Cymantrene Conjugation Modulates the Intracellular Distribution and Induces High Cytotoxicity of a Cell-penetrating Peptide

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Supporting Information

Synthesis of Cym-CO-C_6H_4-COOH, (**1**). The preparation of the cymantrene keto carboxylic acid **1** utilized Friedel-Crafts conditions according to the procedure of Dabard and Plouzennec.[1, 2] In a 100 ml three-necked round-bottom flask equipped with a reflux condenser, dropping funnel, and nitrogen inlet tube is placed cymantrene (2.83 g, 13.9 mmol) and anhydrous dichloromethane (25 ml). To the magnetically stirred and cooled (0 to 5 °C) solution is added phthalic anhydride (2.06 g, 13.9 mmol). Then, anhydrous aluminium chloride (4.00 g, 30.0 mmol) is added in small portions while maintaining the temperature at 0 to 5 °C. Stirring is continued overnight. The reaction mixture is then poured into a mixture of ice-water (100 ml) and concentrated hydrochloric acid (10 ml). The layers are separated and the aqueous phase is extracted with dichloromethane (3x 40 ml). The combined organic extracts are washed with water and finally with aqueous sodium carbonate solution (20%). Upon evaporation of the dichloromethane solution, unreacted cymantrene can be recovered. The aqueous phase is acidified and the cymantrene keto carboxylic acid extracted with ether. The combined ether solutions are washed with water and dried over magnesium sulfate. The solvent is then removed in vacuo and the crude product recrystallized from a tetrahydrofuran / pentane mixture to give the desired product as yellow crystals. Yield: 25% (1.24 g) M_r ($C_{13}H_{11}MnO_6$) 352.18; ESI-MS(CH_3OH, neg. mode): 350.91 $[M-H]^-$, 702.85 $[2M-H]^-$, 1107.70 $[3M-Mn]^-$; Calc. C, 54.57; H, 2.58, Found. C, 54.45; H, 2.54; ^1H NMR (acetone-d_6): 7.95-7.32 (m, 4H, C_6H_4), 5.23 (m, 2H, Cp), 4.97 (m, 2H, Cp); IR ν(CO, cm^{-1}) 2021, 1930, 1686, 1664.

Literature

[1] R. Dabard, M. Le Plouzennec, *Bull. Soc. Chim. Fr.* **1972**, 3594-3599.
[2] M. Le Plouzennec, R. Dabard, *Bull. Soc. Chim. Fr.* **1972**, 3600-3609.