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A THREE CARBON INTERCALATION OF AN ENEDIOL SILYL ETHER; A SHORT ENTRY TO THE BICYCLO[5.3.1]UNDECYL SYSTEM OF TAXANES

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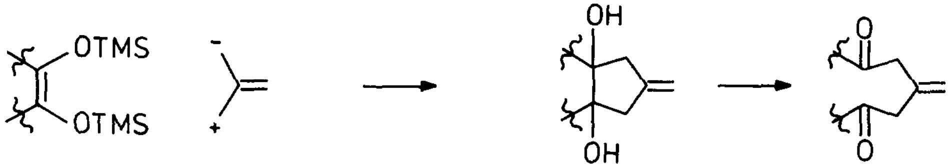
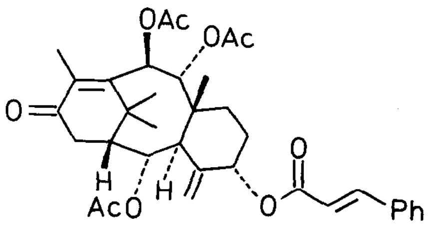
ABSTRACT: A three step synthesis of 11-methylene-bicyclo[5.3.1]undecan-2,6-dione is described.

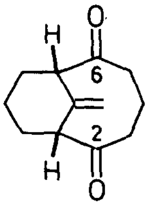
1,2-Bis(trimethylsilyloxy)alkenes, readily available via an acyloin condensation,[1] among other methods, offer a versatile juxtaposition of functionality for further structural manipulations.[2] A three carbon intercalation as outlined in equation (1) is especially attractive because of the facility of an oxidative cleavage of a vicinal diol.

(1) 

The taxanes, e.g. taxinine (1), constitute a large group of structurally intriguing compounds which have not yet yielded to total synthesis.[3,4,5] A novel strategy for the construction of the bicyclo[5.3.1]undecyl system (2),



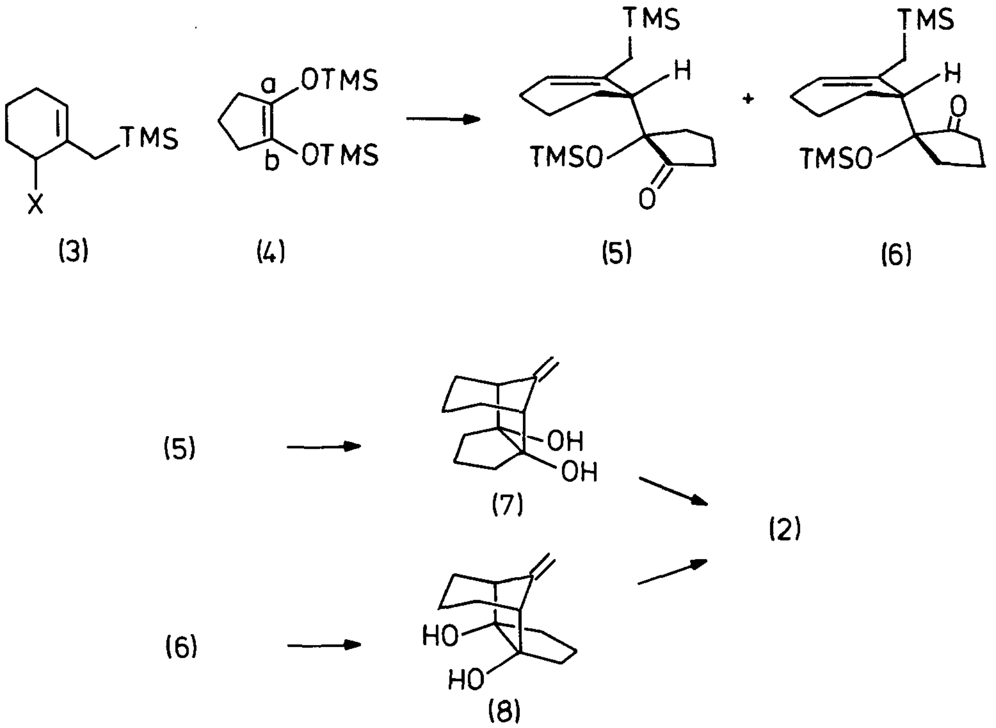
(1)



(2)

which forms the structural nucleus of taxanes and which possesses useful functionality at C2 and C6, would be the intercalation of the bifunctional reagent (3)[4] between the atoms a and b of the enediol silyl ether (4) (see Scheme). We describe here the successful application of this strategy to the efficient three-step synthesis of the bridged bicyclic dione (2).

Scheme



The allylic alcohol (3) (X = OH)[4] was converted to the chloride (3) (X = Cl) in 91% yield by treatment with a mixture of MsCl (1.25 eq.), LiCl (2 eq.) and collidine (1.35 eq.) in DMF at 0°C for 90 min.[6] Reaction of (3) (X = Cl) (ca 1M in dichloromethane) with 1,2-bis(trimethylsilyloxy)cyclopentene (4)[1] in the presence of anhydrous zinc chloride at 0°C for 2 h[7], followed by a pyridine quench, cleanly gave the α-trimethylsilyloxy ketones (5)[8], m.p. 41-2°C, and

(6)[8], an oil, (60%, ratio 1:1), which were separated by flash chromatography. The lack of stereoselectivity in this reaction is of no importance since each diastereomer is ultimately transformed into the same product. Preferential alkylation of (4) in competition with self-annihiliation of the allyl silane was anticipated, and nicely illustrates the differential reactivity of the two functional groups. Ketone (5) cyclized smoothly to give the diol (7)[8], m.p. 58-60°C (85%) when treated with ethylaluminium dichloride[4,9] (2 eq., ca 0.2M in toluene, -78°C, 2 h[10]), followed by hydrolysis (0.5M aqueous sulphuric acid/THF = 1:3, 23°C). Likewise ketone (6) formed diol (8)[8], m.p. 143-4°C (87%) upon shorter exposure to the Lewis acid (2 eq., toluene, -78°C, 30 min). Oxidative cleavage of (7) and (8) using sodium metaperiodate (2 eq., MeOH/H_2O, 23°C) for 22.5 h and 72 h respectively, furnished the same diketone (2)[8], m.p. 133.5-134.5°C, in 89% and 90% yields, respectively. The stereochemistry of compounds (5)-(8) was assigned from the rates of cyclization and ring fragmentation. Thus (5) cyclized to form the more sterically congested tricyclic diol (7) more slowly than (6) afforded diol (8), but (7), having the more accessible hydroxyl groups was cleaved significantly faster than (8).

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8. All new compounds were completely characterized by spectroscopic means and combustion analysis. Spectroscopic data:

   (7) IR ($CHCl_3$) 3470, 3075, 1673, 1114, 892 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 1.45 (1H, m), 1.58-2.16 (11H, m), 2.34 (2H, m), 2.60 (2H, s), 4.78 (2H, s). δ_C (15 MHz, $CDCl_3$) 17.12, 25.77, 31.38, 32.76, 51.98, 88.98, 102.80, 160.72. m/e 194, 100, 95.

   (8) IR ($CHCl_3$) 3490, 3075, 1673, 1138, 890 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 1.40-1.71 (8H, m), 1.84 (2H, m), 2.03 (2H, m), 2.36 (2H, m), 2.44 (2H, s). 4.74 (2H, s). δ_C (15 MHz, $CDCl_3$) 19.71, 23.13, 31.00, 43.33, 52.36, 84.68, 103.90, 155.27. m/e 194, 100, 95.

   (2) IR ($CHCl_3$) 3075, 1710, 1648, 1137, 911 cm^{-1}. δ_H(270 MHz, $CDCl_3$) 1.34 (3H, m), 1.44 (1H, qt, J 13, 4 Hz), 1.72 (1H, qt, J 13, 3 Hz), 1.90 (1H, dtt, J 13, 5.5, 3.5 Hz), 2.14 (2H, ddd, J 11, 5.5, 3 Hz), 2.35 (2H, m), 2.97 (2H, ddd, J 13, 11, 3.5 Hz), 3.14 (2H, m), 5.42 (2H, s). δ_C (15 MHz, $CDCl_3$) 17.34, 24.61, 26.10, 38.60, 57.65, 119.09, 142.22, 209.23. m/e 192, 136, 108, 55.

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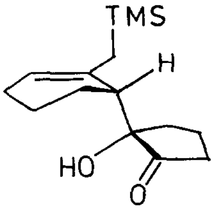
10. Shorter reaction times gave small amounts (ca 10%) of desilylated starting material **(9)** in addition to **(7)**.



(9)

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