

A NOVEL SYNTHETIC METHOD OF DIHYDRO-4-PYRONE DERIVATIVES AND ITS
APPLICATION TO THE SYNTHESSES OF *ax*-ATLANTONE AND (\pm)-*ax*-TURMERONE

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Abstract: Reaction of 1,3-dihalo-3-methyl-2-butanone with *t*-butyl acetoacetate (NaH) gave *t*-butyl 3,4-dihydro-2,2,6-trimethyl-4-oxo-2H-pyran-5-carboxylate *via* the Favorskii-type rearrangement. Michael addition of 4-methylphenyllithium (CuI) followed by ring cleavage with Me₃SiCl-NaI in DMF or PrCN afforded *ax*-atlantone as well as (\pm)-*ax*-turmerone selectively.

Conjugated enones have been widely used as versatile intermediates in organic synthesis. Frequently, the appropriate structures are found in carbon skeletons of terpenoids, e.g. *ax*-atlantone (1)¹ and (\pm)-*ax*-turmerone (2).² We report here a convenient synthetic route to these compounds, which involves two novel reactions. One of them is the Favorskii-type rearrangement of α,α' -dihalo ketones induced by enolates of β -keto ester and acetylacetone, giving dihydro-4-pyrone derivatives in one-pot reaction. The other is the cleavage of tetrahydro-4-pyrone skeleton with Me₃SiCl-NaI reagent³ in DMF or PrCN affording divinyl ketone as well as monovinyl ketone, selectively. By the combination of these procedures, compounds 1 and 2 could be synthesized effectively in three steps.

It has been well known that the Favorskii rearrangement of α,α' -dihalo ketones induced by hydroxide or alkoxide gives α,β -unsaturated acids or their esters, respectively.⁴ The reaction presented here is the first example of extending the base of the Favorskii rearrangement to enolates of β -keto ester and acetylacetone to obtain a variety of dihydro-4-pyrone derivatives as summarized in Table I. Possible mechanism of the reaction represented by those of 3 and 4 is shown below. The Favorskii-type rearrangement may occur initially to give enone intermediate 5,⁵ which then cyclizes to form dihydro-4-pyrone 6a.

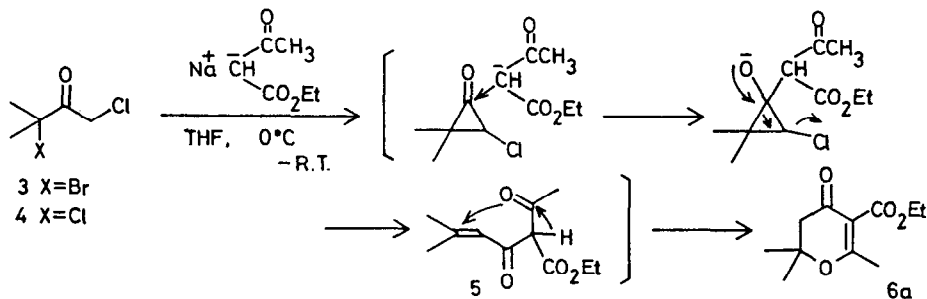
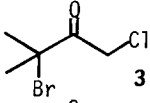
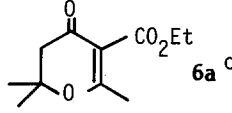
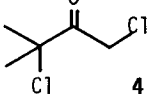
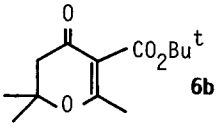
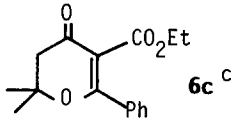
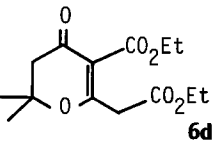
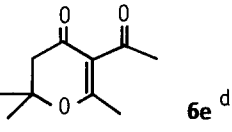
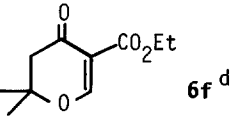
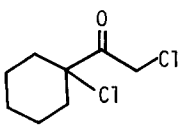
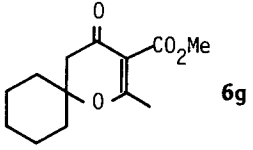


Table I. Synthesis of Dihydro-4-pyrone Derivatives.^a

Dihalo Ketone	$\begin{array}{c} \text{O} \quad \text{Na}^+ \quad \text{O} \\ \parallel \quad \quad \parallel \\ \text{R}^1 - \text{C} - \text{CH} - \text{C} - \text{R}^2 \\ \text{R}^1 \quad \quad \quad \text{R}^2 \end{array}$		Product	Procedure for Isolation ^b	Yield (%)
	CH ₃	OEt		A [bp 106-110 °C (0.18 mmHg)]	71
	CH ₃	OEt	6a^c	A	61
3	CH ₃	OBu ^t		A [bp 92-95 °C (0.12 mmHg)] mp 38.2-38.9 °C (hexane-ether 5:1)	75
4	Ph	OEt		B (hexane-acetone 5:1)	46
4	-CH ₂ CO ₂ Et	OEt		C (hexane-acetone 6:1)	47
4	CH ₃	CH ₃		A [bp 100-110 °C (0.17 mmHg)]	53
4	H	OEt		A [bp 130-150 °C (0.18 mmHg)]	53
	CH ₃	OMe		B (hexane-ether 5:1)	60

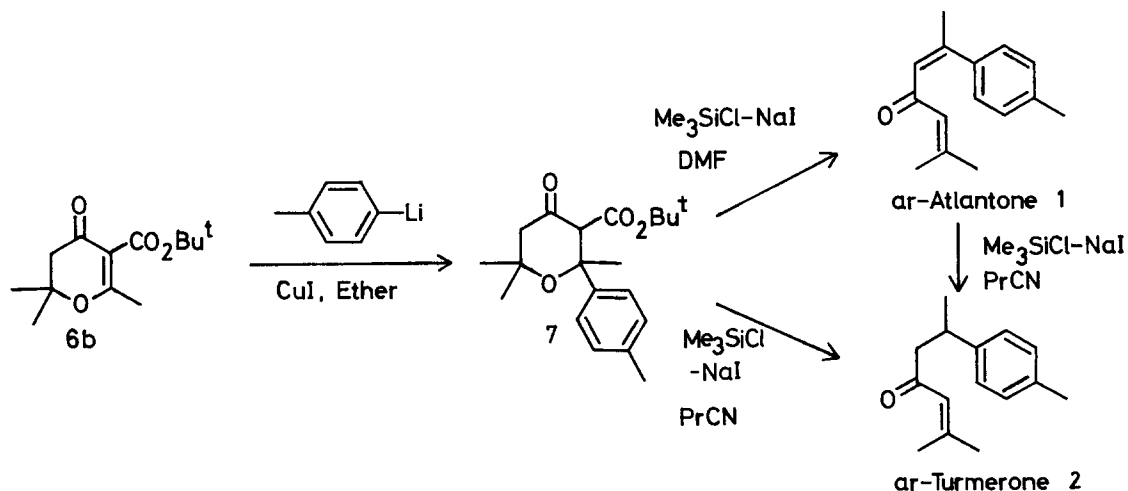
^a See reference 6 (IR and ¹H NMR spectral data).
PF₂₅₄); C, column chromatography (Wakogel C-200).
Fr., 1968, 288. ^d Reaction in dioxane.

^b A, distillation; B, TLC (Merck, Kieselgel
^c S. Gelin and R. Gelin, Bull. Soc. Chim.

A typical procedure for the synthesis of dihydro-4-pyrones is as follows: A suspension of *t*-butyl acetoacetate (16.4 g, 0.103 mol) and NaH (4.7 g, 0.103 mol) in THF (70 mL) was heated under reflux for 2 h and then cooled on an ice bath. To the suspension was added a solution of 3-bromo-1-chloro-3-methyl-2-butanone (3) (11.4 g, 0.0427 mol) in THF (30 mL) dropwise. The mixture was stirred for 2 h at 0 °C and then for additional 12 h at room temperature. The resulting mixture was acidified with 10% HCl and the organic layer was treated in a usual manner to give 7.64 g of *t*-butyl 3,4-dihydro-2,2,6-trimethyl-4-oxo-2H-pyran-5-carboxylate (**6b**) in 75% yield after vacuum distillation.

The carbon skeleton of compounds **1** and **2** was constructed by introducing 4-methylphenyl moiety to C-6 position of the common intermediate **6b**. To a suspension of 4-methylphenyllithium (41.6 mmol) and CuI (4.0 g, 20.8 mmol) in ether (20 mL), was added a solution of **6b** (1.7 g, 6.9 mmol) in ether (20 mL) at -50 °C slowly. The mixture was stirred for 2 h at -50 °C, for 4 h at 0 °C and then for additional 14 h at room temperature to yield *t*-butyl tetrahydro-2,6,6-trimethyl-2-(4-methylphenyl)-4-oxo-4H-pyran-3-carboxylate (**7**)⁷ in 83% yield after purification by column chromatography (Wako gel C-200, hexane-ether 20:1).

Subsequently, the tetrahydro-4-pyrone ring was cleaved to obtain **1** or **2**, selectively, by the use of Me₃SiCl-NaI reagent in different solvent. Compound **7** was allowed to react with Me₃SiCl-NaI (6 equiv. each) in DMF at 120 °C for 0.5 h, affording *ar*-atlantone in 70% yield after purification by TLC (hexane-acetone 3:1). In contrast to the above result, where dehydrative ring opening has merely occurred in parallel with the removal of *t*-butoxycarbonyl group, the similar reaction of **7** with Me₃SiCl-NaI (10 equiv. each) in PrCN⁸ at reflux temperature gave (±)-*ar*-turmerone in 68% yield exclusively. Although the mechanism is still obscure, partial reduction has been achieved in one step during the course of the latter reaction. It is interesting that compounds **1** and **2** can be prepared selectively by the choice of the solvent, i.e. DMF or PrCN. It should be noted here that *ar*-atlantone is transformed to (±)-*ar*-turmerone by the Me₃SiCl-NaI reagent (6 equiv. each) in refluxing PrCN in good yield.⁹ Further study on the mechanism and the scope of the reactions is in progress.



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References and Notes

- Multi-step synthesis of **1**: J. Alexander and G. S. K. Rao, *Ind. J. Chem.*, **10**, 789 (1972).
- P. Gosselin, S. Masson, and A. Thuillier, *J. Org. Chem.*, **44**, 2807 (1979), and references cited therein.
- G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).
- (a) A. S. Kende, "Organic Reactions," Vol. 11, John Wiley & Sons, Inc., N. Y. (1960), p.261; (b) R. B. Wagner, J. A. Moore, *J. Am. Chem. Soc.*, **72**, 974 (1950).
- The similar reaction with diethyl sodiomalonate gave diethyl (3-methyl-2-butenoyl)malonate in good yield. It will be reported elsewhere.
- New compounds such as **6b**, **6d**, **6e**, **6f**, and **6g** showed satisfactory analytical and spectral data. IR and ^1H NMR spectral data are shown in the following:
6b: IR (KBr) 1730, 1680, 1605 cm^{-1} ; ^1H NMR (CCl_4) δ 1.41 (s, 6 H), 1.46 (s, 9 H), 2.07 (s, 3 H), 2.37 (s, 2 H).
6d: IR (neat) 1740, 1695, 1595 cm^{-1} ; ^1H NMR (CCl_4) δ 1.26 (t, 3 H, J = 7 Hz), 1.29 (t, 3 H, J = 7 Hz), 1.45 (s, 6 H), 2.47 (s, 2 H), 3.46 (s, 2 H), 4.12 (q, 2 H, J = 7 Hz), 4.16 (q, 2 H, J = 7 Hz).
6e: IR (neat) 1650, 1545 cm^{-1} ; ^1H NMR (CCl_4) δ 1.45 (s, 6 H), 2.19 (s, 3 H), 2.33 (s, 3 H), 2.46 (s, 2 H).
6f: IR (neat) 1740, 1695, 1590 cm^{-1} ; ^1H NMR (CCl_4) δ 1.32 (t, 3 H, J = 7 Hz), 1.48 (s, 6 H), 2.52 (s, 2 H), 4.12 (q, 2 H, J = 7 Hz), 8.10 (s, 1 H).
6g: IR (neat) 1710, 1670, 1590 cm^{-1} ; ^1H NMR (CCl_4) δ 1.10-2.05 (m, 10 H), 2.12 (s, 3 H), 2.32 (s, 2 H), 3.64 (s, 3 H).
- IR (KBr) 1720, 1640 cm^{-1} ; ^1H NMR (CCl_4) δ 0.87 (s, 3 H), 1.20 (s, 3 H), 1.25 (s, 9 H), 1.76 (s, 3 H), 2.23 (s, 2 H), 7.13 (m, 5 H), 13.05 (s, 1 H, enol OH).
- When the reaction was carried out in CH_3CN , the yield of **2** was less than 20%.
- The reduction occurred regioselectively at the double bond which is conjugated with phenyl group. To the best of our knowledge, such a 1,4-reduction with $\text{Me}_3\text{SiCl-NaI}$ reagent has not been known. Scope of the reductions with similar reagents has been reported: a) G. A. Olah, B. C. B. Gupta and S. C. Narang, *Synthesis*, **1977**, 583 (sulfoxide to sulfide, Me_3SiI in CCl_4); b) J. N. Denis, R. Magnane, M. V. Eenoo, and A. Krief, *Nouv. J. Chem.*, **3**, 705 (1979) (oxirane to olefin, Me_3SiI in CCl_4); c) N. C. Barua and R. P. Sharma, *Tetrahedron Lett.*, **23**, 1365 (1982) (vicinal diol to olefin, $\text{Me}_3\text{SiCl-NaI}$ in CH_3CN); d) J. M. Aizpurua and C. Palomo, *Tetrahedron Lett.*, **25**, 1103 (1984) [aromatic aldehyde to benzyl halide derivative, $\text{Me}_3\text{SiCl-NaI-TMDS}$ (1,1,3,3-tetramethyldisiloxane) in CH_3CN].

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