Tris(dialkylamino)sulfonium Enolates. Synthesis, Structure, and Reactions[1,2]

R. Noyori,* I. Nishida, and J. Sakata

Contribution from the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan. *Received July 26, 1982*

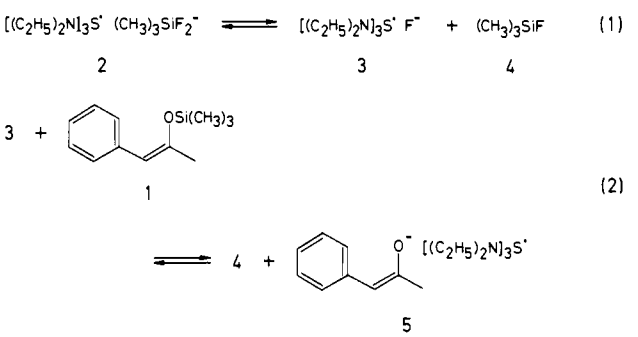
Abstract: A mixture of an enol trimethylsilyl ether and a fluoride salt exists in a dynamic equilibrium with an enolate species and fluorotrimethylsilane. Evacuation of an equimolar mixture of an enol trimethylsilyl ether of benzyl methyl ketone and tris(diethylamino)sulfonium (TAS) difluorotrimethylsiliconate produces fluorotrimethylsilane as the volatile fraction and the corresponding TAS enolate as air-sensitive crystals. The conductivity measurement and the ^1H and ^{13}C NMR analysis have substantiated the ionic nature of the TAS enolate in THF. The NMR chemical shifts are interpreted in terms of the electron distribution. The isolated TAS enolate undergoes O-acetylation with acetic anhydride and C-alkylation with methyl iodide exclusively. TAS enolate intermediates generated in situ from a series of enol silyl ethers and TAS difluorotrimethylsiliconate react with various active organic halides under mild conditions to give the regiospecific C-alkylation products. The in situ formed enolates react with aldehyde substrates to afford the β-trimethylsiloxy ketone adducts. In most cases, the reaction is kinetically controlled and the major products have erythro stereochemistry regardless of enolate configuration. This aldol reaction is postulated to proceed via an acyclic, extended transition state, in contrast to the ordinary aldol reactions of Lewis acid coordinated enolates, which take place by way of six-membered chelate transition states.

The importance of enolates in organic synthesis is attributed to the capability of undergoing a variety of nucleophilic reactions.[3] The structures and reactivities are highly dependent on the nature of the countercations and solvents.[4] A traditional method for the generation of enolates is exposure of carbonyl compounds in aqueous or alcoholic media to basic reagents. Under such reversible conditions, metal-free but hydrogen-bonded species are formed. Recently a number of preformed, metal-coordinated enolates are used in aprotic solvents. We have been intrigued by the chemistry of a new class of enolates, naked enolates in aprotic media. Crown ether complexation of the metal counterion or replacement of the metal ion by an onium ion decreases greatly the degree of ion pairing, thereby enhancing the nucleophilicity of the anionic moiety. In this context, tris(dialkylamino)sulfonium ions are expected to serve as an ideal countercation. This paper describes the synthesis, NMR behavior, and characteristics in the reaction with some nucleophilic agents of such enolates.

Results and Discussion

Synthesis. In view of the great strength of silicon–fluorine bonds (139 kcal/mol),[5] reaction of enol trimethylsilyl ethers and fluoride ion is anticipated to produce the corresponding enolate species and fluorotrimethylsilane.[6-10] In order to test this possibility, quaternary ammonium fluorides have been frequently employed as a fluoride ion source,[6,7] but the inevitable water contamination makes the scrutiny difficult. Therefore we took a tris(dialkylamino)sulfonium difluorotrimethylsiliconate[11,12] as a fluoride ion source that can remove this difficulty and hence is more suitable for the mechanistic and synthetic purpose.[13] As an enolate system, we chose a benzyl methyl ketone enolate, which had been examined in detail by House.[14] ^1H NMR spectrum of the enol silyl ether **1** taken in tetrahydrofuran (THF) showed a Si–CH_3 singlet at δ 0.22. The Si–CH_3 signal of tris(diethylamino)sulfonium (TAS) difluorotrimethylsiliconate (**2**) occurred at δ −0.18 as a singlet. However, when these two components were mixed in a 1:1 ratio in THF, there was observed only one Si–CH_3 singlet at δ 0.21. This indicates the occurrence of dynamic equilibria outlined in

Scheme I



(1) Superanions. 5. Part 4: Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1981**, *22*, 3993.

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(3) Reviews: House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapters 9–12. d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. Stowell, J. C. "Carbanions in Organic Synthesis"; Wiley: New York, 1979; Chapter 5.

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(13) Disadvantages include the high cost and the susceptibility of the TAS moiety to a base-promoted fragmentation.

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Table I. ^{1}H NMR Data of the TAS Enolate 5 and the Metal Enolates[a]

compound	chemical shift, δ				
	para	meta	ortho	vinyl	CH_3
enol silyl ether 1	7.05	7.15	7.45	5.36	1.85
Li enolate[b]				4.93	
Na enolate[b]	6.66	7.09	7.47	4.86	
TAS enolate 5[c]	6.25	6.75	7.57	4.50	1.67

[a] Taken in THF. [b] Reference 14a. [c] Taken in THF-d_8.

Scheme I. The TAS salt **2** is considered to exist in an equilibrium with TAS fluoride (**3**) and fluorotrimethylsilane (**4**), since the latter gives a doublet at δ 0.20 due to the Si–CH_3 groups ($J_{H,F}$ = 7 Hz). Fluoride ion thus generated reacts with the enol silyl ether at the silicon atom via a short-lived pentacoordinate anionic silicon intermediate[15] to produce the TAS enolate **5** and the fluorosilane **4**. Indeed when this mixture was evacuated to 0.01 mmHg at 25 °C, 90% of the theoretical amount of the fluorosilane **4** was collected in a cold trap (liquid nitrogen) as THF solution. There remained the TAS enolate **5** in the reaction vessel. Washing of the residue with a small amount of dry ether gave extremely air-sensitive, yellowish crystals.

Reaction of isolated **5** and fluorosilane **4** gave little **1**, suggesting that the equilibrium of eq 2 lies to the right. In addition, the nonproductive process, **5** + **1** ⇌ **1** + **5**, may also be involved. Notably the enolate **5** has *Z* stereochemistry and no *E* isomer[14] is produced through this synthetic procedure.

Electroconductance. The TAS enolate **5** in THF solution exhibited a molar conductance of 1.8 $cm^2\ mol^{-1}\ ohm^{-1}$ at a concentration of 3.8×10^{-3} M at 25 °C. It is clear that this compound is ionic in nature and dissociates into free ions in THF. The possible sulfurane structure was thus excluded.[16]

NMR Spectral Studies. The ionic structure of **5** was further substantiated by the NMR behavior in the presence of a proton source. When a small amount of benzyl methyl ketone was present in the THF solution, rapid proton exchange between the ketone and the enolate occurred and, as a consequence, significant line broadening of the vinylic and aromatic ring proton signals was observed.[14,17] The signals of the TAS moiety remained sharp, however.

The nature of the ion pairing can be inferred by examining the NMR chemical shift, which is profoundly related to the electron distribution.[18] The TAS exhibited the methyl and methylene signals at δ 1.09 and 3.20, respectively, and the chemical shift values compared well with those of ionic TAS bromide, δ 1.11 (CH_3) and 3.25 (CH_2) (cf. triethylamine, δ 1.00 (CH_3) and 2.53 (CH_2); diethylamine, δ 1.11 (CH_3) and 2.65 (CH_2)). The low-field occurence of the methylene signal indicates that positive charge does not localize on the sulfur atom but spreads over the alkyl groups. Table I lists the NMR spectra of **5**, the corresponding alkali metal enolates, and the silyl analogue **1**. When the data for **5** are compared with those of the neutral compound **1**, the signals of the vinyl proton and aromatic para and meta protons move upfield significantly. The chemical shifts appear to be even higher than those of the lithium and sodium enolates. On the other hand, the ortho proton signal moves downfield to a slight extent.[19]

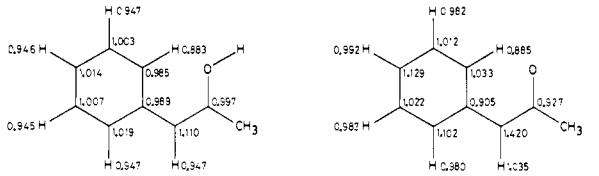

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Figure 1. Calculated electron distribution in enol **6** and enolate **7** (1s for hydrogen and $2p_z$ for carbon).

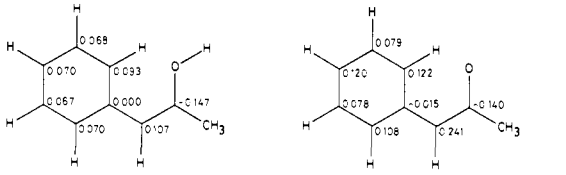

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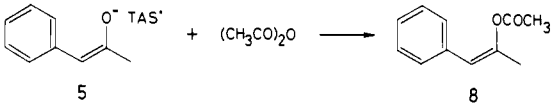
Figure 2. Calculated excess electron densities in enol **6** and enolate **7**.

Scheme II



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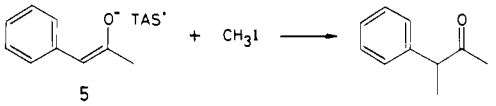
Scheme III



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The ^{13}C NMR spectrum is more useful than the corresponding ^{1}H spectrum in earning structural information. The TAS moiety of **5** gave the signals at δ 13.0 and 42.0 due to the methyl and methylene carbons, respectively. The chemical shifts are very close to those of TAS bromide, δ 13.5 (CH_3) and 42.5 (CH_2). In Table II, the spectrum of the enolate moiety is compared with the data for the related alkali metal enolates and the silyl derivative **1**. In going from the neutral compound **1** to the TAS enolate **5**, the vinylic, ortho, and para carbons are shielded more strongly, whereas the oxygen-linked carbon and the ipso carbon are substantially deshielded. The magnitude of the chemical shift difference, which is sensitive to the nature of ion pairing, appears to be greater than any of the reported systems. For instance, the 20.0 ppm upfield shift of the vinylic carbon signal is even larger than the shift, 18.5 ppm, caused by the crown ether complexation of the sodium enolate.[14b]

Since TAS cation possesses negligible interaction with the counteranion in the THF,[20] the observed chemical shift change is perceived to arise mainly from the delocalization of negative charge.[18] To test the validity of this view, the ab initio MO calculations with STO-3G minimal basis set were carried out on

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(16) Some concentration dependency was observed. However, further precise measurements at lower concentration were not made because of the moisture and air sensitivity of **5**.

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(19) Evacuation of an equimolar mixture of **1** and tetrabutylammonium fluoride left the corresponding quaternary ammonium enolate. The ^{1}H NMR spectrum (THF-d_8) exhibited broad but consistent signals: δ 4.56 (broad, vinylic), 7.00 (t, para), 7.53 (d, ortho); position of the meta signal was obscure. The chemical shifts were intermediate between those of the Na enolate and TAS enolate.

(20) Farnham, W. B.; Middleton, W. J.; Sam, D. J. "Abstracts of Papers", 172nd National Meeting of the American Chemical Society, San Francisco, CA, Aug 30–Sept 3, 1976; American Chemical Society: Washington, D.C., 1976; ORGN 46. Cowley, A. H.; Pagel, D. J.; Walker, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 7065.

Table II. ^{13}C NMR Data of the TAS Enolate 5 and the Metal Enolates

compound	solvent	chemical shift, δ						
		para	meta	ortho	ipso	vinyl	C–O	CH_3
enol silyl ether **1**	THF	125.5	128.3	128.1	137.5	109.2	149.0	23.8
Na enolate[a]	DME	119.2	128.2	124.1	145.1	93.4	169.3	29.4
Na enolate + 18-crown-6[a]	DME	116.4	126.7	123.1	146.0	90.7	170.3	29.7
K enolate[a]	DME	118.6	128.6	123.3	145.6	91.8	170.7	29.5
TAS enolate **5**	THF	116.2	127.6	123.0	149.0	88.9	174.0	29.7

[a] Taken from ref 14b.

Table III. Fluoride Ion Promoted Alkylation of Enol Silyl Ethers[a]

entry	enol silyl ether	alkylating agent (equiv)	reaction conditions		% yield of alkylation product[b]
			2, equiv	T, °C (time, h)	
1	(*Z*)-1-phenyl-2-(trimethylsiloxy)-propene (1)	methyl iodide (1.3)	1.0	−78 (0.25)	89[c]
2	1	cyclopropylmethyl iodide (1.3)	1.0	−74 (7)	83[d]
3	1	cyclopropylmethyl iodide (1.3)	1.0	−74 (12)	51[d,e]
4	1	5-hexenyl iodide (1.0)	1.0	−78 (4) + −40 (0.5)	91[d]
5	1-(trimethylsiloxy)-cyclopentene (**10**)	benzyl bromide (1.2)	1.2	−78 (4)	82
6	**10**	allyl bromide (1.2)	1.2	−78 (4)	60
7	1-(trimethylsiloxy)-cyclohexene (11)	methyl iodide (1.5)	1.2	−78 (4)	95[d]
8	**11**	*n*-butyl iodide (1.1)	1.1	−30 (3)	59
9	**11**	benzyl bromide (1.0)	1.0	−78 (3)	72
10	**11**	(*E*)-cinnamyl bromide (1.2)	1.0	−78 (2.5)	61
11	**11**	methyl bromoacetate (1.2)	1.0	−78 (2)	83
12	5-methyl-1-(trimethylsiloxy)-cyclohexene (12)	benzyl bromide (1.2)	1.0	−78 (3)	66[f]
13	2-methyl-1-(trimethylsiloxy)-cyclohexene (**13**)	benzyl bromide (1.2)	1.0	−78 (3)	60

[a] Unless otherwise stated, reaction was carried out in THF. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by GLPC analysis. [e] Hexamethylphosphoric triamide (10 equiv) was added to the reaction mixture. [f] A 1:5 mixture of the cis and trans isomers.

the model enol **6** and enolate **7**.[21,22] The calculated electron distribution is shown in Figure 1. The result indicates that, in going from the enol to its anion, all of the protons increase their electron density. Likewise, the charge delocalization causes an increase in π electron densities of the vinyl, ortho, meta, and para carbons. Notably, introduction of a negative charge makes the oxygen-bearing carbon and ipso carbon the more *electron deficient*. Thus the direction of the observed signal movement, except for the unusual behavior of the ortho proton,[23] is basically consistent with the electron distribution change.[14b,24,25]

When ^{13}C chemical shifts of the sp^2-hybridized carbons in **5** are plotted against the calculated π electron densities for **8** (as model of **5**), a good correlation was obtained for the ortho, meta, para, and vinyl carbons. However, the ipso and oxygen-linked carbons did not correlate well. On the other hand, the ^{13}C (sp^2) chemical shift bears a linear relationship with excess total electron density (total electron density − *N*, *N* = 6 for carbon)[26] (Figures 2 and 3). The slope, 221 ppm/electron, is very close to that observed with TAS phenoxide (216 ppm/electron).[1]

Reactions with Electrophiles. Enolates are ambident in nature. In a naked enolate, the charge density is greater at the oxygen atom and the HOMO coefficient is larger at the carbon terminus, and the selectivity in the nucleophilic reactions should reflect such electronic characteristics. In most actual reactions that involve metal-coordinated enolates, however, the metal atoms are also playing important roles in determining the reaction course. Described below is chemical behavior of TAS enolates where such metal cations are absent.

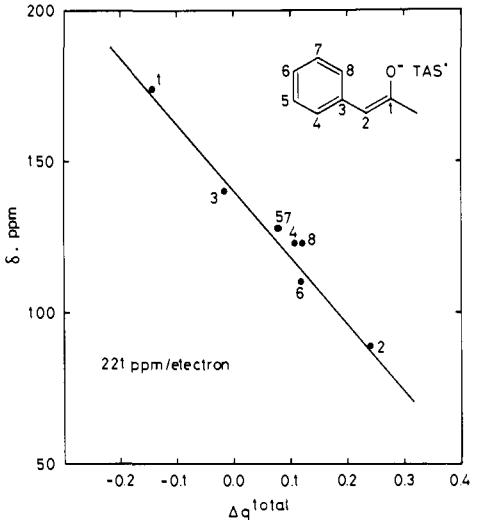


Figure 3. ^{13}C NMR chemical shift vs. excess total electron density in **7**.

When the TAS enolate **5** was treated with 1.2 equiv of acetic anhydride in THF at −78 °C, the O-acylation product **8** was obtained as a sole product in 86% yield (Scheme II).

Unlike the acylation reaction, the alkylation takes place at the carbon terminus of **5**. Thus the preformed **5** upon exposure of 1 equiv of methyl iodide at −78 °C in THF gave the methylated ketone **9** exclusively (85% yield, Scheme III). The TAS enolate generated in situ from the enol silyl ether and the fluoride ion

(21) Since ^1H NMR spectra of phenol and phenyl trimethylsilyl ether exhibit similar signal patterns in the aromatic region, use of the enol silyl ether as a neutral model compound would not be unreasonable.

(22) Planar structures are assumed for the models **6** and **7**, although for the actual compounds **1** and **5** two ortho and meta positions are equivalent in the NMR time scale. The structures for the calculations are derived by using optimized bond lengths (MINDO/3) for vinyloxy anion (1.374 Å for C–C and 1.257 Å for C–O) and standard parameters for other fragments: Baird, N. C.; Dewar, M. J. S. *J. Chem. Phys.* **1969**, *50*, 1262. Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285.

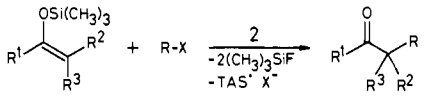
(23) This may be due to magnetic anisotropy of the oxygen atom.

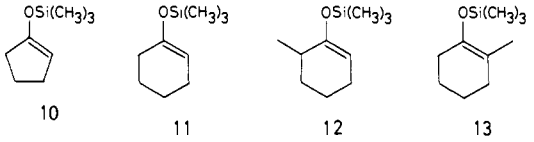
(24) Fellmann, P.; Dubois, J.-E. *Tetrahedron Lett.* **1977**, 247. DePalma, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 3514.

(25) Change in electron distribution is not the sole factor controlling the magnitude of the chemical shift change. The chemical shift for charged species is highly dependent on the nature of substituents, particularly heteroatoms: Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1968**, *90*, 1884. Olah, G. A.; Halpern, Y.; Mo, Y. K.; Liang, G. *Ibid.* **1972**, *94*, 3554.

(26) Bloor, J. E.; Breen, D. L. *J. Phys. Chem.* **1968**, *72*, 716.

Scheme IV





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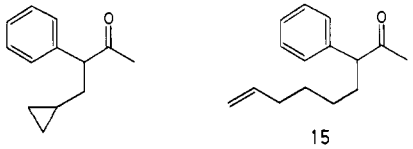
source **2** formed the same product **9** (89% yield). In addition, a variety of enol silyl ethers can be alkylated selectively with active alkylating agents and the aid of **2**. Examples are given in Table III.[27] Although such alkyl halides react readily with **2**, giving the corresponding alkyl fluorides and TAS halides, under the present conditions the enol silyl ethers are even more reactive toward fluoride ion in the generation of the enolate intermediates and **4**. Attempted reaction with secondary alkyl halides such as 2-octyl bromide gave olefinic products predominantly. The overall alkylation via the naked enolates proceeded smoothly at temperatures as low as −78 °C. Usually no appreciable dialkylation took place, although the reaction of cyclopentanone enol trimethyl silyl ether (**10**) produced trace amounts of dialkylation products, which were detected by GC–MS analysis. The reaction is regiospecific with respect to enol silyl ether substrates. Thus, each of the methylated enol silyl ethers **12** and **13** was benzylated only at the sp^2-hybridized C-2 position, and no crossover of the products was noticed (Scheme IV).

Reaction of the enolate **5**, either prepared by vacuum technique or in situ generated, and cyclopropylmethyl iodide proceeded at −78 °C in THF or a THF–hexamethylphosphoric triamide mixture to afford the adduct **14** in good yield. The reaction with 5-hexenyl



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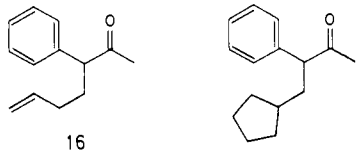
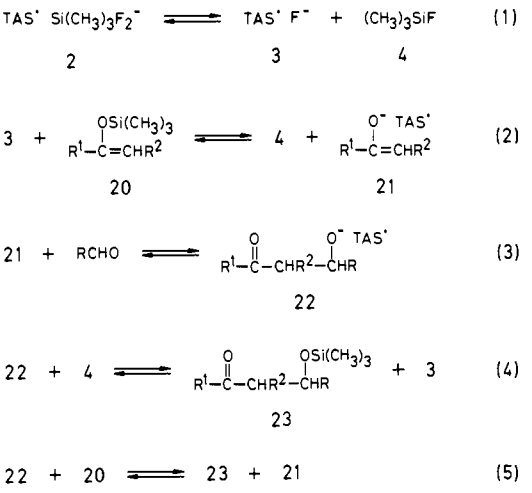


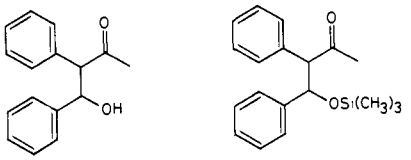
16 17

iodide gave **15**. During these alkylation reactions, neither cyclopropylmethyl nor the 5-hexenyl group as entering group rearranged to allylcarbinyl and cyclopentylmethyl, respectively; no trace of **16** or **17** was detected in the reaction mixture. Therefore, the alkylation reaction, though proceeding by way of highly reactive, naked enolate species, is interpreted in terms of a classical S_N2 type mechanism. Possible mechanisms involving nongeminate, free alkyl radicals formed via electron-transfer processes are excluded.[28,29]

Scheme V



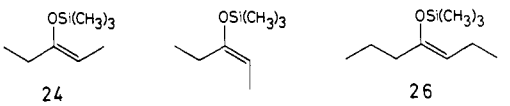
Attempted reaction of the isolated TAS enolate **5** and benzaldehyde in THF at −78 °C failed to give the aldol product **18**



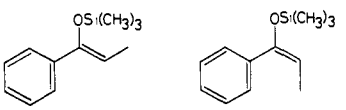
18 19

after aqueous workup. However, when 5 equiv (excess) of fluorotrimethylsilane (**4**) or the enol silyl ether **1** was added to the reaction system, the aldol reaction proceeded smoothly to give the β-trimethylsiloxy ketone **19** in 65 and 80% yield, respectively.

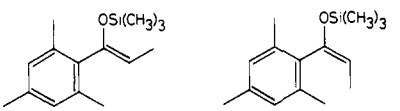
A TAS enolate, generated in situ from an enol silyl ether and fluoride ion, appeared to react readily with an aldehyde substrate, giving rise to the aldol type adduct. Thus, a series of enol silyl ethers can be condensed under mild reaction conditions with aldehydes in the presence of a catalytic amount (0.01–0.1 equiv) of the fluoride ion source **2**, as exemplified in Table IV.[30] This



24 25 26



27 28



29 30

aldol reaction gave no or very little dehydration or self-condensation products.[31] In some cases addition of an excess amount of the fluorosilane **4** was required to produce the β-trimethylsiloxy

(27) For the quaternary ammonium fluoride promoted reaction, see ref 6.
(28) Walling, C. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1963; Vol. 1, p 440. Davies, D. I.; Crostol, S. *Advan. Free-Radical Chem.* **1965**, *1*, 155. Hanack, M.; Schneider, H. J. *Fortschr. Chem. Forsch.* **1967**, *8*, 554. Beckwith, A. L. J. In "Essays on Free Radical Chemistry"; Chemical Society Special Publications, No. 24, London, 1970; p 239. Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. Ingold, K. U. *ACS Symp. Ser.* **1978**, *No. 69*, 187. Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6355. Maillard, B.; Forrest, D.; Ingold, K. U. *Ibid.* **1976**, *98*, 7024. Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *Ibid.* **1980**, *102*, 1734.

(29) For photostimulated $S_{RN}1$ reaction of potassium enolates see: Bunnett, J. F.; Sundberg, J. E. *J. Org. Chem.* **1976**, *41*, 1702. Komin, A. P.; Wolfe, J. F. *Ibid.* **1977**, *42*, 2481. Bunnett, J. F.; Bard, R. R. *Ibid.* **1978**, *43*, 1019. An ESR signal was observed in the reaction of a lithium enolate and methyl *p*-nitrobenzenesulfonate in dioxane: Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.
(30) For the quaternary ammonium fluoride catalyzed aldol reaction, see ref 7.
(31) Reviews on aldol reactions: Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 629–682.

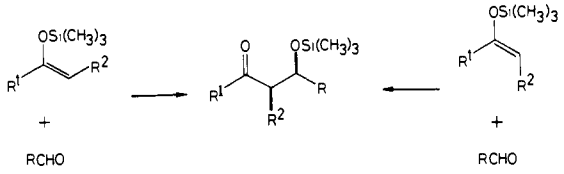
Table IV. Erythro-Selective Aldol Reaction of Enol Silyl Ethers and Aldehydes[a]

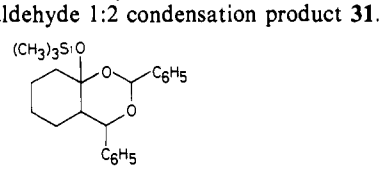
entry	enol silyl ether (configurational purity, %)[b]	aldehyde (equiv)	reaction conditions: 4, equiv	reaction conditions: T, °C (time)	% yield of product[c] (erythro/threo)[d]
1	(Z)-3-(trimethylsiloxy)-2-pentene (24) (100)[d]	benzaldehyde (1.2)	10	−78 (2 h)	89 (86:14)
2	(E)-3-(trimethylsiloxy)-2-pentene (25) (70)[d]	benzaldehyde (1.3)	7	−78 (2 h)	84 (63:37)
3	(Z)-4-(trimethylsiloxy)-3-heptene (26) (100)[d]	benzaldehyde (1.1)		−70 (30 min)[g]	65 (86:14)
4	26	benzaldehyde (1.3)	10	0 (5 min)[h]	90 (73:27)
5	(Z)-1-phenyl-1-(trimethylsiloxy)-propene (27) (99)	benzaldehyde (1.3)		−75 (1 h)	75 (95:5)
6	(E)-1-phenyl-1-(trimethylsiloxy)-propene (28) (91)	benzaldehyde (1.3)		−73 (1 h)	78 (94:6)
7	(Z)-1-(2,4,6-trimethylphenyl)-1-(trimethylsiloxy)-propene (29) (98)	benzaldehyde (1.1)		−78 (4 h)	77[e] (~95:5)
8	29	isobutyraldehyde (1.4)		−70 (11 h)	25[e,i] (~95:5)
9	(E)-1-(2,4,6-trimethylphenyl)-1-(trimethylsiloxy)-propene (30) (97)	benzaldehyde (1.1)		−78 (4 h)	65[e] (~95:5)
10	30	isobutyraldehyde (1.2)		−70 (11 h)	17[e,i] (~95:5)
11	1-(trimethylsiloxy)-cyclohexene (11)	isobutyraldehyde (1.3)	10	−78 (8 h)	67[e] (100:0)[f]
12	1-(trimethylsiloxy)-cyclopentene (10)	isobutyraldehyde (1.3)	10	−78 (35 min)	67[e] (100:0)[f]
13	10	isobutyraldehyde (1.3)	10	−20 − −30 (12 h)	80 (89:11)

[a] All reactions were carried out with 0.1 equiv of 2 as a fluoride ion source. [b] Determined by GLC. [c] Determined by ^{1}H NMR using tetrachloroethane (δ 5.98) as an internal standard. [d] Determined by ^{1}H NMR analysis. [e] Isolated yield. [f] NMR signals due to threo isomer were not observed. [g] 2, 0.01 equiv. [h] 2, 0.05 equiv. [i] The reaction was very slow; a considerable amount of the starting material was recovered.

ketone in high yield. Removal of the silyl group with dilute hydrochloric acid gave the β-hydroxy ketone products. The assignment of the relative configuration (threo or erythro[32]) in the aldol products was made by ^{1}H NMR analysis particularly by using the well-accepted $J_{threo} > J_{erythro}$ relationship.[33,34] The overall reaction is outlined in Scheme V. The failure of the reaction with preformed enolate **5** in the absence of any trimethylsilyl donor is ascribed to the thermodynamic balance of the equilibrium of eq 3 in favor of the starting system rather than the aldol anion formation.[35] This lies in contrast to the reaction of Lewis acid complexes enolates which readily leads to the aldol products. However, the fluorosilane **4** or enol silyl ether **20** present in the reaction system can trap effectively the naked anion **22** to form the aldol silyl ether **23** (eq 4 and 5). The latter pathway makes the reaction autocatalytic. In some cases **22** reacts with another aldehyde molecule. For example, the fluoride ion catalyzed reaction of cyclohexanone enol silyl ether **11** and benzaldehyde formed the enolate/aldehyde 1:2 condensation product **31**.

Scheme VI





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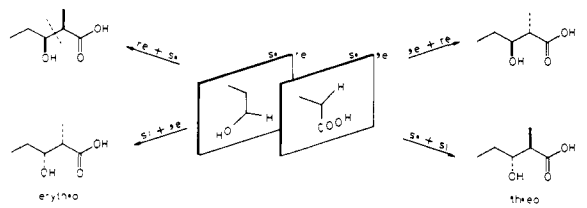
It is worth pointing out that the fluoride-promoted reaction produces, with some exceptions (see below), erythro isomers predominantly.[33] The sense of the stereoselection is independent of enolate geometry, featuring the behavior of TAS enolates (Scheme VI). Under these reaction conditions, configurational integrity of the starting enol silyl ethers or intermediary TAS enolates was unaffected. All the steps given in Scheme V are in principle reversible.[7] Actually, however, the observed erythro selectivity is kinetically controlled by the step depicted by eq 3. The reaction of cyclopentanone enol silyl ether **10** and isobutyraldehyde at −78 °C produced the erythro adduct almost exclusively (entry 12). Exposure of the erythro or threo β-siloxy ketone, prepared independently, to the reaction conditions did not cause stereochemical isomerization. When the same aldol reaction was performed at −20 to −30 °C, the degree of the diastereoselectivity was decreased to give an 89:11 mixture of the erythro and threo isomers (entry 13; compare also entry 3 and 4). The unique erythro-selective reaction of **11** is to be compared with the reaction of cyclopentanone lithium enolate and isobutyraldehyde in aprotic medium, which gives the threo aldol with >95% selectivity.[36] The equilibrium conditions in protic medium are

(32) We have proposed a reasonable, unambiguous nomenclature regarding the threo/erythro relative stereochemistries.[2c] When a diastereomeric compound is cleaved at the single bond that links two adjacent asymmetric carbons, two trigonal radicals are produced. The products arising from the *re* face/*re* face or *si* face/*si* face recombination are referred to as threo diastereomers, and the recombination through *re*/*si* or *si*/*re* interaction affords the erythro diastereomers. This nomenclature procedure accommodates the customary naming for the aldols in most cases and, more conveniently, is applicable to the related diastereomeric compounds other than aldols, even for substances containing more than two asymmetric carbons, in which unambiguous selection of the *skeletal backbone* is difficult.



(33) For an excellent review on stereoselective aldol condensations, see: Heathcock, C. H. "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1981; Vol. II, Chapter 4.

(34) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(35) Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1969; Chapter 13.

(36) Dubois, J. E.; Dubois, M. *Chem. Commun.* **1968**, 1567.

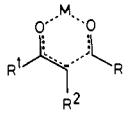
Table V. Nonstereoselective Aldol Reaction of Enol Silyl Ethers and Aromatic Aldehydes[a]

entry	enol silyl ether	aldehyde (equiv)	reaction conditions: 4, equiv	reaction conditions: T, °C (time, min)	% yield of product[b] (erythro/threo)
1	(*Z*)-1-phenyl-2-(trimethylsiloxy)-propene (**1**)[c]	benzaldehyde (1.2)		−78 (135)	90 (38:62)
2	1-(trimethylsiloxy)-cyclopentene (**10**)	benzaldehyde (1.2)	10	−78 (30)	82 (46:54)
3	1-(trimethylsiloxy)-cyclohexene (**11**)	benzaldehyde (1.2)	10	−73 (300)[d]	77 (43:57)
4	**11**	*p*-anisaldehyde (1.2)	10	−30 (5)	19 (41:59)[e]
5	**11**	*p*-nitrobenzaldehyde (1.1)	10	−30 (90)	79 (67:33)
6	**11**	*m*-nitrobenzaldehyde (1.1)	10	−30 (5)	42 (64:36)
7	**11**	furfural (1.2)	10	−78 (15)	54 (40:60)

[a] Unless otherwise stated, reaction was carried out with 0.03 equiv of 2 as a fluoride ion source. [b] Determined by ^{1}H NMR using tetrachloroethane (δ 5.98) as an internal standard. [c] *Z*:*E* = 95:5. [d] 2, 0.05 equiv. [e] The reaction was very slow; a considerable amount of the starting material was recovered.

known to give a 32:68 mixture of the threo and erythro aldols.[36]

The kinetic stereoregulation in the reaction of aldehydes and enolates possessing a Lewis-acidic countercation is defined by the enolate configuration; the *Z* enolates give the products enriched by erythro aldols, whereas the *E* enolates afford the threo aldols predominantly. Here the stereoselectivity is considered to be governed by the relative stabilities of the diastereomeric, metal-linked six-membered transition states of type **32** (M = metallic species).[34,37-44] By contrast, in the reaction of TAS enolates, there



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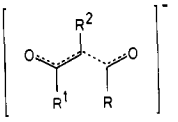
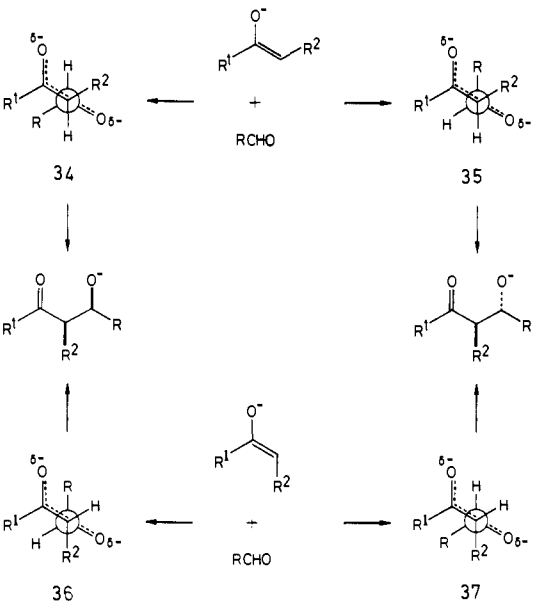


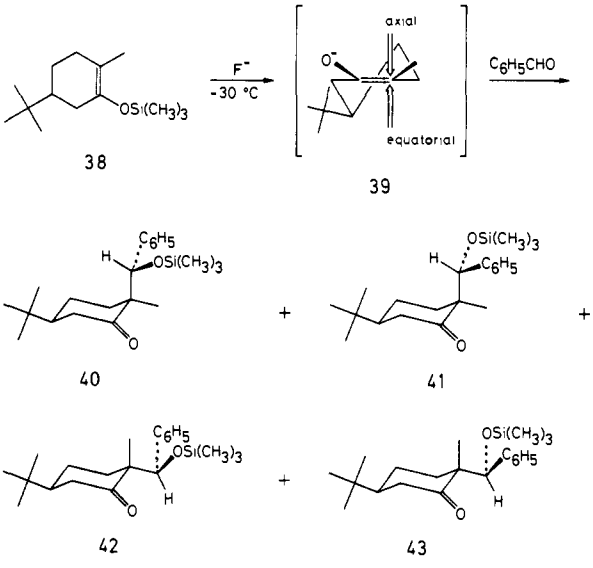
33

exist no cationic species that are capable of assembling the enolate moiety and an aldehyde substrate. In addition, unlike the pericyclic transition state **32** where the charge is neutralized as a whole, the transition state in the TAS enolate reaction is characterized by the development of negative charge. Consequently, we consider, the reaction proceeds via an *acyclic, extended transition state*, **33**,[44-46] among various possible structures, because

Scheme VII



Scheme VIII



(37) (a) Li^+: Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. Buse, C. T.; Heathcock, C. H. *Ibid.* **1977**, *99*, 8109. Heathcock, C. H.; White, C. T. *Ibid.* **1979**, *101*, 7076. Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *Ibid.* **1979**, *101*, 7077. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. Pirrung, M. C.; Heathcock, C. H. *Ibid.* **1980**, *45*, 1727. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, H. C.; White, C. T.; VanDerveer, D. *Ibid.* **1980**, *45*, 3846. Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *Ibid.* **1981**, *46*, 1296. (b) Li^+: Dubois, J. E.; Fellmann, P. *Tetrahedron Lett.* **1975**, 1225. Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.* **1979**, *101*, 2501. Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem.* **1980**, *92*, 573. (c) Li^+, Mg^{2+}, Zn^{2+}: ref 34. (d) Sn^{2+}: Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353. Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467.

(38) B^{3+}: (a) Fenzl, W.; Köster, R.; Zimmerman, H.-J. *Liebigs Ann. Chem.* **1975**, 2201. (b) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Ibid.* **1977**, 153. Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (c) Masamune, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229. Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937. Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568. Choy, W.; Ma, P.; Masamune, S. *Tetrahedron Lett.* **1981**, *22*, 3555. (d) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *Ibid.* **1981**, *103*, 3099. (e) Wada, M. *Chem. Lett.* **1981**, 153.

(39) Al^{3+}: (a) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373. (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. Nozaki, H.; Oshima, K.; Takai, K.; Ozawa, S. *Chem. Lett.* **1979**, 379.

(40) Ti^{4+}: (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029. (c) Reetz, M. T.; Peter, R. *Ibid.* **1981**, *22*, 4691.

(41) Zr^{4+}: Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876.

(42) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(43) For threo-selective aldol reaction via tin enolates see: Shenvi, S.; Stille, J. K. *Tetrahedron Lett.* **1982**, *23*, 627. Cf. ref 37d.

(44) Dubois, J.-E.; Fort, J.-F. *Tetrahedron* **1972**, *28*, 1665.

the electrostatic repulsion of the negatively charged oxygen atoms is minimized through such atomic arrangement. The observed erythro selection is in accord with this consideration. As can be seen from Scheme VII, in the reaction between an aldehyde and the *E* enolate, the erythro transition state **34** arising from the *re/si* face matching[32] is favored over the threo transition state **35** (*si/si* or antipodal *re/re* face matching), which suffers significant steric repulsion between gauche R and R^2 groups. In a like manner, the erythro transition state **36** is more stable than the threo transition state **37**.

It should be added that this reaction is not always kinetically controlled. Reaction of aliphatic aldehydes exhibits general erythro selection, regardless of the structures of enolates. However, some nonstereoselective reactions were noticed when an aromatic aldehyde substrate was combined with the phenylated enol silyl ether **1** or cycloalkanone enol silyl ethers such as **10** or **11** (Table V). It is probable that in such cases the conjugative effect of the aromatic substituents and the rigid structures of the cyclic enolates cooperate in lowering the kinetic barriers, thereby establishing readily the thermodynamic equilibria (eq 3).[7] The facile reaction did not allow examination of time or temperature dependency of the stereoselectivity.

Occurrence of the equilibration was demonstrated by the reaction of the enol silyl ether **38** and benzaldehyde (Scheme VIII). In this reaction, four diastereomers **40–43** are possible to form. When the catalytic reaction was stopped after 5 min, only the axial-threo and axial-erythro adducts, **40** and **41**, were formed in 23 and 10% yield (70:30 ratio), respectively. Apparently, the aldehyde is attacking the six-membered enolate **39** stereoselectively from the axial direction via a kinetically favored chairlike transition state.[47] After a prolonged reaction period (2.5 h), however, some equatorial products, **42** (9%) and **43** (1%), were produced together with **40** (51%) and **41** (21%). Here, notably, the **40/41** ratio, 70:30, remained constant. This indicates that the fluoride ion promoted retrograde reaction of the aldol silyl ethers is indeed involved but the equilibration, TAS enolate + benzaldehyde ⇌ TAS aldolate (eq 3 in Scheme V), is much more facile.

In summary, the fluoride ion catalyzed aldol reaction is reversible in nature and, in some cases, equilibrates quite rapidly, but in most cases the reaction is virtually under kinetic control to afford erythro adducts preferentially.

Experimental Section

General. Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrometer. ^1H NMR spectra were determined on a Varian HA-100 spectrometer, or a JEOL FX-100 spectrometer for the TAS enolate **5**, and the chemical shifts (δ) are reported relative to internal tetramethylsilane (Me_4Si) = 0. ^{13}C NMR spectra were determined at 25 MHz on a JEOL FX-100 spectrometer by using an $^1H/^{13}C$ dual probe, and chemical shifts (δ) are reported relative to internal tetramethylsilane = 0. A 45° pulse was irradiated every 10 s for measurement of ^{13}C NMR spectra of **5**. Electroconductivity measurement was performed at 25 °C under argon atmosphere using a TOA CM-58 instrument connected with a TOA CG-201PL electrode (No. 516021). Mass spectra were determined at 75 eV on a JEOL JMS D-10 spectrometer. For GC–MS analysis, a 2 m × 2 mm column of 3% Silicon OV-1 on Chromosorb WAW was used. Analytical gas–liquid partition chromatography (GLPC) was performed on a Hitachi 163 instrument with a thermal conductivity detector and helium carrier gas (0.5–1.0 kg/cm^2) or a Hitachi 063 instrument with a flame ionization detector and nitrogen carrier gas (1.0 kg/cm^2). Preparative GLPC was carried out on a Varian 1700 instrument with a thermal conductivity detector. The following columns were used: column A (Hitachi 163), a 1 m × 3 mm column of 10% SE-30 on Chromosorb W; column B (Hitachi 163), a 2 m × 3 mm column of 5% FFAP on Chromosorb WAW; column C (Hitachi 063), a 2 m × 3 mm column of 3% DEGS on Uniport B; column D (Hitachi 063), a 2 m × 3 mm column of 5% FFAP on Neopak 1A; column E (Varian 1700), a 4.6 m × 10 mm column of 11% SE-30 on Chromosorb WAW; column F (Varian 1700), a 5 m × 10 mm column of 15% DEGS on Chromosorb WAW. Preparative thin-layer chromatography (TLC) was carried out on glass plates (20 × 20 cm) coated with Merck silica gel PF_{254} (1 mm in thickness). Analytical TLC was carried out on precoated plates (2 × 5 cm) of Merck silica gel 60 F_{254} (0.25 mm in thickness). Column chromatography was performed on Merck silica gel 60 (70–230 mesh) or Fuji-Davison silica gel BW-80 (100–200 mesh). Microanalysis was done in Professor T. Sasaki's laboratory, Faculty of Engineering, Nagoya University. The MO calculations were performed at the Computer Center of Institute for Molecular Science.

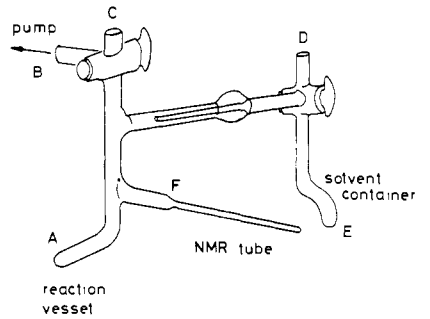


Figure 4. Apparatus for NMR measurement.

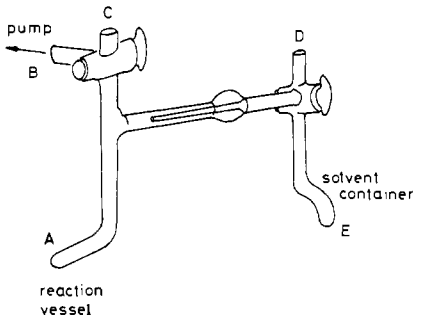


Figure 5. Apparatus for electroconductivity measurement.

Solvents and Reagents. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl immediately before use. Deuterated THF (THF-d_8) was purchased from Nakarai Chemical Co. and used without further purification. All solvents for extraction were used after distillation of the guaranteed reagents (Nakarai). Fluorotrimethylsilane (**4**), bp 18 °C, was synthesized by the known method.[48] After successive washing with cold aqueous ammonia and cold water, the product was distilled over CaH_2 through a 40-cm Vigreux column in a cold room (4 °C), stored in a Schlenck tube under argon atmosphere, and taken by syringe on use. All aldehydes and most organic halides were purchased (Nakarai) and distilled for use. Cyclopropylmethyl iodide[49] and 5-hexenyl iodide[50] were synthesized as described in the literature. Enol silyl ethers **10–13** and **38**,[51] **25** and **28–30**,[52] and **24**, **26**, and **27**[53] were prepared as described or after slight modification. Purification, if necessary, was done by preparative GLPC (column E, 200 °C, or column F, 90–100 °C). The *E* enol silyl ether **1** was synthesized as follows: In a 300-mL round-bottomed flask, sodium hydride (7.40 g, 0.15 mmol) was washed with dry (P_2O_5) hexane and suspended in dry ether (100 mL). Benzyl methyl ketone[54] (14.83 g, 0.111 mmol) was then added dropwise,

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the mixture was heated at reflux for 2 h, and to this was added chlorotrimethylsilane (25.4 mL, 0.20 mmol) at 0 °C. The reaction mixture was diluted with petroleum ether (100 mL) and triethylamine (20 mL) and washed with cold water. The aqueous layer was extracted with petroleum ether. The combined organic extracts were washed with cold 1 N HCl solution (2 × 300 mL), saturated $NaHCO_3$ solution (100 mL), and water (100 mL), then dried (Na_2SO_4), and concentrated in vacuo. Distillation under reduced pressure gave 19.5 g (85%) of 1-phenyl-2-trimethylsiloxypropene (*Z*:*E* = 95:5), bp 120–122 °C (36 mmHg). The *Z* isomer **1** was purified by preparative GLPC (column E, 190 °C).

TAS difluorotrimethylsiliconate (**2**) synthesized according to the patent procedure[11] was dissolved in dry THF and dividedly stored in 1-mL ampules under argon atmosphere. The concentration of the solution was determined by ^1H NMR spectroscopy with benzene as an internal standard; the upper signals of THF (δ 3.63) were used as a lock signal, and the signal intensities at δ 7.25 (C_6H_6) and −0.18 ($Si-CH_3$) were compared to each other.

Synthesis of Tris(diethylamino)sulfonium Enolate 5. The apparatus used for the synthesis of **5** are shown in Figures 4 and 5. In solvent container E was placed molecular sieves 3A. Apiezon L was used for stopcock grease. Openings C and D were capped with rubber septa (SGA Scientific Inc., R 7950) sealed by parafilm (American Can Co.). Evacuation of the inner atmosphere of the apparatus and introduction of argon gas were performed through B. Prior to the enolate synthesis, the apparatus was baked out with a heat gun under reduced pressure (0.01 mmHg) and cooled to room temperature under argon pressure.

Dry ether (2 mL) placed in E was degassed by repeated freezing, pumping, and thawing and stored under argon. The enol silyl ether **1** (95.9 mg, 0.466 mmol) and 0.5 mL of THF was placed in A and cooled to −78 °C. To this was added a THF solution of **2** (1.06 M, 440 μL, 0.466 mmol), and the resulting yellow solution was degassed by repeated freeze–pump–thaw cycles and then evaporated at 0 °C to leave yellow solid, which was cooled in a liquid nitrogen bath. The ether stored in E was then transferred to A by distillation under reduced pressure. The solid in A was vigorously dispersed in a cold (0 °C) ether by vibration with an electric vibrator (Hitachi HV 150). The supernatant was removed by a syringe under argon, and remaining yellow precipitate, which appeared to be the TAS enolate **5**, was dried under reduced pressure at 0 °C. THF-d_8 (containing a small amount of Me_4Si, 0.5 mL) was introduced to E, degassed as described above, and admitted under reduced pressure to A cooled in a liquid nitrogen bath. The mixture was warmed to 0 °C. The resulting TAS enolate solution was transferred into the NMR tube. The tube was then frozen, pumped, sealed at F, and subjected to ^1H and ^{13}C NMR measurements (Tables I and II).

TAS enolate **5**, prepared in container A of Figure 5 and placed under argon atmosphere, was dissolved in 3 mL of THF. The solution was then transferred to a dried 25-mL volumetric flask in a dry bag through a stainless pipe under argon pressure. Then THF was added up to 25-mL total volume. The solution was subjected to electroconductivity measurement, which showed 1.8 $cm^2\ mol^{-1}\ ohm^{-1}$ (3.8×10^{-3} M). Ten milliliters of the solution was diluted with methanol and concentrated in vacuo. ^1H NMR analysis with added tetrachloroethane internal standard revealed the concentration of the resulting ketone.

A THF solution of **1** (42 mg, 0.21 mmol) was placed in a flask connected with a cold (liquid nitrogen) distillation receiver. To this was added **2** (0.95 M THF solution, 0.22 mL, 0.21 mmol) at −78 °C, and the solution was kept at room temperature for 1.5 h under vacuum (0.01 mmHg). Volatile fluorotrimethylsilane (**4**) and THF were collected in the cold receiver. ^1H NMR analysis with added benzene (30 mg, 0.42 mmol) revealed the production of **4** in 90% yield.

Acetylation of TAS Enolate 5. To a solution of **1** (76.8 mg, 0.373 mmol) in THF (2 mL) cooled at −78 °C was added **2** (1.0 M in THF, 336 μL, 0.336 mmol) and the solution was evaporated to dryness. The resulting residue was dissolved in THF (1 mL) and cooled to −78 °C. The solution was mixed with acetic anhydride (53 μL, 0.56 mmol), stirred for 30 min at this temperature, and diluted with hexane (4 mL). The mixture was washed with water, and the aqueous layer was extracted with hexane. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 85 mg of pale yellow oil. GLPC analysis of this oil with added $C_{16}H_{34}$ (41.2 mg, 0.182 mmol) showed that the enol acetate **8** was the sole product formed in 86% yield (column D, 160 °C, t_R 1.6 min ($C_{16}H_{34}$), 6.8 min (**8**)). Then the product was purified by a column chromatography (10:1 petroleum ether–ether) to afford 51 mg of **8** (78%). ^1H NMR and IR spectra of the product were consistent with the assigned structure.[14a]

Methylation of TAS Enolate 5. To **1** (248 mg, 1.20 mmol) placed in a 5 mL round-bottomed reaction tube was added **2** (1.0 M in THF, 1.2 mL, 1.2 mmol), and the solution was evaporated to dryness. The resulting solid was dissolved in THF (3.0 mL) and cooled to −78 °C. The solution was mixed with methyl iodide (170 mg, 1.2 mmol), stirred for 30 min at this temperature, and diluted with hexane. The mixture was washed with water, and the aqueous layer was extracted with hexane. The combined extracts were dried (Na_2SO_4) and concentrated to give 253 mg of a crude oil. ^1H NMR analysis (CCl_4) with added tetrachloroethane internal standard revealed that 3-phenyl-2-butanone (**9**) and benzyl methyl ketone were formed in 85 and 15% yield, respectively. No signals assignable to vinylic protons were observed.

Fluoride Ion Promoted Alkylation of Enol Silyl Ethers. A variety of enol silyl ethers were alkylated under the conditions specified in Table III. The representative examples are as follows.

A. Reaction of 1 and Methyl Iodide. To a cold (−78 °C) solution of the enol silyl ether **1** (194 mg, 0.943 mmol) and methyl iodide (93%, 193 mg, 1.27 mmol) in THF (3 mL) was added **2** (1.085 M in THF, 869 μL, 0.943 mmol). After 15-min reaction, the mixture was diluted with hexane and washed with water. The aqueous layer was extracted with ether and combined organic layers were dried ($MgSO_4$) and concentrated to give a crude oil (162 mg). The ^1H NMR analysis (CCl_4) in the presence of tetrachloroethane (103 mg, 0.616 mmol) revealed that 3-phenylbutan-2-one (**9**) was formed in 89% yield. Column chromatography of the concentrated solution (25:1 hexane–ethyl acetate) afforded the ketonic product (107 mg, 77%):[55] R_f 0.40 (6:1 hexane–ethyl acetate; IR (neat) 1716 cm^{-1}; ^1H NMR (CCl_4) δ 1.37 (d, 3, J = 6 Hz, CH_3), 1.97 (s, 3, CH_3CO), 3.64 (q, 1, J = 6 Hz, CHC_6H_5), 7.0–7.4 (m, 5, C_6H_5); MS, m/z 148 (M^+).

B. Reaction of 1 and Cyclopropylmethyl Iodide. To a cold (−78 °C) solution of **1** (356 mg, 1.73 mmol) and cyclopropylmethyl iodide (424 mg, 2.33 mmol) in THF (3.5 mL) was added **2** (1.085 M in THF, 1.59 mL, 1.73 mmol). The solution was stirred for 7 h at −78 °C, diluted with hexane, and quenched with water. Extractive workup followed by concentration gave a crude oil (396 mg). GLPC analysis (column B, 180 °C) with added methyl laurate (78.4 mg, 0.344 mmol) indicated that 1-cyclopropyl-2-phenylbutan-3-one (**14**) was formed in 83% yield: t_R 2.9 min (benzyl methyl ketone), 3.9 min (methyl laurate), 6.8 min (**14**). Spectral characteristics of **14**: IR (neat) 1708 cm^{-1}; ^1H NMR (CCl_4) δ 0.8 (m, 4, CH_2), 1.3–1.9 (m, 3, CH and CH_2), 1.98 (s, 3, CH_3), 3.64 (t, 1, J = 7 Hz, CHC_6H_5), 7.0–7.4 (m, 5, C_6H_5); MS, m/z 188 (M^+). Anal. ($C_{13}H_{16}O$) C, H.

When the enol silyl ether **1** (510 mg, 2.48 mmol) and cyclopropylmethyl iodide (587 mg, 3.22 mmol) in THF (20 mL) were treated with **2** (1.085 M in THF, 2.28 mL, 2.48 mmol) in the presence of hexamethylphosphoric triamide (4.3 mL, 24.7 mmol) at −74 °C for 12 h, 1.21 g of crude oil was obtained after the extractive workup. GLPC analysis of the oil showed that the ketone **14** was formed in 51% yield.

C. Reaction of 1- and 5-Hexenyl Iodide. To a cold (−78 °C) solution of enol silyl ether **1** (223 mg, 1.08 mmol) and 5-hexenyl iodide (234 mg, 1.11 mmol) in THF (2 mL) was added **2** (0.947 M in THF, 1.145 mL, 1.11 mmol), and the solution was stirred at −78 °C for 4 h and at −40 °C for an additional 30 min. Then the mixture was diluted with hexane and quenched with water. Extractive workup and concentration of the organic solutions afforded a crude oil (290 mg). GLPC analysis with added methyl laurate (42.2 mg, 0.197 mmol) (column A, 150 °C) revealed that 3-phenyl-8-nonen-2-one (**15**) was formed in 91% yield: t_R 6.6 min (methyl laurate), 9.9 min (**15**). The ketonic product was purified by column chromatography (hexane–ethyl acetate): R_f 0.53 (6:1 hexane–ethyl acetate); IR (neat) 1715 cm^{-1}; ^1H NMR (CCl_4) δ 1.1–2.2 (m, 8, CH_2), 1.95 (s, 3, CH_3CO), 3.48 (t, 1, J = 6.6 Hz, CHC_6H_5), 4.88 (m, 1, $=CH_2$), 4.92 (m, 1, $=CH_2$), 5.71 (tdd, 1, J = 5, 11, 19 Hz, $=CH$), 7.0–7.4 (m, 5, C_6H_5); MS, m/z 216 (M^+). Anal. ($C_{15}H_{20}O$) C, H.

D. Reaction of 10 and Allyl Bromide. To a solution of **10** (340.6 mg, 2.14 mmol) and allyl bromide (185 μL, 2.14 mmol) in THF (2.0 mL) cooled at −78 °C was added **2** (1.0 M in THF, 2.15 mL, 2.14 mmol), and the solution was stirred at this temperature for 3 h. Quenching with water and extractive workup with ether gave a crude oil (147.2 mg). GC–MS analysis of this oil indicated the production of trace amounts (<3%) of compounds having molecular weight of 164 (diallylation products) together with the ordinary monoallylation product (60% yield). Purification by column chromatography (10:3 hexane–ether) afforded 2-allylcyclopentanone:[56] R_f 0.37 (10:3 hexane–ether); IR (CCl_4) 1734 cm^{-1}; ^1H NMR (CCl_4) δ 1.3–2.6 (m, 9, CH and CH_2), 4.8–5.1 (m, 2, $=CH_2$), 5.5–5.9 (m, 1, $=CH$); MS, m/Z 124 (M^+).

E. Reaction of 11 and Methyl Iodide. To a cold (−78 °C) solution of **11** (175 mg, 1.03 mmol) and methyl iodide (213 mg, 1.5 mmol) in THF (1.5 mL) was added **2** (0.75 M in THF, 1.6 mL, 1.2 mmol), and the mixture was kept for 4 h at −78 °C. The crude product was analyzed by GLPC with added methyl caplirate (84 mg, 0.53 mmol) (column C, 70 °C) to reveal that 2-methylcyclohexanone[56] was formed in 95% yield: t_R 3.6 min (2-methylcyclohexanone), 5.9 min (methyl caprylate).

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F. Reaction of 12 and Benzyl Bromide. To a cold (−78 °C) solution of **12** (308 mg, 1.67 mmol) and benzyl bromide (343 mg, 2.00 mmol) in THF (2.5 mL) was added **2** (1.0 M in THF, 1.7 mL, 1.7 mmol), and the solution was stirred for 3 h at −78 °C. Quenching with water and extractive workup gave a crude oil (431 mg). TLC separation (10:1 hexane–ethyl acetate) afforded *trans*-2-benzyl-5-methylcyclohexanone[6,57] (185 mg, 55%) and its cis isomer (36 mg, 11%). Trans isomer: R_f 0.37; IR (CCl_4) 1711 cm^{-1}; ^1H NMR (CCl_4) δ 1.06 (d, 3, J = 6.5 Hz, CH_3), 1.3–2.2 (m, 6, CH_2), 2.4–2.8 (m, 3, CH and $CH_2C_6H_5$), 2.9–3.2 (m, 1, $CH_2C_6H_5$), 7.0–7.4 (m, 5, C_6H_5); MS m/z 202 (M^+). Cis isomer: R_f 0.42; IR (CCl_4) 1713 cm^{-1}; ^1H NMR (CCl_4) δ 0.99 (d, 3, J = 6 Hz, CH_3), 1.2–2.7 (m, 9, CH_2 and $CH_2C_6H_5$), 3.0–3.4 (m, 1, $CH_2C_6H_5$), 7.0–7.4 (m, 5, C_6H_5); MS, m/z 202 (M^+).

G. Reaction of 13 and Benzyl Bromide. A solution of **13** (255 mg, 1.38 mmol) and benzyl bromide (284 mg, 1.66 mmol) were dissolved in THF (1.5 mL) and cooled at −78 °C. To this was added **2** (0.75 M in THF, 2.0 mL, 1.40 mmol), and the solution was stirred for 3 h at this temperature, diluted with hexane, and quenched with water. Extractive workup with hexane afforded a crude oil (363 mg). TLC purification (10:1 hexane–ethyl acetate) afforded 2-benzyl-2-methylcyclohexanone (165 mg, 60%):[6,57] R_f 0.38; IR (CCl_4) 1709 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (s, 3, CH_3), 1.4–2.1 (m, 6, CH_2), 2.3–2.5 (m, 2, CH_2CO), 2.72 and 2.90 (ABq, 2, J = 13 Hz, $CH_2C_6H_5$), 7.0–7.4 (m, 5, C_6H_5); MS, m/z 202 (M^+).

Aldol Reaction of TAS Enolate 5 and Benzaldehyde. A. In the Presence of 4. To the TAS enolate **5**, prepared in reaction vessel A (Figure 5) from **1** (44.2 mg, 0.215 mmol) and **2** (2.042 M in THF, 105 μL, 0.215 mmol), was added degassed THF (1.5 mL) from B by distillation and then **4** (0.9 mL, 1.1 mmol) in the same manner. The solution was cooled at −78 °C and to this was added benzaldehyde (1.98 M in THF, 119 μL, 0.237 mmol). After being kept at −78 °C for 30 min, the solution was diluted with dry pentane (10 mL), and the resulting mixture was poured into water (20 mL) through a stainless pipe under argon pressure. The reaction vessel was washed with pentane (5 mL), THF (3 mL), and ether (5 mL), successively. The organic solutions were combined and washed with water. The aqueous layer was extracted with ether. Organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give a crude oil (63 mg). Column chromatography of this oil (petroleum ether–ether) afforded a 28:72 mixture of *erythro*- and *threo*-3,4-diphenyl-4-trimethylsiloxybutan-2-one (**19**) (37.5 mg, 52%), R_f (2:1 hexane–ethyl acetate) 0.62 and 0.52, respectively, and an 11:89 mixture of *erythro*- and *threo*-4-hydroxy-3,4-diphenylbutan-2-one (**18**) (10.2 mg, 13%). ^1H NMR of *erythro*-**18** (CCl_4) δ 1.92 (s, 3, CH_3CO), 2.74 (d, 1, J = 2.0 Hz, OH), 3.79 (d, 1, J = 5.5 Hz, C*H*OH), 5.26 (dd, 1, J = 2.0, 5.5 Hz, C_6H_5CHCO), 6.8–7.4 (m, 10, C_6H_5). ^1H NMR of *threo*-**18** (CCl_4) δ 2.07 (s, 3, CH_3CO), 3.27 (br s, 1, OH), 3.78 (d, 1, J = 9.5 Hz, C*H*OH), 5.08 (dd, 1, J = 4.0, 9.5 Hz, C_6H_5CHCO), 6.8–7.4 (m, 10, C_6H_5). ^1H NMR characteristics of a 28:72 mixture of *erythro*- and *threo*-**19** (CCl_4) δ 1.83 and 2.22 (two s, 3:7 ratio, 3, CH_3CO), 4.00 and 4.01 (two d, 3:7 ratio, 1, J = 8, 10 Hz, CHOSi), 5.18 and 5.23 (two d, 3:7 ratio, 1, J = 8, 10 Hz, C_6H_5CHCO), 6.8–7.4 (m, 10, C_6H_5).

B. In the Presence of 1. The TAS enolate **5**, synthesized from **1** (43.8 mg, 0.213 mmol) and **2** (2.042 M in THF, 104 μL, 0.213 mmol), was dissolved in THF (2.0 mL). To this was added **1** (213 mg, 1.032 mmol), the solution was cooled at −78 °C, and then benzaldehyde (1.98 M in THF, 118 μL, 0.234 mmol) was added. After stirring for 30 min at −78 °C, the mixture was subjected to extractive workup as described above to give a crude oil (167 mg). ^1H NMR analysis of this oil with added tetrachloroethane (55.1 mg, 0.328 mmol) revealed the formation of a 22:78 mixture of *erythro*- and *threo*-**19** (δ 1.83 and 2.22, respectively, s, CH_3CO) in 80% yield.

When the reaction of **5** and benzaldehyde (1:1 to 1:1.5 mol ratio, −104 to 32 °C, 10 min) was conducted without added **1** or **4**, substantial amounts of benzyl methyl ketone (40–60%) and benzaldehyde were recovered. Some untractable materials were produced but no aldol or its dehydration products were formed.

Fluoride Ion Catalyzed Aldol Reaction of Enol Silyl Ethers and Aldehydes. A number of aldol reactions were carried out under the conditions given in Tables IV and V. Some typical procedures are given below.

A. Reaction of 24 (or 25) and Benzaldehyde. To a solution of **4** (1.060 g, 11.52 mmol) in THF (1 mL) cooled at 0 °C was added the *Z* enol silyl ether **24** (186 mg, 1.18 mmol, 100% pure) and benzaldehyde (153 mg, 1.45 mmol). After cooling to −78 °C, **2** (0.908 M in THF, 130 μL, 0.118 mmol) was added in a dropwise manner. The solution was stirred for 2 h at −78 °C, diluted with hexane, and then quenched with water. The aqueous layer was extracted with ether. The organic solutions were combined, dried (Na_2SO_4), and concentrated in vacuo to give a crude oil. This oil was then treated at 0 °C for 20 min with a 1:10 mixture of 1 N HCl and THF, diluted with hexane, and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether. The organic solutions were combined, dried (Na_2SO_4), and concentrated in vacuo to give a crude ketol product (240 mg). Tetrachloroethane (51.7 mg, 0.308 mmol, δ 5.98) was added to this oil dissolved in CCl_4, and the solution was subjected to NMR analysis. 2-(Hydroxyphenylmethyl)-pentan-3-one[50] was formed in 89% yield as an 86:14 mixture of the erythro and threo isomers, which exhibited the signals due to C*H*OH at δ 4.85 (d, J = 5 Hz) and 4.68 (d, J = 9 Hz), respectively.

In a similar manner, the reaction of the *E* enol silyl ether **25** (284 mg, 1.79 mmol, 70% pure) and benzaldehyde (245 mg, 2.31 mmol) was performed in the presence of fluorotrimethylsilane (1.88 g, 12.91 mmol) and **2** (0.908 M in THF, 197 μL, 0.179 mmol) in THF (1 mL). After the acidic hydrolysis of the reaction product was obtained 369 mg of a crude oil. Tetrachloroethane (48.7 mg, 0.290 mmol, δ 5.98) was added to this oil dissolved in CCl_4, and the solution was then subjected to NMR analysis; the aldol product was formed in 84% yield as a 63:37 mixture of the erythro (δ 4.85, d, J = 5 Hz, C*H*OH) and threo (δ 4.68, d, J = 9 Hz, C*H*OH) isomers.

B. Reaction of 26 and Benzaldehyde. A solution of the enol silyl ether **26** (262 mg, 1.41 mmol, 100% pure) and benzaldehyde (157 mg, 1.48 mmol) in THF (2.0 mL) was cooled at −70 °C, and to this was added **2** (0.908 M in THF, 16 μL, 0.015 mmol). After being stirred at −70 °C for 30 min, the solution was diluted with hexane and quenched with water. The extractive workup with ether and concentration of the organic solutions gave a crude oil (397 mg). When this oil was treated at room temperature for 15 min with a 1:40 mixture of 1 N HCl and THF, 237 mg of a crude aldol product was obtained after ordinary workup. ^1H NMR analysis with added tetrachloroethane (57.5 mg, 0.343 mmol, δ 5.98) revealed that 3-(hydroxyphenylmethyl)heptan-4-one was formed in 65% yield as an 86:14 mixture of the erythro (δ 4.74, C*H*OH) and threo (δ 4.63, C*H*OH) isomers.

In a similar manner, the reaction of the enol silyl ether **26** (208 mg, 1.12 mmol) and benzaldehyde (153 mg, 1.44 mmol) was performed at 0 °C for 5 min in the presence of **4** (1.022 g, 11.11 mmol) and **2** (0.908 M in THF, 70 μL, 0.064 mmol) in THF (1.5 mL). The aldol product (254 mg) was obtained from the reaction mixture after hydrolysis with 1:10 1 N HCl–THF at 0 °C for 15 min. The ^1H NMR analysis revealed that the aldol product, formed in 90% yield, consisted of the erythro and threo isomers in 73:27 ratio. Column chromatography (15:1 benzene–ethyl acetate and 5:1 petroleum ether–ether) afforded a 4:1 mixture of erythro and threo aldols: IR (neat) 3450, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 0.65–0.95 (m, 6, CH_3), 1.2–2.8 (m, 8, CH and CH_2), 4.63 and 4.74 (two d, 1:4 ratio, 1, J = 7.0, 5.7 Hz, C*H*OH), 7.23 (s, 5, C_6H_5). Anal. ($C_{14}H_{20}O_2$) C, H.

C. Reaction of 27 (or 28) and Benzaldehyde. A solution of the *Z* enol silyl ether **27** (130 mg, 0.630 mmol, 99% pure) and benzaldehyde (89.5 mg, 0.844 mmol) in THF (1.5 mL) was cooled at −75 °C and to this was added the THF solution of **2** (0.908 M, 69 μL, 0.63 mmol) in a dropwise manner. After being stirred at −75 °C for 1 h, the solution was diluted with hexane and quenched with water. The extractive workup with ether and concentration of the organic solutions gave a crude oil, which was heated at reflux for 10 min in CH_3OH containing a small amount of pyridinium *p*-toluenesulfonate (PPTS). The reaction mixture was then cooled to room temperature and evaporated in vacuo. The resulting residue was suspended in water and extracted with ether three times. The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give an oily product (150 mg). Tetrachloroethane (62.6 mg, 0.373 mmol, δ 5.98) was added to this oil dissolved in CCl_4 and the solution was subjected to ^1H NMR analysis. 2-(Hydroxyphenylmethyl)-1-phenylpropan-1-one[50] was formed in 75% yield as a 95:5 mixture of erythro and threo isomers, which exhibited the signals due to C*H*OH at δ 5.21 (d, J = 3 Hz) and 4.94 (d, J = 8 Hz), respectively.

In a similar manner, the reaction of the *E* enol silyl ether **28** (21.9 mg, 0.106 mmol, 91% pure) and benzaldehyde (14.5 mg, 0.137 mmol) was performed at −73 °C for 1 h in the presence of **2** (0.908 M in THF, 12 μL, 0.011 mmol) in THF (0.5 mL). After the hydrolysis of the reaction product in refluxing methanol containing PPTS was obtained a crude oil (22.5 mg). The ^1H NMR analysis with added tetrachloroethane (29.2 mg, 0.174 mmol, δ 5.98) revealed that the aldol product was formed in 78% yield and was a 94:6 mixture of the erythro (δ 5.21, d, J = 3 Hz, C*H*OH) and threo (δ 4.94, d, J = 8 Hz, C*H*OH) isomers.

D. Reaction of 29 (or 30) and Isobutyraldehyde. A mixture of the *Z* enol silyl ether **29** (47.2 mg, 0.318 mmol, 98% pure) and isobutyraldehyde (31.7 mg, 0.44 mmol) in THF (2.0 mL) was cooled to −70 °C, and to this was added **2** (0.908 M in THF, 35 μL, 0.032 mmol). After being stirred for 11 h at this temperature, the solution was quenched with water and extracted with ether. The crude product was treated with a

(57) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.

1:4 mixture of 1 N HCl and THF for 15 min at room temperature and quenched with saturated $NaHCO_3$ to give after extractive workup an oil (56 mg). Column chromatography (15:1 hexane–ethyl acetate) separated 3-hydroxy-2,4-dimethyl-1-(2,4,6-trimethylphenyl)pentan-1-one (19.8 mg, 25% yield). Judging from the ^1H NMR signal due to C*H*OH proton, the erythro isomer was the sole product (δ 3.59 (dd)), but the TLC analysis indicated the formation of a trace amount of the threo isomer.

When the *E* enol silyl ether **30** (139 mg, 0.558 mmol, 97% pure) was reacted with isobutyraldehyde (48.7 mg, 0.676 mmol) as described above, 24 mg (17%) of the aldol product was obtained together with recovered 1-(2,4,6-trimethylphenyl)propan-1-one (77 mg, 78%). Only the erythro isomer was detectable by ^1H NMR, but TLC analysis suggested the formation of a trace amount of the threo aldol.

Authentic samples of the stereoisomeric aldol were prepared by the known method.[50] *erythro*-3-Hydroxy-2,4-dimethyl-1-(2,4,6-trimethylphenyl)pentan-1-one: R_f 0.20 (1:4 ether–petroleum ether); mp 52 °C; IR ($CHCl_3$) 3540, 1679 cm^{-1}; ^1H NMR (CCl_4) δ 0.82 (d, 3, J = 6.4 Hz, CH_3), 1.04 (d, 3, J = 6.4 Hz, CH_3), 1.08 (d, 3, J = 7.3 Hz, CH_3), 1.4–1.9 (m, 1, CH), 2.20 (s, 6, CH_3), 2.28 (s, 3, CH_3), 3.02 (dq, 1, J = 1.7, 7.3 Hz, CH), 3.58 (dd, 1, J = 9.5, 1.7 Hz, CHO), 6.77 (s, 2, =CH). Anal. ($C_{16}H_{24}O_2$) C, H. *threo*-3-Hydroxy-2,4-dimethyl-1-(2,4,6-trimethylphenyl)pentan-1-one: R_f 0.29 (1:4 ether–petroleum ether); IR ($CHCl_3$) 3600, 1680 cm^{-1}; ^{1} H NMR (CCl_4) δ 0.88 (d, 3, J = 6.2 Hz, CH_3), 1.00 (d, 3, J = 7.3 Hz, CH_3), 1.15 (d, 3, J = 6.4 Hz, CH_3), 1.4–1.9 (m, 1, CH), 2.21 (s, 6, CH_3), 2.26 (s, 3, CH_3), 3.01 (quint, 1, J = 7.3 Hz, CH), 3.70 (dd, 1, J = 7.5, 3.0 Hz, CHO), 6.76 (s, 2, =CH).

Attempted reaction of **30** (106 mg, 0.427 mmol) and butanal (40.1 mg, 0.557 mmol) with added **2** (0.908 M in THF, 24 μL, 0.022 mmol) and **4** (1.089 g, 11.84 mmol) in THF (1.5 mL) at −78 °C for 6 h resulted in recovery of **30**. ^1H NMR of the enol silyl ether indicated that no *E* to *Z* isomerization occurred under such conditions.

E. Reaction of 11 and Isobutyraldehyde. To a solution of **4** (1.598 g, 17.37 mmol) in THF (2.0 mL) cooled at 0 °C was added the enol silyl ether **11** (295 mg, 1.73 mmol) and isobutyraldehyde (163 mg, 2.27 mmol). After cooling to −78 °C, **2** (0.908 M, 191 μL, 0.173 mmol) was added in a dropwise manner. After stirring for 8 h at −78 °C, the solution was diluted with hexane and quenched with water. An oil, obtained by extractive workup, was hydrolyzed in a 1:3 1 N HCl–THF mixture at room temperature for 10 min to give a crude oily product (257 mg). Column chromatography of this oil (20:1 benzene–ethyl acetate) afforded the erythro β-hydroxy ketone (199 mg, 67%). No signals assignable to threo isomer were detected in ^1H NMR spectrum of the crude product. *erythro*-2-(1-Hydroxy-2-methylpropyl)cyclohexan-1-one:[40a] R_f 0.47 (20:1 benzene–ethyl acrylate); IR (neat) 3500, 1702 cm^{-1}; ^1H NMR (CCl_4) δ 0.79 (d, 3, J = 6 Hz, CH_3), 1.02 (d, 3, J = 6 Hz, CH_3), 1.4–2.6 (m, 11, CH, CH_2, and OH), 3.61 (dd, J = 2.5, 9 Hz, C*H*OH).

F. Reaction of 10 and Isobutyraldehyde. A solution of the enol silyl ether **10** (204 mg, 1.41 mmol) and isobutyraldehyde (136 mg, 1.88 mmol) was treated with **2** (0.908 M in THF, 156 μL, 0.141 mmol) in the presence of **4** (1.306 g, 14.20 mmol) in THF (2.0 mL) at −78 °C for 35 min. After hydrolysis of the product with a 1:2 mixture of 1 N HCl and THF at room temperature for 10 min was obtained a crude oil (173 mg). Column chromatography (benzene–ethyl acetate) afforded *erythro*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one[7b,56] (149 mg, 65%) as the sole product: R_f 0.21 (5:1 benzene–ethyl acetate); IR (neat) 3440, 1730 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (d, 3, J = 7 Hz, CH_3), 0.97 (d, 3, J = 7 Hz, CH_3), 1.4–2.4 (m, 8, CH and CH_2), 2.13 (br s, 1, OH), 3.63 (dd, 1, J = 2, 8 Hz, C*H*OH).

Reaction of **10** (170 mg, 1.18 mmol) and isobutyraldehyde (111 mg, 1.54 mmol) was performed at −20 to −30 °C for 12 h in the presence of **2** (0.908 M in THF, 130 μL, 0.118 mmol) and **4** (1.103 g, 11.99 mmol) in THF (1.0 mL). ^1H NMR analysis of the crude product with added tetrachloroethane (78.5 mg, 0.468 mmol) revealed the formation of a mixture of *erythro*- and *threo*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one (δ 3.63 and 3.41, respectively, dd, C*H*OH) in 80% total yield and in 89:11 ratio.

The β-siloxy ketone products did not undergo threo/erythro isomerization under the reaction conditions, as confirmed by TLC analysis after 15- to 30-h duration. *erythro*-2-(2-Methyl-1-(trimethylsiloxy)propyl)-cyclopentanone: ^1H NMR (CCl_4) δ 0.15 (s, 9, $Si(CH_3)_3$), 0.81 (d, 3, J = 7 Hz, CH_3), 0.88 (d, 3, J = 7 Hz, CH_3), 1.4–2.4 (m, 8, CH_2 and CH), 3.80 (d, 1, J = 8 Hz, C*H*OSi). *threo*-2-(2-Methyl-1-(trimethylsiloxy)-propyl)cyclopentanone: ^1H NMR (CCl_4) δ 0.10 (s, 9, $Si(CH_3)_3$), 0.77 (d, 1, J = 7 Hz, CH_3), 0.86 (d, 3, J = 7 Hz, CH_3), 1.5–2.5 (m, 8, CH_2 and CH), 3.56 (dd, 1, J = 4, 7 Hz, C*H*OSi).

G. Reaction of 11 and Benzaldehyde in the Absence of 4. To a solution of **2** (0.908 M in THF, 20 μL, 0.02 mmol) in THF (1.5 mL) cooled at −78 °C was added a solution of **11** (305 mg, 1.79 mmol) and benzaldehyde (192 mg, 1.81 mmol) in THF (0.5 mL). After stirring for 5 min at −78 °C, the solution was diluted with hexane (15 mL) and quenched with water. The aqueous layer was extracted with ether. The organic solutions were combined and concentrated. The residue was treated at room temperature for 15 min with 1:20 1 N HCl–THF. Neutralization and extraction afforded a crude oil (108 mg). ^1H NMR analysis with added tetrachloroethane (70.2 mg, 0.418 mmol, δ 5.98) revealed that a 43:57 mixture of the erythro and threo aldols (δ 5.29, d, J = 2 Hz, and δ 4.68, d, J = 8 Hz, respectively, for C*H*OH) was formed in 18% yield. In this case, some enol silyl ether–benzaldehyde 1:2 adduct remained in the product mixture. Preparative TLC (10:1 hexane–ethyl acetate) separated 2,4-dioxa-5,6-*erythro*- and -5,6-*threo*-3,5-diphenyl-1-(trimethylsiloxy)-*trans*-bicyclo[4.4.0]decane (**31**). Erythro isomer (3.6 mg, 0.5%): R_f 0.58 (10:1 hexane–ethyl acetate); ^1H NMR (CCl_4) δ 0.24 (s, 9, $SiCH_3$), 1.4–1.8 (m, 9, CH_2 and CH), 5.51 (s, 1, C_6H_5CHO), 6.05 (s, 1, $OCH(C_6H_5)O$), 7.1–7.6 (m, 10, C_6H_5). Threo isomer (3.9 mg, 0.5%): R_f 0.53 (10:1 hexane–ethyl acetate); ^1H NMR (CCl_4) δ 0.25 (s, 9, $SiCH_3$), 1.4–2.0 (m, 9, CH_2 and CH), 4.72 (d, 1, J = 10 Hz, C_6H_5CHO), 6.10 (s, 1, $OCH(C_6H_5)O$), 7.1–7.6 (m, 10, C_6H_5).

H. Reaction of 38 and Benzaldehyde. A solution of the enol silyl ether **38** (176 mg, 0.73 mmol) and benzaldehyde (93 mg, 0.88 mmol) in THF (2 mL) was placed in a 10-mL round-bottomed reaction tube. After being cooled to −78 °C, the solution was mixed with **4** (920 mg, 10 mmol) and **2** (1.0 M in THF, 30 μL, 0.03 mmol) successively, and stirred for 5 min at −30 °C. Then the mixture was cooled again to −78 °C and diluted with precooled (−78 °C) hexane (5 mL). The resulting mixture was poured into cold hexane (−78 °C, 15 mL) and washed with water. The aqueous layer was extracted with hexane. The combined hexane extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a crude oil (230 mg), which was treated with 1:10 mixture of 2 N HCl and THF for 1.5 h at room temperature. The solution was diluted with a 1:1 mixture of hexane and ethyl acetate and washed with water. The aqueous phase was extracted with the same solvent repeatedly, and the combined extracts afforded after concentration a crude oil (161 mg). ^1H NMR analysis with added tetrachloroethane (31 mg, 0.37 mmol) showed the axial-threo and axial-erythro aldol adducts, **40** and **41**,[34] were formed in 23 and 10% yield, respectively. The yields were determined on the basis of relative signal intensities at δ 5.98 (tetrachloroethane), 5.08 (C*H*OH of **40**, and 4.81 (C*H*OH of **41**); no signals due to the equatorial adducts were observed. However, prolonged reaction brought about the equatorial adducts, **42** and **43**,[34] in addition to **40** and **41**. A solution of **38** (158 mg, 0.66 mmol), benzaldehyde (84 mg, 0.79 mmol), **4** (610 mg, 6.6 mmol), and **2** (1.0 M in THF, 30 μL, 0.03 mmol) in THF (3 mL) was kept at −30 °C for 2.5 h. The crude oily product was hydrolyzed to give aldols (186 mg, crude), whose ^1H NMR with added tetrachloroethane (55 mg, 0.33 mmol) (CCl_4) exhibited characteristic signals at δ 5.98 (tetrachloroethane), 5.08 (C*H*OH of **40**), 4.81 (**41**), 4.71 (**42**), and 4.96 (**43**). The relative intensities indicated that **40**, **41**, **42**, and **43** were formed in 51, 21, 9, and 1% yield, respectively.

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Registry No. (*Z*)-**1**, 19980-24-6; (*E*)-**1**, 19980-25-7; **2**, 59201-86-4; **4**, 420-56-4; **5**, 73334-39-1; **8**, 19980-46-2; **9**, 769-59-5; **10**, 19980-43-9; **11**, 6651-36-1; **12**, 19980-33-7; **13**, 19980-35-9; **14**, 76355-24-3; **15**, 76355-25-4; *erthryo*-**18**, 60418-00-0; *threo*-**18**, 60418-02-2; *erythro*-**19**, 84624-32-8; *threo*-**19**, 84624-33-9; **24**, 51425-54-8; **25**, 51425-53-7; **26**, 72551-28-1; **27**, 66323-99-7; **28**, 71268-59-2; **29**, 72658-08-3; **30**, 72658-15-2; **31**, 84624-34-0; **3**, 62572-34-3; **40**, 62572-37-6; **41**, 62623-74-9; **42**, 84680-50-2; **43**, 84680-51-3; 2-allylcyclopentanone, 30079-93-7; 2-methylcyclohexanone, 583-60-8; 2-benzylcyclopentanone, 2867-63-2; 2-butylcyclohexanone, 1126-18-7; 2-benzylcyclohexanone, 946-33-8; (*E*)-cinnamyl bromide, 26146-77-0; (*E*)-2-(3-phenyl-2-propenyl)cyclohexanone, 84624-35-1; methyl cyclohexanone-2-ylacetate, 13672-64-5; *trans*-2-benzyl-5-methylcyclohexanone, 84624-36-2; *cis*-2-benzyl-5-methylcyclohexanone, 84624-37-3; 2-benzyl-2-methylcyclohexanone, 1206-21-9; *erythro*-2-(hydroxyphenylmethyl)pentan-3-one, 71699-15-5; *threo*-2-(hydroxyphenylmethyl)pentan-3-one, 71699-16-6; *erthro*-3-(hydroxyphenylmethyl)heptan-4-one, 84624-38-4; *threo*-3-(hydroxyphenylmethyl)heptan-4-one, 84624-39-5; *erythro*-2-(hydroxyphenylmethyl)-1-

phenylpropan-1-one, 71908-03-7; *threo*-2-(hydroxyphenylmethyl)-1-phenylpropan-1-one, 71908-02-6; *erythro*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-66-8; *threo*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-67-9; *erythro*-3-hydroxy-2,4-dimethyl-1-(2,4,6-trimethylphenyl)pentan-1-one, 71699-37-1; *threo*-3-hydroxy-2,4-dimethyl)-1-(2,4,6-trimethylphenyl)pentan-1-one, 71699-38-2; *erythro*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-66-8; *threo*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-67-9; *erythro*-2-(1-hydroxy-2-methylpropyl)cyclohexan-1-one, 81640-04-2; *erythro*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one, 26620-52-0; *threo*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one, 26662-85-1; *erythro*-2-(2-methyl-1-(trimethylsiloxy)propyl)cyclopentanone, 77504-15-5; *threo*-2-(2-methyl-1-(trimethylsiloxy)propyl)cyclopentane, 84624-40-8; *erythro*-3-(hydroxyphenylmethyl)-3-phenylpropan-2-one, 60418-00-0; *threo*-3-(hydroxyphenylmethyl)-3-phenylpropan-2-one, 60418-02-2; *erythro*-2-(α-hydroxybenzyl)cyclopentanone, 43108-70-9; *threo*-2-(α-hydroxybenzyl)cyclopentanone, 43108-71-0; *erythro*-2-(α-hydroxybenzyl)cyclohexanone, 13161-18-7; *threo*-2-(α-hydroxybenzyl)cyclohexanone, 42052-56-2; *erythro*-2-(α-hydroxy-*p*-methoxybenzyl)cyclohexanone, 84624-41-9; *threo*-2-(α-hydroxy-*p*-methoxybenzyl)cyclohexanone, 84624-42-0; *erythro*-2-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone, 71444-29-6; *threo*-2-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone, 71444-30-9; *erythro*-2-(α-hydroxy-*m*-nitrobenzyl)cyclohexanone, 04624-43-1; *threo*-2-(α-hydroxy-*m*-nitrobenzyl)cyclohexanone, 84624-44-2; *erythro*-α-(2-oxocyclohexyl)furanmethanol, 84624-45-3; *threo*-α-(-2-oxocyclohexyl)-furanmethanol, 84624-46-4; benzyl methyl ketone, 103-79-7; chlorotrimethylsilane, 75-77-4; acetic anhydride, 108-24-7; methyl iodide, 33574-02-6; cyclopropylmethyl iodide, 33574-02-6; 5-hexenyl iodide, 18922-04-8; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; butyl iodide, 542-69-8; methyl bromoacetate, 96-32-2; benzaldehyde, 100-52-7; isobutylaldehyde, 78-84-2; butanol, 123-72-8; π-anisaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; furfural, 98-01-1.

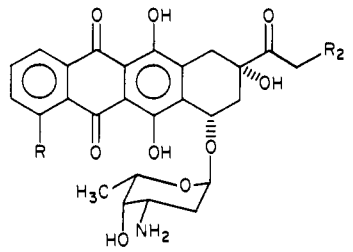
An Improved Route to 4-Demethoxydaunomycinone. A-Ring Functionalization and Resolution Studies of Tetracyclic Precursors

Domingo Domínguez, Robert J. Ardecky, and Michael P. Cava*

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received July 23, 1982*

Abstract: A detailed study has been made of the conversion of the readily prepared 4-demethoxy-7,9-dideoxydaunomycinone (**4**) and its dimethyl ether (**5**) into 4-demethoxydaunomycinone (**24**). Procedures have been developed that are suitable for the preparation of **24** in multigram quantities. In addition, racemic 4-demethoxy-7-deoxydaunomycinone (**16**) has been resolved into its enantiomers by using Enders' hydrazine reagent.

The discovery of the improved antineoplastic activity of the synthetic anthracycline 4-demethoxydaunomycin (**1**),[1] as compared



1, $R_1 = R_2 = H$
2, $R_1 = OMe$; $R_2 = H$
3, $R_1 = OMe$; $R_2 = OH$

with the naturally occurring daunomycin (**2**) and adriamycin (**3**), has stimulated considerable synthetic effort toward the corresponding aglycon 4-demethoxydaunomycinone (**24**).[2] In many of these studies, the tetracyclic red ketone **4** was the target molecule.[3] Early work by Sih[3f] provided a method of 9-hydroxylation, and Wong,[15] Kende[4], and Smith[5] have described the introduction of the second hydroxy group in the 7-position of the A-ring. In our hands the above-mentioned hydroxylation methods were not satisfactory for large-scale preparations of the desired aglycon **24**. Because of this, we decided to reinvestigate the problem of the ring A functionalization of anthracyclinones. Here we report detailed procedures for the introduction of the *cis*-7,9-diol functionality of the A-ring, in addition to the resolution of the racemic tetracyclic hydroxy ketone **16**, a result which allows the preparation of optically active aglycons.

Results and Discussion

The trapping by methyl vinyl ketone of transient *o*-quinodimethane derivatives of bis(bromomethyl)quinizarins provided us with a practical and very efficient route for the preparation of large quantities of the tetracyclic ketones **4** to **6**.[6] With these compounds in hand, we addressed the next challenge of the anthracyclinone synthesis, i.e., the functionalization of the A-ring by a stepwise introduction of the *cis*-diol functionality by procedures applicable to larger scale syntheses.

(a) 9-Hydroxylation. We have earlier reported the one-step preparation of 7-deoxyaglycones using 3-acyloxy-3-buten-2-ones as trapping agents in our *o*-quinodimethane synthesis of anthracyclinones. This procedure gave variable yields (2–46%) of 9-oxy derivatives, the results being highly dependent on the electronic properties of both the diene and the dienophile.[6] Since the above procedure can only be applied for that particular Diels–Alder

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