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SYNTHESIS OF 2,2-DIMETHYL-4-CYCLOPENTENE-1,3-DIONE AND 5,5-DIMETHYL-4-HYDROXY-2-CYCLOPENTEN-1-ONE.

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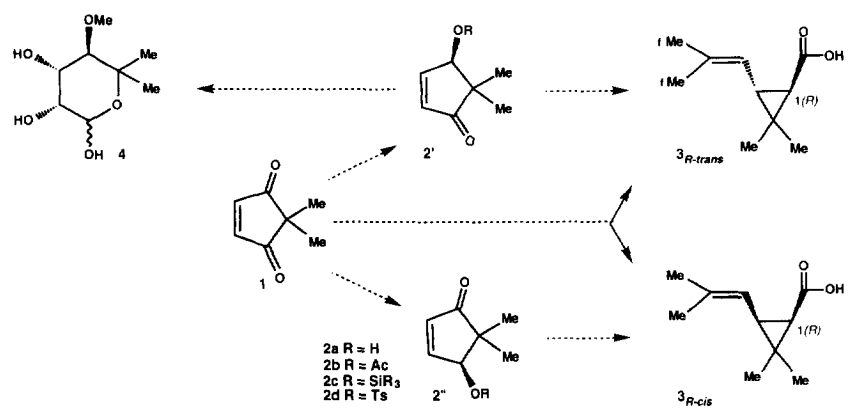
Abstract : Enedione **1** and related *rac-* and optically active enones **2** bearing a hydroxyl- **2a** or a protected- **2b-c** or an activated- **2d** 4-hydroxyl group at C-4 have been efficiently synthesized from cheap and readily available starting materials. Copyright © 1996 Elsevier Science Ltd

Enedione **1** and related enones **2** bearing a hydroxyl- **2a** or a protected- **2b-c** or an activated- **2d** 4-hydroxyl group at C-4,[1,2] are prochiral or chiral building blocks we planned to use for the synthesis of *rac-* and *optically active-* (i) *(1R)-cis-* and *(1R)-trans*-chrysanthemic acids **3**,[3] precursors of powerful insecticides[4,5] and (ii) Noviose, a rare sugar **4**[4,6] (Scheme 1).

Scheme 1

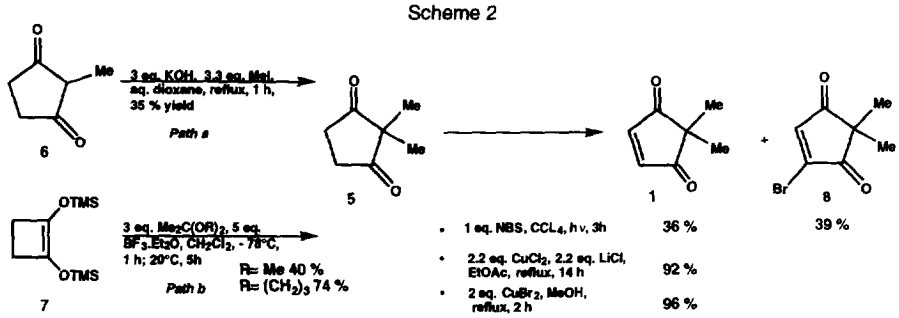


Enedione **1** has been previously synthesized by dehydrogenation of 2,2-dimethyl cyclopentane-1,3-dione **5** which has been generated (i) by alkylation of commercially available 2-methyl cyclopentane-1,3-dione **6** (3 equiv. KOH, 3 equiv. MeI, dioxane-water 3/1, 20°C, 24 h, 31%)[1b] or (ii) from 1,2-(bis)trimethylsilyoxy) cyclobut-1-ene **7**,[7] readily available from succinic acid [7], and the acetals derived from acetone and methanol[1a] or 1,3-propanediol[8] (Scheme 2).

These routes suffer however from the oxidation step which has been performed (i) expensively with stoichiometric amount of palladium chloride in *t*-butanol[1a] or (ii) more cheaply but inefficiently by photochemical oxidation with NBS[1b] which leads, besides the desired compound **1**, to substantial amounts of 4-bromo-2,2-dimethyl cyclopent-4-ene **8** arising from further uncontrolled oxidation of **1** (1 equiv. NBS, CCl_4, hv, **1**: 36%, **8**: 39%).

We have now found that the oxidation of **5** is more conveniently and quantitatively achieved by heating **5** with $CuBr_2$ (2 equiv., reflux, 2 h, 96 %)or $CuCl_2$-LiCl (2 equiv. $CuCl_2$, 2 equiv. LiCl, reflux, 14 h, 92 %).

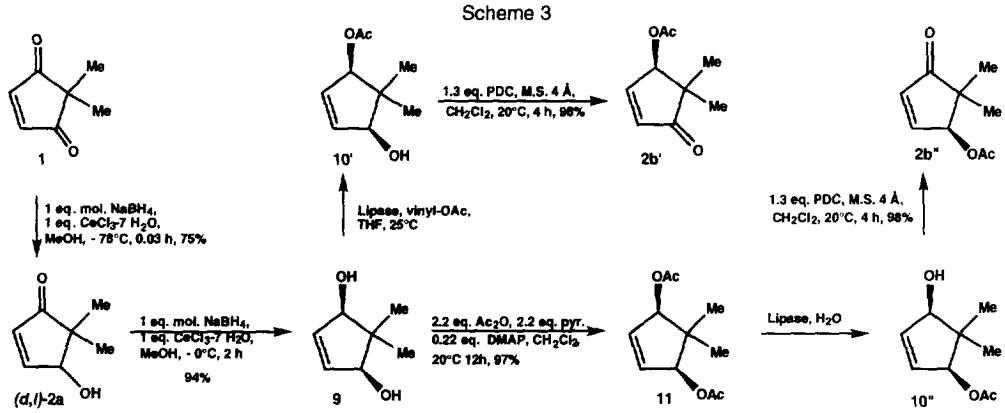
Scheme 2



Enedione **1** proved to be a valuable precursor of 5,5-dimethyl-4-hydroxy-2-cyclopenten-1-one **2a**. Thus mono-reduction of **1** with sodium borohydride and cerium trichloride[9] allows the synthesis of *(d,l)*-**2a** (1 equiv. mol. $NaBH_4$, 1 equiv. $CeCl_3$-7 H_2O , MeOH, - 78°C, 0.03 h, 75%) besides 10% of the diol **9** from which it can be easily separated. Use of the Luche's reagent proved to be crucial for the success of the desired transformation since in the absence of $CeCl_3$, a mixture of products resulting from 1,2- and 1,4-addition of the hydride, are instead produced. [9] Further reduction of *(d,l)*-**2a** with the same reagent, but at higher temperature, provides the diol **9** almost quantitatively (0.7 equiv. mol. $NaBH_4$, 1.5 equiv. $CeCl_3$-7 H_2O, MeOH, 0°C, 2 h, 94%).[2b] The diol **9** can be even more conveniently prepared by direct di-reduction of the enedione **1** with a slight excess of sodium borohydride and cerium trichloride (2 equiv. mol. $NaBH_4$, 2 equiv. $CeCl_3$-7 H_2O, MeOH, - 78°C, 3 h, 85%).

This prochiral diol **9** has in turn been used for the synthesis of optically active *(d)*- and *(l)*-4-acetoxy-5,5-dimethyl-2-cyclopenten-1-one **2b** which has been achieved by lipase desymmetrization of the diol **9** or its diacetate **11** followed by oxidation of the resulting optically active hydroxy acetates **10** (1.3 equiv. PDC, M.S. 4 Å, CH_2Cl_2, 20°C, 4 h, 98%).

Scheme 3



Mono-acetylation of **9** to *(1S,4R)*-4-acetoxy-5,5-dimethyl-2-cyclopentene-1-ol **10'** has been achieved by acetylation with vinyl acetate in the presence of lipases (7 equiv. vinyl acetate, 38-128 mg lipase/ mmol., THF, 20°C). Best results have been obtained from Amano PS [10,11] and PFL but PFL immobilized on saw[12] proved to be the most convenient, especially if the reaction is carried out in the presence of triethylamine (Table 1, entry e).[10] After filtration of the organic layer, the lipase on its solid support can be washed and reused several times without loss of activity.[4b]

The other enantiomer *(1R,4S)*-4-acetoxy-5,5-dimethyl-2-cyclopentene-1-ol **10"** has been produced by enantioselective, lipase catalyzed, mono-deacetylation of *meso*-1,4-diacetoxy-5,5-dimethyl-cyclopent-2-ene **11**, itself synthesized by peracetylation of 1,4-dihydroxy-5,5-dimethyl-2-cyclopentene **9** (2.2 equiv. Ac_2O, 2.2 equiv. pyr., 0.22 equiv. DMAP, CH_2Cl_2, 20°C, 12h, 97%).

Table 1

Entry	Starting Material	Lipase (11)	Amount of lipase (mg / mmol.)	Reaction time (d)	Yield in **10'** (%)	$[\alpha]_D^{20}$ (e.e. %)
a	**9**	PPL	51	25	100	- 67.5 (82)
b	**9**	Pancreatin	51	26	50	- 73.3 (89)
c	**9**	PFL	51	7	50	- 75.6 (92)
d	**9**	PFL / saw	38	7	100	- 78.1 (95)
e	**9**	PFL / saw-NEt_3	38	7	93	- 81.5 (99)
f	**9**	PS	102	11	90	- 81.8 (99.4)[2b]

The reaction is best achieved with PPL (34 mg lipase/ mmol. **11**, H_2O-*t*-BuOMe 5-1, pH 7.3, 20°C, table 2, entry d). No reaction took place with PLE (0.1 M. phosphate buffer pH 7, methanol-water 1-9 , 24°C, 90 h, 0 %) but use of PLAP instead leads to (1R,4S)-4-acetoxy-5,5-dimethyl-2-cyclopentene-1-ol **10"** in good yield but with relatively modest enantiomeric excess (0.1 M. phosphate buffer pH 7, methanol-water 1-9, 24°C, h, 84 % of **10"** : e.e. 84% , 12 % of **9**, table 2, entry e). Finally, the desired monoacetate **10"** has been obtained in reasonably high enantiomeric excess by deacetylation of **11** by a mixture of PLAP and PLE (**10"** / **10'** = 92/8, e.e. 84 %, table 2, entry e, 67%). We do not understand the reasons of such surprising results but we have proved that it is not due to the selective hydrolysis by PLE of the unwanted enantiomer **10'** produced concomitantly to **10"** by PLAP (a 50/50 mixture of **10"** / **10'** does not react under the conditions disclosed above with PLE and is recovered unchanged).

Anyhow, this unusual procedure could be an original solution to some desperate cases or an economical solution if the cheapest PLAP can be used instead of PLE.

Table 2

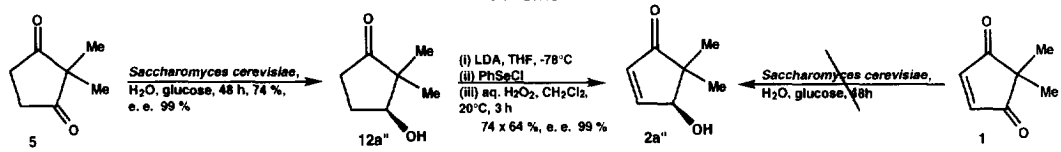
Entry	Starting Material	Lipase	Amount of lipase (mg / mmol. of **11**)	Reaction time (h)	Yield in **10"** (%)	$[\alpha]_D^{20}$ (e.e. %)
a	**11**	PFL	64	3	-	-
b	**11**	PLE	1	90	-	-
c	**11**	PS	64	84	23	+ 71 (86.4)
d	**11**	PPL	34	24	75	+ 74.1 (90.2)
e	**11**	PLAP	50	48	86	(84)
f	**11**	PLAP + PLE	50 + 0.4	43	67	+ 77.8 (95)

In the course of this work, we have also tried to perform the enantioselective acetylation of the saturated *cis*-diol (resulting from the di-reduction of **5** by DIBAH) or the mono-deacetylation of its diacetate with lipases, hoping to introduce the unsaturation leading to **2'** and **2"** at a later stage. None of the various lipases tested, however, allow the desired transformations.[13]

An even more convenient route to the 4-hydroxyenone **2a** would involve the enantioselective reduction of the enediones **1**. Unfortunately however, we have been unable to reduce it using *Saccharomyces cerevisiae*. Nevertheless, the same reaction performed on **5**, the saturated analog of **1**, produces the saturated hydroxy ketone **12a"** with very high enantioselection ($[\alpha]_D^{20}$= +13.0, $CHCl_3$, c = 1.23) (Scheme 4).[14] The synthesis of the optically active hydroxy-enone **2b"** was efficiently achieved by sequential selenenylation α-to the carbonyl group followed by selenoxide elimination reaction ((i) 3 equiv. LDA, -78°C, 2 equiv. PhSeCl, 74 % (ii) 2 equiv. H_2O_2, CH_2Cl_2, 20°C, 0.3 h, 64 %, $[\alpha]_D^{20}$ = 94.03, MeOH, c = 0.876).[15] Interestingly the reaction does not require protection of the free hydroxyl group and proceeds without concomitant retroaldol reaction. We have nevertheless observed that the use of two equivalents of phenylselenenyl chloride is essential for the success of the reaction. In fact, when the reaction is carried out under similar conditions with stoichiometric amounts of phenylselenenyl chloride, the colour of the latter disappeared once it is added

to the intermediate γ-alkoxy-enolate but the starting material is delivered back after hydrolysis. This leads us to suggest that phenylselenenyl chloride firstly reacts chemoselectively on the alkoxide group rather than on the enolate moiety of the intermediate.

Scheme 4



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3. Krief, A.; Swinnen, D. accompanying paper.

4. (a) Most of the work described in this paper has been performed unintentionally in duplicate in Dortmund [4b] and Namur. We have been aware also of a related work when it appeared in a recent paper.[2b] The Dortmund and Namur groups decided to merge their results and to present them together (b) Wiggermann, A. *Ph.D. Thesis*, November **1994**.

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10. PS : Lipase from *Pseudomonas* (Amano)[12] ; PFL : Lipase from *Pseudomonas fluorescens* (Fluka); PPL : Lipase from *Porcine Pancreas* (Fluka).

11. We thank Mr Nakai, K. from Amano Enzyme Europe LTD (England) , for a generous gift of several lipases.

12. Kindly provided by Dr. Kerscher, V. c/o Röhm GmbH-Chem. Fabrik-Kirschenallee, 64293 DARMSTAT (Germany)

13. Several related derivatives behave differently. We are working to understand the reasons of these results.

14. (a) We have ascertained this result (e.e. 99 %) by NMR on the MTPA ester of **12a"** . The $[\alpha]_D^{20}$ = +13.0 ($CHCl_3$, c = 1.23) of the ketoalcohol **12a"** is however much higher than the one reported by Djerassi for the same compound under similar conditions $[\alpha]_D^{20}$ = +8.0 ($CHCl_3$)) (14b) . (b) Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1981**, *103*, 295.

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