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β-KETOLACTONE SYNTHONS. SHORT EFFICIENT SYNTHESES OF JASMONOIDS.

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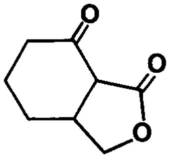
Summary: The cyclopentanoid β-ketolactone 2, serving as the equivalent of a specific enolate of a 3-alkyl cyclopentanone, has been converted to several jasmonoid substances.

A key process in synthesis is the alkylation of unsymmetrically substituted cycloalkanones. For 2-substituted cyclic ketones the enolization and substitution steps necessary for this process are often easily achieved in a regiospecific fashion[1]. In the case of β-alkyl substituted cycloalkanones little evidence seems to exist regarding the regiochemical course of either kinetic or thermodynamic enolate formation[2]. This uncertainty has stimulated the development of a variety of indirect methods employing cyclic enones for the preparation of specific enolates[3].

In a previous paper[4] we reported the preparation of ketolactone 1, and showed how this compound through the use of its mono and dianions could be used as the synthetic equivalent of either enolate of a 3-substituted cyclohexanone. In this report we describe an extension of this methodology to the alkylation of a cyclopentanoid system[5], and illustrate its utility for the short, highly efficient synthesis of several jasmonoid substances[6].



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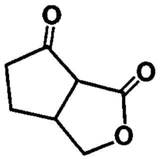

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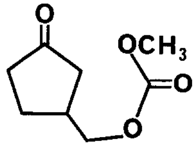

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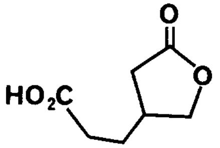

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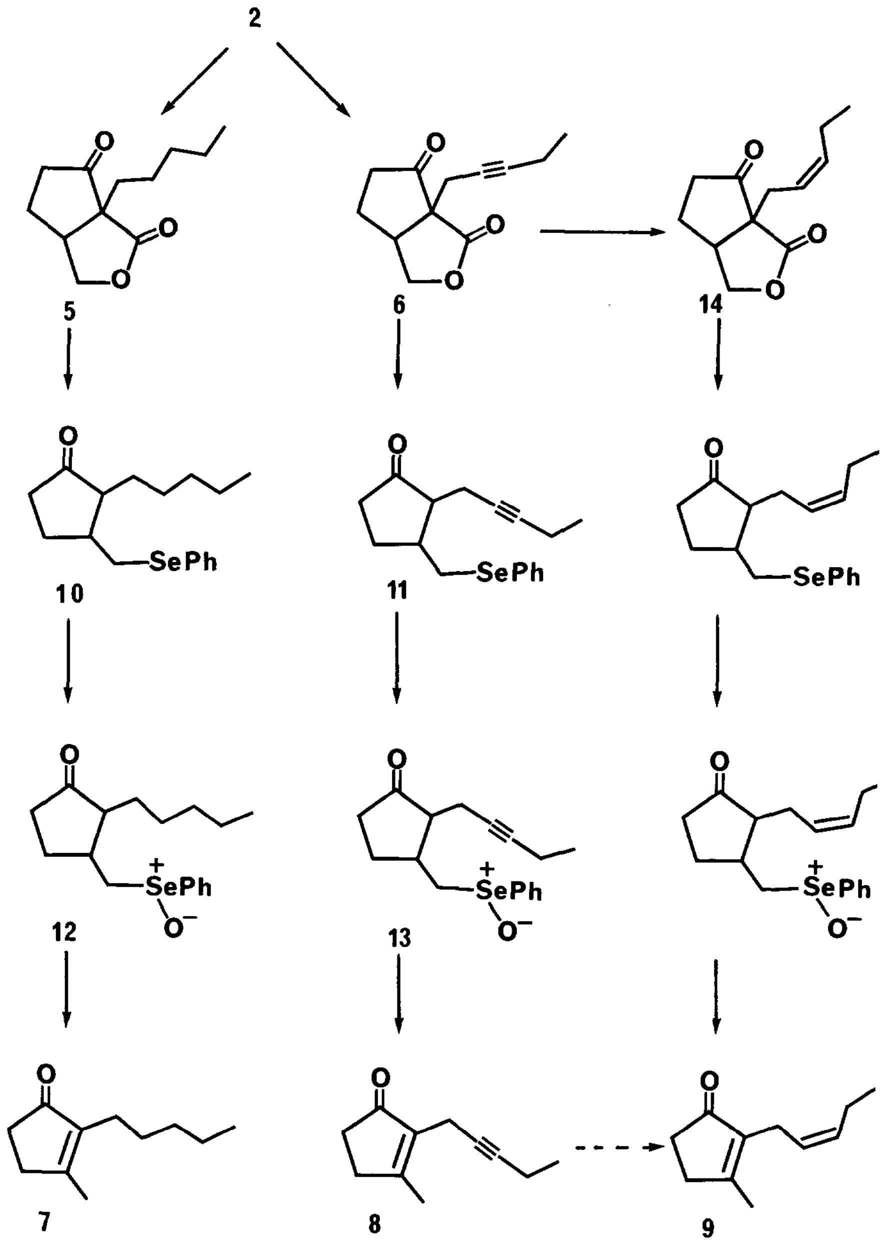
Ketolactone 2 was prepared by cyclization of methyl carbonate ester 3 (t-BuOK, t-BuOH-Et_2O, 25°C, 20 min), and the latter was obtained in straightforward fashion from cyclopentanone 3-car-

Scheme I



boxylic acid[7]. Depending on the manner of the work-up of the condensation reaction the yield of 2 varies from zero to nearly quantitative. For example, quenching of the reaction with concentrated HCl gave 2 in 93% yield after purification on silica gel. In contrast, when the mixture is first diluted with water only the cleavage product 4[8] can be obtained.

Alkylation of ketolactone 2 occurs exclusively at carbon, and as expected for the monoanion, exclusively at the α-position flanked by the two carbonyl groups. Thus, as shown in Scheme I, treatment of 2 with K_2CO_3 and either n-amyl iodide or 1-bromo-3-pentyne in DMF (25°C, 30 min, N_2 atm.) gave alkylation products 5 and 6 in yields of 87% and 90%, respectively.

For the conversion of 5 and 6 to the jasmonoid substances 7, dihydrojasmone, 8, dehydrojasmone, and 9, cis-jasmone the lactone ring was cleaved using sodium phenylselenide[9]. We have found this process to be applicable to a variety of functionalized polycyclic lactone systems including those containing several carbonyl groups[10]. In the present case, treatment of 5 and 6 with NaSePh (PhSeH, NaH, THF-HMPA, 25°C(2h), reflux(16h)) resulted in both the cleavage of the lactone at the alkyl oxygen position, and subsequent decarboxylation. Phenylselenenyl ketones 10 and 11 were thus obtained in yields of 99% and 97%, respectively, after purification on silica gel. These substances, in turn, were oxidized ($10 \rightarrow 12$: O_3, CH_2Cl_2, -78°C)($11 \rightarrow 13$: m-ClPBA, CH_2Cl_2, -78°C(1h), -20°C(15 min)) to the corresponding selenoxides, and the latter substances were subjected to thermal decomposition in refluxing chloroform containing diethylamine. These conditions suffice not only to cause the usual elimination reaction to occur but to also effect migration of the initially formed exocyclic double bond to the tetrasubstituted conjugated endocyclic position[11]. Thus 12 and 13 respectively were converted to dihydrojasmone, 7, in 89% yield (62% conversion) and dehydrojasmone, 8, in 85% yield (62% conversion). Partial hydrogenation of 8 to cis-jasmone has been reported previously[12].

In an alternative and complete synthesis of the fragrant substance itself we have also carried lactone 6 through to cis-jasmone, 9, by (a) controlled reduction (Pd-$BaSO_4$, quinoline, EtOAc, H_2 (atmospheric press.)) to the cis-olefin 14, and (b) subsequent application of the selenide cleavage, oxidation-elimination-isomerization sequence.

Further applications of these β-ketolactones to the synthesis of natural products will be reported in forthcoming publications.

Acknowledgment: This work was supported in part by a generous grant from the National Institute of Environmental Health Sciences (ES01615).

References and Footnotes

1. For a recent review see J. d'Angelo, Tetrahedron, 32, 2979 (1976).

2. Both kinetic and thermodynamic enolization of 3-methylcyclohexanone appears to be favored at the α-position remote from the substituent. (a) J. Ficini, J. d'Angelo and J. Noiré, J. Am. Chem. Soc., 96, 1213 (1974). (b) G. Stork and J. d'Angelo, ibid, 96, 7114 (1974). (c) K. Inomata, Y. Nakayama, M. Tsutsumi, and H. Kotake, Heterocycles, 12, 1467 (1979). However in the case of equilibrium aldol condensation the yield was only 20% (2b) and only 57% in the case of the kinetically controlled process (2c).

3. (a) G. Stork and M. Isobe, J. Am. Chem. Soc., 97, 4745, 6260 (1975). (b) R. Davis and K. G. Untch, J. Org. Chem., 44, 3755 (1979). (c) G. Zima, C. Barnum and D. Liotta, ibid, 45, 2736 (1980). (d) R. A. Lee, C. McAndrews, K. M. Patel and W. Reusch, Tetrahedron Lett., 965 (1973).

4. D. J. Goldsmith, T. K. John and F. VanMiddlesworth, Syn. Commun., 10, 551 (1980).

5. Substituted cyclopentanoid β-ketolactones have been used in the synthesis of prostaglandin analogues. See O. Oda, K. Kojima and K. Sakai, Tetrahedron Lett. 3709 (1975) and references therein.

6. For a review of some of the many syntheses of these compounds see T-L Ho, Syn. Commun., 4, 265 (1974).

7. H. K. Hall, Jr., Macromolecules, 4, 139 (1971).

8. The methyl ester of 4 has been cyclized to 2 by R. K. Boeckman, Jr., P. C. Naegly, and S. D. Arthur, J. Org. Chem., 45, 754 (1980), and the ketolactone employed for the synthesis of the cyclopentanoid antibiotic sarcomycin.

9. (a) D. Liotta, H. Santiesteban, and W. Markiewicz, Tetrahedron Lett., 4365, 4369 (1977). (b) R. M. Scarborough, Jr., and A. B. Smith, III, J. Am. Chem. Soc., 99, 7085 (1977).

10. It has been reported that the oxidative elimination of phenylselenides fails in the presence of carboxyl groups, and that the γ-lactone cleavage produces complex mixtures with epoxide containing substrates; R. M. Scarborough, Jr., B. H. Toder and A. B. Smith, III, J. Am. Chem. Soc., 102, 3904 (1980).

11. Some disproportionation of the selenoxides occurs under these conditions. Yields are based on the amounts of 10 and 11 recovered. Satisfactory elemental analyses were obtained for all new compounds reported herein. The spectroscopic properties (nmr, ir, and ms) of all compounds were fully compatible with and specific for the structures described.

12. J. E. McMurry and J. Melton, J. Am. Chem. Soc., 93, 5309 (1971).

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