A New Route to ± Quadrone

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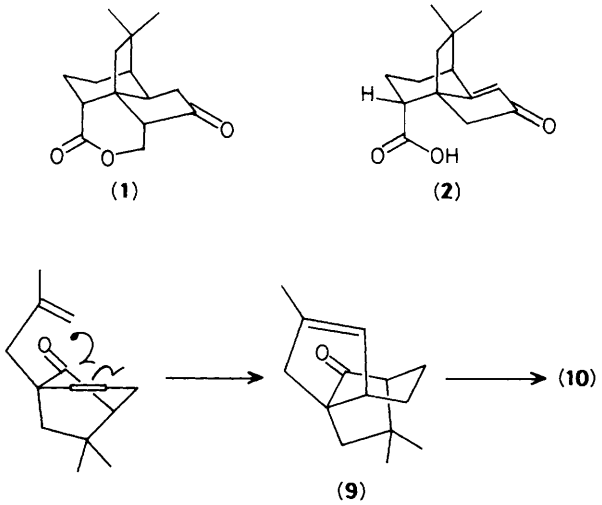
A new route to ± quadrone (**1**) is reported which relies on an intramolecular radical cyclisation to provide the required axial carboxylic acid in the Danishefsky intermediate (**2**).

The fused tetracyclic sesquiterpene lactone quadrone (**1**) was isolated from fermentation broths of the fungus *Aspergillis terreus* by Ranieri and Carlton in 1978.[1] Quadrone was found to exhibit inhibitory activity *in vitro* against human epidermoid carcinoma of the nasopharynx (KB) (ED_{50} 1.3 μg ml^{-1})[2] and *in vivo* against P388 lymphocytic leukaemia in mice (PS) (the intraperitoneal LD_{50} value in mice was found to be >340 mg kg^{-1}). The unusual structure of quadrone coupled with its important biological activity has led to intense chemical interest from groups worldwide.[3] We have been interested in this molecule for several years and we now present a short and efficient route to the Danishefsky intermediate (**2**).

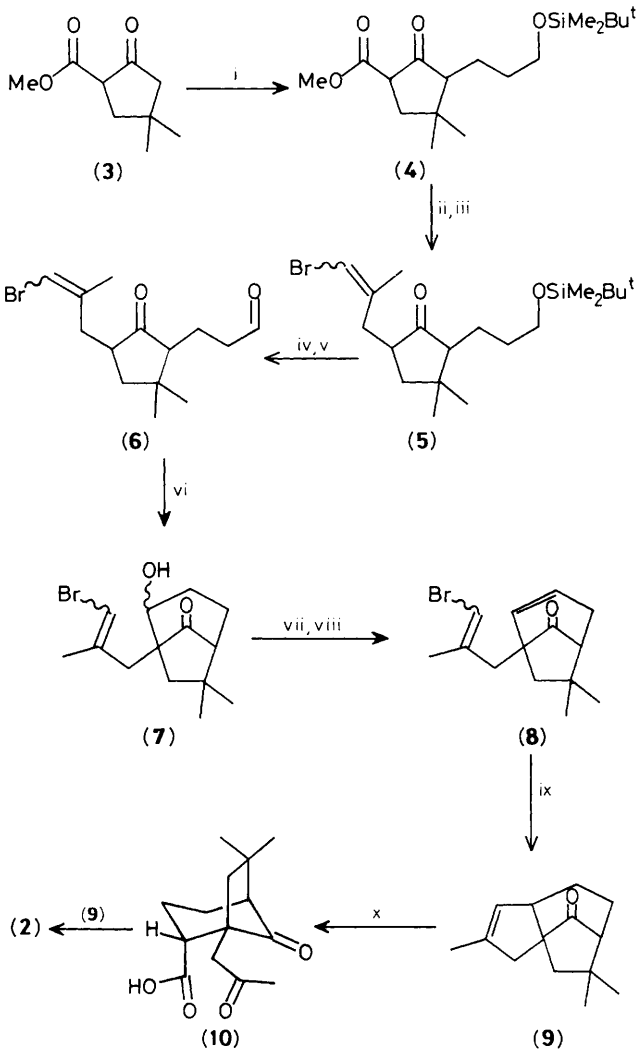
The key step in our approach to quadrone (**1**) involves the intramolecular addition of an alkenyl radical[4] to a double bond to form the substituted cyclopentane (**9**). Oxidative cleavage of the cyclopentane was used to provide the desired axial carboxylic acid; thus overall the axial carboxylic acid has been introduced by radical cyclisation (Scheme 1).

Our route has the advantage that all the stereoisomers formed in the synthetic sequence are converted into a single racemate at the end of the scheme (Scheme 2).

The dianion derived from the keto ester (**3**)[5] was alkylated in tetrahydrofuran (THF) at −60 °C by the slow addition of the t-butyldimethylsilyl ether of 3-iodopropanol (1 equiv.). The esters (**4**) were isolated as a mixture of diastereoisomers in 75% yield: these isomers and subsequent isomers were not separated since they were eventually converted into one racemate in the radical cyclisation step. Treatment of the esters (**4**) with sodium hydride in toluene followed by the dropwise addition of 1,3-dibromo-2-methylprop-2-ene gave an alkylated product which was converted into the ketones (**5**) by treatment with lithium iodide in lutidine [88% from (**3**)]. Protodesilylation of (**5**) with aqueous HF in acetonitrile followed by pyridinium chlorochromate (PCC) oxidation in dichloromethane gave the aldehyde (**6**) in 64% yield for the two steps. Many attempts to cyclise the aldehyde (**6**) to the bicyclic ketol (**7**) failed, and we eventually found that exposure of (**6**) to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10 mol % in benzene) at room temperature overnight gave the desired alcohols (**7**) (72%). The epimeric mixture of alcohols (**7**) was treated with sodium hydride (1 equiv.) in THF and then a solution of *p*-toluyl thiochloroformate[6] was added, giving the corresponding thiocarbonate esters. Ther-



Scheme 1



Scheme 2. *Reagents:* i, lithium di-isopropylamide (LDA) (2 equiv.) THF/°C then $ICH_2CH_2CH_2OSiMe_2Bu^t$ 0 °C to room temp.; ii, NaH, toluene, room temp., then $BrCH_2(Me)=CHBr$, reflux; iii, LiI lutidine, 120 °C; iv, HF, MeCN, room temp.; v, PCC, NaOAc, CH_2Cl_2, room temp.; vi, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene, room temp.; vii, NaH, toluene, *p*-toluyl thiochloroformate, room temp. to reflux; viii, 180 °C; ix, Bu_3SnH, azoisobutyronitrile (AIBN), benzene, reflux; x, RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN, room temp.

molysis of the esters at 180 °C as a thin film afforded the alkenes (**8**)† in 30% yield from the alcohols (**7**).

When the mixture of alkenes (**8**) was treated with tri-n-butyltin hydride in boiling benzene, the desired radical cyclisation occurred giving the crystalline alkene (**9**)† in 80% yield. Ruthenium tetroxide[7] oxidation of the alkene (**9**) gave the desired axial acid (**10**)† quantitatively. Base catalysed cyclisation of (**10**)[5] lead to the isolation of the Danishefsky intermediate (**2**) which has already been converted into (±)-quadrone (**1**).[8]

Thus, we have demonstrated a new approach to (±)-quadrone (**1**) overcoming the problem of introducing the key carboxylic acid residue. The procedure is also simple to carry out on a large scale, providing gramme quantities of intermediates.

† All new compounds possess satisfactory analytical purity. Compound (**8**): $C_{14}H_{19}BrO$ requires 203.1435 (M − Br), found 203.1436. 32.84, 40.14, 49.90, 52.38, 56.18, 64.14, 126.13, 139.21, 220.03. Compound (**10**): ^{13}C n.m.r. ($CDCl_3$) δ 21.33, 23.39, 29.40, 31.15, 32.33, 32.65. 45.48, 46.68, 50.16, 53.20, 56.37, 76.72, 77.20, 77.66, 179,30, 207.17, 217.97.

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