

## Synthesis of 6-Hydroxy-5,5-dialkyl Substituted Cyclohexenones *via* (Bistrifluoroacetoxyiodo)benzene mediated Cyclization of 1,3-Dithiane and Ethyl Enol Ether

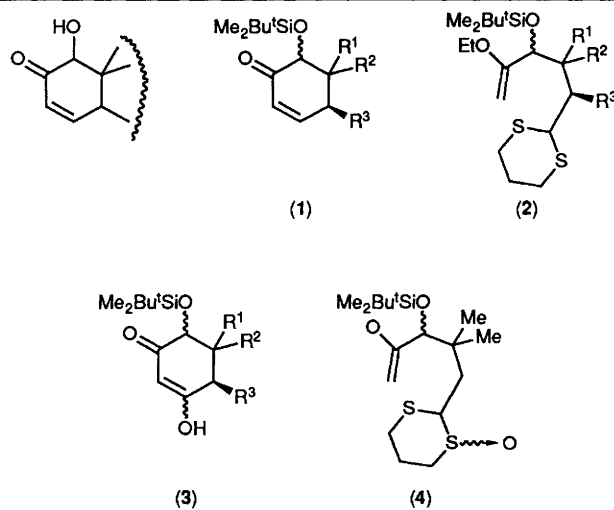
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A novel type of intramolecular aldol reaction of 1,3-dithiane and ethyl enol ethers in the same molecule mediated by (bistrifluoroacetoxyiodo)benzene was used for synthesis of 6-hydroxy-5,5-dialkyl substituted cyclohexenones.

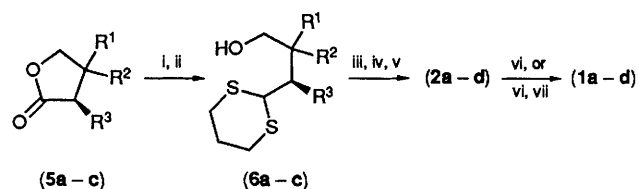
A number of compounds containing the 6-hydroxy-5,5-dialkyl substituted cyclohexenone ring system are present in biologically important terpenoids, *e.g.* triticones (spirostaphylotrichin)<sup>1</sup> and quassinoids,<sup>2</sup> this ring system being essential for potent activity.<sup>3</sup> The preparation of this ring is not easy by ordinary methods because of tautomerism of the  $\alpha$ -hydroxyketone,<sup>4</sup> and the construction of the tertiary carbon centre at the 5-position would be difficult after ring formation.

We now describe a new preparation of 6-hydroxy-5,5-dialkyl substituted cyclohexenones (1) *via* a novel intramolecular reaction of 1,3-dithiane and ethyl enol ether units mediated by PIFA [(bistrifluoroacetoxyiodo)benzene] as the key carbon-carbon bond formation step. PIFA is an excellent reagent for various types of oxidation,<sup>5</sup> and is also effective for hydrolysis of dithioacetals and enol ethers.<sup>6</sup> When 1,3-dithiane and ethyl enol ether functionalities are both present at an appropriate position in the same molecule (2), the use of PIFA led to carbon-carbon bond formation. The  $\gamma$ -1,3-dithianyl ethyl enol ether (2a)<sup>†</sup> was treated with PIFA (1.2 equiv.) in anhydrous acetonitrile (0.05–0.08 M) at  $-20^\circ\text{C}$  for



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	OSiBu <sup>t</sup> Me <sub>2</sub>
a;	CH <sub>2</sub> OCH <sub>2</sub> Ph	CH <sub>2</sub> OSiBu <sup>t</sup> Me <sub>2</sub>	H	$\alpha : \beta$ (1 : 1)
b;	Me	Me	H	—
c;	Me	Me	OCH <sub>2</sub> Ph	$\alpha$
d;	Me	Me	OCH <sub>2</sub> Ph	$\beta$

<sup>†</sup> All new compounds reported here gave satisfactory spectroscopic data (NMR, IR, and mass), which were available as supplementary material to the referees.



**Scheme 1.** Chromatographic separation of the diastereoisomeric  $\alpha$  and  $\beta$  alcohols. *Reagents and conditions*: i,  $\text{Bu}^i_2\text{AlH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; ii, propane-1,3-dithiol,  $\text{SnCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ ; iii, pyridinium chlorochromate, molecular sieves, 4 Å,  $\text{CH}_2\text{Cl}_2$ , room temp., or  $\text{BaMnO}_4$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,  $70^\circ\text{C}$ ; iv,  $\alpha$ -ethoxyvinyl-lithium,  $\text{LiBr}$ , ether,  $-78^\circ\text{C}$ ; v,  $\text{Me}_2\text{Bu}^t\text{SiOSO}_2\text{CF}_3$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; vi, PIFA,  $\text{MeCN}$ ,  $-20^\circ\text{C}$  then  $\text{H}_2\text{O}$ ,  $0^\circ\text{C}$  to room temp.; vii,  $\text{MeSO}_2\text{Cl}$ ,  $\text{EtNPr}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ .

5 min then hydrolysed with water (100 equiv.) at  $0^\circ\text{C}$  giving rise to the cyclohexenone (**1a**) in 67% yield. In the reaction of (**2b**), (**2c**), and (**2d**) with PIFA the aldol condensation stopped at the  $\beta$ -hydroxyketone stage, giving (**3b**), (**3c**), and (**3d**) in 35, 90, and 85% yields in a ca. 3:1 diastereoisomeric ratio. No significant amounts of by-products were isolated except in the case of (**2b**) in which the dithiane sulphoxide (**4**) was obtained in 54% yield. The  $\beta$ -hydroxyketones (**3**) were treated with methanesulphonyl chloride in the presence of *N,N*-di-isopropylethylamine, leading to the corresponding cyclohexenones (**1b**), (**1c**), and (**1d**) in 90–95% yields. This PIFA-promoted cyclization is mild and complete in several minutes in all cases.‡ This reaction is unusual because aldehyde and methyl ketone components masked as the 1,3-dithiane and

‡ This reaction does not take place intermolecularly in which the simple hydrolysed product, having aldehyde and methyl ketone units, is obtained quantitatively.

ethyl enol ether respectively have both reacted intramolecularly without any deprotection.§

The substrates (**2a–d**) were efficiently derived from  $\gamma$ -butyrolactones (**5a–c**) as shown in Scheme 1. Reduction of the  $\gamma$ -butyrolactone (**5**) with di-isobutylaluminium hydride gave the lactol, treatment of which with propane-1,3-dithiol in the presence of  $\text{SnCl}_4$  afforded the 1,3-dithianes (**6a–c**) in 70–85% yields in two steps. The primary alcohols (**6**) were transformed to the  $\alpha$ -silyloxy ethyl enol ethers (**2a–d**) in three steps in 56–65% yields.

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§ Acetyl or benzoyl groups may also be used to protect the secondary alcohol; the corresponding cyclic aldol is obtained in 70–90% yield in 4:1 diastereoisomeric ratio.