug of silica gel, washing of the latter with Et_2O (60 mL), concentration of the combined filtrates, and column chromatography of the residue on silica gel yielded **25** as a colorless oil (175 mg, 54%); R_f = 0.09 (cyclohexane–Et_2O, 95:5).

IR (ATR): 2924, 2853, 1760, 1465, 1260, 1092 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 1.72 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3), 2.54 (d, *J* = 7.4 Hz, 2 H, H-1′), 2.65 (d, *J* = 13.7 Hz, 1 H, H-1″a), 3.00 (d, *J* = 13.7 Hz, 1 H, H-1″b), 4.25 (d, *J* = 17.1 Hz, 1 H, H-5a), 4.32 (d, *J* = 17.1 Hz, 1 H, H-5b), 5.11 (d, *J* = 10.1 Hz, 1 H, H-3′), 5.14 (d, *J* = 17.0 Hz, 1 H, H-3′), 5.60 (ddt, *J* = 17.0, 10.1, 7.4 Hz, 1 H, H-2′), 5.83 (d, *J* = 18.7 Hz, 1 H, H-5″), 6.89 (d, *J* = 18.7 Hz, 1 H, H-4″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.3, 14.3, 21.6, 39.4, 40.1, 53.7, 73.4, 121.1, 127.7, 129.2, 130.2, 133.9, 141.1, 176.1, 209.6.

MS: *m*/*z* (%) = 306 (5, [M^+]), 265 (13), 213 (5), 197 (12), 181 (11), 175 (8), 151 (9), 107 (9), 75 (40), 73 (100).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{26}O_3Si$: 306.1651; found: 306.1657.

(*Z*)-3-Allyl-3-(2′,3′-dimethylpenta-2′,4′-dienyl)furan-(5*H*)-2,4-dione (4)

A solution of **25** (34 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (0.02 mL, 0.24 mmol) and the mixture was stirred at r.t. for 75 min. Aq $KHCO_3$ (30 mL, 10% w/w) was added, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **4** as a yellow oil (23 mg, 91%); R_f = 0.40 (cyclohexane–EtOAc, 4:1).

IR (ATR): 2940, 1755, 1435, 1379, 1353, 1262, 1215, 1161, 1088, 1051, 994, 929, 840, 798, 667 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.74 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3), 2.55 (d, *J* = 7.6 Hz, 2 H, H-1′), 2.67 (d, *J* = 13.6 Hz, 1 H, H-1″a), 2.94 (d, *J* = 13.6 Hz, 1 H, H-1″b), 4.32–4.36 (m, 2 H, H-5), 5.09 (d, *J* = 10.9 Hz, 1 H, H-5″), 5.13 (d, *J* = 10.0 Hz, 1 H, H-3′), 5.15 (d, *J* = 17.2 Hz, 1 H, H-3′), 5.19 (d, *J* = 17.1 Hz, 1 H, H-5″), 5.59 (ddt, *J* = 17.2, 10.0, 7.6 Hz, 1 H, H-2′), 6.75 (dd, *J* = 17.1, 10.9 Hz, 1 H, H-4″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.0, 39.6, 40.2, 53.8, 73.4, 113.8, 121.3, 127.3, 130.2, 132.9, 134.4, 176.2, 210.0.

MS: *m*/*z* (%) = 234 (17, [M^+]), 205 (4), 193 (7), 176 (20), 113 (7), 93 (36), 77 (35), 67 (83), 55 (100).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.56; H, 7.52.

(*Z*)-3-Allyl-3-(3,4-dimethylpenta-2,4-dienyl)furan-2,4(5*H*)-dione (11)[2]

Analogous to the synthesis of **25**, compound **11** (114 mg, 22%) was obtained from **3a** (354 mg, 2.20 mmol) and **2** (360 mg, 2.22 mmol) as a colorless oil after column chromatography on silica gel; R_f = 0.14 (cyclohexane–Et_2O, 95:5).

IR (ATR): 2933, 1804, 1758, 1437, 1344, 1217 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.78 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3), 2.55 (d, *J* = 7.5 Hz, 2 H, H-1′), 2.62 (dd, *J* = 13.8, 7.5 Hz, 1 H, H-1″a), 2.71 (dd, *J* = 13.8, 8.7 Hz, 1 H, H-1″b), 4.30 (d, *J* = 17.2 Hz, 1 H, H-5a), 4.37 (d, *J* = 17.2 Hz, 1 H, H-5b), 4.95 (s, 1 H, H-5″), 5.03 (s, 1 H, H-5″), 5.15 (d, *J* = 9.9 Hz, 1 H, H-3′), 5.16 (d, *J* = 17.1 Hz, 1 H, H-3′), 5.39 (dd, *J* = 8.7, 7.5 Hz, 1 H, H-2″), 5.64 (ddt, *J* = 17.1, 9.9, 7.5 Hz, 1 H, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 20.8, 34.5, 38.9, 54.2, 73.3, 113.4, 118.0, 121.2, 130.1, 140.4, 143.7, 176.0, 210.3.

MS: *m*/*z* (%) = 234 (5, [M^+]), 219 (11), 201 (6), 193 (10), 175 (10), 147 (8), 139 (10), 133 (13), 122 (20), 121 (89), 114 (74), 107 (57), 96 (28), 95 (100).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1251.

3-Spiro[2′-(1′,3′,3a′,4′,5′,7a′-hexahydro-6′,7′-dimethyl)indenyl]furan-(5*H*)-2,4-dione (26)

A mixture of **11** (71 mg, 0.30 mmol), toluene (15 mL), and BHT (10 mg, 0.05 mmol) was sealed in a 20 mL bomb tube and heated at 190 °C for 25 h. The solvent was removed and the crude product was purified by column chromatography (silica gel, cyclohexane–Et_2O, 2:1) to yield an inseparable crystalline 6:6:1:1 mixture (GC) of unassigned stereoisomers of **26** (69 mg, 97%); R_f = 0.26 (cyclohexane–Et_2O, 2:1).

IR (ATR): 2924, 1799, 1753, 1437, 1338, 1260, 1091, 1048, 798, 747 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.56–1.62 (m, 6 H), 1.64–2.40 (m, 10 H), 4.60 (d, *J* = 16.9 Hz, 1 H, H-5a), 4.68 (d, *J* = 16.9 Hz, 1 H, H-5b).

^{13}C NMR (75 MHz $CDCl_3$): δ = 15.80, 15.85, 18.5, 27.1, 27.2, 33.6, 33.7, 38.8, 39.3, 40.8, 41.3, 44.2, 44.4, 48.7, 48.8, 51.6, 71.9, 72.3, 126.3, 126.4, 127.4, 127.5, 178.8, 210.6.

MS: *m*/*z* (%) = 234 (14, [M^+]), 219 (4), 121 (97), 114 (100), 107 (31), 105 (39), 95 (43), 93 (19), 91 (18), 79 (16), 77 (15).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1253.

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