Michael Reaction of Conjugated Nitro Olefins with Carboxylic Acid Dianions and with Ester Enolates: New Synthesis of γ-Keto Acids and γ-Keto Esters

Masaaki Miyashita, Ryuji Yamaguchi, and Akira Yoshikoshi*

Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

Received November 3, 1983

Base-sensitive conjugated nitro olefins **2** reacted with lithium dianions of carboxylic acids **3** or with lithium enolates of esters **4** at a low temperature of ca. −100 °C, and subsequent treatment of the Michael adducts with aqueous acid yielded γ-keto acids **5** or esters **5'** in a one-pot operation, respectively. Results of both the reactions have been compared. Some applications of the resulting γ-keto esters in organic synthesis have also been demonstrated in lactone synthesis and cyclenone annulation.

γ-Keto acids and esters are highly useful compounds in organic synthesis because five-membered carbocycles (cyclopentane-1,3-diones, cyclopentenones, etc.) and various heterocycles (γ-lactones, butenolides, γ-lactams, thiophenes, etc.) are readily accessible from them. In consequence, a variety of synthetic methods of γ-keto acids (esters) have been published hitherto,[1] however with these methods, levulinic acid derivatives bearing substituents on their α-, β-, and/or γ-positions were not necessarily readily accessible due to their methodological limitations. In the previous paper,[2] as a solution of this problem, we reported the synthetic method of γ-keto esters by the reaction of conjugated nitro olefins **2** with ketene methyl trimethylsilyl acetals **1**, and demonstrated that various α- and/or β-substituted γ-keto esters **5'** were obtainable in moderate to good yields except for an α,α,β,β-tetrasubstituted γ-keto derivative.

On account of the high susceptibility of aliphatic conjugated nitro olefins to bases, acidic conditions employing Lewis acid were selected in the above reaction. Although we have thus secured the useful and general method of α,β-substituted γ-keto esters, the direct use of carboxylic acids or esters themselves as reactants seemed to be more preferable than that of ketene silyl acetals **1**.

In this paper we describe our study on the Michael reaction of aliphatic conjugated nitro olefins **2** with dianions of carboxylic acids **3**[3] and also with ester enolates **4** for the synthesis of γ-keto acids **5** and γ-keto esters **5'**.[4,5]

As a model study, we first examined the reaction of 2-nitropropene (**11**)[6] and the lithium dianion of hexanoic acid (**6**), and soon found that both addition of hexamethylphosphoric triamide (HMPT) to the dianion solution and low temperature were crucial to realize the desired reaction (Table I, entry 1). The dianion was generated from **6** and 2 mol equiv of lithium diisopropylamide (LDA) in tetrahydrofuran at ca. −50 °C as usual, and after addition of 1 mol equiv of HMPT, the resulting clear solution was cooled to ca. −100 °C in a liquid nitrogen–methanol bath. After addition of the nitro olefin **11** (1.5 mol equiv) followed by gradual warming to room temperature, the reaction mixture was treated with dilute mineral acid in a one-pot operation. The resulting γ-keto acid **15** was purified after esterification with diazomethane to **15'**. The remarkable observation was that no addition of HMPT caused the formation of a complex mixture and that at slightly higher temperature, even at −78 °C, the yield lowered considerably.

The one-pot synthesis of γ-keto acids from carboxylic acid dianions and nitro olefins was thus proved feasible; hence we examined this reaction in a variety of combinations of carboxylic acids and nitro olefins. The results are summarized in Table I.

When 1-nitrocyclohexene (**13**) was employed in the reaction (entries 3 and 4), lower yields of γ-keto acids were obtained in comparison with those obtained with nitro olefins **11** and **12** (entries 1 and 2). It is also observable from Table I that dianions of α-branched carboxylic acids, prepared at 50 °C according to the known procedure,[7] added sluggishly to nitro olefins and that yields of γ-keto acids were generally lower than those with primary carboxylic acid dianions (entries 5–7).

It is noteworthy that butyllithium could be employed to generate the dianions of phenylacetic acid (**8**) much more effectively than LDA, and keto acid **22**, without addition of HMPT, was obtained in high yield (entry 8). The reaction of **8** with other nitro olefins **12** and **13** also afforded the corresponding α-phenyl-γ-keto acids **23** and **24** in good yields (entries 9 and 10).

(1) Recent synthetic methods: Lukes, R.; Zobakova, A. *Collect Czech. Chem. Commun.* **1959**, *24*, 3189. Putterbauch, W. H.; Readshow, R. L. *Chem. Ind. (London)* **1959**, 255. Pomomarev, A. A.; Sedavkina, V. A. *Zh. Obshch. Khim.* **1961**, *31*, 984; *Chem. Abstr.* **1961**, *55*, 25905b. Chiusoli, G. P.; Merzoni, S.; Mondelli, G. *Tetrahedron Lett.* **1964**, 2777. Reinheckel, H.; Haage, K.; Gensike, R. *Angew. Chem.* **1965**, *77*, 810. Takeda, A.; Takahashi, K., Torii, S., Morikawa, T. *J. Org. Chem.* **1966**, *31*, 3436. Chavdrian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822. Manas, A.-R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216. Stetter, H.; Schreckenberg, M., Wiemann, K. *Chem. Ber.* **1976**, *109*, 541. Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166. Boeckman, R. K., Jr.; Bruza, K. J. *Ibid* **1979**, *44*, 4781. Andersen, W. K.; Lee, G. E. *Synth. Commun.* **1980**, *10*, 351. Cerfontain, H.; van Noort, P. C. M. *Synthesis* **1980**, 490. Hirai, K.; Suzuki, H.; Kashiwagi, H.; Moro-oka, Y.; Ikawa, T. *Chem. Lett.* **1982**, 23.

(2) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Chem. Lett.* **1980**, 1043. Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149.

(3) Preliminary account: Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *Chem. Lett.* **1982**, 1505.

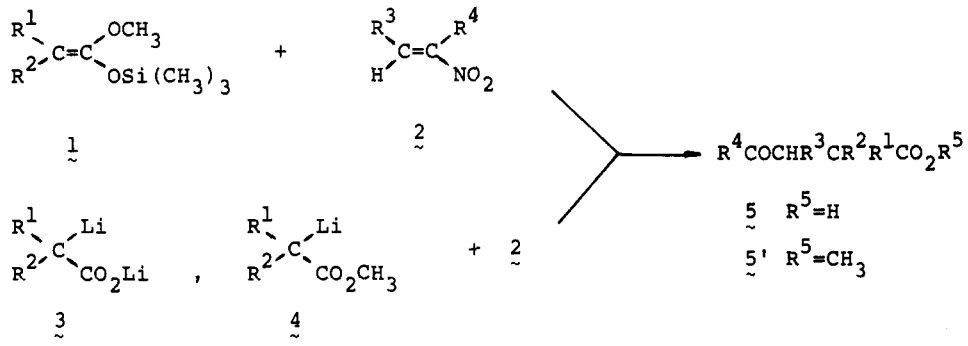
(4) Prior to our publication, the reaction of nitro olefins with anions of *N,N*-dialkylamides, ketones, and esters was reported to give nitro amides, nitro ketones, and nitro esters, respectively. (a) Seebach, D.; Leitz, H. F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924. (b) Züger, M.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005.

(5) Throughout this paper, primed compound numbers indicate methyl esters of carboxylic acids with the corresponding nonprimed numbers.

(6) For a large scale preparation of other nitro olefins used here other than 1-nitrocyclohexene, see: Miyashita, M.; Yanami, T.; Yoshikoshi, A. *Org. Synth.* **1981**, *60*, 101.

(7) Pfeffer, P. E.; Silbert, L. S. Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.

0022-3263/84/1949-2857$01.50/0



We then proceeded to the reaction of nitro olefins with α-phenylthio carboxylic acids to obtain α-(phenylthio)-γ-keto acids, which were useful intermediates for the synthesis of α,β-unsaturated γ-keto esters as will be discussed later. Again, butyllithium was an effective base[8] to generate dianions of (phenylthio)acetic and α-(phenylthio)-propionic acids **9** and **10**, and in the reaction with nitro olefins **11**, **12**, **13**, and **14**, the former acid provided the desired α-(phenylthio)-γ-keto acids **25–28** in good yields (entries 11–14), while the latter α-branched acid gave somewhat lower yields than did the former acid (entries 15–17).

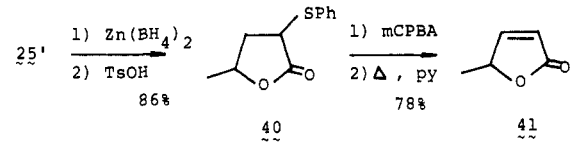
For comparison, we also examined the Michael reaction of ester enolates with nitro olefins. The anions were generated in tetrahydrofuran from esters with LDA in the customary manner, and the reaction with nitro olefins was conducted at ca. −100 °C. The reaction mixtures were then treated with dilute mineral acid at ice–water temperature to give γ-keto esters. Results are summarized in Table II from which one can see that primary and α-branched esters afforded better yields of γ-keto esters than those obtained in the reaction with the dianions (entries 1–7). Methyl phenylacetate (**35**) and methyl (phenylthio)acetate (**36**) gave α-phenyl-γ-keto and α-(phenylthio)-γ-keto esters in comparable yields with those obtained by the dianion method (entries 8–13).

The above-mentioned fruitful outcome prompted us to set about the reaction of *aliphatic nitro olefins* and monoketone enolates, which would be a more preferable synthetic method of 1,4-diones than the silyl enol ether method described in the previous paper.[2] A reaction of this type was reported by Seebach et al. with an *aryl-conjugated nitro olefin*, which yielded the Michael adducts, i.e., nitro ketones, in the reaction with the lithium enolates of cyclohexanone and camphor.[4a]

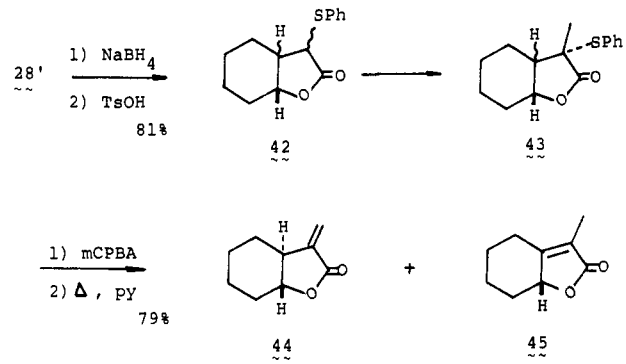
We observed, unfortunately, no formation of the desired 2-acetonylcyclohexanone in the reaction of cyclohexanone lithium enolate with 2-nitropropene, which was employed as a model experiment, under various reaction conditions.

α-Sulfenylation–dehydrosulfenylation[9] of carbonyl compounds and the similar procedure of seleno analogues[10] have been reported as efficient methods for the introduction of unsaturation into the corresponding saturated carbonyl compounds at their α–β-positions, and in fact these methods have been substituted for the classical bromination–dehydrobromination method. In our synthesis, α-(phenylthio)-γ-keto esters **5′** (R′ = PhS) are, as described, readily obtainable in high yields, and α,β-unsaturated-γ-keto esters and related unsaturated compounds could be synthesized from them without protection of ketone carbonyl, which was required in the sulfenylation–dehydrosulfenylation route of keto esters. From the above point of view, we attempted the application of the present method to the synthesis of some simple systems of α,β-unsaturated esters and lactones, and also to cyclenone annulation reaction.

Scheme I



Scheme II



Methyl α-(phenylthio)levulinate (**25′**) was reduced with zinc borohydride and the resulting crude hydroxy ester was heated in refluxing benzene containing a catalytic amount of *p*-toluenesulfonic acid, yielding γ-lactone **40** as an epimeric mixture in an approximate ratio of 1:1 (Scheme I). The mixture was oxidized with 1 mol eqiv of *m*-chloroperoxybenzoic acid, and the crude sulfoxides were refluxed in benzene containing pyridine to give β-angelica lactone (**41**) in good overall yield (67%).

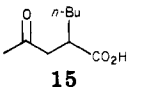
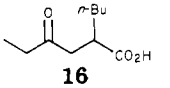
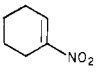
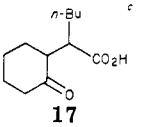
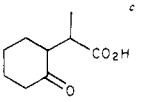
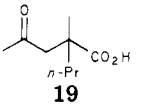
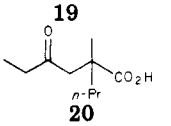
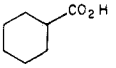
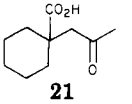
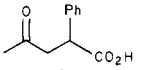
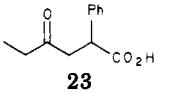
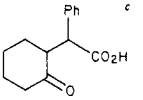
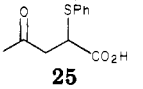
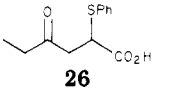
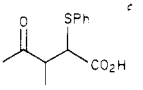
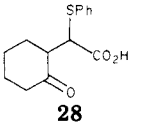
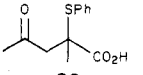
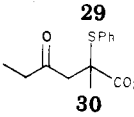
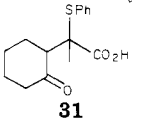
Our methodology was next applied to the synthesis of fused lactones **44** and **45**. Sodium borohydride reduction of methyl α-(phenylthio)acetate (**28′**) followed by acid treatment provided a diastereomeric mixture of γ-lactones **42**, and the product was then methylated to give **43** in high overall yield. After oxidation of the phenylthio group to sulfoxide, the product was heated in refluxing benzene containing pyridine to afford a mixture of **44** and **45** in a ratio of 18:82[11] (see Scheme II).

(8) Although LDA was reported as an excellent base for the dianion generation from **9** (Yamagiwa, S.; Hoshi, N.; Sato, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 214), the yield of **25**, despite of optimization, did not exceed 67% with this base in the reaction with **11**, which was carried out as a model experiment. A similar observation was made in the nitration of this acid with an alkyl nitrite (Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.

(9) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6480. Trost, B. M.; Salzmann, T. N.; Hiroi, K. *Ibid.* **1976**, *98*, 4887.

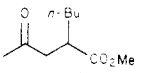
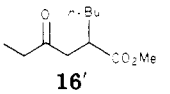
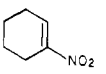
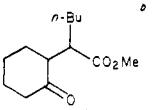
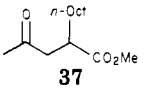
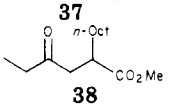
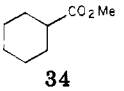
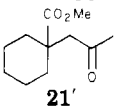
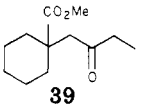
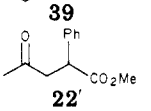
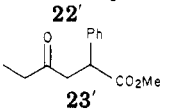
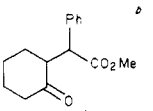
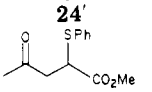
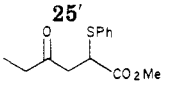
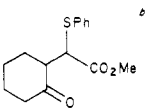
(10) Reich, H.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813. Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137. Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695.

Table I. Synthesis of γ-Keto Acids from Conjugated Nitro Olefins and Carboxylic Acid Dianions

entry	carboxylic acid	base[a]	nitro olefin	product	isolated yield,[b] %
1	$CH_3(CH_2)_4CO_2H$ **6**	A	 **11**	 **15**	65
2		A	 **12**	 **16**	55
3		A	 **13**	 **17** [c]	24
4	$CH_3CH_2CO_2H$	A	13	 **18** [c]	43
5	$CH_3(CH_2)_2CH(CH_3)CO_2H$ **7**	A	11	 **19**	46
6		A	12	 **20**	38
7		A	11	 **21**	37
8	$C_6H_5CH_2CO_2H$ **8**	B	11	 **22**	88
9		B	12	 **23**	73
10		B	13	 **24** [c]	72
11	$C_6H_5SCH_2CO_2H$ **9**	B	11	 **25**	80
12		B	12	 **26**	76
13		B	 **14**	 **27** [c]	64
14		B	13	 **28** [c]	76
15	$C_6H_5SCH(CH_3)CO_2H$ **10**	B	11	 **29**	55
16		B	12	 **30**	39
17		B	13	 **31** [c]	37

[a] A, lithium diisopropylamide; B, butyllithium. [b] The product was isolated as a methyl ester, and the yield given was calculated based on the starting carboxylic acid. [c] Diastereomeric mixture.

Table II. Synthesis of γ-Keto Esters from Conjugated Nitro Olefins and Ester Enolates

entry	ester	nitro olefin	product	isolated yield,[a] %
1	$CH_3(CH_2)_4CO_2Me$ **32**	 **11**	 **15′**	81
2		 **12**	 **16′**	56
3		 **13**	 **17′** [b]	54
4	$CH_3(CH_2)_8CO_2Me$ **33**	11	 **37**	61
5		12	 **38**	53
6	 **34**	11	 **21′**	53
7		12	 **39**	41
8	$C_6H_5CH_2CO_2Me$ **35**	11	 **22′**	79
9		12	 **23′**	75
10		13	 **24′** [b]	61
11	$C_6H_5SCH_2CO_2Me$ **36**	11	 **25′**	65
12		12	 **26′**	66
13		13	 **28′** [b]	52

[a] Calculated based on the starting ester. [b] Diastereomeric mixture.

Our attention then focused on the cyclenone annulation. McMurry and Blaszczak[12] observed that ethyl 4-oxopentenoate and 2-methylcyclohexanone gave an annulation product (ethyl ester of **49a**) in 21% yield only under acidic conditions (*p*-toluenesulfonic acid in refluxing benzene). Since the carboxyl group in **49a** could be decarboxylated by lead tetraacetate oxidation to give the enone system in good yield, this carboxylic acid is the attractive intermediate in the reported transformation into crossed dienone **50** and enones **51a** and **51b**,[12] provided the yield of the annulation product can be improved.

Although our method may provide a variety of α,β-unsaturated γ-keto esters from the readily accessible α-(phenylthio)-γ-keto esters listed in Table I, we chose α-phenylthio esters **25′** and **26′** to compare with McMurry's observation (Scheme III). From both the α-phenylthio esters, the corresponding *E*-α,β-unsaturated esters **46a** and **46b** were exclusively obtained[9] in acceptable yields (60–68%) by oxidation with sodium periodate or *m*-chloroperoxybenzoic acid followed by the subsequent thermal elimination reaction of the resulting sulfoxides in benzene containing pyridine at reflux.

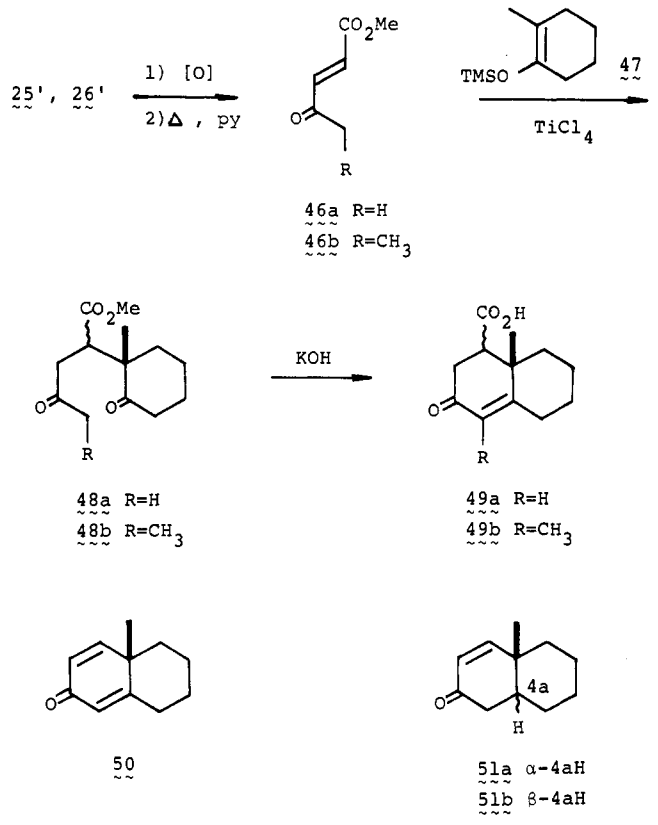
With these unsaturated esters in hand, the first problem to be solved was to improve the reported low yield[12] in the annulation with 2-methylcyclohexanone. We found that the titanium tetrachloride catalyzed conjugate addition[13]

(11) For the detailed study of this unsaturated lactone synthesis, see: Grieco, P. A.; Reap, J. J. *Tetrahedron Lett.* **1974**, 1097.

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

(13) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.

Scheme III



of silyl enol ether **47**,[14] readily obtainable from the cyclohexanone, to the above unsaturated esters proceeded smoothly to give adducts **48a** and **48b**, and that on treatment of the adducts with base, cyclenone carboxylic acids **49a** and **49b** were obtained in high overall yields (73% and 61%, respectively) as epimeric mixtures with respect to the carboxyl groups.

In conclusion, we succeeded in finding satisfactory reaction conditions that provided γ-keto acids or esters in a one-pot operation from base-sensitive nitro olefins and carboxylic acids or esters *under conventional, strong basic conditions*. One can expect a further extension of the present γ-keto acid and ester syntheses, and such studies are now in progress.

Experimental Section

All melting points were uncorrected and boiling points indicate bath temperatures on evaporative distillation of liquid products. IR spectra were recorded, except where noted, with liquid film on a Jasco A-3 spectrophotometer, and ^{1}H NMR were taken in deuteriochloroform on a Jeol FX-90Q (90 MHz) or a Jeol PS-100 (100 MHz) spectrometer. Chemical shift values are expressed in δ values relative to Me_4Si as internal standard. Coupling constants (J) are given in hertz.

General Procedure for the Synthesis of Methyl γ-Keto Carboxylates 5b from Nitro Olefins 2 and Dianions of Carboxylic Acids 3 (Table I). Under an Ar atmosphere, a carboxylic acid **3** (0.5 mmol) was added dropwise to a stirred tetrahydrofuran (THF) solution (3.5 mL) of LDA (1.2 mmol) at −50 °C, and stirring was continued at the same temperature for an additional 30 min. HMPT (0.5 mmol) was added to the solution, and the mixture was further stirred at room temperature for 30 min. When an α-alkyl carboxylic acid was used (Table I, entries 5, 6, and 7), without addition of HMPT,[7] the solution was stirred at 50 °C for 2 h.

Dianions of phenylacetic acid (**8**), (phenylthio)acetic acid (**9**), and α-(phenylthio)propionic acid (**10**) were generated by butyllithium in place of LDA, i.e., a commercial hexane solution of butyllithium (1.2 mmol) was added dropwise to a solution of the carboxylic acid (0.5 mmol) in THF (3.5 mL) at −78 °C, and stirring was continued at the same temperature for 45 min under Ar.

The dianion solution thus obtained was cooled to ca. −100 °C in a liquid nitrogen–methanol bath, and a nitro olefin **2** (1.5 mmol)[16] was added dropwise. After the mixture had been gradually warmed to 0–10 °C over 5 h, dilute hydrochloric acid (17%, 3 mL) was added, and the mixture was further stirred in an ice bath overnight. Then water was added, and the product was extracted with dichloromethane. The extract was washed with water and then brine. After drying, the extract was concentrated to leave the crude product, which was then esterified with ethereal diazomethane. The product was purified by preparative silica gel layer chromatography (TLC) with dichloromethane–hexane (7:1) as eluent. Analytical samples were obtained by evaporative distillation in vacuo.

General Procedure for the Synthesis of Methyl γ-Keto Carboxylate 5b from Nitro Olefins 2 and Anions of Esters 4 (Table II). An ester (0.5 mmol) was added dropwise to a stirred THF solution (3 mL) of LDA (0.6 mmol) at −78 °C under Ar, and stirring was continued for an additional 30 min. The mixture was then cooled to ca. −100 °C in a liquid nitrogen–methanol bath, and a nitro olefin (**2**, 0.75 mmol) was added dropwise. Stirring was continued while the temperature was allowed gradually to raise to 10 °C over 5 h. Dilute hydrochloric acid (17%, 3 mL) was added at 0 °C, and the mixture was stirred overnight at this temperature. After dilution with water, the product was extracted with dichloromethane, and the extract was washed with water and then brine and dried. Removal of the solvent left the crude product, which was purified by TLC with dichloromethane–hexane (7:1) as eluent. Most of the resulting γ-keto esters were spectroscopically identified with samples obtained by the dianion method.

Methyl 2-butyl-4-oxopentanoate (15′):[17] bp 75 °C (1.2 mmHg); IR 1740–1710 cm^{-1} (br); ^{1}H NMR[18] 0.88 (t, 3 H, J = 6), 1.05–1.8 (m, 6 H), 2.14 (s, 3 H), 2.3–3.1 (m, 3 H), 3.66 (s, 3 H). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.71; H, 9.92.

Methyl 2-butyl-4-oxohexanoate (16′): bp 95 °C (5 mmHg); IR 1740–1720 cm^{-1} (br); ^{1}H NMR 0.96 (t, 3 H, J = 6), 1.12 (t, 3 H, J = 7), 1.2–1.8 (m, 4 H), 2.3–3.1 (m, 5 H), 2.52 (q, 2 H, J = 6), 3.72 (s, 3 H). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.59; H, 10.26.

Methyl 2-(2-oxocyclohexyl)hexanoate (17′): bp 90 °C (3 mmHg); IR 1735, 1710 cm^{-1}; ^{1}H NMR 0.88 (br t, 3 H, J = 6), 1.0–3.0 (m, 16 H), 3.68 (s, 3 H). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.02; H, 9.79.

Methyl 2-(2-oxocyclohexyl)propionate (18′):[19] bp 80 °C (1 mmHg); IR 1730, 1705 cm^{-1}; ^{1}H NMR 1.12 and 1.18 (d each, 3 H in total), 1.3–2.9 (m, 10 H), 3.66 and 3.70 (two s in 2:1 ratio, 3 H in total). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.07; H, 8.97.

Methyl 2-methyl-4-oxo-2-propylpentanoate (19′): bp 85 °C (3 mmHg); IR 1740, 1720 cm^{-1}; ^{1}H NMR 0.89 (br t, 3 H, J = 6.5), 1.20 (s, 3 H), 1.0–1.8 (m, 7 H), 2.50 (d, 1 H, J = 17), 2.94 (d, 1 H, J = 17), 3.64 (s, 3 H). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.24; H, 9.53.

(14) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(15) From the reported spectral data (ref 12), the acid-catalyzed Robinson annulation of 2-methylcyclohexanone with ethyl 4-oxopentenoate seems, unlike our outcome, to give the single isomer, although they have not assigned the stereochemistry of the ethoxycarbonyl group to the isomer.

(16) 1-Nitrocyclohexene (**13**): Hayama, T.; Tomoda, S.; Takeuchi, Y.; Nomura, Y. *Chem. Lett.* **1982**, 1109. Sakakibara, T.; Ikeda, Y.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 635. Dampawan, P.; Zajac, W. W., Jr. *Tetrahedron Lett.* **1982**, *23*, 135. Sakakibara, T.; Takai, I.; Ohara, E.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1981**, 261. Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294 and references therein. Other nitro olefins used: ref 5.

(17) Boehm, I.; Hirsch, E.; Reissig, H. V. *Angew. Chem.* **1981**, *93*, 593.

(18) Data at 100 MHz.

(19) Stork, G.; Brizzolara, A.; Landesman, H.; Azmuszkowicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

Methyl 2-methyl-4-oxo-2-propylhexanoate (20′): bp 80 °C (5 mmHg); IR 1740–1720 cm^{-1}; ^1H NMR 0.96 and 1.04 (t, 3 H, J = 7 each), 1.20 (s, 3 H); 1.2–1.7 (m, 4 H), 2.37 (q, 2 H, J = 6.8), 2.50 (d, 1 H, J = 17), 2.97 (d, 1 H, J = 17), 3.64 (s, 3 H). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.91; H, 9.97.

Methyl 1-(2-Oxopropyl)cyclohexanecarboxylate (21′).[2] This ester was identified by spectral comparison with those of the authentic compound.

Methyl 4-oxo-2-phenylpentanoate (22′):[20] mp 70–71 °C; IR (supercooled liquid) 1740–1710 cm^{-1}; ^1H NMR[18] 2.12 (s, 3 H), 2.67 (dd, 1 H, J = 4 and 18), 3.36 (dd, 1 H, J = 10 and 18), 3.60 (s, 3 H), 4.07 (dd, 1 H, J = 4 and 10), 7.22 (s, 5 H). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62; H, 6.92.

Methyl 4-oxo-2-phenylhexanoate (23′):[2] bp 120 °C (4 mmHg); IR 1740, 1710 cm^{-1}; ^1H NMR 1.03 (t, 3 H, J = 6.8), 2.46 (q, 2 H, J = 6.8), 2.68 (dd, 1 H, J = 4.2 and 17), 3.38 (dd, 1 H, J = 8.5 and 17), 3.64 (s, 3 H), 4.13 (dd, 1 H, J = 4.2 and 8.5), 7.23 (s, 5 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.58; H, 7.40.

Methyl 2-(2-oxocyclohexyl)-2-phenylacetate (24′): mp 99–100 °C; IR ($CHCl_3$) 1790, 1710 cm^{-1}; ^1H NMR 0.9–2.6 (m, 9 H), 3.19 (dt, 1 H, J = 5 and 10), 3.64 (s, 3 H), 7.28 (s, 5 H). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.16; H, 7.46.

Methyl 4-oxo-2-(phenylthio)pentanoate (25′): bp 148 °C (2 mmHg); IR 1740, 1720 cm^{-1}; ^1H NMR[18] 2.12 (s, 3 H), 2.88 (dd, 1 H, J = 4 and 18), 3.12 (dd, 1 H, J = 10 and 18), 3.64 (s, 3 H), 4.02 (dd, 1 H, J = 4 and 10), 7.2–7.6 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.33; H, 6.10; S, 13.49.

Methyl 4-oxo-2-(phenylthio)hexanoate (26′): bp 160 °C (2 mmHg); IR 1740, 1715 cm^{-1}; ^1H NMR[18] 1.02 (t, 3 H, J = 8), 2.42 (q, 2 H, J = 8), 2.78 (dd, 1 H, J = 4 and 18), 3.12 (dd, 1 H, J = 8 and 18), 3.67 (s, 3 H), 4.07 (dd, 1 H, J = 4 and 8), 7.4–7.6 (m, 5 H). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; S, 12.71. Found: C, 62.13; H, 6.55; S, 12.62.

Methyl 3-methyl-4-oxo-2-(phenylthio)pentanoate (27′): bp 135 °C (3 mmHg); IR 1740, 1710 cm^{-1}; ^1H NMR[18] 1.20 and 1.40 (two d in 2:1 ratio, 3 H in total), 2.24 and 2.28 (two s in 2:1 ratio, 3 H in total), 2.8–3.4 (m, 1 H), 3.72 and 3.76 (two s in 1:2 ratio, 3 H in total), 3.98 (d, 1 H, J = 8), 7.2–7.8 (m, 5 H). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.64; H, 6.13; S, 12.98.

Methyl 2-(2-oxocyclohexyl)-2-(phenylthio)acetate (28′): bp 163 °C (1.8 mmHg); IR 1740, 1710 cm^{-1}; ^1H NMR 1.0–3.2 (m, 9 H), 3.64 and 3.66 (two s in3:2 ratio, 3 H in total), 4.04 (d, 1 H, J = 6.8), 7.1–7.7 (m, 5 H). Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52; S, 11.52. Found: C, 64.91; H, 6.63; S, 11.61.

Methyl 2-methyl-4-oxo-2-(phenylthio)pentanoate (29′): bp 120 °C (4 mmHg); IR 1740–1720 cm^{-1}; ^1H NMR[18] 1.44 (s, 3 H), 2.02 (s, 3 H), 2.72 (d, 1 H, J = 16), 3.19 (d, 1 H, J = 16), 3.54 (s, 3 H), 7.2–7.6 (m, 5 H). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.64; H, 6.61.

Methyl 2-methyl-4-oxo-2-(phenylthio)hexanoate (30′): bp 125 °C (2.8 mmHg); IR 1740–1720 cm^{-1}; ^1H NMR 1.0 (t, 3 H, J = 6.8), 1.52 (s, 3 H), 2.38 (q, 2 H, J = 6.8), 2.72 (d, 1 H, J = 17), 3.20 (d, 1 H, J = 17), 3.64 (s, 3 H), 7.1–7.6 (m, 5 H). Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.03; H, 6.98.

Methyl 2-(2-oxocyclohexyl)-2-(phenylthio)propionate (31′): bp 150 °C (4.5 mmHg); IR 1730, 1710 cm^{-1}; ^1H NMR 1.44 (s, 3 H), 1.5–3.2 (m, 9 H), 3.54 and 3.60 (two s in 2:1 ratio, 3 H in total), 7.2–7.6 (m, 5 H). Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.90. Found: C, 65.89; H. 7.13.

Methyl 2-octyl-4-oxopentanoate (37):[2] bp 80 °C (0.5 mmHg); IR 1735, 1720 cm^{-1}; ^1H NMR 0.88 (t, 3 H, J = 7), 1.24 (br s, 14 H), 2.22 (s, 3 H), 2.4–3.2 (m, 3 H), 3.72 (s, 3 H). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.14; H, 11.11.

Methyl 2-octyl-4-oxohexanoate (38):[2] bp 120 °C (3 mmHg); IR 1740, 1720 cm^{-1}; ^1H NMR 0.88 (t, 3 H, J = 7), 1.04 (t, 3 H, J = 6.8), 1.24 (br s, 14 H), 2.44 (q, 2 H, J = 6.8), 2.5–3.0 (m, 3 H), 3.66 (s, 3 H). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.16; H, 11.08.

(20) Goldberg, M. W.; Sullivan, W. R.; Scott, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 2810. Eskola, S. *Suom. Kemistil. B*, **1956**, *29*, 39; *Chem. Abstr.* **1957**, *51*, 288. Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Takanashi, H. *Tetrahedron Lett.* **1980**, *21*, 1047.

Methyl 1-(2-Oxobutyl)cyclohexanecarboxylate (39).[2] This ester was identified by spectral comparison with those of the authentic compound.

4,5-Dihydro-5-methyl-3-(phenylthio)furan-2(3*H*)-one (40). An ethereal solution (9 mL) of $Zn(BH_4)_2$ (1.35 mg, 1.4 mmol) was added to a stirred solution of the keto ester **25′** (84 mg, 0.35 mmol) in the same solvent (9 mL) at 0 °C, and stirring was continued for 3 h. The solvent was removed in vacuo, water was added to the residue, and the product was extracted with CH_2Cl_2. The extract was washed with water, and dried. The residue obtained on evaporation was dissolved in benzene containing a catalytic quantity of *p*-toluenesulfonic acid (TsOH), and the solution was heated at 50 °C for 2 h. After workup, the product was purified by TLC with CH_2Cl_2 as eluent to give 63 mg (86% yield) of the lactone **40**: bp 130 °C (3 mmHg); IR 1770 cm^{-1}; ^1H NMR[18] 1.30 and 1.38 (two d in ca. 1:1 ratio, 3 H in total, J = 4 each), 1.6–2.9 (m, 2 H), 3.8–4.1 (m, 1 H), 4.3–4.7 (m, 1 H), 7.2–7.7 (m, 5 H). Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.14; H, 6.09.

When $NaBH_4$ was used as the reducing agent, a slightly lower yield (77%) of **40** was obtained.

β-Angelica Lactone (41). *m*-Chloroperoxybenzoic acid (mCPBA) (80% assay, 106 mg, 0.49 mmol) was added to a CH_2Cl_2 solution (3 mL) of the lactone **40** (93 mg, 0.45 mmol) at 0 °C and the solution was stirred at the same temperature for 2 h. The solution was successively washed with water, aqueous $NaHCO_3$, and brine and evaporated after drying. The residue was dissolved in benzene (3 mL) containing pyridine (150 μL, 1.9 mmol) and heated at 110–120 °C for 1.5 h with stirring. After evaporation, the residue was purified by TLC with CH_2Cl_2 as eluent to give **41** (34 mg, 78% yield): IR 1780–1730 cm^{-1}; ^1H NMR 1.42 (d, 3 H, J = 6.8), 5.12 (q t, 1 H, J = 6.8 and 1.7), 6.08 (dd, 1 H, J = 5.1 and 1.7), 7.44 (dd, 1 H, J = 5.1 and 1.7).

Epimer Mixture of 3a,4,5,6,7,7aβ-Hexahydro-3-methyl-3-(phenylthio)-1-benzofuran-2(3*H*)-one (43). $NaBH_4$ (90% assay, 27 mg, 0.63 mmol) was added to a solution of **28′** (176 mg, 0.63 mmol) in methanol (6 mL) at 0 °C, and the mixture was stirred for 2 h at the same temperature. After dilution with water, the product was extracted with CH_2Cl_2, and the residue obtained by evaporation was dissolved in benzene (5 mL) containing a catalytic quantity of TsOH. The mixture was refluxed for 1 h. The benzene was removed in vacuo, and the residue was purified by TLC with CH_2Cl_2 as eluent to give **42** (127 mg, 81% yield): IR 1770 cm^{-1}.

A THF solution (1 mL) of **42** (66 mg, 0.27 mmol) was added dropwise to LDA (0.32 mmol) in THF (1 mL) at −78 °C and stirred for 30 min at the same temperature. The mixture was gradually warmed to −40 °C, and MeI (33.5 μL, 0.53 mmol) in THF (0.5 mL) was added. While stirring was continued, the mixture was further warmed to 0 °C. The reaction was quenched by addition of water, and the product was extracted with CH_2Cl_2. Workup gave the residue, which was purified by TLC with CH_2Cl_2 as eluent to yield **43** (60 mg, 87% yield): bp 160 °C (3 mmHg); IR 1770 cm^{-1}; ^1H NMR 1.0–2.8 (m, 12 H including two sharp s at 1.36 and 1.40 ppm), 3.84 (m, 0.75 H), 4.62 (m, 0.25 H), 7.0–8.0 (m, 5 H). Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.92. Found: C, 68.50; H, 7.15.

3aα,4,5,6,7,7aβ-Hexahydro-3-methylene-1-benzofuran-2(3*H*)-one (44) and 5,6,7,7a-Tetrahydro-3-methyl-1-benzofuran-2(4*H*)-one (45). A solution of mCPBA (85% assay, 67 mg, 0.33 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of **43** (87 mg, 0.33 mmol) in CH_2Cl_2 (4 mL) at −78 °C, and the mixture was stirred for 3 h at the same temperature. Water was added, and the product was extracted with ether. When successive washing of the extract with water, aqueous $NaHCO_3$, water, and brine was complete, the residue obtained by evaporation was dissolved in a mixture of benzene (3 mL) and pyridine (107 μL, 1.42 mmol), and the solution was refluxed for 2 h. The benzene was evaporated, and the residue was purified by TLC with CH_2Cl_2 as eluent to give **44** (7 mg, 14% yield) and **45** (33 mg, 65% yield). These lactones were identified by spectroscopic comparison with authentic samples.[11]

Methyl 4-Oxo-2-pentenoate (46a). To an aqueous solution (3.2 mL) of $NaIO_4$ (153 mg, 0.72 mmol) was added **25′** (114 mg, 0.48 mmol) dissolved in a mixture of benzene (0.57 μL) and methanol (7.3 mL) and the whole mixture was stirred at room temperature for 3 days. After dilution with water, the product

was extracted with CH_2Cl_2. After workup, the crude product was dissolved in benzene (3 mL) containing pyridine (155 μL) and refluxed for 2 h. The residue obtained by evaporation was purified by TLC with CH_2Cl_2 as eluent to afford **46a** (36 mg, 60%): IR (CCl_4) 1705, 1730, 1640, 1624 cm^{-1}; ^1H NMR 2.36 (s, 3 H), 3.80 (s, 3 H), 6.62 (d, 1 H, J = 16), 7.03 (d, 1 H, J = 16).

Methyl 4-Oxo-2-hexenoate (46b). A solution of mCPBA (85% assay, 108 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of **26′** (126 mg, 0.5 mmol) in the same solvent (3 mL) at −78 °C, and stirring was continued for 3 h at the same temperature. Water was added, and the product was extracted with ether. The extract was washed with aqueous $NaHCO_3$, water, and then brine. The residue obtained by evaporation was heated in a mixture of benzene (4 mL) and pyridine (161 μL, 2 mmol) for 2 h, and then the benzene was removed by evaporation. The unsaturated ester **46b** (48 mg, 68%) was obtained from the residue by TLC with CH_2Cl_2 as eluent: IR (CCl_4) 1730, 1705, 1690, 1640, 1628 cm^{-1}; ^1H NMR 1.14 (t, 3 H, J = 6), 2.68 (d, 2 H, J = 6), 3.80 (s, 3 H), 6.68 (d, 1 H, J = 16), 7.07 (d, 1 H, J = 16).

Methyl 2-(1-Methyl-2-oxocyclohexyl)-4-oxopentanoate (48a) and Methyl 2-(1-Methyl-2-oxocyclohexyl)-4-oxohexanoate (48b). $TiCl_4$ (110 μL, 1.0 mmol) was added to a stirred solution of **46a** (128 mg, 1 mmol) at −78 °C under Ar, and the mixture was stirred for 30 min. 2-Methyl-1-((trimethylsilyl)oxy)cyclohexene (**47**) (330 μL, 1.5 mmol)[14] was then added dropwise to the above solution at the same temperature, and the mixture was allowed gradually to raise to room temperature over 3 h. After addition of water, the product was extracted with ether, and the extract was washed with water and brine. The residue obtained by evaporation of the solvent was purified by TLC with CH_2Cl_2 as eluent to yield **48a** (197 mg, 82% yield): bp 120 °C (1.5 mmHg); IR 1725, 1710 cm^{-1}; ^1H NMR[18] 1.02 and 1.04 (two s in ca. 1:1 ratio, 3 H in total), 1.2–2.1 (m, 7 H), 2.08 and 2.16 (two s in ca. 1:1 ratio, 3 H in total), 2.2–3.5 (m, 4 H), 3.52 and 3.62 (two s in ca. 1:1 ratio, 3 H in total). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.70; H, 8.77.

By the same manner, **48b** (64 mg, 71% yield) was obtained from **46b** (51 mg): bp 120 °C (3 mmHg); IR 1740–1705 cm^{-1}; ^1H NMR[18] 0.9–1.2 (overlapped singlet and triplet, 6 H in total), 1.2–2.2 (m, 7 H), 2.42 (q, 2 H, J = 7), 2.2–3.2 (m, 4 H), 3.56 and 3.65 (two s in 1:1 ratio, 3 H in total). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.33; H, 8.98.

4,4a,5,6,7,8-Hexahydro-4a-methyl-4-carboxy-2(3*H*)-naphthalenone (49a) and 4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-4-carboxy-2(3*H*)-naphthalenone (49b). A mixture of **48a** (96 mg, 0.4 mmol), KOH (86% assay, 261 mg, 4.0 mmol), water, (0.4 mL), and ethanol (4 mL) was heated at 70 °C for 4 h. After dilution with water, the product was extracted with ether, and the aqueous layer was acidified with dilute HCl. Acidic product **49a** (74 mg, 89% yield) was obtained by extraction with ether: ^1H NMR 1.29 and 1.42 (two s in ca. 1:1 ratio, 3 H in total), 1.0–3.1 (m, roughly 11 H), 5.80 and 5.82 (two s in ca. 1:1 ratio, 1 H in total), 8.64 (br s, 1 H).

By the same procedure, **49b** (106 mg, 86% yield) was obtained from **48b** (141 mg): ^1H NMR 1.24 and 1.40 (two s in ca. 1:1 ratio, 3 H in total), 1.0–3.0 (m, approximately 11 H), 1.78 (s, 3 H), 8.80 (br s, 1 H).

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (56430010) and by a Grant-in-Aid for Special Project Research (57118006).

Registry No. **6**, 142-62-1; **7**, 97-61-0; **8**, 103-82-2; **9**, 103-04-8; **10**, 17431-94-6; **11**, 4749-28-4; **12**, 2783-12-2; **13**, 2562-37-0; **14**, 4812-23-1; **15**, 26817-75-4; **15′**, 77903-61-8; **16**, 84796-99-6; **16′**, 84796-95-2; **17** (isomer 1), 84797-00-2; **17** (isomer 2), 84797-01-3; **17′** (isomer 1), 84805-09-4; **17′** (isomer 2), 55311-10-9; **18** (isomer 1), 90670-05-6; **18** (isomer 2), 90670-06-7; **18′** (isomer 1), 88869-02-7; **18′** (isomer 2), 88869-03-8; **19**, 84797-02-4; **19′**, 84796-96-3; **20**, 84797-03-5; **20′**, 84796-97-4; **21**, 72349-79-2; **21′**, 75436-61-2; **22**, 4439-87-6; **22′**, 74457-44-6; **23**, 13122-69-5; **23′**, 84796-94-1; **24** (isomer 1), 84805-10-7; **24** (isomer 2), 84796-98-5; **24′** (isomer 1), 84805-07-2; **24′** (isomer 2), 84805-08-3; **25**, 84796-81-6; **25′**, 84796-82-7; **25′**-ol, 90670-14-7; **26**, 84796-89-4; **26′**, 84796-83-8; **27** (isomer 1), 84796-90-7; **27** (isomer 2), 84796-91-8; **27′** (isomer 1), 84796-84-9; **27′** (isomer 2), 84796-85-0; **28** (isomer 1), 84805-03-8; **28** (isomer 2), 84805-04-9; **28′** (isomer 1), 84796-86-1; **28′** (isomer 2), 84805-00-5; **28′**-ol, 90670-09-0; **29**, 84796-92-9; **29′**, 84796-87-2; **30**, 84796-93-0; **30′**, 84796-88-3; **31** (isomer 1), 84805-05-0; **31** (isomer 2), 84805-06-1; **31′** (isomer 1), 84805-01-6; **31′** (isomer 2), 84805-02-7; **32**, 106-70-7; **33**, 110-42-9; **34**, 4630-82-4; **35**, 101-41-7; **36**, 17277-58-6; **37**, 75436-60-1; **38**, 88869-08-3; **39**, 88869-09-4; **40**, 53138-46-8; **41**, 591-11-7; **42**, 53183-56-5; **43** (isomer 1), 53390-35-5; **43** (isomer 2), 90670-15-8; **44**, 3727-53-5; **45**, 15174-78-4; **46a**, 2833-24-1; **46b**, 90670-10-3; **47**, 19980-35-9; **48a** (isomer 1), 90670-11-4; **48a** (isomer 2), 90670-07-8; **48b** (isomer 1), 90670-12-5; **48b** (isomer 2), 90670-08-9; **49a** (isomer 1), 67800-09-3; **49a** (isomer 2), 90670-16-9; **49b** (isomer 1), 90670-13-6; **49b** (isomer 2), 90670-17-0; propanoic acid, 79-09-4; cyclohexanecarboxylic acid, 98-89-5.

Charge–Carbon-13 Empirical Relationships in Organic Ions: An Improvement Extending the Access to Experimental Charge Maps

Silvia Bradamante and Giorgio A. Pagani*

Centro C.N.R. and Istituto di Chimica Industriale dell'Università, via Golgi 19, 20133 Milano, Italy

Received October 26, 1983

An improved empirical relationship between ^{13}C shifts and local π electron densities is proposed for organic ions. Accordingly, the ^{13}C shifts can be predicted by summing two terms: the first takes into account the shielding contributions of neighboring groups and represents the shift of a hypothetically uncharged trigonal carbon with the same chemical environment as that of the ion, while the second term accounts for the effect of π charge upon this shift. The validity and generality of the relationship are tested in a number of carbanions and carbenium ions constituted of a hydrocarbon skeleton only and in which the charge is fully delocalized. A good accord is generally found between empirical and theoretically computed local π electron densities: exceptions, in particular those relative to triphenylmethyl ions, are discussed in detail. The proposed relationship represents an easy and expeditious method for obtaining experimental, empirical charge maps in organic ions starting from their ^{13}C shifts.

Carbanions and carbenium ions are key intermediates in many reactions of organic chemistry. When the charge is delocalized over an extended π system, structure–reactivity relationships require in the first step a detailed knowledge of charge density maps. Although theoretical calculations provide one access to charge distribution, in

0022-3263/84/1949-2863$01.50/0