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A DIRECT α-METHYLENE LACTONE SYNTHESIS VIA AN ITACONIC ACID ESTER

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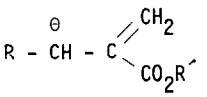
α-Methylene-γ-butyrolactones and δ-valerolactones have recently engendered considerable interest due to the discovery of several naturally-occurring cytotoxic or anti-tumor agents (e.g., euparotin, elephantin, vernolepin, etc.) that possess this characteristic α-methylene lactone system.[1,2] A variety of other natural products also contain this structural feature, some of which show antibiotic activity (e.g., protolichesterinic acid).[3] In this preliminary report, we wish to describe the use of the dianion of p-methoxybenzyl itaconate in the synthesis of protolichesterinic acid, nephrosterinic acid, and related α-methylene-γ-butyrolactones.

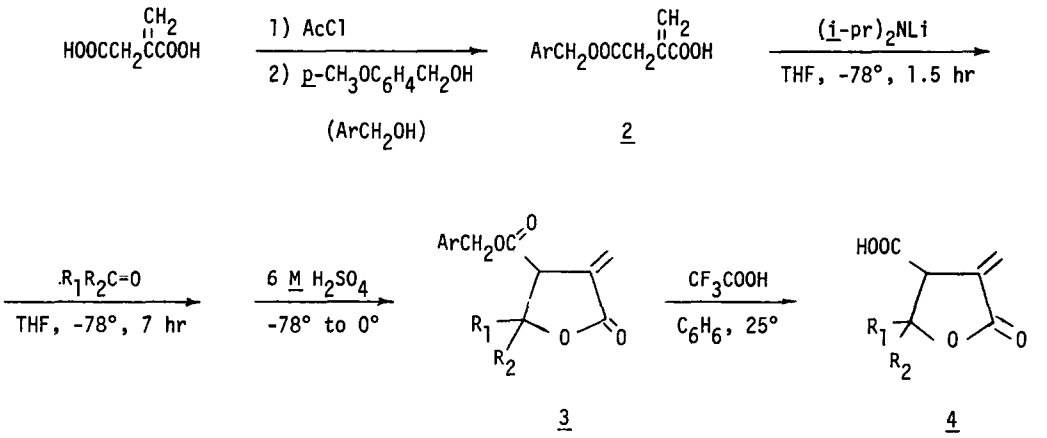
The general approach considered in the current program was to evaluate the possible resonance stabilized carbanions derived from appropriately substituted α-methylacrylic acid derivatives.[4,5] The ability to generate such a carbanionic species would permit the selective and direct synthesis of a series of α-methylene-γ-butyrolactones by the addition of the anion (1) to aldehydes and ketones.



≡ 1

Itaconic acid was recognized as an example of such a potential carbanion precursor and upon an examination of a variety of itaconic acid derivatives,[6] it was found the p-methoxybenzyl itaconate[7] (2) offered the best combination of acceptable yields in the anion formation and addition steps, ready separation of lactones from impurities and/or diastereomers, and ease of ester hydrolysis. The observed products were only those resulting from addition of the α carbon[8] of the itaconic acid ester to the various aldehydes and ketones (Scheme 1). Subsequent hydrolysis of the lactonized p-methoxybenzyl esters (3) with trifluoroacetic acid[9] provided the corresponding carboxylic acids (4) (Table 1).

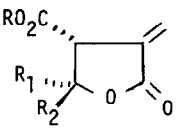
Scheme 1



The extension of this particular synthetic process and the development of structurally related syntheses are currently in progress.

Acknowledgement: The antibacterial screening was performed in these laboratories by Mr. Kevin Costley.

TABLE I[a]



Ref. #	R	R_1	R_2	% Yield	Mp, °C
1	$ArCH_2$-	CH_3-	CH_3-[b,c]	78[d]	54.5-55.5
2	H-	CH_3-	CH_3-[c]	69[d]	150-152
3	$ArCH_2$-	-$CH_2CH_2CH_2CH_2$-[e]		73[d]	---
4	H	-$CH_2CH_2CH_2CH_2$-[c]		54[d]	107-109
5	$ArCH_2$-	CH_3CH_2-	CH_3CH_2-[e]	30[d]	---
6	H	CH_3CH_2-	CH_3CH_2-[c]	17[d]	74-75
7	$ArCH_2$-	H	$CH_3(CH_2)_{12}$-[c]	25[f]	53.5-54.5
8	$ArCH_2$-	$CH_3(CH_2)_{12}$-	H[c]	16[f]	38.0-39.5
9	H	H	$CH_3(CH_2)_{12}$-[g]	20[d]	91-92[h]
10	H	$CH_3(CH_2)_{12}$-	H[c,g,i]	13[d]	87-88
11	$ArCH_2$-	H	$CH_3(CH_2)_{10}$-[c]	13[f]	46.8-47
12	$ArCH_2$-	$CH_3(CH_2)_{10}$-	H[c]	13[f]	34-35
13	H	H	$CH_3(CH_2)_{10}$-[c,j,k]	11[d]	83.5-84.5
14	H	$CH_3(CH_2)_{10}$-	H[c,k,l]	5[d]	81.5-82.5

a) In our laboratory compounds 1, 3, 9, 10, 13, and 14 show 7-10 mm inhibition zones (100 μg) against S. aureus. A. W. Bauer, W. M. Kirby, J. Sherris, and M. Turek, Am. J. Clin. Pathol., 45, 493 (1966); "Quality Control in Bacteriology with Bactrol Disks," Difco Technical Information, Feb., 1973.
b) Nmr ($CDCl_3$) δ 1.25 (3H, s), 2.56 (3H, s), 3.41 (1H, t), 3.81 (3H, s), 5.17 (2H, s), 5.85 (1H, d, J = 2.6 Hz), 6.48 (1H, d, 2.8 Hz), 7.15 (4H, m). Other compounds listed in this table exhibited similar spectra.
c) Satisfactory elemental analysis was obtained for this compound.
d) Initial yield based on itaconic ester; >90% pure by nmr and/or HPLC.
e) Corroborated by mass spec.
f) Yield of single diastereomer, based on itaconic ester-after purification by HPLC.
g) For a discussion of stereochemistry and nmr spectra see E. van Tamelen and S Bach, J. Amer. Chem. Soc., 80, 3079 (1958) and reference 4a.
h) dl-Protolichesterinic acid. Lit. mp 92-93.5 [F. Johnson et al., J. Org. Chem., 39, 1676 (1974)].
i) dl-Alloprotolichesterinic acid.
j) "trans-nephrosterinic acid."
k) (+)-Nephrosterinic acid has been isolated from Centraria endocrocea [Y. Asahina and M. Yanagita, Chem. Ber., 70B, 227 (1937)] but the stereochemistry has not yet been assigned.
l) "cis-nephrosterinic acid."

References and Notes:

1) For reviews see: P. A. Grieco, Synthesis, 67 (1975), R. B. Gammill, C. A. Wilson, and T. A. Bryson, Syn. Commun., 5, 245 (1975).

2) K. -H Lee, E. -S Huang, C. Piantodosi, J. Pagano, and T. A. Geissman, Cancer Res., 31, 1649 (1971).

3) For references see: M. W. Miller, "The Pfizer Handbook of Microbial Metabolites," McGraw-Hill, New York, 1961; W. B. Turner, "Fungal Metabolites," Academic Press, New York, 1971, pp. 288-289; C. Culberson, Bryologist, 73, 177-377 (1970), and C. F. Culberson, "Chemical and Botanical Guide to Lichen Products," U. of N. Carolina Press, Chapel Hill, NC, 1969. A recent synthesis is described by F. Johnson et al., J. Org. Chem., 39, 1576 (1974).

4) The related Reformatsky reactions have been previously reported: a) A. Loffler, R. D. Pratt, L. Pucknot, G. Geibard, A. S. Dreiding, Chimia, 23, 413 (1969); b) Ohler, et al., Angew. Chem. Int. Ed., 9, 457 (1970).

5) A malonic ester synthesis is described by V. B. Piskov, J. Gen. Chem. USSR, 30, 1421 (1960).

6) Attempts to generate the trianion of itaconic acid and add it to aldehydes and ketones resulted in diminished yields of lactones which were not easily purified. The dianion derived from methyl itaconate gave acceptable yields of lactones but the methyl ester could not be hydrolized without isomerization at the α-methylene system (see reference 4a). The use of dimethyl itaconate did not provide the desired products (see C. Katsuta and N. Sugiyama, Bull. Chem. Soc. Japan, 35, 1194 (1962).

7) This hitherto unknown compound was prepared by a modification of the procedure reported by B. Baker, et al., J. Org. Chem., 17, 116 (1952) for methyl itaconate. In the present case, the p-methoxybenzyl alcohol was allowed to react with the itaconic anhydride for 30 hr. at 55-60°. mp 86.8-87.2 Nmr ($CDCl_3$) δ 3.38 (2H, s), 3.74 (3H, s), 5.08 (2H, s), 5.82 (1H, m), 7.05 (4H, m), 68% overall yield.

8) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, Tetrahedron Lett., 26, 2433 (1973); P. E. Pfeffer, L. S. Silbert, and E. Kinsel, Tetrahedron Lett., 14, 1163 (1973); G. Cainelli, G. Cardello, M. Contento, and A. U. Ronchi, Gazz. Chim. Ital., 104, 625 (1974) M. W. Rathke and D. Sullivan, Tetrahedron Lett., 4249 (1972); C. A. Henrick, W. E. Willy, D. R. Mckean, E. Baggiolini, and J. B. Siddall, J. Org. Chem., 40, 8 (1975).

9) J. Webber, E. Van Heyningen, and R. Vasileff, J. Amer. Chem. Soc., 91, 5674 (1969).