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An Improved Synthesis of *trans*-3, 3b, 4, 9b, 10, 11-Hexahydro -6-methoxy-9b-methyl-7- (1-methylethyl) phenanthro {1,2-c[furan-1,5-dione]}

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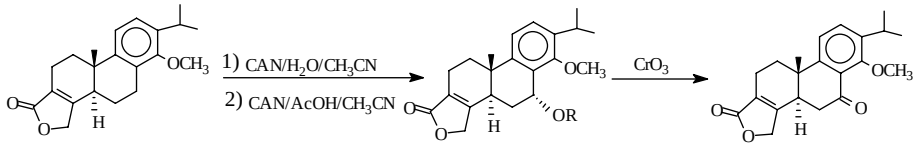
Abstract: *trans*-3, 3b, 4, 9b, 10, 11-Hexahydro-6-methoxy-9b-methyl-7-(1-methylethyl) phenanthro {1,2-c[furan-1,5-dione]} was synthesized with good yield in two steps from triptophenolide methyl ether under mild conditions.

Keywords: *Tripterygium wilfordii*, triptolide**,** triptophenolide methyl ether .

The diterpenoid triexpoxides lactone triptolide is a potent antileukemic, antiflammatory, immunosuppressive and antifertile principle of *Tripterygium wilfordii* Hook *f.*[1,2]. Many methods of synthesis of this compound have been reported in which *trans*-3,3b,4,9b,10, 11-hexahydro-6-methoxy-9b-methyl-7- (1-methylethyl) phenanthro {1,2-c [furan-1,5-dione]} **4** was an important intermediate. In one reported synthesis, compound **4** was obtained by CrO_3/AcOH oxidation of triptophenolide methyl ether **1**, but with poor yield[1]. We tried ammonium ceric nitrate (CAN) as oxidant in H_2O/CH_3CN and found that **2** was the major product with a 80% yield, **4** was obtained from **2** in a much better yield under mild conditions. Oxidation of **1**in AcOH led to the formation of **3** in 81%.



1 **2** R=H **4**
3 R=$COCH_3$

Experimental

*Oxidation of **1** with CAN in H_2O/CH_3CN:*

At room temperature with stirring, the solution of CAN (1.172g, 2mmol) in H_2O (5mL) was added to the solution of **1** (326 mg, 1 mmol) in CH_3CN (10mL). After 0.5 h, the reaction mixture was diluted with CH_2Cl_2 and the yellow precipitates were removed by

filtration. The filtrate was washed with saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification by chromatography (ethyl acetate: petroleum ether, 1:3) gave **2** (272 mg, 80%). ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 0.99 (s, 3H, 18-CH_3), 1.17 (d, 3H, J=6.9Hz, 17-CH_3), 1.29 (d, 3H, J=6.9Hz, 16-CH_3), 1.64-1.73 (m, 1H, C_1-α H), 2.00-2.14 (m, 2H, 6-CH_2), 2.34-2.43 (m, 1H, C_1-β H), 2.45-2.52 (m, 2H, 2-CH_2), 3.05-3.12 (m, 1H, 5-H), 3.27 (m, 1H, 15-H), 3.87 (s, 3H, O-CH_3), 4.72-4.90 (m, 2H, 19-CH_2), 5.06-5.08 (m, 1H, C_7-β H), 7.16 (d, 1H, J=8.4Hz, 11-H or 12-H), 7.20 (d, 1H, J=8.4Hz , 11-H or12-H); MS (*m/z*): 342 (M^+), 324 (M^+-H_2O), 309, 281; IR (KBr cm^{-1}): 3469.4, 1754.9, 1675.9, 1020.2, 817.7; HRMS: calcd for $C_{21}H_{26}O_4$ M^+, 342.1830, found 342.1820.

*Oxidation of **2** with Pyridinium dichromate*:

CrO_3 (60 mg, 6 mmol) was added to a mixture of anhydrous pyridine (9.49 g, 12 mmol) in anhydrous CH_2Cl_2 (10 mL) with stirring. The deep red reaction mixture was stirred for 15 minutes at room temperature, and then a solution of **2** (72 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (3 mL) was added in one portion. After stirring an additional 15 minutes, the solution was decanted from the residue, which was washed with CH_2Cl_2 (10 mL). The combined extracts were washed with 5% HCL (10 mL×3), 5% Na_2CO_3 solution (10 mL) and brine successively, and dried over $MgSO_4$. Evaporation of the solvent at reduced pressure and purification by chromatography afforded **4** (63 mg, 90%). The spectroscopic data of **4** was the same as those described in the literature[1].

*Oxidation of **1** with CAN in AcOH/CH_3CN:*

The procedure was the same as **1**, the only difference is that MeOH is substituted with AcOH, and purification by column chromatography to give **3** (282 mg, 81%). **3** ^{1}HNMR (400MHz，$CDCl_3$) δ ppm: 0.98 (s, 3H, 18-Me), 1.21 (d, 3H, J=7Hz, 16-Me), 1.23 (d, 3H, J=6.9Hz, 17-Me), 1.60 (m, 1H, C_1-α H), 1.80 (m, 1H, C_6-β H), 1.95 (d, 1H, J=4.7Hz, C_6-α H), 2.10 (s, 3H, $COCH_3$), 2.40 (m, 1H, C_1-β H), 2.53 (m, 2H, 2-CH_2), 3.10 (m, 1H, 5-CH), 3.22 (m, 1H, 15-CH), 3.75 (s, 3H, OCH_3)，4.68 (d, 1H, J=17.0, 19-CH_a), 4.80 (d, 1H, J=17, 19-CH_b), 6.25 (t, 1H, J=2.4Hz, 7-H), 7.18 (d, 1H, J=8.1Hz, 11-H or 12-H), 7.45 (d, 1H, J=8.1, 11-H or 12-H)； MS (*m/z*)：384 (M^+)，341 (M^+-$COCH_3$)； HRMS: calcd for $C_{23}H_{28}O_5$ M^+, 384.1990, found 384.1925.

References

1. C. K. Lai, R. S. Buckanin, S. J. Chen, D. F. Zimmerman, F. T. Sher, G. A. Berchtold, *J. Org. Chem.*, **1982**, *47*, 2364.
2. L. C. Garver, E. E. J. Tamelen, *J. Am. Chem. Soc.*, **1982**, *104*, 867.

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