$TiCl_4$-Mediated Reactions of the Silyl Ketene Acetals Derived from *N*-Methylephedrine Esters: An Asymmetric Variant of the Mukaiyama Reaction[1]

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The $TiCl_4$-mediated reaction between silyl ketene acetals **2** and benzaldehyde was chosen as a model for mechanistic studies. The influence of the silyl ketene acetal double-bond geometry, the C-1/C-2 relative configuration of *N*-methylephedrine, and different modes of addition and molar ratios of the reagents on the stereochemical outcome of the reaction was investigated. On the basis of these results and of literature data, an octahedral, six-coordinate titanium complex was proposed as the transition-structure model. This model helps to rationalize some of the experimental data (e.g., the anti–syn ratios with aldehydes and imines). The $TiCl_4$-mediated additions of the *E* silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate **1** (R = Me) to racemic 3-(benzyloxy)-2-methylpropionaldehyde (**11**) (kinetic resolution), (+)-(*S*)-**11** (mismatched pair), and (−)-(*R*)-**11** (matched pair) were studied. In the matched pair case three contiguous stereocenters were established with complete selectivity. The Mukaiyama–Michael additions of **1** (R = Me) to vinyl ketones were also studied. By this route α-methyl-δ-keto esters were obtained in 72–75% ee.

Since its discovery, the Lewis acid mediated reaction of enol silanes with aldehydes (Mukaiyama reaction)[2a,b] has attracted the interest of synthetic organic chemists and has provoked considerable research and interpretation.[2c,3] During the past 10 years this methodology has been extended to several different electrophiles,[4-6] including acetals,[7] ortho esters,[8] thioacetals,[9] S_N1-type electrophiles,[10] enones,[11] and imines.[12]

We recently introduced an asymmetric variant of this reaction by the use of $TiCl_4$ as a stereochemical template and of the silyl ketene acetals derived from *N*-methylephedrine esters. By this route anti α-methyl-β-hydroxy esters,[13] 3-(benzyloxy)-2-methylpropionaldehyde,[14] α-amino and α-hydrazino acids,[15] and trans β-lactams[16] were synthesized in high enantiomeric excess and good chemical yields (Scheme I). Remarkable features of this new methodology are the following: (a) enantiomeric excess exceeding 90% in most cases and good chemical yields; (b) both enantiomers of the chiral auxiliary are inexpensive, commercially available materials;[17] (c) the chiral auxiliary can be recycled; (d) the absolute configuration of the reaction products is easily predictable.

Some aspects of this high selectivity, however, remained obscure and intriguing and prompted us to a more detailed investigation of the reaction mechanism. In this paper we report these mechanistic studies together with new applications of the reagent.

(1) Part of this work was presented as "Ciamician medal lecture" (C. Gennari) at the 16th National Meeting of the Organic Division of the Italian Chemical Society, Urbino, September 7–12, 1986.

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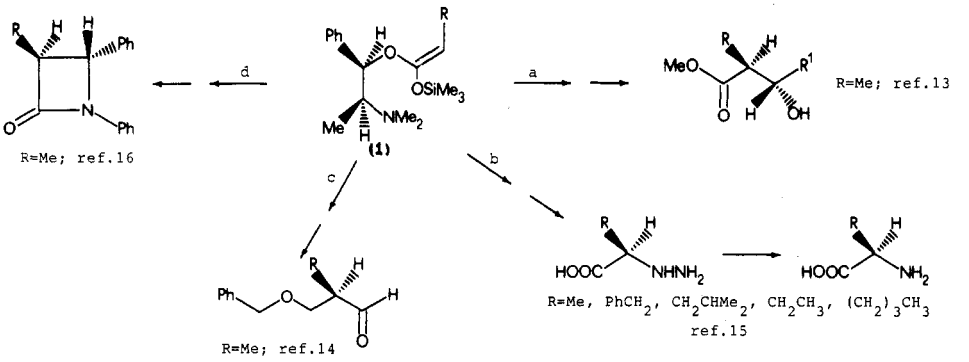
Scheme I[a]



[a] (a) $R^1CHO/TiCl_4/CH_2Cl_2$; (b) *t*-BuOCON=NCOOBu-*t*/ $TiCl_4/CH_2Cl_2$; (c) $HC(OMe)_3/TiCl_4/CH_2Cl_2$; (d) PhCH=NPh/ $TiCl_4/CH_2Cl_2$.

Table I

entry	2	Lewis acid	anti/syn	*anti*-3/ *anti*-4	*syn*-5/*syn*-6	% yield	methyl ester 7		methyl ester 9	
							% yield	% ee	% yield	% ee
1	R = Ph, R^1 = H (R^2 = Me, R^3 = H)[a]	$TiCl_4$	85:15	34:1	4.5:1	80	60	94	10	64
2	R = Ph, R^1 = H (R^2 = Me, R^3 = H)[a]	$TiCl_4$–PPh_3	≥96:4	≥30:1		90	70	94		
3	R = Ph, R^1 = H (R^2 = H, R^3 = Me)[b]	$TiCl_4$	80:20	22:1	3.5:1	65	52 methyl ester 8	91	13 methyl ester 10	55
4	R = H, R^1 = Ph (R^2 = Me, R^3 = H)[a]	$TiCl_4$	77:23	1:13.5	1:1.5	65	50	86	15	20

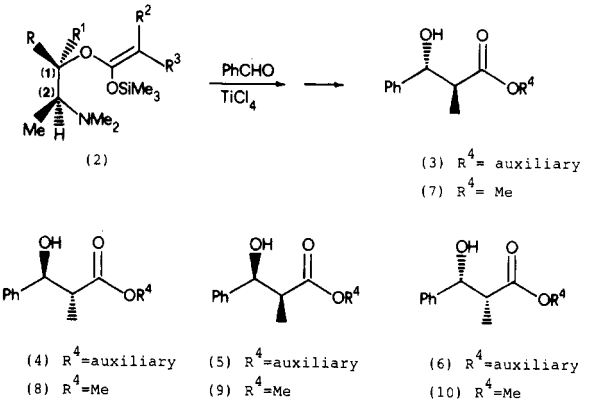
[a] $E/Z \geq 95:5$. [b] Z/E 65:35.

Mechanistic Studies

The reaction between silyl ketene acetals **2** and benzaldehyde in the presence of $TiCl_4$ was chosen as a model for mechanistic studies (Scheme II, Table I). First of all we examined the influence of the silyl ketene acetal double-bond geometry on the stereochemical outcome of the reaction. It is interesting to observe that both the anti–syn ratios and the enantiomeric excesses were found to be relatively independent of the double-bond geometry. In fact the *Z*/*E* 65:35 silyl ketene acetal obtained by using $LiN(SiMe_3)_2$ as base instead of LDA gave almost the same results (but slightly worse) as the pure *E* (compare entries 1 and 3, Table I). We then examined which of the two stereocenters of *N*-methylephedrine is responsible for the asymmetric induction and for the absolute configuration of the reaction products. By the use of (1*S*,2*S*)-*N*-methyl-ψ-ephedrine (entry 4, Table I), the enantiomers of the methyl esters synthesized by using (1*R*,2*S*)-*N*-methylephedrine (entry 1, Table I) were obtained, though with less stereoselectivity. Carbon-2 configuration has therefore a minor effect on steric control (positive in the 1*R**,2*S** case, negative in the 1*S**,2*S** case), while the chiral center responsible for the overall sense of the asymmetric induction is carbon-1.

The influence of different modes of addition of the reagents on the stereochemical outcome was then investigated. In the first two entries of Table I, the *E* silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine was used under normal reaction conditions, i.e., addition of 1 molar equiv of the silyl ketene acetal in methylene chloride to 1 molar equiv of the Lewis acid–aldehyde complex at −78 °C in CH_2Cl_2. Treatment of the silyl ketene acetal first with $TiCl_4$ (30 min, −78 °C) and then with benzaldehyde gave the same results as in Table I, entry 1, thus showing that yield and selectivity are not affected by inverse order of addition of the reagents. This transformation was followed by ^1H NMR spectroscopy (CD_2Cl_2, −78 °C): after the addition of $TiCl_4$ to the silyl ketene acetal a new signal

Scheme II



at δ 0.30, most likely Me_3SiCl, was clearly observed. The dependence of yields and diastereoselectivities on the molar ratios of $TiCl_4$–electrophile–silyl ketene acetal 1 was then investigated. An optimum was found at ca. 1:1:1, while excess $TiCl_4$ (2:1:1) markedly decreased the selectivities (reaction with aldehydes, trimethyl orthoformate, *tert*-butyl azadicarboxylate, see Scheme I) and did not improve the yields. These results support the assumption of a 1:1:1 $TiCl_4$–1–electrophile complex as reacting species under the conditions of optimum selectivity.

Based on these results, and on the reasonable expectation that both the aldehyde carbonyl[18] and the ephedrine NMe_2 group tend to bind to $TiCl_4$, which usually ligates two electron-donating molecules to form cis-octahedral, six-coordinate complexes, we propose for this reaction the transition-structure models shown in Scheme III. The

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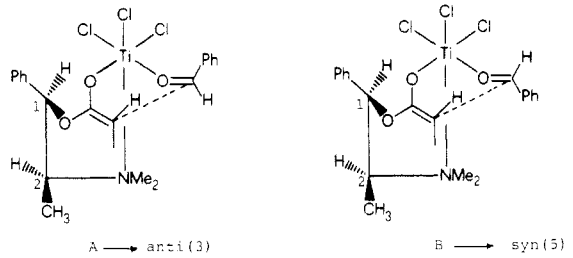
Scheme III. Transition-Structure Models Deriving from (1*R*,2*S*)-*N*-Methylephedrine Propionate *E* Silyl Ketene Acetal: Reaction with Benzaldehyde



Scheme IV

crystal structure of a cis-octahedral, six-coordinate titanium complex containing a similar seven-membered ring chelate structure was recently reported by Helmchen.[19] Starting from (1*R*,2*S*)-*N*-methylephedrine, eight different transition structures can be modeled by varying the double-bond geometry (*E*,*Z*), the type of coordination between titanium and benzaldehyde (C_{Ph}—C=O—Ti cis or trans), and the chirality at the metal. Geometries and relative energies of these structures are at present under careful evaluation by use of theoretical methods;[20] however, the unoptimized models shown in Scheme III can also be useful to tentatively rationalize some of the experimental results. While the silyl ketene acetal π-facial selectivity is usually very high ($\geq$ 20:1), [13-16] there is only a moderate preference (85:15) for the anti vs. the syn isomer (model A vs. B), and the anti–syn ratios have been shown to worsen with increasing aldehyde steric hindrance. For example, with isobutyraldehyde the anti–syn ratio is only 67:33.[13a] This result can be interpreted by models A and B (Scheme III): aldehyde steric bulkiness destabilizes A (C—C=O—Ti cis) compared to B(C—C=O—Ti trans).

On the other hand, the enhancement of the anti–syn selectivity observed when $TiCl_4$–PPh_3[13b] is used as Lewis acid instead of plain $TiCl_4$ (Table I, entry 2) is at present beyond our rationalization. The electrophile π-facial selectivity is increased passing from aldehydes to imines (anti–syn 92:8),[16] probably because of the more pronounced energy difference between the two Ti–imine coordination complexes (Scheme IV; *trans*-phenyls (C) more stable than *cis*-phenyls (D).[21]

Additions to 3-(Benzyloxy)-2-methylpropionaldehyde: Matching and Mismatching

Due to its structural features (chirality and the possibilty of β-chelation), 3-(benzyloxy)-2-methylpropionaldehyde (11) has been widely used in organic synthesis, and its optically active forms are important intermediates in the total synthesis of natural products.

We recently reported an asymmetric synthesis of (−)-(*R*)-11 in 91% enantiomeric excess and high chemical yield by the use of the silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me; Scheme I).[14] The 1:1 complex between aldehyde 11 and $TiCl_4$ has recently been characterized by NMR spectroscopy and shown to be rigid and essentially "conformationally locked".[22] Stereoselective aldol additions of propionate-derived silyl ketene acetals to the $TiCl_4$–aldehyde 11 complex is a practical way to establish three contiguous stereocenters with high selectivity: addition of the thio ester silyl ketene acetal 12 and subsequent reduction gave the known alcohol 13 in 50% overall yield as a single diastereoisomer (capillary VPC, HPLC, ^1H and ^{13}C NMR) in 85–90% enantiomeric excess (Scheme V, eq 1).[3a,14] Formation of the syn-chelated isomer can be rationalized by the transition-structure model A (Scheme VI), where the methyl of the silyl ketene acetal is oriented outside the six-membered ring containing titanium.[3a,14]

By reaction of an excess of the complex between racemic aldehyde 11 and $TiCl_4$ (3 molar equiv) with the *E* silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me) (1 molar equiv), a kinetic resolution experiment was tried. The results are shown in eq 2 of Scheme V: after LAH reduction the syn-chelated alcohol 13 was obtained in 58% overall yield as the major isomer (syn-chelated/anti-chelated $\geq$ 10:1) and in 65–70% enantiomeric excess. The preference for the syn-chelated isomer can again be interpreted by transition-structure model B (methyl outside the titanium-containing ring), while the absolute configuration is determined by the preference of the silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me) for creating *S* stereocenters at C-2 (*R* after reduction) upon reaction with aldehydes.[13]

(+)-(*S*)-3-(Benzyloxy)-2-methylpropionaldehyde was synthesized in 91% ee starting from (1*S*,2*R*)-*N*-methylephedrine and following our published procedure.[14] Reaction of (+)-(*S*)-11 with the silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me) and subsequent reduction gave low overall yields (22%) of a 1.3:1 mixture of the syn-chelated alcohol 14 and the anti-chelated alcohol 15 (eq 3, Scheme V). This reaction is the coupling of a mismatched pair: in fact formation of the anti-chelated isomer (transition-structure model C, Scheme VI) is in accord with the silyl ketene acetal preference (*S* stereocenter at C-2) but against the aldehyde preference (Me *inside* the titanium containing ring). On the other hand, formation of the syn-chelated isomer (transition-structure model D, Scheme VI) is in accord with the aldehyde preference (Me *outside* the ring) but against the silyl ketene acetal preference (*R* stereocenter formed at C-2). It is also interesting to observe that while the anti-chelated alcohol (+)-15 is optically pure ($[\alpha]_D$, Mosher derivatization[23]), the enantiomeric excess of the syn-chelated alcohol (+)-14 is only 65–70%. This means that, as the starting aldehyde is a 95.5:4.5 *S*/*R* mixture, almost all the minor *R* enantiomer has been consumed to produce the syn-chelated alcohol (−)-13 with consequent loss of optical purity.

The great affinity of the silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me) for (−)-*R* aldehyde 11 has been used to synthesize the syn-

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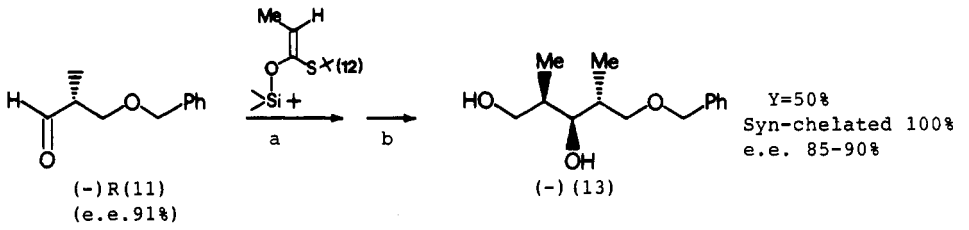
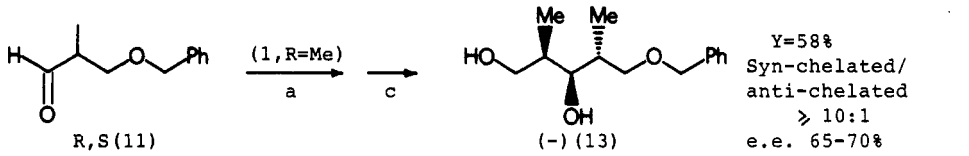
Scheme V[a]

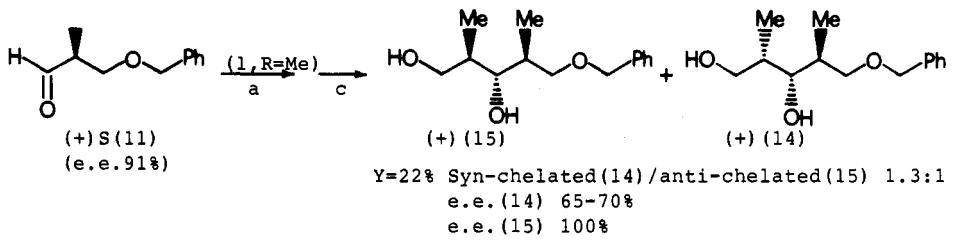
ALDEHYDE PREFERENCE (eq. 1)



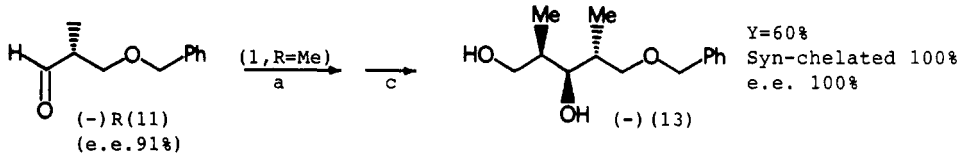
SILYL KETENE ACETAL PREFERENCE, KINETIC RESOLUTION (eq. 2)



MISMATCHED PAIR (eq. 3)

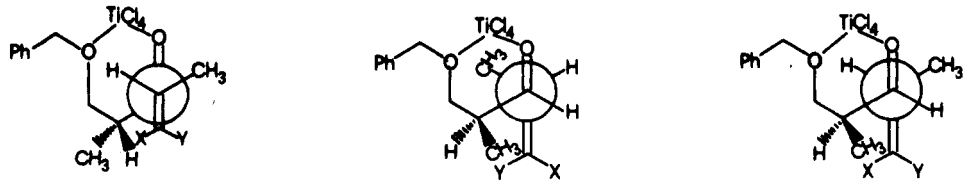


MATCHED PAIR (eq. 4)



[a] (a) $TiCl_4$, CH_2Cl_2, -78 °C; (b) Raney-Ni, H_2, MeOH; (c) $LiAlH_4$,Et_2O.

Scheme VI



A [X = S-Bu^t; Y = O-SiMe$_2$Bu^t]

B [X = O-SiMe$_3$; Y = O-Ephedrine (1R,2S)]

C [X = O-SiMe$_3$; Y = O-Ephedrine (1R,2S)]

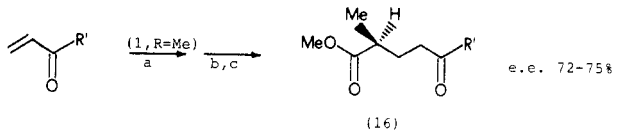
D [X = O-SiMe$_3$; Y = O-Ephedrine (1R,2S)]

chelated alcohol (-)-**13** in 60% overall yield as a single diastereoisomer and in 100% optical purity (eq 4, Scheme V; model B, Scheme VI). Therefore, using the silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate twice—the first time for the synthesis of (*R*)-**11**,[14] the second time for the matched pair coupling—three contiguous stereocenters were established with complete selectivity.

Conjugate Addition to Enones

The enantioselective Michael additions of chiral propionate equivalents to unsaturated carbonyl compounds

Scheme VII[a]



[a] (a) $TiCl_4$, CH_2Cl_2; (b) NaOH, H_2O–MeOH, or HCOOH, Pd/C, MeOH; (c) CH_2N_2.

are useful reactions for the synthesis of various natural products. Additions of chiral lithium ester or amide enolates to conjugated esters were recently reported by Corey and Peterson[24a] and Yamaguchi and co-workers[24b] to proceed with high enantioselectivity.

We explored the enantioselective Mukaiyama–Michael[11] additions of reagent **1** (R = Me) to unsaturated ketones, focusing on vinyl ketones, which had not been studied in the above-mentioned methodologies.[24,25]

$TiCl_4$-mediated addition of the *E* silyl ketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine propionate **1** (R = Me) to ethyl vinyl ketone (R^1 = Et) gave, after saponification and diazomethane treatment, δ-keto ester **16** in 45% overall yield and 72% ee. Methyl vinyl ketone (R^1 = Me) gave the same ee (75%) but a much lower yield (20%) because of extensive polymerization during the condensation step[11d] (Scheme VII). In order to be sure that no racemization had occurred during the NaOH treatment, the saponification was substituted with a mild hydrogenolysis (HCOOH, MeOH, Pd/C)[26] to give the methyl esters with the same enantiomeric excess as the ones previously obtained. The absolute configuration at carbon-2 was assumed on the basis of our mechanistic studies (see relevant paragraph) and by analogy with all the previous cases (see Scheme I), where the absolute configuration at C-2 was proven. It is worth noting that, although the enantiomeric excesses are far from satisfactory, this methodology is the only one available at present for the asymmetric synthesis of **16**-type δ-keto esters.[25]

In summary, we have shown that our asymmetric bond-forming reaction successfully complements other available methods. Efforts to further expand the scope and utility of this methodology are presently under active investigation in our laboratory.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded with Varian XL-200 or Bruker WP-80 instruments in the FT mode, with tetramethylsilane as internal standard. Optical rotations were measured in 1-dm cells of 1-mL capacity on a Perkin-Elmer Model 241 polarimeter. IR spectra were recorded with a Perkin-Elmer Model 681 spectrophotometer. Elemental analyses were performed with a Perkin-Elmer Model 240 instrument. Silica gel 60 F_{254} plates (Merck) were used for TLC; 273–400-mesh silica gel (Merck) was used for flash chromatography. VPC analyses were performed with a Dani-3800 instrument (capillary OV-1 column) using a Hewlett-Packard-3390 A integrator. HPLC analyses were performed with a Varian-5000 instrument (LiChroCART-Manufix 15543 column) and UV (250 nm) detector. Organic extracts were dried over Na_2SO_4. Dry solvents were distilled under nitrogen immediately before use: THF and ethyl ether from sodium/benzophenone, CH_2Cl_2 and diisopropylamine from CaH_2. All reactions were run under nitrogen atmosphere (from liquid nitrogen).

***N*-Methylephedrine Propionate.** A solution of *N*-methylephedrine (5.0 g, 27.90 mmol) in CH_2Cl_2 (140 mL) was treated with propionyl chloride (41.85 mmol) at 0 °C, under nitrogen, with stirring. After 3 h at room temperature the mixture was quenched with 5% aqueous NaOH and extracted several times (5 × 50 mL) with 5% aqueous NaOH. The organic phase was then dried and evaporated to give a pale yellow oil (27.80 mmol; >99% yield).

(1*R*,2*S*)-*N*-Methylephedrine propionate: $[\alpha]^{23}_D$ −46.3° ($CHCl_3$, *c* 1.19); ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, *J* = 6.7 Hz), 1.15 (t, 3 H, *J* = 7.7 Hz), 2.25 (s, 6 H), 2.38 (q, 2 H, *J* = 7.7 Hz), 2.88 (dq, 1 H, *J* = 5.4, 6.7 Hz), 5.94 (d, 1 H, *J* = 5.4 Hz), 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.02 (q), 9.36 (q), 27.95 (t), 41.11 (q), 63.73 (d), 75.00 (d), 126.13 (d), 127.27 (d), 128.07 (d), 140.12 (s), 172.81 (s); IR ($CHCl_3$) 2980, 2940, 1735, 1460, 1450, 1375, 1185 cm^{-1} (selected values). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.30; H, 9.11; N, 5.87.

(1*S*,2*S*)-*N*-Methyl-ψ-ephedrine propionate: $[\alpha]^{23}_D$ +102.0° ($CHCl_3$, *c* 1.0); ^1H NMR ($CDCl_3$) δ 0.70 (d, 3 H, *J* = 6.7 Hz), 1.10 (t, 3 H, *J* = 8.0 Hz), 2.31 (s, 6 H), 2.36 (m, 2 H), 2.98 (dq, 1 H, *J* = 8.0, 6.7 Hz), 5.72 (d, 1 H, *J* = 8.0 Hz), 7.30 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.09 (q), 10.12 (q), 27.99 (t), 40.95 (q), 62.70 (d), 76.99 (d), 127.53 (d), 127.89 (d), 128.32 (d), 139.52 (s), 173.38 (s); IR ($CHCl_3$) 2980, 2940, 1735, 1460, 1450, 1375, 1185 cm^{-1} (selected values). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.35; H, 9.05; N, 5.90.

Silyl Ketene Acetals from *N*-Methylephedrine Propionate. A solution of diisopropylamine (1.45 mL, 10.2 mmol) in THF (20.5 mL) was treated with *n*-BuLi (1.5 M in *n*-hexane, 6.8 mL, 10.2 mmol), at 0 °C, under nitrogen, with stirring. After 30 min at 0 °C, the solution was cooled to −78 °C, and a solution of *N*-methylephedrine propionate (8.5 mmol) in THF (17.0 mL) was slowly added. After 1 h at −78 °C, Me_3SiCl (1.29 mL, 10.2 mmol) was slowly added. After 1.0 h at −78 °C, the mixture was slowly warmed up to room temperature (during 1 h). The mixture was then evaporated and pumped. The residue (*THF free*!) was taken up in CH_2Cl_2 (8.5 mL), and the 0.8 M solution so obtained could be stored at −20 °C for several weeks and used as stock solution.

***E* Silyl ketene acetal from (1*R*,2*S*)-*N*-methylephedrine propionate 1 (R = Me) and 2 (Table I, entries 1 and 2):** ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 1.10 (d, 3 H, *J* = 6.7 Hz), 1.55 (d, 3 H, *J* = 6.7 Hz), 2.30 (s, 6 H), 2.80 (dq, 1 H, *J* = 4.0, 6.7 Hz), 3.48 (q, 1 H, *J* = 6.7 Hz), 5.29 (d, 1 H, *J* = 4.0 Hz), 7.27 (s, 5 H); spectroscopic yield (^1H NMR) ≥95%; *E*/*Z* ratio (^1H NMR) ≥ 95:5.

***Z* Silyl ketene acetal from (1*R*,2*S*)-*N*-methylephedrine propionate 2 (Table I, entry 3):** ^1H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 1.03 (d, 3 H, *J* = 6.7 Hz), 1.33 (d, 3 H, *J* = 6.7 Hz), 2.32 (s, 6 H), 2.80 (m, 1 H), 3.34 (q, 1 H, *J* = 6.7 Hz), 4.95 (d, 1 H, *J* = 3.5 Hz), 7.27 (s, 5 H). This compound was obtained by following the procedure described above, but using $LiN(SiMe_3)_2$ as base instead of LDA: spectroscopic yield (^1H NMR) 80%; *Z*/*E* ratio (^1H NMR) 65:35.

***E* Silyl ketene acetal from (1*S*,2*S*)-*N*-methyl-ψ-ephedrine propionate 2 (Table I, entry 4):** ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.74 (d, 3 H, *J* = 7.0 Hz), 1.48 (d, 3 H, *J* = 7.0 Hz), 2.39 (s, 6 H), 3.00 (dq, 1 H, *J* = 8.0, 7.0 Hz), 3.45 (q, 1 H, *J* = 7.0 Hz), 5.03 (d, 1 H, *J* = 8.0 Hz), 7.27 (s, 5 H); spectroscopic yield (^1H NMR) ≥95%; *E*/*Z* ratio (^1H NMR) ≥95:5.

General Procedure for the Aldol Condensation (Scheme II). A solution of benzaldehyde (3 mmol) in CH_2Cl_2 (9 mL) was treated with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (3 mL), at −78 °C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of the silyl ketene acetal in CH_2Cl_2 (3.75 mL) was slowly added at −78 °C. After 2 h at −78 °C, the mixture was quenched with 5% $NaHCO_3$ and 1.5 N NaOH aqueous solution and filtered through Celite. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried and evaporated to

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give the crude aldol condensation product.

Adducts 3–6 derived from (1*R*,2*S*)-*N*-methylephedrine (Table I, entries 1–3): ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 6 H), 2.30 (s, 6 H), 2.90 (m, 2 H). 4.63 (d, *J* = 8.8 Hz, C*H*OH, adduct 4), 4.78 (d, *J* = 9.3 Hz, C*H*OH, adduct 3), 5.14 (d, *J* = 3.0 Hz, C*H*OH, adduct 5), 5.48 (d, *J* = 3.7 Hz, C*H*OH, adduct 6), 6.22 (d, *J* = 4.0 Hz, PHC*H*, adduct 5), 6.30 (d, *J* = 3.0 Hz, PhC*H*, adduct 4), 6.34 (d, *J* = 4.0 Hz, PhC*H*, adduct 6), 6.40 (d, *J* = 3.0 Hz, PhC*H*, adduct 3), 7.30 (s, 10 H).

Adducts 3–6 derived from (1*S*,2*S*)-*N*-methyl-ψ-ephedrine (Table I, entry 4): ^{1}H NMR ($CDCl_3$) δ 0.70 (d, 3 H, *J* = 6.5 Hz), 0.90 (d, 3 H, *J* = 7.0 Hz), 2.30 (s, 6 H), 2.6–3.3 (m, 2 H), 4.55 (d, *J* = 9.0 Hz, C*H*OH, adduct 3), 4.76 (d, *J* = 9.8 Hz, C*H*OH, adduct 4), 5.18 (d, *J* = 1.9 Hz, C*H*OH, adduct 6), 5.58 (d, *J* = 3.4 Hz, C*H*OH, adduct 5), 5.72 (d, 1 H, *J* = 8.0 Hz), 7.30 (s, 5 H), 7.40 (s, 5 H).

General Procedure for the Synthesis of Methyl Esters 7–10. A solution of the aldol condensation product (2.0 mmol) in 4:1 MeOH–H_2O (20 mL) was treated with NaOH (400 mg, 10.0 mmol) at room temperature, with stirring. After 15 h at room temperature the mixture was diluted with water (3 mL), and MeOH was evaporated in vacuo. The resulting aqueous mixture was treated with 1 N HCl (20 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give the crude acid. A solution of the crude acid in 9:1 Et_2O–MeOH was treated with CH_2N_2 to give the methyl ester, which was purified by flash chromatography (*n*-hexane–EtOAc, 4:1). The aqueous phase containing *N*-methylephedrine hydrochloride was treated with NaOH and extracted with CH_2Cl_2: the combined organic extracts were dried and evaporated to give optically pure *N*-methylephedrine.

***anti*-Methyl 2-methyl-3-hydroxy-3-phenylpropanoate (7, 8):** ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 6.9 Hz), 2.80 (dq, 1 H, *J* = 6.9, 9.0 Hz), 3.0 (br s, 1 H), 3.70 (s, 3 H), 4.73 (d, 1 H, *J* = 9.0 Hz), 7.30 (s, 5 H); IR ($CHCl_3$) 3600, 2980, 1725, 1450, 1180 cm^{-1} (selected values). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.99; H, 7.19. Optically pure methyl ester **7**: $[\alpha]^{23}_D$ +57.0° ($CHCl_3$, *c* 0.17).[13] Optically pure methyl ester **8**: $[\alpha]^{23}_D$ −57.1° ($CHCl_3$, *c* 0.12).[13] ^{1}H NMR ($CDCl_3$ + Eu(hfc)$_3$): δ 4.1 (s, OCH_3, methyl ester **8**), 4.2 (s, OCH_3, methyl ester **7**).

***syn*-Methyl 2-methyl-3-hydroxy-3-phenylpropanoate (9, 10):** ^{1}H NMR ($CDCl_3$) δ. 1.13 (d, 3 H, *J* = 6.9 Hz), 2.80 (dq, 1 H, *J* = 6.9, 3.9 Hz), 2.90 (br s, 1 H). 3.66 (s, 3 H), 5.08 (d, 1 H, *J* = 3.9 Hz), 7.30 (s, 5 H); IR ($CHCl_3$) 3600, 2980, 1725, 1450, 1180 cm^{-1} (selected values). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.97; H, 7.20. Optically pure methyl ester **9**: $[\alpha]^{23}_D$ −23.1° ($CHCl_3$, *c* 1.5).[13] Optically pure methyl ester **10**: $[\alpha]^{23}_D$ +23.1° ($CHCl_3$, *c* 1.5).[13] ^{1}H NMR ($CDCl_3$ + Eu(hfc)$_3$): δ 3.7 (d, CH_3CH, methyl ester **10**), 3.9 (d, CH_3CH, methyl ester **9**).

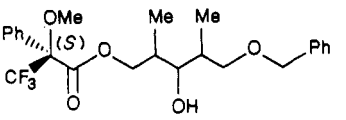
Additions to 3-(Benzyloxy)-2-methylpropionaldehyde (11). Kinetic Resolution (eq 2, Scheme V). A solution of racemic 3-(benzyloxy)-2-methylpropionaldehyde (**11**) (9 mmol) in CH_2Cl_2 (27 mL) was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (9 mL), at −78 °C, under nitrogen, with stirring. Immediately after a 0.8 M solution of the silyl ketene acetal **1** (R = Me) in CH_2Cl_2 (3.75 mL) was slowly added at −78 °C. After 2 h at −78 °C, the mixture was quenched and worked up as described above.

Mismatched Pair and Matched Pair (eq 3, 4, Scheme V). A solution of (+)-*S*)-**11** ($[\alpha]^{25}_D$ +25.8°, *c* 1, $CHCl_3$)[14] or (−)-(*R*)-**11** ($[\alpha]^{25}_D$ −25.8°, *c* 1, $CHCl_3$)[14] (4.5 mmol) in CH_2Cl_2 (13.5 mL) was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (4.5 mmol), at −78 °C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of the silyl ketene acetal **1** (R = Me) in CH_2Cl_2 (3.75 mL) was slowly added at −78 °C. After 2 h at −78 °C, the mixture was quenched and worked up as described above.

Reduction and Analysis of the Product Stereoisomeric Composition (Scheme V). The crude products derived from the condensation reaction (see above) (3 mmol) were dissolved in dry ethyl ether (15 mL) and treated with excess $LiAlH_4$ (9 mmol) at 0 °C, under nitrogen, with stirring. After being stirred for 1 h at room temperature, the mixture was quenched (0.3 mL of H_2O, 0.3 mL of 15% NaOH, 0.6 mL of H_2O) and worked up as usual. The stereoisomeric ratios were determined on the crude reaction mixtures by HPLC (*n*-hexane-EtOAc, 60:40), ^{1}H NMR ($CDCl_3$ and C_6D_6–D_2O), ^{13}C NMR ($CDCl_3$), by comparison with authentic samples previously synthesized.[3a,14] Then the products were isolated by flash chromatography (*n*-hexane–EtOAc, 70:30).

Syn-chelated compounds (−)-13 and (+)-14: ^{1}H NMR (C_6D_6 + D_2O, 200 MHz) δ 0.52 (d, 3 H, *J* = 7.0 Hz), 1.01 (d, 3 H, *J* = 7.0 Hz), 1.51 (m, 1 H), 1.85 (m, 1 H), 3.21 (A part of ABX system, 1 H, J_{AB} = 9.0 Hz, J_{AX} = 8.0 Hz), 3.28 (B part of ABX system, 1 H, J_{AB} = 9.0 Hz, J_{BX} = 4.5 Hz), 3.6–3.7 (m, 3 H), 4.18 (s, 2 H), 7.17 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 8.72, 13.10, 35.91, 36.36, 67.81, 73.60, 76.75, 79.49, 127.73, 127.90, 128.51, 137.43. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.58; H, 9.24. Found: C, 70.51;, H, 9.29. IR (neat): 3375 cm^{-1}. Optically pure (−)-**13** $[\alpha]^{25}_D$ −38.5° (*c* 1, $CHCl_3$); reported optically pure (+)**14** $[\alpha]^{25}_D$ +38.4° (*c* 0.94, $CHCl_3$), see ref 27.

(−)-**13** and (+)-**14** were converted into the Mosher derivatives, under usual conditions.[23]



Mosher derivative of (+)-14: ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3 H, *J* = 7.0 Hz), 0.90 (d, 3 H, *J* = 7.0 Hz), 1.95 (m, 2 H), 3.34–3.62 (m, 3 H), 3.54 (q, 3 H, *J* = 1.0 Hz), 4.27–4.35 (m, 2 H), 4.50 (s, 2 H), 7.25–7.60 (m, 10 H).

Mosher derivative of (−)-13: ^{1}H NMR ($CDCl_3$) δ 0.75 (d, 3 H, *J* = 7.0 Hz), 0.91 (d, 3 H, *J* = 7.0 Hz), 1.95 (m, 2 H), 3.34–3.62 (m, 3 H), 3.54 (q, 3 H, *J* = 1.0 Hz), 4.18 (1 H, A part of ABX system, J_{AB} = 10.5 Hz, J_{AX} = 6.5 Hz), 4.44 (1 H, B part of ABX system, J_{AB} = 10.5 Hz, J_{BX} = 7.5 Hz), 4.50 (s, 2 H), 7.25–7.60 (m, 10 H).

Anti-chelated compound (+)-15: ^{1}H NMR (C_6D_6 + D_2O, 200 MHz) δ 0.82 (d, 3 H, *J* = 7.0 Hz), 0.88 (d, 3 H, *J* = 7.0 Hz), 1.68 (m, 1 H), 1.81 (m, 1 H), 3.21 (dd, 1 H, *J* = 6.0, 9.0 Hz), 3.33 (t, 1 H, *J* = 6.0 Hz), 3.35 (dd, 1 H, *J* = 9.0, 4.5 Hz), 3.58 (dd, 1 H, *J* = 11.0, 6.0 Hz), 3.75 (dd, 1 H, *J* = 11.0, 3.5 Hz), 4.15 (s, 2 H), 7.17 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.47, 14.67, 35.49, 37.16, 66.92, 74.30, 76.75, 82.56, 127.73, 127.90, 128.51, 137.43. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.58; H, 9.24. Found: C, 70.50; H, 9.34. IR (neat): 3375 cm^{-1}. Optically pure (+)-**15** $[\alpha]^{25}$D +3.69 (*c* 1, $CHCl_3$); reported optically pure (+)-**15** $[\alpha]^{25}_D$ +3.63° (*c* 2.67, $CHCl_3$), see ref 27. (+)-**15** were converted into the Mosher derivative, under usual conditions.[23]

Mosher derivative of (+)-15: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6 H, *J* = 7.8 Hz), 1.8–2.1 (m, 2 H), 3.30–3.52 (m, 1 H), 3.42 (dd, 1 H, *J* = 9.5, 6.5 Hz), 3.55 (q, 3 H, *J* = 1.0 Hz), 3.61 (dd, 1 H, *J* = 9.5, 4.0 Hz), 4.23 (dd, 1 H, *J* = 7.0, 11.0 Hz), 4.48 (s, 2 H), 4.58 (dd, 1 H, *J* = 4.5, 11.0 Hz), 7.27–7.55 (m, 10 H).

Addition to Ethyl Vinyl Ketone (Scheme VII). A solution of ethyl vinyl ketone (4.5 mmol) in CH_2Cl_2 (13.5 mL) was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (4.5 mL), at −100 °C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of the silyl ketene acetal **1** (R = Me) in CH_2Cl_2 (3.75 mL) was slowly added at −100 °C. After 2 h of stirring at −78 °C, the mixture was quenched and worked up as described above. The crude product can be purified by flash chromatography (CH_2Cl_2–MeOH, 96:4) to give the pure adduct (60%): ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, *J* = 7.4 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 1.15 (d, 3 H, *J* = 7.0 Hz), 1.6–2.7 (m, 7 H), 2.25 (s, 6 H), 2.88 (m 1 H), 5.87 (d, 1 H, *J* = 5.5 Hz), 7.27 (s, 5 H). The crude product was dissolved in 8:2 MeOH–H_2O (30 mL) and treated with NaOH (15 mmol). After being stirred at room temperature for 15 h, the mixture was diluted with water (4.5 mL), and MeOH was evaporated in vacuo. The resulting aqueous mixture was treated with 1 N HCl (30 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated to give the crude acid. Alternatively the crude product was dissolved in 10:1 MeOH–HCOOH (30 mL) and treated with 10% Pd/C (636 mg) under nitrogen, with stirring. The mixture was stirred overnight; then more HCOOH (1.5 mL) was added. After 1 h the mixture was filtered and evaporated in vacuo. The residue was treated with 1 N HCl (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to give the crude acid. A solution of the crude acid in 9:1 Et_2O–MeOH was treated with CH_2N_2 to give the crude methyl ester, which was purified by flash chromatography (*n*-hexane–EtOAc, 9:1) to give pure **16** (R^1 = Et) (0.24 g, 45%) as a volatile oil: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3 H, *J* = 7.5 Hz), 1.13

(d, 3 H, J = 6.6 Hz), 1.6-2.0 (m, 2 H), 2.1-2.7 (m, 5 H), 3.63 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 7.78, 17.15, 27.45, 35.94, 38.69, 39.64, 51.57, 176.61, 210.71; $[\alpha]^{25}_D$ +16.8° (c 1.1, $CHCl_3$); IR ($CHCl_3$) 2960, 1735, 1715, 1165 (selected values). Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.68; H, 9.44. ^1H NMR ($CDCl_3$ + $Eu(hfc)_3$): δ 5.50 (s, OCH_3, minor, 0.42 H), 5.58 (s, OCH_3, major, 2.58 H).

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An Unusual Cyclization of a Homoallyl Oxyacetic Acid Dianion[1]

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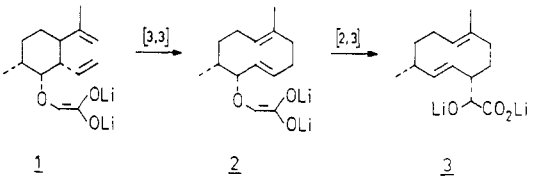
Treatment of the homoallyl oxyacetic acid **7** with excess LDA at −78 °C followed by thermolysis at 185 °C in HMPA provided the unusual cyclization product **8a**. A single-crystal X-ray structure was obtained for the derivative **8c**.

Recently in connection with projects directed toward the synthesis of germacrane sesquiterpenes,[3] we examined a strategy for the synthesis of the 1,6-cyclodecadiene **3** that involved the tandem [3,3]-[2,3]-sigmatropic rearrangement of the homoallyl oxyacetic acid dianion **1**. In this approach, the unfavorable Cope equilibrium between **1** and **2** was to be driven by the [2,3]-sigmatropic rearrangement[4] of the allyl oxyacetic acid dianion **2** to **3** (Scheme I). This strategy is related to our previously reported synthesis of 1,6-cyclodecadienes by tandem Cope-Claisen rearrangements.[5] We now wish to report the results of these studies which led to an unusual cyclization rather than the desired tandem [3,3]-[2,3] transformation.

The requisite acid **7** was prepared as shown in Scheme II. (*R*)-(−)-Carvone (**4**) was converted to **5** in 76% overall yield by reaction first with LDA and (phenylseleno)acetaldehyde and then with triethylamine and methanesulfonyl chloride, by using the procedure of Kowalski.[6] The known axial alcohol **6**[5] was prepared in 45% overall yield by a one-pot procedure which involved 1,4-reduction of **5** with 1 equiv of K-Selectride,[7] addition of 1 equiv of acetic acid, reduction of the resulting ketone with L-Selectride,[8] and workup with basic hydrogen peroxide. This procedure for the preparation of **6** was more convenient than that previously reported.[5] Reaction of **6** with excess chloroacetic acid and NaH gave **7** in 98% yield.

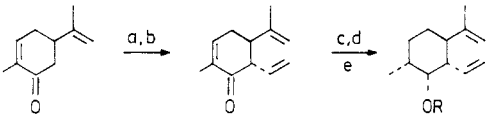
Treatment of **7** with excess LDA at −78 °C, followed by thermolysis in HMPA at 185 °C provided a new isomeric carboxylic acid as the major product. Since purification proved to be difficult, the crude reaction mixture was esterified with diazomethane and purified by flash chromatography to give a 33% yield of a methyl ester which was assigned as **8b** on the basis of NMR, IR, and MS.

Scheme I



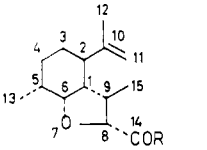
1 2 3

Scheme II[a]



4 5 6 R = H; 7 R = CH_2CO_2H

[a] (a) LDA, $PhSeCH_2CHO$; (b) MsCl, Et_3N; (c) K-Selectride, HOAc; (d) L-Selectride, H_2O_2, NaOH; (e) NaH, $ClCH_2CO_2H$.



8a R = OH
8b R = OCH_3
8c R = NHC_6H_4Br

The 500-MHz ^1H NMR of **8b** showed the isopropylidene protons as singlets at 4.75 and 4.62 ppm. An apparent triplet at 3.92 ppm was assigned to H-6, and a doublet at 3.90 ppm was assigned to H-8. The methyl ester appeared as a singlet at 3.73 ppm. A doublet of quartets at 2.22 ppm was assigned to H-9. The isopropylidene methyl appeared as a singlet at 1.67 ppm. The C-15 methyl group appeared as a doublet at 1.15 ppm, and the C-13 methyl group appeared as a doublet at 1.13 ppm.

Homonuclear decoupling studies with **8b** established the connectivity between C-8, C-9, and C-15. When H-8 was

(1) Synthesis via Sigmatropic Rearrangements. 13. For previous paper in this series see ref 5b.
(2) (a) Recipient of NIH Research Career Development Award (1983-1988) and Fellow of the Alfred P. Sloan Foundation (1980-1984). (b) Department of Biological Structure.
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