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Synthesis of the *N*-((1*E*)-Alkenyl)-(2*Z*,4*Z*)-heptadienamide Side Chain of Salicylihalamide A and Apicularens A and B

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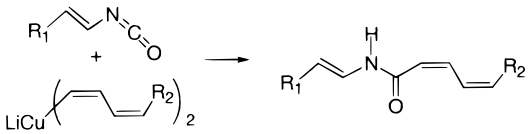
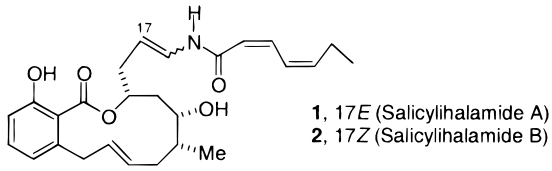
ABSTRACT

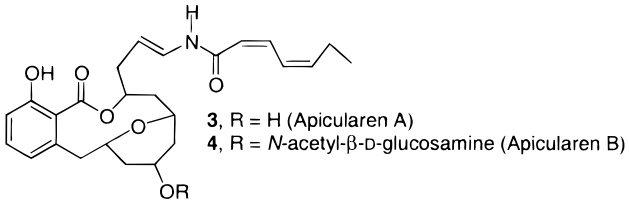


The unstable *N*-((1*E*)-alkenyl)-(2*Z*,4*Z*)-heptadienamide side chain of salicylihalamide A (1) and apicularens A and B (3 and 4) has been prepared in one pot by the addition of (1*Z*,3*Z*)-hexadienylcuprate, prepared in situ from EtLi, CuBr·SMe$_2$, and acetylene, to a (1*E*)-alkenyl isocyanate.

Erickson and co-workers reported the isolation of the potent antitumor agents salicylihalamides A and B (**1** and **2**) from the marine sponge *Haliclona* sp. in 1997.[1] These compounds



1, 17*E* (Salicylihalamide A)
2, 17*Z* (Salicylihalamide B)



3, R = H (Apicularen A)
4, R = *N*-acetyl-β-D-glucosamine (Apicularen B)

show a striking pattern of differential cytotoxicity at a mean activity GI$_{50}$ level of 15 nM without any significant correlation to the profiles shown by other known antitumor compounds. In 1998, Kunze and co-workers reported the isolation of the cytostatic macrolides apicularens A and B (**3** and **4**) from several species of myxobacteria of the genus *Chondromyces*.[2] Apicularen A showed no antimicrobial activity but was highly cytotoxic for cultivated human and animal cells, with IC$_{50}$ values ranging between 0.1 and 3 ng/mL.

The unusual, reactive, unstable *N*-((1*E*)-alkenyl)-(2*Z*,4*Z*)-heptadienamide side chain of these antitumor agents probably plays an important role in their biological activity. Since this side chain is known to be unstable (salicylihalamides decompose in $CDCl_3$), it must be introduced by a mild procedure late in the synthesis. We report here a one-step method for the production of this side chain in moderate yield by the addition of a (1*Z*,3*Z*)-alkadienylcuprate to a vinyl isocyanate.

Taylor reported that organocuprates add to acetylene at −50 °C to give the (1*Z*)-alkenylcuprate.[3] At 0 °C, the (1*Z*)-alkenylcuprate adds to a second equivalent of acetylene to give the (1*Z*,3*Z*)-alkadienylcuprate **5**.[3] The dienylcuprate was trapped by a variety of electrophiles, including carbon

(1) Erickson, K. L.; Beutler, J. A.; Cardellina, J. A., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192.

(2) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080.

(3) Furber, M.; Taylor, R. J. K.; Burford, S. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809−1815.

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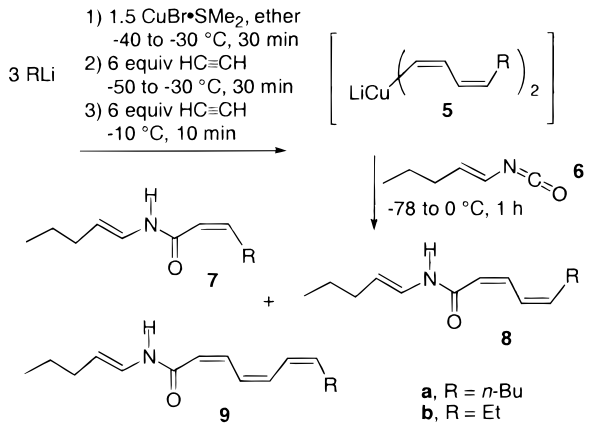
dioxide, iodine, alkyl halides, aldehydes, and enones. We reasoned that addition of the dienylcuprate to a (1*E*)-alkenyl isocyanate should lead directly to the desired *N*-((1*E*)-alkenyl)-(2*Z*,4*Z*)-heptadienamide side chain of salicylihalamide A and the apicularens.

Initial experiments were conducted with the cuprate prepared from readily available *n*-BuLi (see Scheme 1).

Scheme 1



Addition of 3 equiv of *n*-BuLi to 1.5 equiv of CuBr·SMe$_2$ in ether at −40 °C gave the organocuprate. Acetylene (6 equiv) was added at −50 °C, and the solution was warmed to −10 °C and treated with 6 equiv more of acetylene to generate the dienylcuprate **5a**, containing some alkenylcuprate and some trienylcuprate. Excess cuprate was used to optimize the yield based on the isocyanate, which will be the expensive component in the synthesis of **1**, **3**, and **4**. The solution was cooled to −78 °C and treated with HMPA, P(OEt)$_3$, and (1*E*)-pentenyl isocyanate (**6**).[4−6] The solution was warmed to 0 °C over 1 h. Normal workup and flash chromatography on silica gel afforded 65% of a 3:1:1 mixture of the desired dienamide **8a**, enamide **7a**, and trienamide **9a**. Chromatography on silica gel impregnated with 5% silver nitrate afforded 12% of pure enamide **7a**, followed by 28% of the desired dienamide **8a**, 8% of trienamide **9a**, and a trace of the 4*E* isomer of **8a**, resulting from isomerization during chromatography. Taylor also noted the formation of minor amounts of products analogous to **7**, but not trienes analogous to **9**.[3]

EtLi needed for the preparation of the dienamide **8b** was prepared in situ from EtI and 2.2 equiv of *t*-BuLi.[7] Addition of CuBr·SMe$_2$ and acetylene at −40 °C, additional acetylene at −10 °C, and then isocyanate **6** at −78 °C as described above gave 60% of a 3:1:1 mixture of **8b**, **7b**, and **9b**. Chromatography on silica gel impregnated with 5% silver nitrate gave 15% of **7b**, followed by 28% of **8b**, and 6% of **9b**.[8]

The ^{1}H and ^{13}C NMR spectral data of **8b** in both CD$_3$OD and benzene-d_6 correspond closely to those reported for salicylihalamide A (**1**), except for the expected differences due to the different *N*-alkenyl side chain.

This sequence provides efficient access to the unsaturated side chain of salicylihalamide A (**1**) and apicularens A and B (**3** and **4**) under mild conditions that should be compatible with the functionality of these macrolides. Application of this method to the total synthesis of salicylihalamide A is currently in progress.

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(4) (2*E*)-Hexenoyl azide (92%) was prepared from the acid and DPPA.[5] Heating the acyl azide in benzene at reflux for 3 h and distillation afforded isocyanate **6** in 61% yield after distillation.[6]

(5) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2157.

(6) (a) Hocking, M. B. *Can. J. Chem.* **1968**, *46*, 2275−2282. (b) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224−228.

(7) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−5406. (b) Bratovanov, S.; Bienz, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1587−1603.

(8) *tert*-Butyllithium (1.9 mL, 1.5 M solution in pentane, 2.85 mmol) was added dropwise to a solution of iodoethane (203 mg, 1.3 mmol) in 5 mL of pentane and 3.5 mL of ether at −78 °C. The solution was stirred at −78 °C for 10 min and then at room temperature for 1 h. The resulting solution was added by cannula to a suspension of CuBr·SMe$_2$ (133 mg, 0.65 mmol) in 1.0 mL of ether at −40 °C. The mixture was stirred at −30 °C for 30 min. The solution was cooled to −50 °C, and gaseous acetylene (50 mL, 2.0 mmol) was slowly passed into the solution through a syringe needle. The resulting solution was stirred at −30 °C for 20 min. The solution was warmed to −10 °C, and the temperature was carefully maintained at −10 °C while more acetylene (60 mL, 2.45 mmol) was added over 10 min. The resulting solution was cooled in a dry ice−acetone bath. HMPA (89 μL, 0.5 mmol), (EtO)$_3$P (10 μL), and then 33 mg (0.30 mmol) of **6** were added to the cold solution. The temperature was slowly raised to 0 °C over 1 h. The reaction was quenched with 5 mL of 5% aqueous NH$_3$ and filtered through Celite. The filtrate was extracted with three portions of ether. The combined extracts were washed with 5% aqueous NH$_3$ and dried over Na$_2$SO$_4$. The solvent was removed, and the residue was purified on silica gel (12:1 hexanes/EtOAc) to give 37 mg (60%) of a 1:3:1 mixture of **7b**, **8b**, and **9b**. Chromatography on silica gel impregnated with 5% AgNO$_3$ (7:1 pentane/Et$_2$O) gave **7b** (8 mg, 15%), followed by **8b** (17 mg, 28%) and **9b** (4 mg, 6%). Data for **7b**: ^{1}H NMR (CD$_3$OD) δ 6.70 (d, 1, J = 14.0 Hz), 6.08 (dt, 1, J = 11.6, 7.3 Hz), 5.75 (dt, 1, J = 11.6, 1.8 Hz), 5.28 (dt, 1, J = 14.0, 7.3 Hz), 2.67 (ddq, 2, J = 1.8, 7.3, 7.3 Hz), 2.02 (ddt, 2, J = 1.2, 7.3, 7.3 Hz), 1.41 (tq, 2, J = 7.3, 7.3 Hz), 1.04 (t, 3, J = 7.3 Hz), 0.92 (t, 3, J = 7.3 Hz); ^{13}C NMR (CD$_3$OD) δ 165.9, 150.0, 124.0, 122.1, 115.3, 33.3, 24.3, 23.4, 14.2, 14.0; IR (neat) 3276, 1651, 952 cm^{-1}. Data for **8b**: mp 55−56 °C; ^{1}H NMR (CD$_3$OD) δ 7.31 (dd, 1, J = 11.6, 11.6 Hz), 6.87 (ddd, 1, J = 1.2, 11.6, 11.6 Hz), 6.72 (d, 1, J = 14.0 Hz), 5.82 (dt, 1, J = 11.6, 7.6 Hz), 5.69 (d, 1, J = 11.6 Hz), 5.30 (dt, 1, J = 14.0, 7.3 Hz), 2.29 (ddq, 2, J = 1.2, 7.6, 7.6 Hz), 2.03 (ddt, 2, J = 1.2, 7.3, 7.3 Hz), 1.41 (tq, 2, J = 7.3, 7.3 Hz), 1.03 (t, 3, J = 7.6 Hz), 0.92 (t, 3, J = 7.3 Hz); ^{13}C NMR (CD$_3$OD) δ 165.9, 142.6, 137.6, 125.5, 124.1, 120.6, 115.5, 33.4, 24.3, 21.7, 14.5, 14.0; IR (neat) 3278, 1654, 1522, 954 cm^{-1}. Data for **9b**: ^{1}H NMR (CD$_3$OD) δ 7.37 (dd, 1, J = 10.4, 12.2 Hz), 7.05 (dd, 1, J = 11.6, 12.2 Hz), 6.73 (d, 1, J = 14.4 Hz), 6.62 (dd, 1, J = 10.4, 12.2 Hz), 6.57 (d, 1, J = 10.4, 12.2 Hz), 5.72 (d, 1, J = 11.6 Hz), 5.70 (dt, 1, J = 7.3, 12.2 Hz), 5.31 (dt, 1, J = 7.3, 14.4 Hz), 2.28 (dt, 2, J = 7.3, 7.3 Hz), 2.03 (ddt, 2, J = 1.2, 7.3, 7.3 Hz), 1.42 (tq, 2, J = 7.3, 7.3 Hz), 1.03 (t, 3, J = 7.3 Hz), 0.93 (t, 3, J = 7.3 Hz); ^{13}C NMR (CD$_3$OD) δ 165.8, 139.3, 137.4, 131.7, 125.7, 124.1, 123.3, 121.0, 115.6, 33.3, 24.3, 22.0, 14.5, 14.0; IR (neat) 3290, 1642, 1516, 953 cm^{-1}.