slowly added a cold solution (−70 °C) of 1 mmol of $(HMDS)_3UR$ (from 5 mmol of $HMDS)_3UCl$ and 5 mmol of RLi, see above) in 10 mL of THF. After mixture was stirred for 2 h, 5 mL of 10% aqueous THF was added, and the reaction mixture was allowed to warm to room temperature. Water (100 mL) was added. THF was partially removed under vacuum, and the mixture was extracted with 3 × 10 mL of pentane. The organic phase was dried over sodium sulfate, concentrated to 10 mL, and analyzed (GC).

Typical Stereoselective Reactions. (A) Hydratropic Aldehyde. To a stirred solution of 1 mmol of 2-phenylpropanal in 10 mL of pentane was added dropwise a solution of $(HMDS)_3UCH_3$ (0.37 g, 0.5 mmol) in 10 mL of pentane. After 1 h, the solution was hydrolyzed with 10 mL of saturated aqueous NH_4F. The organic layer was washed twice with water, dried over sodium sulfate, concentrated to 5 mL, and analyzed (GC).

(B) 4-*tert*-Butylcyclohexanone. A solution of 1 mmol of 4-*tert*-butylcyclohexanone in 20 mL of pentane was poured onto solid $(HMDS)_3UCH_3$ (0.735 g; 1 mmol), and the solution was stirred 24 h at 20 °C. After hydrolysis and workup, the organic phase was concentrated to 10 mL and analyzed (GC).

Registry No. 1, 69517-44-8; **1a**, 112460-13-6; **1b**, 112460-14-7; **1c**, 112460-15-8; **2** (R_1 = H, R_2 = C_2H_5), 107145-73-3; **2** (R_1 = H, R_2 = n-C_4H_9), 107145-74-4; **2** (R_1 = H, R_2 = C_6H_5), 107164-07-8; **2** (R_1 = H, R_2 = $C_5H_5FeC_5H_4$), 107241-38-3; **2** (R_1 = R_2 = CH_3), 99646-25-0; **2** (R_1 = R_2 = C_2H_5), 107145-75-5; **2** (R_1 = CH_3, R_2 = n-C_4H_9), 112460-17-0; **2** (R_1 = R_2 = n-C_3H_7), 112460-18-1; **2** (R_1 = CH_3, R_2 = C_6H_5), 107164-08-9; **2** (R_1 = CH_3, R_2 = $C_6H_5CH_2$), 107145-76-6; **2** (R_1 = CH_3, R_2 = $C_5H_5FeC_5H_4$), 107222-01-5; **2** (R_1 = C_6H_58 R_2 = $C_5H_5FeC_5H_4$), 112460-24-9; **2** (CR_1R_2 = *cis*-4-*tert*-butylcyclohexyl), 112572-75-5; **2** (CR_1R_2 = *trans*-4-*tert*-butylcyclohexyl), 112460-25-0; **2** (CR_1R_2 = *cis*-2-methylcyclohexyl), 112460-26-1; **2** (CR_1R_2 = *trans*-2-methylcyclohexyl), 112530-32-2; **2** (CR_1R_2 = bornyl), 112460-19-2; **2** (CR_1R_2 = frenchyl), 112460-20-5; **3a**, 112460-08-9; **3b**, 112460-09-0; **3c**, 112460-10-3; **3** (R = $CH(CH_3)_2$), 112460-16-9; **3** (R = t-C_4H_9), 112460-11-4; **4a**, 112460-21-6; **4b**, 112460-22-7; **4c**, 112460-23-8; UCl_4, 10026-10-5; $U(HMDS)_3Cl$, 69517-42-6; $(HMDS)_2\overline{UCH_2SiMe_2NSiMe_3}$, 72472-77-6; UCl_3Cp, 112460-12-5; C_2H_5CHO, 123-38-6; n-$C_6H_{11}CHO$, 66-25-1; C_6H_5CHO, 100-52-7; $C_5H_5FeC_5H_4CHO$, 12093-10-6; $(CH_3)_2CO$, 67-64-1; $(C_2H_5)_2CO$, 96-22-0; $CH_3COC_4H_9$-n, 591-78-6; $(n$-$C_9H_7)_2CO$, 123-19-3; $C_6H_5COCH_3$, 98-86-2; $C_6H_5CH_2COCH_3$, 103-79-7; $C_5H_5FeC_5H_4COCH_3$, 1271-55-2; $C_5H_5FeC_5H_4COC_6H_5$, 1272-44-2; $C_2H_5CH(OH)CH_3$, 78-92-2; n-$C_5H_{11}CH(OH)CH_3$, 543-49-7; $C_6H_5CH(OH)CH_3$, 98-85-1; $C_5H_5FeC_5H_4CO(OH)CH_3$, 1277-49-2; t-C_4H_9OH, 75-65-0; $(C_2H_5)_2C(OH)CH_3$, 77-74-7; n-$C_4H_9C(CH_3)_2OH$, 625-23-0; $(n$-$C_3H_7)_2C(OH)CH_3$, 598-01-6; $C_6H_5C(CH_3)_2OH$, 617-94-7; $C_6H_5CH_2C(CH_3)_2OH$, 100-86-7; $C_5H_5FeC_5H_4C(CH_3)_2OH$, 12093-87-7; $C_6H_5CH(CH_3)CHO$, 93-53-8; (*R**,*R**)-$C_6H_5CH(CH_3)CH(OH)CH_3$, 1502-79-0; (*R**,*S**)-$C_6H_5CH(CH_3)CH(OH)CH_3$, 1502-80-3; (*R**,*R**)-$C_6H_5CH(CH_3)CH(OH)C_2H_5$, 1502-77-8; (*R**,*S**)-$C_6H_5CH(CH_3)CH(OH)C_2H_5$, 1502-78-9; (*R**,*R**)-$C_6H_5CH(CH_3)CH(OH)CH(CH_3)_2$, 1502-75-6; (*R**,*S**)-$C_6H_5CH(CH_3)CH(OH)CH(CH_3)_2$, 1502-76-7; (*R**,*R**)-$C_6H_5CH(CH_3)CH(OH)C_4H_9$-$n$, 96929-99-6; (*R**,*S**)-$C_6H_5CH(CH_3)CH(OH)C_4H_9$-$n$, 96930-05-1; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclohexanone, 583-60-8; camphor, 76-22-2; (*R*)-(−)-fenchone, 7787-20-4; 4-methylcyclohexanone, 589-92-4; *cis*-4-*tert*-butyl-1-methylcyclohexanol, 16980-55-5; *trans*-4-*tert*-butyl-1-methylcyclohexanol, 16980-56-6; *cis*-1,2-dimethylcyclohexanol, 19879-11-9; *trans*-1,2-dimethylcyclohexanol, 19879-12-0; *cis*-1,4-dimethylcyclohexanol, 16980-61-3; *trans*-1,4-dimethylcyclohexanol, 16980-60-2.

Generation of [α-(Alkoxycarbonyl)vinyl]aluminum and Aluminum Allenolates by the Hydroalumination of α,β-Acetylenic Carbonyl Compounds and Their Reaction with Carbonyl Compounds

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[α-(Alkoxycarbonyl)vinyl]aluminum and aluminum allenolate intermediates were generated by the hydroalumination of α,β-acetylenic ester and ketone, respectively, with DIBAH–HMPA. The [α-(methoxycarbonyl)vinyl]aluminum generated from methyl propynoate reacted with aldehydes and ketones to produce methyl α-(1-hydroxyalkyl)acrylates in good yields although its reaction with ketones required Lewis acid activation by BF_3·Et_2O. In contrast, the nucleophilic reactivity of the aluminum allenolate intermediates from α,β-acetylenic ketones was not high. Their reaction with aldehydes produced α-(1-hydroxyalkyl) α,β-enones in relatively low yield.

Very recently, we have reported the hydroalumination of α,β-acetylenic carbonyl compounds with diisobutylaluminum hydride (DIBAH) in the presence of the hexamethylphosphoric triamide (HMPA) ligand.[1] On hydrolysis, the organoaluminum intermediates generated afford α,β-olefinic carbonyl compounds, i.e., the conjugate reduction products of the α,β-acetylenic carbonyl compounds. The organoaluminum obtained from methyl propynoate (1) reacts with a variety of allylic bromides to give synthetically useful methyl α-allylacrylates. To expand the scope of the hydroalumination reaction of the α,β-acetylenic carbonyl compounds with DIBAH–HMPA, we have explored here the reaction of the organoaluminum intermediates with carbonyl compounds.

Another interesting problem concerns the structure of the organoaluminum intermediate. The possible structures of the organoaluminums from α,β-acetylenic ester 1 and ketones 4 are [α-(alkoxycarbonyl)vinyl]aluminum **2** and (α-acylvinyl)aluminum **5**, aluminum allenolates **3** and **6**, and their equilibrated mixtures (Scheme I). Here we have also investigated spectroscopically the structures of the organoaluminum intermediates, which are thermally stable at room temperature to permit the spectroscopic study.

In the spectroscopic study of the organoaluminum intermediates, methyl propynoate (1), 1-hexyn-3-one (**4a**), 2-methyl-4-nonyn-3-one (**4b**), and 1-phenyl-2-hexyn-1-one (**4c**) were used as α,β-acetylenic carbonyl compounds. The results are summarized in Table I. The [α-(alkoxycarbonyl)vinyl]- and (α-acylvinyl)aluminums **2** and **5** and

(1) Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 1624.

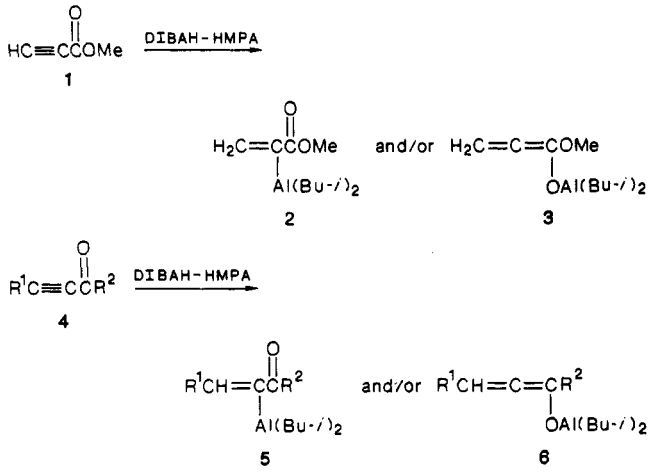
0022-3263/88/1953-1037$01.50/0

Table I. Spectroscopic Data of the Organoaluminum Intermediates Generated from α,β-Acetylenic Carbonyl Compounds

α,β-acetylenic carbonyl compound	assigned structure of the organoaluminum intermediate	NMR chemical shift, ppm: ^{1}H NMR[a] olefinic and allenic proton	^{13}C NMR[b] C_3	C_2	C_1	IR stretching frequency, cm^{-1}[a]
HC≡CCO$_2$Me (1)	$H_2C^3=C^2(CO_2Me)^1$, Al(Bu-*i*)$_2$ **2**	5.62 (d, ^2J = 6.0)[c] 6.26 (d, ^2J = 6.0)[c]	132.6 (t)[d]	134.7	175.5[a]	1695, 1620
HC≡CCOPr-*n* (**4a**)	$H_2C^3=C^2=C^1HCH_2Et$, OAl(Bu-*i*)$_2$ **6a**	4.85 (t, ^5J = 2.4)[c]	80.5 (t)[d]	208.2	130.8	1950
BuC≡CCOPr-*i* (**4b**)	*n*-PrCH$_2$CH^3=C^2=C^{1}CHMe$_2$, OAl(Bu-*i*)$_2$ **6b**	5.23 (dt, ^5J = 1.9 and ^3J = 6.3)[c]	97.5 (d)[d]	197.4	136.1	1940
BuC≡CCOPh (**4c**)	*n*-PrCH$_2$CH^3=C^2=C^{1}HPh, OAl(Bu-*i*)$_2$ **6c**	5.69 (t, ^3J = 6.3)[c]	100.7 (d)[d]	200.6	140.9	1920

[a] Measured at room temperature. Measurement at −3 °C gave identical results in the ^{1}H NMR experiments of **4a–c**. [b] Measured at −3 °C. [c] ^nJ:*n*-bond proton–proton coupling constant in hertz. [d] One-bond carbon–proton coupling pattern.

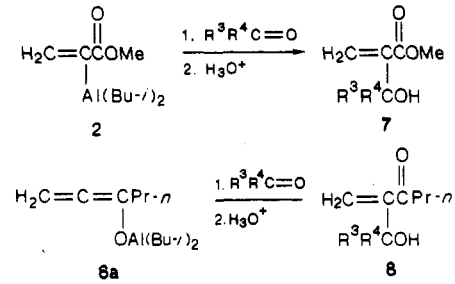
Scheme I



the aluminum allenolates **3** and **6** are readily distinguished by NMR and IR spectroscopies.[2] The former two are expected to show a β-olefinic proton absorption (^{1}H NMR, around δ 6.0), an olefinic carbon absorption (^{13}C NMR, around δ 130), a carbonyl carbon absorption (^{13}C NMR, around δ 190), and a carbonyl stretching frequency (IR, around 1700 cm^{-1}). On the other hand, the latter two should exhibit an allenic proton absorption (^{1}H NMR, around δ 5.0), a terminal allenic carbon absorption (^{13}C NMR, around δ 90), a central allenic carbon absorption (^{13}C NMR, around δ 200), and an asymmetric stretching absorption for the allene portion (C=C=C) (IR, around 1950 cm^{-1}).

The spectral data[3] of the organoaluminum generated from **1** indicate the presence of the α,β-olefinic carbonyl moiety and are consistent with the [α-(alkoxycarbonyl)-vinyl]aluminum structure **2**. In contrast, the NMR and IR data of the organoaluminums from α,β-acetylenic ketones **4a–c** are consistent with the aluminum allenolate structure **6**. The *n*-bond proton–proton coupling constant ^nJ(HH) and the one-bond carbon–proton coupling pattern are compatible with the allenolate structure **6** (Table I). Thus, it is interesting to note that two different kinds of organoaluminums are generated by the hydroalumination of α,β-acetylenic carbonyl compounds with DIBAH–HMPA. To our knowledge, the present study provides the first example of the structurally defined [α-(alkoxycarbonyl)vinyl]metal and metal allenolate.[4]

Scheme II



[α-(Alkoxycarbonyl)vinyl]metals and (α-acylvinyl)metals or their allenic tautomers are useful organometallic reagents in organic synthesis although their examples are not abundant. For instance, lithium [α-(alkoxycarbonyl)vinyl]- and (α-acylvinyl)cuprates generated by the conjugate addition of lithium organocuprates to α,β-acetylenic esters and ketones, respectively, are well known.[5] This method, however, cannot afford β-unsubstituted lithium [α-(alkoxycarbonyl)vinyl]- and (α-acylvinyl)cuprates.[6] Thus, it

(2) (a) Munson, J. W. *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; Part 1, pp 172–183. (b) Runge, W. *The Chemistry of the Allenes*; Landor, S. R., Ed; Academic: New York, 1982; Vol. 3, pp 777–848.

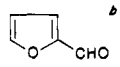
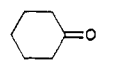
(3) The NMR spectral data are similar to those of methyl methacrylate. Methyl methacrylate: ^{1}H NMR (CCl_4) δ 1.91, 3.69, 5.47, 6.00 (*The Sadtler Standard Spectra*; Sadtler Research Laboratories: Philadelphia, PA, 1971); ^{13}C NMR (dioxane) δ 18.3, 51.5, 124.7, 136.9, 167.3 (*Carbon-13 NMR Spectra*; Johnson, L. F., Jankowski, W. C., Eds.; Wiley: New York, NY, 1972).

(4) IR study has been reported on copper and lithium compounds. See: (a) Klein, J.; Levene, R. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 1971. (b) Adlington, R. M.; Barret, A. G. M. *J. Chem. Soc., Chem. Commun.* **1981**, 65.

(5) (a) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621. (c) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.*, in press. The structure of lithium [α-(alkoxycarbonyl)vinyl]- and (α-acylvinyl)cuprates has not been established although IR study has been reported. See ref 4a.

(6) Lithium β-unsubstituted [α-(alkoxycarbonyl)vinyl]cuprate has been generated from alkyl α-bromoacrylate and lithium methyl(1-hexynyl)cuprate. Its generation, however, needs multistep manipulations and is not efficient. See: (a) Marino, J. P.; Floyd, D. M. *J. Am. Chem. Soc.* **1974**, *96*, 7138. (b) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1975**, 3897.

Table II. Reactions of the Organoaluminums 2 and 6a with Carbonyl Compounds

organoaluminum	carbonyl compound (R^3R^4C=O)	product (%)[a]	
H_2C=C(CO$_2$Me)–Al(Bu-*i*)$_2$ (**2**)	*n*-PrCHO	H_2C=C(CO$_2$Me)–CR^3R^4OH	**7a** (87)
	i-PrCHO		**7b** (87)
	PhCHO		**7c** (83)
	 [b]		**7d** (80)
	(*E*)-*n*-PrCH=CHCHO		**7e** (90)
	(*n*-Pr)$_2$CO		**7f** (68)[c]
			**7g** (72)[c]
H_2C=C=C(Pr-*n*)–OAl(Bu-*i*)$_2$ (**6a**)	*n*-PrCHO	H_2C=C(COPr-*n*)–CR^3R^4OH	**8a** (23)
	PhCHO		**8b** (31)

[a] Isolated yield by column chromatography or preparative layer chromatography. [b] Furfural/**2** = 1.1. [c] The reaction in the presence of BF_3–Et_2O. BF_3–Et_2O/carbonyl compound = 1.

is noteworthy that the hydroalumination of β-unsubstituted α,β-acetylenic carbonyl compounds with DIBAH–HMPA produces readily the β-unsubstituted [α-(alkoxycarbonyl)vinyl]aluminum such as **2** and the terminally unsubstituted aluminum allenolate such as **6a**.

The reaction of **2** and **6a** with carbonyl compounds producing synthetically important α-substituted acrylates[7] and α-methylene ketones[8] was examined (Scheme II). The reaction of **2** with a variety of aldehydes proceeded smoothly at room temperature to produce methyl α-(1-hydroxyalkyl)acrylates **7a–e** in good yields. The results are summarized in Table II. In the reaction of **2** with (*E*)-2-hexenal, a 1,2-carbonyl addition took place with no conjugate addition. The reaction of **2** with ketones requires activation of a ketone carbonyl group by a Lewis acid. This finding indicates a relatively low nucleophilic reactivity of **2**. In the presence of an equimolar amount of BF_3·Et_2O to ketones, the reaction of **2** with ketones gave methyl α-(1-hydroxyalkyl)acrylates **7f** and **7g** in good yields (Table II). Without the Lewis acid, a trace amount of the addition product was obtained. In the reaction with 2-cyclohexenone, no major product was produced. In contrast, **6a** did not react readily with aldehydes to give α-(1-hydroxyalkyl) α,β-enones **8a** and **8b** in relatively low yields (Table II).

The decreased nucleophilic reactivity of the aluminum allenolate also has been previously found in the reaction with allyl bromide.[1] The reaction of **6a** and **6b** with allyl bromide affords no allylation product[9] under conditions where **2** produces the allylation production in high yield. The remarkable difference between the nucleophilic reactivity of the [α-(alkoxycarbonyl)vinyl]aluminum and the aluminum allenolate may be correlated with their structures. In comparison with an ester carbonyl group, the more polar and electron-withdrawing character of a ketone carbonyl group converts the (α-acylvinyl)aluminum **5** into the more stable aluminum allenolate **6** in which the central allenic carbon atom is less nucleophilic than the α-carbon atom of the [α-(alkoxycarbonyl)vinyl]aluminum **2**.

Experimental Section

IR spectra was determined on a Hitachi 260-50 grating spectrophotometer. ^{1}H NMR spectra was recorded in $CDCl_3$ on a Hitachi R-20B (60 MHz) instrument unless otherwise stated. ^{13}C NMR spectra were obtained on a JEOL JNM-JX-400 instrument. Chemical shifts are reported in δ downfield from internal tetramethylsilane except the chemical shifts shown in Table II where benzene is used as an NMR internal standard, and the calculated chemical shifts based on tetramethylsilane are reported. Coupling constants (*J*) are reported in hertz. Mass spectra were obtained on a JEOL DX-300 instrument. Elemental analyses were performed by the Microanalytical Center of Kyoto University.

Reactions were carried out under an atmosphere of nitrogen. Diisobutylaluminum hydride (DIBAH) in hexane was obtained from Aldrich Chemical Co. Tetrahydrofuran (THF) and THF-d_8 were distilled from lithium aluminum hydride under nitrogen. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride under reduced pressure. Methyl propynoate (**1**) was a commercial reagent and was distilled under nitrogen after drying over calcium sulfate (Drierite). 1-Hexyn-3-one (**4a**) was prepared by the oxidation of 1-hexyn-3-ol.[10] α,β-Acetylenic ketones **4b** and **4c** were prepared according to the published method.[11] Carbonyl compounds (R^3R^4C=O) were commercial reagents and were distilled under nitrogen after drying over Drierite except for furfural, which was distilled from calcium hydride.

General Procedure for the Spectroscopic Study of the Organoaluminum Intermediates Generated by the Hydroalumination of α,β-Acetylenic Carbonyl Compounds. A hexane solution of DIBAH (0.45 mmol) was placed in an NMR tube, and the hexane was evaporated by a stream of nitrogen. THF-d_8 (0.25 mL), benzene (0.005 mL) as an NMR internal standard, and HMPA (0.078 mL, 0.45 mmol) were added successively at 0 °C. After 10 min, α,β-acetylenic ester **1** or ketone **4** (0.30 mmol) was added to the mixture cooled to 0 °C. The tube was closed by flame and allowed to stand at 0 °C for 2 h. Then the ^{1}H and ^{13}C NMR spectra of the resulting solution were recorded at the temperature indicated in Table I on a JEOL JNM-JX-400 (400 MHz) instrument. A portion of the solution was transferred by a syringe to an IR cell (NaCl, thickness 0.20 mm), and its IR spectrum was taken at room temperature.

Reaction of the [α-(Methoxycarbonyl)vinyl]aluminum 2 with Butyraldehyde. To a stirred THF (8 mL) solution of HMPA (0.391 mL, 2.25 mmol) cooled to 0 °C was added a hexane solution of DIBAH (1.65 mmol). After 0.5 h, methyl propynoate (**1**) (0.133 mL, 1.50 mmol) was added. The reaction mixture was stirred for 1 h, and then butyraldehyde (0.265 mL, 3.00 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 5 mL of 1 N HCl solution, and extracted with 100 mL of ether. The organic layer was washed three times with 10 mL of 1 N HCl solution and then 10 mL of saturated $NaHCO_3$ solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexane = 1:5 v/v) to give **7a**:[7] 207 mg (87%); IR (neat, cm^{-1}) 3420, 1720, 1630, 955; ^{1}H NMR δ 0.7–1.1 (m, 3 H), 1.1–1.7 (m, 4 H), 2.65 (br s, 1 H), 3.76 (s, 3 H), 4.2–4.6 (m, 1 H), 5.80 (s, 1 H), 6.20 (s, 1 H); MS, *m/e* (relative intensity) 158 (M^+, 1), 143 (1), 140 (2), 115 (100), 83 (82). The reaction of **2** with other aldehydes was carried out as described above to give the products **7b–e**, which were identified as follows. The spectral data of **7a**,[7] **7b**,[12] and **7c**[13] are compatible with those of the literature. **7b**:[12] IR (neat, cm^{-1}) 3470, 1720, 1630, 955; ^{1}H NMR δ 0.89 (d, *J* = 6.6, 3 H), 0.95 (d, *J* = 6.6, 3 H), 1.6–2.1 (m, 1 H), 2.63 (br d, *J* = 6.6,

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(8) Tsuji, J.; Nisar, M.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 2483 and references therein.
(9) A hydrolytic workup of the attempted allylation reaction of **6b** produced a conjugate reduction product of 2-methyl-4-nonyn-3-one (*E*/*Z* = 88/12) in 67% yield.
(10) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. L. L. *J. Chem. Soc.* **1946**, 39.
(11) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.
(12) Miyakoshi, T.; Omichi, H.; Saito, S. *Nippon Kagaku Kaishi*, **1979**, 748.
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1 H), 3.78 (s, 3 H), 4.10 (br t, J = 6.6, 1 H), 5.78 (s, 1 H), 6.26 (s, 1 H); MS, m/e (relative intensity) 158 (M^+, 1), 143 (1), 140 (2), 115 (100), 83 (79). **7c**:[13] IR (neat, cm^{-1}) 3410, 1720, 1625, 1490, 955; ^1H NMR δ 3.13 (br s, 1 H), 3.70 (s, 3 H), 5.57 (br d, J = 5.4, 1 H), 5.83 (s, 1 H), 6.33 (s, 1 H), 7.34 (s, 5 H); MS, m/e (relative intensity) 192 (M^+, 100), 191 (73), 160 (72), 132 (41), 105 (25). **7d**: IR (neat, cm^{-1}) 3425, 1720, 1630, 955; ^1H NMR δ 3.17 (br s, 1 H), 3.75 (s, 3 H), 5.60 (br d, J = 6.6, 1 H), 5.95 (s, 1 H), 6.2–6.4 (m, 3 H), 7.36 (s, 1 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.32; H, 5.62. **7e**: IR (neat, cm^{-1}) 3450, 1730, 1635, 970; ^1H NMR δ 0.89 (t, J = 6.0, 3 H), 1.1–1.7 (m, 2 H), 1.9–2.3 (m, 2 H), 2.80 (d, J = 6.0, 1 H), 3.78 (s, 3 H), 4.91 (t, J = 6.0, 1 H), 5.6–5.9 (m, 2 H), 5.84 (s, 1 H), 6.21 (s, 1 H); MS, m/e (relative intensity) 184 (M^+, 1), 166 (1), 141 (51), 109 (100). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.31; H, 9.02.

Reaction of the [α-(Methoxycarbonyl)vinyl]aluminum 2 with 4-Heptanone in the Presence of BF_3·OEt_2. To **2**, generated in a similar way as above from **1** (1.50 mmol), in THF (8 mL) at 0 °C were added 4-heptanone (0.419 mL, 3.00 mmol) and BF_3·OEt_2 (0.369 mL, 3.00 mmol). The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 5 mL of 1 N HCl solution, and extracted with 100 mL of ether. The organic layer was washed three times with 10 mL of 1 N HCl solution and then 10 mL of saturated $NaHCO_3$ solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexane = 1:10 v/v) to give **7f**: 206 mg (68%); IR (neat, cm^{-1}) 3510, 1710, 1610, 965; ^1H NMR δ 0.7–1.1 (m, 6 H), 1.1–1.5 (m, 4 H), 1.5–2.0 (m, 4 H), 3.05 (s, 1 H), 3.76 (s, 3 H), 5.76 (s, 1 H), 6.23 (s, 1 H); MS, m/e (relative intensity) 157 (100), 71 (32), 55 (22). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.92; H, 10.35. The compound **7g** was similarly obtained and identified as follows. **7g**: IR (neat, cm^{-1}) 3510, 1710, 1620, 960; ^1H NMR δ 1.3–1.9 (m, 10 H), 3.57 (s, 1 H), 3.78 (s, 3 H), 5.76 (s, 1 H), 6.15 (s, 1 H); MS, m/e (relative intensity) 184 (M^+, 3), 166 (8), 152 (58), 141 (49), 109 (100); HRMS, m/e calcd for $C_{10}H_{16}O_3$ 184.1100, found 184.1086.

Reaction of the Aluminum Allenolate 6a with Butyraldehyde. To a stirred solution of THF (8 mL) and HMPA (0.391 mL, 2.25 mmol) cooled to 0 °C was added a hexane solution of DIBAH (1.65 mmol). After 0.5 h, 1-hexyn-3-one (**4a**) (0.169 mL, 1.50 mmol) was added. The reaction mixture was stirred for 1 h, and the butyraldehyde (0.265 mL, 3.00 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 5 mL of 1 N HCl solution, and extracted with 100 mL of ether. The organic layer was washed three times with 10 mL of 1 N HCl solution and then 10 mL of saturated $NaHCO_3$ solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by preparative layer chromatography (PLC) on a silica gel plate (20 × 20 × 0.2 cm) to give **8a**: IR (neat, cm^{-1}) 3400, 1670, 1630; ^1H NMR δ 0.94 (t, J = 7.2, 6 H), 1.1–1.9 (m, 6 H), 2.68 (t, J = 7.2, 2 H), 2.89 (br s, 1 H), 4.45 (m, 1 H), 5.95 (s, 1 H), 6.08 (s, 1 H); MS, m/e (relative intensity) 170 (M^+, 1), 152 (2), 127 (100). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.43; H, 10.83. The compound **8b** was similarly obtained and identified as follows. **8b**: IR (neat, cm^{-1}) 3430, 1675, 1630, 1600, 1500, 955; ^1H NMR δ 0.86 (t, J = 7.0, 3 H), 1.58 (sext, J = 7.0, 2 H), 2.64 (t, J = 7.0, 2 H), 3.22 (d, J = 5.4, 1 H), 5.61 (d, J = 5.4, 1 H), 5.93 (s, 1 H), 6.15 (s, 1 H), 7.32 (s, 5 H); MS, m/e (relative intensity) 204 (M^+, 62), 203 (100), 161 (63); HRMS, m/e calcd for $C_{13}H_{16}O_2$ 204.1151, found 204.1142.

Registry No. **1**, 922-67-8; **2**, 107270-46-2; **4a**, 689-00-9; **4b**, 63098-60-2; **4c**, 18998-78-2; **6a**, 112247-17-3; **6b**, 112247-18-4; **6c**, 112247-19-5; **7a**, 18020-64-9; **7b**, 71385-30-3; **7c**, 18020-59-2; **7d**, 87102-10-1; **7e**, 112247-20-8; **7f**, 112247-21-9; **7g**, 112247-22-0; **8a**, 112247-23-1; **8b**, 112247-24-2; *n*-PrCHO, 123-72-8; *i*-PrCHO, 78-84-2; PhCHO, 100-52-7; (*E*)-*n*-PrCH=CHCHO, 6728-26-3; $(n\text{-Pr})_2CO$, 123-19-3; furfural, 98-01-1; cyclohexanone, 108-94-1.

Triply Convergent Synthesis of 1α,25-Dihydroxy-24(*R*)-fluorocholecalciferol

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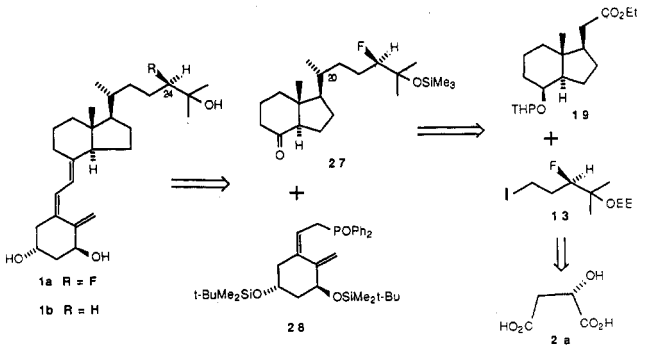
A triply convergent approach to the stereoselective synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) is described. The key step in the synthesis is the Wicha alkylation of the C,D-ring synthon **19** with the properly substituted side chain synthon **13**, producing stereoselectively the natural configuration at C-20.

Since the discovery of the physiologically active vitamin D_3 metabolite, 1α,25-dihydroxycholecalciferol [1,25-(OH)$_2$D$_3$][1] (**1b**), we have been interested in the synthesis of an analogue with a longer half-life and increased antirachitogenic activity. As a part of this program, the synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) was undertaken. This substance was first synthesized via the conventional cholesterol → 5,7-diene → previtamin → vitamin route.[2] 1α,25-Dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) contains a fluorine atom specifically located at the 24*R* position, one of the principal sites of the calcitriol catabolism. As anticipated, the plasma half-life of this 24(*R*)-monofluoro analogue **1a**, after iv administration in dogs, was 14.4 h, compared to 3.6 h for calcitriol (**1b**). Potent antirachitogenic activity was also demonstrated. An oral dose of this analogue in vitamin D deficient chicks

Scheme I



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