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Use of an Acetylenic Sulfone as an Alkene Dipole Equivalent in the Synthesis of (±)-Pumiliotoxin C

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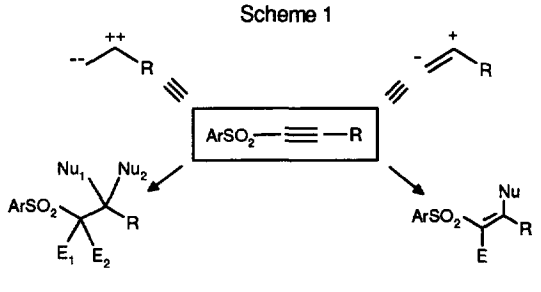
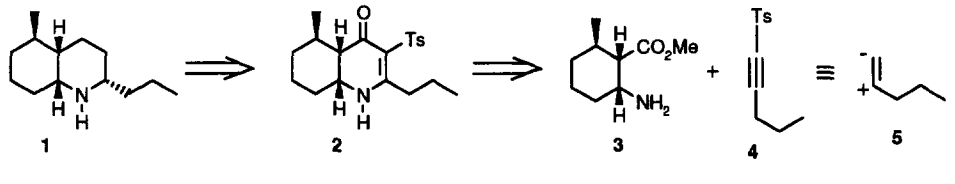
Abstract: The cycloaddition of methyl *cis*-2-amino-*trans*-6-methylcyclohexanecarboxylate (**3**) with 1-p-(toluenesulfonyl)-1-pentyne (**4**) afforded the corresponding enaminone **2**, that was in turn reduced to (±)-pumiliotoxin C (**1**). The acetylenic sulfone **4** thus functions as the synthetic equivalent of the alkene dipole **5** in this process.

Acetylenic sulfones are versatile synthetic reagents[1] that can undergo one or more conjugate additions at the β-position, followed by reaction with one or more electrophiles at the α-position. The sulfone group can be removed reductively at the end of the desired transformations. Thus, acetylenic sulfones act as the synthetic equivalents of dipoles or "multipoles" (Scheme 1).[2] When the nucleophile in the initial conjugate addition is an amine, the product is an enamine sulfone[3] that in turn has nucleophilic character at the α-position, providing a potential site for alkylation or acylation. The retrosynthesis in Scheme 2 shows how these features can be combined in the novel stepwise cycloaddition of β-amino ester **3** with acetylenic sulfone **4** (Ts= *p*-toluenesulfonyl) to afford enaminone **2**, which then serves as a key intermediate for the preparation of pumiliotoxin C (**1**), an alkaloid that occurs in the skin secretions of the Panamanian poison-dart frog *Dendrobates pumilio*.[4,5] Thus, **4** behaves as the equivalent of the alkene dipole **5** in the cycloaddition.

Scheme 1



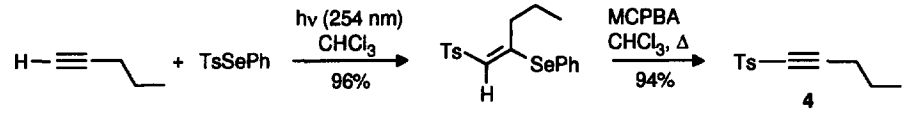
Scheme 2



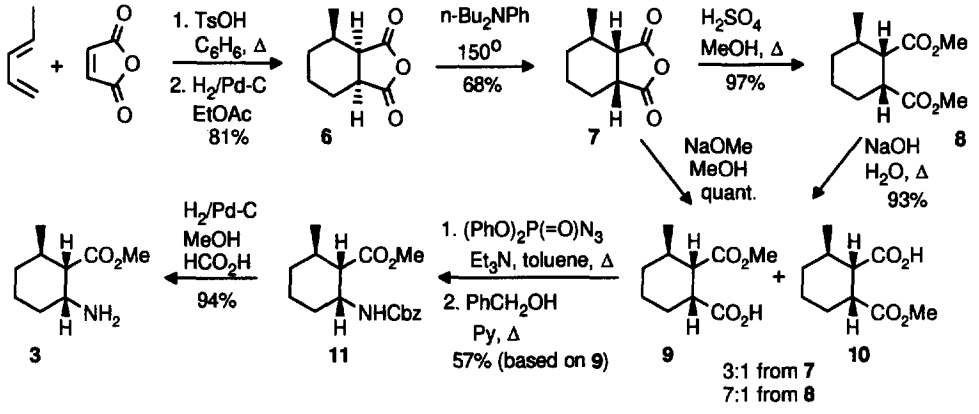
The acetylenic sulfone **4** was prepared by the selenosulfonation of 1-pentyne, followed by selenoxide elimination (Scheme 3), using a procedure reported previously for the selenosulfonation of other acetylenes.[6]

The β-amino ester **3** was obtained as shown in Scheme 4. The cyclic anhydride **7** was prepared by the Diels-Alder cycloaddition of piperylene with maleic anhydride, followed by hydrogenation to **6**, and base-catalyzed epimerization to **7**.[7] The direct methanolysis of anhydride **7** proceeded with poor regioselectivity to furnish the half esters **9** and **10** in the ratio of 3:1. However, selective partial saponification of the diester **8** afforded **9** and **10** in an improved ratio of 7:1. Since the half-esters **9** and **10** were difficult to separate, the 7:1 mixture was subjected to a Curtius rearrangement effected with diphenylphosphoryl azide,[8] and the resulting isocyanates were trapped *in situ* with benzyl alcohol to afford the Cbz-protected amine **11**, which was easily separated from the regioisomer derived similarly from **10**. Finally, hydrogenolysis produced the desired amino ester **3**.[9]

Scheme 3

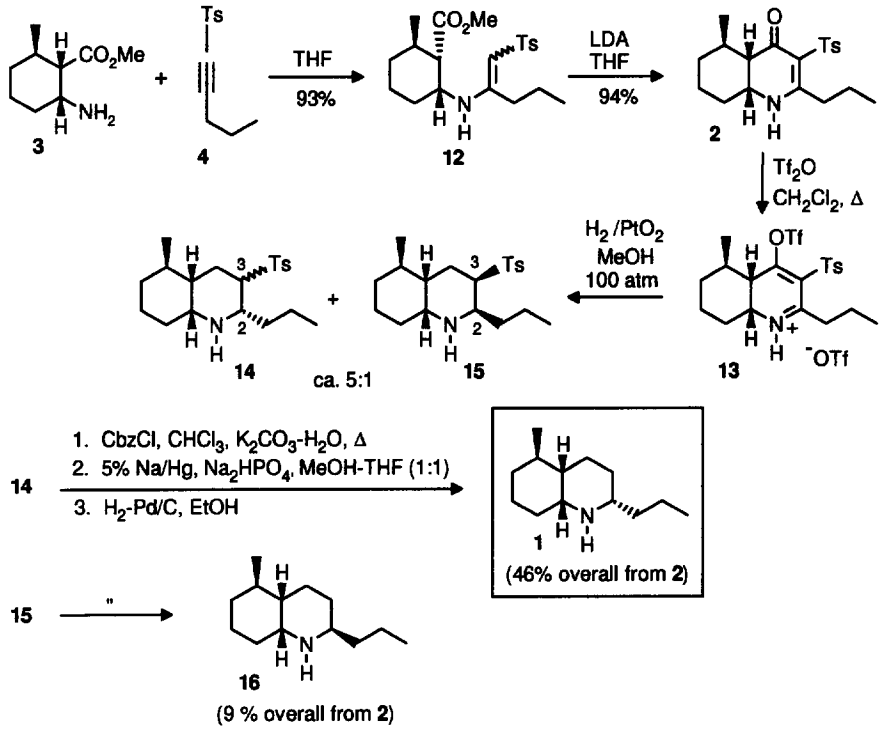


Scheme 4



The conjugate addition of **3** to **4** in THF at room temperature afforded a 2:1 mixture of the Z and E isomers of **12**, respectively. Ring-closure was effected in 94% yield (based on the recovery of 33% of unreacted starting material) by treatment with LDA to provide the enaminone **2** (Scheme 5).[10] Hydrogenation of the corresponding enol triflate **13** occurred stereoselectively from the *exo* side, producing the C-2 epimers **14** and **15** in the ratio of ca. 5:1. The desired C-2 isomer **14** was obtained as an unseparable mixture of C-3 epimers, whereas the 2-epi derivative **15**, which was separated chromatographically from **14**, was a single C-3 stereoisomer, tentatively identified as the 3-*exo* sulfone. Reductive desulfonylation[11] of the Cbz derivatives of **14** with 5% sodium amalgam, followed by hydrogenolysis of the Cbz group, afforded (±)-pumiliotoxin C (**1**) in 46% overall yield from enaminone **2**. Similarly, the N-Cbz derivative of **15** gave (±)-2-epipumiliotoxin C (**16**) in 9% overall yield from **2**. Both products **1** and **16** had properties[12,13] in close agreement with the literature.[5] The present synthesis of pumiliotoxin C illustrates how an acetylenic sulfone can be employed as an alkene dipole synthon in a novel cyclization of a β-amino ester to a synthetically useful enaminone.

Scheme 5



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9. For a different synthesis of **3**, see Davies, S.G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595.
10. New compounds **2** and **12** were fully characterized by their IR, NMR and mass spectra, and gave satisfactory elemental analyses. The *Z*-isomer of **12** was identified by an NOE between the olefinic CH and allylic CH_2 groups.
11. For examples of reductive desulfonylations with Na/Hg, see: Trost, B.M.; *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107, and references cited therein.
12. (±)-Pumiliotoxin C (**1**): oil; IR (film) 3300, 1117, 1089, 754 cm^{-1}; ^{1}H-NMR (400 MHz) δ 2.87-2.83 (m, 1 H), 2.58-2.50 (m, 1 H), 2.00-1.80 (m, 2 H), 1.75-0.88 (m, 15 H), 0.91 (t, J= 6.9 Hz, 3 H), 0.85 (d, J= 6.6 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 57.8, 56.0, 42.6, 39.6, 35.9, 33.3, 27.4, 27.2, 27.0, 21.2, 19.9, 19.1, 14.3; mass spectrum, *m/z* (relative intensity, %) 195 (M^+, 4), 194 (8), 166 (60), 152 (100). (±)-(**1**) Hydrochloride: mp 242-245 °C (sealed capillary), lit.[5m] mp 245 °C, lit.[5n] mp 232 °C; ^{1}H-NMR (400 MHz) δ 9.60 (m, 1 H), 8.30 (m, 1 H), 3.33 (m, 1 H), 3.00 (m, 1 H), 2.55-2.30 (m, 2 H), 2.23-1.95 (m, 4 H), 1.92-1.84 (broad d, 1 H), 1.83-1.75 (broad d, 1 H), 1.72-1.35 (m, 6 H), 1.32-1.20 (m, 1 H), 1.04-0.95 (m, 1 H), 0.92 (t, J= 7.4 Hz, 3 H), 0.90 (d, J= 6.2 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 60.1, 58.0, 40.9, 34.8, 34.3, 29.1, 27.2, 25.2, 23.1, 20.6, 19.7, 19.1, 13.7.
13. (±)-2-Epipumiliotoxin C (**16**): oil; IR (film) 3352, 1145, 1080, 742 cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.13 (dt, J= 10.5, 4.1 Hz, 1 H), 2.84-2.75 (m, 1 H), 1.90-1.01 (m, 17 H), 0.99 (d, J= 7.2 Hz, 3 H), 0.91 (t, J= 7.0 Hz, 3 H); ^{13}C-NMR (100 MHz) δ 50.0, 49.5, 42.0, 38.4 (br), 32.5 (br), 31.6 (br), 29.7 (br), 28.4 (br), 25.3 (br), 20.5, 19.4, 19.3, 14.2; mass spectrum, *m/z* (relative intensity, %) 195 (M^+, 2), 194 (3), 166 (5), 152 (100).

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