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Synthesis of alkylphenols and alkylcatechols from the marine mollusc *Haminoea callidegenita*

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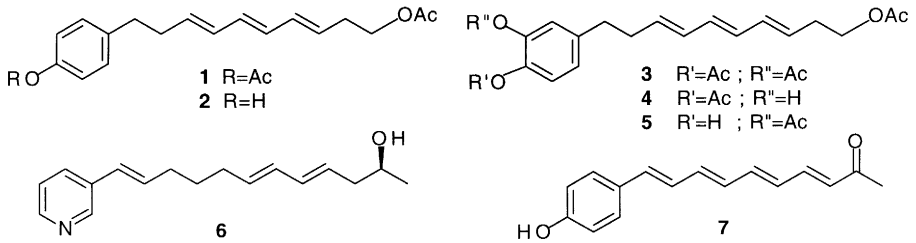
Abstract

Alkylphenols **1**–**5**, potential alarm pheromones of the marine mollusc *Haminoea callidegenita*, have been synthesized using a convergent approach centred on a Stille coupling reaction.

Keywords: Haminoea callidegenita; alkylphenols; pheromones; palladium catalysts.

Alkylphenols and alkylcatechols **1**–**5** are marine metabolites recently isolated from the cephalaspidean mollusc *Haminoea callidegenita*.[1] These molecules are particularly interesting because both their origin and structure strongly suggest a potential role as semiochemicals. In fact, it has been shown that some metabolites of *Haminoea* species, e.g. **6**,[2] are responsible for an alarm pheromone based defensive behaviour. Furthermore, the compounds isolated from *H. callidegenita* are clearly structurally related to navenone C (**7**), isolated from the Pacific cephalaspidean *Navanax inermis*, belonging to the first group of chemically described alarm pheromones from a marine mollusc.[3]



Another aspect which makes these molecules intriguing synthetic targets is related to the interesting biological activities exhibited by several alkylphenols and alkylcatechols (e.g. cytotoxic, antibacterial and DNA strand scission activities).[4] This prompted us to produce adequate quantities of compounds **1**–**5** in order to start a wide bioassay investigation.

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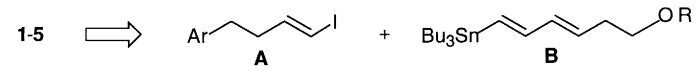
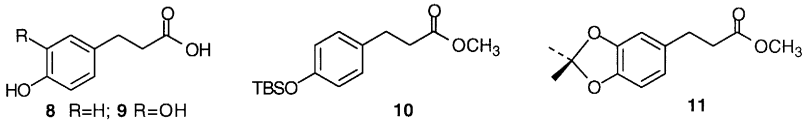
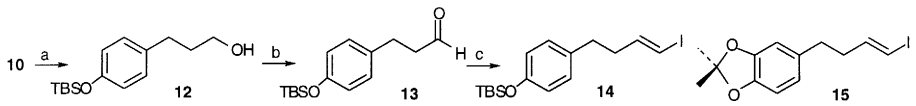
In this paper we describe a synthesis of these molecules using a convergent route in which the key step is the Stille coupling between the building blocks **A** and **B**.



Alkenyl iodides corresponding to block **A** were prepared starting from protected esters **10**[5] and **11** derived from commercially available starting materials such as 4-hydroxydihydrocinnamic (**8**) and 3,4-dihydroxydihydrocinnamic (**9**) acids. In particular, **10** was obtained from 4-hydroxydihydrocinnamic acid after Fischer esterification (MeOH, H_2SO_4) followed by silylation with *tert*-butyldimethylsilyl chloride (TBS-Cl) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[6] Acetal **11** was prepared by treating the methyl ester, easily obtained from 3,4-dihydroxydihydrocinnamic acid (**9**), with 2,2-dimethoxy propane.[7]

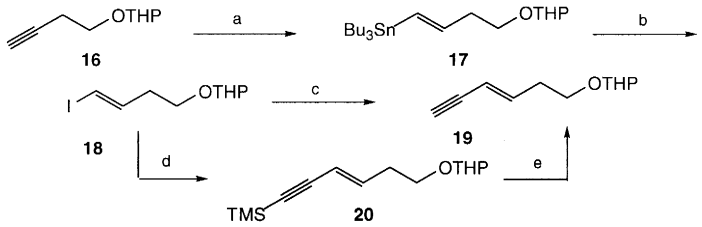


Our route to alkenyl iodides **14** and **15** is shown in Scheme 1. Ester **10** was reduced with $LiAlH_4$ to afford the alcohol **12** in quantitative yield. Oxidation of **12** with pyridinium dichromate (PDC)[8] gave the aldehyde **13**. This was subjected to reaction with chromium(II) chloride and iodoform[9] to afford a 90:10 mixture of *E*-alkenyl iodide **14** and its *Z* isomer (not shown).[10] The application of the same procedure to ester **11** gave alkenyl iodide **15** (41% overall yield from **9**, *E*:*Z ratio* 90:10).[11]



Scheme 1. (a) 1.0 equiv of $LiAlH_4$, THF, 0°C, 0.5 h 100%; (b) 1.3 equiv of PDC, 3 Å molecular sieves, CH_2Cl_2, rt, 1 h, 71%; (c) 6.0 equiv. of $CrCl_2$, 2 equiv. of CHI_3, 1,4-dioxane:THF (6:1), 15°C, 24 h, 72%

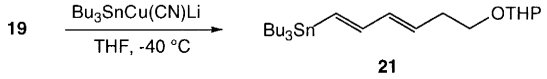
The synthesis of the block **B** started with hydrostannylation[12] of the THP protected 3-butyn-1-ol (**16**, Scheme 2). This reaction afforded the tributylstannane **17** which, after treatment with iodine,[13] gave **18** (80% yield, two steps). Enyne **19** was assembled from vinylic iodide **18** and tributyl(ethynyl)tin using a $(CH_3CN)_2PdCl_2$ catalyzed Stille coupling[13] reaction (45% yield; *E*:*Z ratio* 95:5). The yield of **19** was improved with a two step procedure involving a Sonogashira coupling[14] of iodide **18** with (trimethylsilyl)acetylene[13] (81% yield) followed by removal of the silyl group with tetrabutylammonium fluoride (TBAF, 72% yield; *E*:*Z ratio* 97:3).



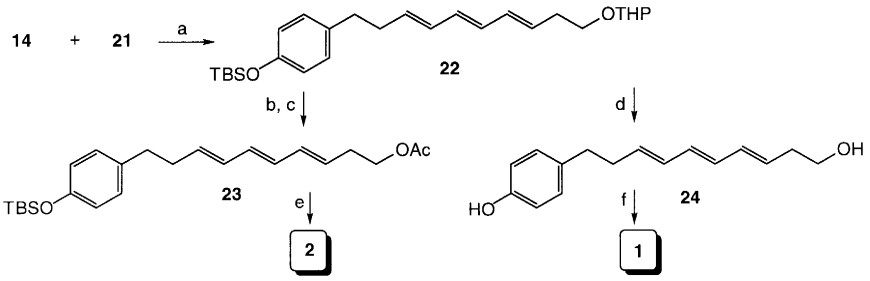
Scheme 2. (a) 0.9 equiv of Bu_3SnH, 0.02 equiv of AIBN, toluene, reflux, 4 h (b) 1.0 equiv of I_2, CH_2Cl_2, 0.5 h, 80% (two steps); (c) 0.07 equiv of $(CH_3CN)_2PdCl_2$, 1.1 equiv of $HCCSnBu_3$, 25°C, 0.5 h, DMF, 45%; (d) 2.0 equiv of $HCCSiMe_3$, 0.07 equiv of $(CH_3CN)_2PdCl_2$, 0.3 equiv of CuI, 2.0 equiv of Et_3N, 0°C, 1 h, 81%, (e) 2.0 equiv of TBAF, THF, rt, 0.5 h, 72%

With enyne **19** in hand, we tried the conventional hydrostannylation reaction[12] with 2,2-azobis(isobutyronitrile) (AIBN) as radical initiator. Unfortunately this reaction proved to be inefficient

giving a low yield of **21**. The enyne **19** was successfully metalated with the stannyl cuprate donor, prepared in situ with CuCN, *n*-BuLi and Bu_3SnH.[15] The dienylstannane **21**[16] was thus obtained in decent yield (60%) and good isomeric purity ((*E*,*E*)>97%, ^{1}H NMR analysis).

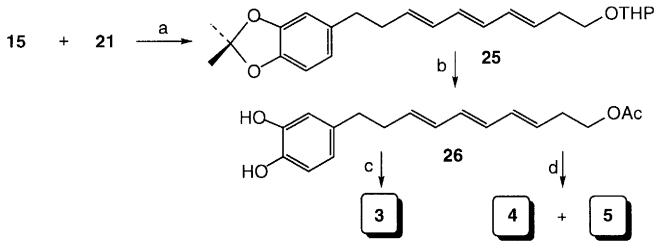


Finally, alkenyl iodide **14**, on coupling with stannane **21** using Stille's conditions (Scheme 3), provided, after careful column chromatography on silica gel, the isomerically enriched triene **22** (95% pure, ^{1}H NMR analysis).[17,18] Deprotection of the THP group with pyridinium *p*-toluenesulfonate (PPTS) and subsequent acetylation gave the silyl ether **23**. Removal of *tert*-butyldimethylsilyl group with TBAF in THF afforded target alkylphenol **2** in 15% overall yield from **8**. Stronger deprotective conditions on **22** (PPTS, *p*-TsOH) afforded **24** which, after acetylation, gave **1** (8% overall yield from **8**).



Scheme 3. (a) 0.05 equiv. of $(CH_3CN)_2PdCl_2$, DMF, rt, 0.5 h, 53%; (b) 0.1 equiv. of PPTS, EtOH, 55°C, 7 h, 80%; (c) 4.0 equiv. of Ac_2O, 6.0 equiv. of pyridine, 0.02 equiv. of DMAP, CH_2Cl_2, rt, 2 h, 81%; (d) 0.3 equiv. of PPTS, 0.3 equiv. *p*-TsOH, EtOH, 55°C, 40%; (e) 2.0 equiv. of TBAF, THF, rt, 0.5 h, 95%; (f) 4.0 equiv. of Ac_2O, 6.0 equiv. of pyridine, 0.02 equiv. of DMAP, CH_2Cl_2, rt, 2 h, 80%

The synthesis of catechols **3**–**5** started from the palladium-catalyzed cross-coupling[12] of the alkenyl-iodide **15** with the stannane **21** (Scheme 4) to afford, after a careful purification, triene **25** (95% pure, ^{1}H NMR analysis).[17,19] Exposure of **25** to aqueous acetic acid gave the monoacetylated catechol **26**. Target **3** (12% overall yield from **9**) was obtained after acetylation of **26**. A 1:1 mixture of catechols **4** and **5** (9% overall yield from **9**) was obtained by acetylating **26** using 0.8 equivalents of acetic anhydride.



Scheme 4. (a) 0.05 equiv. of $(CH_3CN)_2PdCl_2$, DMF, rt, 3 h, 56%; (b) CH_3COOH:H_2O (8:2), 80°C, 16 h, 63%; (c) 4.0 equiv. of Ac_2O, 6.0 equiv. of pyridine, 0.02 equiv of DMAP, CH_2Cl_2, rt, 2 h, 84%; (d) 0.8 equiv. of Ac_2O, 3.0 equiv. of pyridine, CH_2Cl_2, rt, 2 h, 65%

Synthetic compounds **1**–**5** showed ^{1}H and ^{13}C NMR spectra identical to those reported for the natural products.[1] An investigation into the biological activities of these compounds is now in progress and the results will be given in due course.

In conclusion, a straightforward synthetic route to alkylphenols **1**, **2** and alkylcatechols **3**–**5** from *H. callidegenita* has been developed in fair overall yields, starting from quite inexpensive dihydrocinnamic acid derivatives **8** and **9**, using a convergent approach centred on the Stille coupling reaction.

Acknowledgements

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10. Configurational assignment of the (*Z*) and (*E*) isomers was based on the 400 MHz ^{1}H NMR resonance of their vinylic protons (*E* isomer: δ 6.01, d, *J*=14.3 Hz and 6.54, dt, *J*=14.3, 7.3 Hz; *Z* isomer: δ 6.21, m, and 7.07, d, *J*=8.2 Hz).
11. Configurational assignment of the (*Z*) and (*E*) isomers was based on the 400 MHz ^{1}H NMR resonance of their vinylic protons (*E* isomer:δ 6.03, d, *J*=14.4 Hz and 6.52, m; *Z* isomer: δ 6.22, m and 6.64, d, *J*=8.2 Hz).
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16. Compound **21**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.49 (1H, dd, *J*=18.0, 10.0 Hz), 6.12 (1H, dd, *J*=10.0, 15.2 Hz), 6.11 (1H, d, *J*=18.0 Hz), 5.67 (1H, dt, *J*=15.2, 7.2 Hz), 4.60 (1H, t, *J*=4.3 Hz), 3.87 (1H, m), 3.77 (1H, m), 3.48 (1H, m), 3.46 (1H, m), 2.39 (2H, dt, *J*=7.2, 6.8 Hz), 1.70–1.45 (12H, m), 1.30 (6H, m), 0.88 (15H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.9, 135.4, 131.7, 129.6, 98.8, 66.9, 62.3, 32.9, 30.7, 29.1 (×3), 27.2 (×3), 25.5, 19.6, 13.6 (×3), 9.5 (×3).
17. The stereochemistry of the triene moiety was deduced from the coupling constants of the higher field protons which were carefully measured through ^{1}H homodecoupling experiments and comparison of the ^{13}C NMR values with literature data (Wehrli, F. W.; Nishida, T. *Progr. Chem. Org. Nat. Products* **1979**, *36*, p. 128).
18. Compound **22**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02 (2H, bd, *J*=8.4 Hz), 6.74 (2H, bd, *J*=8.4 Hz), 6.17–6.04 (4H, m), 5.70 (1H, dt, *J*=14.1, 7.0 Hz), 5.68 (1H, dt, *J*=14.6, 7.2 Hz), 4.59 (1H, t, *J*=3.6 Hz), 3.86 (1H, m), 3.78 (1H, dt, *J*=9.7, 7.0 Hz), 3.48 (1H, m), 3.45 (1H, dt, *J*=9.7, 6.7 Hz), 2.63 (2H, t, *J*=8.3 Hz), 2.38 (4H, m), 1.85–1.50 (6H, m), 0.98 (9H, s), 0.18 (6H, s); ^{13}C–NMR ($CDCl_3$, 100 MHz): δ 153.7, 134.4, 133.7, 132.2, 131.3, 131.0, 130.9, 130.2, 129.2 (×2), 119.8 (×2), 98.8, 67.0, 62.3, 35.0, 34.8, 33.2, 30.7, 25.7 (×3), 25.5, 19.6, 18.2, –2.8 (×2).
19. Compound **25**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (1H, bd, *J*=8.0 Hz), 6.58 (1H, bd, *J*=8.0 Hz), 6.57 (1H, bs), 6.15–6.06 (4H, m), 5.74–5.65 (2H, m), 4.59 (1H, t, *J*=3.8 Hz), 3.86 (1H, m), 3.76 (1H, dt, *J*=9.7, 7.0 Hz), 3.51 (1H, m) 3.44 (1H, dt, *J*=9.7, 6.7 Hz), 2.60 (2H, t, *J*=8.1 Hz), 2.38 (4H, m), 1.80–1.50 (6H, m), 1.65 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.3, 145.5, 134.9, 133.5, 132.2, 131.2, 131.0, 130.8, 130.1, 120.4, 117.4, 108.6, 107.8, 98.7, 66.9, 62.2, 35.5, 34.9, 33.2, 30.6, 25.8 (×2), 25.4, 19.5.