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Synthesis and reactions of functionalized spirocyclopropanes by cyclization of dilithiated β-ketosulfones, α-cyanoacetone and diethyl 2-oxopropylphosphonate with 1,1-diacetylcyclopropane

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Abstract

The cyclization of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1,1-diacetylcyclopropane afforded 1-hydroxyspiro[5.2]-cyclooct-4-en-3-ones, which were transformed, by reaction with tetrabutylammonium halides, into functionalized phenols containing a remote halide function.

1. Introduction

Cytotoxic natural products are important lead structures for the synthesis of new anticancer agents.[1] Notably, the search for new cytotoxic compounds is of ongoing importance since tumours, similar to bacteria, may become resistant to known chemotherapeutics.[2] In addition, several types of tumours have not yet been efficiently addressed by chemotherapeutic methods. Spiro[2.5]cycloocta-4,7-dien-6-ones and related spirocyclopropanes constitute an important structural motif of cytotoxic and cancerostatic natural and non-natural products. This includes, for example, the illudins S and M (Fig. 1), which possess a 1-hydroxyspiro[5.2]cyclooct-4-en-2-one skeleton.[3] The cytotoxic natural products CC-1065 and duocarmycin SA contain a spiro[2.5]cycloocta-4,7-dien-6-one moiety containing aromatic rings fused to a heterocyclic ring system.[4] Most of the chemotherapeutic agents used today belong to alkylating compounds (chlorambucil, melphalan, thiotepa and busulfan), platinum derivatives (cisplatin, carboplatin), inhibitors of topoisomerases (camptothecin, etoposide, doxorubicin), antimetabolic compounds (5-fluoruracil, methotrexate, hydroxyurea) or inhibitors of mitosis (taxol, vinblastine). The illudins belong to the group of alkylating agents: The reaction of a nucleophile (such as glutathione) with the unsaturated ketone moiety results in formation of a cyclohexadiene, which rapidly undergoes an aromatization with concurrent ring opening of the cyclopropane moiety and alkylation of the DNA (Chart 1).[3]

In their pioneering work, Baird and Winstein studied the synthesis of spiro[2.5]cycloocta-4,7-dien-6-ones and their reaction with various nucleophiles.[5] Padwa and co-workers reported interesting cyclization reactions of diazo compounds, which allow a convenient synthesis of illudins.[6] We reported[7] the synthesis of ester-substituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones based on cyclization reactions of 1,3-dicarbonyl dianions. Noteworthy, the products showed a considerable antiproliferative activity against human leukaemia HL60 cells. Herein, we report the synthesis and reactions of novel spirocyclopropanes

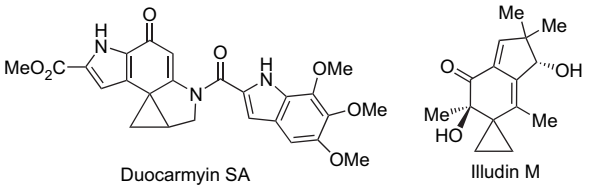

Chart 1. Natural cancerostatic spirocyclopropanes.

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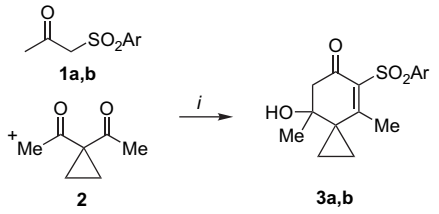
based on cyclizations of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1,1-diacetylcyclopropane. These reactions provide a convenient access to functionalized phenols, which are not readily available by other methods.

2. Results and discussion

2.1. β-Ketosulfones

Dianions of β-ketosulfones are useful synthetic building blocks, which have been previously used in cyclization reactions. This includes, for example, the synthesis of 2-(sulfonylmethylidene)tetrahydrofurans[8] and 7-sulfonyl-2,3,3a,4,5,6-hexahydrobenzofurans[9] by cyclization of β-ketosulfone dianions with cyclic sulfates and 1,4-dibromobut-2-ene, respectively. The cyclization of the dianions of β-ketosulfones **1a**,**b**, generated by means of LDA (2.0 equiv), with 1,1-diacetylcyclopropane (**2**) afforded the 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **3a**,**b** (Scheme 1, Table 1). The relatively low isolated yields can be explained by the fact that the products are, due to their high reactivity, rather unstable and readily decompose during the chromatographic purification. However, it proved possible to directly use the crude spirocyclopropane for the next synthetic step (vide infra) without chromatographic purification.

Despite its unstable nature, it proved to be possible to grow a single crystal of spirocyclopropane **3b** and to independently confirm its structure by X-ray crystal structure analysis (Fig. 1).[10]



Scheme 1. Synthesis of **3a**,**b**, (i): (1) LDA (2.0 equiv), **1a**,**b** (1.0 equiv), THF, 1 h 0 °C; (2) **2** (1.0 equiv), −78→20 °C, 14 h.

Table 1
Synthesis of **3a**,**b**

3	Ar	Yield[a] (%)
a	Ph	30
b	4-MeC_6H_4	32

[a] Yields of isolated products.

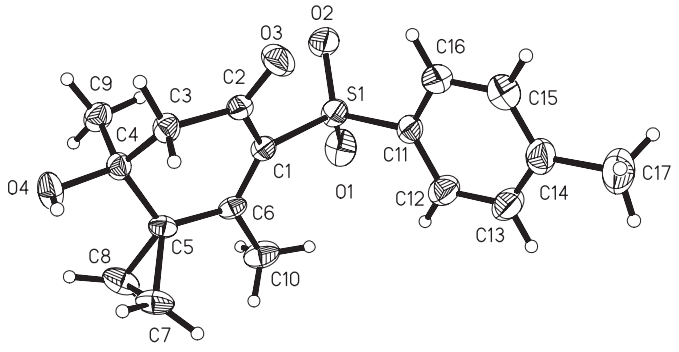
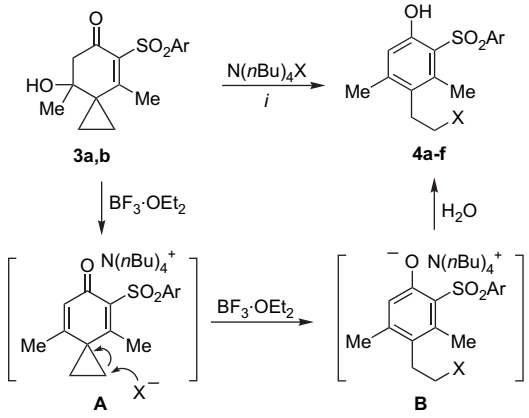


Figure 1. Ortep plot of **3b**.

The $BF_3\cdot OEt_2$-mediated reaction of pure **3a**,**b** with tetrabutylammonium halides afforded the sulfonyl-substituted phenols **4a**–**f** containing a remote chloride, bromide, and iodide group (Scheme 2, Table 2). Alternatively, the crude material could be successfully employed (vide supra). Products **4a**–**f** were presumably formed by Lewis acid mediated elimination of water to give a highly reactive spiro[2.5]cycloocta-4,7-dien-6-one (intermediate **A**). The cyclopropane moiety is subsequently cleaved by Lewis acid mediated attack of the halide ion to give a phenolate (intermediate **B**), which is protonated upon addition of water (aqueous work-up). The structure of **4f** was independently confirmed by X-ray crystal structure analysis (Fig. 2).



Scheme 2. Synthesis of **4a**–**f**, (i): $BF_3\cdot OEt_2$, CH_2Cl_2, −78→20 °C, 6 h, then 20 °C, 6 h.

Table 2
Reaction of **3a**,**b** with N(*n*-Bu)$_4$X

4	Ar	X	Yield[a] (%)
a	Ph	Cl	80
b	Ph	Br	75
c	Ph	I	81
d	4-MeC_6H_4	Cl	78
e	4-MeC_6H_4	Br	68
f	4-MeC_6H_4	I	84

[a] Yields of isolated products.

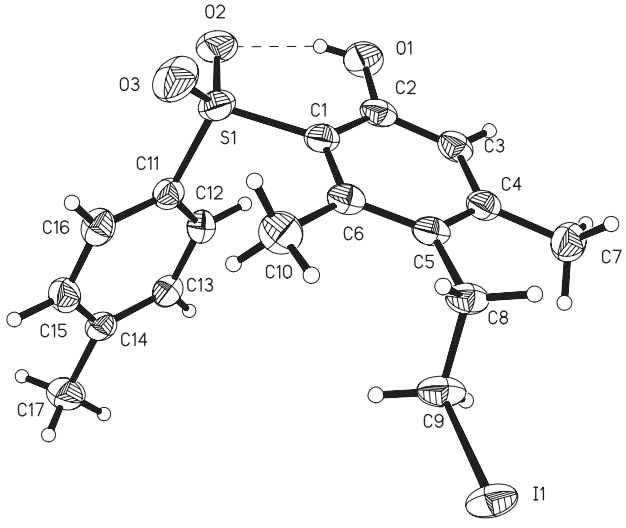


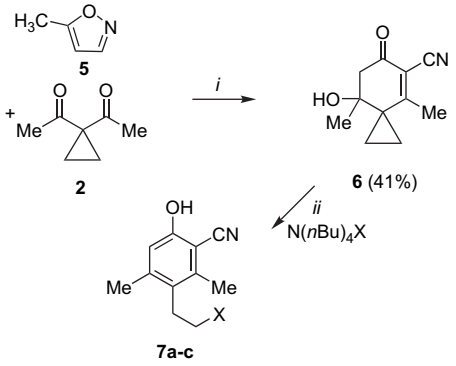
Figure 2. Ortep plot of **4f**.

2.2. α-Cyanoacetone

The cyclization of **2** with the dianion of α-cyanoacetone, generated by treatment of 5-methylisoxazole (**5**) with LDA,[11] afforded 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **6** (Scheme 3). The $BF_3 \cdot OEt_2$-mediated reaction of **6** with tetrabutylammonium halides gave the 2-cyanophenols **7a–c** containing a remote halide group (Scheme 3, Table 3). The formation of **7a–c** can be explained by a similar mechanism as discussed for **4a–f**. The structure of **7b** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[10]

2.3. Diethyl 2-oxopropylphosphonate

The cyclization of **2** with the dianion of diethyl 2-oxopropylphosphonate (**8**), generated by means of LDA, afforded the novel unsubstituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **9**



Scheme 3. Synthesis of **7a–c**, (i): (1) LDA (2.0 equiv), **5** (1.0 equiv), THF, 1 h, 0 °C; (2) **2** (1.0 equiv), −78→20 °C, 14 h; (ii): *n*-Bu_4NX (1.0 equiv), $BF_3 \cdot OEt_2$ (0.5 equiv), −78→20 °C, 12 h.

Table 3
Products and yields

7	X	Yield[a] (%)
a	Cl	64
b	Br	67
c	I	75

[a] Yields of isolated products.

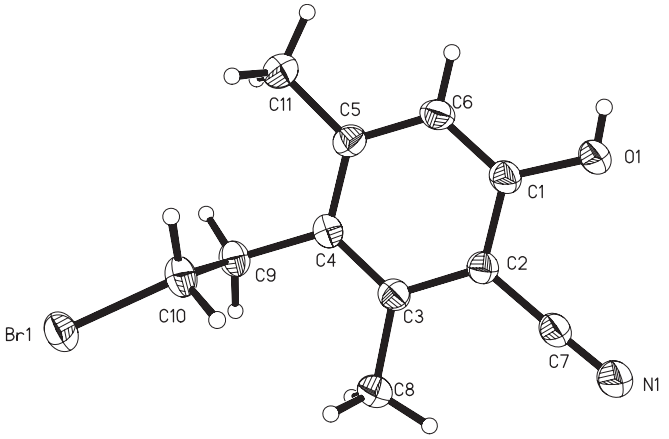
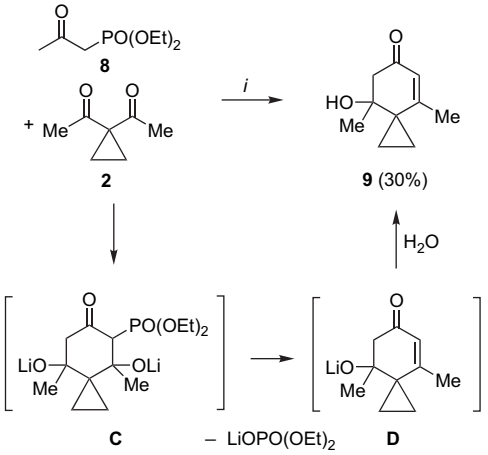
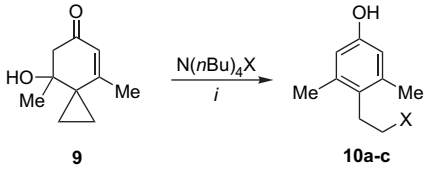


Figure 3. Ortep plot of **7b**.



Scheme 4. Synthesis of spirocyclopropane **9**, (i): (1) LDA (2.0 equiv), **8** (1.0 equiv), THF, 1 h, 0 °C; (2) **2** (1.0 equiv), −78→20 °C, 14 h.

(Scheme 4). The formation of **9** can be explained by cyclization (intermediate **C**), elimination of lithium diethylphosphate (intermediate **D**) and subsequent protonation upon addition of water. Alternatively, the reaction can be regarded as a domino 'aldol/Horner–Wadsworth–Emmons (HWE)' reaction. The $BF_3 \cdot OEt_2$-mediated reaction of **9** with tetrabutylammonium halides afforded the functionalized phenols **10a–c** (Scheme 5, Table 4).



Scheme 5. Reaction of **9** with *n*-Bu_4NX, (i): *n*-Bu_4NX (1.0 equiv), $BF_3 \cdot OEt_2$ (0.5 equiv), −78→20 °C, 12 h.

Table 4
Products and yields

10	X	Yield[a] (%)
a	Cl	73
b	Br	68
c	I	63

[a] Yields of isolated products.

3. Conclusion

In conclusion, 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones were prepared by cyclization of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1,1-diacetylcyclopropane. These products were transformed into functionalized phenols by Lewis acid mediated reaction with tetrabutylammonium halides. The reactions reported provide a convenient two-step approach to functionalized phenols, which are not readily available by other methods.

4. Experimental section

4.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and

^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

4.2. Typical procedure for the cyclization of β-ketosulfone dianions with 1,1-diacetylcyclopropane

A THF solution (8.5 mL) of LDA was prepared by addition of *n*-BuLi (3.10 mL, 7.7 mmol, 2.5 M solution in hexane) to a THF solution of diisopropylamine (1.0 mL, 7.76 mmol) at 0 °C. After stirring for 1 h, β-ketosulfone **1** (768 mg, 3.88 mmol) was added at −78 °C and the solution was stirred for 1 h. To the solution was added 1,1-diacetylcyclopropane (**2**) (490 mg, 3.88 mmol) at −78 °C and the solution was allowed to warm to 20 °C for 14 h. To the reaction mixture was added an aqueous solution of HCl (1 M) and the organic and aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **3a** as a yellow solid (230 mg, 30%).

4.2.1. 8-Hydroxy-4,8-dimethyl-5-(phenylsulfonyl)spiro-[2.5]oct-4-en-6-one (*3a*)

Mp=165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–0.97 (m, 1H, CH_2), 1.13 (s, 3H, CH_3), 1.28–1.32 (m, 1H, CH_2), 1.50–1.54 (m, 1H, CH_2), 2.22 (s, 3H, CH_3), 2.45 (d, 1H, J=15.8 Hz, CH_2), 2.55 (d, 1H, J=15.8 Hz, CH_2), 7.40–7.49 (m, 3H, ArH), 7.83–7.87 (dd, 2H, J=8.4, 3.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 13.6 (CH_2), 16.5, 25.8 (CH_3), 38.8 (C), 52.4 (CH_2), 69.7 (C), 128.0 (2C, CH), 128.9 (2C, CH), 133.3 (CH), 136.5, 149.0, 173.8, 191.4 (C); IR (KBr): $\tilde{\nu}$ = 3407(s), 2967 (w), 2924 (w), 1664 (m), 1544 (s), 1447 (m), 1375 (m), 1334 (s), 1301 (s), 1088 (s), 732 (s) cm^{-1}; MS (CI): *m/z* (%): 307 ([M+1]$^+$) (100), 289 (11.21), 247 (6.07), 199 (2.82); HRMS (CI): calcd for $C_{16}H_{19}SO_4$ ([M+1]$^+$) 307.0996, found 307.1001.

4.2.2. 8-Hydroxy-4,8-dimethyl-5-(4-methylphenylsulfonyl)-spiro[2.5]oct-4-en-6-one (*3b*)

Starting with *n*-BuLi (31 mL, 78.4 mmol, 2.5 M solution in hexane), diisopropylamine (11 mL, 78.4 mmol), 1,1-diacetylcyclopropane (**2**) (5.00 g, 39.7 mmol), and *p*-tolylsulfonylacetone (8.41 g, 39.7 mmol) in THF (86 mL), **3b** was isolated as a colourless solid. Mp=160–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06–1.10 (m, 1H, CH_2), 1.29 (s, 3H, CH_3), 1.32–1.36 (m, 1H, CH_2), 1.42–1.46 (m, 1H, CH_2), 1.66–1.70 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.66 (d, 1H, J=13.4 Hz, CH_2), 2.72 (d, 1H, J=16.4 Hz, CH_2), 7.38 (d, 2H, J=8.0 Hz, ArH), 7.94 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.3, 13.5 (CH_2), 16.6, 22.0, 25.8 (CH_3), 37.1 (C), 52.5 (CH_2), 71.6 (C), 128.2 (2C, CH), 129.6 (2C, CH), 136.8, 140.0, 144.2, 173.8, 191.5 (C); IR (KBr): $\tilde{\nu}$ = 3489(m), 2974 (m), 2929 (m), 1718 (m), 1679 (s), 1597 (m), 1373 (m), 1301 (s), 1186 (s), 1086 (s), 981 (s), 815 (m), 543 (s) cm^{-1}; MS (CI, 70 eV): *m/z* (%): 321 ([M+1]$^+$) (100), 303 (10.21), 253 (11), 213 (9); HRMS (CI): calcd for $C_{17}H_{21}SO_4$ ([M+1]$^+$): 321.11521, found: 321.11551.

4.3. Typical procedure for the reaction of 8-hydroxy-4,8-dimethyl-5-(phenylsulfonyl)spiro[2.5]oct-4-en-6-ones with tetraalkylammonium halides

To a CH_2Cl_2 solution (12.4 mL) of **3a** (500 mg, 1.63 mmol) and of *n*-Bu_4NCl (526 mg, 1.6 mmol) was dropwise added $BF_3\cdot OEt_2$ (0.10 mL, 0.8 mmol) at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C over 6 h and was stirred for additional 6 h at 20 °C. The solution was filtered and the filtrate was poured into an aqueous solution of HCl (1.0 M). The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **4a** as a yellow solid (435 mg, 75%).

4.3.1. 4-(2-Chloroethyl)-3,5-dimethyl-2-(phenylsulfonyl)-phenol (*4a*)

Starting with **3a** (300 mg, 1.0 mmol), *n*-Bu_4NCl (272 mg, 1.0 mmol), CH_2Cl_2 (7.4 mL) and $BF_3\cdot OEt_2$ (0.06 mL, 0.5 mmol), **4a** was isolated (355 mg, 80%) as a colourless solid. Mp=192–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.27(s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.89 (t, 2H, J=7.6 Hz, CH_2), 3.40 (t, 2H, J=6.9 Hz, CH_2), 6.79 (s, 1H, CH), 7.50–7.54 (m, 2H, ArH), 7.60–7.65 (m, 1H, ArH), 7.83–7.87 (m, 1H, ArH), 10.45 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=16.5, 20.8 (CH_3), 32.6, 41.7 (CH_2), 118.6 (C), 119.1 (CH), 126.4 (2C, CH), 128.3 (C), 129.2 (2C, CH), 133.5 (CH), 137.2, 142.1, 145.6, 157.1 (C); IR (KBr): $\tilde{\nu}$ = 3265(s), 2957 (w), 2920 (w), 1601 (s), 1445 (s), 1342 (s), 1295 (m), 1109 (s), 1157 (m), 762 (m), 691 (s), 649 (s), 568 (s) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 324 (M$^+$, ^{35}Cl, 22), 275 (100), 133 (19), 91 (12), 77 (15); HRMS (EI): calcd for $C_{16}H_{17}O_3ClS$ [M$^+$, ^{35}Cl]: 324.05814, found: 324.057851.

4.3.2. 4-(2-Bromoethyl)-3,5-dimethyl-2-(phenylsulfonyl)-phenol (*4b*)

Starting with **3a** (500 mg, 1.6 mmol), *n*-Bu_4NBr (526 mg, 1.63 mmol), CH_2Cl_2 (12.4 mL) and $BF_3\cdot OEt_2$ (0.1 mL, 0.8 mmol), **4b** was isolated (435 mg, 75%) as a colourless solid. Mp=144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.31 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.05 (t, 2H, J=7.7 Hz, CH_2), 3.23 (t, 2H, J=6.9 Hz, CH_2), 6.79 (s, 1H, CH), 7.50–7.55 (m, 2H, ArH), 7.60–7.65 (m, 1H, ArH), 7.83–7.87 (m, 1H, ArH), 10.62 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.9, 21.2 (CH_3), 29.5, 33.4 (CH_2), 119.1 (C), 119.7 (CH), 127.1 (2C, CH), 129.6 (2C, CH), 129.9 (C), 133.9 (CH), 137.5, 142.5, 146.1, 157.5 (C); IR (KBr): $\tilde{\nu}$ = 3264(s), 2955 (w), 1601 (s), 1558 (s), 1445 (s), 1342 (s), 1278 (m), 1126 (s), 1083 (s), 865 (w), 761 (m), 730 (s), 642 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 368 (M$^+$, ^{79}Br, 22), 289 (22), 275

(100), 133 (19), 91 (10), 77 (17); HRMS (EI): calcd for $C_{16}H_{17}O_3BrS$ [M^+, ^{79}Br]: 368.00763, found: 368.007146.

*4.3.3. 4-(2-Iodoethyl)-3,5-dimethyl-2-(phenylsulfonyl)-phenol (**4c**)*

Starting with **3a** (500 mg, 1.6 mmol), *n*-Bu_4NI (603 mg, 1.6 mmol), CH_2Cl_2 (12.4 mL) and $BF_3{\cdot}OEt_2$ (0.1 mL, 0.8 mmol), **4c** was isolated (425 mg, 81%) as a colourless solid. Mp=170–171 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.94–2.98 (m, 2H, CH_2), 3.05–3.10 (m, 2H, CH_2), 6.78 (s, 1H, CH), 7.50–7.54 (m, 2H, ArH), 7.58–7.62 (m, 1H, ArH), 7.83–7.87 (m, 1H, ArH), 10.54 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=0.0 (CH_2), 15.8, 20.0 (CH_3), 33.5 (CH_2), 117.9 (C), 118.4 (CH), 125.7 (2C, CH), 128.4 (2C, CH), 131.0 (C), 132.7 (CH), 136.0, 141.3, 144.5, 156.2 (C); IR (KBr): $\tilde{\nu}$ = 3262(s), 2950 (w), 1598 (s), 1559 (s), 1445 (s), 1341 (s), 1291 (s), 1207 (m), 1125 (s), 1082 (s), 866 (m), 727 (s), 690 (s), 667 (m), 548 (s) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 416 (M^+, 6), 289 (100), 275 (7), 196 (5), 148 (11), 91 (10), 77 (15); HRMS (EI): calcd for $C_{16}H_{17}O_3IS$ [M^+]: 415.99376, found: 415.99368.

*4.3.4. 4-(2-Chloroethyl)-3,5-dimethyl-2-[(4-methylphenyl)-sulfonyl]phenol (**4d**)*

Starting with **3b** (300 mg, 0.9 mmol), *n*-Bu_4NCl (260 mg, 0.9 mmol), CH_2Cl_2 (7.0 mL) and $BF_3{\cdot}OEt_2$ (0.06 mL, 0.5 mmol), **4d** was isolated (248 mg, 78%) as a colourless solid. Mp=118–121 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.11 (t, 2H, *J*=8.0 Hz, CH_2), 3.53 (t, 2H, *J*=6.6 Hz, CH_2), 6.96 (s, 1H, CH), 7.43 (d, 2H, *J*=8.0 Hz, ArH), 8.37 (d, 2H, *J*=8.0 Hz, ArH), 10.74 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.9, 21.3, 22.0 (CH_3), 33.0, 42.1 (CH_2), 119.4 (C), 119.5 (CH), 126.5 (2C, CH), 129.7 (C), 130.2 (2C, CH), 137.7, 139.4, 144.9, 145.8, 157.8 (C); IR (KBr): $\tilde{\nu}$ = 3193(m), 2960 (w), 2854 (w), 1605 (m), 1566 (m), 1463 (m), 1240 (s), 1124 (s), 1085 (s), 811 (w), 684 (s), 548 (m), 555 (s) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 338 (M^+, ^{35}Cl, 28), 289 (100), 197 (11), 133 (23), 91 (14), 77 (10); HRMS (EI): calcd for $C_{17}H_{19}O_3ClS$ [M^+, ^{35}Cl]$^+$: 338.07379, found: 338.07326.

*4.3.5. 4-(2-Bromoethyl)-3,5-dimethyl-2-[(4-methylphenyl)-sulfonyl]phenol (**4e**)*

Starting with **3b** (500 mg, 1.5 mmol), *n*-Bu_4NBr (503 mg, 1.5 mmol), CH_2Cl_2 (11.8 mL) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol), **4e** was isolated (395 mg, 68%) as a colourless solid. Mp=135–137 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.46 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.24 (t, 2H, *J*=7.8 Hz, CH_2), 3.66 (t, 2H, *J*=6.1 Hz, CH_2), 6.97 (s, 1H, CH), 7.49 (d, 2H, *J*=8.0 Hz, ArH), 8.37 (d, 2H, *J*=8.4 Hz, ArH), 10.76 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.5, 18.9, 20.8 (CH_3), 34.2, 41.8 (CH_2), 119.1 (C), 119.7 (CH), 126.5 (2C, CH), 128.2 (C), 129.8 (2C, CH), 139.2, 141.3,144.5, 145.5, 160.0 (C); IR (KBr): $\tilde{\nu}$ = 3194(m), 2955 (w), 2853 (w), 1605 (m), 1565 (m), 1462 (m), 1239 (s), 1124 (s), 1085 (s), 811 (m), 685 (s), 548 (m), 555 (s) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 382 (M^+, ^{79}Br, 29), 303 (25), 289 (100), 197 (12), 133 (27), 91 (13), 65 (10); HRMS (EI): calcd for $C_{17}H_{19}O_3BrS$ [M^+, ^{79}Br]: 382.02328, found: 382.02340.

*4.3.6. 4-(2-Iodoethyl)-3,5-dimethyl-2-[(4-methylphenyl)-sulfonyl]phenol (**4f**)*

Starting with **3b** (400 mg, 1.3 mmol), *n*-Bu_4NI (461 mg, 1.3 mmol), CH_2Cl_2 (9.5 mL) and $BF_3{\cdot}OEt_2$ (0.08 mL, 0.6 mmol), **4f** was isolated (520 mg, 84%) as a colourless solid. Mp=136–139 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.23 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.94–2.98 (m, 2H, CH_2), 3.03–3.07 (m, 2H, CH_2), 6.75 (s, 1H, CH), 7.30 (d, 2H, *J*=7.8 Hz, ArH), 7.70 (d, 2H, *J*=8.4 Hz, ArH), 10.47 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=0.0 (CH_2I), 15.6, 19.9, 20.7 (CH_3), 33.4 (CH_2), 118.1 (C), 118.4 (CH), 126.7 (2C, CH), 128.9 (2C, CH), 130.8, 135.9, 138.3, 143.7, 144.2. 155.0 (C); IR (KBr): $\tilde{\nu}$ = 3206(m), 2900 (s), 1597 (s), 1562 (s), 1493 (m), 1348 (m), 1259 (m), 1166 (w), 1125 (s), 709 (s), 696 (s), 648 (w), 523 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 430 (M^+, 7), 303 (100), 289 (10), 209 (7), 133 (10), 91 (18), 77 (8); HRMS (EI): calcd for $C_{17}H_{19}O_3IS$ [M^+]: 430.00872, found 430.00864.

*4.3.7. 8-Hydroxy-4,8-dimethyl-5-cyanospiro[2.5]oct-4-en-6-one (**6**)*

Starting with *n*-BuLi (48.8 mL, 122.0 mmol, 2.5 M solution in hexane), diisopropylamine (17.2 mL, 122.0 mmol), 1,1-diacetylcyclopropane (**2**) (7.70 g, 61.4 mmol), and 5-methylisoxazole (**5**) (5.00 g, 61.4 mmol) in THF (134 mL), **6** was isolated as yellow oil (4.80 g, 41%); ^1H NMR (300 MHz, $CDCl_3$): δ=0.94–1.07 (m, 2H, CH_2), 1.25–1.32 (m, 1H, CH_2), 1.22 (s, 3H, CH_3), 1.61–1.68 (m, 1H, CH_2), 2.03 (s, 3H, CH_2), 2.69 (d, 2H, *J*=5.7 Hz, CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): δ=12.1, 13.7 (CH_2), 19.6, 25.4 (CH_3), 34.2 (C), 51.0 (CH_2), 70.1 (C), 114.1 (CN), 128.7, 171.9, 191 (C); IR (neat): $\tilde{\nu}$ = 3488(m), 2969 (w), 2931 (w), 2228 (m), 1678 (s), 1573 (m), 1383 (s), 1295 (s), 1164 (w), 1089 (m), 965 (w), 740 (w) cm^{-1}; GC–MS (CI, 70 eV): *m/z* (%) 191 ($[M+1]^+$) (100), 148 (11), 125 (7), 74 (6); HRMS (CI): calcd for $C_{11}H_{13}O_2N$ ($[M+1]^+$): 191.09408, found: 191.093758.

*4.3.8. 4-(2-Chloroethyl)-3,5-dimethyl-2-cyanophenol (**7a**)*

Starting with **6** (300 mg, 1.6 mmol), *n*-Bu_4NCl (436 mg, 1.6 mmol), CH_2Cl_2 (11.9 mL) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol), **7a** was isolated (205 mg, 64%) as a colourless solid. Mp=124–126 °C; ^1H NMR (300 MHz, acetone-d_6): δ=2.40 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.20–3.25 (m, 2H, CH_2), 3.64–3.68 (m, 2H, CH_2), 6.92 (s, 1H, CH), 9.90 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=18.2, 20.7 (CH_3), 29.7, 43.1 (CH_2), 100.0 (C), 116.2 (CH), 116.6, 129.0, 142.1, 146.6, 159.3 (C); IR (KBr): $\tilde{\nu}$ = 3194(s), 2961 (w), 1605 (s), 1566 (m), 1463 (s), 1350 (m), 1240 (m), 1224 (s), 684 (s), 555 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 209 (M^+, ^{35}Cl, 13), 160 (100), 77 (5); HRMS (EI): calcd for $C_{11}H_{12}ONCl$ [M^+, ^{35}Cl]: 209.06019, found: 209.06040.

*4.3.9. 4-(2-Bromoethyl)-3,5-dimethyl-2-cyanophenol (**7b**)*

Starting with **6** (400 mg, 2.0 mmol), *n*-Bu_4NBr (674 mg, 2.0 mmol), CH_2Cl_2 (15.2 mL) and $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol), **7b** was isolated (142 mg, 67%) as a colourless solid; ^1H NMR (300 MHz, acetone-d_6): δ=2.57 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.40 (t, 2H, J=7.6 Hz, CH_2), 3.72 (t, 2H, J=7.4 Hz, CH_2), 6.98 (s, 1H, CH), 9.82 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=18.1, 20.6 (CH_2), 30.7, 33.4 (CH_3), 100.4 (C), 116.2 (CH), 116.6, 129.0, 142.0, 144.6, 159.3 (C); IR (KBr): $\tilde{\nu}$ = 2958(m), 2928 (m), 2858 (m), 1728 (s), 1464 (m), 1286 (s), 1124 (m), 1073 (w), 742 (m), 704 (w) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 253 (M^+, ^{79}Br, 16), 174 (49), 160 (100), 77 (6); HRMS (EI): calcd for $C_{11}H_{12}ONBr$ [M^+, ^{79}Br]: 253.00968, found: 253.00949.

*4.3.10. 4-(2-Iodoethyl)-3,5-dimethyl-2-cyanophenol (**7c**)*

Starting with **6** (400 mg, 2.0 mmol), *n*-Bu_4NI (738 mg, 2.0 mmol), CH_2Cl_2 (15.2 mL) and $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol), **7c** was isolated (475 mg, 75%) as a colourless solid. Mp=185–188 °C; ^1H NMR (300 MHz, acetone-d_6): δ=2.50 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.34–3.38 (m, 2H, CH_2), 3.43–3.47 (m, 2H, CH_2), 6.89 (s, 1H, CH), 9.85 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=2.7 (CH_2), 18.5, 20.9 (CH_3), 35.1 (CH_2), 100.0 (C), 116.6 (CH), 117.6, 131.6, 141.9, 144.5, 159.6 (C); IR (KBr): $\tilde{\nu}$ = 3223(s), 2923 (w), 2232 (s), 1598 (s), 1443 (m), 1312 (m), 1168 (m), 1090 (w), 867 (m), 705 (w) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 300 (M^+, 5), 174 (100), 160 (18), 77 (5); HRMS (EI): calcd for $C_{11}H_{12}ONI$ [M^+]: 300.99581, found: 300.995296.

*4.3.11. 8-Hydroxy-4,8-dimethylspiro[2.5]oct-4-en-6-one (**9**)*

Starting with *n*-BuLi (28.6 mL, 57.2 mmol, 2.5 M solution in hexane), diisopropylamine (8.6 mL, 57.2 mmol), 1,1-diacetylcyclopropane (**2**) (7.70 g, 61.4 mmol), and diethyl 2-oxophosphonate **8** (5.55 g, 28.6 mmol) in THF (62 mL), **9** was isolated as gummy compound (2.20 g, 29%); ^1H NMR (300 MHz, $CDCl_3$): δ=0.76–0.80 (m, 1H, CH_2), 0.97–1.02 (m, 2H, CH_2), 1.22 (s, 3H, CH_3), 1.34–1.38 (m, 1H, CH_2), 1.68 (s, 3H, CH_3), 2.54 (d, 2H, J=15.8 Hz, CH_2), 2.65 (d, 2H, J=15.8 Hz, CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): δ=9.0, 10.2 (CH_2), 19.9, 25.3 (CH_3), 32.1 (C), 51.8 (CH_2), 72.5 (C), 126.5 (CH), 161.5, 198.4 (C); IR (neat): $\tilde{\nu}$ = 3403(s), 2975 (m), 1648 (s), 1604 (s), 1444 (m), 1387 (m), 1286 (m), 1144 (m), 1028 (m), 963 (m), 860 (m), 641 (w) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 166 (M^+, 41), 148 (50), 138 (40), 123 (38), 107 (85), 79 (100), 43 (85); HRMS (EI): calcd for $C_{10}H_{14}O_2$ [M^+]$^+$: 166.09883, found: 166.09916.

*4.3.12. 4-(2-Chloroethyl)-3,5-dimethylphenol (**10a**)*

Starting with **9** (334 mg, 2.0 mmol), *n*-Bu_4NCl (554 mg, 2.0 mmol), CH_2Cl_2 (16 mL) and $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol), **10a** was isolated (170 mg, 68%) as a colourless solid; ^1H NMR (300 MHz, $CDCl_3$): δ=2.22 (s, 6H, CH_3), 2.98–3.02 (m, 2H, CH_2), 3.38–3.43 (m, 2H, CH_2), 6.43 (s, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.2 (2C, CH_3), 30.1, 42.4 (CH_2), 115.0 (2C, CH), 126.9 (C), 138.2 (2C, C), 153.8 (C); IR (KBr): $\tilde{\nu}$ = 3355(m), 3423 (s), 2920 (m), 1712 (m), 1621 (s), 1582 (m), 1449 (s), 1315 (m), 1180 (m), 1161 (s), 1112 (w), 834 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 184 (M^+, ^{35}Cl, 13), 148 (6), 135 (100), 105 (10), 91 (14), 77 (9); HRMS (EI): calcd for $C_{10}H_{13}OCl$ [M^+, ^{35}Cl]: 184.05432, found: 184.05631.

*4.3.13. 4-(2-Bromoethyl)-3,5-dimethylphenol (**10b**)*

Starting with 8-hydroxy-4,8-dimethylspiro[2.5]oct-4-en-6-one (**9**) (180 mg, 1.0 mmol), *n*-Bu_4NBr (322 mg, 1.0 mmol), CH_2Cl_2 (7.6 mL) and $BF_3{\cdot}OEt_2$ (0.074 mL, 1.0 mmol), **10b** was isolated (170 mg, 68%) as a colourless solid. Mp=76–79 °C;^1H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 6H, CH_3), 3.12 (t, 2H, J=6.3 Hz, CH_2), 3.34 (t, 2H, J=6.5 Hz, CH_2), 6.40 (s, 2×1H, CH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=19.2 (2C, CH_3), 30.0, 32.7 (CH_2), 115.2 (2C, CH), 126.9 (C), 138.2 (2C, C), 153.8 (C); IR (KBr): $\tilde{\nu}$ = 3314(s), 2966 (S), 2855 (w), 1596 (s), 1475 (s), 1318 (m), 1213 (w), 1191 (m), 1138 (s), 1025 (s), 852 (m), 633 (s) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 228 (M^+, ^{79}Br, 19), 149 (60), 135 (100), 105 (10), 91 (16), 77 (10); HRMS (EI): calcd for $C_{10}H_{13}OBr$ [M^+, ^{79}Br]$^+$: 228.01444, found: 228.01429.

*4.3.14. 4-(2-Iodoethyl)-3,5-dimethylphenol (**10c**)*

Starting with **9** (135 mg, 0.8 mmol), *n*-Bu_4NI (298 mg, 0.8 mmol), CH_2Cl_2 (6.1 mL) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol), **10c** was isolated (170 mg, 68%) as a colourless solid. Mp=69–72 °C; ^1H NMR (250 MHz, $CDCl_3$): δ=2.23 (s, 6H, CH_3), 3.01 (t, 2H, J=4.7 Hz, CH_2), 3.06 (t, 2H, J=4.7 Hz, CH_2), 6.40 (s, 2H, CH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=0.00 (CH_2) 17.7 (2C, CH_3), 32.1 (CH_2), 112.6 (2C, CH), 128,1 (C), 135.8 (2C, C), 151.1 (C); IR (KBr): $\tilde{\nu}$ = 3362(s), 3402 (S), 2960 (w), 1705 (m), 1606 (s), 1595 (m), 1460 (s), 1312 (s), 1190 (m), 1166 (s), 1133 (s), 1024 (s), 850 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 276 (M^+, 8), 149 (100), 135 (21), 105 (10), 91 (13), 77 (9); HRMS (EI): calcd for $C_{1o}H_{13}OI$ [M^+]$^+$: 276.00056, found: 276.07548.

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