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New reactions with CrO_3/3,5-dimethylpyrazole reagent: Formation of Cross-conjugated Dienones from β-Cyclocitral and Safranal Derivatives .

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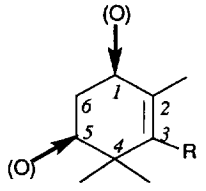
Abstract: Oxidation of the enol diphenylphosphate ester derived from a 3-substituted 2,4,4-trimethylcyclohex-2-en-1-one by the CrO_3-DMP reagent affords in high yield the cross-conjugated dienone **8**. The same dienone can be obtained from safranal derivative **10** by reaction with the same reagent.

Recent convergent strategies for the synthesis of taxol use the coupling of A and CD ring moieties followed by the formation of the B ring, and thus require the efficient and economical synthesis of complex building blocks for the A and CD rings. In continuation of our ongoing program to provide versatile synthons or chirons for the elaboration of active natural substances [1], we have directed our efforts toward the elaboration of an effective A ring synthon, involving a 3-substituted 2,4,4-trimethylcyclohex-2-ene, oxidized (or hydroxylated) in positions -1 and/or -5 (**1**).



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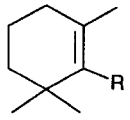
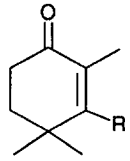
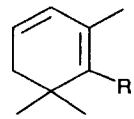


2 : R= CH_2OH
3 : R= CH_2-CH_2OH



4 : R= CH_2OH or CH_2-CH_2OH

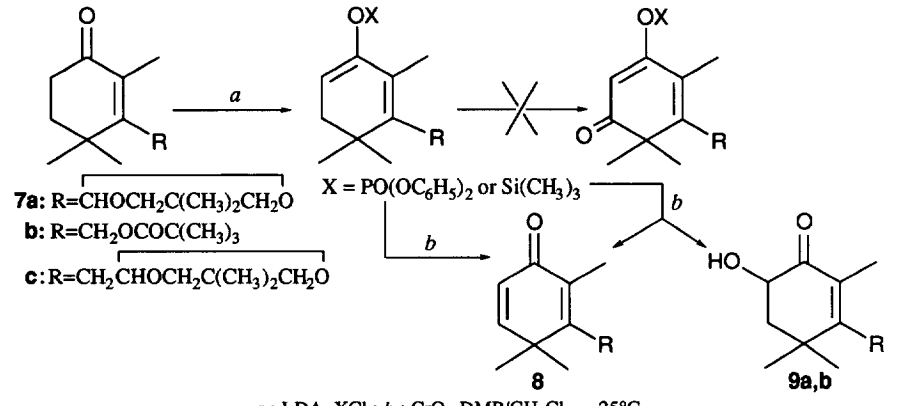


5: R= CHO
6: R= CH_2OH

We have already investigated the allylic oxidation of various 2,4,4-trimethylcyclohexenes [1d] : the allylic oxidation of readily available β-ionone with CrO_3-3,5-dimethylpyrazole (CrO_3-DMP), at low temperature, gave, in almost quantitative yield, the corresponding 1-keto derivative (which was obtained in only 60 % yield [2] by oxidation with CrO_3 in DMSO at 100°C). Similar results were obtained with β-cyclocitrol **2**, or its homologous alcohol **3**, or their protected derivatives, affording in acceptable yields the corresponding 1-keto compounds **4**. CrO_3-DMP is a well known allylic oxidizing reagent, providing conjugated enones [2-11] and sometimes, in minor amounts, epoxides [4].

The idea was thus to extend this reaction to the allylic oxidation of a conjugated diene, either an enol-derivative of **4**, or safranal(ol) (**5/6**) related compounds. To the best of our knowledge, there is no reported example of allylic oxidation using CrO_3-DMP applied to conjugated monocyclic dienes. We wish to report here our results using this oxidation methodology with such dienic substrates.

When the enol derivatives of **7a-c** [X = $PO(OC_6H_5)_2$ or $Si(CH_3)_3$] were treated with CrO_3-DMP in CH_2Cl_2 at –25°C (*Scheme 1*), unexpectedly, dienones **8** were isolated as major products together with variable amounts of **7a-c**, arising from the hydrolysis of unreacted starting material during the workup. The best result was obtained with the diphenylphosphate esters (Table), affording 90% pure dienones as a crude product [12]. Using the silyl enol ethers of **7a** or **7b**, 10-12% of a new hydroxylated product was also isolated, identified as the hydroxy ketone **9** [13].



a : LDA, XCl ; *b* : CrO_3-DMP/CH_2Cl_2, - 25°C.

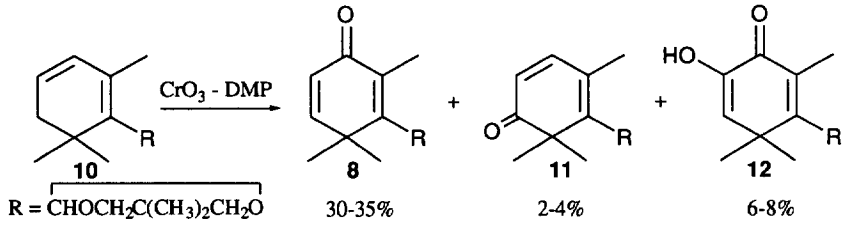
Scheme 1

Table: Oxidation Products Obtained from Enol Derivatives of **7a** - **c** using the CrO_3-DMP reagent

	R	X	CrO_3-DMP equivalents	**7** (%)[a]	**8** (%)[a]	**9** (%)[a]
7a	$CH(OCH_2)_2C(CH_3)_2$	$PO(OC_6H_5)_2$	6-8	0-1	>90	–
7a	$CH(OCH_2)_2C(CH_3)_2$	$Si(CH_3)_3$	2	40-45	40-45	10-12
7b	$CH_2OCOC(CH_3)_2$	$Si(CH_3)_3$	2	40-45	40-45	10-12
7c	$CH_2CH(OCH_2)_2C(CH_3)_2$	$PO(OC_6H_5)_2$	6-8	0-1	>90	–

[a] The indicated yields were evaluated from ^{1}H-NMR spectra measurements on crude products.

We then decided to investigate the allylic oxidation of safranal [14] or its protected derivatives. We had previously attempted the functionalization of safranal **5**, or safranol **6** (easily obtained from **5** by DIBAL reduction at –78°C) by oxidation with a SeO_2-pyridine-N-oxide reagent [1e] or by microbial hydroxylation [15], but with disappointing results. The aldehyde group was first protected as a 2,2-dimethyl-1,3-dioxane derivative [16] **10** and oxidation with CrO_3-DMP was performed under the usual conditions. Results are reported in *Scheme 2* and show again the main formation of the cross conjugated dienone **8**, together with small amounts of the dienone **11** and enolized diketone **12** [17].



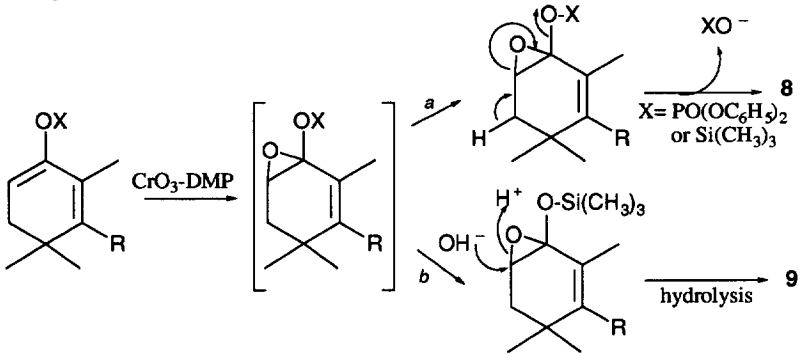
Scheme 2

Dienones **8** and **11** are easily distinguished by their NMR spectra [13]: C-1 resonated at 186 ppm for the cross conjugated dienone **8**, and 199 ppm for the 5-ketodiene **11**. The synthesis of **8** in six steps starting from β-ionone was recently reported [18], but no spectroscopic data were reported. An unambiguous identification resulted from the baker's yeast-mediated reduction [19] of the pivaloyl ester **8b**: the reduced compound was identical to the enone **7b**, synthesized by allylic oxidation of the β-cyclocitrol pivalic ester.

The synthetic utility of oxidation reactions of enol derivatives is attested by many examples: formation of α-hydroxy ketones by hydroperoxy reagents [20], or α,β-unsaturated enones by tritylfluoroborate [21], DDQ [22,23] or

stoichiometric amounts of palladium(II) acetate [24]. However, in most cases, DDQ or the trityl cation gave rise to a substantial amount of recovered saturated ketone. Moreover, enones do not react [22]. In comparison, our results, using the CrO_3-DMP reagent, show that a cross conjugated dienone can be easily obtained from the enolphosphate ester, providing an 80% yield of **8** from a β-cyclocitral(ol) derivative in three steps.

A mechanistic explanation for this reaction can be derived from the previously reported CrO_3-DMP allylic oxidation scheme [3], suggesting a hydrogen abstraction at the allylic position (involving assistance of the pyrazole group) with formation of a 5-hydroxy chromate ester, followed by a 1,3-migration (previously observed in the pyridinium chlorochromate oxidation of tertiary allylic alcohols [25]) and elimination of the phosphate ester (silyl ether) group. However, the observed formation of small amounts of **9** from silyl enolate derivatives is reminiscent of the classical oxidation of enol ethers (or esters) to α-hydroxy ketones [20], suggesting (*Scheme 3*) the formation of **8** *via* 1,6-epoxide formation (see [4]), followed by opening of the epoxide by abstraction of H-5 and elimination of the diphenylphosphate group (pathway *a*); conversely, epoxide hydrolysis during the alkaline workup leads to **9** (pathway *b*).



Scheme 3

The oxidation of **10** by CrO_3-DMP corresponds to a different situation. The conjugated enones are possibly formed through the allylic 5-chromate ester, effectively attested by the isolation of dienone **11**.

Synthetic studies using dienone **8**, involving a $\Delta^{5,6}$ regioselective epoxidation affording functionalized structures related to taxol-ring A synthons, are in progress.

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12. It is advisable to use the crude dienone for further reactions to avoid a significant loss of material during chromatographic steps. Only 60-80% of pure crystalline **8a** or **8c** can be recovered after a Florisil column.
13. **8a**: M.p. 75-76°C (from pentane). IR (neat) cm^{-1}: 2956, 2527, 2850, 1663, 1635, 1471, 1395, 1373, 1144, 1119, 1085, 1024, 984, 833. ^{1}H-NMR ($CDCl_3$), δ ppm, J Hz: 0.80 (3H, s, 4-CH_3), 1.34 (9H, s, 4-CH_3 and C(CH_3)$_2$), 2.16 (3H, s, 2-CH_3), 3.55 and 3.78 (4H, AB system, J_{AB}= 11.0, OCH_2), 5.20 (1H, s, 3'-CH), 6.18 and 6.71 (2H, AB system, J_{AB}= 9.90, 5- and 6-CH). ^{13}C-NMR ($CDCl_3$), δ ppm: 187.1 (C-1), 157.6 (C-5), 153.1 and 135.0 (C-3 and C-2), 125.1 (C-6), 101.6 (C-3'), 78.3 (CH_2O), 39.2 (C-4), 30.3 (OCH_2-C(CH_3)$_2$), 25.4 (4-CH_3), 23.9 and 22.1 (OCH_2-C(CH_3)$_2$, 11.8 (2-CH_3) MS (CI, NH_3) m/z: 251 $[M+H]^+$.
8b: Colorless oil. IR (neat) cm^{-1}: 2972, 2933, 2873, 1792, 1665, 1633, 1480, 1464, 1406, 1397, 1374, 1279, 1144, 1033, 967, 832. ^{1}H-NMR ($CDCl_3$), δ ppm, J Hz: 1.13 (9H, s, C(CH_3)$_3$), 1,20 (6H, s, 4-CH_3), 1.87 (3H, s, 2-CH_3), 4.75 (2H, s, 3'-CH_2), 6.16 and 6.73 (2H, AB system, J_{AB}= 10.0, 5- and 6-CH). ^{13}C-NMR ($CDCl_3$), δ ppm: 186.0 (C-1), 178.1(OCO), 156.9 (C-5), 152.6 and 136.5 (C-3 and C-2), 125.9 (C-6), 60.4 (C-3'), 39.6 (C-4), 38.4 (C(CH_3)$_3$), 27.1 (OC(CH_3)$_3$), 25.3 (4-CH_3), 11.1 (2-CH_3). MS (EI) m/z: 250 $[M^+]$.
8c: M.p. 66.5-67°C (from pentane). IR (neat) cm^{-1}: 2958, 2930, 2849, 1665, 1634, 1608, 1470, 1391,1298, 1128, 1090, 1021, 988. ^{1}H-NMR ($CDCl_3$), δ ppm, J Hz: 0.69 (3H, s, 4-CH_3), 1.18 (3H, s, 4-CH_3), 1.21 (6H, s, C(CH_3)$_2$), 1.91 (3H, s, 2-CH_3), 2.77 (2H, d, J= 5.0, 3'-CH_2), 3.35 and 3.56 (2H, AB system, J_{AB}= 10.9, OCH_2), 4.58 (1H, t, J= 5.0, CHO_2), 6.16 and 6.74 (2H, AB system, J_{AB}= 9.8, 5- and 6-CH). ^{13}C-NMR ($CDCl_3$), δ ppm: 186.4 (C-1),157.5 (C-5), 156.3 and 134.0 (C-2 and C-3), 125.7 (C-6), 101.7 (CHO_2), 78.3 (CHO), 77.4 (CH_2O), 40.6 (C-4), 36.7 (C-3'), 30.0 (OCH_2-C(CH_3)$_2$) 26.0 (OCH_2-C(CH_3)$_2$, 23.1 and 21.8 (4-CH_3), 23.1 and 21.8 (4-CH_3), 12.3 (2-CH_3). MS (CI, NH_3) m/z: 265 $[M+H]^+$.
9b: colorless oil. IR (CCl_4) cm^{-1}: 3508, 2969, 2933, 2870, 1733, 1683, 1479, 1397, 1367, 1277, 1146, 1086, 1031. ^{1}H-NMR ($CDCl_3$), δ ppm, J Hz: 1.17 (3H, s, 4-CH_3), 1.20 (9H, s, C(CH_3)$_3$), 1.28 (3H, s, 4-CH_3), 1.81 (1H, t, J= 12.8, H-5ax), 1.86 (3H, s, 2-CH_3), 2.16 (1H, dd, J= 12.8 and 5.7, H-5eq), 3.62 (1H, br.s, OH), 4.35 (1H, dd, J= 12.8 and 5.7, H-6ax), 4.65 and 4.70 (2H, AB system, J_{AB}= 12.1, 3'-CH_2). ^{13}C-NMR ($CDCl_3$), δ ppm: 200.6 (C-1), 178.2 (CO), 156.8, 132.6 (C-2, C-3), 68.5 (C-6), 60.5 (C-3'), 45.3 (C-5), 39.0 (C(CH_3)$_3$), 36.6 (C-4), 29.0 and 25.1 (4-CH_3), 27.1 (C(CH_3)$_3$), 11.6 (2-CH_3). MS (CI, NH_3) m/z: 269 $[M+H]^+$.
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