Stereospecific and Stereoselective Reactions. V.[1] Alkylation of Active Methylene Compounds by the Use of Alcohols, Diethyl Azodicarboxylate, and Triphenylphosphine[2]

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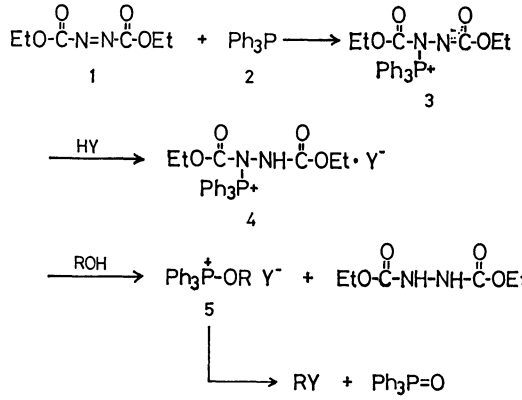
The reagent formed by the reaction of diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**) reacted with alcohols and ethyl cyanoacetate (**6**) to give alkylated products in 30—80% yields. When ethyl acetoacetate, 1,3-cyclopentanedione, or 1,3-cyclohexanedione was used in place of **6**, the corresponding *O*-alkylated products were obtained. The reaction of either (*S*)-(−)-ethyl lactate or (*S*)-(−)-ethyl 2-hydroxy-3-phenylpropionate with **1**, **2**, and **6**, followed by hydrolysis resulted in the formation of (*S*)-(−)-methylsuccinic acid or (*S*)-(−)-benzylsuccinic acid. The results indicate that nearly complete inversion of the configuration takes place in the alkylation step.

Alkylation of anions derived from active methylene compounds furnishes a synthetically useful reaction producing carbon to carbon bonds. A number of bases are effective for removing a proton from the carbon atom alpha to an electron-withdrawing group, but only a few alkylating reagents are utilized in the alkylation of the carbanions.[3]

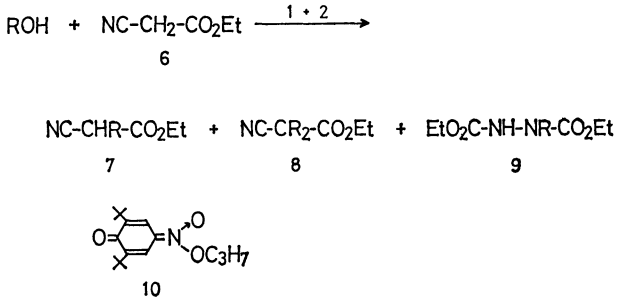
It was reported that the reaction of diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**) in the presence of an alcohol and an acidic component gives an alkoxyphosphonium salt intermediate (**5**) which functions as a versatile alkylating reagent.[4] The reaction seems to proceed through (a) addition of **2** to **1** giving a quaternary phosphonium salt (**3**),[5] (b) protonation of **3**, (c) formation of an alkoxyphosphonium salt (**5**), and (d) S_N2 type displacement of the resulting species **5** as shown in Scheme 1.



Scheme 1.

Acidic components (Scheme 1; YH) alkylated by this method include phosphoric mono- and diesters, carboxylic acids, imides, phenols, and oximes. Not only simple alcohols but also complex hydroxy compounds such as nucleosides, carbohydrates, and steroids can be used.[4] This paper deals with the alkylation of acyclic and cyclic active methylene compounds by the above reaction.

Alkylation of Ethyl Cyanoacetate. The alkylation of ethyl cyanoacetate (**6**) was carried out under the same conditions as for the preparation of carboxylic esters.[6] Thus, **1** was added to a solution of 1-propanol, **2**, and **6** in tetrahydrofuran (THF) at room temperature (Procedure A). No alkylation of **6** took place, 45% of **6** being recovered. Similarly, no alkylated product was obtained when the reaction was carried out at −10——15 °C. On the other hand, when **1** was added to **2** in THF at −10——15 °C, followed by the addition of **6** and 1-propanol (Procedure B) and the reaction was continued for 1 h, ethyl 2-cyanopentanoate (**7**; R=C_3H_7) was isolated in 29% yield along with dialkylated product, ethyl 2-cyano-2-propylpentanoate (**8**; R=C_3H_7; 3—4%). A small amount of diethyl *N*-propylhydrazine-*N*,*N*′-dicarboxylate (**9**; R=C_3H_7) was also obtained (Scheme 2).



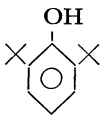
Scheme 2.

In Procedure B, a white fine precipitate is sometimes observed in the initial 5—10 min (1—2 mmol each of **1** and **2**/2—3 ml of THF). Complete disolution takes place on addition of alcohol and **6**, **7** (R=C_3H_7) being obtained in a comparable yield as above. No identification has yet been made but the precipitate seems to be an intermediate in the reaction. Since stirring of the slurry of the adduct is difficult, the alcoholic and acidic components are added preferably before the precipitation of adduct.

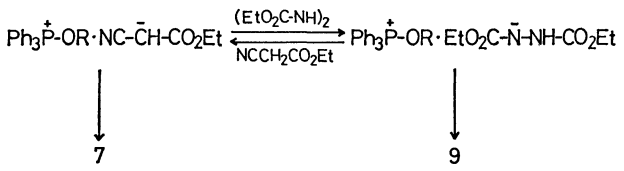
It was found that various alcohols can also enter into the reaction under similar conditions. The results are summarized in Table 1.

The formation of **9** suggests that both ethyl cyanoacetate anion and diethyl hydrazinedicarboxylate anion exist in the reaction mixture at equiliblium, the product ratio (**7**/**9**) depending on relative acidity of **6** and diethyl hydrazinedicarboxylate as well as the nucleophilicity of their anions (Scheme 3).[7]

TABLE 1. ALKYLATION OF ETHYL CYANOACETATE (**6**) BY PROCEDURE B

Reactant (mmol)						NC-CHR-$CO_2C_2H_5$	
R	ROH	**1** and **2**	**6**		Reaction time/h (°C; rt, room temperature)	Yield %	NMR (CCl_4) δ/ppm
C_3H_7	2	3	2	0	1(−20), 7(−20—0), 10(rt)	51[a]	0.8—1.2(m, $C\underline{H}_3CH_2CH_2$-), 1.35(t, $CH_3C\underline{H}_2O$-), 1.1—2.2(m, $CH_3C\underline{H}_2C\underline{H}_2$-), 3.35 (t, NCC$\underline{H}$-), 4.3(q, $CH_3C\underline{H}_2O$-)
	4	3	2	0	1(−20)[b]	29[c]	
	4	3	2	0	48(−20)[b]	30[d]	
CH_2=$CHCH_2$	4	2	2	0	2(rt)	43[e]	1.3(t, CH_3), 2.5—2.75(3 lines, =$CHC\underline{H}_2$-), 3.4—3.65(3 lines, NCC$\underline{H}$-), 4.22(q, CH_2O-), 4.9—6.2(m, vinyl H)
	1.3	1.5	1	1	10(rt)	24[f]	
EtO_2C, CH_3, CH (*dl*)	3	4.5	3	0	24(rt)	45[g]	1.3 and 1.32(two t, $C\underline{H}_3CH_2$-), 1.4(d, $C\underline{H}_3CH$〈), 2.7—3.35(m, $CH_3C\underline{H}$〈), 3.45—3.9(4 lines, NCC$\underline{H}$-), 4.15 and 4.25 (two q, $CH_3C\underline{H}_2O$-)
	3	4.5	3	3	24(rt)	62[g]	
EtO_2C, C_5H_{11}, CH (*dl*)	54	70	54	0	5(−30——20), 12(−10), 10(0), 120 (rt)	83	0.9(m, $C\underline{H}_3(CH_2)_4$-), 1.3 and 1.35(two t, $C\underline{H}_3CH_2O$-), 1—2.2(m, $CH_3(C\underline{H}_2)_4$-, 2.7—3.2(m, $C_5H_{11}C\underline{H}$-), 3.65—3.95(4 lines, NCC$\underline{H}$-), 4.18 and 4.25(two q, $CH_3C\underline{H}_2$-)
	30	40	30	40	12(0), 120(rt)	74	
MeO_2C, CH_3CH (*dl*)	2	1.5	1	0	24(rt)	67	1.15 and 1.2(two t, $C\underline{H}_3CH_2$-), 1.5(d, $C\underline{H}_3C\underline{H}$-), 3.25—3.8(m, NC-C$\underline{H}C\underline{H}$-), 4.1 and 4.15(two q, $CH_3C\underline{H}_2$-), 7.35 and 7.95 (AA'BB', aromatic H)
	2	1.5	1	1.5	24(rt)	79	

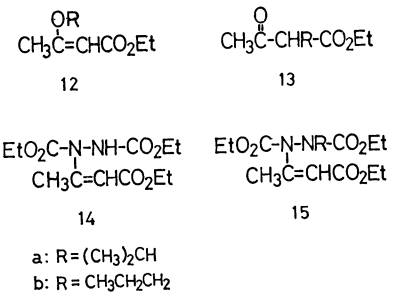
a) 12 and 17% yields of **8**(R=C_3H_7) and **9**(R=C_3H_7), respectively, 23% of **6** recovered. b) Procedure C. c) 3—4% yield of **8**(R=C_3H_7). d) 7% yield of **8**(R=C_3H_7). e) 10% yield of **8**(R=CH_2=$CHCH_2$-). f) 21% yield of **8**(R=CH_2=$CHCH_2$-), 29% of **6** recovered. g) 10% yield of **9**(R=$EtO_2C(CH_3)CH$).



Scheme 3.

The yields of the alkylated products are not so high as compared with those obtained in the alkylation of relatively strong acid such as phosphoric diesters,[8] carboxylic acids,[6] or imides.[9] A possible explanation of the difference is obtained if a protonated phosphonium salt (**4**) is assumed to be an active intermediate for the formation of an alkoxyphosphonium salt (**5**). In the reaction of **6**, equilibrium is not favorable to protonated form (**4**; Y=CH(CN)CO_2Et) because of its low acidity. In order to increase the concentration of the protonated form in equilibrium, alkylation of **6** by various alcohols was examined in the presence of 2,6-di-*t*-butylphenol as a proton source. The yields of alkylated products increased to some extent, but no marked effect of the proton source was observed (Table 1). When 2,6-di-*t*-butyl-4-nitrophenol was used in place of 2,6-di-*t*-butylphenol, an *aci*-nitro ester (**10**)[10] was obtained in 70% yield with a 67% recovery of **6**.

Alkylation of Ethyl Acetoacetate. The reaction of ethyl acetoacetate (**11**) with **1**, **2**, and 2-propanol was carried out by Procedure B giving ethyl 3-isopropoxy-2-butenoate (**12a**), 3-[1,2-bis(ethoxycarbonyl)hydrazino]-2-butenoate (**14**), and 3-[2-isopropyl-1,2-bis(ethoxycarbonyl)hydrazino]-2-butenoate (**15a**) in 17, 16, and 12% yields, respectively. Contrary to the case of alkylation of **6**, that of **11** took place even at room temperature by Procedure A giving **12a**, **14**, and **15a** in 6, 40, and 8% yields, respectively (Scheme 4). No *C*-alkylated product (**13a**) could be isolated in these reactions.



Scheme 4.

The side product **14** would be formed *via* a vinyloxyphosphonium salt (**16**) which arises from the reaction of **3** with **11** (enol form). Collapse of **16** by an addition-elimination process gave rise to **14** and triphenylphosphine oxide (Scheme 5). The assumption is supported by the reaction of **11** with **1** and **2** in

Table 2. Alkylation of ethyl acetoacetate (**11**)

R	ROH	1 and 2	11	Procedure	Reaction time/h (°C; rt, room temperature)	Products yield/% 12	13
$(CH_3)_2CH$	4	3	2	A	48 (rt)	6[a]	0
	4	3	2	B	48 (−20)	17[b]	0
	4	3	2	C	48 (−20)	35	0
C_3H_7	4	3	2	A	24 (rt)	18[c]	0
	8	5	4	B	24 (−20)	18	0
	8	5	4	C	48 (−20)	37	0
	40	5	4	A	72 (rt)	29	6
	40	5	4	C	72 (−20)	30	6

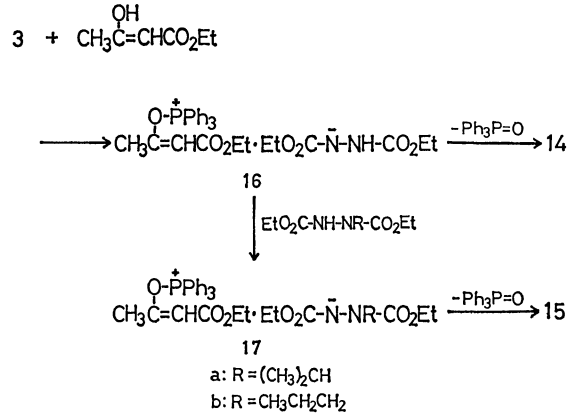
a) 40 and 8% yields of **14** and **15a**, respectively. b) 16 and 12% yields of **14** and **15a**, respectively. c) 8 and 6% yields of **14** and **15b**, respectively.

Table 3. Alkylation of 1,3-cyclohexanedione

ROH	Reactant (mmol)[a] 1 and 2	Procedure	Reaction time/min (°C; rt, room temperature)	Products yield/% 18	19
$(CH_3)_2CH$	2 2	A	35 (rt)	81	
	2 2	B	50 (−20)	74	
C_2H_5>CH / CH_2=CH	3 3	A	60 (rt)	36	8
	3 3	B	60 (−20)	40	13

a) 1,3-Cyclohexanedione; 1.5 mmol.

the absence of an alcoholic component where **14** was obtained in 68% yield. Compound **15** would be produced through a similar intermediate **17**.

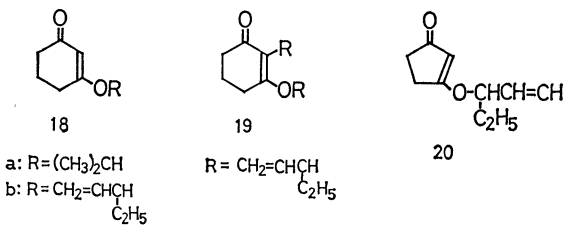


Scheme 5.

In order to suppress the formation of undesirable **14** and **15a**, 2-propanol (2 equivalents) and **11** were successively added to the reaction mixture of **1** with **2** at −10——20 °C (Procedure C). By this procedure, the yield of **12a** increased to 35%.

Similarly, the reaction of 1-propanol with **11** by Procedure A or B resulted in the formation of *O*-alkylated product (**12b**) in 18% yield, the yield increasing to 37% by Procedure C. When 1-propanol was used in large excess (10 equivalents), the *C*-alkylated product (**13b**) was formed in 6—10% yield along with **12b** (30%). The results are summarized in Table 2.

Alkylation of Cyclic 1,3-Diketone. In contrast to the case of acyclic active methylene compounds, the alkylation of cyclic 1,3-diketones proceeded smoothly in a perior of 0.5—1 h, giving *O*-alkylated products in good yields. Thus, when 1,3-cyclohexanedione was allowed to react with 2-propanol, **1**, and **2**, 3-isopropoxy-2-cyclohexenone (**18a**) was isolated by Procedures A and B in 74% and 81% yields, respectively. When 1-penten-3-ol was used in this reaction (Procedure B), 3-(1-ethyl-2-propenyloxy)-2-cyclohexenone (**18b**) and 3-(1-ethyl-2-propenyloxy)-2-(1-ethyl-2-propenyl)-2-cyclohexenone (**19**) were obtained in 40 and 13% yields, respectively (Scheme 6; Table 3). The reaction of 1,3-cyclopentanedione with 1-penten-3-ol by Procedure A resulted in the formation of 3-(1-ethyl-2-propenyloxy)-2-cyclopentenone (**20**) in nearly quantitative yield.

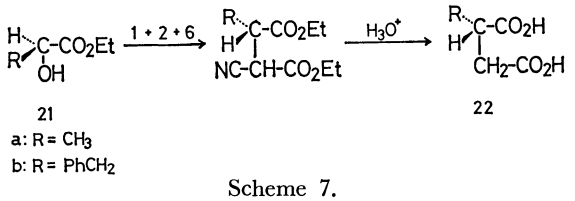


Scheme 6.

Stereochemistry. Intermolecular dehydration between an optically active alcohol and active hydrogen compounds by the use of **1** and **2** proceeds through the inversion of the configuration at the carbon atom bonded to hydroxyl group.[4]

The inversion of configuration was observed in the alkylation of **6**. Thus, (*S*)-(−)-ethyl lactate (**21a**) reacted with **6** in the presence of **1** and **2** to give diethyl 2-cyano-3-methylsuccinate in 61% yield. On hydrolysis, methylsuccinic acid (**22a**) with $[\alpha]_D$ −15.1° was obtained. This indicates that complete or nearly complete inversion of the configuration at the reaction site takes place in the alkylation step. Similarly, (*S*)-

(−)-ethyl 2-hydroxy-3-phenylpropionate (**21b**) was converted into opticcally pure (*S*)-(−)-benzylsuccinic acid (**22b**) (Scheme 7).



Scheme 7.

Concluding Remarks. The reagent formed by the reaction of **1** and **2** could be utilized in direct condensation between alcohols and active methylene compounds. The reaction proceeds under mild neutral conditions with inversion of configuration at the reaction site. In spite of some reduced yields, a high degree of stereospecificity is observed. The reaction might provide an effective procedure for the synthesis and transformation of natural products.

The fact that the alkylation of 1,3-dicarbonyl compounds mainly gives *O*-alkylated products suggests that the alkoxyphosphonium salt intermediate is a harder alkylating reagent than alkyl halides and alkyl sulfonates.[11] Steric interaction between alkoxyphosphonium salt having three bulky phenyl groups and ambident anion derived from the dicarbonyl compound would also favor *O*-alkylation.

Diethyl malonate can not enter into the alkylation reaction,[2b] suggesting that an active methylene compound to be alkylated should be more acidic than diethyl hydrazinedicarboxylate for achievement of the reaction.

Experimental

The reaction was carried out under anhydrous conditions. Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl. Unless otherwise stated, the products were isolated by preparative layer chromatography (PLC) carried out on Kieselgel 60 PF_{254} (Merck) or Wakogel-B5 plates (20 cm×20 cm or 20 cm×30 cm), visualization being made by UV light or iodine vapor. Nuclear magnetic resonance spectra were measured on a Hitachi R-20 spectrometer (60 MHz) using tetramethylsilane as an internal standard.

Alkylation of Ethyl Cyanoacetate. Procedure A: A solution of **1** (522 mg, 3 mmol) in THF (2 ml) was added dropwise to a solution of **2** (787 mg, 3 mmol), **6** (226 mg, 2 mmol), and 1-propanol (240 mg, 4 mmol) in THF (6 ml) at room temperature. The solution was stirred at room temperature for 2 d. No alkylated product could be obtained, 45% of **6** being recovered.

Procedure B: A solution of **1** (1.3—1.5 mmol) in THF (0.5 ml) was added dropwise to a solution of an equimolar amount of **2** in THF (3 ml) stirred in an ice–salt bath. The intermediate formed in solution by this procedure will be referred to as "adduct." A few min after mixing the components, a solution of **6** (1 mmol) and an alcohol (1—2 mmol) in THF (3 ml) was added at this temperature. Stirring was continued under the conditions shown in Table 1.

Reaction in the Presence of 2,6-Di-t-butylphenol. To the adduct was added a solution of 1 mmol each of **6**, 2,6-di-*t*-butylphenol, and an alcohol in THF (3 ml) at −20 °C. The solution was stirred for appropriate periods of time (Table 1).

Reaction in the Presence of 2,6-Di-t-butyl-4-nitrophenol. To the adduct prepared from 3 mmol each of **1** and **2** in THF (4.5 ml) was added all at once a solution of 1-propanol (4 mmol) and 2,6-di-*t*-butyl-4-nitrophenol (754 mg, 3 mmol) in THF (3 ml). A solution of **6** (2 mmol) in THF (2.5 ml) was then immediately added over a period of 20 min and the resulting solution was kept standing at −20 °C for 10 h. The products were separated by PLC (benzene) giving **10** in 70% (617 mg) yield and recovered **6** (67%). Compound **10** was again applied to silica-gel plates and developed with ether–petroleum ether (1:5) to give semicrystalline sirup which crystallized on trituration with petroleum ether, subliming at 138—141 °C. NMR (CCl_4) δ 1.8—2 (m, $C\underline{H}_3C\underline{H}_2$), 1.13 (s, *t*-$C_4H_9$), 4.25 (t, CH_2O), 7.28 and 7.5 (AB q, J=3 Hz, 2H, vinyl H).

Preparative Scale Experiment. Reaction with Ethyl 2-Hydroxyheptanoate. A solution of **6** (54 mmol) and ethyl 2-hydroxyheptanoate (9.387 g, 54 mmol) in THF (25 ml) was added dropwise at −20——30 °C to a solution of the adduct prepared from 70 mmol each of **1** and **2** in THF (20 ml). After the solution had been stirred at −30——20 °C for 5 h, −10 °C for 12 h, at 0 °C for 10 h, and then at room temperature for 5 d, the solvent was removed under reduced pressure. Ether (30 ml) was added to the residue and precipitate was filtered off. The filtrate was evaporated and the residue was applied to a silica-gel column (Wakogel C-200, 4 cm×30 cm) and eluted with benzene. Diethyl 2-cyano-3-pentylsuccinate was obtained in 83% yield and purified by distillation; 64%, bp 119—122 °C/0.25 Torr (1 Torr=133.322 Pa).

The ester was treated with concd HCl under reflux for 15 h. The mixture was extracted with ether and organic layer was evaporated giving pentylsuccinic acid which was recrystallized from hexane; 84% yield, mp 82—83 °C (lit,[12] mp 82.5—83.5 °C) (*R*-(+)-form). NMR (acetone-d_6) δ 1.6—2.0 (m, 11H, C_5H_{11}), 2.3—3.2 (m, 3H, $CHCH_2$), 9.51 (s, 2H, COOH).

Alkylation of Ethyl Acetoacetate. Procedure A: A solution of **1** (3 mmol) in THF (3 ml) was added dropwise to a solution of **2** (3 mmol), **11** (260 mg, 2 mmol), and 2-propanol (4 mmol) in THF (7 ml) at room temperature, and the solution was stirred at room temperature for 2 d. After removal of the solvent *in vacuo*, the residue was applied to silica-gel plates, developed with benzene giving **12a** in 6% (20 mg) yield. The zone containing **14** and **15a** was rechromatographed (AcOEt–CCl_4=1:3) affording chromatographically homogeneous **14** and **15a** in 40% (231 mg) and 8% (55 mg) yields, respectively. NMR, **12a** (CCl_4) δ 1.20 (t, $C\underline{H}_3CH_2$) and 1.25 (d, $(CH_3)_2CH$); total 9H, 2.15 (s, $C\underline{H}_3$–$\underline{C}$=C<), 3.9 (q, $CH_3C\underline{H}_2$) and 4.3 (septet, $(CH_3)_2C\underline{H}$); total 3H, 4.7 (s, >C=C$\underline{H}$). **14** ($CDCl_3$) δ 1.25 (superimposed t, 9H, three $C\underline{H}_3CH_2$), 2.45 (s, $C\underline{H}_3$–$\underline{C}$=C<), 3.84—4.4 (superimposed q, 6H, $CH_3C\underline{H}_2$), 5.85 (s, >C=C$\underline{H}$–), 7.2—7.5 (br s, NH). **15a** (CCl_4) δ 1.1 (d, $(C\underline{H}_3)_2CH$) and 1.25 (superimposed t, three $C\underline{H}_3CH_2$); total 15H, 2.35 (s, $C\underline{H}_3$–C=C<), 3.7—4.35 (septet and superimposed q, total 7H, three $CH_3C\underline{H}_2$ and $(CH_3)_2C\underline{H}$), 5.5 (s, >C=CH–).

Procedure B: A solution of **1** (3 mmol) in THF (3 ml) was added dropwise to a solution of **2** (3 mmol) in THF (3 ml) stirred in an ice–salt bath. A few min after the components had been mixed, a solution of **11** (2 mmol) and 2-propanol (4 mmol) in THF (4 ml) was added and stirring was continued for 5 h. After the solution had been kept standing for 2 d at *ca.* −20 °C, **12a** **14**, and **15a** were obtained in 17, 16, and 12% yields, respectively.

Procedure C: A solution of 2-propanol (4 mmol) in THF (2 ml) was added all at once at −20 °C to a solution of the adduct prepared from 3 mmol each of **1** and **2** in THF (4 ml). Immediately after the addition of 2-propanol, a solution of **11** (2 mmol) in THF (2 ml) was added dropwise over a period of 15 min at −20 °C. The reaction mixture was stirred for 1.5 h and then kept standing at −20 °C for 2 d. The products were separated by PLC giving **12a** in 35% yield. Small amounts of **14** and **15a** were also formed as indicated by thin layer chromatography of the crude reaction mixture, no attempt being made to isolate them.

When 1-propanol was used in large excess (10 equivalents), a mixture of *C*-alkylated and *O*-alkylated products were obtained. The ratio was estimated from integration of the signal of NMR spectrum.

*Preparation of **14***. Compound **1** (3 mmol) in THF (2 ml) and **11** (2 mmol) in THF (2 ml) were successively added to a solution of **2** (3 mmol) in THF (3.5 ml) at −20 °C, and the mixture was kept standing at −20 °C for 2 d. Compound **14** was isolated by PLC (AcOEt–CCl_4=1:3) in 68% (390 mg) yield.

Alkylation of 1,3-Cyclohexanedione. *Procedure A*: A solution of **1** (2 mmol) in THF (3 ml) was added dropwise over a period of 10 min to a solution of **2** (2 mmol), 2-propanol (2 mmol), and 1,3-cyclohexanedione (1.5 mmol) in THF (6 ml) at room temperature. After the solution had been stirred at room temperature for 35 min, water (4 ml) was added, and extracted with $CHCl_3$. The organic layer was evaporated and the residue was separated by PLC (AcOEt–petroleum ether=1:1) giving **18a** which was contaminated with a small amount of diethyl hydrazinedicarboxylate. The crude product was suspended in CCl_4, stirred, and filtered in order to remove undissolved diethyl hydrazinedicarboxylate to give practically pure **18a**, 188 mg (81%). A pure sample was obtained by distillation, bp (oven temperature) 58—68 °C/35 Torr. NMR (CCl_4) δ 1.25 (d, $(C\underline{H}_3)_2CH$), 1.6—2.5 (m, $-(CH_2)_3-$), 4.4 (septet, $(CH_3)_2C\underline{H}$), 5.13 (s, $>C{=}C\underline{H}-$).

Procedure B: A solution of 1-penten-3-ol (258 mg, 3 mmol) and 1,3-cyclohexanedione (168 mg, 1.5 mmol) in THF (3 ml) was added over a period of 15 min to a solution of the adduct prepared from 3 mmol each of **1** and **2** in THF (7 ml) cooled in an ice–salt bath. Thin layer chromatography of the reaction mixture revealed that the cyclohexanedione disappeared in 10 min after the addition. The reaction mixture was stirred for 1 h and water was added. The mixture was extracted with $CHCl_3$ and the organic layer was evaporated. The residue was applied to silica-gel plates and developed with ether–petroleum ether=3:1 giving **18b** (108 mg, 40%) and **19** (48 mg, 13%). NMR; **18b** (CCl_4) δ 0.9 (t, CH_3), 1.25—2.55 (m, CH_3CH_2 and $-(CH_2)_3-$), 4.37 (q, CH–O), 4.85—5.95 (m, 4H, vinyl H). **19** (CCl_4) δ 0.75 (t, CH_3), 0.95 (t, CH_3), 0.9—2.6 (m, two $CH_3C\underline{H}_2$ and $-(CH_2)_3-$), 3.35 (q, $=C-C\underline{H}(C_2H_5)CH{=}CH_2$), 4.4 (q, CH–O), 4.5—6.2 (m, 6H, vinyl H).

Alkylation of 1,3-Cyclopentanedione. A solution of 1,3-cyclopentanedione (147 mg, 1.5 mmol) and 1-penten-3-ol (172 mg, 2 mmol) in *N*,*N*-dimethylformamide (1 ml) was added at −17 °C to the adduct prepared by the reaction of 2 mmol each of **1** and **2** in THF (2 ml). The solution was stirred at −17—−12 °C for 1.5 h and then at room temperature overnight. The products were separated by PLC (ether) to give **20** in 93% yield. NMR (CCl_4) δ 1.0 (t, CH_3), 1.7 (m, $CH_3C\underline{H}_2$), 2.1—2.8 (A_2B_2, $-CH_2CH_2-$), 4.5 (q, CH–O), 5—6.15 (m, 5H, vinyl H).

Preparation of (S)-(−)-*Methylsuccinic Acid*. A solution of (*S*)-(−)-ethyl lactate [1.53 g, 13 mmol, $[\alpha]_D^{19}$ −10.9° (neat)], **6** (1.13 g, 10 mmol), and 2,6-di-*t*-butylphenol (2.06 g, 10 mmol) in THF (17 ml) was added dropwise to a solution of the adduct prepared from 15 mmol each of **1** and **2** in THF (5 ml) at −20 °C. After the solution had been stirred at −20 °C for 3 h and then at room temperature for 1 d the solvent was removed *in vacuo*. Ether was added and the precipitate was filtered off. The filtrate was concentrated and the products were separated by PLC ($CHCl_3$) giving diethyl 2-cyano-3-methylsuccinate in 61% (1.29 g) yield, $[\alpha]_D^{20}$ −2.76° (*c* 6.03, CCl_4). The product was contaminated by small amounts of two side products as indicated by gas chromatography (OV-1, 1 m, column temperature was 140 °C in initial 6 min and then raised at a rate of 5 °C/min, retention time; the succinate, 2.3 min, unknown side products, 4 and 12.5 min, respectively).

The succinate (1.13 g, 5.3 mmol) was treated with acetic acid (1 ml) and concd HCl (4 ml) under reflux for 6 h and then 4 ml of concd HCl was added. After the mixture had been refluxed for 10 h, ether was added. Organic layer was concentrated to dryness giving crude methylsuccinic acid (502 mg, mp 80—85 °C). Recrystallization from hexane–CH_2Cl_2 (1:1) caused a rise in the melting point to 100—103 °C, $[\alpha]_D^{20}$ −12.5° (*c* 1.82, EtOH). Recrystallization for the second time from the same solvent system gave a pure sample, mp 109—109.5 °C, $[\alpha]_D^{19}$ −15.1° (*c* 0.818, EtOH) [lit,[13] mp 111—113 °C, $[\alpha]_D^{24.2}$ −15.0 (*c* 1.89, EtOH)].

Preparation of (S)-(−)-Benzylsuccinic Acid. (*S*)-(−)-Ethyl 2-hydroxy-3-phenylpropionate [1.94 g, 10 mmol, $[\alpha]_D$ −22.7° (*c* 0.852, benzene), lit[14] $[\alpha]_D$ −22.6° (*c* 4.33, benzene)] was allowed to react with 10 mmol each of **1**, **2**, and **6** by Procedure B. After the addition of the hydroxy ester and **6**, the solution was stirred at room temperature for 2 h. Diethyl 2-benzyl-3-cyanosuccinate was isolated by distillation (250 mg, 8.7%, bp 130 °C/0.25 Torr). The succinate was treated with a mixture of acetic acid (2.5 ml) and concd HCl (11.3 ml) under reflux for 10 h giving (*S*)-(−)-benzylsuccinic acid (159 mg, 88%) which was recrystallized from water, mp 153—154 °C, $[\alpha]_D^{21}$ −28.9° (*c* 0.665, AcOEt) [lit,[14] mp 159—161 °C, $[\alpha]_D^{28}$ −26° (*c* 1.5, AcOEt)].

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