combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford **62** (0.015 g) as a pale brown solid: R_f 0.39 in 1:1 hexane–CH_2Cl_2; NMR δ 8.95, 7.42 (AB q, 2 H, J = 9 Hz), 7.79, 7.19 (AB q, 2 H, J = 10 Hz), 7.51 (s, 1 H), 4.45 (br s, 2 H), 3.93 (s, 3 H), 2.55 (s, 3 H), 2.50 (s, 3 H); IR λ_{max} ($CHCl_3$) 2.92, 2.95 μm; mass spectrum (EI), m/e 329, 331 (M^+, base), 314, 316, 286, 288.

Photolysis of 52 in *tert*-Butyl Alcohol: Preparation of Phenanthrenes 63 and 64. A solution of **52** (0.229 g, 0.57 mmol) and iodine (ca. 0.010 g) in *tert*-butyl alcohol (120 mL) and CH_2Cl_2 (5 mL) was prepared in a 250-mL flask equipped with a stir bar, water-cooled condenser, and calcium sulfate drying tube. It was irradiated for 23.5 h with a 450-W Hanovia lamp contained in a water-cooled quartz housing located ca. 4 in. from the flask. The resulting dark red solution was concentrated in vacuo and the residue partitioned between ether and $NaHSO_3$ solution. The aqueous layer was reextracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried, filtered, and concentrated. Preparative TLC (two elutions with CH_2Cl_2) gave three fractions.

Band 1 (0.040 g) contained a TLC-inseparable mixture of starting material **52** and a new phenanthrene **64** (14% yield): NMR δ 9.57, 7.08 (AB q, 2 H, J = 10 Hz), 8.08 (s, 1 H), 7.81, 7.10 (AB q, 2 H, J = 9 Hz), 6.60 (br s, 1 H), 6.40–6.80 (m), 4.25 (q, 2 H, J = 7 Hz), 3.95 (s, 3 H), 2.57, 2.60 (two s, 6 H), 1.35 (t, 3 H, J = 7 Hz). Anal. ($C_{20}H_{21}NO_4$).

Band 2 contained another new phenanthrene tentatively identified as **63** (0.015 g): NMR δ 9.49, 7.17 (AB q, 2 H, J = 10 Hz), 8.09 (s, 1 H), 7.80, 7.58 (AB q, 2 H, J = 10 Hz), 6.55 (br s, 1 H), 4.25 (q, 2 H, J = 7 Hz), 3.95 (s, 3 H), 2.55 (s, 3 H), 2.40 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz), 1.17 (s, 9 H); IR λ_{max} ($CHCl_3$) 2.85, 5.80 μm; mass spectrum (EI), m/e 395 (M^+), 339 (base).

Band 3 contained 0.053 g (23%) of **61** which was identical with a sample prepared from stilbene **55**.

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General Synthetic Route to Malonamic Acids and 3-Thiomalonamic Acids. Amidations and Thioamidations of α Anions of Carboxylate Salts with Alkyl and Aryl Isocyanates and Isothiocyanates[1]

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Treatment of α anions of carboxylate salts **2** with alkyl or aryl isocyanates and isothiocyanates leads to substituted malonamic acids (**4**, X = O) and 3-thiomalonamic acids (**4**, X = S), respectively. Lithium naphthalenide is utilized as the base in the formation of the α anions **2** in order to circumvent the problem of a competitive reaction involving diisopropylamine (if lithium diisopropylamide is used to generate **2**) and the highly electrophilic isocyanates and isothiocyanates. A study of the generality of this type of reaction and a comparison of the two base systems are made.

During the past decade, α anions of carboxylate salts have found many synthetic applications.[2] As part of our continued interest in the synthetic uses of these α anions,[3] the present research was undertaken to investigate the reaction of carboxylic acids (via their α anions) with alkyl or aryl isocyanates and isothiocyanates as a possible general route to malonamic acids and 3-thiomalonamic acids, respectively.

The Ivanov reagent, $C_6H_5CH(MgCl)CO_2MgCl$, prepared from phenylacetic acid and isopropylmagnesium chloride, reacts with isocyanates to yield N-substituted malonamic acids.[4] However, treatment of this Ivanov reagent with isothiocyanates leads to decarboxylated products. This method suffers from the limitation that it cannot be applied to aliphatic and alicyclic carboxylic acids.

Malonamic acids have been prepared from amide α anions by treatment with CO_2,[5] from arylamines and diethyl malonate,[6] from acylals derived from substituted malonic acids,[7] from half-acid acyl chlorides,[8] by hydrolysis of spiro-1,3-oxazinones,[9] and by hydrogenation of a 1,3-oxazine-4,6-dione.[10]

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Scheme I

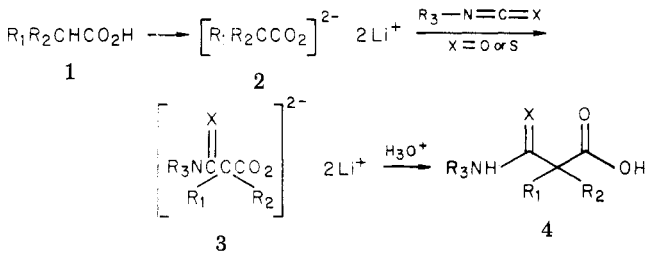

Table I. Malonamic Acids (4, X = O) and 3-Thiomalonamic Acids (4, X = S) Prepared via Scheme I

	R_1	R_2	R_3	X	% yield
4a	CH_3	CH_3	C_6H_5	O	65
4b	CH_3	CH_3	*n*-Pr	O	77
4c	C_6H_5	H	C_6H_5	O	80
4d	C_6H_5	H	*n*-Pr	O	75
4e	CH_3	H	C_6H_5	O	65
4f	CH_3	H	*n*-Pr	O	66
4g	$-(CH_2)_5-$		C_6H_5	O	62
4h	$-(CH_2)_5-$		*n*-Pr	O	60
4i	CH_3	CH_3	CH_3	S	61
4j	C_6H_5	H	CH_3	S	70
4k	$-(CH_2)_5-$		CH_3	S	60
4l	CH_3	CH_3	α-$C_{10}H_7$	S	65
4m	C_6H_5	H	α-$C_{10}H_7$	S	68

An attempt to convert malonamic acids into 3-thiomalonamic acids has been unsuccessful.[7] In one isolated example, a 1,3-oxathia 4,6-dione was converted into *N*-benzyl-2,2-dimethyl-3-thiomalonamic acid.[11]

Malonamic acids have found use in the preparation of 2,4-dihydroxyquinolines.[6] The esters show sedative properties[7] and have found use as intermediates in the syntheses of benzodiazepines[12] and aminonaphthopyranones.[13]

Results and Discussion

We wish to report a general two-step synthetic procedure in which an isocyanate or isothiocyanate is treated with a carboxylic acid (α anion) to produce a malonamic acid or 3-thiomalonamic acid via the formal transformation shown in eq 1 where X = O or S.

$$R_1R_2CHCOOH + R_3N{=}C{=}X \rightarrow R_3NHCXCR_1R_2COOH \quad (1)$$

Treatment of carboxylic acids 1 with 2 equiv each of lithium naphthalenide (LNAP) and tetramethylethylenediamine (TMEDA) in dry THF produces the dilithiated species **2**. Subsequent treatment of **2** with 1 equiv of the isocyanate or isothiocyanate at −75 °C leads to the salts **3** of the malonamic and 3-thiomalonamic acids, respectively. After the reaction mixture is quenched with water and acidified the malonamic acids (**4**, X = O) and 3-thiomalonamic acids (**4**, X = S) are obtained in 60–80% yields. The acids are readily obtained by extraction of the acidic aqueous phase with CH_2Cl_2, and the crude products which are obtained by evaporation of the solvent are quite pure. The products can be further purified by recrystallization from CH_2Cl_2–pentane. The products obtained via the reaction sequence in Scheme I are tabulated in Table I.

From the data presented in Table I, it can readily be discerned that alkyl or aryl isocyanates and isothiocyanates can be successfully utilized in the reaction, thus allowing the synthesis of a wide variety of N-substituted malonamic and 3-thiomalonamic acids.

Table II. Base Comparisons in Reactions with $C_6H_5N{=}C{=}O$

	acid 1			% yield	
entry	R_1	R_2	base	4	5
1	CH_3	CH_3	LDA	50	49
2	CH_3	CH_3	LNAP	55	0
3	CH_3	CH_3	LNAP/TMEDA	65	0
4	CH_3	CH_3	NNAP/TMEDA	55	0
5	C_6H_5	H	LDA	50	50
6	C_6H_5	H	LNAP	80	0
7	C_6H_5	H	NNAP	78	0
8	$-(CH_2)_5-$		LDA	37	60
9	$-(CH_2)_5-$		LNAP	45	0
10	$-(CH_2)_5-$		LNAP/TMEDA	62	0

Our initial studies showed that if the α anions **2** derived from propionic, isobutyric, or phenylacetic acids were formed by using lithium diisopropylamide (LDA) and then treated with phenyl isocyanate, the corresponding malonamic acids were formed in about 50% yields along with the side product *N,N*-diisopropyl-*N'*-phenylurea (**5**, eq 2) in a comparable yield (vide infra, Table II, entries 1, 5, and 8). This competitive side reaction was found to proceed

$$C_6H_5N{=}C{=}O + [(CH_3)_2CH]_2NH \rightarrow C_6H_5NHCON[CH(CH_3)_2]_2 \quad (2)$$
5

quite consistently regardless of the manipulations made on reaction conditions in attempts to avoid or prevent it. Such a competition between diisopropylamine and an electrophile was also reported by Krapcho and co-workers with α anions which were insoluble in the reaction medium.[2] The competitive reaction reported here proceeded regardless of the solubility of the α anions. The rapidity of the urea formation was determined by treating diisopropylamine with phenyl isocyanate in THF at −75 °C. It was found that within 10 min a quantitative yield of **5** was formed.

In the research reported here, the use of LNAP as the metalating agent circumvented the formation of urea **5** in the reaction. The use of aromatic hydrocarbon radical anions as metalating agents in the formation of α anions has been previously reported,[14] and the literature has recently been reviewed.[15] A summary of various reactions using LDA, LNAP (with and without TMEDA), and sodium naphthalenide (NNAP) is tabulated in Table II.

The use of LNAP also leads to higher yields of the malonamic acids (entries 2 and 9, Table II). A further increase in the yields could be realized if TMEDA was present in the reaction mixture. The role of TMEDA in these reactions is presumed to be twofold: (1) to lower the aggregation number of the lithium naphthalenide, thereby facilitating the metalation of the carboxylic acid, and (2) decreasing the degree of aggregation of the α anion, which enhances its reactivity toward the electrophile.[16]

In the case of phenylacetic acid, LNAP or NNAP yield equal amounts of the malonamic acid (entries 6 and 7, Table II). In the case of isobutyric acid, LNAP leads to a higher yield (entries 3 and 4, Table II).

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To determine the metalating efficiency of lithium naphthalenide compared to LDA, we studied the alkylation of cyclohexanecarboxylic acid. Generation of the anion by either base followed by addition of *n*-butyl bromide led to 85% yields of α-*n*-butylcyclohexanecarboxylic acid. Both bases appear to be of comparable metalation efficiency.

Conclusions

The procedure described allows a general two-step synthesis of malonamic acids and 3-thiomalonamic acids with a wide variety of substitution patterns. We have also shown that inexpensive lithium naphthalenide is a useful base for the preparations of the α anions of carboxylate salts. Equal in metalating efficiency to LDA but producing a far less nucleophilic reaction product, LNAP becomes a particularly attractive base for use in those systems employing reactive electrophiles.

Experimental Section

All melting points were determined by using a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined by using a JEOL JNM-MH-100 or a JEOL C-60HL spectrometer. Microanalyses were performed by Robertson Laboratories.

All carboxylic acids were distilled from P_2O_5 prior to use with the exception of phenylacetic acid which was used as received. All the isocyanates and isothiocyanates were commercial products. The THF was pretreated with NaOH and then refluxed over sodium in the presence of benzophenone sodium ketyl and used immediately upon distillation. TMEDA was distilled from 1-naphthyl isocyanate prior to use.

General Procedures. A. Lithium Naphthalenide–TMEDA. Lithium naphthalenide was prepared by dissolving naphthalene (1.28 g, 10 mmol) in 50 mL of dry THF (distilled from sodium–benzophenone ketyl directly into the reaction flask) under a nitrogen blanket. Lithium ribbon (0.07 g, 10 mmol), weighed under mineral oil and washed with pentane prior to addition to the reaction flask, was added in small pieces at room temperature. The reaction mixture was stirred for 2 h over which period the lithium metal dissolved and a dark black-green solution of LNAP remained. TMEDA (1.1 mL, 10 mmol) was then added at room temperature and the reaction mixture stirred for 30 min. The reaction mixture was cooled to −75 °C, and the carboxylic acid (5 mmol) was added as a solution in 10 mL of dry THF. The reaction mixture was then heated to 50 °C for 1 h and cooled to −75 °C, and the isocyanate or isothiocyanate (5 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 1–4 h and then poured over 30 g of ice layered with 30 mL of pentane. The layers were separated, and the pentane layer was washed with a 10-mL portion of $NaHCO_3$. The combined aqueous layers were acidified (H_2SO_4) and extracted ten times with CH_2Cl_2. On removal of the solvent, the crude malonamic or 3-thiomalonamic acids were crystallized from a CH_2Cl_2–pentane mixture. The melting points and the ^1H NMR data for the malonamic acids (4, X = O) and the 3-thiomalonamic acids (4, X = S) prepared by this procedure are tabulated in Table III.

B. Lithium Naphthalenide. Identical with general procedure A, except the addition of TMEDA was omitted.

C. Lithium Diisopropylamide. Diisopropylamine (1.40 mL, 10 mmol) was added to 50 mL of dry THF under a nitrogen blanket, and the mixture was cooled to −75 °C. A 2.31 M *n*-butyllithium solution (4.33 mL, 10 mmol) was added, and the mixture was stirred 0.5 h at −75 °C. The carboxylic acid (5 mmol) was added as a solution in 10 mL of dry THF at −75 °C, and the reaction mixture was then heated for 1 h at 50 °C. The mixture was recooled to −75 °C, and phenyl isocyanate (5 mmol) was added. The reaction mixture was then stirred at room temperature for 2 h and then poured over 30 g of ice layered with 30 mL of pentane. The pentane layer was washed with aqueous $NaHCO_3$. On removal of the pentane the urea **5**, mp 110–122 °C (lit.[17] mp 110–112 °C), could be obtained (50% yield from propionic, isobutyric, and phenylacetic acids). The isolation of the malonamic acids followed procedure A.

***N,N*-Diisopropyl-*N'*-phenylurea (5).** Phenyl isocyanate (0.60 g, 5 mmol) and diisopropylamine (0.50 g, 5 mmol) were dissolved in 25 mL of dry THF at −75 °C and the mixture was stirred for 10 min. After the mixture warmed to room temperature, the THF

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Table III. Data for the Malonamic Acids (4, X = O) and the Thiomalonamic Acids (4, X = S)

Melting Point and NMR Data

compd[a]	mp, °C	^1H NMR (δ, $CDCl_3$-Me_2SO-d_6)
4a	133–133.5	1.56 (s, 6 H), 7.12–7.60 (m, 6 H), 9.16–9.60 (br s, 1 H)
4b	88.5–89	0.88 (t, 3 H), 1.40–1.70 (m, 8 H), 3.20 (m, 2 H), 6.8–6.9 (br s, 1 H), 10.8–11.0 (br s, 1 H)
4c	129.5–130	4.92 (s, 1 H), 6.6–7.0 (br s, 1 H), 7.3–7.9 (m, 10 H), 10.0–10.2 (br s, 1 H)
4d	97.5–98	0.8 (t, 3 H), 1.44 (m, 2 H), 3.16 (m, 2 H), 4.24 (s, 1 H), 7.24 (s, 5 H), 10.3–10.9 (br s, 1 H)
4e	157.5–158	1.44 (d, 3 H), 3.60 (q, 1 H), 7.2–8.0 (m, 6 H), 9.8–10.0 (br s, 1 H)
4f	103.5–104	0.96 (t, 3 H), 1.4–1.7 (m, 5 H), 3.16–3.48 (m, 3 H), 7.2–7.6 (br s, 1 H), 9.8–10.0 (br s, 1 H)
4g	151–151.5	1.2–2.4 (m, 10 H), 7.2–8.0 (br m, 5 H), 8.6–8.8 (br s, 1 H), 10.1–10.4 (br s, 1 H)
4h	119–119.5	0.98 (t, 3 H), 1.2–2.0 (br m, 12 H), 3.21 (m, 2 H), 6.9–7.2 (br s, 1 H), 10.5–10.8 (br s, 1 H)
4i	105.0–106	1.56 (s, 6 H), 3.16 (d, 3 H), 8.9–9.2 (br s, 1 H), 10.0–10.3 (br s, 1 H)
4j	95.5–96.0	3.12 (d, 3 H), 5.04 (s, 1 H), 7.1–7.3 (m, 5 H), 9.2–9.6 (br s, 1 H), 9.7–10.0 (br s, 1 H)
4k	116–116.5	1.2–2.2 (m, 10 H), 3.16 (d, 3 H), 7.6–7.8 (br s, 1 H), 10.0–10.4 (s, 1 H)
4l	90.5–91.0	1.80 (s, 6 H), 6.0–6.4 (br s, 1 H), 7.3–7.5 (m, 4 H), 7.7–8.0 (m, 3 H), 10.4–10.6 (br s, 1 H)
4m	132.5–133	4.32 (s, 1 H), 7.2–7.6 (m, 9 H), 7.7–8.0 (m, 4 H), 10.0–10.2 (br s, 1 H)

Analytical Data

	calcd		found	
compd	C	H	C	H
4a	63.75	6.32	63.49	6.28
4b	55.47	8.73	55.48	8.49
4c	70.58	5.13	70.16	5.36
4d	65.14	6.83	65.05	6.83
4e	62.16	5.74	62.29	5.80
4f	52.81	8.23	52.91	8.40
4g	67.99	6.93	67.66	7.25
4h	61.94	8.98	61.89	9.14
4i	44.71	6.88	44.71	6.98
4j	57.41	5.30	57.75	5.42
4k	53.72	7.51	53.89	7.68
4l	65.92	5.53	65.84	5.50
4m	71.02	4.71	70.80	4.65

[a] Satisfactory analytical data were obtained for all compounds.

was removed at reduced pressure, yielding 1.06 g (97%) of the urea **5**, mp 112-113 °C (lit.[17] mp 110-112 °C). The NMR spectrum of the urea fit the structure nicely.

Preparation of α-n-Butylcyclohexanecarboxylic Acid. A. Using LDA. Diisopropylamine (1.40 mL, 10 mmol) was added to 50 mL of dry THF at -75 °C. To this solution was added 4.33 mL (10 mmol) of 2.3 M *n*-butyllithium, and the mixture stirred at -75 °C for 0.5 h. Cyclohexanecarboxylic acid (0.64 g, 5 mmol) was added as a THF solution, and the mixture was heated to 50 °C for 1 h. The reaction was cooled to -75 °C and *n*-butyl bromide (0.54 mL, 5 mmol) added neat. The mixture was stirred for 2 h at room temperature, and the product was isolated as in general procedure A. An 85% yield of alkylated acid (0.79 g) was isolated.

B. Using Lithium Naphthalenide-TMEDA. Lithium metal (0.69 g, 10 mmol) was added to a solution of naphthalene (1.28 g, 10 mmol) in 50 mL of dry THF. The mixture was stirred at room temperature for 2 h, TMEDA (1.5 mL, 10 mmol) was added at room temperature, and the mixture was stirred for 0.5 h. Cyclohexanecarboxylic acid (0.64 g, 5 mmol) was added at room temperature, and the mixture was heated to 50 °C for 1 h. The reaction was cooled to -75 °C, and *n*-butyl bromide (0.54 mL, 5 mmol) was added. The mixture was stirred at room temperature for 2 h, and the product was isolated as described in general procedure A. An 85% yield of the alkylated acid (0.79 g) was isolated.

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Registry No. **1** ($R_1 = R_2 = CH_3$), 79-31-2; **1** ($R_1 = C_6H_5$, $R_2 = H$), 103-82-2; **1** ($R_1 = R_2 = (CH_2)_5$), 98-89-5; **1** ($R_1 = CH_3$, $R_2 = H$), 79-09-4; **4a**, 72708-59-9; **4b**, 72708-60-2; **4c**, 41951-10-4; **4d**, 72708-61-3; **4e**, 15601-92-0; **4f**, 72708-62-4; **4g**, 2719-28-0; **4h**, 72708-63-5; **4i**, 72708-64-6; **4j**, 72708-65-7; **4k**, 72708-66-8; **4l**, 72708-67-9; **4m**, 72708-68-0; **5**, 1461-81-0; phenyl isocyanate, 103-71-9; propyl isocyanate, 110-78-1; methyl isothiocyanate, 556-61-6; 1-naphthyl isothiocyanate, 551-06-4; diisopropylamine, 108-18-9; α-*n*-butylcyclohexanecarboxylic acid, 62410-48-4.

Conversion of Secondary Furfuryl Alcohols and Isomaltol into Maltol and Related γ-Pyrones

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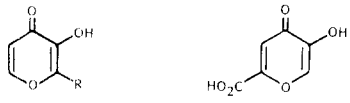
A one-pot synthesis of maltol and ethylmaltol is reported. Treatment of methylfurfuryl alcohol with 2 equiv of halogen affords good yields of 4-halo-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-ones (**8**), which need not be isolated and can be converted to maltol by aqueous hydrolysis in the same vessel. A similar sequence employing ethylfurfuryl alcohol yields ethylmaltol. By a related series of reactions, isomaltol (**9**) can be converted to maltol.

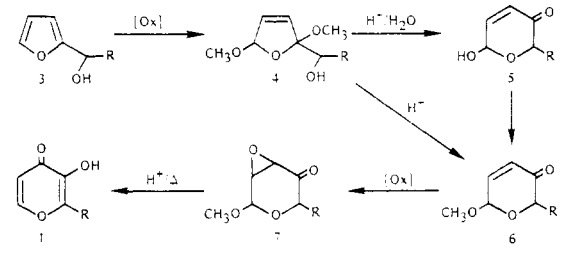
Maltol (**1**, R = CH_3; 2-methyl-3-hydroxy-4*H*-pyran-4-one) is a naturally occurring substance found in the bark of young larch trees, pine needles, and chicory.[1] Maltol and its homologue ethylmaltol (**1**, R = CH_2CH_3) are important commercial flavor and aroma agents used in a variety of food products. Early commercial production of maltol was from the destructive distillation of wood. The



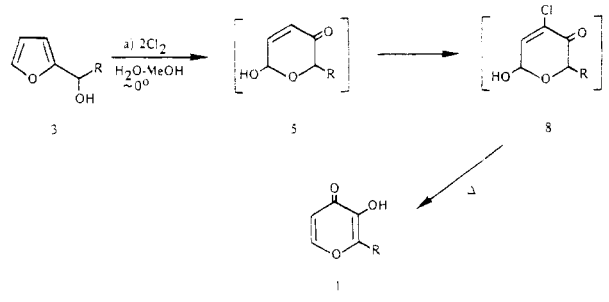
1 **2**

first synthesis of maltol was reported by Spielman and Freifelder[2] and involved the alkylation of pyromeconic acid (**1**, R = H), which had been derived from comenic acid (**2**), a fermentation product. A superior modification of this process was developed by Tate and Miller of these laboratories.[3] Subsequently, several novel syntheses of the γ-pyrone derivatives **1** have appeared in the patent literature;[4] in addition, several carbohydrate routes have been published.[5,6] Recently two similar furfuryl alcohol based syntheses have appeared, one[7] employing the known[8] **4** to **5** rearrangement and the other[9] employing the direct conversion of **4** to **6** as outlined in Scheme I.

Scheme I



Scheme II



Inasmuch as 3-hydroxy-4*H*-pyran-4-ones **1** are formally only two oxidations and a rearrangement removed from

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(2) M. A. Spielman and M. Freifelder, *J. Am. Chem. Soc.*, **69**, 2908 (1947).
(3) B. E. Tate and R. L. Miller, U.S. Patent 3 130 204 (1964).
(4) (a) A. A. Schleppnik and M. L. Oftedahl, U.S. Patents 3 621 063 (1971), 3 491 122 (1970), 3 949 959 (1970), 3 455 960 (1969), 3 468 914 (1969), 3 476 778 (1969), 3 474 113 (1969). (b) I. Takasa, M. Higuchi, and H. Hotta, U.S. Patent 3 665 015 (1972).
(5) R. K. Chawla and W. E. McGonigal, *J. Org. Chem.*, **39**, 3281 (1974).
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(8) O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, *Tetrahedron*, **27**, 1973 (1971).
(9) R. P. Allingham and P. D. Weeks, Belgium Patent 843 953 (1977); P. D. Weeks, D. E. Kuhla, R. P. Allingham, H. A. Watson, and B. Wlodecki, *Carbohydr. Res.*, **56**, 195 (1977).

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