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Carboalumination/Ni-catalyzed couplings. A short synthesis of verticipyrone

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ABSTRACT

Verticipyrone (**1**) has been synthesized in six overall steps from commercially available ethyl-2-methylacetoacetate. This represents the first successful application of a modified Negishi carboalumination-nickel-catalyzed cross-coupling reaction to a chloromethylated pyrone.

Verticipyrone (**1**, Fig. 1) is a potent and selective complex I inhibitor of helminth mitochondrial electron transport, where protein NADH-fumarate reductase is responsible for the reduction of fumarate to succinate, coupled with the oxidation of NADH to NAD^+.[1,2] The recent isolation and identification of verticipyrone (**1**) as a potential antiparasitic have prompted its preparation via a modified Julia olefination, ultimately obtained as a mixture of *E*/*Z* isomers.[1] The structural attributes of **1** are generally similar to those of the methallylated heterocyclic bacterial metabolites actinopyrone A (**2**)[3] and the complex I (NADH dehydrogenase) inhibitor piericidin A1 (**3**),[4] with recent synthetic work having appeared on the latter.[5] In this Letter we report a significantly improved, stereoselective synthesis of verticipyrone (**1**) utilizing a modified Negishi carboalumination/nickel-catalyzed cross-coupling reaction.[6]

Retrosynthetic analysis (Scheme 1) of **1** suggests a disconnection to chloromethylpyrone (**4**) and the corresponding vinylalane **5**, generated in situ from a modified Negishi carboalumination of 1-decyne.[7] Coupling partners **4** and **5** are subsequently joined by a Ni-catalyzed cross-coupling. This approach mirrors our recent synthesis of piericidin A1 (**3**),[8] expanding the scope of this one-pot coupling reaction to include chloromethylated pyrones.[9]

The heterocyclic chloromethyl-γ-pyrone coupling partner **4** was prepared in four steps from known diketoester **6** (Scheme 2).[10] Monoalkylation of **6** with methyl iodide followed by treating diketoester **7** with DBU and refluxing the mixture in benzene for one hour gave the α-pyrone **8** in acceptable yield. As reported for similar substrates, cyclization of ester **7** to pyrone **8** consistently gave lower yields as the reaction was allowed to reflux for longer reaction times, and when run at reflux in toluene.[11] A modification of the known alkylation[1] conditions for the conversion of α-pyrone **8** to γ-pyrone **9** led to a significant decrease in the amount of methyl fluorosulfonate needed for complete conversion (from 10 to 2 equiv), thereby reducing exposure to this acutely toxic alkylating agent. Chlorination at the desired α′-position was subsequently achieved by treatment of **9** with LHMDS in THF in the presence of *p*-toluenesulfonyl chloride.

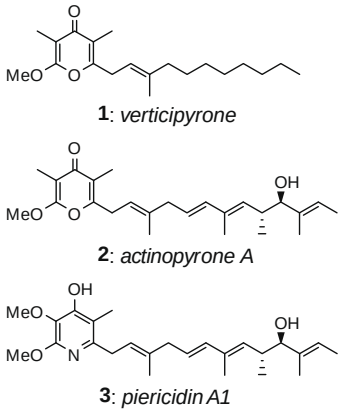
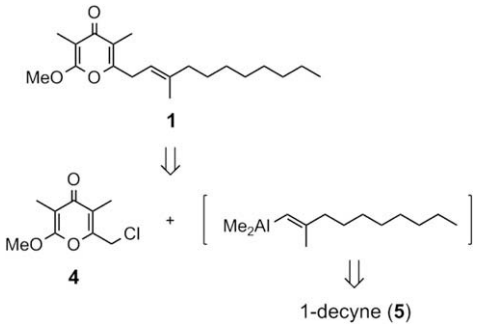


Figure 1. Verticipyrone (**1**), and analogous bacterial metabolites actinopyrone A (**2**) and piericidin A1 (**3**).



Scheme 1. Retrosynthetic analysis of verticipyrone: modified Negishi carboalumination/nickel-catalyzed cross-coupling.

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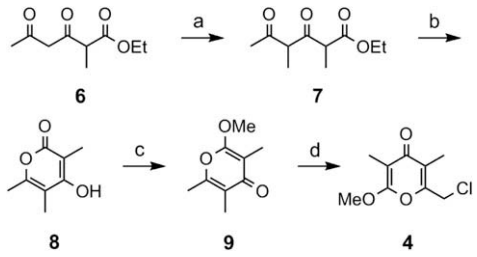
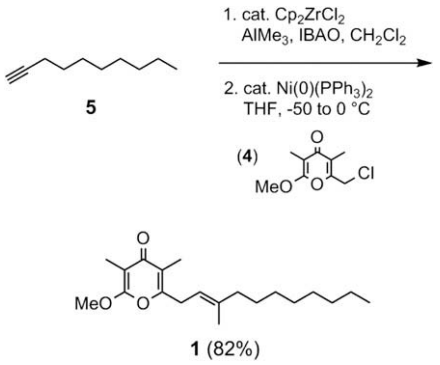


Scheme 2. Preparation of γ-pyrone **4**. Reagents and conditions: (a) CH_3I, K_2CO_3, acetone, rt, 16 h; (b) DBU, benzene, reflux, 1 h, 60% for two steps; (c) $MeOSO_2F$, CH_2Cl_2, rt, 3 h, then 40 °C, 30 min, 88%; and (d) LHMDS, THF, −40 to −5 °C, then TsCl, THF, −78 °C to rt, 91%.

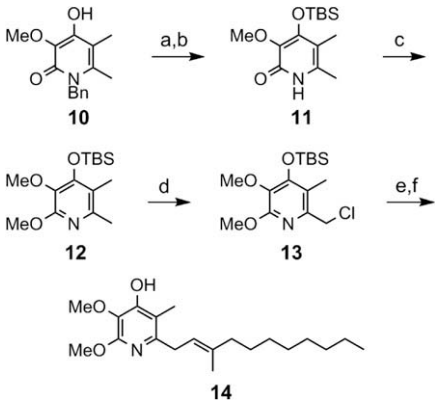
Carboalumination of 1-decyne **5** (1.2 equiv) was effected with catalytic Cp_2ZrCl_2 (10 mol %), trimethylaluminum (2 equiv), and isobutylaluminoxane (IBAO, 20 mol %) in DCM (Scheme 3). Once TLC analysis of a quenched aliquot (in MeOH) indicated complete conversion of terminal alkyne to 2-methyl-1-decene (~2 h). The Ni(0) catalyst (10 mol %) was then added at −50 °C followed by the heterocyclic chloride **4** (1 equiv), after which the mixture was warmed to 0 °C. The reaction was then quenched with an aqueous mixture of Rochelle's salt and K_2CO_3, extracted with ether, dried over anhydrous Na_2SO_4, and then chromatographed on silica to provide verticipyrone (**1**) in 82% yield. Comparison of spectral data for this material with those published confirms the assignment of our synthetic material.[1]

Carboalumination/nickel-catalyzed cross-coupling provides an attractive alternative to traditional cross-coupling strategies applied particularly to the synthesis of methallylated natural products. In this case, the synthesis of verticipyrone (**1**) expands its utility to include chloromethylated derivatives of pyrone heterocycles as substrates. Further applications to related analogues could also be envisioned. Heterocyclic analogue **14** (Scheme 4) could also be readily prepared, a derivative that shares common structural motifs between pyrone **4** and the fully substituted pyridine derivative **13**. Silyl protected 4-pyridinol **13**[8] was prepared from the known *N*-benzyl-2-pyridone[12] utilizing a modified protocol. Thus, treatment of **10** with H_2 (1 atm), Pd/C in HOAc followed by O-silylation provided 2-pyridone **11**. O-Alkylative aromatization followed by selective benzylic-like chlorination provided heteroaromatic **13**. 1-Decyne carboalumination of 1-decyne followed by Ni-catalyzed cross-coupling, with subsequent standard desilylation, afforded the mixed analogue of **1** and **2**, product **14**.

In summary, an efficient and relatively short synthesis of verticipyrone (**1**) has been accomplished requiring only six overall steps from commercially available ethyl 2-methylacetoacetate. This represents another successful application of a one-pot modified Negishi carboalumination/Ni-catalyzed cross-coupling reaction to a chloromethylated heteroaromatic nucleus, in this case to a pyrone. The 2-pyridyl analogue **14** was also prepared using this technology.[13]



Scheme 3. One-pot 1-alkyne carboalumination/nickel-catalyzed cross-coupling of pyrone **4** providing verticipyrone (**1**).



Scheme 4. Preparation of the analogous pyridyl heterocycle **14**. Reagents and conditions: (a) H_2 (1 atm), Pd/C, HOAc, rt, 16 h, 78%; (b) TBSCl, Et_3N, CH_2Cl_2, rt, 4 h, 95%; (c) CH_3I, Ag_2CO_3, CH_2Cl_2, rt, 16 h, 90%; (d) *t*-BuLi, hexane, 0 °C, 1 h, then Cl_3CCCl_3, THF, −78 to 0 °C, 82%; (e) 1-decyne (**5**), Cp_2ZrCl_2, $AlMe_3$, IBAO, CH_2Cl_2, then **13**, $(PPh_3)_2NiCl_2$, *n*-BuLi, THF, −50 to 0 °C; (f) TBAF, THF, rt, 1 h, 71% for two steps.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.167.

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13. *Selected data*: compound **4**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (s, 2H), 4.01 (s, 3H), 2.03 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 162.4, 151.9, 121.6, 100.6, 55.9, 39.6, 10.1, 7.2; HRMS (ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_9H_{11}ClO_3Na$: 225.0295, found: 225.0294. Verticipyrone (compound **1**, see Ref. 1 for spectra comparison): ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (t, 1H, J = 6.0 Hz), 3.93 (s, 3H), 3.29 (d, 2H, J = 7.2 Hz), 2.00 (t, 2H, J = 7.6 Hz), 1.95 (s, 3H), 1.84 (s, 3H), 1.71 (s, 3H), 1.42–1.34 (m, 2H), 1.32–1.18 (m, 10H), 0.87 (t, 3H, J = 6.8 Hz); HRMS (ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{20}H_{32}O_3Na$: 343.2249, found:

343.2253. Compound **11**: mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H), 0.99 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 156.2, 136.9, 134.4, 109.5, 59.2, 26.1, 19.1, 17.2, 11.5, −4.1; HRMS (ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{14}H_{25}NO_3SiNa$: 306.1501, found: 306.1489. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.71 (s, 3H), 2.33 (s, 3H), 2.06 (s, 3H), 1.01 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.2, 148.3, 132.2, 117.6, 60.3, 53.4, 26.1, 22.5, 19.0, 12.5, −4.1; HRMS (ESI/TOF) *m/z*: $(M+H)^+$ calcd for $C_{15}H_{27}NO_3SiH$: 298.1838, found: 298.1819. Compound **13**: mp 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 2H), 3.96 (s, 3H), 3.78 (s, 3H), 2.20 (s, 3H), 1.01 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 154.5, 145.5, 134.1, 119.9, 60.3, 53.6, 46.3, 26.1, 19.0, 11.9, −4.0; HRMS (ESI/TOF) *m/z*: $(M+H)^+$ calcd for $C_{15}H_{26}ClNO_3SiH$: 332.1449, found: 332.1448. Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (br s, 1H), 5.31 (td, 1H, J = 6.8, 1.2 Hz), 3.96 (s, 3H), 3.85 (s, 3H), 3.35 (d, 2H, J = 6.8 Hz), 2.09 (s, 3H), 1.99 (t, 2H, J = 7.2 Hz), 1.73 (s, 3H), 1.41–1.33 (m, 2H), 1.31–1.19 (m, 10H), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.7, 151.4, 136.5, 128.0, 121.1, 112.1, 60.8, 53.3, 39.9, 34.7, 32.1, 29.7, 29.54, 29.52, 28.2, 22.9, 16.5, 14.3, 10.6; HRMS (ESI/TOF) *m/z*: $(M+H)^+$ calcd for $C_{20}H_{34}NO_3H$: 336.2539, found: 336.2537.