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A New Approach to Furan-Containing Macrolactones

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Furan and tetrahydrofuran heterocycles are part of many natural products, like the Galerucella pheromone, furano epothilones, bipinnatin, and amphidinolides. This paper describes a short and efficient synthetic approach to furan-containing macrolactones in 4 steps, including as key steps a Sonogashira reaction and an olefin metathesis. The resulting compounds were tested at the National Cancer Institute for their cytotoxicity, but did not exhibit significant cytotoxicity in the human tumour cell line screen.

Key Words: Sonogashira reaction, Mitsunobu reaction, metathesis, cytotoxicity.

Introduction

Furan heterocycles are partial structures of numerous natural products. The Galerucella pheromone from the beetle *Galerucella calmariensis* is a 14-carbon bicyclic dimethylfuran lactone.[1] The furano epothilone family is an interesting group of derivatives of the bacterial macrolides, epothilone A and epothilone B, and represents a biological analogues of paclitaxel.[2,3] Bipinnatins are natural marine products with interesting activities against several tumour cell lines.[4]

Likewise, tetrahydrofuran rings are a part of many natural products, such as the amphidinolide family, that was first isolated from various strains of the microscopic marine dinoflagellate *Amphidinium* sp., which lives inside the marine flatworm *Amphiscolopes* sp. The compounds exhibit significant antineoplastic activity against several human carcinoma cell lines.[5]

Herein, we describe a short and efficient approach to furan-containing macrolactones. The strategy we describe opens up the possibility of preparing numerous analogues with different ring sizes.

Results and Discussion

Hex-5-ynoic acid (**1**) was reacted in a Sonogashira reaction[6] with 5-iodofurancarbaldehyde (**2**) to give the alkyne **3**. The carboxyl group of **3** was esterified with hex-5-en-1-ol under Mitsunobu conditions[7] to give the corresponding ester **4**. The formyl group of **4** was allowed to react in a Grignard reaction with allyl magnesium bromide[8,9] to give the alkenol **5**. The yield of **5** was only 40% since the Grignard reagent, in part, was also added to the ester group, giving the corresponding tertiary alcohol. The alkenol **5** was cyclized by

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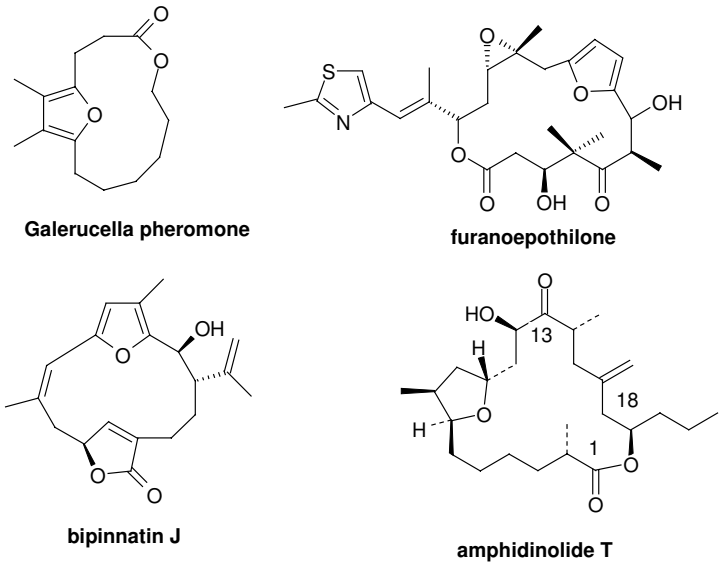
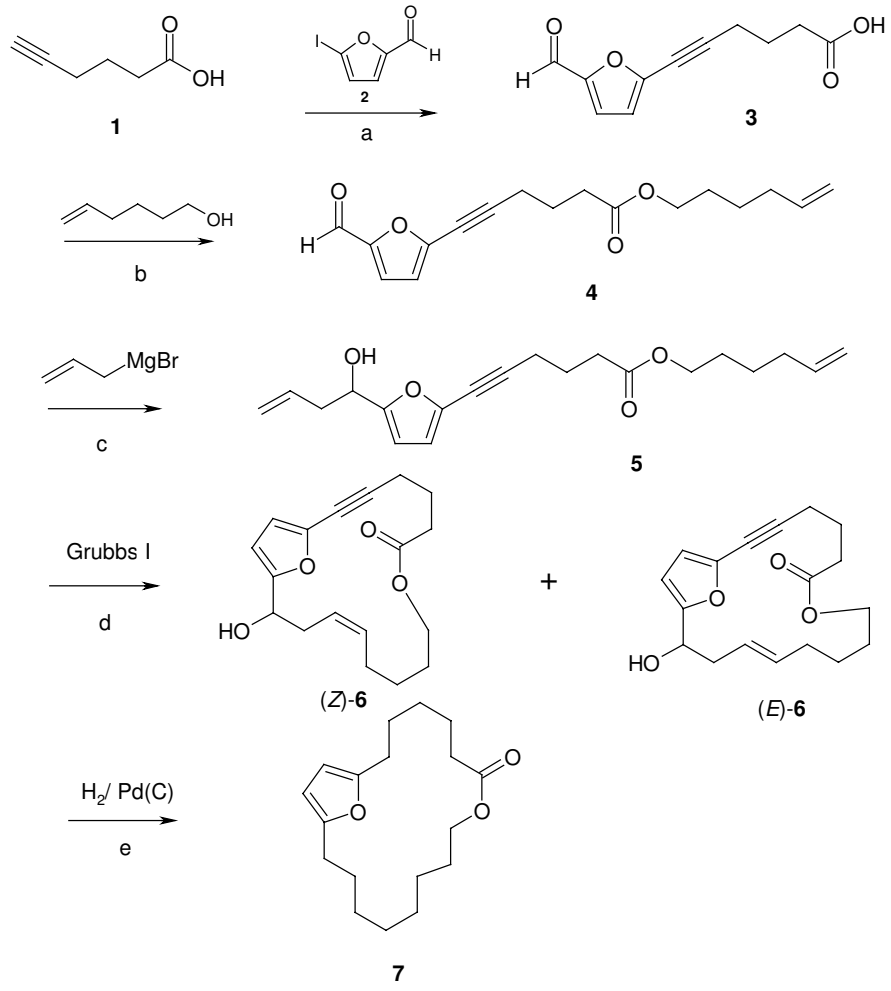


Figure 1. Naturally occurring macrolactones containing furan or tetrahydrofuran heterocycles.



Scheme 1. a: EDMA, $PdCl_2(PPh_3)_2$, CuI; b: Ph_3P, toluene, DIAD; c: THF, d: CH_2Cl_2; e: THF-mentioning of Lindlar cat-Pd/C cat mixture.

a ring-closing olefin metathesis using Grubbs I catalyst[10,11] to give the lactone **6** as a 7:3 E/Z mixture. The composition of the mixture was determined by GLC-MS. Subsequent hydrogenation of both the triple and the double bonds with a mixture of Pd/C and Lindlar catalyst led to the lactone **7** with an amphidinolide T skeleton.

Experimental

General

Elemental analysis: Heraeus CHN–Rapid; IR-Spectra: Perkin-Elmer FT-IR Paragon 1000; MS: Hewlett Packard MS-Engine; electron ionisation (EI): 70 eV, chemical ionisation (CI) with CH_4 (300 eV); NMR: Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz); melting points: Büchi Melting Point B-540 (not corrected); flash column chromatography (FCC): silica gel 60 (230-400 mesh, E. Merck, Darmstadt, Germany); GLC-MS: Shimadzu GC.

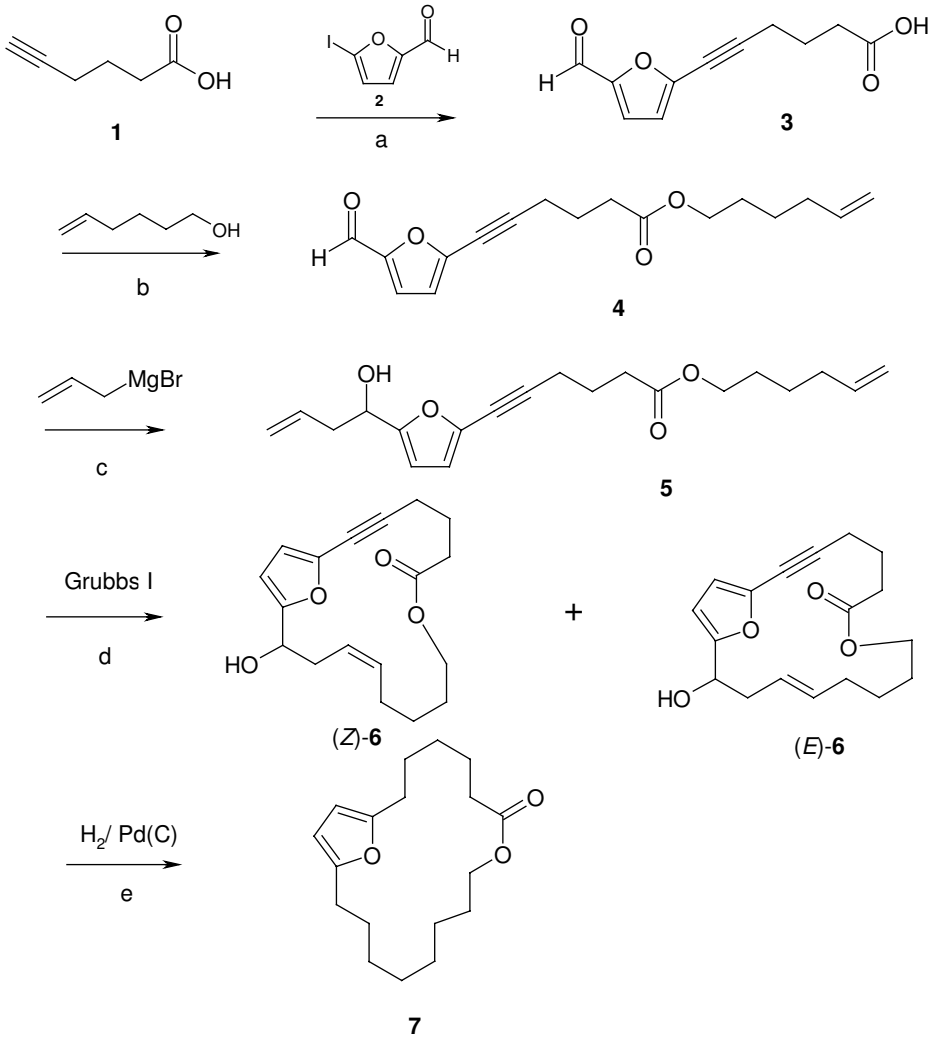
6-(5-Formyl-furan-2-yl)-hex-5-ynoic acid (3)

We dissolved 0.15 g (0.79 mmol) CuI in 70 mL of dry ethyldimethylamine (EDMA) and 2.72 g (17.3 mmol) hex-5-ynoic acid, 200 mg (0.25 mmol) $PdCl_2(PPh_3)_2$, and 3.84 g (17.3 mmol) 5-iodo furan-2-carbaldehyde (**2**) were added. The mixture was stirred for 48 h under N_2 atmosphere. The solvent was evaporated and the residue dissolved in 50 mL of 5% $Na_2S_2O_3$ solution. Then, 1 mL of 2 M NaOH was added and extracted with diethyl ether (3 × 50 mL). The organic layer was rejected. Then, conc. HCl was added to the aqueous to get a pH value of 3. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4. The organic solvent was evaporated and the residue purified by FCC (diethyl ether/iso-hexane 1:1) to give 2.36 g (66%) of **3**. Melting point: 90.6-91.2 °C. Elemental analysis: $C_{11}H_{10}O_4$ (M_r = 206 g/mol) Calc. (%) C: 64.08 H: 4.89 Found (%) C: 63.72 H: 4.90. IR (KBr): ν[cm^{-1}] = 3142, 3104, 2220, 1716, 1639, 1508, 1428, 1407, 1382, 1329, 1260, 1182, 1030, 966, 920, 876, 815, 765, 654. MS (EI): m/z (%) = 206 (M^+ (59)), 188 (20), 159 (82), 147 (92), 146 (92), 103 (33), 94 (81), 77 (100), 63 (41), 55 (62), 51 (65). MS (CI): m/z (%) = 207 (M^++1, 100), 189 (28) ^{1}H-NMR ($CDCl_3$)δ(ppm) = 1.89 (tt, J = 7.1 Hz, J = 7.1 Hz, 2 H, 3-H), 2.49 (t, J = 7.2, 2 H, 2-H), 2.51 (t, J = 7.0 Hz, 2 H, 4-H), 6.55 (d, J = 3.7 Hz, 1 H, aromat. CH), 7.14 (d, J = 3.7 Hz, 1 H, aromat. CH), 9.51 (s, 1 H, CHO). ^{13}C-NMR ($CDCl_3$)δ(ppm) = 18.84 (C-4), 22.88 (C-3), 32.56 (C-2), 71.25 (C-5), 96.99 (C-6), 116.20 (aromat. CH), 121.31 (aromat. CH), 142.14 (quart. C), 151.99 (quart. C), 177.19 (CHO), 178.69 (C-1).

6-(5-Formyl-furan-2-yl)-hex-5-ynoic acid hex-5-enyl ester (4)

We dissolved 1.00 g (4.85 mmol) of **3**, 0.53 g (5.30 mmol) hex-5-en-1-ol and 1.31 g (5.00 mmol) triphenylphosphine in 60 mL of dry THF. The mixture was stirred under N_2 atmosphere and cooled to 0 °C. Then, 1.01 g (4.95 mmol) diisopropyl azodicarboxylate (DIAD) was added dropwise through a syringe. Afterwards, the mixture was stirred for 15 h and then quenched with 30 mL of water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over Na_2SO_4. Then, the solvent was evaporated and the residue was purified by FCC (hexane/diethyl ether 8:2) to give 1.01 g (72%) of **4** as a yellow oil. Elemental analysis: $C_{17}H_{20}O_4$ (M_r = 288 g/mol) Calc. (%)

C: 70.81 H: 6.99. Found (%) C: 71.02 H: 7.05. IR (KBr): ν [cm^{-1}] = 3146, 3076, 2938, 2860, 2231, 1732, 1678, 1642, 1570, 1503, 1455, 1390, 1351, 1314, 1278, 1159, 1022, 969, 913, 804, 760. MS (EI): m/z (%) = 288 (M$^+$, (8)), 206 (44), 188 (46), 164 (38), 159 (100), 103 (17). ^{1}H-NMR ($CDCl_3$)δ(ppm) = 1.45 (m, 2 H, 3′-H), 1.64 (m, 2 H, 2′-H), 1.93 (tt, J = 7.2 Hz, J = 7.2 Hz, 2 H, 3-H), 2.07 (m, J = 7.1 Hz, 2 H, 4′-H), 2.47 (t, J = 7.3 Hz, 2H, 2-H), 2.54 (t, J = 7.1 Hz, 2H, 4-H), 4.08 (t, J = 6.7 Hz, 2 H, 1′-H), 4.99 (m, 2 H, 6′-H), 5.80 (m, 1 H, 5′-H), 6.61 (d, J = 3.7 Hz, 1 H, aromat. CH), 7.20 (d, J= 3.7 Hz, 1 H, aromat. CH), 9.58 (s, 1 H, CHO). ^{13}C-NMR ($CDCl_3$)δ(ppm) = 18.99 (C-4), 23.28 (C-3), 25.21 (C-3′), 28.06 (C-2′), 32.98 (C-4′), 33.27 (C-2), 64.52 (C-1′), 71.13 (C-5), 97.31 (C-6), 114,88 (C-6′), 116.15 (aromat. CH), 121.5 (aromat. CH), 138.31 (C-5′), 142.24 (C quart.), 152.05 (C quart.), 172.58 (C-1), 177.11 (CHO).



Scheme 1. a: EDMA, $PdCl_2(PPh_3)_2$, CuI; b: Ph_3P, toluene, DIAD; c: THF, d: CH_2Cl_2; e: THF-mentioning of Lindlar cat-Pd/C cat mixture.

6-[5-(1-Hydroxy-but-3-enyl)-furan-2-yl]-hex-5-ynoic acid hex-5-enyl ester (5)

We dissolved 0.44 g (1.53 mmol) of **4** in dry THF and stirred at -80 °C under N_2-atmosphere. Using a syringe, 1.9 mL (1.9 mmol) of an allylmagnesium bromide solution (1 M in diethyl ether) was added dropwise. The temperature was slowly advanced to room temperature over 3 h. At this temperature the mixture was stirred for another 11 h. The mixture was quenched with 20 mL of saturated NH_4Cl solution and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by FCC (n-hexane/diethyl ether 8:2) to give 177 mg (40%) of **5** as a yellow oil. Elemental analysis: $C_{20}H_{26}O_4$ (M_r = 330 g/mol) Calc. (%) C: 72.70 H: 7.93. Found (%) C: 72.68 H: 7.59. IR (KBr): ν [cm^{-1}] = 3441, 3077, 2933, 2860, 2232 (very small), 1732, 1641, 1434, 1316, 1192, 1011, 914. MS (EI): m/z (%) = 312 (M^+-18, 28), 289 (43), 229 (27), 207 (52), 189 (100), 161 (43), 128 (27). ^{1}H-NMR ($CDCl_3$)δ(ppm) = 1.45 (m, 2 H, 3′-H), 1.64 (m, 2 H, 2′-H), 1.92 (tt, J = 7.2 Hz,J = 7.2 Hz, 2 H, 3-H), 2.08 (m, 2 H, 4′-H), 2.48 (t, J = 7.5 Hz, 2 H, 2-H), 2.51 (t, J = 6.9 Hz, 2 H, 4-H), 2.62 (m, 2H, C-2″ of 1-hydroxy-but-3-enyl), 4.09 (t, J = 6.7 Hz, 2H, 1′-H), 4.71 (t, J = 6.6 Hz, 1 H, 1-H), 4.99 (m, 2 H, 6′-H), 5.17 (m, 2 H, H_2C=), 5.80 (m, 2 H, 2 -HC=), 6.21 (d, J = 3.4 Hz, 1 H, aromat. CH), 6.42 (d, J = 3.4 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$)δ(ppm) = 18.97 (C-4), 23.58 (C-3), 25.19 (C-3′), 28.05 (C-2′), 33.10 (C-4′), 33.27 (C-2), 40.06 (CH_2), 64.44 (C-1′), 67.00 (-HCOH-), 71.73 (C-5), 93.56 (C-6), 107.11 (aromat. CH), 114.74 (aromat. CH), 114.86 (C-6′), 118.85 (CH_2 allyl of 1-hydroxy-but-3-enyl), 133.43 (CH_1 allyl of 1-hydroxy-but-3-enyl), 136.69 (C quart.), 138.34 (C-5′), 156.44 (C quart.), 173.11 (C-1).

***(Z)*-16-Hydroxy-8,20-dioxa-bicyclo[15.2.1]icosa-1(19),13,17-trien-2-yn-7-one((*Z*)-6) and (*E*)-16-hydroxy-8,20-dioxa-bicyclo[15.2.1]icosa-1(19),13,17-trien-2-yn-7-one((*E*)-6)**

We dissolved 0.19 g (0.58 mmol) of **5** and 0.16 g (0.20 mmol) of Grubbs I catalyst separately in 5 mL of dry toluene. Using 2 syringes these solutions were simultaneously added dropwise to 120 mL of dry boiling toluene over 10 h. The mixture was heated under reflux for 2 h under a N_2-atmosphere. Then, the solvent was evaporated and the residue was purified by FCC (cyclohexane/diethyl ether 9:1) to give 35 mg (20 %) of (*Z*)-**6** and (*E*)-**6** as a yellow oil. IR (KBr): ν[cm^{-1}] = 3425, 2927, 2859, 2362, 2336, 1725, 1710, 1630, 1210, 1155, 1016. MS (EI): m/z (%) = 302 (M^+ (24)), 284 (8), 206 (13), 189 (19), 188 (23), 159 (49), 146 (34), 134 (34), 105 (43), 82 (43), 55 (100). HR-MS (EI): $C_{18}H_{22}O_4$ Calc.: 302.1518 Found: 302.1542. ^{1}H-NMR ($CDCl_3$)δ(ppm) = 1.27 (m, 2 H, 11-H), 1.49 (m, 2H, 10-H), 1.92 (m, 2H, 6-H), 1.98 (m, 2H, 12-H), 2.54 (m, 6 H, 4-H + 6-H + 15-H), 4.06 (m, 2 H, 9-H), 4.73 (m, 1 H, 16-H), 5.25 (dtt, J = 1.5 Hz, J = 7.5 Hz, J = 10.8 Hz, 0.3 H, *Z* 13-H), 5.39 (m, 0.7 H, *E* 14-H and 0.3 H, *Z* 14-H), 5.50 (dt, J = 15.3 Hz, J = 6.5 Hz, 0.7 H, *E* 14-H), 6.17 (d, J = 3.4 Hz, 1 H, 19-H), 6.37 (d, J = 3.4 Hz, 0.3 H, *Z*18-H), 6.39 (d, J = 3.4 Hz, 0.7 H, *E*18-H). ^{13}C-NMR ($CDCl_3$)δ(ppm) = 18.51 (C-4), 22.62 (C-5), 25.38 (C-11), 27.72 (C-10), 31.72 (C-12), 32.46 (C-6), 40.26 (C-15), 64.30 (C-9), 67.06 (C-16), 72.85 (C-3), 92.90 (C-2), 107.01 (aromat. C-19), 114.38 (aromat. C-18), 123.11 (*Z* C-14), 123.86 (*E* C-14), 132.56 (*Z* C-13), 134.25 (*E* C-13), 136.55 (quart. C-1), 138.34 (C-5′), 157.26 (quart. C-17), 173.11 (C-7).

8,20-Dioxa-bicyclo[15.2.1]icosa-1(19),17-dien-7-one (7)

We dissolved 15 mg (0.05 mmol) of **6** in 60 mL of dry THF. To this were added 10 mg of Pd/C and 10 mg of Lindlar-catalyst. The suspension was stirred under H_2 atmosphere for 42 h at room temperature. The suspension was filtered and the solvent was evaporated. The residue was purified by FCC (diethyl ether/iso-hexane 1:1) to give 13.9 mg (95%) of **7** as a yellow oil. IR (KBr): $\nu[cm^{-1}]$ = 2926, 2857, 1733, 1458, 1258, 1092, 1021, 798. MS (EI): m/z (%) = 292 (M^+ (19)), 207 (6), 191 (7), 149 (18), 135 (19), 121 (34), 107 (100). MS (CI): m/z (%) = 293 (M^++1, 100). HR-MS (EI): $C_{18}H_{28}O_3$ Calc.: 292.2039, Found: 292.2047. ^{1}H-NMR ($CDCl_3$)δ (ppm) = 1.30 (m, 10 H, 4-H, 11-H, 12-H, 13-H, 14-H), 1.62 (m, 8 H, 3-H, 5-H, 10-H, 15-H), 2.30 (t, J = 6.8 Hz, 2 H, 6-H), 2.60 (m, 4 H, 2-H, 16-H), 4.08 (t, J = 5.78 Hz, 2 H, 9-H), 5.85 (m, 2 H, 2 aromat. CH). ^{13}C-NMR ($CDCl_3$)δ(ppm) = 24.75 (CH_2), 25.57 (CH_2), 27.32 (CH_2), 27.41 (CH_2), 27.57 (CH_2), 27.74 (CH_2), 27.80 (CH_2), 27.99 (CH_2), 28.16 (CH_2), 28.27 (CH_2), 28.31 (CH_2), 34.46 (CH_2), 64.37 (CH_2), 105.67 (2 aromat. CH), 153.84 (quart. C), 154.38 (quart. C), 173.95 (C-7).

Conclusion

In summary, we worked out a short and convenient approach to furan-containing macrolactones. This methodology offers the possibility of preparing numerous analogues with different ring sizes and different positions of the furan moiety in the macrolactone by using homologues of the building blocks **1**, the alkenol and the Grignard reagents.

Compounds **3**, **4**, **5**, **6,** and **7** were tested for their cytotoxic activity at the National Cancer Institute (NCI). None of the compounds showed significant cytotoxic activity in the NCI pretest.[12]

Acknowledgements

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