92623-31-9; **6**, 92623-09-1; **7**, 92623-10-4; **10a**, 92623-11-5; **10a** (bromide), 92623-23-9; **10b**, 92623-12-6; **10b** (bromide), 92623-24-0; **10c**, 92623-13-7; **10c** (bromide), 92623-25-1; D_2, 7782-39-0; T_2, 10028-17-8; $CH_3CH_2NMe_3^+$, 15302-88-2; $CH_3CH_2CH_2NMe_3^+$, 20064-29-3; $CH_3CH(CH_3)CH_2NMe_3^+$, 76965-80-5; $CH_3CH_2NMe_2$, 598-56-1; $CH_3CH_2CH_2NME_2$, 926-63-6; $CH_3CH(CH_3)CH_2NMe_2$, 7239-24-9; sodium 1-butoxide, 2372-45-4; ethanol-*1,1-d*$_2$, 1859-09-2; propionitrile-α,α-d_2, 24300-23-0; 1-propylamine-*2,2-d*$_2$, 24300-24-1; *N*-1-propyl-*2,2-d*$_2$-isobutyramide, 92623-14-8; isobutyl-1-propyl-*2,2-d*$_2$-amine, 92623-15-9; isobutyl-1-propyl-*2,2-d*$_2$-dimethylammonium iodide, 92623-16-0; 2-propanol-*2-d*, 3972-26-7; 2-bromopropane-2-*d*, 4067-80-5; 2-methylpropanoic-*2-d* acid, 19136-93-7; *N*-propyl-2-methylpropanamide-*2-d*, 92623-17-1; (2-methyl-1-propyl-*2-d*)-1-propyldimethylammonium iodide, 92623-18-2; ethanol-*1-t*, 13326-02-8; 1-propanol-1-*t*, 3820-19-7; 2-methyl-1-propanol-*1-t*, 92623-19-3; ethyl-*1-t* bromide, 92623-20-6; 1-propyl-*1-t* bromide, 92623-21-7; 2-methyl-1-propyl-*1-t* bromide, 92623-22-8; acetyl chloride, 75-36-5; ethanol-*1,1-d*$_2$ tosylate, 60835-92-9; isobutyryl chloride, 79-30-1; 2-methylpropanoyl-*2-d* chloride, 92623-26-2; acetic-d_4 acid, 1186-52-3; ethanol-*2,2,2-d*$_3$, 1759-87-1; ethanol-*2,2,2-d*$_3$ tosylate, 24344-87-4; ethyl-*2,2,2-d*$_3$ iodide, 7439-87-4; propionyl chloride, 79-03-8; ethyl-*2,2,2-d*$_3$-1-propyldimethylammonium iodide, 92623-27-3; methyl 1-butyl ether, 628-28-4; acetone, 67-64-1.

Asymmetric Synthesis via Acetal Templates. 10. [1] Aldol-Type Reactions. Preparation of a Nonactic Acid Intermediate

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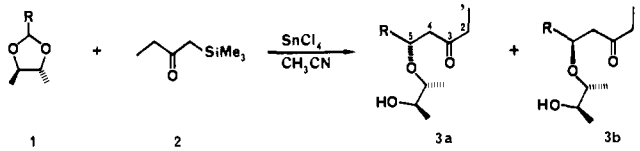
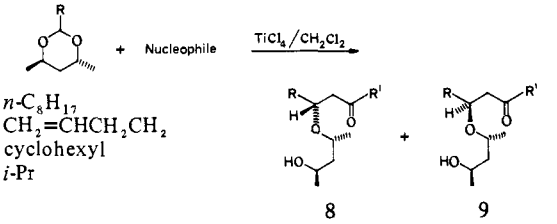
Abstract: A procedure has been developed for the coupling of acetals **4–7** derived from (*R,R*)-2,4-pentanediol with α-silyl ketones or enol silyl ethers to give aldol ethers **8/9** in excellent yield and high diastereoselectivity, **8:9** = >95:5. This methodology has been applied to a total asymmetric synthesis of (2*S*,4*R*)-2,4-dihydroxyoct-7-ene, a key intermediate in the Bartlett synthesis of nonactic acid.

McNamara and Kishi[2] were the first to disclose the use of chiral acetals in aldol-type reactions.[3] Thus for the coupling **1** + **2**, the diastereoselectivity of **3a**:**3b** was excellent (91:9–94:6) with aromatic acetals **1** (R = aryl), while it was lower (50:50–76:24) with aliphatic acetals. The absolute configuration of the major aldol products **3a** was the same as that observed by us for a variety of asymmetric acetal coupling reactions.[1,4]



The present paper includes an account of some of our work in this area which differs from the Harvard study[2] in that excellent diastereoselectivity (>95:5) can now be realized with aliphatic acetals. We have used six-membered ring acetals derived from 2,4-pentanediol which affords the advantage of being readily available in the *S,S* as well as the *R,R* forms.[5] These acetals have already been shown to react highly diastereoselectively with a variety of nucleophilic partners to give products from which the chiral auxiliary is easily removed.[1,4] Some of our studies of the $TiCl_4$-catalyzed aldol reaction are summarized in Table I.

Table I. Aldol Coupling of Chiral Acetals



4, R = *n*-C_8H_{17}
5, R = CH_2=$CHCH_2CH_2$
6, R = cyclohexyl
7, R = *i*-Pr

8 9

a, R = *n*-C_8H_{17}; R′ = Me
b, R = *n*-C_8H_{17}; R′ = *t*-Bu
c, R = CH_2=$CHCH_2CH_2$; R′ = Me
d, R = cyclohexyl; R′ = Me
e, R = *i*-Pr; R′ = Et
f, R = *n*-C_8H_{17}; R′ = Et

entry	acetal[4a,b,6]	nucleophile[7,8]	% yield[9]	product[10]	ratio[11]
1	**4**	$CH_3COCH_2SiMe_3$ (**10**)	92	**8a**/**9a**	97:3
2	**5**	$CH_3COCH_2SiMe_3$	93	**8c**/**9c**	97:3
3	**6**	$CH_3COCH_2SiMe_3$	93	**8d**/**9d**	98:2
4	**5**	CH_2=$C(OSiMe_3)Me$	89	**8c**/**9c**	97:3
5	**7**[10]	**2**	48	**8e**/**9e**	95:5
6	**7**	CH_2=$C(OSiMe_3)Et$	84	**8e**/**9e**	96:4
7	**4**	CH_2=$C(OSiMe_3)Et$	95	**8f**/**9f**	97:3
8	**4**	CH_2=$C(OSiMe_3)$-*t*-Bu	96	**8b**/**9b**	96:4

After extensive experimentation a procedure has been developed for obtaining excellent results using enol silyl ethers as the nucleophile (entries 4 and 6–8). Trimethylsilylacetone (**10**) is just as effective in the condensations (entries 1–3) as the enol silyl ether of acetone (entry 4), and it is easier to prepare, handle, and store. No attempt was made to optimize the yield of the coupling with trimethylsilylbutanone (entry 5), which is a slower process than with the corresponding enol silyl ether (entry 6). Use of the latter

(1) Paper 9. Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, 3951–3954.

(2) (a) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371–7372. (b) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372–7374.

(3) The $TiCl_4$-catalyzed aldol reaction of achiral acetals is well-known. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817–826.

(4) (a) Bartlett, P. A.; Johnson, W. S.; Elliott; J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088–2089. (b) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904–2905. (c) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294–2295. (d) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1974**, *106*, 1138–1139. (e) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591–594. (f) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, 3947–3950.

(5) Both enantiomeric forms of 2,4-pentanediol are readily available through asymmetric hydrogenation of acetylacetone. See: Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367–3368.

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isomer is preferred, and it is easily prepared regiospecifically by isomerization of **2** with HgI_2.[8] Isopropenyl acetate is a less reactive nucleophile than trimethylsilylacetone requiring more strenuous conditions and resulting in poorer selectivity; e.g., in the condensation with **5**, the ratio **8c/9c** was 88;12.

The diastereoselectivity and yield can be significantly affected by procedural changes, i.e., time, temperature, concentrations of reagents, and even the order of addition of reagents; thus in the reaction of entry 6, when the enol ether was added slowly to a solution of acetal **4** and $TiCl_4$ (instead of the reverse), the ratio of **8e/9e** dropped to 90:10. Obtaining attenuated diastereoselection in this way, or by using isopropenyl acetate (see above), however, does have the advantage of affording access to products sufficient in the minor isomer **9** so that it can be unequivocally identified in the mixture by 300-MHz ^1H NMR.

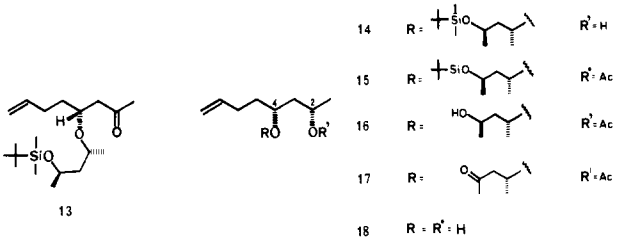
The coupling reaction shown in entry 5 (Table I) represents the direct counterpart of the reported example, i.e., **1** (R = *i*-Pr) + **2** → **3a/3b**.[2] The diastereoselectivity in our system (95:5) represents a marked improvement over the reported (50:50)[2] value. Using the enol silyl ether in place of **2**, moreover, gives even better results (entry 6, Table I), particularly with respect to the yield.

The coupling products in most cases do not lend themselves to direct removal of the chiral auxiliary without destruction of the aldol product by β-elimination. As shown below, however, the chiral auxiliary can be removed after reduction of the carbonyl group, and this expedient can be deployed for preparation of intermediates that are comparable to the aldols in synthetic utility. In the case of the coupling product **8b/9b** (entry 8), the reaction sequence, i.e., oxidation (PCC) to give the diketone **11**[9,10] followed by β-elimination (0.5 M piperidinium acetate in C_6H_6, reflux 8 h), afforded the free aldol **12**[9,10] in 90% overall yield. The stability

11 **12**

of **12** to piperidinium acetate is suggestive of involvement of an enamine (readily produced from the methyl ketone) in the mechanism of β-elimination.

The aldol product **8c/9c** (entry 2) was made with the aim of using it to synthesize the diol **18**, which is an intermediate for Bartlett's elegant synthesis of nonactic acid[12] —the basic unit of the ionophore nonactin. Substance **8c** was readily obtained free of the contaminant **9c** by conversion of the mixture to the *tert*-butyldimethylsilyl ethers followed by a single-pass HPLC (Du Pont Zorbax SIL, 4:1, hexane/EtOAc). Pure **13**,[10] thus obtained in 93% yield, was reduced (L-Selectride, THF, −78 °C, 4 h) to give in 95% yield a 4:1[11] mixture[9,10] of syn (**14**) and anti (2-*epi*-**14**) isomers. This mixture was converted (Ac_2O, Pyr, DMAP, 25



13

14 R = R' = H

15 R = R' = Ac

16 R = R' = Ac

17 R = R' = Ac

18 R = R' = H

°C, 2 h) to the corresponding acetate[10] **15** + 2-*epi*-**15** (99% yield). Desilylation (*n*-Bu_4NF, THF, 25 °C, 8 h) afforded the hydroxy acetate[9,10] **16** + 2-*epi*-**16** (91% yield), which was oxidized[4a] (PCC) to the keto acetate[9,10] **17** + 2-*epi*-**17** (98% yield). Base treatment[4a] to effect β-elimination and deacetylation gave the mixture of diols **18** + 2-epi-**18**, which was cleanly separated by chromatography[9] to give **18**[10a] (75% yield). Substance **18** was identical (^1H NMR, IR, GC coinjection) with authentic 2*R*,4*S* diol (enantio-**18**).[13] The $[\alpha]^{25}_D$ (CCl_4) for **18** was +18.4° (*c* 1) and for enantio-**18**[13] was -18.3° (*c* 0.75). It should be noted that both enantiomeric forms of nonactic acid are components of nonactin, and that our asymmetric synthesis of Bartlett's diol also lends itself to the preparation of enantio-**18** by use of the *S*,*S*-chiral auxiliary. Thus the aldol reaction of **5** was shown to proceed so as to develop the *R* configuration at the newly formed chiral center in **8c**, a consequence that is entirely consistent with the stereochemical course of related processes as predicted by theory[4e] as well as established by experiment.[1,2,4] Similarly the absolute configuration of **8d** was confirmed by its preparation via ozonolysis of the known olefinic alcohol (**8d**, CH_2= in place of O=).[1] Accordingly the other aldol reactions may be presumed, with considerable certainty, to proceed in the same stereochemical sense, as indicated by the formulas (Table I).

Experimental Section

Acetals 4-7. Compounds **4–7** were prepared from the corresponding aldehyde and 2(*R*),4(*R*)-pentane-2,4-diol[6] in the presence of a catalytic quantity of *p*-toluenesulfonic acid.

(4*R*,6*R*)-4,6-Dimethyl-2-octyl-1,3-dioxan (4). $[\alpha]^{25}_D$ +22° (*c* 1.4, CCl_4); ^1H NMR 0.8–2.1 (m, 25, 3 × CH_3 and 8 × CH_2), 3.62–4.58 (m, 2, 2 × CHO), 4.87 (t, *J* = 4 Hz, 1, OCHO).

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found, C, 73.68; H, 12.29.

(4*R*,6*R*)-2-(But-3′-en-1-yl)-4,6-dimethyl-1,3-dioxan (5). $[\alpha]^{25}_D$ +26° (*c*, 1.1, CCl_4); IR (film), 3085, 1640, 940 cm^{-1} (C=CH_2); ^1H NMR 1.1–2.3 (m, 12, 2d at 1.2 and 1.34, *J* = 6, 7 Hz, respectively, 2 × CH_3 superimposed upon m, 3 × CH_2), 3.75–4.55 (m, 2, 2 × CHO), 4.8–6.05 (m, 4, t at 4.85, *J* = 5 Hz, OCHO, superimposed upon m, CH=CH_2).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.47.

(4*R*,6*R*)-2-Cyclohexyl-4,6-dimethyl-1,3-dioxan (6). $[\alpha]^{25}_D$ +25° (*c* 0.5, CCl_4); ^1H NMR 0.9–2.00 (m, 19, 2d at 1.20 and 1.30, each, *J* = 7 Hz, 2 × CH_3, superimposed upon m, 6 × CH_2, CH), 3.70–4.45 (m, 2, 2 × CHO), 4.55 (d, *J* = 6 Hz, 1, OCHO).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found: C, 72.49; H, 11.38.

(4*R*,6*R*)-4,6-Dimethyl-2-(2′-propyl)-1,3-dioxan (7). ^1H NMR 0.91 (d, *J* = 6.8 Hz, 6, CH_3CHCH_3), 1.19 (d, *J* = 6.2 Hz, 3, CH_3), 1.33 (d, *J* = 6.9 Hz, 3, CH_3), 1.55–1.96 (m, 3, CH_3CHCH_3 and $CHCH_2CH$), 3.75–4.05 (m, 1, CH_3CHO), 4.07–4.42 (m, 1, CH_3CHO), 4.51 (d, *J* = 5.2 Hz, 1, OCHO).

Coupling of Acetal 4 with 1-(Trimethylsilyl)propan-2-one. A solution of freshly distilled titanium tetrachloride (0.135 mL, 1.23 mmol) in dichloromethane (1.6 mL) was instilled via motorized syringe over 35 min into a stirred, cooled (−40 °C) solution of acetal **4** (0.093 g, 0.41 mmol) and 1-(trimethylsilyl)propan-2-one[7] (0.35 mL, 2.0 mmol) in dichloromethane (7.7 mL) under argon. After an additional 25 min, 1:1 methanol/dichloromethane (1.5 mL) was added dropwise (1 min) at −40 °C; then the mixture was poured rapidly into water (30 mL) and shaken with ether (30 mL). The aqueous layer was saturated with sodium chloride and extracted with two 35-mL portions of ether. The combined extracts were dried (anhydrous magnesium sulfate), filtered, and evaporated.

(6) The 2(*R*),4(*R*)-pentanediol employed for producing these acetals was obtained from the Aldrich Chemical Co. and shown, by GC analysis of the MTPA esters, to be of ee 97.5% (see footnote 6 of ref 1).

(7) The trimethylsilyl ketones were prepared according to: Hauser, C. R.; Hance, C. R. *J. Am. Chem. Soc.* **1952**, *74*, 5091–5096. See also: Musker, W. K.; Ashby, R. W. *J. Org. Chem.* **1966**, *31*, 4237–4239.

(8) The enol silyl ethers of acetone and butanone were prepared by isomerization (HgI_2, 40–45 °C) of the silyl ketones (see ref 7) according to: Lutsenko, I. F.; Baukov, Yu. I.; Dudukina, O. V.; Kramarova, E. N. *J. Organomet Chem.* **1968**, *11*, 35–48. The enol silyl ether of pinacolone was prepared according to: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.

(9) The product was purified by low-pressure column chromatography using "Merck silica gel 60 H for thin-layer chromatography".

(10) (a) ^1H NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(11) The diastereomeric ratio was determined by GC on a 15-m SE-54 capillary column, which showed a base line separation of the two peaks. In the case of **8a/9a** it was necessary to prepare the *tert*-butyl dimethylsilyl ether[14] to obtain a base line resolution. For **8b/9b**, **8d/9d**, and **8f/9f** base line resolution was observed only after oxidation (PCC) to the corresponding diketone mixtures.

(12) Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, *21*, 1607–1610.

(13) Obtained by saponification of the corresponding cyclic carbonate which was in turn prepared from (*S*)-(−)-malic acid by a stereorational synthesis. Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304–5311.

Column chromatography[9] (gradient elution, 0–40% ether/*n*-hexane gave **(4*RS*,1′*R*,3′*R*)-4-(3′-hydroxy-1′-methylbutoxy)dodecan-2-one (8a/9a)** as a colorless oil (0.107 g, 92% yield).

IR (film) 3440 (OH), 1715 cm^{-1} (C=O); ^1H NMR 0.88 (t, J = 7 Hz, 3, CH_3CH_2), 1.14 (d, J = 6 Hz, 3, CH_3CH), 1.17 (d, J = 6 Hz, 3, CH_3CH), 1.22–1.70 (m, 16, 8 × CH_2), 2.17 (s, 3, CH_3C=O), 2.43 (ABq, J = 13, 4.5 Hz, 1, CHHC=O), 2.66 (ABq, J = 13, 7 Hz, 1, CHHC=O), 2.85–2.95 (br s, 1, OH), 3.80–3.95 (m, 2, 2 × CHO), 4.02–4.15 (m, 1, CHO).

Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 71.42; H, 11.75.

A crude sample of **8a/9a** prepared as detailed above was quantitatively converted to the mixture of *tert*-butyldimethylsilyl ethers by the procedure of Corey.[14]

GC (170 °C) showed two peaks, ratio 97:3.

Coupling of Acetal 4 with 3,3-Dimethyl-2-[(trimethylsilyl)oxy]but-1-ene. By the same coupling procedure used to prepare **8a/9a**, the acetal **4** (0.044 g, 0.19 mmol) and 3,3-dimethyl-2-[(trimethylsilyl)oxy]but-1-ene[8] gave **8b/9b**. Column chromatography[9] (gradient elution, 0–20% ether/*n*-hexane) provided **(5*RS*,1′*R*,3′*R*)-2,2-dimethyl-5-(3′-hydroxy-1′-methylbutoxy)tridecan-3-one (8b/9b)** as a colorless solid (0.061 g, 96% yield).

IR (film) 3460 (OH), 1705 cm^{-1} (C=O); ^1H NMR 0.87 (t, J = 6 Hz, 3, CH_3CH_2), 1.11 (s, 9, $(CH_3)_3C$), 1.12 (d, J = 6 Hz, 3, CH_3CH), 1.16 (d, J = 6 Hz, 3, CH_3CH), 1.19–1.37 (m, 12, 6 × CH_2), 1.47–1.64 (m, 4, CH_2CH_2CHO and $OCHCH_2CHO$), 2.38 (ABq, J = 17, 5 Hz, 1, CHHC=O), 2.81 ABq, J = 17, 7 Hz, CHHC=O), 3.04 (d, J = 3 Hz, 1, OH), 3.72–4.26 (m, 3, 3 × CHO).

Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.34; H, 12.07.

GC of **8b/9b** failed to show a base-line separation of diastereoisomers, accordingly a sample of crude **8b/9b**, prepared as detailed above, was oxidized quantitatively by the method of Corey[15] using PCC. GC of crude diketone product (170 °C) showed two peaks, ratio 96:4.

Column chromatography[9] (gradient elution, 0–20% ether/pentane) provided **(5*RS*,1′*R*)-2,2-dimethyl-5-(1′-methyl-3′-oxobutoxy)tridecan-3-one (11)** (0.069 g, 100% yield). IR (film) 1705 cm^{-1} (C=O); ^1H NMR 0.86 (t, J = 7 Hz, 3, CH_3CH_2), 1.07 (d, J = 6 Hz, 3, $CHCH_3$), 1.10 (s, 9, $(CH_3)_3C$), 1.25 (br s, 12, $CH_3(CH_2)_6$), 1.3–1.5 (m, 2, CH_2CH_2CHO), 2.13 (s, 3, CH_3C=O), 2.20–2.86 (m, 4, 2 × CH_2C=O), 3.75–3.99 (m, 2, 2 × CHO).

Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.64; H, 11.56.

Preparation of (5*R*)-2,2-Dimethyl-5-hydroxytridecan-3-one (12). The diastereoisomeric mixture (96:4) of diketones **11** (0.044 g, 0.13 mmol) and a 0.5 M benzene solution of piperidinium acetate (2.35 ml, 1.18 mmol) were refluxed for 2 h then left to stir at ambient temperature overnight. Column chromatography[9] (gradient elution, 0–10% ether/hexane) gave the title compound **12** as a pale yellow oil (0.029 g, 90% yield).

$[\alpha]^{20}_D$ −34° (*c* 0.78, CCl_4); IR (film) 3405 (OH), 1705 cm^{-1} (C=O); ^1H NMR 0.88 (br t, J = 6 Hz, 3, CH_3CH_2), 1.15 (s, 9, $(CH_3)_3C$), 1.18–1.46 (br s, 15, 7 × CH_2 and OH), 2.54 (ABq, J = 18, 8 Hz, 1, CHHC=O), 2.65 (ABq, J = 18, 3.5 Hz, 1, CHHC=O), 3.87–4.07 (m, 1, CHOH).

The optical purity of **12** was confirmed by conversion to the diastereoisomeric mixture of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters.[16] ^1H NMR showed two clearly separated resonances due to the methoxy group in the pair of diastereomers (closely spaced multiplets at δ 3.54 and 3.49), ratio (by integration) 96:4. The identity of the methoxy resonance due to the minor diastereomer was established from the ^1H NMR of the (+)-MTPA ester of (±)-**12** (prepared by coupling nonaldehyde with 3,3-dimethyl-2-[(trimethylsilyl)oxy]but-1-ene in a manner similar to that used to obtain **8a/9a**).

Coupling of Acetal 5 with 2-[(trimethylsilyl)oxy]propene. By the same coupling procedure used to obtain **8a/9a**, acetal **5** (0.111 g, 0.65 mmol) and 2-[(trimethylsilyl)oxy]propene[8] (0.435 g, 3.26 mmol) gave **8c/9c**. GC (100 °C) showed two peaks, ratio 97:3. Column chromatography[9] (gradient elution, 0–55% ether/*n*-hexane) gave **(4*RS*,1′*R*,3′*R*)-4-(3′-hydroxy-1′-methylbutoxy)oct-7-en-2-one (8c/9c)** as a colorless oil (0.132 g, 89% yield).

IR (film) 3440 (OH), 1715 cm^{-1} (C=O); ^1H NMR 1.14 (d, J = 6.7 Hz, 3, CH_3CH), 1.17 (d, J = 6.6 Hz, 3, CH_3CH), 1.45–1.75 (m, 4, CH_2CH_2), 1.95–2.3 (m, 2, $OCHCH_2CHO$) 2.16 (s, 3, CH_3C=O), 2.3–2.8 (m, 2, CH_2C=O), 3.65–4.25 (m, 4, 3 × CHO and OH), 4.9–5.15 (m, 2, CH_2=CH), 5.6–6.0 (m, 1, CH_2=CH). An identical diastereomeric ratio (i.e., 97:3) was observed when 1-(trimethylsilyl)-propan-2-one[7] (**10**) was used in place of 2-[(trimethylsilyl)oxy]propane[8] to obtain **8c/9c** (see entry 2, Table *I*).

Coupling of Acetal 6 with 1-(Trimethysilyl)propan-2-one (10). By the same coupling procedure used to prepare **8a/9a**, acetal **6** (0.0565 g, 0.29 mmol) and 1-(trimethylsilyl)propan-2-one[7] **10** (0.190 g, 1.43 mmol) gave **8d/9d**. Column chromatography[9] (gradient elution, 10–55% ether/*n*-hexane) afforded **8d/9d** as a colorless oil which solidified on standing (0.068 g, 93% yield).

IR (film) 3430 (OH), 1710 cm^{-1} (C=O); ^1H NMR 0.9–1.8 (2d, each J = 6 Hz, superimposed upon m, 19, 2 × CH_3, 6 × CH_2,CH), 2.17 (s, 3, CH_3CO), 2.38 (ABq, J = 15, 4 Hz, 1, CHHC=O), 2.59 (ABq, J = 15, 8.5 Hz, 1 CHHC=O), 2.98–3.08 (br s, 1, OH), 3.70–3.90 (m, 2, 2 × CHO), 4.03–4.17 (m, 1, CHO).

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.15; H, 10.88.

GC (150 °C) of the corresponding diketones (prepared by oxidation of a crude sample of **8d/9d** quantitatively with PCC[15]) showed two peaks, ratio 98:2.

Coupling of Acetal (7) with 2-[(Trimethylsilyl)oxy]but-1-ene. A modification of the procedure used to prepare **8a/9a** was employed in which the solution of titanium tetrachloride in dichloromethane was added over a period of 1 h and the resulting mixture stirred at −40 °C for a further 1 h before workup. Care was then excercised during the extraction procedure due to the water solubility of the product.

Thus acetal **7** (0.046 g, 0.029 mmol) and 2-[(trimethylsilyl)oxy]but-1-ene[8] (0.27 mL, 1.46 mmol) gave **8e/9e**. GC (130 °C) two peaks, ratio 96:4.

Column chromatography[9] (gradient elution, 0–35% ether/*n*-hexane) provided **(3*RS*,1′*R*,3′*R*)-3-(3′-hydroxy-1′-methylbutoxy)-2-methylheptan-5-one (8e/9e)** as a colorless oil (0.0565 g, 84% yield).

IR (film) 3440 (OH), 1710 cm^{-1} (C=O); ^1H NMR 0.87 (d, J = 7 Hz, 3, CH_3CHCH_3), 0.91 (d, J = 7 Hz, 3, CH_3CHCH_3), 1.04 (t, J = 7 Hz, 3, CH_3CH_2), 1.10 (d, J = 6 Hz, 3, CH_3CHO), 1.17 (d, J = 6 Hz, 3, CH_3CHO), 1.48–1.64 (m, 2, $CHCH_2CH$), 1.88–2.01 (m, 1, CH_3CHCH_3), 2.29 (ABq, J = 15.4, 3.4 Hz, 1, CHHC=O), 2.47 (q, J = 7 Hz, 2, CH_3CH_2), 2.54 (ABq, J = 15.4, 6.6 Hz, 1, CHHC=O), 2.97 (d, J = 3 Hz, 1, OH), 3.77–3.85 (m, 2, 2 × CHO), 4.05–4.17 (m, 1, CHO).

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.77; H, 11.19.

Coupling of Acetal 4 with 2-[(Trimethylsilyl)oxy]but-1-ene. By the same coupling procedure used to prepare **8a/9a**, acetal **4** (0.104 g, 0.46 mmol) and 2-[(trimethylsilyl)oxy]but-1-ene[8] (0.43 mL, 2.28 mmol) provided **8f/9f**. Column chromatography[9] (gradient elution, 5–25% ether/*n*-hexane) gave **(5*RS*,1′*R*,3′*R*)-5-(3′-hydroxy-1′-methylbutoxy)-tridecan-3-one (8f/9f)** as a colorless oil (0.13 g, 95% yield).

IR (film) 3450 (OH), 1710 cm^{-1} (C=O); ^1H NMR 0.88 (t, J = 6 Hz, 3, CH_3CH_2), 1.04 (t, J = 7 Hz, 3, CH_3CH_2C=O), 1.12 (d, J = 6 Hz, 3, CH_3CHO), 1.17 (d, J = 6 Hz, 3, CH_3CHO), 1.22–1.70 (m, 16, 8 × CH_2), 2.37–2.65 (m, 4, CH_2COCH_2), 2.85–3.05 (br s, 1, OH), 3.78–3.93 (m, 2, 2 × CHO), 4.02–4.13 (m, 1, CHO).

Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.96; H, 11.86.

A crude sample of **8f/9f** prepared as detailed above was quantitatively oxidized using PCC.[15] GC (150 °C) of the corresponding diketones, thus obtained, showed two peaks, ratio 97:3.

(4*R*,1′*R*,3′*R*)-4-(3′-[(*tert*-Butyldimethylsilyl)oxy]-1′-methylbutoxy)-oct-7-en-2-one (13). The coupling product **8c/9c** (0.44 g, 0.19 mmol) was converted to the *tert*-butyldimethylsilyl ether **13** according to the procedure of Corey.[14] Single-pass HPLC (eluant 4:1 *n*-hexane/ethyl acetate) provided diastereoisomerically pure **13** (0.061 g, 93% yield).

IR (film) 1720 cm^{-1} (C=O); ^1H NMR 0.04 (s, 6, $Si(CH_3)_2$), 0.86 (s, 9, $(CH_3)_3C$), 1.06 (d, J = 6 Hz, 3, CH_3CH), 1.11 (d, J = 6 Hz, 3, CH_3CH), 1.42–1.69 (m, 4, CH_2CH_2), 2.03–2.12 (m, 2, $OCHCH_2CHO$), 2.15 (s, 3, CH_3C=O), 2.46 (ABq, J = 15, 5 Hz, 1, CHHC=O), 2.62 (ABq, J = 15, 7 Hz, 1, CHHC=O), 3.5–3.61 (m, 1, CHO), 3.78–3.96 (m, 2, 2 × CHO), 4.93–5.06 (m, 2, CH_2=CH), 5.71–5.87 (m, 1, CH_2CH).

Anal. Calcd for $C_{19}H_{38}SiO_3$: C, 66.61; H, 11.18. Found: C, 66.88; H, 10.95.

(2*RS*,4*R*,1′*R*,3′*R*)-4-(3′-[(*tert*-Butyldimethylsilyl)oxy]-1′-methylbutoxy)oct-7-en-2-ol (14). To a vigorously stirred solution of **13** (0.174 g, 0.51 mmol) in dry THF (170 ml) at −78 °C under argon was added L-Selectride (1 M in THF; 1.27 mL, 1.27 mmol) dropwise (5 min).[17]

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After 4 h at −78 °C the mixture was warmed rapidly to ambient temperature, quenched cautiously with water, and stirred for a further 10 min. The THF was evaporated and the product extracted into ether. The ether extract was dried (anhydrous magnesium sulfate), filtered, and evaporated to give a colorless oil. Column chromatography[9] (gradient elution, 0–30%, ether/*n*-pentane) gave the title product, **14**, as a colorless oil (0.167 g, 95% yield).

GC (150 °C) showed two peaks, ratio 4:1. The ^{1}H NMR spectra of **14–17** were consistent with the assigned structures but were complex due to the fact that these intermediates were 4:1 mixtures of diastereoisomers at C-2.

Anal. Calcd. for $C_{19}H_{40}SiO_3$: C, 66.22, H, 11.70. Found: C, 65.94; H, 11.64.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(3′-[(*tert*-butyldimethylsilyl)oxy]-1′-methylbut-1′-oxy)oct-7-ene (15). A sample of the crude acetylation product was purified by column chromatography[9] (gradient elution, 0–20% ether/*n*-pentane) to give **15** as a colorless oil.

Anal. Calcd for $C_{21}H_{42}SiO_4$: C, 65.24; H, 10.95. Found: C, 65.35; H, 10.66.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(3′-hydroxy-1′-methylbutoxy)oct-7-ene (16). The crude desilylation product was purified by column chromatography[9] (gradient elution, 0–30% ether/*n*-pentane) to give **16** as a colorless oil.

Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.29; H, 10.27.

(2*RS*,4*R*,1′*R*,3′*R*)-2-Acetoxy-4-(1′-methyl-3′-oxobutoxy)oct-7-ene (17). The crude oxidation product was purified by column chromatography[9] (gradient elution, 0–30% ether/*n*-pentane) to give **17** as a colorless oil.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.49; H, 9.58.

(2*RS*,4*R*)-2,4-Dihydroxyoct-7-ene (18). Column chromatography[9] of the crude product of base treatment of **17**[4a] (gradient elution, 10–70% ether/*n*-pentane) gave (2*S*,4*R*)-**18** (75% yield) and (2*R*,4*R*)-**18** (19% yield). (2*S*,4*R*)-**18** was a pale yellow oil with the following characteristics:

$[\alpha]^{25}_D$ +18.4 (*c* 1.0, CCl_4); IR (film) 3350 (OH), 1640, 910 cm^{-1} (CH_2=CH). ^{1}H NMR 1.19 (d, *J* = 6.2 Hz, 3, CH_3CH), 1.39–1.66 (m, 4, CH_2CH_2), 2.04–2.24 (m, 2, OCHCH_2CHO), 3.19 (br s, 2, 2 × OH), 3.83–3.91 (m, 1, CHO), 3.98–4.08 (m, 1, CHO), 4.96 (ddt, *J* = 10.2, 1.9, 1.2 Hz, 1, H_EH_ZC=CHCH$_2$), 5.03 (dq, *J* = 17.1, 1.9 Hz, 1, H_EH_ZC=CHCH$_2$), 5.75–5.88 (m, 1, CH$_2$=C*H*).

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. We also thank Professor P. A. Bartlett for supplying us with a specimen of the cyclic carbonate of the 2(*R*),4(*S*)-diol (enantio-**18**).[13]

Evidence for a Single Transition State in the Transfer of the Phosphoryl Group ($-PO_3^{2-}$) to Nitrogen Nucleophiles from Pyridino-*N*-phosphonates[1a]

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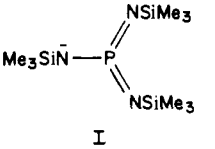
Received April 17, 1984

Abstract: The reaction of pyridinio-*N*-phosphonates with pyridines in aqueous buffers has been demonstrated to involve nucleophilic attack at phosphorus. The second-order rate constants obey the equation log k_{xpy} = 0.15pK_{xpy} − 0.86 for attack on isoquinolinio-*N*-phosphonate over a wide range of pyridine basicity indicating a *single* transition state; this is consistent with a concerted transfer of the phosphoryl group rather than with a stepwise mechanism involving metaphosphate ion in a ternary encounter complex with donor and acceptor. Transfer of the phosphoryl group to pyridine from substituted pyridinio-*N*-phosphonates obeys the equation log k = −0.92pK_{xpy} + 5.24 and leads to a β_{eq} of 1.07 for substituent effect on the equilibrium constant for transfer. The effective charge at nitrogen, in the transition state, indicated by these values favors weak P–N bonding. An imbalance of −0.77 effective charge units between entering and leaving nitrogen in the transition state is proposed to derive from the charge on the PO_3 atoms, which therefore do not bear a full negative charge in the transition state. Transfer of the phosphoryl group from isoquinolinio-*N*-phosphonate to amines has been investigated kinetically, and the results are also consistent with weak bonding between phosphorus and nitrogen in the transition state.

The existence of unsaturated, metaphosphate-like, intermediates has been established for many phosphyl-transfer reactions.[1b–k]

The isolation and characterization of such intermediates are not so far advanced, and we know of only two well-characterized compounds: a nitrogen (I)[2] and a sulfur (II)[3] analogue of monomeric metaphosphate. The transfer of the phosphoryl group ($-PO_3^{2-}$)[4] between nucleophiles has been studied recently for enzyme and model systems using stereochemical probes.[5] Single phosphoryl transfers, such as from donor to enzyme or donor to acceptor,[6] have been found in all cases to exhibit inversion at the phosphorus. It is possible that in the enzyme reactions a meta-



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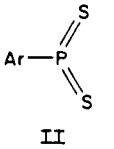

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