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A new approach to (±)-heritonin. The preparation of β-tetralones from allylsilanes and acid chlorides

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Abstract—A new method for the preparation of 4-alkyl-β-tetralones is described, by reaction of arylacetic acid chlorides with allylsilanes. Employing β-tetralone **5**, the synthesis of (±)-heritonine and (±)-*epi*-heritonine, natural piscicides isolated from *Heritiera littoralis*, was achieved in four steps and 22% overall yield. The key step of this synthesis involved the selenocarbenium ion-mediated elaboration of the butenolide ring of the natural product.

Heritonin (**1**), heritol (**2**), heritianin (**3**), and vallapin (**4**) are cadinane sesquiterpenes (Fig. 1) isolated from *Heritiera littoralis*, a mangrove plant of Philippines and other tropical countries, used by native fishermen to kill fish.[1] Unlike rotenoid-yielding mangrove plants used by South American Indians for fishing, in which ichtiotoxic properties are attributed to rotenone,[2] it was shown that piscicidal activity of *Heritiera* resides mainly in lactones **1**–**4**.

Four syntheses of lactones **1** and **2** have been reported to date, all of them involving α-tetralone intermediates; they differ in the way how the butenolide ring was accomplished.[3] Thus, intramolecular Wittig reaction,[3a] osmylation,[3b] and oxidative cyclization of β,γ-unsaturated esters with ceric ammonic nitrate[3c] have been used for that purpose and a 'green' synthesis of heritonin, heritol, and analogs, by cyclization of β,γ-dihydroxyesters to butenolide employing Amberlyst-15, was also described.[3d]

Recently, we disclosed the Lewis acids-mediated alkylation of silyl enolethers with α-halo-α-phenyl selenoesters.[4b] Continuing our studies on the use of

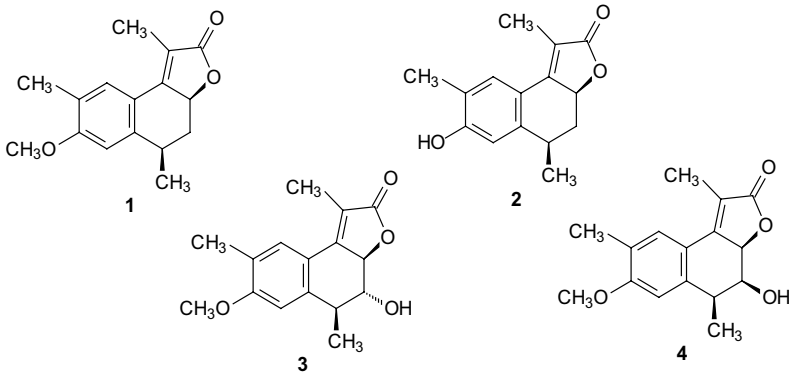

Figure 1. Cadinane sesquiterpenes isolated from *Heritiera littoralis*.

Keywords: Selenocarbenium ions; Heritonin; 2-Tetralones; Natural products.
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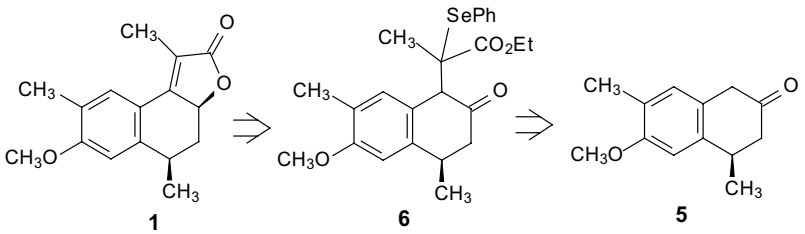


Scheme 1. Retrosynthetic analysis of (±)-heritonin (**1**).

organochalcogenium stabilized carbocations for the regiospecific construction of C–C bonds,[4] we report here the synthesis of (±)-heritonin (**1**) using this alkylation strategy for the construction of the butenolide ring of the natural product (Scheme 1). We also disclose a new approach to 4-alkyl-β-tetralones, employed for the elaboration of **5**, which embodies the tetraline unit of (±)-**1**.

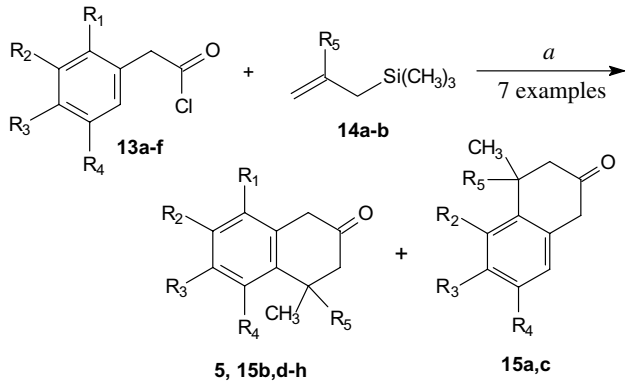
Initially, it was envisioned to prepare key β-tetralone **5** from α-tetralone **7** (Scheme 2). In spite of the increasing use of β-tetralones as intermediates for dopamine antagonists[5] and spasmolytic agents[6] and other compounds, methods for accessing 4-substituted-β-tetralones are scarce and of rather narrow scope. In addition, high cost and poor purity of commercial β-tetralones constitute interesting incentives to develop new syntheses for these compounds.

The most common methods for the preparation of β-tetralones involve 1,2-transposition of the carbonyl group of α-tetralones,[7] reduction of substituted 2-methoxy-naphthalenes,[8] cyclization of diazoketones, and β-keto-sulfoxides,[9] and the Friedel–Crafts reaction of aromatic acyl chlorides with olefins.[10] The 1,2-carbonyl transposition of α-tetralone **7** to **5** showed satisfactory results (Scheme 2, steps a–b).[11,12]

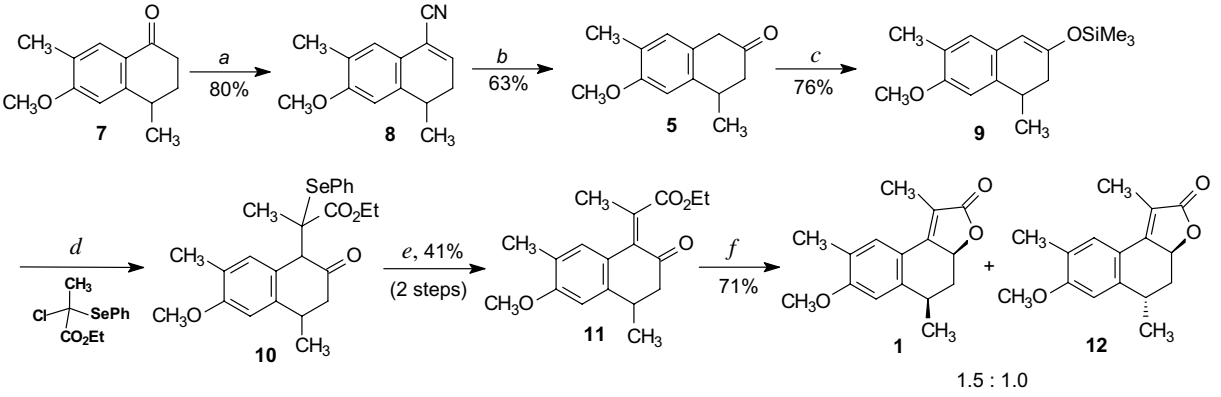
Nevertheless, preparation of **7** according to Ayyangar et al.,[3b] (43% overall yield, six steps from 2-methyl anisole), resulted lengthy and tedious, many steps requiring anhydrous conditions, which prompted us to study a more direct approach to β-tetralone **5**.

We discovered that the $AlCl_3$-mediated Friedel–Crafts reaction of aromatic acyl chlorides with allyl trimethylsilanes furnishes 4-methyl-β-tetralones directly and in reasonable to good yields[13] (Scheme 3, Table 1). The use of acyl chlorides and olefins in the presence of Lewis acids to prepare β-tetralones was first described by Burckhalter and Campbell[14] and is well documented. Recently, Gray and Smith[15] disclosed an improvement of this procedure, using trifluoroacetic anhydride/H_3PO_4 instead of $AlCl_3$. However, the use of allylsilanes as the olefin component has not been reported and the synthesis of aryl-substituted-4-methyl-β-tetralones exploiting a Friedel–Crafts reaction has no literature precedent.

Tetralone **5** was obtained together with its isomer **15a** from which it was easily separated by crystallization



Scheme 3. Reagents and conditions:[13] (a) $AlCl_3$ (3 equiv), CH_2Cl_2, −20 °C → reflux, 90 min.



Scheme 2. Reagents and conditions: (a) (1) TMSCN, ZnI_2, reflux, 24 h; (2) $POCl_3$/pyridine, reflux, 12 h; (b) (1) $Bu_4N^+HSO_4^-$, NaOH, H_2O_2, CH_2Cl_2, rt;[11] 2.3 N HCl, reflux, 12 h; (c) (1) LDA, THF, −78 °C; (2) TMSCl; (d) CH_2Cl_2, $ZnBr_2$, 0 °C → rt; (e) *m*-CPBA, CH_2Cl_2, −78 °C → rt; (f) (1) $NaBH_4$, EtOH, 0 °C, 5 min, rt, 1 h; (2) 12 N HCl, 60 °C, 40 min.

Table 1. Synthesis of 4-methyl-β-tetralones

Entry	Acyl chloride	Allylsilane (equiv)	β-Tetralone	R_1	R_2	R_3	R_4	R_5	Yield (%)[a]
1	**13a**	**14a** (1.6)	**5** + **15a** (2:1)[b]	**5**: H	CH_3	CH_3O	H	H	25[c]
				15a: –	H	CH_3O	CH_3	H	16
2	**13b**	**14a** (1.6)	**15b** + **15c** (2:1)[b]	**15b**: H	CH_3	H	H	H	47[d]
				15c: –	H	H	CH_3	H	
3	**13c**	**14a** (3.0)	**15d**	H	H	CH_3	H	H	23
4	**13d**	**14a** (1.6)	**15e**	H	H	Br	H	H	35
5	**13e**	**14a** (1.6)	**15f**	Cl	H	H	H	H	60
6	**13f**	**14a** (1.6)	**15g**	H	H	H	H	H	71
7	**13f**	**14b** (5.0)	**15h**	H	H	H	H	^{n}Pentyl	34

[a] After purification by silica gel column chromatography.
[b] Determined by GC and ^{1}H NMR of the crude reaction and compared after purification.
[c] Purified by crystallization from petroleum ether.
[d] Yield of the mixture.

(petroleum ether, 25% yield). A similar behavior was observed during the cyclization of **13b** (Table 1, entries 1 and 2). Yields of β-tetralones prepared as shown in Scheme 3 are satisfactory, compared to those arising from cyclization of β,γ-unsaturated ketones with $AlCl_3$.[16] Moreover, the aryl acetic acids and allyltrimethylsilane are easily available, the method described here allows the preparation of several 4-methyl-β-tetralones in a short sequence, and acyl chlorides with electron withdrawing groups can be used (entry 5).

A reaction that exploits the ability of the selenium atom in stabilizing an adjacent carbocation, which is part of an extensive study of selenocarbenium ions developed by our group,[4] served for the synthesis of the butenolide unit of (±)-heritonin (**1**). Thus, silyl enol ether **9** was prepared in 76% yield from the β-tetralone **5** and treated with α-chloro-α-phenylseleno-ethyl propionate in the presence of $ZnBr_2$,[4b] furnishing γ-keto ester **10**. Reaction of crude ester **10** with *m*CPBA at −78 °C provided 41% of α,β-unsaturated ester **11**,[17] together with 16% of its isomeric *trans* ester, easily separated by silica gel column chromatography (hexane/EtOAc, 95:5). Finally, ester **11** was cyclized upon reduction with $NaBH_4$ and acid hydrolysis to give 75% of (±)-heritonin **1** and (±)-*epi*-heritonin **12** as a 1.5:1 diastereomeric mixture (Scheme 2), purified by fractional crystallization (petroleum ether). Isomer **12** was the first to crystallize, while (±)-**1** was obtained from the mother liquors, as described in the literature.[3b] Spectral data of **1** and **12** perfectly agreed with those reported.[3] Demethylation of (±)-**1** to (±)-heritol (**2**) with BCl_3 or BBr_3 is well established and can be achieved in 59–81% yield.[3b,d]

In conclusion, we described here a new method for the synthesis of 4-alkyl-β-tetralones and a new route to (±)-heritonin **1**, which constitutes a good alternative to other described protocols, especially if the easy access of the β-tetralone intermediate is considered.

Acknowledgements

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12. *1,2-Carbonyl transposition of* **7**: *1,6-dimethyl-7-methoxy-1,2-dihydro-4-naphthylcyanide* **8**. Me_3SiCN (1.38 mL,

11.51 mmol) and ZnI_2 (80 mg, 0.25 mmol) were added to a solution of α-tetralone **7** (1.56 g, 7.7 mmol) in benzene (3 mL), and the mixture was refluxed for 24 h. Then, pyridine (12.4 mL) and $POCl_3$ (2.08 mL) were added and the mixture was refluxed another 12 h. The crude was poured over ice-cold 12 N HCl (50 mL) and extracted with EtOAc (3 × 25 mL). The extract was dried ($MgSO_4$) and concentrated under reduced pressure affording a dark oil. Chromatographic purification (hexane/EtOAc, 95:5) furnished cyanide **8** (1.31 g, 80%) as a light nut-brown solid, mp 60–61 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (d, $J = 7.0$ Hz, 3H), 2.20 (s, 3H), 2.18–2.35 and 2.51–2.69 (m, 2H), 2.94 (sex, $J = 7.0$ Hz, 1H), 3.86 (s, 3H), 6.64 (t, $J = 5.2$ Hz, 1H), 7.23 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.6, 20.4, 31.1, 31.4, 55.4, 108.5, 113.3, 117.4, 120.1, 124.9, 127.3, 138.5, 139.3, 158.4. GC/MS m/z (relative intensity, %): 213(51), 198(100), 183(51), 154(11), 140(13), 127(10), 77(5), 63(4). IR (KBr, cm^{-1}): 2926, 2221, 1610, 1565, 1505, 1464, 1353, 1258, 1137, 1047, 885, 823. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84, H, 7.09, N, 6.57; found: C, 78.81, H, 6.98, N, 6.49. *4,7-Dimethyl-6-methoxy-β-tetralone* **5**. 30% Bu_4NHSO_4 (0.544 g, 1.59 mmol), H_2O_2 (3.75 mL), and 5 N NaOH (3.0 mL) were added to a solution of **8** (1.34 g, 6.14 mmol) in CH_2Cl_2 (2.8 mL) at 25 °C. After stirring 15 min. at rt, the mixture was extracted with EtOAc (3 × 25 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo, to afford a brown solid, which was treated 12 h under reflux with 3 N HCl (25 mL) and then extracted with EtOAc (3 × 25 mL); the extract was washed (H_2O), dried ($MgSO_4$) and concentrated under reduced pressure, to afford a dark orange oil. Chromatographic purification (hexane/EtOAc, 90:10), provided β-tetralone **5** (0.74 g, 59%) as a white solid, mp 48–49 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.24 (d, $J = 7.0$ Hz, 3H), 2.11 (s, 3H), 2.26 (dd, $J = 6.8$ and 16 Hz, 1H), 2.62 (dd, $J = 5.4$ and 16.2 Hz, 1H), 3.16 (sex, $J = 6.8$ Hz, 1H), 3.43 (s, 2H), 3.77 (s, 3H), 6.65 (s, 1H), 6.81 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.7, 20.6, 33.9, 43.4, 46.5, 55.5, 108.1, 123.9, 125.2, 130.6, 139.5, 156.7, 210.9. GC/MS m/z (relative intensity %) 204(100), 177(37), 162(82), 135(16), 91(25). IR (KBr, cm^{-1}): 2925, 1715, 1609, 1501, 1463, 1253, 1052. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44, H, 7.90; found: C, 76.20, H, 7.72.

13. *Synthesis of-β-tetralones* **5** *and* **15a**. 3-Methoxy-2-methylphenyl acetyl chloride **13a** (0.20 g 1 mmol) was added to a two-necked 25 mL round-bottom flask equipped with a reflux condenser and containing $AlCl_3$ (0.399 g, 3 mmol) in CH_2Cl_2 (4 mL) at −20 °C under N_2. After stirring for 30 min at −20 °C, allyltrimethylsilane **14a** (0.182 g, 1.6 mmol) was added dropwise, and the mixture was stirred 2 h at −20 °C and refluxed during 1.5 h. The reaction was cooled to rt, poured over cold 2 N HCl (25 mL) and extracted with EtOAc (3 × 25 mL); the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, to afford a dark oil. Chromatography (hexane/EtOAc, 90:10), gave a 2:1 mixture of β-tetralone **5** and its isomer **15a** (80 mg, 41%). Recrystallization (petroleum ether) furnished pure **5** (50 mg, 25%).
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17. Compound **11**: white solid, mp 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (d, $J = 6.5$ Hz, 3H), 1.36 (t, $J = 7.1$ Hz, 3H), 2.20 (s, 3H), 2.22 (s, 3H), 2.36 (dd, $J = 17$ and 6.5 Hz, 1H), 2.63 (dd, $J = 17$ and 4.7 Hz, 1H), 3.10–3.18 (m, 1H), 3.88 (s, 3H), 4.32 (q, $J = 7.1$ Hz, 2H), 6.71 (s, 1H), 7.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 16.0, 18.6, 19.9, 32.8, 44.6, 55.3, 61.2, 107.6, 123.1, 124.4, 130.1, 131.3, 133.1, 142.8, 157.8, 171.9, 200.7. GC/MS m/z (relative intensity, %): 302 (M^+ 25), 256(66), 228(100), 171(14), 115(14), 84(49), 49(47). IR (KBr, cm^{-1}): 2926, 1699, 1609, 1502, 1464, 1255, 1126, 1033.