H)$^+$ = 332, calculated molecular weight = 331.19. Elemental analysis: C, 65.2 (65.3); H, 6.3 (6.3); N, 4.2 (4.2); O, 24.4 (24.2) (calculated values are given in parentheses). Optical rotation: $[\alpha]^{23.5}_D$ = −17.1° (c 2.5; CH_3CN). ^1H NMR (200 MHz, $CDCl_3$): 1.1 (3 H, t, $J \sim 7.6$ Hz, CH_3), 2.2 (2 H, q, $J \sim 7.6$ Hz, CH_2CH_3), 2.9 (2 H, m, $CH_2C_6H_4$), 4.2 (2 H, m, CH_2O), 4.5 (1 H, m, >CH), 5.7 (1 H, d, $J \sim 9$ Hz, NH), 5.8–6.7 (6 H, m, $CH{=}CH_2$), 7.0–7.3 (4 H, m, C_6H_4).

Carbon-14-Labeled Substrates. ^{14}C-Labeled D- and L-*p*-aminophenylalanine ethyl esters were synthesized by esterification of free amino acid with [C-1,^{14}C]ethanol using a slightly modified standard procedure for amino acid ester synthesis,[8] a method known to yield no racemization of the product formed in the esterification step.

The following describes the method applied to make L-*p*-NH_2PheO[C-1,^{14}C]Et (D-*p*-NH_2PheO[C-1,^{14}C]Et was synthesized in an identical manner). The monohydrate of L-*p*-NH_2PheOH·HCl (126.6 mg, 0.54 mmol) was added to 7.5 mL of EtOH (99.5%) containing 250 μCi [C-1,^{14}C]ethanol. Dry HCl gas was bubbled through the mixture, placed on ice, to yield a saturated HCl solution. This solution was left for 40 h at room temperature, affording a product that had precipitated out from the solution during the reaction. The product formed was dissolved in "cold" ethanol (99.5%), and the solvent was evaporated under reduced pressure. This washing procedure using cold ethanol was repeated several times. The radiolabeled ethyl ester synthesized was purified by dissolving it in 15 mL of 0.2 M $NaHCO_3$ (pH adjusted to 9.5) and extracting the water phase with ethyl acetate (2 × 50 mL). The organic phase was saved and taken down to dryness, and the residue afforded in the evaporation step was dried over P_2O_5 under vacuum. Yield: 0.36 mmol (75 mg, 66%).

In order to remove small amounts of [^{14}C]ethanol remaining in the purified ^{14}C-labeled ester preparations, the product obtained was chromatographed twice on a silica gel column (1.6 × 20 cm, 33 mL) using chloroform/methanol (50:1, v/v) as the eluent. The product isolated was pure as judged from analysis by TLC, UV, specific radioactivity, and optical rotation. TLC: R_f = 0.51 on silica in chloroform/methanol (9:1, v/v); R_f = 0.63 on cellulose in 1-butanol/acetic acid/water (50:20:30, v/v). Optical rotation: $[\alpha]^{23}_D$ = +17.3° (c 2.5; CH_3CN) for the L enantiomer; $[\alpha]^{23}_D$ = −16.6° (c 4.2; CH_3CN) for the D-enantiomer. Specific radioactivity: L-*p*-NH_2PheO[C-1,^{14}C]Et, 1.79 nCi/μmol; D-*p*-NH_2PheO[C-1,^{14}C]Et, 2.11 nCi/μmol. UV: λ_{max} = 284 nm (in 0.1 M sodium phosphate, pH 7.5).

Nonlabeled L-*p*-NH_2PheOEt used as a print molecule was prepared similarly as described above for the preparation of the radiolabeled ethyl ester.

Preparation of Print Polymers. Polymer A. Following a procedure described previously,[2a] 1 (2.9 mol %) was copolymerized with an excess of DVB (technical grade containing 55.5 mol % of DVB and 41.6 mol % of ethylstyrene) in acetonitrile (1.28 mL/g of monomer mixture) in the presence of azobis(isobutyronitrile) (0.8% w/w of the monomers). After polymerization, the polymers were extracted continuously in toluene for 24 h using a Soxhlet extractor. Washing of the polymers was repeated once in acetonitrile. The polymers were then treated with 10 M NaOH/methanol (1:1, v/v) under reflux conditions for 20 h. After the hydrolysis step, they were washed successively in acetonitrile/water (1:1, v/v) and in acetonitrile using the Soxhlet extractor. Finally, the polymers were dried in an oven at 60 °C overnight. Prior to use, dried polymers were stored in a desiccator over P_2O_5 under vacuum. Elemental analyses of hydrolyzed and unhydrolyzed polymers were carried out. The nitrogen content of the polymers (0.44% before hydrolysis, 0.27% after hydrolysis, and about 0.1% for a blank polymer without print molecule) showed that approximately 50% of added print molecules had been split off from the polymers by the treatment with concentrated NaOH.

Polymer B. A print polymer was prepared by using instead of 1 a mixture of PVB (5.8 mol % of vinyl monomers) and L-*p*-NH_2PheOEt (2:1 molar ratio) in the polymerization step but otherwise under identical conditions as for polymer A except that the hydrolysis step was omitted.

Binding Experiments. Dry polymers (0.5 g) and acetonitrile (3 mL) containing D- or L-*p*-NH_2PheO[C-1,^{14}C]Et (1.7 mM) were equilibrated overnight at room temperature in centrifugation tubes placed on an end over end rocking table. The mixtures were then subjected to centrifugation. (In this context, it should be mentioned that in binding experiments similar to those described here, based on ammonium carboxylate ion-pair formation in highly cross-linked DVB polymers, the time dependence of ligand binding to the polymers indicated that equilibrium was reached within an hour at room temperature.) By measuring the radioactivity of the supernatant (in a liquid scintillation counter, LKB, rackbeta), the amount of bound and free substrate could be calculated. Used polymers were freed from bound ligand by washing the polymers with acetonitrile in the Soxhlet extractor. When the polymers were treated in this fashion, they could be reused two or three times.

Acknowledgment. We are grateful to Professor Klaus Mosbach for valuable discussions. This work was supported by Ferring Pharmaceuticals, the Swedish Natural Science Research Council, and the National Swedish Board for Technical Development.

Registry No. 1, 126257-05-4; 2, 126257-06-5; H-L-(*p*-NH_2)-Phe-OH·*x*HCl, 120482-21-5; H-D-(*p*-NH_2)Phe-OH·*x*HCl, 126257-07-6; H-L-(*p*-NH_2)Phe-OEt, 114422-51-4; H-D-(*p*-NH_2)-Phe-OEt, 126257-08-7; L-tyrosinol, 5034-68-4; polymer A, 126257-09-8.

(8) Greenstein, J. P.; Winitz, M. In *Chemistry of the Amino Acids*; Wiley: New York, 1961; p 925.

Trifluoromethyl-Substituted Carbethoxy Carbene as a Novel CF_3-Containing a^2 Synthon Equivalent for the Preparation of 2-(Trifluoromethyl)-4-oxo Carboxylic Ester Derivatives: Highly Functionalized Synthetic Building Blocks Bearing a CF_3 Group

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Received September 25, 1989

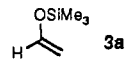
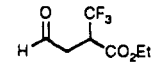
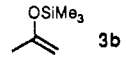
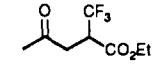
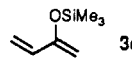
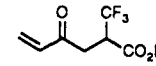
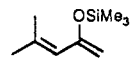
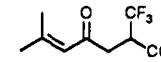
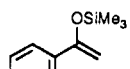
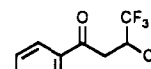
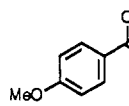
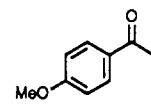
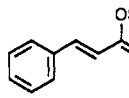
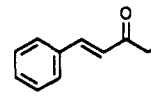
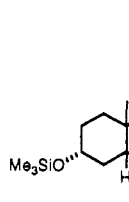
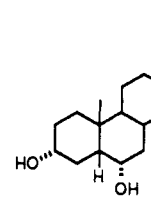
The synthesis of specifically trifluoromethylated molecules is an ongoing area of research due to the unique physical and biological properties imparted by the CF_3 group.[1] While for the synthesis of trifluoromethylated aromatic compounds, direct transformations of certain functional groups to the CF_3 group have been employed,[2] the preparation of trifluoromethylated aliphatic compounds, on the other hand, is not straightforward because of the requirement of milder reaction conditions and limited intrinsic reactivity of various trifluoromethylating reagents. Therefore, the development of a simple method for the preparation of trifluoromethylated building blocks and their further utilization for the synthesis of desired CF_3-containing aliphatic compounds are essential to organofluorine chemistry. Previously, we reported the easy preparation of a novel CF_3-containing diazo compound 1 from readily available inexpensive starting materials and established its feasibility as a CF_3-substituted carbenoid

(1) (a) *Carbon-fluoride Compounds, A CIBA Foundation Symposium*; Elsevier: Amsterdam, 1972. (b) Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha: Tokyo, 1983. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (d) Fuchigami, T. *J. Synth. Org. Chem. Jpn.* **1984**, *42*, 775.

(2) Hudlicky, M. In *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: Chichester, 1976.

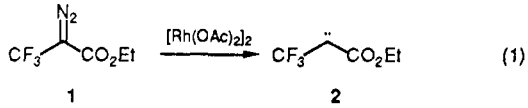
0022-3263/90/1955-3383$02.50/0

Table I. 2-(Trifluoromethyl)-4-oxo Carboxylic Ester Derivatives Prepared

entry	silyl enol ethers	procedure[a]	products[b]	yield,[c] %
1	 3a	B	 5a	73
2	 3b	A or B	 5b	83
3	 3c	B or C	 5c	85
4	 3d	A or B	 5d	87
5	 3e	A or B	 5e	90
6	 3f	A or B	 5f	94
7	 3g	A or B	 5g	97
8	 3h	D	 5h[d]	77

[a] See Experimental Section. [b] All the products (**5a–h**) are hitherto unknown and are fully characterized by ^{1}H NMR, IR, MS and C, H, F elemental analyses. [c] Yield of the isolated product based on **3**. The yield is slightly varied with different procedures and the better one is presented. [d] Obtained as a pair of epimers (1:1) as revealed by two doublets in the ^{19}F NMR spectrum due to the absorption of two epimeric CF_3 groups.

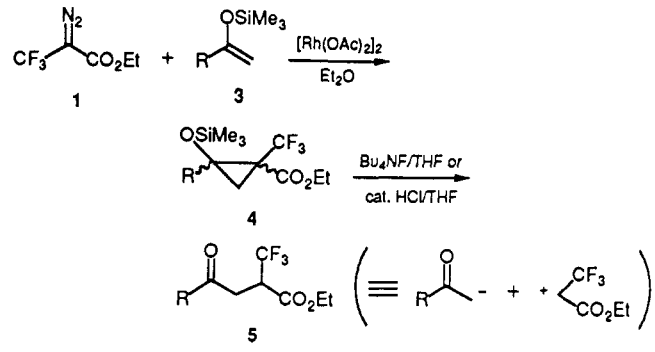
precursor.[3] We describe here further synthetic utility of **1** based on its rhodium-catalyzed decomposition to produce in situ a CF_3-substituted carbethoxy carbenoid **2** and its subsequent synthetic manipulations.



1 2 (1)

The inherent problems associated with the carbon–carbon bond formation on a trifluoromethyl-substituted anionic or cationic carbon[4] have largely accounted for the scarcity of practical CF_3-containing building blocks, especially those with adequate functionalities for the assembly of complex molecules. We envisaged that the interaction of **2** with silyl enol ethers to produce a siloxycyclopropane derivative and its subsequent unravelling might constitute an interesting carbon–carbon bond forming reaction in which **2** act as a CF_3-containing a[2] synthon equivalent. Indeed, we found that the rhodium-catalyzed reaction of **1** with electron-rich and sterically undemanding silyl enol ether **3** readily afforded a cyclopropane product[5] **4**, which, being installed with a donor–acceptor system,[6] underwent facile unidirectional ring

Scheme I



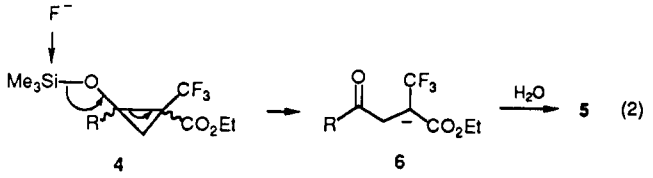
scission on treatment with Bu_4NF or a catalytic amount of hydrochloric acid to afford a variety of synthetically valuable 2-(trifluoromethyl)-4-oxo carboxylic ester derivatives in good overall yield (Scheme I).

The results were summarized in Table I. Cyclopropanation proceeded smoothly with a variety of silyl enol ethers possessing a terminal enolic double bond and furnished **4** as a pair of *E* and *Z* isomers in unequal amount as revealed by ^{19}F NMR analysis of the reaction mixture. In all cases, the intermediary product **4**, which was rendered unstable by the "push and pull" action of the ring substituents, needed not to be isolated, for they could undergo instantaneous ring opening when the reaction mixture was subjected to desilylation even below room temperature. Somewhat surprisingly, when silyl enol ethers derived from cyclohexanone and 3-pentanone, which possess an internal enolic double bond and are consequently more sterically demanding, were used as substrates, no preparatively useful yield of the corresponding

(3) Shi, G.; Xu, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 607.
(4) (a) Young, J. A. *Fluorine Chem. Rev.* **1967**, *1*, 359. (b) Drakesmith, F. G.; Steward, O. J.; Tarrant, P. *J. Org. Chem.* **1967**, *33*, 280. (c) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987 and 3991. (d) Morikawa, T.; Nishiwaki, T.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 2407.
(5) For rhodium-catalyzed cyclopropanation, see: Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919 and references cited therein.
(6) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

products could be obtained even though more than 2 equiv of 1 was used. In these two cases, it was found that the competing dimerization reaction and intermolecular C–H insertion of 2 into the solvent[7] became predominant, indicating that due to CF_3 substitution, 2, among other considerations, is much more sterically sensitive in cyclopropanation than those derived from other diazo esters, notably, ethyl diazoacetate.[8]

The reaction of Bu_4NF with 4 deserves further comments: ring opening by this reagent was believed to proceed via fluoride anion promoted desilylation and subsequent formation of an anionic intermediate 6 whose defluorination, as will be the case otherwise,[9] was presumably impeded by a quaternary ammonium countercation[10] and the presence of a fluoride anion in the reaction medium, thus making the ring-opening reaction a safe one. Besides,



in the case of entry 3, it was found that the yield of **5c** was substantially lowered when the ring-opening reaction, as had been done in the other cases, was performed in dry THF medium.[11] This anomaly could be rationalized by invoking the involvement of 6 (R = vinyl) whose combination with a reactive Michael acceptor, i.e., the double-bond moiety of **5c** (compare **5d** whose corresponding part was relatively unreactive due to steric congestion), might have initiated a series of intermolecular processes and, as a result, a considerable amount of polymeric byproducts was produced. However, this problem could be circumvented by running the reaction in moist THF so that the anionic intermediate 6 (R = vinyl) was rapidly protonated on its formation. Furthermore, it should be noted that in entry 1 the presence of a base-sensitive aldehyde group in the product precluded the use of Bu_4NF because of its incurrence of a basic reaction medium so that only acid could be used for the ring unravelling.

In contrast with the fluoride-induced ring opening, that catalyzed by acid probably involved an initial regiospecific attack of a proton at the carbon–carbon bond of the ring followed by the ring scission in a cationic fashion, and consequently no complications, as was encountered in the former case, had arisen therefrom.

It is noteworthy that the present reaction can be exploited for the introduction of a CF_3-containing side chain to a steroidal compound (entry 8) whose further elaboration should provide some interesting CF_3 analogues of bioactive natural products.

In conclusion, we have developed a facile synthesis of highly functionalized trifluoromethylated building blocks which could be utilized in a variety of ways such as appropriate stepwise functionalization at 1,4 termini, formation of lactone system, etc. Synthetic application of these functionalized building blocks for preparing trifluoromethylated organic compounds of biological interest are being pursued.

Experimental Section

^1H NMR spectra were recorded on a Varian EM-360A spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (δ 0.00) as an external standard; downfield shifts were designated as negative. Infrared spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra were done on a Finnigan 4021 GC/MS/DC instrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or ^{19}F NMR spectroscopy.

Ether was dried over sodium wire, and THF was distilled from $LiAlH_4$. Bu_4NF (1 M solution) was purchased from Aldrich and used as received. $[Rh(OAc)_2]_2$ was prepared by the method of Wilkinson.[12] Silyl enol ether **3a** was prepared as previously described.[13] A modified procedure[14] was used to prepare **3d**, **3g**, and **3h**; other silyl enol ethers were prepared according to a general procedure described by Cazeau et al.[15]

Preparation of Ethyl 3,3,3-Trifluoro-2-diazopropionate (1). Ethyl 3,3,3-trifluoro-2-oxopropionate[3,16] (20 g, ca. 0.1 mol) and tosyl hydrazide (18.6 g, 0.1 mol) were mixed in CH_2Cl_2 (120 mL). The mixture was briefly refluxed and then stirred at room temperature overnight. Pyridine (50 mL) was added, and then with the exclusion of moisture $POCl_3$ (9.4 mL, 0.1 mol) was added at such a rate that a gentle reflux was maintained. After addition, refluxing of the reaction mixture was continued for an additional 20 min. Water (200 mL) was added, and the organic layer was separated. The water layer was extracted with ether (80 mL × 3). The combined organic layer was washed with 1 N HCl solution to remove the pyridine and then washed successively with saturated $NaHCO_3$ solution and brine and dried over Na_2SO_4. The bulk of the solvent was removed in a rotary evaporator, and the remaining solvent was carefully distilled off under atmospheric pressure. Further distillation under reduced pressure[17] gave 14 g (77%) of 1 as a yellow liquid: bp 60–62 °C (100 mmHg); ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 4.20 (q, J = 7 Hz, 2 H); ^{19}F NMR (CCl_4) δ −20.0 (s); IR (neat) 2200 (s), 1750 (s); MS m/z (relative intensity) 183 (M + 1, 3), 80 (100), 52 (11). Anal. Calcd for $C_5H_5N_2O_2F_3$: C, 33.00; H, 2.75; N, 15.38. Found: C, 33.05; H, 2.75; N, 15.06.

General Procedures for the Preparation of 2-(Trifluoromethyl)-4-oxo Carboxylic Ester Derivatives. Procedure A. A solution of 1 (4 mmol) in dry ether (10 mL) was added dropwise within 4 h under N_2 to a suspension of $[Rh(OAc)_2]_2$ (0.005 mmol) in silyl enol ether 3 (2 mmol) kept at reflux. The resulting reaction mixture was then diluted with dry THF (15 mL) and treated with Bu_4NF in THF (2 mL) at room temperature for a few minutes. Water (30 mL) was added, and three extractions with ether were

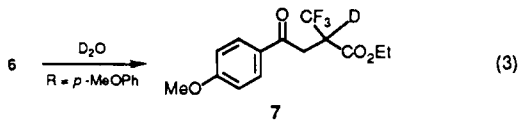
(7) The insertion product was found to be exclusively the one which resulted from insertion of 2 into C–H bond to the ether oxygen. The same has been reported for other carbenoids. Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.

(8) (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778. (b) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Justus Liebigs Ann. Chem.* **1984**, 512.

(9) Kitazume, T. K.; Ohnogi, T. *Synthesis* **1988**, 614.

(10) Fuchigami, T.; Nakagawa, Y. *J. org. Chem.* **1987**, *52*, 5276.

(11) Although it was found that the drying of THF was not necessary for the production of 5 (vide infra), it did offer advantage in that a discrete anion 6 could be generated which had been quenched by D_2O other than H_2O and might be further diverted to other synthetic purposes.



(12) Rempel, G. A.; Legzdins, P.; Smith, H.; Wilkinson, G. *Inorg. Synth.* **1972**, *13*, 90.

(13) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791.

(14) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

(15) Cazeau, P.; Ouboudin, F.; Moulines, F.; Babot, O.; Dunogus, J. *Tetrahedron* **1987**, *43*, 2075.

(16) Francese, C.; Toxdeux, M.; Wakeselman, C. *Tetrahedron Lett.* **1988**, *29*, 1029. The compound is prone to exist in its hydrated form which, it was found, was unnecessary to dehydrate and could be directly used in the present experiment.

(17) The distillation can also be carried out with safety at the atmospheric pressure, although some decomposition was noticed when the final bath temperature was raised above 150 °C in order to drive out the product from the high boiling residue. Unlike some other diazo compound, 1 is quite stable and can be stored in a refrigerator for several months without any deterioration.

carried out. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a residue which was subjected to silica gel chromatography using 9:1 petroleum ether/ethyl acetate as the eluent.

Procedure B. The procedure is similar to A with the difference that a catalytic amount of concentrated hydrochloric acid was used instead of Bu_4NF in THF (2 mL).

Procedure C. The procedure is similar to A except that the reaction mixture was diluted with moist THF (10 mL) instead of dry THF (10 mL).

Procedure D. The procedure is similar to B with the differences that 5 equiv of 1 (10 mmol) was employed instead of 2 equiv of 1 (2 mmol) and 5:2:3 petroleum ether/ethyl acetate/acetone was used as the eluent for chromatography.

Ethyl 2-(trifluoromethyl)-4-oxobutanoate (5a): ^1H NMR (CCl_4) δ 1.20 (t, J = 7 Hz, 3 H), 2.7–3.83 (m, 3 H),[18] 4.20 (q, J = 7 Hz, 2 H), 9.7 (s, 1 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1750 (broad s), 2870 (m); MS m/e (relative intensity) 199 (M + 1, 75), 179 (2), 170 (15), 153 (100), 102 (38), 45 (38). Anal. Calcd for $C_7H_9O_3F_3$: C, 42.42; H, 4.55; F, 28.78. Found: C, 41.95; H, 4.59; F, 28.77.

Ethyl 2-(trifluoromethyl)-4-oxopentanoate (5b): ^1H NMR (CCl_4) δ 1.10 (t, J = 7 Hz, 3 H), 1.95 (s, 3 H), 2.75–3.90 (m, 3 H), 4.23 (q, J = 7 Hz, 2 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1755 (s), 1730 (s); MS m/e (relative intensity) 213 (M + 1, 86), 197 (4), 167 (64), 147 (33), 43 (100). Anal. Calcd for $C_8H_{11}O_3F_3$: C, 45.28; H, 5.19; F, 26.88. Found: C, 45.29; H, 5.21; F, 26.85.

Ethyl 2-(trifluoromethyl)-4-oxohex-5-enoate (5c): ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 2.70–3.90 (m, 3 H), 4.24 (q, J = 7 Hz, 2 H),5.76–6.10 (m, 1 H), 6.2–6.50 (m, 2 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1750 (s), 1690 (s), 1620 (s); MS m/z (relative intensity) 225 (M + 1, 72), 192 (26), 180 (100), 159 (20). Anal. Calcd for $C_9H_{11}O_3F_3$: C, 48.21; H, 4.91; F, 25.45. Found: C, 48.26; H, 4.93; F, 25.57.

Ethyl 6-methyl-2-(trifluoromethyl)-4-oxohex-5-enoate (5d): ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 1.85 (s, 3 H), 2.05 (s, 3 H), 2.40–3.72 (m, 3 H), 4.20 (q, J = 7 Hz, 2 H), 6.05 (s, 1 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1750 (s), 698 (s), 1620 (s); MS m/z (relative intensity) 252 (M, 10), 207 (21), 117 (20), 109 (14), 84 (100), 96 (12), 55 (40). Anal. Calcd for $C_{11}H_{15}O_3F_3$: C, 52.35; H, 5.95; F, 22.62. Found: C, 51.85; H, 5.93; F, 22.67.

Ethyl 4-phenyl-2-(trifluoromethyl)-4-oxobutanoate (5e): ^1H NMR (CCl_4) δ 1.15 (t, J = 7 Hz, 3 H), 2.75–3.85 (m, 3 H), 4.10 (q, J = 7 Hz, 2 H), 7.10–7.50 (m, 3 H), 7.58–7.95 (m, 2 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1750 (s) 1695 (s); MS m/z (relative intensity) 275 (M + 1, 1), 229 (11), 209 (4), 105 (100), 77 (17). Anal. Calcd for $C_{13}H_{13}O_3F_3$: C, 56.93; H, 4.74; F, 20.80. Found: C, 56.47; H, 4.46; F, 20.40.

Ethyl 4-(4′-methoxyphenyl)-2-(trifluoromethyl)-4-oxobutanoate (5f): ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 2.75–3.85 (m, 3 H), 3.80 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.85 (d, J = 8.5 Hz, 2 H); ^{19}F NMR (CCl_4) δ −9.0 (d, J_{H-F} = 6.6 Hz); IR (neat) 1750 (s), 1680 (s); MS m/z (relative intensity) 304 (M, 11), 239 (2), 259 (17), 135 (100), 92 (7), 63 (2). Anal. Calcd for $C_{14}H_{15}O_4F_3$: C, 55.26; H, 4.93; F, 18.75. Found: C, 55.37; H, 5.25; F, 18.75.

Ethyl 6-phenyl-2-(trifluoromethyl)-4-oxohex-5-enoate (5g): mp 65–67 °C; ^1H NMR (CCl_4) δ 1.16 (t, J = 7 Hz, 3 H), 2.58–3.80 (m, 3 H), 4.10 (q, J = 7 Hz, 2 H), 6.55 (d, J = 16.8 Hz, 1 H) 7.10–7.65 (m, 6 H); ^{19}F NMR (CCl_4) δ −9.1 (d, J_{H-F} = 6.6 Hz); IR (KCl) 1740 (s), 1685 (s), 1660 (m), 1615 (m); MS m/z (relative intensity) 300 (M, 9), 255 (16), 144 (17), 132 (12), 131 (100), 103 (32), 77 (17), 51 (7). Anal. Calcd for $C_{15}H_{15}O_3F_3$: C, 60.00; H, 5.00; F, 19.00. Found: C, 59.58; H, 4.89; F, 19.25.

25-Ethoxy-3α,6α-dihydroxy-24-(trifluoromethyl)-26,27-dinor-5β-cholestane-22,25-dione (5h): mp 85–87 °C; ^1H NMR (CD_3COCD_3) δ 0.72 (s, 3 H, 18-H_3), 0.95 (s, 3 H, 19-H_3), 3.30 (broad s, 2 H, 2 OH), 4.20 (q, J = 7 Hz, 2 H), 2.50–4.25 (m, 5 H, 23-H_2, 24-H, 3-H, and 6-H); ^{19}F NMR (CD_3COCD_3) δ −9.4 (d, J_{H-F} = 6.8 Hz), −9.3 (d, J_{H-F} = 6.8 Hz), IR (KCl) 1750 (s), 1720 (s), 3100–3650 (s); MS m/z (relative intensity) 517 (M + 1, 5), 498 (M − H_2O, 14), 480 (M − 2H_2O, 18), 465 (6), 435 (5), 273 (11), 255 (21), 231 (21), 226 (20), 213 (37), 169 (43), 95 (100), 81 (64). Anal. Calcd for $C_{28}H_{43}O_5F_3$: C, 65.12; H, 8.33; F, 11.05. Found: C, 65.62; H, 8.24; F, 11.50.

Quench of the Anion 6 (R = *p*-MeOPh) with Deuterium Oxide. The cyclopropanation reaction of **3f** (2 mmol) with **1** (4 mmol) was performed as described above. The resulting reaction mixture was diluted with THF (15 mL) and treated successively with Bu_4NF in THF (1 M, 2 mL)[19] and deuterium oxide (1 mL); 1% aqueous HCl solution (30 mL) was then added, and the remaining workup was the same as described in the general procedure. The product was identified as ethyl 2-deuterio-4-(4′-methoxyphenyl)-2-(trifluoromethyl)-4-oxobutanoate (**7**): ^1H NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 3.12 and 3.60 (2 d, AB system, J = 18 Hz, 2 H), 3.78 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.85 (d, J = 8.5 Hz, 2 H); ^{19}F NMR (CCl_4) δ −9.0 (s); MS m/z (relative intensity) 305 (M, 6), 260 (7), 239 (1), 135 (100), 92 (7), 69 (2), 64 (6).

Acknowledgment. We gratefully acknowledge financial support from National Natural Science Foundation of China and from Academia Sinica.

(18) For compound **5a–g**, the signals appearing in the range of 2.5–3.9 ppm have similar absorption patterns and can be assigned to the protons on C-2 (1 H) and C-3 (2 H) carbons which constitute the ABM portion of a complicated $ABMX_3$ system (X = F).

(19) Commercial Bu_4NF in THF usually contains a small amount of water. To avoid incomplete deuteration, the reagent employed in this procedure was freshly prepared with careful drying.

Effect of Cation, Temperature, and Solvent on the Stereoselectivity of the Horner–Emmons Reaction of Trimethyl Phosphonoacetate with Aldehydes

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Received September 21, 1989

It is known that the E/Z ratio of olefinic products formed in the Horner–Emmons reaction of dialkyl 2-phosphonopropionates and 2-phosphonopropionitriles with aldehydes increases as the metal cation is changed from K^+ to Na^+ to Li^+ and as the reaction temperature is increased.[1] This effect has been attributed to an increase in the "reversibility factor" (e.g., k_{-E}/k'_E in Scheme I) for more coordinating cations and at higher temperatures.[1a,2,3] It has been assumed that the same effects operate in the Horner–Emmons reaction of dialkyl 2-phosphonoacetates with aldehydes and the effects of metal cation and reaction temperature on the E/Z ratio have been reported for an isolated example.[4] However, no effect on the E/Z ratio by a change of solvent from tetrahydrofuran (THF) to 1,2-dimethoxyethane (DME) has been reported. We report here a study of the effects of the metal cation, reaction

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