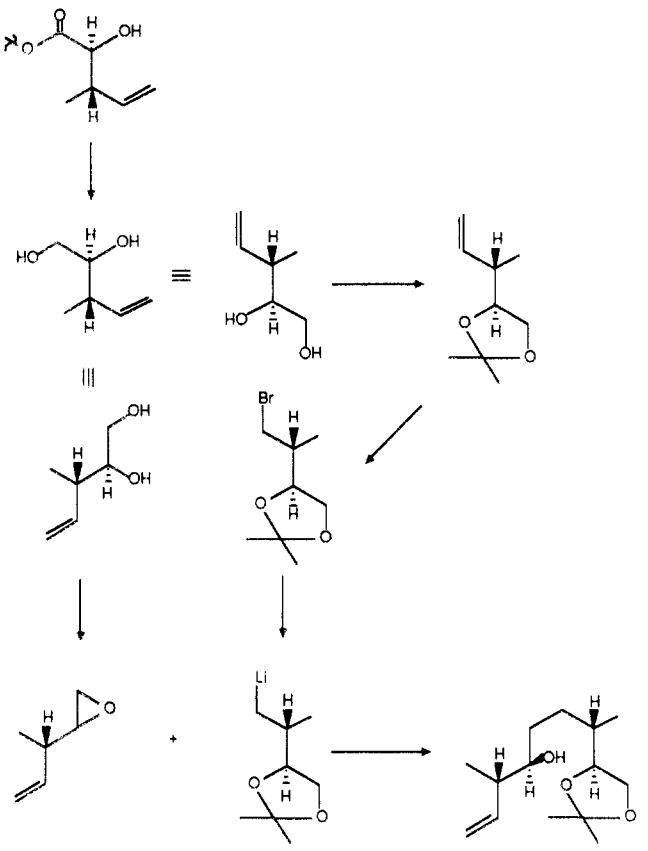
Scheme XV



Application to Total Synthesis

The implementation of the ene reaction process within the framework of absolute asymmetric synthesis is well illustrated by the synthesis of the left half of the antibiotic X-14547-A.[19] Each of the subunits that are illustrated in Scheme XIV had previously been prepared in racemic form.[20] As a consequence, their combination resulted in a mixture of four stereoisomers (as two mirror-image pairs) where only approximately one fourth of the product mixture is constituted with both the correct relative as well as absolute stereochemistry. Application of asymmetric induction to the synthesis of each of these fragments results in essentially a single stereoisomer, and thus only one stereoisomer can be formed upon their combination. It is important to note that the ability to select for either the threo or the erythro diastereomer in the ene reaction and the fact that epoxides can be formed from glycols with either retention or inversion of stereochemistry combine to provide access with essentially equal facility to any one of the 16 possible stereoisomers of the pyran ring with its four stereochemical centers. Thus, the question of both relative as well as absolute stereochemical control has thus been lifted from the confines of a specific target and has been solved in a quite general way.

It should be clear that significant progress has occurred in the past decade in the design and application of asymmetric induction to synthetic endeavors, and indeed the results described here represent only a portion the growing arsenal of methods for carbon–carbon bond formation with antisymmetric induction. However, much remains to be accomplished and the area of stereochemical control will reach maturity only when a full cornucopia of techniques are available.

It has been my pleasure during the course of many years to have been associated with a loyal, dedicated, and perseverant group of researchers to whom belongs the credit for the successful chemistry described above. Funding has been provided by the Research Corp., the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Robert A. Welch Foundation (F-626), and the National Institutes of Health (GM-31750).

(19) Westley, J. W.; Evans, R. H.; Sello, L. H.; Troupe, N.; Liu, C. H.; Blount, J. F. *J. Antibiot.* **1979**, *32*, 100.

(20) Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90.

Oxoalkylation of Carbonyl Compounds with Conjugated Nitro Olefins

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Carbon–carbon bond-forming processes involving nitro aliphatics are of increasing importance because of the remarkable versatility of nitro groups in their conversion into a variety of organic functional groups. For example, nitro olefins have been well documented as versatile and prominent acceptors in conjugated addition reactions.[1] The addition of a nucleophile (NuH) to a nitro olefin **1** results in the formation of a saturated nitro compound **2**, which is readily convertible

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(1) For general reviews on the synthesis and chemistry of conjugated nitro olefins, see H. H. Bauer and L. Urbas, "The Chemistry of the Nitro and Nitroso Groups", part 2, H. Feuer, Ed., Interscience, New York, 1970, pp 75–200. (b) O. Schickh, G. Apel, H. G. Padeken, H. H. Schwarz, and A. Segnitz, "Methoden der Organischen Chemie (Houben-Weyl)", E. Müller, Ed.; Georg Thieme Verlag, Stuttgart, 1971, Vol. 10/1, pp 9–462. (c) J. Kochany. *Wiad. Chem.*, **32**, 723 (1978). (d) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979).

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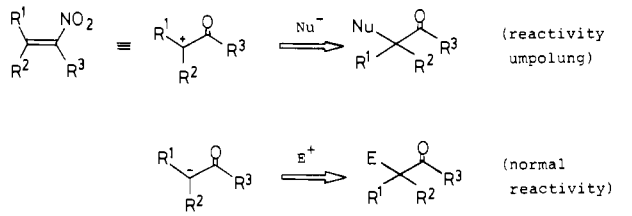
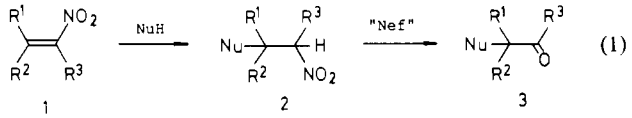


Figure 1. Reactivity umpolung of the carbonyl α-carbon with nitro olefin vs. normal reactivity.

to a variety of compounds such as amines, aldehydes, ketones, oximes, amides, nitriles, etc. (eq 1). Among



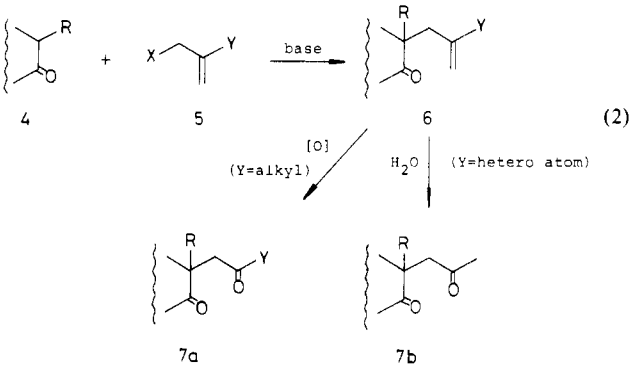
(1)

these compounds, ketones **3**, inter alia, are useful intermediates in organic synthesis. Nitro groups are synthetically equivalent to carbonyl groups because of the ready accessibility of ketones **3** from **2** by the Nef reaction or other methods;[1d] hence the overall transformation of NuH into **3** thus constitutes an oxoalkylation of the former. The nitro olefins **1**, in this sense, are masked electrophilic oxoalkylating agents. In other words, **3** can be regarded as the nucleophilic α-substitution product of carbonyl compounds with NuH. This reaction sequence illustrates a reactivity umpolung of the carbon α to carbonyl (Figure 1).[1d]

On the basis of this concept, we have intensively investigated the reaction of nitro olefins as oxoalkyl synthons with reactivity umpolung and their practical utility for a new development of nitro aliphatic chemistry.

If a carbanion is employable in eq 1 as the Nu, this reaction should provide an efficient means for carbon–carbon bond formation. At the outset of our study, however, such a conjugate addition of carbanions generated from *monofunctional carbonyl compounds* such as ketones, esters, lactones, amides, etc. to aliphatic nitro olefins was unprecedented,[2] presumably because of the high susceptibility of these nitro olefins to conventional, strong alkaline media requisite for the generation of such carbanions, although the addition of active methylene compounds including malonates, acetoacetates, and 1,3-diones to nitro olefins is known.[1a] To circumvent this difficulty, our first attention was focused on finding alternative, nonbasic reaction conditions that effect the expected addition reaction.

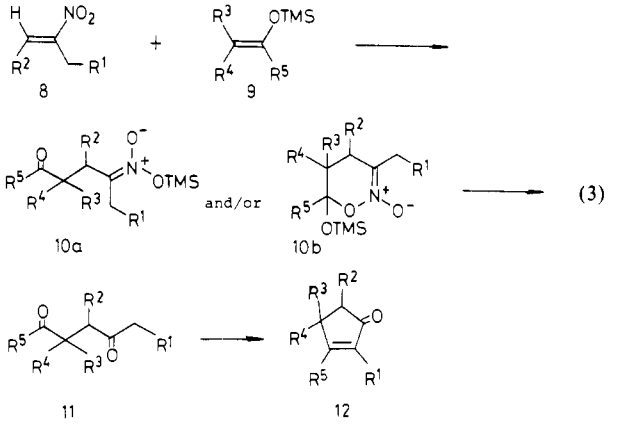
Lewis Acid-Promoted Addition of Silyl Enol Ethers or Ketene Silyl Acetals to Nitro Olefins. Novel Synthesis of 1,4-Dicarbonyl Compounds.[3] Cyclopentenones and furans are useful intermediates for the synthesis of a variety of organic molecules and are most conveniently prepared by intramolecular condensation of 1,4-dicarbonyl compounds. While many synthetic methods of 1,4-diones are known, those using monoketones are relatively limited in number. A representative method is the alkylation of monoketones **4** with allylic halides **5** in which Y is a hetero atom[4a] or a group connected with the double bond through a heteroatom.[4b] In order to obtain 1,4-diones **7a** or **7b**, alkylation product **6** must be oxidized when Y is an alkyl substituent or hydrolyzed when Y is a heteroatom or a heteroatom group (eq 2). This method is an in-



(2)

direct multistep synthesis, and one can readily see that the second step may not be applicable to **6** involving other functional groups susceptible to oxidative or hydrolytic treatment. In addition, the alkylation of **4** generally suffers from its ambiguous regiospecificity (C- vs. O-alkylation and regioselectivity in the C-alkylation of unsymmetrically substituted ketones).

Having the above problem in mind, we set about the straightforward oxoalkylation of monoketones employing nitro olefins under nonbasic conditions. Since nitro olefins, fortunately, are fairly stable in acidic media, our attention was attracted to the Lewis acid promoted reaction of silyl enol ethers, which are synthetically equivalent to ketone enolates,[5] with nitro olefins (eq 3). If the conjugate addition of a silyl enol



(3)

ether **9** to a nitro olefin **8** is feasible, silyl nitronate **10a** or **10b** would be the product, which has the structure similar to a Nef reaction intermediate. We thus presumed that the adduct should be readily hydrolyzed in the same flask by simply treating with water to give a 1,4-dione **11**.

To find optimal reaction conditions, 1-((trimethylsilyl)oxy)-1-cyclohexene and 2-nitropropene were employed as model substrates. The reaction, conducted in the presence of a Lewis acid in dichloromethane at −78 °C, followed by treatment with water at reflux gave,

(2) Independently of us, Seebach and co-workers reported the Michael addition of lithium *N,N*-dialkylacetamides to aliphatic nitro olefins (D. Seebach, H. F. Leitz, and V. Ehrig, *Chem. Ber.*, **108**, 1924 (1975)) and to aromatic nitro olefins (D. Seebach and H. F. Leitz, *Angew. Chem., Int. Ed. Engl.*, **10**, 501 (1971). D. Seebach, V. Ehrig, H. F. Leitz, and R. Henning, *Chem. Ber.*, **108**, 1946 (1975)).

(3) M. Miyashita, T. Yanami, T. Kumazawa, and A. Yoshikoshi. *J. Am. Chem. Soc.*, **106**, 2149 (1984).

(4) For example, see (a) M. Kobayashi and T. Matsumoto, *Chem. Lett.*, 957 (1973) and references cited; (b) R. M. Jacobson, R. A. Rath, and J. H. McDonald III, *J. Org. Chem.*, **42**, 2545 (1977) and references cited.

(5) (Review) J. K. Rasmussen, *Synthesis*, 91 (1977).

Table I.
Synthesis of 1,4-Diones and Cyclopentenones from Nitro Olefins and Silyl Enol Ethers

8		silyl enol ether 9			Lewis	% yield	
R^1	R^2	R^3	R^4	R^5	acid[a]	11	12
H	H				$SnCl_4$	85	83
Me	H	H		$-(CH_2)_4-$	$TiCl_4$	76	89
H	Me				$AlCl_3$	63	80
H	H				$TiCl_4$	70	93
Me	H	Me		$-(CH_2)_4-$	$TiCl_4$	82	87
H	Me				$SnCl_4$	71	85
H	H	H		$-(CH_2)_3CHMe-$	$SnCl_4$	63	81
H	H	H	H	$Me(CH_2)_5-$	$SnCl_4$	65	80
H	H	H		$-(CH_2)_3-$	$SnCl_4$	70	
H	H	Me		$-(CH_2)_3-$	$SnCl_4$	41	79
Me	H					41	88

[a] Only the Lewis acid which gave the best results are listed (ref 3 for details).

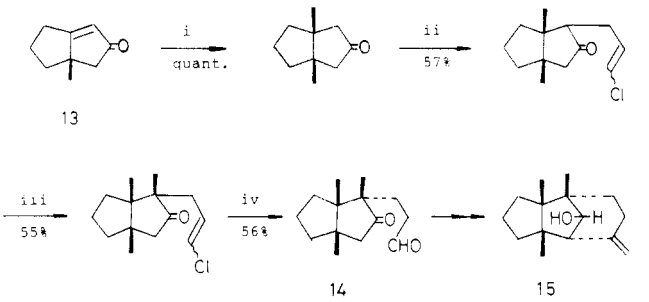
as anticipated, 2-acetonylcyclohexanone in a one-pot operation. A variety of Lewis acids and solvents were screened, and we found that $TiCl_4$ or $SnCl_4$ afforded an excellent yield of the dione. $AlCl_3$ was somewhat less effective, while BF_3 etherate, benzyltrimethylammonium fluoride,[6] trimethylsilyl triflate,[7] and trimethylsilyl iodide[8] were all noneffective in this reaction. Dichloromethane was the preferred solvent.

With these optimum conditions in hand, a variety of combinations of nitro olefins[9] and silyl enol ethers were submitted to the reaction, and various 1,4-diones were obtained in good yields (Table I).[10] The diones obtained here were submitted to alkaline cyclization to provide various cyclopentenones **12**. Thus a sequence of these reactions was proven an efficient and regiospecific cyclopentenone annulation method starting with ketones because silyl enol ethers are readily available from ketones in a regiospecific manner.[5]

An important feature of the present method is that nitro olefins are available from nitro alkanes via an aldol-type addition with carbonyl compounds (Henry reaction) followed by dehydration[1] or by other methods recently reported,[1d,11] whereas other oxoalkylating agents known hitherto are not always readily accessible.

Our interest was then directed to the disclosure of the reaction intermediates, silyl nitronates **10**, but these were susceptible to hydrolysis and were difficult to isolate in pure form.[12-14] In an experiment of the

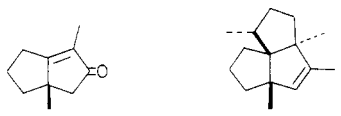
Chart I.[a] Total Synthesis of Gymnomitrol



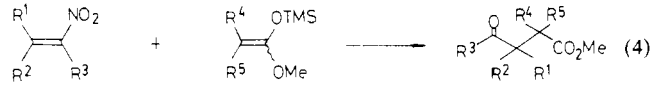
[a] i, Me_2CuLi; ii, 1,3-dichloropropene, $NaNH_2$; iii, MeI, $NaNH_2$; iv, $Hg(OAc)_2$, HCO_2H.

aforementioned model substrates using $AlCl_3$ as the Lewis acid, the silyl nitronate was isolated by working up with aqueous K_2CO_3 as a gum, free from the hydrolysis product. Its IR and ^1H NMR spectra revealed the presence of nitronate, trimethylsilyl, and olefinic methyl groups, demonstrating unequivocal intermediacy of **10a** and/or **10b** ($R^1 = R^2 = R^3 = H$, R^4–$R^5 = (CH_2)_4$) in the reaction.[13]

The versatility of the present cyclopentenone annulation sequence was demonstrated by the following syntheses of natural polyquinanes. Bicyclic ketone **13**, obtained from 2-methylcyclopentanone, was transformed into keto aldehyde **14**[15] which has been reported by two groups[16] as the key intermediate for the synthesis of gymnomitrol (**15**) (Chart I). The same ketone **13** was also employed in an alternative synthesis of **15**.[17] Another bicyclic ketone **16** was used by Paquette and Han as the starting material in the synthesis of isocomene (**17**).[18]



The present methodology was then extended to the reaction of ketene silyl acetals **18** with nitro olefins **1** in the hope of the one-step formation of γ-keto esters **19**, which are potential synthetic precursors for γ-lactones, 1,3-cyclopentanediones, and cyclopentenones as well as heterocycles such as pyrrolidines, 1,2-pyrazines, etc. (eq 4). Although a number of synthetic methods



for γ-keto esters are available, they are not necessarily satisfactory for the preparation of α- and/or β-alkylated

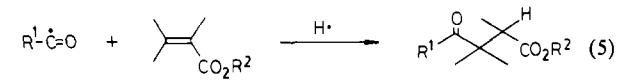
(6) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975).
(7) (Review) R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, **37**, 3899 (1981).
(8) (Review) A. Hosomi, *Yuki Gosei Kagaku Kyokaishi*, **40**, 545 (1982).
(9) Volatile aliphatic nitro olefins frequently used in this work were conveniently prepared by dehydration of the corresponding β-nitro alcohols by distilling them from phthalic anhydride (G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1974)), and we enabled to considerably improve their yields by the use of a slight excess (1.3 equiv) of phthalic anhydride (M. Miyashita, T. Yanami, and A. Yoshikoshi, *Org. Synth.*, **60**, 101 (1981)). 2-Nitro-1-propanol and 3-nitro-2-butanol are commercially available (Aldrich Chemicals, No. 14759-1 and 14664-1).
(10) (Preparation in a large scale) M. Miyashita, T. Yanami, and A. Yoshikoshi, *Org. Synth.*, **60**, 117 (1981).
(11) E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, **100**, 6294 (1978); P. Knochel and D. Seebach, *Nouv. J. Chim.*, **5**, 75 (1981); T. Hayama, S. Tomoda, and Y. Takeuchi, *Tetrahedron Lett.*, **23**, 4733 (1982) and references cited.
(12) Trimethylsilyl nitronates of secondary nitroalkanes are known to be less stable than those derived from primary ones. E. W. Colvin and D. Seebach, *J. Chem. Soc., Chem. Commun.*, 689 (1978).
(13) Stable cyclic silyl nitronates were very recently prepared from 1-((trimethylsilyl)oxy)cyclohexene and β-nitrostyrene. D. Seebach and M. A. Brook, *Helv. Chim. Acta*, **68**, 319 (1985).
(14) Analogous cyclic nitronic esters prepared from enamines and 2-nitropropene have been known. A. Risalti, M. Forchiassin, and E. Valentin, *Tetrahedron*, **24**, 1889 (1968).
(15) M. Miyashita, T. Yanami, S. Yonishi, and A. Yoshikoshi, unpublished results.
(16) L. A. Paquette and Y.-K. Han, *J. Am. Chem. Soc.*, **103**, 1831 (1981); R. M. Coates, S. K. Shah, and R. W. Mason, *ibid.*, **104**, 2198 (1982).
(17) S. C. Welch, S. Chayabunjonglerd, and A. S. C. Prakasa Rao, *J. Org. Chem.*, **45**, 4086 (1980).
(18) L. A. Paquette and Y.-K. Han, *J. Org. Chem.*, **44**, 4014 (1979).

Table II.
Selected Examples of the γ-Keto Ester Synthesis from Nitro Olefins and Ketene Methyl Trimethylsilyl Acetals

entry	nitro olefin 1 R¹	R²	R³	ketene silyl acetal 18 R⁴	R⁵	% yield of γ-keto ester 19
1	H	H	Me			64
2	H	-(CH₂)₄-		Me	H	70
3	Me	-(CH₂)₄-				73
4	H	H	Et			68
5	H	-(CH₂)₄-		Me	Me	25
6	Me	-(CH₂)₄-				0
7	H	H	Me	Ph	H	82
8	H	H	Me	Me(CH₂)₇-	H	84
9	H	H	Me	-(CH₂)₅-		79
10	H	H	Me	CH₂=CH-	Me	46

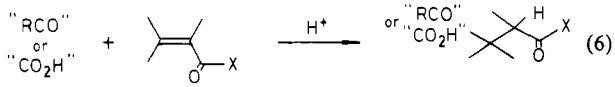
derivatives due to their intrinsic methodological limitations.

The known one-step construction of γ-keto esters is the addition of acyl radicals generated from aldehydes to unsaturated esters (eq 5).[19] Obviously α,α-dialkyl



(5)

γ-keto esters are out of the scope of its application. Another methodology, which one can more frequently encounter in the literature, is the conjugate addition of acyl- or carboxy-equivalent nucleophiles to unsaturated carbonyl counterparts giving masked γ-keto acid derivatives, which are then hydrolyzed to afford the desired keto acids (eq 6).[20] In these multistep syntheses,



(6)

the attendant problem is limited availability of the unsaturated compounds.

Some improvements of reaction conditions were necessary to perform the oxoalkylation of ketene silyl acetals with nitro olefins. Since ketene silyl acetals are generally more sensitive to acidic environment than silyl enol ethers, the reaction conditions applied to the latters caused hydrolysis of the formers. Ultimately we found that a mixture of $TiCl_4$ and $(i\text{-PrO})_4Ti$ in a molar ratio of 1:1[21] most effectively promoted the desired reaction in CH_2Cl_2 at −78 °C and that subsequent hydrolysis of the adduct was smoothly conducted in aqueous DME. Yields of γ-keto esters obtained under the optimized conditions were listed in Table II.

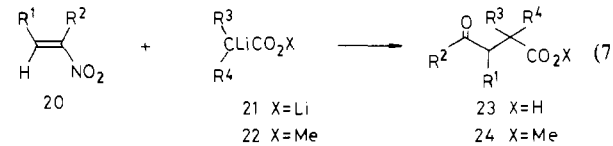
Table II demonstrates that β-substituents of nitro olefins are not large obstacles in the reaction with β-monosubstituted ketene silyl acetals (entries 2 and 3), whereas in the reaction with β-disubstituted ketene silyl acetals, β-substituents considerably impeded the addition reaction (entries 5 and 6). It was noteworthy that methylvinylketene silyl acetal, a conjugated silyloxy diene, added regiospecifically to 2-nitropropene at the β-position of the former yielding methyl α-methyl-α-vinyllevulinate (entry 10). This product was successfully applied to the total synthesis of curzerenone and its analogues (vide post).

Table III.
Selected Examples of the γ-Keto Acid Synthesis from Nitro Olefins and Carboxylic Acid Dianions

nitro olefin 20 R¹	R²	carboxylic acid dianion 21 R³	R⁴	% yield of γ-keto acid 23
H	Me	H	Me(CH₂)₄-	65
-(CH₂)₄-		H	Et	43
H	Me	Me	Me(CH₂)₂-	46
H	Me	-(CH₂)₅-		37
H	Me	H	Ph	88
-(CH₂)₄-				72
H	Me			80
Me	Me	H	PhS	64
-(CH₂)₄-				76
H	Me	Me	PhS	55
-(CH₂)₄-				37

We thus secured a new and efficient preparation of α- and/or β-substituted γ-keto esters involving α,α-disubstituted ones from various ketene silyl acetals.[22]

Conjugate Addition of Carboxylic Acid Dianions or Ester Enolates to Nitro Olefins.[23] While we had established the Lewis acid promoted oxoalkylation of silyloxy olefin-type substrates with nitro olefins as mentioned above, our effort was also devoted to finding appropriate reaction conditions that allow the addition of carbanion themselves to nitro olefins for the facile synthesis of the 1,4-dicarbonyl function (eq 7).



(7)

Model experiments using the lithium dianion **21** of a typical carboxylic acid generated in THF with LDA demonstrated that a low temperature (−100 °C) is required to suppress the polymerization of nitro olefin **20**[24] and also that the addition of HMPT is essential to effect the reaction. Hydrolysis of the reaction mixture with dilute HCl afforded the expected γ-keto acid **23**. A variety of γ-keto acids were thus obtained as listed in Table III.

As a remarkable observation, both dianions of phenylacetic and (phenylthio)acetic acids were more efficiently generated by means of BuLi than LDA and gave, without HMPT, the corresponding γ-keto acids in good yields, respectively. Potential Michael acceptors **25** for the cyclenone annulation[23,25] were easily prepared

(19) (Recent example) H. Cerfontain and P. C. M. Noort, *Synthesis*, 490 (1980).

(20) A variety of acyl- and carboxy-equivalent reagents have recently been reported. For example, J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973); A.-R. B. Manas, and R. A. J. Smith, *J. Chem. Soc., Chem. Commun.*, 216 (1975); C. G. Chavdarian and C. H. Heathcock, *J. Am. Chem. Soc.*, **97**, 3822 (1975); R. K. Boeckman, Jr. and K. J. Bruza, *J. Org. Chem.*, **44**, 4781 (1979).

(21) K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).

(22) C. Ainsworth, F. Chen, and Y.-N. J. Kou, *J. Organomet. Chem.*, **46**, 59 (1972).

(23) M. Miyashita, R. Yamaguchi, and A. Yoshikoshi, *J. Org. Chem.*, **49**, 2857 (1984).

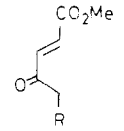
(24) Such a low temperature also enabled the conjugate addition of lithium anions of *N,N*-dialkylamides, ketones, and esters to nitro olefins.[2]

(25) J. E. McMurry and L. C. Blaszczak, *J. Org. Chem.*, **39**, 2217 (1974).

Table IV.
Selected Examples of the γ-Keto Ester Synthesis from Nitro Olefins and Ester Enolates

nitro olefin 20		ester enolate 22		% yield of
R^1	R^2	R^3	R^4	
H	Me	H	$Me(CH_2)_3$-	81
$-(CH_2)_4$-				54
H	Me	$-(CH_2)_5$-		53
H	Me	H	Ph	79
$-(CH_2)_4$-				61
H	Me	H	Ph	65
$-(CH_2)_4$-				52

from these products **23** (R^1 = H, R^2 = Me or Et, R^3 = SPh, R^4 = H) on oxidation followed by thermal elimination of phenylsulfenic acid.

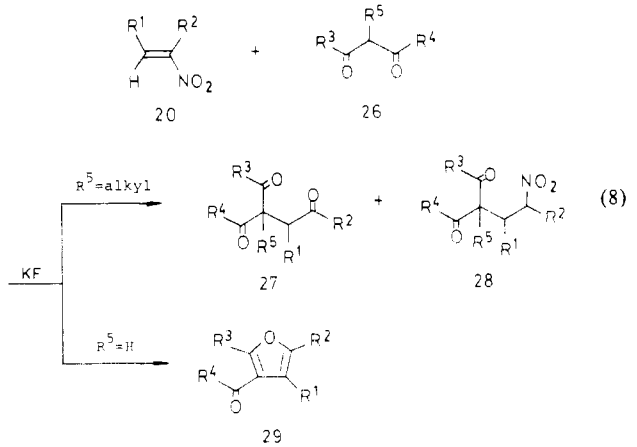


25 R=H or Me

On the other hand, ester lithium enolates **22** reacted with nitro olefins **20** in a similar fashion at low temperature yielding γ-keto ester **24** (eq 7, Table IV).

Attempted oxoalkylation of the lithium enolate of cyclohexanone with 2-nitropropene, however, was fruitless under similar conditions, and we were frustrated in effecting the reaction of aliphatic monoketone enolates with nitro olefins.[26]

Reaction of Nitro Olefins with 1,3-Dicarbonyl Compounds: Synthesis of Tricarbonyl Compounds and Acylfurans. We found that the dicarbonyl compounds **26** themselves successfully reacted with nitro olefins **20** by use of KF as a base to afford tricarbonyl compounds **27**[27,28] or acylfurans **29**[27,29] depending on the presence or the absence of 2-alkyl substituents on the substrates, respectively (eq 8).



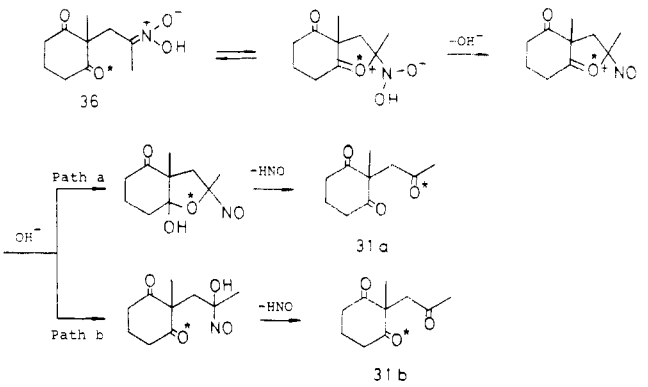
20 26 27 28 29 (8)

While 2-methylcyclohexane-1,3-dione, a typical 2-alkyl-1,3-dione, gave initially a mixture of nitro dione

Table V.
Synthesis of Tricarbonyl Compounds from Nitro Olefins and 2-Alkyl 1,3-Dicarbonyl Compounds

	nitro olefin 20		dicarbonyl compd 26			% yield tricarbonyl compd	% yield nitro dione
entry	R^1	R^2	R^3	R^4	R^5	27	28
1	H	Me				96	
2	H	Et	$-(CH_2)_3$-		Me	96	
3	Me	Me				63	
4	H	Me	$-(CH_2)_3$-		Me	14	13
5	H	Me	Me	Me	Me	13	17
6	H	Me	EtO	$-(CH_2)_4$-		11	30
7	H	Me	EtO	$-(CH_2)_3$-		20	47

Chart II. Postulated Paths for the Single-Step Formation of 2-Acetonylcyclohexane-1,3-dione



36 31a 31b

30 and trione **31** in the reaction with 2-nitropropene in toluene, the prolonged reaction (19 h) provided **31** almost quantitatively at the expense of the former product (Table V, entry 1). The reaction with other nitro olefins also gave the corresponding triones in good yields (entries 2 and 3). However, yields of tricarbonyl compounds **27** were largely dependent on the nature of dicarbonyl substrates **26**, and other diones provided nitro diones **28** as the major product even in prolonged reactions (entries 4–7).

The trione **31** was converted into enedione **34** by aldol cyclization with NaH in benzene.[28] This enedione is a five-membered-ring analogue of the Wieland–Miescher ketone **35**, a valuable starting material for the synthesis of various organic compounds, and hence is a useful starting material for the synthesis of cyclopentanoids.

30 R=CH(NO$_2$)Me
31 R=COMe
32 R=CH$_2$NO$_2$
33 R=CHO

34 n=1
35 n=2

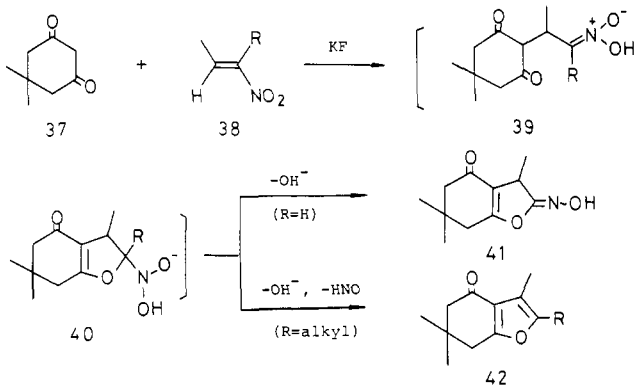
The high-yield and single-step formation of the trione **31** from 2-methylcyclohexane-1,3-dione prompted us to study the detailed mechanism of this novel Michael reaction. Both the observations that about 65% of the isotopic oxygen in the substrate **36** was transferred to the acetonyl side chain on **31a** in ^{18}O-labeled experiments[30] and that 2-methylcyclohexane-1,3-dione reacted with nitroethylene, an α-unsubstituted nitro olefin, to give only **32** instead of aldehyde **33** support two reaction

(26) Conjugate addition of monofunctional ketone enolates to base-stable, aryl-conjugated nitro olefins was reported.[2]
(27) T. Yanami, M. Kato, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 726 (1975).
(28) T. Yanami, A. Ballatore, M. Miyashita, M. Kato, and A. Yoshikoshi, *Synthesis*, 407 (1980).
(29) T. Yanami, A. Ballatore, M. Miyashita, M. Kato, and A. Yoshikoshi, *J. Chem. Soc., Perkin Trans. 1*, 1144 (1978).
(30) T. Yanami, M. Kato, M. Miyashita, A. Yoshikoshi, Y. Itagaki, and K. Matsuura, *J. Org. Chem.*, **42**, 2779 (1977).

Table VI.
Selected Examples of the 3-Acylfuran Synthesis from Nitro Olefins and 2-Unsubstituted 1,3-Dicarbonyl Compounds

nitro olefin 20		dicarbonyl compd 26 (R^5 = H)			% yield of
R^1	R^2	R^3	R^4	solv	29
		Me	Me	xylene	81
H	Me	$-(CH_2)_3-$		DME	42
		$-CH_2CMe_2CH_2-$		xylene	52
H	Et	$-CH_2CMe_2CH_2-$		xylene	48
Me	Me			DME	58
H	Me	EtO	Me	xylene	64
H	Et			DME	58
Me	Me	EtO	Me	xylene	0
				DME	65

Chart III. KF-Promoted Reactions of Dimedone with 1-Nitropropene and with Its α-Alkyl Derivatives

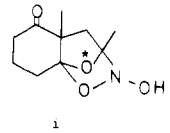


paths a and b as shown in Chart II.[31]

On the other hand, when 2-unsubstituted 1,3-dicarbonyl compounds **26** (R^5 = H) were submitted to the KF-promoted reaction, 3-acylfurans **29** were obtained directly (Table VI).[29] In the formal sense, **29** may be regarded as the product produced by an one-pot consecutive sequence of reactions, i.e., conjugate addition–Nef reaction–furan ring formation.

An interesting outcome was obtained in the KF-promoted reaction of dimedone (**37**) with 1-nitropropene **38** (R = H) which has no α-alkyl substituent.[32] The product (81% yield) was a stereoisomeric mixture of (hydroxyimino)dihydrofurans **41** instead of 3-methylfuran **42** (R = H) surmizable from the reaction with α-alkylated nitro olefins (Chart III). This result provided a mechanistic insight into the reaction as follows. The adduct **39** arising from the conjugate addition of **37** to a nitro olefin **38** cyclizes to give **40**. When R in **40** is hydrogen, elimination of hydroxide anion followed by facile nitroso–oxime tautomerization results in the formation of **41**. While an alkyl substituent (R) in **40** obviously prevents such a tautomerization, an acylfuran **42** is formed on elimination of hydroxide anion and nitroxyl.

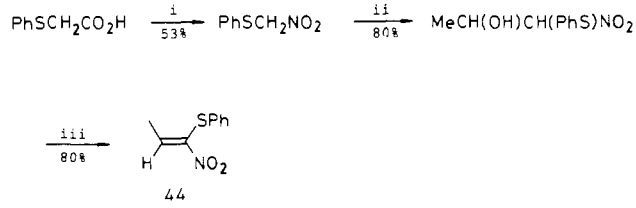
(31) As a reviewer has suggested, the dioxazolidine structure i can not be ruled out from plausible structures of the intermediate.



i

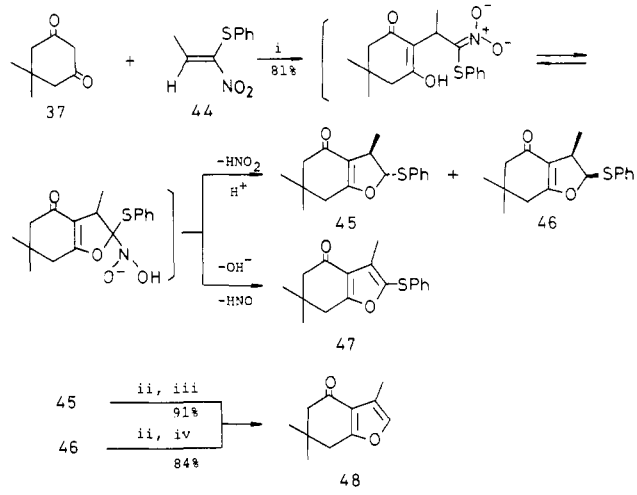
(32) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *J. Org. Chem.*, **45**, 2945 (1980).

Chart IV.[a] Preparation of 1-Nitro-1-(phenylthio)propene



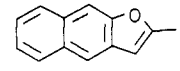
[a] i, BuLi (2.3 equiv), $PrONO_2$ and then HOAc; ii, KOH, MeCHO and then HOAc; iii, MsCl, Et_3N.

Chart V.[a] Synthesis of 3-Methylfuran with 1-Nitro-1-(phenylthio)propene



[a] i, KF, xylene; ii, $NaIO_4$; iii, Δ, pyridine, CCl_4; iv, Δ, pyridine, Al_2O_3, CCl_4.

Reaction of Phenols with 2-Nitropropene.[33] β-Naphthol gave naphtho[2,3-*b*]furan (**43**) in the KF-promoted reaction with 2-nitropropene in refluxing benzene (55% yield). This reaction was rather exceptional, and α-naphthol and orcinol gave no anticipated furans under similar reaction conditions, while phenol itself was inert to this reaction. We have not investigated this reaction in detail.



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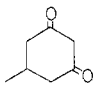
1-Nitro-1-(phenylthio)propene (44), a New Nitro Olefin Reagent for 3-Methylfuran Synthesis.[32] The mechanistic insight discussed above led us to a new nitro olefin reagent **44**. If R in **42** is not an alkyl substituent but an atom or a functional group replaceable with hydrogen, the 2-unsubstituted 3-methylfuran structure, which is widely distributed in natural products, should be readily accessible from the present furan-annulation method. We made choice of the phenylthio group as such a substituent. The required nitro olefin **44** was synthesized as shown in Chart IV.

With the desired nitro olefin in hand, we examined its reaction with dimedone (**37**) under the standard conditions (KF, toluene, 120 °C) (Chart V). Contrary to our expectations, however, the anticipated furan **47**

(33) M. Miyashita, R. Yamaguchi, and A. Yoshikoshi, unpublished results.

was only the minor product, and the major one was a separable mixture of the corresponding dihydrofurans **45** and **46** (**45**/**46**/**47** = 18:70:12). Evidently, this outcome demonstrates that the anion-stabilizing effect of the sulfur substituent accelerated elimination of nitrous acid rather than that of nitroxyl. These dihydrofurans **45** and **46**, fortunately, are potential precursors of the desired 3-methylfuran **48**, and they were transformed into **48** by the conventional procedure via the corresponding sulfoxides as shown in Chart V.

A straightforward application of this method was the synthesis of evodone (**50**), a monoterpene, from dione **49**. More complex natural furanoterpenoids, ligularone



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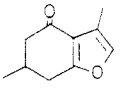

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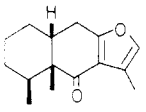
(**51**) and isoligularone (**52**), were also synthesized by the same strategy.[32] The total synthesis of curzerenone (**53**), epicurzerenone (**54**), and isocurzerenone (**55**) were also achieved by a combination of the present oxoalkylation method starting from methyl α-methyl-α-vinyllevulinate (vide ante).[34]



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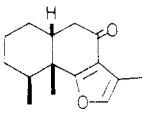

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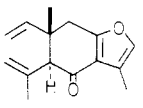

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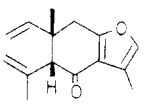

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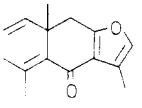

55

(34) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *J. Org. Chem.*, **49**, 3728 (1984).

Concluding Remarks

As outlined above, conjugate nitro olefins are highly efficient oxoalkylating agents, which produce a variety of oxoalkylation products depending on substrates in a one-pot operation. In comparison with the conjugate addition of carbon nucleophiles to unsaturated carbonyl systems, another characteristic feature of the present oxoalkylation lies in the formation of products which are one-carbon shorter congeners of those derived from the former reaction. In other words, oxoalkylation products obtainable by the reaction of unsaturated carbonyl electrophiles are 1,5-dicarbonyls, cyclohexenones, pyrans, etc., while those obtained by nitro olefin electrophiles are, in contrast, 1,4-dicarbonyls, cyclopentenones, furans, etc. The present oxoalkylation utilizing nitro olefins thus provides a useful methodology complementary to the reactions of unsaturated carbonyl systems.

Many functional groups seem to be compatible with the reaction conditions employed due to mildness.

Another interest lies in nitro olefins involving heteroatom substituents. As observed in the reaction of dicarbonyl compounds with nitro olefin **44**, the sulfur substituent distinctly altered the reaction course. Preparation of other heteroatom-substituted nitro olefins and their reactions await further investigation.[35]

We are grateful to acknowledge the skillful contribution of the collaborators whose names are mentioned in the references. Much of this work was supported by Grants-in-Aid for Scientific Research.

(35) (Preparations and reactions of some heteroatom-substituted nitro olefins)(nitro enamines) S. Rajappa, *Tetrahedron*, **37**, 1453 (1981); M. Faulques, L. Rene, and R. Royer, *Synthesis*, 260 (1982); A. Krôwczyński and L. Kozerski, *ibid.*, 489 (1983); (sulfur-substituted nitro olefins) W. D. Emmons and J. P. Freeman, *J. Org. Chem.*, **22**, 456 (1057); H. Fugimoto, Y. Tominaga, Y. Natsuda, and G. Kobayashi, *Heterocycles*, **6**, 376 (1977): (selenium-substituted nitro olefins) T. Sakakibara, M. D. Manadhar, and Y. Ishido, *Synthesis*, 920 (1983).