of **10b** (0.10 g, 0.42 mmol), triethylamine (50 mg, 0.49 mmol), and acetic anhydride (50 mg, 0.50 mmol) in anhydrous acetone (5 mL) during 1.15 h. The red solution thus obtained was quenched on ice yielding **12** (90 mg, 90%) as white needles, mp 166–8 °C (dec). Acetate **12** was thermally unstable and could not be recrystallized; ^{1}H NMR (60 MHz, $DCCl_3$) δ 2.4 (s, 3 H, Me), 6.9 (q, 1 H, J_1 = 7.5 Hz, J_2 = 4.1 Hz, H6), 7.3 (d, 2 H, J = 9.0 Hz, Ar), 7.9 (d, 2 H, J = 9.0 Hz, Ar), 8.0 (q, 1 H, J_1 = 7.5 Hz, J_2 = 2.0 Hz, H5), 8.4 (q, 1 H, J_1 = 4.10 Hz, J_2 = 2.0 Hz, H7); ^{13}C NMR ($DCCl_3$) δ 167.0 (CO), 149.5 (C7), 142.6 (C3), 131.7 (C9), 130.3 (C2), 129.0 (C5), 134.1, 128.7, 128.0, 123.7 (Ar), 108.5 (C6), 20.1 (Me); IR (KBr) ν 1790 (CO), 1615 (C=N) cm^{-1}; UV (MeOH) λ (log ϵ) 340 (3.96), 302 (3.86), 245 (4.39), 212 (4.33).

Synthesis of 1-Aryl-2-hydroxy-2-(2′-heteroarylamino)-ethanones 5 and 9. Method A. Arylglyoxal hydrate (**1g**) was added in one portion over a solution (or slurry) of the equimolecular amount of the corresponding aminopyridine in benzene (15 mL) at room temperature. The resulting suspension was stirred at room temperature until complete reaction. Carbinolamines **5** were isolated by filtration of the reaction mixture and used without subsequent purification. All compounds **5** were white amorphous solids, stable for months at −20 °C but decomposed to generate complex mixtures after a few hours at room temperature.

Method B. 2-Amino heterocycle (2.0 g) was disolved in dry methylene chloride (25 mL), the equimolar amount of arylglyoxal hydrate was added, and the mixture was heated under reflux until complete reaction. Analytically pure carbinolamines **9** crystallized by cooling from the reaction crude and were used without subsequent purification. All compounds **9** were white amorphous solids stable for months at −20 °C.

Oxidation of 4a in Basic Medium. A solution of 0.5 g (2.38 mmol) of **4a** in ethanol (250 mL) and aqueous 30% NaOH (1 mL) was stirred in an open flask for 4 h. After this time the solvent was evaporated under vacuum, and the residual white solid dissolved in water (15 mL). The resulting clear solution was extracted with methylene chloride (3 × 25 mL). The organic layers were dried ($MgSO_4$) and evaporated under vacuum. After chromatography (silica gel, benzene/ethyl acetate 10:1) *N*-(2-pyridyl)benzamide (0.32 g, 67%) was obtained. Benzoic acid (70 mg, 25%) was recovered from the aqueous layer after acidic workup and methylene chloride extraction.

Oxidation of 4a in Neutral Medium. A solution of **4a** (0.5 g, 2.38 mmol) in methanol (125 mL) was irradiated in an open flask under direct sunlight for 15 h on a sunny day in an open vessel. After this time the solution was clear and the former yellow color had disappeared. The solvent was removed under vacuum and the crude material chromatographied (silica gel, benzene/ethyl acetate 10:1). In order of elution, methylphenylglyoxalate (50 mg 15%) and *N*-(2-pyridyl)benzamide (0.19 g, 40%) were obtained.

Reaction of 4a in MeOH/$HClO_4$. Synthesis of the Amino Ester 16. A solution of **4a** (1 g, 4.76 mmol) in methanol (5 mL) and 60% $HClO_4$ (2 mL) was heated under reflux for 24 h. The reaction mixture was cooled at 0 °C and neutralized with saturated sodium carbonate solution. Compound **16** was isolated after methylene chloride extraction and methylene chloride recrystallization in a 65% yield, mp 101–2 °C; ^{1}H NMR (60 MHz, $DCCl_3$) δ 3.7 (s, OMe), 5.6 (s, br, 2 H, CHNH), 6.3–6.7, 7.1–7.6, 8.0–8.2 (m, 9 H, Ar); ^{13}C NMR (DMSO-d_6) δ 172.2 (CO), 157.6, 147.2, 137.5, 136.7, 128.7, 128.1, 127.9, 112.2, 109.6, 58.1 (NHCH), 51.9 (Me); IR (KBr) ν 3240 (br, NH), 1750 (CO). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.31; H, 5.55; N, 11.34.

Catalytic Hydrogenation of 4a. A solution of 0.5 g (2.38 mmol) of **4a** in methanol (10 mL) and 35% HCl (1 mL) was hydrogenated in the presence of 10% palladium on charcoal (20 mg) under 35 psi of hydrogen. After 2.5 h the catalyst was filtered, and the solvent removed under vacuum. Compound **17** was obtained from the crude hydrochloride by treatment with aqueous sodium carbonate solution followed by recrystallization from methanol; yield 70%; mp (dec) 224–28 °C (MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.5–2.2 (m, 4 H, H6, H7), 2.6–3.1 (m, 2 H, H8), 3.7–4.1 (m, 2 H, H5), 6.8–7.8 (m, 5 H, Ar); ^{13}C NMR (DMSO-d_6) 139.6 (C9), 138.3 (C3), 128.9, 127.7, 127.2, 124.6 (Ar), 111.1 (C2), 41.7 (C5), 21.2 (C8), 20.6 (C7), 17.8 (C6); UV (MeOH) λ (log ϵ) 264 (4.24), 206 (4.08); mass spectrum (ei), m/z 214 (M). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.90; H, 6.54; N, 13.08. Found: C, 72.88; H, 6.40; N, 13.18.

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Lewis Acid Promoted Condensation of Allylalkoxysilanes with Carbonyl Compounds. Synthesis of Tetrahydropyrans[1]

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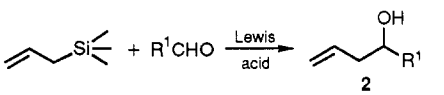
Allylalkoxysilanes **1** condense with aldehydes under Lewis acid conditions to give cis-2,4,6-trisubstituted tetrahydropyrans **3** or the homoallylic alcohols **2**. Factors affecting the reaction have been examined. The enantioselective synthesis of **2** using optically active **1** has also been studied. The reaction is applied to the enantioselective synthesis of (6′-methyl-2′-tetrahydropyranyl)acetic acid (**11**), a natural compound that has been isolated from the glandular secretion of the civet cat.

Introduction

The condensation of allylsilanes with carbonyl compounds (eq 1) under Lewis acid conditions to give homoallylic alcohols **2**, first reported by Sakurai and Hosomi,[2] has been found to be quite useful in organic synthesis. The silyl moiety usually bears three methyl groups. As



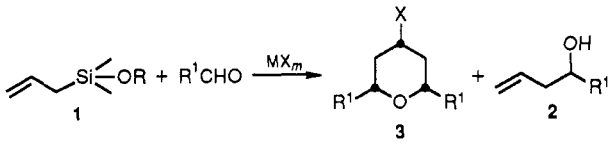
(1)

part of our program to examine the effect of substituents on reactions remote from silicon,[3-6] we studied the Lewis

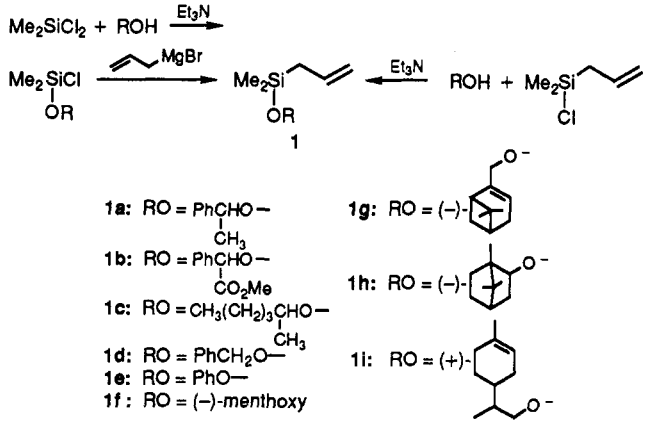
(1) A preliminary account of this work has been reported: Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441.
(2) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.

0022-3263/89/1954-5768$01.50/0

Scheme I



Scheme II



acid promoted reaction of carbonyl compounds with allylsilanes **1** where one of the substituent on silicon was an alkoxy (or aryloxy) group. We were surprised to find that the products were mainly 2,4,6-trisubstituted tetrahydropyrans and not the expected homoallylic alcohols (Scheme I).[1] Because of the rather ubiquitous presence of the tetrahydropyran structure in natural products, we carried out a systematic study of this reaction.

We found that the relative distribution of the two possible products, **2** and **3**, can be selectively controlled, depending on the nature of the alkoxy group OR, the nature and quantity of the Lewis acid used, and the temperature of the reaction. Furthermore, because optically active alcohols can be conveniently introduced as the OR group, the enantioselective formation of homoallylic alcohols has been investigated. Finally, we completed an enantioselective synthesis of (6′-methyl-2′-tetrahydropyranyl)acetic acid (**11**), a component of the glandular secretion of the civet cat.[7] Independant of our work, Ricci et al. have reported preliminary results[8,9] of similar nature.

Results and Discussion

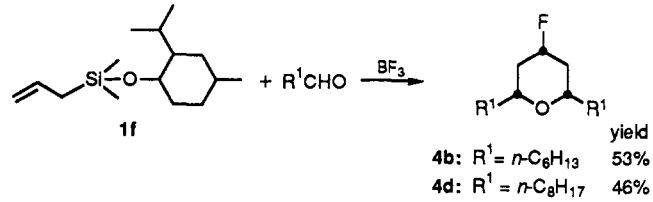
I. Synthesis of Allylalkoxysilanes 1. Allylalkoxydimethylsilanes can be conveniently prepared by one of two routes starting from dimethyldichlorosilane or dimethylallylchlorosilane according to Scheme II. Dimethyldichlorosilane was first converted to the intermediate chloroalkoxysilane followed by reaction with allylmagnesium bromide. Compounds **1a**, **1c**, and **1f** were synthesized by this route. Alternatively, allyldimethylchlorosilane was reacted directly with different alcohols and triethylamine in tetrahydrofuran (THF) to give **1b**, **1d**, **1e**, **1g**, **1h**, and **1i**.

Table I. Synthesis of *cis*-4-Chloro-2,6-disubstituted-tetrahydropyrans[a]

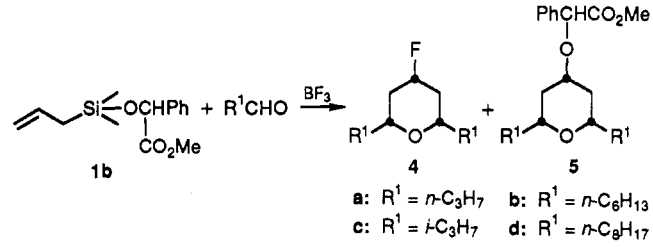
entry	allylalkoxysilane	carbonyl compounds	MX_m (1.1 mol)	product 3, R^1	% yield
1	**1a**	n-$C_6H_{13}CHO$	$AlCl_3$	n-C_6H_{13}, **3b**	84
2	**1a**	n-C_3H_7CHO	$TiCl_4$	n-C_3H_7, **3a**	80
3	**1a**	n-C_3H_7CHO	$AlCl_3$	n-C_3H_7, **3a**	73
4	**1a**	n-C_3H_7CHO	$SnCl_4$	n-C_3H_7, **3a**	52
5	**1a**	i-C_3H_7CHO	$AlCl_3$	i-C_3H_7, **3c**	75
6	**1a**	$C_6H_{11}CHO$	$AlCl_3$	c-C_6H_{11}, **3d**	81
7	**1a**	PhCHO	$AlCl_3$		0
8	**1a**	cyclohexanone	$AlCl_3$		0
9	**1a**		$AlCl_3$		0
10	**1c**	n-$C_6H_{13}CHO$	$AlCl_3$	n-C_6H_{13}, **3b**	81
11	**1c**	n-C_3H_7CHO	$AlCl_3$	n-C_3H_7, **3a**	80
12	**1e**	n-$C_6H_{13}CHO$	$AlCl_3$	n-C_6H_{13}, **3b**	84
13	**1d**	n-$C_6H_{13}CHO$	$AlCl_3$	n-C_6H_{13}, **3b**	78

[a] For general procedure, see Experimental Section.

Scheme III



Scheme IV



II. Influence of Various Parameters on the Condensation Reaction. II.1. Lewis Acid. In the condensation of **1** with carbonyl compounds, the amount of Lewis acid used has a critical effect on the distribution of products. This was demonstrated by the reaction of **1a** with n-butanal, using $AlCl_3$ as the Lewis acid. When the ratio of $AlCl_3$/**1a** was less than 0.5, the product was mainly the homoallylic alcohol **2a**. On the other hand, when $AlCl_3$ was used in excess (>1 mol), the product was exclusively the tetrahydropyran **3a**, with little homoallylic alcohol **2a** according to analysis by gas chromatography and ^1H NMR spectroscopy. Stannic chloride and titanium tetrachloride behaved more or less the same as $AlCl_3$, with $TiCl_4$ perhaps giving the better isolated yield (Table I, entries 2–4). With the metal chlorides as the Lewis acid, the product **3** has a chlorine substitution in the 4-position. When BF_3·OEt_2 was used as the Lewis acid, the tetrahydropyran obtained has a fluorine substituent (**4**). This was illustrated in the reaction of **1f** with aldehydes as shown in Scheme III.

II.2. Alkoxy Substituent. In general, change in the alkoxy substituent does not affect the reaction to any significant extent. Using the same standard reaction conditions (n-heptanal, 1.1 mol of $AlCl_3$, −78 °C), compounds **1a**, **1c**, **1d**, or **1e** all reacted to give nearly the same yield (80%) of the tetrahydropyran product (Table I, entries 1, 10, 12, and 13). On the other hand, for the mandelate substituent (**1b**), only 0.1 mol of $AlCl_3$ was

(3) Chan, T. H.; Koumaglo, K.; Horvath, R.; Wang, D.; Wei, Z. Y.; Yi, G. L.; Li, J. S. In *Silicon Chemistry*; Corey, Y. J., Corey, E. R., Gaspar, P. P., Eds.; Ellis Horwood Ltd.: Chichester, 1988; Chapter 5.
(4) Chan, T. H.; Chen, L. M.; Wang, D. *J. Chem. Soc., Chem. Commun.* **1988**, 1281.
(5) Horvath, R.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 317.
(6) Chan, T. H.; Peng, Q. J.; Wang, D.; Guo, J. A. *J. Chem. Soc. Chem. Commun.* **1987**, 325.
(7) Maurer, B.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 1096. van Dorp, S. A.; Ward, J. P. *Experientia* **1981**, *37*, 917.
(8) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973.
(9) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911.

Table II. Product Distribution in the Reaction According to Scheme IV

entry	R^1CHO, R^1 =	reagents used $1b/R^1CHO/BF_3$	product 4 (yield, %)[a]	product 5 (yield, %)[b]
1	n-C_6H_{13}	1:1:3	**4b** (25)	**5b** (32)
2	n-C_6H_{13}	1:2:6	**4b** (35)	**5b** (48)
3	i-C_3H_7	1:2:6	**4c** (35)	**5c** (43)
4	n-C_3H_7	1:2:6	**4a** (35)	**5a** (45)
5	n-C_8H_{17}	1:2:6		**5d** (40)

[a] Yield determined by ^1H NMR. [b] Isolated yield.

Table III. Effect of Temperature on Yield of 3 According to Scheme I Using 1a and 1.1 mol of $AlCl_3$

entry	aldehyde	reactn temp, °C	yield, of 3, %
1	n-C_3H_7CHO	−78	73
2	n-C_3H_7CHO	−40	82
3	n-C_3H_7CHO	0	21
4	n-$C_6H_{13}CHO$	−78	84
5	n-$C_6H_{13}CHO$	−40	20
6	n-$C_6H_{13}CHO$	0	20

required to give an 85% yield. The mandelate substituent is also the only alkoxy group (in **1b**) that could participate in the reaction to give 4-alkoxytetrahydropyrans **5** when BF_3 was used as the Lewis acid. This is illustrated in Table II and Scheme IV.

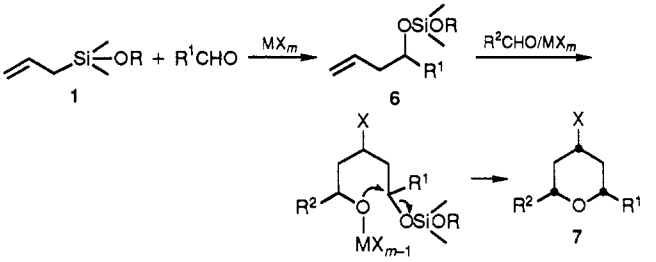
II.3. Carbonyl Compounds. The reaction to form tetrahydropyrans could be carried out with a number of aldehydes. However, the reaction did not seem to work with aromatic aldehydes such as benzaldehyde or with acrolein or with cyclohexanone (see below).

II.4. Reaction Temperature. The reaction temperature appeared to have an effect on the yield of tetrahydropyrans. In general, a lower reaction temperature gave better yield of tetrahydropyrans. This was demonstrated by the reaction of **1a** with n-heptanal with $AlCl_3$ as the Lewis acid. The yield of the product declined from 84% at −78 °C to less than 20% at 0 °C. The same was true in the reaction with n-butanal (Table III).

II.5. Order of Addition of Reagents. For reactions using $AlCl_3$, $SnCl_4$, or $TiCl_4$, the Lewis acid was first mixed with the aldehyde, followed by the addition of the alkoxyallylsilane. This gave then the tetrahydropyran. If, however, the Lewis acid was first mixed with the alkoxyallylsilane for an extended period, this usually led to the cleavage of the alkoxysilane and the yield of **3** diminished. In the case of $BF_3{\cdot}OEt_2$ as Lewis acid, mixing of aldehyde with BF_3 first seemed to favor the formation of the fluoro-substituted tetrahydropyran. On the other hand, if BF_3 was mixed with the alkoxysilane **1b** first followed by addition of the aldehyde, the formation of homoallylic alcohol was favored.

III. Unsymmetrical Tetrahydropyrans. The reactions examined so far gave symmetrically substituted tetrahydropyrans with the substituents at C-2 and C-6 derving from the same aldehyde. Since by reducing the quantity of Lewis acid the reaction gave mainly the homoallylic alcohol, it seemed reasonable to assume that the first step of the reaction involved the formation of the mixed silyl acetal **6** according to Scheme V. To confirm this possibility, we synthesized compound **6** from dimethyldichlorosilane by substituting the chlorines stepwise with the appropriate alcohols.[6] We were indeed able to isolate the same mixed acetal from the reaction of alkoxyallylsilane **1a** with n-butanal. Furthermore, starting from the mixed acetal **6**, and reacting it with a different aldehyde or ketone under the same reaction conditions with more Lewis acid, a series of unsymmetrically substituted tetrahydropyrans **7** could be obtained in good yields. It is interesting to note that in this condensation, ketones or aromatic aldehydes reacted equally well (Table IV). From these results, it seemed that the previously observed reluctance of ketones or aromatic aldehydes to undergo cyclization must be due to difficulty associated with the first step of the reaction in forming the mxied silyl acetal intermediate. We also developed a one-pot process to synthesize unsymmetrical tetrahydropyrans based on these observations. The alkoxyallylsilane was first reacted with 1 mol of aldehyde with a limited amount of Lewis acid. After the first step of condensation was completed, the intermediate mixed silyl acetal was not isolated but allowed to react with a second, different carbonyl compound with more Lewis acid. The yield of the unsymmetrical tetrahydropyrans obtained was quite satisfactory.

Scheme V



IV. Stereochemistry. The 2,4,6-trisubstituted tetrahydropyrans formed can, in principle, have four stereoisomers. Only one single isomer was formed as judged from ^1H and ^{13}C NMR spectroscopy. The stereochemistry was found to be the all-cis compound in all cases. The assignment was based on the coupling constants of the protons at the C-2, C-4, and C-6 positions. A coupling of about 11 Hz was found for all such protons, indicating the presence of axial–axial coupling. The three substituents are therefore all in the equatorial positions, in agreement with the all-cis stereochemistry.

V. Enantioselective Synthesis of Homoallylic Alcohols Using Chiral Alkoxyallylsilanes. The synthetic usefulness of the reaction of allylsilanes with aldehydes to give homoallylic alcohols would be much enhanced if the reaction can be induced to give chiral alcohols with high enantioselectivity. Several approaches have been applied to this reaction. The most successful to date has been the work of Johnson et al.,[10] who used a chiral aux-

Table IV. Synthesis of Unsymmetrical Tetrahydropyrans According to Scheme V

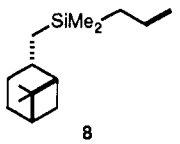
entry	method[a]	R^1CHO	$R^2R^3{=}O$	Lewis acid	reactn temp, °C	product 7 yield, %
1	A		n-C_3H_7CHO	$AlCl_3$	−78	64
2	A		n-$C_6H_{13}CHO$	$AlCl_3$	−78	81
3	A		PhCHO	$AlCl_3$	−78	58
4	A		cyclohexanone	$AlCl_3$	−78	90
5	B	n-C_3H_7CHO	n-$C_6H_{13}CHO$	$AlCl_3$	−78	77
6	B	CH_3CHO	$PhCH_2OCH_2CH_2CHO$	$AlCl_3$	−78	65

[a] Method A: via silyl acetal **6**. Method B: one-pot synthesis starting from **1a** in entry 5, from **1f** in entry 6.

Table V. Enantioselective Synthesis of Homoallylic Alcohols

entry	chiral allylsilane used	R'CHO used	chem yield of 2, %	optical purity of 2 $[\alpha]^{20}_D$ (CCl_4), deg	optical purity of 2 % ee	abs confgn of 2
1	1f	n-$C_6H_{13}CHO$	72	−2.24 (c = 1.4)		S
2	1f	n-$C_8H_{17}CHO$	66	−2.20 (c = 8.0)	19.3	S
3	1g	n-$C_8H_{17}CHO$	73	−1.99 (c = 0.8)	18.1	S
4	1h	n-$C_8H_{17}CHO$	77	−2.57 (c = 1.1)	23.3	S
5	1i	n-$C_8H_{17}CHO$	75	−2.52 (c = 2.0)	22.8	S
6	1i	n-$C_6H_{13}CHO$	70	−1.68 (c = 0.7)		S

iliary at the aldehyde site in the form of acetals. One drawback of the reaction is that the product obtained is the ether of the homoallylic alcohol. A deprotection step with destruction of the chiral auxiliary must be used to liberate the desired alcohol. An alternative approach is to anchor the chiral auxiliary on the silicon site. Optically active silanes with four different groups attached to silicon are of course well known since the work of Sommer.[11] Sporadic attempts to use optically active silanes of this type in enantioselective reactions have not been met with much success. For example, Hathaway and Paquette[12] examined the reaction of optically active α-naphthylphenylmethylallylsilane with aldehydes and acetals and failed to observe significant chirality transfer (5% ee). We have concentrated our effort in examining the reactions of otically active silicon compounds where the chirality resides not on silicon but away from silicon.[13] A first attempt was carried out with compound 8, derived from the hydrosilylation of (−)-β-pinene.[13,14] Reaction of 8 with aldehydes under Lewis acid conditions gave homoallylic alcohols with 10–15% enantiomeric excess (ee).



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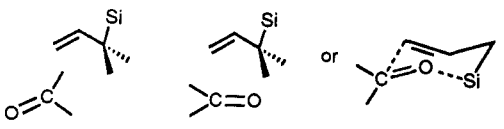
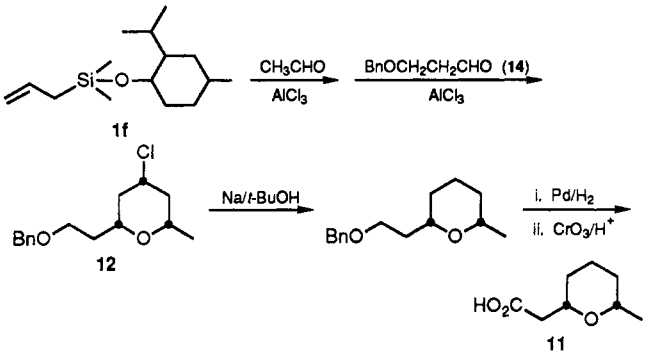
The modest ee obtained in these reactions are not totally unexpected if one considers the mechanism generally accepted for the reactions of allylsilanes with carbonyl compounds. From the work of Kumada[15] and Fleming,[16] it has been concluded that the reaction proceeds through antiperiplanar transition state 9. That being the case, it would



9 10

not be surprising that any chiral auxiliary, either at silicon or attached to silicon, would have little influence on the stereochemical outcome of the reaction. While the antiperiplanar transition state may well be the prefered pathway in most reactions of allylsilanes with electrophiles, the work of Denmark[17] suggests that the synclinal transition state 10 is also operative under certain conditions. It is possible that in the synclinal transition state, the silyl group may have a greater effect on the stereochemistry of the reaction. Since the alkoxy group in alkoxyallylsilanes can be derived from readily available optically active alcohols, we investigated the reaction of chiral alkoxyallylsilanes with aldehydes under Lewis acid conditions. The rationale is that the alkoxy group, in addition to being attached to silicon, may bind with the Lewis acid as well, which may then induce the reaction to proceed through the synclinal transition state.

Scheme VI



Optically active alkoxyallylsilanes **1f**, **1g**, **1h** and **1i** were reacted with n-heptanal or n-nonanal with BF_3·OEt_2 to give the homoallylic alcohols in good isolated yields of about 70%. In all cases, the homoallylic alcohols were found to have optical activity. The enantiomeric excess was found to be in the range of 18–23% (Table V). Use of other Lewis acids did not measurably improve the ee of the products. The optically active alcohols used as the chiral auxiliary could be recovered from the reaction nearly quantitatively and with essentially no loss of optical purity.

Since compound **1g** is quite similar structurally to compound 8, the improved ee in the homoallylic alcohol formed could be attributed to the presence of the oxygen atom in **1g**. Nevertheless, judging from the still modest ee, an alkoxy group directly attached to silicon as in 1 is still insufficient to steer the reaction of the synclinal pathway to any significant extent. Future design of chiral auxiliary on silicon will have to incorporate heteroatoms properly positioned to complex with the Lewis acid in order to obtain an even better ee.[18]

VI. Enantioselective Synthesis of (6′-Methyl-2′-tetrahydropyranyl)acetic Acid. As an example of the application of the present reaction, we completed a synthesis of *cis*-(6′-methyl-2′-tetrahydropyranyl)acetic acid (11), a natural compound that was isolated from the glandular secretion of the civet cat (*Veverra civetta*).[7,19]

Starting from the optically active alkoxyallylsilane **1f**, the tetrahydropyran 12 was prepared in a one-pot synthesis using acetaldehyde and 3-(benzyloxy)propanal (14) as the aldehyde components and aluminum chloride as the Lewis acid (Scheme VI). Compound 12 was obtained in 65%

(10) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951.
(11) Sommer, L. H. *Stereochemistry, Mechanism and Silicon*; McGraw Hill: New York, 1965.
(12) Hathaway, S. J.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 3351.
(13) Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1573.
(14) Yi, G. L.; Wang, D.; Chan, T. H. *Youji Huaxue* **1988**, *8*, 115.
(15) Hagashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.
(16) Fleming, I.; Terrett, N. V. *Tetrahedron Lett.* **1983**, *24*, 4153.
(17) Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am. Chem. Soc.* **1987**, *109*, 2512 and references therein.
(18) Chan, T. H.; Wang, D. *Tetrahedron Lett.* **1989**, *30*, 3041.
(19) For recent syntheses of this compound (11) in its optically active form, see: Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1988**, *53*, 3723 and references cited therein.

yield and it had an optical rotation of $[\alpha]_D^{20} = -2.01°$ (c = 2.7, $CHCl_3$). Sodium reduction removed the chlorine substituent. Catalytic hydrogenolysis followed by oxidation of the liberated hydroxy group gave the desired compound 11 in an overall yield of 38% from **1f**. By comparison with the optical rotation of the natural product synthesized by an enzymic method,[19] the optical purity of 11 from the present synthesis is 29% and the compound has the 2*R*,6*R* stereochemistry.

Since compound **1f** reacted with aldehydes to give homoallylic alcohols with *S* configurations, and assuming that acetaldehyde reacted in the same way as other aldehydes, the fact that 11 has the 2*R* stereochemistry suggests that an inversion must have occurred. This is in agreement with the expectation that the ring-formation step involved an S_N2 displacement at the C-2 position as depicted in Scheme V.

Experimental Section

All the chemicals used were reagent grade. Solvents were dried prior to use: ether, THF, or hexanes were dried over sodium metal, pyridine was dried over sodium hydride. Nuclear magnetic resonance spectra were taken with a Varian EM-360L or JEOL FX-100 spectrometer using tetramethylsilane as internal standard. NMR spectra are reported in ppm with respect to TMS and in parentheses are the multiplicity and the number of hydrogens. IR spectra were taken with a Perkin-Elmer 782 or a Carl Zeiss Specord 751R spectrophotometer and are reported in cm^{-1}. Mass spectra were taken at 60 eV with a AEI MS-50/PS-30 instrument and are reported as m/z (relative intensity). Microanalyses were performed on a Calro 1102 Element Analysis instrument. All reactions were usually run in a nitrogen atmosphere and all equipment dried in an oven. Purifications involving column chromatography were performed with a silica gel G using flash chromatography.

Allylalkoxydimethylsilanes 1. Method A. General Procedure. To a solution of dimethyldichlorosilane (0.20 mol) in THF (100 ml) at room temperature was added a solution of the alcohol (0.10 mol) and triethylamine (0.22 mol) in THF (60 mL) dropwise. After the addition was completed, the reaction mixture was refluxed for 3 h and cooled to room temperature. The mixture was filtered and the filtrate as evaporated to remove excess dimethyldichlorosilane (bp < 120 °C). The residue was diluted with THF (100 mL). To the mixture was added dropwise a solution of allylmagnesium bromide in ether (140 mL, 1.4 M). After the addition, the mixture was refluxed for 3 h. The mixture was hydrolyzed with saturated aqueous ammonium chloride. The organic phase was washed with brine and dried ($MgSO_4$) and distilled under reduced pressure to give product 1.

Allyl(1′-phenylethoxy)dimethylsilane (1a) was obtained in 64% yield: bp 90–94 °C/1 mm; IR (neat) 1620, 1490, 1250, 1150, 1090; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 1.3 (d, J = 6.0 Hz, 3 H), 1.5 (d, J = 8.0 Hz, 2 H), 4.5–4.9 (m, 3 H), 5.2–5.9 (m, 1 H), 7.1 (m, 5 H). Anal. Found for $C_{13}H_{20}OSi$: C, 70.98; H, 9.34. Calcd: C, 70.85; H, 9.15.

Allyl(2′-hexyloxy)dimethylsilane (1c) was obtained in 62% yield: bp 61–62 °C/0.5 mm; IR (neat) 1630, 1250, 1150, 1070; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 0.7–1.6 (m, 14 H), 3.7 (m, 1 H), 4.6–5.0 (m, 2 H), 5.3–6.1 (m, 1 H).

Allyl[(−)-menthoxy]dimethylsilane (1f) was obtained in 84% yield: bp 102–103 °C/1 mm; $[\alpha]_D^{25} = 28.4°$ (EtOH); IR (neat) 1620, 1250, 1150, 1100; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 0.6–2.3 (m, 20 H), 3.3 (m, 1 H), 4.6–4.8 (m, 2 H), 5.2–5.9 (m, 1 H); MS 254 (2), 239 (2), 213 (75), 75 (100). Anal. Found for $C_{15}H_{30}OSi$: C, 70.88; H, 12.38. Calcd: C, 70.79, H, 11.88.

Method B. To a solution of dimethyldichlorosilane (0.50 mol) in ether (250 mL) was added a solution of allylmagnesium bromide in ether (400 mL, 1.25 M) dropwise. After addition (about 8 h), the mixture was refluxed for 2 h. The mixture was distilled under reduced pressure to give allyldimethylchlorosilane (43.5 g, 66% yield). To a solution of allyldimethylchlorosilane (0.22 mol) in THF (80 mL) was added dropwise a solution of alcohol (0.2 mol) and triethylamine (0.22 mol) in THF (100 mL). The mixture was stirred in room temperature for 2 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the product as residue without further purification.

Allyl[[α-(methoxycarbonyl)benzyl]oxy]dimethylsilane (1b) was obtained in quantitative yield: IR (neat) 1750, 1730, 1620, 1490, 1250, 1150, 1100; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 1.5 (d, J = 8.0 Hz, 2 H), 3.5 (s, 3 H), 4.5–4.9 (m, 2 H), 5.0 (s, 1 H), 5.2–5.9 (m, 1 H), 7.0–7.3 (m, 5 H); MS 264 (2), 263 (4), 249 (40), 205 (18), 89 (100). Anal. Found: C, 63.70; H, 7.71. Calcd for $C_{14}H_{20}O_3Si$: C, 63.60; H, 7.62.

Allyl(benzyloxy)dimethylsilane (1d) was obtained in 93% yield: IR (neat) 1630, 1490, 1250, 1150, 1090; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 1.5 (d, J = 8.0 Hz, 2 H), 4.6 (s, 2 H), 4.5–4.9 (m, 2 H), 5.3–6.0 (m, 1 H), 7.2 (m, 5 H); MS 206 (1), 191 (1), 165 (30), 115 (95), 91 (100).

Allylphenoxydimethylsilane (1e) was obtained in 86% yield: bp 56–58 °C/0.5 mm; IR (neat) 1630, 1590, 1490, 1250, 1160; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 1.5 (d, J = 8.0 Hz, 2 H), 4.5–4.9 (m, 2 H), 5.3–6.0 (m, 1 H), 6.5–7.3 (m, 5 H); MS 192 (45), 177 (6), 151 (85), 99 (1), 77 (2), 28 (100).

Allyl[(1*R*)-(−)-myrtenoxy]dimethylsilane (1g) was obtained in 92% yield: $[\alpha]_D^{20} = -35.1°$ ($CHCl_3$); IR (neat) 3080, 1625, 1255, 1130, 1090; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 0.7 (s, 3 H), 1.2 (s, 3 H), 1.45 (d, J = 8.0 Hz, 2 H), 1.8–2.4 (m, 6 H), 3.8 (m, 2 H), 4.5–6.0 (m, 4 H); MS 250 (1), 209 (60), 151 (4), 135 (50), 115 (5), 99 (75), 28 (100).

Allyl[(1*S*)-(−)-bornoxy]dimethylsilane (1h) was obtained in 95% yield: $[\alpha]_D^{20} = -31.8°$ ($CHCl_3$); IR (neat) 1620, 1245, 1150, 1100; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 0.7 (s, 3 H), 0.8 (s, 6 H), 1.45 (d, J = 8.0 Hz, 2 H), 0.8–2.2 (m, 7 H), 3.9 (m, 1 H), 4.6–6.0 (m, 3 H); MS 252 (2), 211 (30), 137 (25), 99 (4), 28 (100).

Allyl[(*R*,*R*)-(+)-*p*-menth-1-en-9-oxy]dimethylsilane (1i) was obtained in 94% yield: $[\alpha]_D^{20} = +46.6°$ ($CHCl_3$); IR (neat) 1620, 1250, 1145, 1090; ^1H NMR ($CDCl_3$) 0.0 (s, 6 H), 0.8 (d, J = 6.0 Hz, 3 H), 1.2–2.0 (m, 13 H), 3.4 (m, 2 H), 4.5–6.0 (m, 4 H); MS 252 (1), 211 (30), 137 (5), 115 (4), 99 (2), 28 (100).

Synthesis of *cis*-4-Chloro-2,6-(symmetrically disubstituted)tetrahydropyrans 3. General Procedure. To a solution of $AlCl_3$ (5.5 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a solution of aldehyde (5.5 mmol) in CH_2Cl_2 (10 mL). After 15 min, a solution of allylalkoxydimethylsilane 1 (5.0 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was allowed to react at −78 °C for 4 h and then warmed to 0 °C. The mixture was hydrolyzed with 20 mL of saturated aqueous ammonium chloride solution and extracted twice with 100 mL of ether. The ether solution was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated in vacuo and the residue purified by column chromatography using petroleum ether (30–60)–ethyl acetate (100:1) as eluent to give product 3.

***cis*-4-Chloro-2,6-dipropyltetrahydropyran (3a)**: IR (neat) 1148, 1085, 765; ^1H NMR ($CDCl_3$) 0.6–2.3 (m, 18 H), 3.3 (m, 2 H), 4.0 (tt, J = 5, 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 13.9, 18.7, 37.9, 42.7, 56.0, 76.2; MS 206 (1.6), 204 (5), 169 (2), 161 (100). Anal. Found: C, 64.68; H, 10.35; Cl, 17.25. Calcd for $C_{11}H_{21}ClO$: C, 64.53; H, 10.34; Cl, 17.34.

***cis*-4-Chloro-2,6-dihexyltetrahydropyran (3b)**: IR (neat) 1140, 1080, 760; ^1H NMR ($CDCl_3$) 1.0 (t, 6 H), 1.2–2.3 (m, 24 H), 3.2 (m, 2 H), 4.0 (tt, J = 5, 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.1, 22.5, 25.5, 29.3, 31.8, 35.9, 42.7, 56.1, 76.6; MS 290 (1), 288 (3), 253 (2), 203 (100).

***cis*-4-Chloro-2,6-diisopropyltetrahydropyran (3c)**: IR (neat) 1150, 1075, 743; ^1H NMR ($CDCl_3$) 0.85 (d, J = 6 Hz, 6 H), 0.95 (d, J = 6 Hz, 6 H), 1.3–2.3 (m, 6 H), 2.9 (ddd, J = 2, 6, 12 Hz, 2 H), 4.0 (tt, J = 5, 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 18.4, 33.0, 39.6, 57.3, 81.5; MS 206 (0.5), 204 (1.5), 169 (4), 161 (2), 28 (100).

***cis*-4-Chloro-2,6-dicyclohexyltetrahydropyran (3d)**: IR (neat) 1150, 1080, 750; ^1H NMR ($CDCl_3$) 0.9–2.3 (m, 26 H), 2.9 (m, 2 H), 3.9 (tt, J = 5, 12 Hz, 1 H); MS 286 (0.5), 284 (1.5), 248 (4), 203 (3), 201 (9), 83 (60), 28 (100).

Dimethyl(1-phenylethoxy)(hept-1-en-4-oxy)silane (6). To a solution of dimethyldichlorosilane (110 mmol) in ether (300 mL) at room temperature was added dropwise a solution of 1-phenylethanol (50 mmol) and triethylamine (110 mmol) in ether (50 mL). After addition, the mixture was refluxed for 3 h. The mixture was cooled and filtered. The filtrate was evaporated under reduced pressure to remove the excess dimethyldichlorosilane. The residue was dissolved in ether (100 mL). To the solution was

added a mixture of hept-1-en-4-ol (50 mmol) and triethylamine (100 mmol). The reaction mixture was refluxed for 3 h, cooled, and filtered. The filtrate was rotary evaporated and the residue was distilled under reduced pressure to give 12.3 g of **6** (84% yield): bp 120–124 °C/1 mm; ^{1}H NMR ($CDCl_3$) 0.1 (s, 3 H), 0.2 (s, 3 H), 0.7–1.6 (m, 10 H), 2.1 (m, 2 H), 3.6 (m, 1 H), 4.7–5.1 (m, 3 H), 5.4–6.1 (m, 1 H), 7.3 (m, 5 H).

Synthesis of *cis*-4-Chloro-2,6-(unsymmetrically substituted)tetrahydropyrans 7. General Procedure. To a solution of $AlCl_3$ (5.5 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a solution of the carbonyl compound (5.5 mmol) in CH_2Cl_2 (10 mL), followed by a solution of compound **6** (5.5 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to react at −78 °C for 5 h and then warmed to 0 °C. The mixture was hydrolyzed with saturated aqueous ammonium chloride solution and extracted twice with ether (100 mL). The ether solution was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified with column chromatography using petroleum ether–ethyl acetate as eluent.

***cis*-4-Chloro-2-propyl-6-hexyltetrahydropyran (7a):** IR (neat) 1142, 1080, 762; ^{1}H NMR 1.0 (m, 6 H), 1.2–2.3 (m, 18 H), 3.3 (m, 2 H), 4.0 (tt, J = 5, 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.1, 18.9, 22.7, 25.6, 29.3, 31.9, 36.1, 38.1, 42.8, 56.2, 76.4, 76.7; MS 248 (0.5), 246 (1.5), 211 (2), 205 (25), 203 (75), 163 (10), 61 (30), 28 (100).

***cis*-4-Chloro-2-propyl-6-phenyltetrahydropyran (7b):** IR (neat) 1600, 1490, 1142, 1080, 754; ^{1}H NMR ($CDCl_3$) 0.87 (t, 3 H), 1.2–2.5 (m, 8 H), 3.4 (m, 1 H), 4.0 (tt, J = 5, 12 Hz, 1 H), 4.2 (dd, J = 2, 10 Hz, 1 H), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) 14.4, 18.9, 38.3, 42.5, 44.7, 56.2, 77.0, 78.5, 126.0, 127.8, 128.6, 141.9; MS 240 (5), 238 (15), 203 (22), 197 (6), 195 (18), 163 (2.5), 161 (7.5), 28 (100).

***cis*-4-Chloro-2-propyl-6,6-pentamethylenetetrahydropyran (7c):** IR (neat) 1140, 1070, 790; ^{1}H NMR ($CDCl_3$) 0.9–2.5 (m, 21 H), 3.4 (m, 1 H), 4.0 (tt, J = 5, 12 Hz, 1 H); MS 232 (0.5), 230 (1.5), 195 (3), 189 (1.5), 187 (4.5), 28 (100).

One-Pot Synthesis of 7a. To a solution of $AlCl_3$ (0.5 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a solution of butanal (2.0 mmol) in CH_2Cl_2 (10 mL). Ten minutes later, compound **1a** (5.0 mmol) was added dropwise. The mixture was stirred at −78 °C for 4 h. To the mixture was added a solution of *n*-heptanal (2.0 mmol) in CH_2Cl_2 (10 mL) dropwise, followed by the addition of $AlCl_3$ (3.0 mmol). The mixture was stirred at −78 °C for a further 4 h. After being warmed to 0 °C, the mixture was hydrolyzed with saturated aqueous ammonium chloride solution and extracted twice with ether (100 mL). The organic phase was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by column chromatography to give compound **7a** in 77% yield.

Synthesis of *cis*-4-Fluoro-2,6-disubstituted-tetrahydropyrans 4. General Procedure. To a solution of aldehyde (6 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise BF_3·OEt_2 (6 mmol). After 15 min, a solution of compound **1f** (6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the mixture. The mixture was allowed to react at −78 °C for 4 h and then warmed to room temperature. The mixture was hydrolyzed with water and extracted three times with ether. The ether extract was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue chromatographed on column with 0.2% of ethyl acetate in petroleum ether as the eluent to give compound **4**.

***cis*-4-Fluoro-2,6-dioctyltetrahydropyran (4a)** was obtained in 46% yield: IR (neat) 1155, 1080, 1000; ^{1}H NMR ($CDCl_3$) 0.9 (t, 6 H), 1.0–2.1 (m, 32 H), 3.1 (m, 2 H), 4.5 (dtt, J = 5.5, 11, 50 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.0, 22.6, 25.5, 29.2, 29.5, 31.8, 35.9, (39.0, 38.3), (74.6, 75.0), (86.0, 93.0); MS 328 (0.5), 309 (1), 215 (10), 196 (80), 113 (90).

***cis*-4-Fluoro-2,6-dihexyltetrahydropyran (4b)** was obtained in 53% yield: IR (neat) 1155, 1080, 1000; ^{1}H NMR ($CDCl_3$) 0.9 (t, 6 H), 1.0–2.1 (m, 24 H), 3.1 (m, 2 H), 4.5 (dtt, J = 5.5, 11, 50 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 13.5, 22.1, 25.2, 28.9, 31.4, 35.6, (38.0, 38.7), (74.7, 74.3), (85.8, 92.8); MS 272 (3), 253 (3), 187 (30), 186 (100), 168 (40).

Synthesis of *cis*-4-[[α-(Methoxycarbonyl)benzyl]oxy]-2,6-disubstituted-tetrahydropyrans 5. General Procedure. To a solution of aldehyde (4.0 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise BF_3·OEt_2 (12 mmol). After 15 min, a solution of **1b** (2.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 4 h at −78 °C and allowed to warm to room temperature. The mixture was hydrolyzed with water and extracted three times with ether. The ether extract was washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated. The residue was purified by column chromatography using petroleum ether/ethyl acetate (100:2) as eluent to give compound **5**.

***cis*-4-[[α-(Methoxycarbonyl)benzyl]oxy]-2,6-diisopropyltetrahydropyran (5c)** was obtained in 43% yield: IR (neat) 3030, 3060, 1735, 1755, 1460, 1385, 1370, 1160, 1070, 735, 700; ^{1}H NMR ($CDCl_3$) 0.9 (dd, 12 H), 1.0–2.2 (m, 6 H), 2.8 (m, 2 H), 3.5 (tt, J = 11, 5 Hz, 1 H), 3.65 (s, 3 H), 4.95 (s, 1 H), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) 17.8, 32.3, 34.1, 51.4, 74.9, 77.0, 79.4, 126.3, 127.7, 136.2, 170.9, 211.0; MS 275 (10), 169 (38), 149 (18), 125 (22), 97 (100). Anal. Found: C, 71.86; H, 8.80. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04.

***cis*-4-[[α-(Methoxycarbonyl)benzyl]oxy]-2,6-dihexyltetrahydropyran (5b)** was obtained in 32% yield: IR (neat) 3030, 3060, 1730, 1750, 1460, 1270, 1170, 1100, 730, 700; ^{1}H NMR ($CDCl_3$) 0.95 (m, 6 H), 1.3 (br, 22 H), 1.95 (m, 2 H), 3.0–3.7 (m, 3 H), 3.65 (s, 3 H), 4.95 (s, 1 H), 7.3 (m, 5 H); MS 359 (15), 253 (90), 149 (20), 85 (5), 28 (100).

***cis*-4-[[α-(Methoxycarbonyl)benzyl]oxy]-2,6-dipropyltetrahydropyran (5a)** was obtained in 45% yield: IR (neat) 3030, 3060, 1745, 1450, 1270, 1170, 1100, 730, 700; ^{1}H NMR ($CDCl_3$) 0.95 (m, 6 H), 1.4 (br, 10 H), 1.95 (m, 2 H), 3.0–3.7 (m, 3 H), 3.65 (s, 3 H), 4.95 (s, 1 H), 7.3 (m, 5 H); MS 275 (45), 169 (100), 149 (30).

***cis*-4-[[α-(Methoxycarbonyl)benzyl]oxy]-2,6-dioctyltetrahydropyran (5d)** was obtained in 40% yield: IR (neat) 3030, 3055, 1740, 1460, 1270, 1165, 1095, 725, 700; ^{1}H NMR ($CDCl_3$) 0.95 (m, 6 H), 1.3 (br, 30 H), 1.95 (m, 2 H), 3.0–3.7 (m, 3 H), 3.65 (s, 3 H), 4.95 (s, 1 H), 7.3 (m, 5 H); MS 474 (2), 415 (30), 309 (55), 195 (25), 167 (95), 83 (100).

Enantioselective Synthesis of Homoallylic Alcohol 2 Using Chiral Allylalkoxydimethylsilanes. General Procedure. To a solution of chiral allylalkoxydimethylsilane (**1f–i**, 3.0 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise BF_3·OEt_2 (3.0 mmol). After 10 min, a solution of aldehyde (3.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at −78 °C for 4 h and warmed to −5 °C. The mixture was hydrolyzed with water and extracted three times with ether. The ether solution was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by column chromatography using petroleum ether–ethyl acetate (100:2) as eluent to give the product **2**. The yield and the enantiomeric excess of **2** are summarized in Table V.

3-(Benzyloxy)propanol (13). A mixture of 1,3-propanediol (0.2 mol) and sodium hydride (3.0 g, 80%, 0.1 mol) in dimethyl sulfoxide (200 mL) was stirred at room temperature for 30 min. To the mixture was added benzyl chloride (0.1 mol). The mixture was stirred at room temperature for 2 h. The mixture was quenched with water (50 mL) and extracted three times with ether. The ether solution was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified with column chromatography using petroleum ether–ethyl acetate (80:20) as eluent to give 13.9 g of compound **13** (84% yield): IR (neat) 3380, 3090, 3070, 3030, 1705, 1085; ^{1}H NMR ($CDCl_3$) 1.8 (m, 2 H), 3.6 (m, 4 H), 4.4 (s, 2 H), 7.2 (m, 5 H).

3-(Benzyloxy)propanal (14). A mixture of compound **13** (6.64 g, 40 mmol) and CrO_3·pyridinium hydrochloride (15 g) in CH_2Cl_2 (100 mL) was stirred at room temperature for 4 h. The mixture was washed with 10% sodium hydroxide, dilute hydrochloric acid, and then brine. The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography using petroleum ether–ethyl acetate (9:1) as eluent to give 5.6 g of compound **14**: ^{1}H NMR ($CDCl_3$) 2.2 (dt, J = 2, 6 Hz, 2 H), 3.6 (t, J = 6 Hz, 2 H), 4.4 (s, 2 H), 7.2 (m, 5 H), 9.6 (t, J = 2 Hz, 1 H).

***cis*-4-Chloro-6-methyl-2-[2-(benzyloxy)ethyl]tetrahydropyran (12).** To a solution of $AlCl_3$ (2.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise a solution of freshly distilled acetaldehyde (5.5 mmol) in CH_2Cl_2 (5 mL). After 15 min, compound **1f** (5.5 mmol) was added dropwise. The mixture was stirred

at −78 °C for 4 h. To the mixture was added a solution of compound 14 (5.0 mmol) and $AlCl_3$ (5.0 mmol) in CH_2Cl_2 (15 mL) dropwise. The mixture was stirred at −78 °C for 4 h and allowed to warm to room temperature. The mixture was hydrolyzed with water and extracted three times with ether. The ether phase was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by column chromatography using petroleum ether–ethyl acetate (100:2) as eluent to give 0.87 g of compound **12** (65% yield): $[\alpha]^{20}_D = -2.01$ ($CHCl_3$); IR (neat) 3090, 3070, 3030, 1715, 1140, 1100, 745; ^1H NMR ($CDCl_3$) 1.15 (d, J = 6 Hz, 3 H), 1.0–2.2 (m, 6 H), 3.4 (m, 4 H), 3.9 (tt, J = 5, 11.5 Hz, 1 H), 4.4 (s, 2 H), 7.2 (m, 5 H). Anal. Found: C, 67.02; H, 7.85. Calcd for $C_{15}H_{21}ClO_2$: C, 67.03; H, 7.87.

***cis*-6-Methyl-2-[2-(benzyloxy)ethyl]tetrahydropyran (15).** To a mixture of sodium (0.3 g), *tert*-butyl alcohol (0.5 mL), and ether (10 mL) was added dropwise a solution of compound **12** (0.15 g) in ether (5 mL). The mixture was refluxed for 8 h. The excess sodium was destroyed with methanol and then water (5 mL). The mixture was extracted three times with ether. The ether phase was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified with column chromatography using petroleum ether–ethyl acetate (100:2) as eluent to give 0.10 g of compound **15** (76% yield): ^1H NMR ($CDCl_3$) 1.1 (d, J = 6 Hz, 3 H), 1.0–1.8 (m, 8 H), 3.4 (m, 4 H), 4.4 (s, 2 H), 7.2 (m, 5 H); MS 234 (15), 216 (20), 143 (35), 107 (60), 99 (85), 77 (1), 28 (100).

(2*R*,6*R*)-(−)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid (11). Compound **15** (0.10 g) was hydrogenolyzed in ethanol (5 mL) with Pd–C (0.060 g) under hydrogen (2 atm) for 40 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in acetone (5 mL). To the acetone solution was added Jones reagent (3 mL) dropwise. The mixture was stirred at room temperature for 1 h. The excess oxidant was destroyed with 2-propanol (2 mL) and the mixture was extracted with ether. The organic phase was washed with brine twice, dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by column chromatography to give 0.052 g of compound **11** (77% yield): $[\alpha]^{21}_D = -5.47°$ ($CHCl_3$) [lit.[20] $[\alpha]^{22}_D = +18.6°$ ($CHCl_3$)]. The spectroscopic data of **11** were in agreement with those reported in the literature.[20]

(20) Keinan, E.; Seth, K. S.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474.

Competing [2 + 3] and [4 + 3] Cycloadditions of *C,N*-Diphenylnitrone with 1,3-Dienes. Evidence for Thermally Nonequilibrated Intermediates†

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C,N-Diphenylnitrone (1) reacts with the 1,3-dienes **2a–f** to give the regular 1,3-dipolar cycloaddition products **3a–f** and **4a–f** as well as several other products (**5–8**), which are explained by the intermediacy of diradicals. The tetrahydrooxazepines **5a–d**, which are obtained in 3–21% yield from **1** and the dienes **2a–d**, are the first [4 + 3] cycloadducts obtained in intermolecular reactions of 1,3-dipoles with 1,3-dienes. Two conformational isomers of **5a** are identified by low-temperature NMR spectroscopy. Thermolyses of the compounds **3a,b**, **4a,b**, and **5a,b** were studied in toluene solution. While **4a** isomerizes into **5a** at 100 °C, the stereoisomeric isoxazolidine **3a** undergoes decomposition under these conditions. For the nonmethylated homologues, the relative stability of the [3 + 2] and [4 + 3] cycloadducts is reversed, and **5b** rearranges into **4b** and traces of **3b**. The stereoselectivity of the **4a,b** ⇌ **5a,b** isomerizations is interpreted by the intermediacy of thermally nonequilibrated diradicals.

Introduction

In agreement with the orbital symmetry rules,[1] 1,3-dipoles and 1,3-dienes usually undergo [$_\pi 4_s$ + $_\pi 2_s$] cycloadditions with formation of five-membered ring compounds,[2] and examples for the generation of seven-membered rings are rare.[3] Two years ago, we described the [4 + 3] cycloaddition of *C,N*-diphenylnitrone (**1**) with 1,1,2,2,3,3-hexamethyl-4,5-dimethylenecyclopentane (**2a**), the first example of an intermolecular [4 + 3] cycloaddition of a 1,3-dipole with a 1,3-diene.[4] This reaction was interpreted by the intermediacy of diradicals, and from a kinetic comparison with "normal" dienes, we had concluded that in reactions of **1** with 1,3-dienes, the stepwise mechanism should generally be accessible. We now report that small amounts of [4 + 3] cycloadducts are also formed from nitrone **1** and other 1,3-dienes, and we discuss the mechanistic impact of these observations.

Reaction Products and Structural Assignments

When diphenylnitrone **1** and the dienes **2a–f** were combined in toluene at 80 °C, the compounds **3–8** were produced (Table I). The ^1H and ^{13}C NMR spectra (Table II and Supplementary Material) reveal the regiochemistry of the [3 + 2] cycloadducts **3** and **4**, which are formed by attack of the benzylic carbon of **1** at the CH_2 termini of the 1,3-dienes. Two regioisomers (**3d**,**4d** and **3d′**,**4d′**) are generated from **2d**, which possesses two nonequivalent CH_2 termini, while in all other cases only one pair of diastereoisomeric [3 + 2] cycloadducts (**3** and **4**) with opposite relative configuration at C-3 and C-5 is formed.

In compounds **3a,b** and **4a,b** the stereochemical assignment was based on NOE difference spectroscopy:

† Dedicated to Professor Ch. Rüchardt on the occasion of his 60th birthday.

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(1) Woodward, R. B.; Hoffmann, R. *Angew. Chem.* **1969**, *81*, 797; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(2) (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604, 742; *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565, 633. (b) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984.

(3) Crabb, J. N.; Storr, R. C. In ref 2b, Vol. II, p 545.

(4) Preliminary communication: Baran, J.; Mayr, H. *J. Am. Chem. Soc.* **1987**, *109*, 6519. Experimental details of this investigation will be reported in this article.

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