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Regiospecific substitution of the carbon–boron bond of tris-(4-methylfuran-3-yl)boroxine: a model ring C→BC→ABC approach towards eudesmanolides☆

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Dedicated to Dr Douglas Lloyd of the University of St. Andrews on the occasion of his 80th birthday

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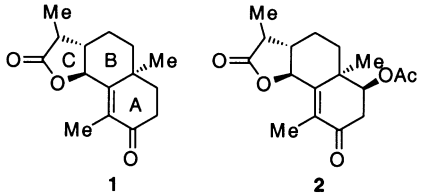
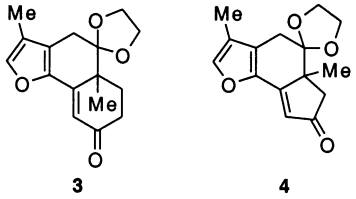
Abstract—A synthetic study of eudesmanolides was performed utilizing a Suzuki coupling reaction of tris(4-methylfuran-3-yl)boroxine (**6**) as the pivotal step. The other key reactions involved Friedel–Crafts acylation, Wacker–Tsuji reaction and aldol condensation. In this Ring C→BC→ABC approach, a model compound **3** towards the synthesis of eudesmanolides 11,13-dihydrotubiferin (**1**) and artogallin (**2**) was realized. In another model study, the five-membered analog **4** was also obtained.

1. Introduction

An organosilicon–organoboron protocol directed to the synthesis of 3,4-disubstituted furans was recently established in our laboratory.[1,2] The same method was subsequently extended to the realization of polysubstituted furans.[3] Herein, we would like to report the application of this strategy as a pivotal step in the synthetic study of eudesmanolides, e.g. 11,13-dihydrotubiferin (**1**)[4] and artogallin (**2**).[5] Our initial target molecule is furan **3** because the oxidative conversion of furans to butanolides is well documented.[6] By employing a model Ring C→BC→ABC approach, the construction of **3** as well as its related compound **4** utilizing the title compound tris(3-methylfuran-4-yl)boroxine (**5**) as a precursor is delineated below. It is noteworthy that a compound structurally similar to **4** was recently used to synthesize the cyathin core of diterpenes erinacine and scabronine.[7]





2. Results and discussion

As depicted in Scheme 1, the title compound tris(4-methylfuran-3-yl)boroxine (**6**) was prepared from 3-methyl-4-trimethylsilylfuran (**5**),[1f] which in turn, was synthesized through Diels–Alder reaction between trimethylsilyl-1-propyne and 4-phenyloxazole[8] after extrusion of benzonitrile.[1f] The Suzuki coupling of boroxine **6** with ethyl 4-bromo-3-methoxycrotonate (**7**)[9] was not trivial due primarily to the unexpected formation of the self-coupling product 4,4′-dimethyl-3,3′-bifuran (**8**). After much experimentation, we were able to obtain the desired product **9** in 60% yield, together with 20% yield of **8**, by employing palladium bis(dibenzylideneacetone) as catalyst through a slow addition of **6** to **7**. With **9** (Ring C) in hand, we then proceeded to the formation of Ring B.

The methyl enol ether moiety of **9** was first converted with *p*-TsOH·H_2O in aqueous EtOH, providing the β-ketoester **10** in 87% yield (Scheme 2). Methylation of **10** then led to the methyl-substituted ketoester **11** in 75% yield. Consecutive alkylation of **11** was also achieved through the use of KO-*t*-Bu as base. In this way, a butenyl group as well as an allyl group were introduced, affording the dialkylation products **12** and **13**, respectively (Scheme 2).

☆ Taken in part from the Ph.D. thesis of C.-Y. Y., The Chinese University of Hong Kong, 1999.

Keywords: aldol reactions; Friedel–Crafts reactions; furans; Suzuki reactions; terpenes and terpenoids.

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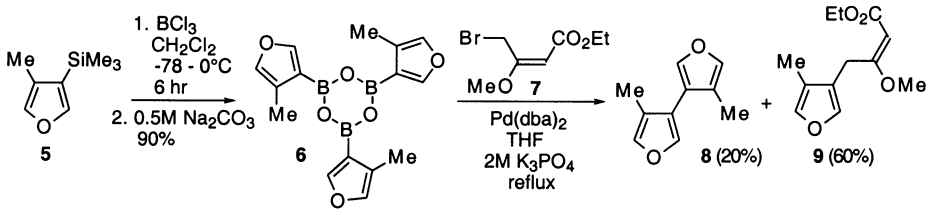
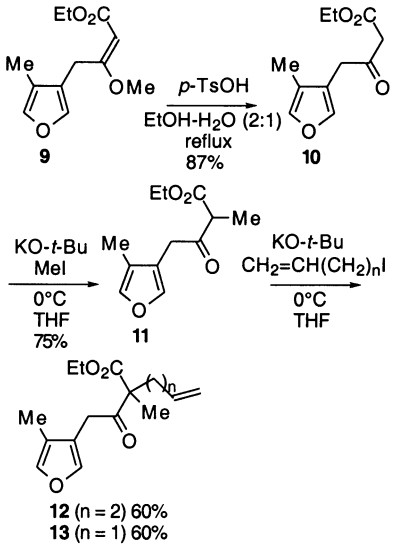
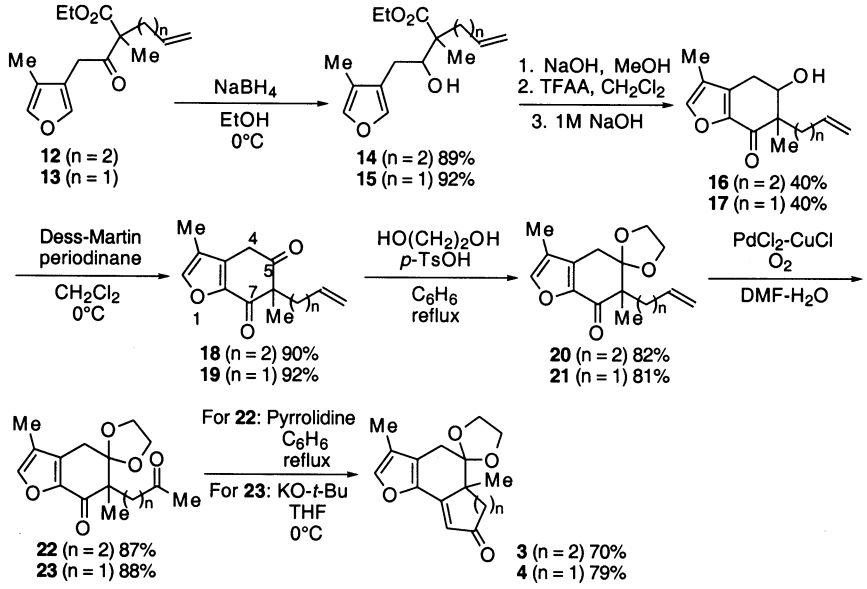


Scheme 1.

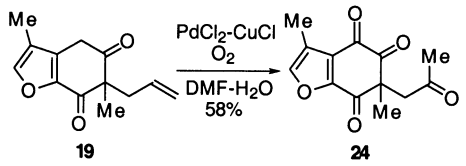


Scheme 2.

Since β-ketoacid is vulnerable to decarboxylation, ketoester **12** was firstly reduced to hydroxyester **14** by $NaBH_4$. Saponification of **14** with NaOH was followed immediately without further purification by a Friedel–Crafts acylation (Scheme 3). Trifluoroacetic anhydride was found to be effective in promoting the cyclization, providing the cyclohexenone (Ring B). Treatment of the resulting product with an aqueous 1 M NaOH was, however, needed to hydrolyze all the resulting trifluoroacetate to hydroxycyclohexenone **16**. The hydroxy group of **16** was oxidized to a carbonyl group with Dess–Martin periodinane[10] to give the diketone **18** in 90% yield. Oxidation of the terminal double bond was expected to lead to a methyl ketone on the side-chain. However, to suppress the possible oxidation of the enolizable methylene group (C-4) of the cyclohexenone ring (vide infra), the C-5 carbonyl was selectively protected with ethylene glycol to afford **20**. Due to the crowding around C-7 and the lower reactivity arising from the conjugation with the furan ring, the C-5 carbonyl reacted preferentially while the C-7 carbonyl remained intact. This route is supported by ^{1}H NMR spectral data of **20** because the H-2 of the furan ring shows a slightly down-field absorption[11] at δ 7.36 because of the deshielding effect of the C-7 carbonyl group. Wacker-Tsuji oxidation[12] of **20** was then carried out to afford the diketone **22** in 87% yield. Our first target molecule **3** was eventually obtained through an aldol cyclization reaction of **22** with pyrrolidine in benzene as solvent (Scheme 3). The use of KO-*t*-Bu as base was found to only lead to a dismal yield of **3**. The successful conversion of **22** to **3** was presumably due to the formation of an enamine at the less sterically demanding carbonyl group. The ^{1}H NMR spectrum of compound **3** exhibits absorptions of the alkene proton and the furan proton at δ 6.18 and 7.26, respectively, as two sharp singlets, and the two isolated methylene protons appear as two doublets at δ 2.71 and 2.84 with J=16.8 Hz because of geminal coupling. It is anticipated that a similar entry resembling that for the model synthesis of **3** will in due course provide key



Scheme 3.



Scheme 4.

intermediates for the synthesis of the tricyclic sesquiterpenoids 11,13-dihydrotubiferin (**1**) and artogallin (**2**).

In order to widen the synthetic scope of our route for the realization of **3**, compound **13** was also subjected to a similar procedure as illustrated also in Scheme 3. As can be seen, reduction of **13** gave alcohol **15**, which was cyclized through the same saponification–Friedel–Crafts acylation–hydrolysis of trifluoroacetate steps to provide **17**. Oxidation of **17** to **19** was followed by the protection of the less hindered and more reactive C-5 carbonyl (vide supra), leading to the monoketone **21**. A Wacker–Tsuji reaction was carried out for **21**, from which the diketone **23** was obtained in 88% yield. In contrary to **22**, KO-*t*-Bu was found to be effective in the aldol reaction. In this manner, **23** was smoothly cyclized to **4** in 79% yield. The structure of **4** is supported by its ^{1}H NMR spectrum that reveals characteristic alkene and furan absorptions at δ 6.01 and 7.36, respectively. The ^{13}C NMR spectrum of **4** shows a quaternary signal at δ 206.9 that corresponds to the enone carbonyl carbon.

An attempt was also initiated in the hope of oxidizing the terminal double bond of **19** by a Wacker–Tsuji reaction in the presence of the enolizable C-4 methylene group (Scheme 4). However, only over-oxidized product **24** was isolated. The ^{1}H NMR spectrum of **24** shows clearly the absence of the signal corresponding to the two protons at C-4, and its ^{13}C NMR spectrum expectedly exhibits four carbonyl carbon absorptions.

The avenue for the successful synthesis of compounds **3** and **4** will serve as a model pathway in our future quest for the sesquiterpenoid eudesmanolides.

3. Experimental

3.1. Data for compounds

3.1.1. 4-Methyl-3-trimethylsilylfuran (5).[1f] A sealed tube containing trimethylsilyl-1-propyne (10 g, 90 mmol), 4-phenyloxazole[8] (12.9 g, 90 mmol) and anhydrous DBU (1.5 g, 10 mmol) was heated at 300°C for 7 days to give a dark brown mixture. Vacuum distillation (bath temperature 30–60°C/65–80 pa) of the resulting mixture gave a colorless liquid, which was flash chromatographed on silica gel (100 g, hexanes) to afford **5** as a colorless oil (11 g, 80%). ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.99 (d, J=0.7 Hz, 3H), 7.16 (s, 2H); MS (EI) m/z 154 (M^+). Anal. Calcd for $C_8H_{14}OSi$: C, 62.30; H, 8.69. Found: C, 62.86; H, 9.03.

3.1.2. Tris(4-methylfuran-3-yl)boroxine (6).[1f] To a solution of **5** (462 mg, 3 mmol) in CH_2Cl_2 (100 mL) was added a solution of BCl_3 (1.0 M) in CH_2Cl_2 (5 mL) under N_2 at −78°C. After stirring for 6 h, the reaction was quenched with 0.5 M Na_2CO_3 (5 mL) and the mixture was extracted with Et_2O (3×50 mL). The organic extract was dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel (200 g, hexanes–Et_2O, 2:1) to give **6** (292 mg, 90%) as colorless crystals, mp 130–131°C. ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 9H), 7.21 (s, 3H), 7.90 (d, J=1.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 10.0, 123.8, 140.5, 154.6; MS (EI) m/z 324 (M^+). Anal. Calcd for $C_{15}H_{15}B_3O_6$: C, 55.66; H, 4.67. Found: C, 55.45; H, 4.58.

3.1.3. 4,4′-Dimethyl-3,3′-bifuran (8) and ethyl 4-(4-methylfuran-3-yl)-3-methoxycrotonate (9). To a refluxing mixture of **7** (4 g, 18 mmol), 2 M aq. K_3PO_4 (30 mL) and $Pd(dba)_2$ (0.5 g, 0.9 mmol) in THF (60 mL) was added a solution of **6** (2 g, 6 mmol) in THF (60 mL) under N_2 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 the organic extract was dried ($MgSO_4$). After evaporation, the residue was chromatographed on a silica gel column (100 g, hexanes–EtOAc, 50:1) to afford **8** (290 mg, 20%) as colorless crystals, mp 43.5–44°C and **9** (2.4 g, 60%) as a pale yellow oil.

Compound **8**: ^{1}H NMR ($CDCl_3$) δ 2.06 (d, J=1.2 Hz, 6H), 7.28 (s, 2H), 7.47 (d, J=1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.4, 117.7, 119.5, 139.7, 140.0; MS m/z 162 (M^+); HRMS (EI) Calcd for $C_{10}H_{10}O_2$: 162.0680. Found: 162.0677.

Compound **9**: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J=7.2 Hz, 3H), 1.97 (d, J=1.2 Hz, 3H), 3.62 (s, 3H), 3.88 (d, J=0.6 Hz, 2H), 4.14 (q, J=7.2 Hz, 2H), 5.05 (s, 1H), 7.12 (s, 1H), 7.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.1, 14.3, 25.7, 55.5, 59.5, 90.9, 120.3, 121.0, 139.1, 140.5, 167.3, 173.5; MS (EI) m/z 224 (M^+); HRMS (FAB) Calcd for $C_{12}H_{17}O_4$ (MH^+): 225.1127. Found: 225. 1132.

3.1.4. Ethyl 4-(4-methylfuran-3-yl)acetoacetate (10). To a solution of **9** (2.1 g, 10 mmol) in EtOH–H_2O (2:1) (200 mL) was added a catalytic amount of *p*-TsOH·H_2O. The mixture was refluxed for 6 h. EtOH was removed under reduced pressure and the aqueous residue was extracted with Et_2O (4×60 mL). After drying ($MgSO_4$) and evaporation, the crude product was subjected to flash column chromatography on silica gel (100 g, hexanes–EtOAc, 10:1) to afford **10** (1.8 g, 87%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H), 1.90 (s, 3H), 3.46 (s, 2H), 3.59 (s, 2H), 4.16 (q, J=7.2 Hz, 2H), 7.18 (s, 1H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.7, 13.8, 37.8, 47.8, 61.2, 117.3, 119.8, 139.8, 140.9, 166.9, 199.8; MS (EI) m/z 210 (M^+); HRMS (EI) Calcd for $C_{11}H_{14}O_4$ (M^+) 210.0892. Found: 210.0887.

3.1.5. Ethyl 2-methyl-4-(4-methylfuran-3-yl)acetoacetate (11). To a solution of **10** (1.5 g, 7.1 mmol) in anhydrous THF (15 mL) at 0°C was added KO-*t*-Bu (800 mg, 7.1 mmol). The mixture was allowed to stir for 30 min. MeI (0.5 mL, 8.5 mmol) was then added. White precipitate appeared immediately. After stirring for a further 1 h, the precipitate was filtered off with Celite. The filtration cake was washed with Et_2O (100 mL), and the filtrate was dried

($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column (80 g, hexanes–EtOAc, 15:1) to afford **11** (1.2 g, 75%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J=7.2 Hz, 3H), 1.34 (d, J=7.2 Hz, 3H), 1.90 (d, J=0.9 Hz, 3H), 3.62 (s, 2H), 3.64 (q, J=7.2 hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 7.19 (s, 1H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9, 12.9, 14.0, 36.7, 51.6, 61.4, 117.4, 120.0, 139.9, 141.1, 170.3, 202.8; MS (EI) *m/z* 224 (M^+). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.30; H, 6.87.

3.1.6. Ethyl 2-methyl-2-(but-3-en-1-yl)-4-(4-methylfuran-3-yl)acetoacetate (12). Similar to the preparation of **11**, compound **12** was prepared from **11** (1.2 g, 5.4 mmol) in anhydrous THF (15 mL), KO-*t*-Bu (670 mg, 5.9 mmol) and 4-iodobut-1-ene (1.1 g, 5.9 mmol). Column chromatography on silica gel (80 g, hexane–EtOAc, 30:1) afforded **12** (900 mg, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J=7.2 Hz, 3H), 1.39 (s, 3H), 1.88 (s, 3H), 1.92–2.06 (m, 4H), 3.53 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 4.93–5.04 (m, 2H), 5.70–5.81 (m, 1H), 7.16 (d, J=1.2 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 13.9, 18.9, 28.4, 33.1, 34.1, 59.1, 61.3, 115.0, 117.6, 120.0, 137.4, 139.5, 140.8, 172.7, 204.2; MS (EI) *m/z* 279 (MH^+); HRMS (EI) Calcd for $C_{16}H_{22}O_4$ (M^+): 278.1518. Found: 278.1515.

3.1.7. Ethyl 2-methyl-2-(prop-2-en-1-yl)-4-(4-methylfuran-3-yl)acetoacetate (13). Similar to the preparation of **11**, compound **13** was prepared from **11** (1.2 g, 5.4 mmol) in anhydrous THF (15 mL), KO-*t*-Bu (670 mg, 5.9 mmol) and allyl iodide (0.5 mL, 5.9 mmol). Column chromatography on silica gel (80 g, hexanes–EtOAc, 30:1) afforded **13** (855 mg, 60%). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H), 1.39 (s, 3H), 1.89 (d, J=0.3 Hz, 3H), 2.56 (dd, J=14.1, 7.5 Hz, 1H), 2.69 (dd, J=14.1, 7.5 Hz, 1H), 3.50 (d, J=18.0 Hz, 1H), 3.57 (d, J=18.0 Hz, 1H), 4.19 (dq, J=7.2, 1.2 Hz, 2H), 5.08 (s, 1H), 5.13 (dd, J=6.0, 1.2 Hz, 1H), 5.61–5.70 (m, 1H), 7.18 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 13.9, 19.1, 33.3, 39.5, 59.1, 61.4, 117.6, 119.1, 120.0, 132.4, 139.5, 140.8, 172.3, 203.9; MS (EI) *m/z* 264 (M^+); HRMS (EI) Calcd for $C_{15}H_{20}O_4$ (M^+): 264.1362. Found: 264.1361.

3.1.8. Ethyl 2-methyl-2-(but-3-en-1-yl)-3-hydroxy-4-(4-methylfuran-3-yl)butanoate (14). To a stirred solution of **12** (280 mg, 1 mmol) in EtOH (10 mL) at 0°C was added $NaBH_4$ (42 mg, 1 mmol). After stirring for 30 min, the reaction was quenched with saturated NH_4Cl (5 mL). EtOH was removed under reduced pressure and the aqueous residue was extracted with Et_2O (5×5 mL). The ethereal extract was dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (20 g, hexanes–EtOAc 10:1) gave **14** (253 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.28 (t, J=7.2 Hz, 3H), 1.62–1.68 (m, 1H), 1.82–1.92 (m, 1H), 1.97 (d, J=0.9 Hz, 3H), 2.08–2.11 (m, 1H), 2.29–2.41 (m, 2H), 2.54–2.60 (m, 1H), 3.81–3.86 (m, 1H), 4.18 (q, J=7.2 Hz, 2H), 4.94–5.06 (m, 2H), 5.74–5.83 (m, 1H), 7.18 (s, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.2, 14.2, 16.5, 25.8, 28.8, 31.3, 35.6, 50.5, 60.7, 114.8, 119.9, 121.7, 138.0, 139.6, 140.5, 176.3; MS (FAB) *m/z* 281 (MH^+); HRMS (EI) Calcd for $C_{16}H_{24}O_4$ (M^+): 280.1675. Found: 280.1676.

3.1.9. Ethyl 2-methyl-2-(prop-2-en-1-yl)-3-hydroxy-4-(4-methylfuran-3-yl)butanoate (15). Similar to the preparation of **14**, compound **15** was prepared from **13** (260 mg, 1 mmol) in EtOH (10 mL) and $NaBH_4$ (42 mg, 1 mmol). Column chromatography on silica gel (20 g, hexanes–EtOAc, 10:1) afforded **15** (240 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.27 (t, J=7.2 Hz, 3H), 1.94 (d, J=1.2 Hz, 3H), 2.30–2.38 (m, 2H), 2.48–2.61 (m, 3H), 3.78–3.81 (m, 1H), 4.14 (q, J=7.2 Hz, 2H), 5.07 (s, 1H), 5.12 (dd, J=6.0, 1.8 Hz, 1H), 5.69–5.75 (m, 1H), 7.17 (s, 1H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.2, 14.2, 17.0, 25.8, 40.7, 50.6, 60.7, 74.9, 118.5, 120.0, 121.7, 133.3, 139.6, 140.5, 176.0; MS (EI) *m/z* 266 (M^+); HRMS (EI) Calcd for $C_{15}H_{23}O_4$ (MH^+): 267.1591. Found: 267.1592.

3.1.10. 3,6-Dimethyl-6-(but-3-en-1-yl)-4,5,6,7-tetrahydro-5-hydroxybenzo[*b*]furan-7(6*H*)-one (16). To a solution of **14** (900 mg, 3.2 mmol) in MeOH (20 mL) was added slowly an aqueous solution of 2 M NaOH (5 mL). The mixture was then refluxed for 10 h. After that H_2O (10 mL) was added and the resulting mixture was washed with CH_2Cl_2 (10 mL). The aqueous layer was acidified with 3N HCl 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 re-dissolved in anhydrous CH_2Cl_2 (20 mL). Trifluoroacetic anhydride (1.3 mL, 9.6 mmol) was slowly added. After stirring for 4 h, 1 M NaOH solution (15 mL) was added. The mixture was allowed to stir for a further 4 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 column chromatography on silica gel (30 g, hexanes–EtOAc, 1:1) to afford **16** (300 mg, 40%) as a viscous yellow oil. Compound **16** shows very complex ^{1}H- and ^{13}C NMR spectra due to the presence of a pair of diastereomers. The structure of **16** was confirmed after its oxidation to **18**. MS (EI) *m/z* 234 (M^+); HRMS (EI) Calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256. Found: 234.1256.

3.1.11. 3,6-Dimethyl-6-(prop-2-en-1-yl)-4,5,6,7-tetrahydro-5-hydroxybenzo[*b*]furan-7(6*H*)-one (17). Similar to the preparation of **16**, compound **17** was prepared from **15** (900 mg, 3.4 mmol) and was obtained (300 mg, 40%) after column chromatography on silica gel (30 g, hexanes–EtOAc, 1:1). The ^{1}H- and ^{13}C NMR spectra of **17** are again very complex and its structure was confirmed after its oxidation to **19**. MS (EI) *m/z* 221 (MH^+); HRMS (EI) Calcd for $C_{13}H_{16}O_3$ (M^+): 220.1099. Found: 220.1100.

3.1.12. 3,6-Dimethyl-6-(but-3-en-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (18). To a stirred solution of **16** (240 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane[10] (636 mg, 1.5 mmol) and the mixture was stirred for 10 min at room temperature under N_2. After the addition of sat. aq. $NaHCO_3$ solution (10 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic solution was dried ($MgSO_4$) and evaporated to give a residue which was chromatographed on a silica gel column (30 g, hexanes–EtOAc, 3:1) to give **18** (220 mg, 90%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.90–

2.01 (m, 4H), 2.04 (d, J=0.9 Hz, 3H), 3.59 (d, J=20.7 Hz, 1H), 3.67 (d, J=20.7 Hz, 1H), 4.89–4.96 (m, 2H), 5.64–5.77 (m, 1H), 7.50 (d, J=0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.6, 19.0, 29.0, 35.5, 36.0, 62.1, 115.2, 120.7, 132.8, 137.2, 145.9, 146.1, 185.3, 205.8; MS (EI) m/z 232 (M^+). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 7.02.

3.1.13. 3,6-Dimethyl-6-(prop-2-en-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (19). Similar to the preparation of **18**, compound **19** was prepared from **17** (220 mg, 1 mmol) and Dess–Martin periodinane (635 mg, 1.5 mmol). Column chromatography on silica gel (30 g, hexanes–EtOAc, 3:1) gave **19** (200 mg, 92%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 2.00 (s, 3H), 2.48 (dd, J=13.8, 7.2 Hz, 1H), 2.57 (dd, J=13.8, 7.2 Hz, 1H), 3.57 (s, 2H), 4.97–5.06 (m, 2H), 5.52–5.61 (m, 1H), 7.46 (d, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.6, 8.3, 5.8, 41.5, 62.3, 119.2, 120.7, 132.0, 133.0, 142.0, 146.0, 184.9, 205.3; MS (EI) m/z 219 (MH^+). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.52; H, 6.03.

3.1.14. 3,6-Dimethyl-6-(but-3-en-1-yl)-5,5-(1,3-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (20). A solution of **18** (220 mg, 0.9 mmol), ethylene glycol (0.1 mL, 1.8 mmol) and a catalyst amount of p-TsOH·H_2O in anhydrous C_6H_6 (20 mL) was heated to reflux with a Dean–Stark trap for 24 h. The mixture was diluted with Et_2O (20 mL) and washed successively with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). After drying ($MgSO_4$) and evaporation, the residue was chromatographed on silica gel (30 g, hexanes–EtOAc, 3:1) to afford **20** (215 mg, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.63–1.71 (m, 1H), 1.79–1.96 (m, 2H), 1.98 (d, J=1.2 Hz, 3H), 2.12–2.19 (m, 1H), 2.76 (d, J=16.8 Hz, 1H), 2.97 (d, J=16.8 Hz, 1H), 3.93–4.10 (m, 4H), 4.87–5.00 (m, 2H), 5.66–5.79 (m, 1H), 7.36 (d, J=0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.7, 12.4, 28.4, 34.1, 56.0, 65.1, 65.8, 114.0, 114.4, 120.8, 134.1, 138.3, 144.7, 146.3, 187.8; MS (EI) m/z 276 (M^+); Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.28; H, 7.49.

3.1.15. 3,6-Dimethyl-6-(prop-2-en-1-yl)-5,5-(1,3-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (21). Similar to the preparation of **20**, compound **21** was prepared from **19** (220 mg, 1 mmol), ethylene glycol (0.1 mL, 1.8 mmol) and a catalytic amount of p-TsOH·H_2O. Chromatography on a silica gel column (30 g, hexanes–EtOAc 3:1) afforded **21** (215 mg, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 2.00 (s, 3H), 2.41–2.50 (m, 2H), 2.88 (d, J=17.1 Hz, 1H), 2.94 (d, J=17.1 Hz, 1H), 3.95–4.09 (m, 4H), 4.94–5.01 (m, 2H), 5.74–5.83 (m, 1H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.6, 13.9, 30.0, 38.9, 55.9, 65.0, 65.6, 113.6, 117.0, 120.7, 133.8, 134.1, 144.7, 146.3, 187.4; MS (EI) m/z 262 (M^+); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; C, 68.30; H, 6.95.

3.1.16. 3,6-Dimethyl-6-(3-oxobut-1-yl)-5,5-(1,3-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (22). To a solution of $PdCl_2$ (12 mg, 0.07 mmol) and CuCl (69 mg, 0.7 mmol) in DMF–H_2O (7:1) (5 mL) under an atmosphere of O_2 was added **20** (200 mg, 0.7 mmol) in the same solvent mixture (5 mL) over 30 min. The mixture was allowed to stir for 3 h. Then it was poured into 3N HCl (3 mL) and the mixture was extracted with EtOAc (5×10 mL). The combined extract was washed successively with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). After drying ($MgSO_4$) and evaporation, the residue was chromatographed on silica gel (20 g, hexanes–EtOAc 1:1) to give **22** (184 mg, 87%) as colorless crystals, mp 161–162.5°C. ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.80–2.03 (m, 2H), 1.95 (s, 3H), 2.06 (s, 3H), 2.34–2.45 (m, 1H), 2.51–2.63 (m, 1H), 2.78 (d, J=17.1 Hz, 1H), 2.97 (d, J=17.1 Hz, 1H), 3.91–4.08 (m, 4H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.5, 12.9, 27.7, 29.6, 29.8, 38.3, 54.9, 65.0, 65.5, 113.6, 120.8, 134.5, 144.8, 146.0, 187.5, 207.9; MS (EI) m/z 292 (M^+); Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.57; H, 6.77.

3.1.17. 3,6-Dimethyl-6-(2-oxoprop-1-yl)-5,5-(1,3-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]furan-5(4*H*),7(6*H*)-dione (23). Similar to the preparation of **22**, compound **23** was prepared from **21** (180 mg, 0.7 mmol), $PdCl_2$ (12 mg, 0.07 mmol) and CuCl (69 mg, 0.7 mmol) in DMF–H_2O (7:1) (5 mL). Chromatography on silica gel (20 g, hexanes–EtOAc, 1:1) afforded **23** (169 mg, 88%) as colorless crystals, mp 148–149°C. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.99 (d, J=1.2 Hz, 3H), 2.06 (s, 3H), 2.49 (d, J=13.5 Hz, 1H), 2.81 (d, J=18 Hz, 1H), 2.89 (d, J=18 Hz, 1H), 2.92 (d, J=13.5 Hz, 1H), 3.87–4.02 (m, 4H), 7.42 (d, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.7, 21.2, 29.7, 31.2, 45.8, 56.9, 64.9, 65.1, 113.0, 121.0, 134.9, 145.6, 186.4, 207.3; MS (EI) m/z 278 (M^+); Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.72; H, 6.52. Found: C, 64.07; H, 6.63.

3.1.18. 3,5a-Dimethyl-5,5-(1,3-dioxolan-2-yl)-4,5,5a,6,7,8-hexahydronaphtho[1,2-*b*]furan-8(7*H*)-one (3). A solution of **22** (180 mg, 0.6 mmol) and pyrrolidine (0.05 mL, 0.6 mmol) in anhydrous C_6H_6 (20 mL) was refluxed with a Dean–Stark trap for 12 h. The mixture was then diluted with Et_2O (20 mL) and washed successively with 3N HCl (10 mL), H_2O (10 mL) and brine (10 mL). After drying ($MgSO_4$) and evaporation, the residue was chromatographed on silica gel (20 g, hexanes–EtOAc, 1:1) to afford **3** (115 mg, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.76–1.83 (m, 1H), 1.97 (s, 3H), 2.25–2.36 (m, 1H), 2.51–2.57 (m, 2H), 2.71 (d, J=16.8 Hz, 1H), 2.84 (d, J=16.8 Hz, 1H), 3.94–4.11 (m, 4H), 6.18 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.8, 20.4, 26.0, 29.6, 33.3, 43.1, 65.5, 65.8, 112.4, 116.5, 121.4, 126.8, 142.9, 146.2, 150.2, 198.2; MS (EI) m/z 274 (M^+); HRMS (EI) Calcd for $C_{16}H_{18}O_4$ (M^+): 274.1205. Found: 274.1201.

3.1.19. 3,5a-Dimethyl-5,5-(1,3-dioxolan-2-yl)-4,5,5a,6-tetrahydroindeno[4,5-*b*]furan-7-one (4). To a solution of **23** (140 mg, 0.5 mL) in anhydrous THF (5 mL) was added KO-*t*-Bu (67 mg, 0.6 mmol) at 0°C. The mixture was allowed to stir for 1 h. It was then poured into H_2O (10 mL) and extracted with EtOAc (3×10 mL). The combined extract was washed with dil. aq. NH_4Cl (5 mL) and brine (5 mL). After drying ($MgSO_4$) and evaporation, the residue was chromatographed on silica gel (15 g, hexanes–EtOAc, 1:1) to afford **4** (104 mg, 79%) as colorless crystals, mp 138–138.5°C. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 2.00 (s, 3H), 2.09 (d, J=17.1 Hz, 1H), 2.70 (d, J=17.4 Hz, 1H), 2.73 (d, J=17.1 Hz, 1H), 2.86 (d, J=17.1 Hz, 1H),

3.98–4.14 (m, 4H), 6.01 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9, 25.4, 30.0, 43.7, 50.6, 65.4, 65.6, 111.6, 118.1, 121.6, 128.4, 144.1, 145.1, 164.7, 206.9; MS (EI) *m/z* 260 (M^+); Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.86; H, 6.39.

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