of N-fluoropyridinium salts. Thus, contrary to unsubstituted salt 1, 2,4,6-trimethyl salt 2 failed to produce any  $9\alpha$ -fluoro steroid 74 from 73. The bulkiness of 2 appears quite likely the reason for this. Thus, 2 was unable to approach the crowded 9-position.

Stereoselectivity also remarkably varied according to the structure of N-fluoropyridinium salts. As shown in Table X, 1 reacted with steroid 57 to give a 1:2 mixture of  $6\alpha$ - and  $6\beta$ -isomeric steroids, and bulky 2 or 7 almost exclusively gave the  $6\beta$ -isomer, possibly as a result of the fluorination at the less hindered  $\beta$ -side. Stereoselective fluorination regulated by structural variation should thus find useful application.

The fluorination yields of enamines 59a-c showed considerable variation according to the electronic nature of the amine part. The  $pK_a$  values of enamines of isobutyraldehyde have been shown to increase in the order of morpholino  $(pK_a 5.47)$ , piperidino (8.35), and pyrrolidino (8.84).44 Steroid enamines should show essentially the same order. Consistent with this, the least basic morpholino steroid 59a afforded the best yield of fluorinated product 75, while the most basic pyrrolidino 59c gave the lowest yield and large amounts of unidentified products. The milder N-fluoropyridinium salt 2 gave better yields.

A comparison was made of the regioselectivity in the 4- and 6-fluorinations of steroids with salt 1 among enamines 59, vinyl ester 57, enol alkyl ether 56, and enol silyl ether 58. The most electron-deficient 57 produced 6-fluoro steroids exclusively, while

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the most electron-rich 59 gave only the 4-fluoro steroid. Intermediate electron-rich 58 and 56 yielded ca. 1:2 and 1:1 mixtures of 4- and 6-isomers, respectively. Similar regioselectivity has been found in fluorination with CF<sub>3</sub>OF<sup>45</sup> or FClO<sub>3</sub>.<sup>46</sup> Differences in electron distribution in the conjugated diene moiety of the substrates themselves rather than the nature of N-fluoropyridinium salt 1 may thus be the reason for this regioselectivity.

## Conclusions

N-Fluoropyridinium salts provide a new system of fluorinating agents by which a wide range of nucleophilic substrates differing in reactivity can be fluorinated due to the varying degree of fluorinating power and also fluorinated very selectively through structural alteration. The scope of selective fluorination should be broadened considerably on the basis of the present results. The N-fluoropyridinium salt system should thus make possible the preparation of many useful organofluoro compounds.

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## Communications to the Editor

## New Synthetic Route to Unsymmetrically Substituted Pentacoordinated Phosphorus. Hydrolytically Stable **Chiral Monocyclic Oxyphosphoranes**

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Pentacoordinated phosphorus (phosphoranes) are of interest as models for the intermediate or transition state for phosphoryl transfer occurring in the hydrolysis of phosphates and phosphonates.<sup>1a-d</sup> Such intermediates have been proposed for an increasing number of reactions catalyzed by phosphoryl- and nucleotidyl-transfer enzymes.<sup>1c,2</sup> Monocyclic oxyphosphoranes represent an important stable model system for such intermediates. The stereochemical course of phosphoryl-transfer reactions has been discussed in terms of structure, stereochemistry, and pseudorotational processes observed for model phosphoranes.1b However, the monocyclic phosphoranes synthesized to date are invariably "symmetric" phosphoranes in the sense that at least two or three identical alkoxy substituents are bound to phosphorus. The proposed intermediates or transition states in phosphoryltransfer reactions frequently involve "unsymmetric" oxyScheme I<sup>4</sup>



<sup>e</sup>Reagents and conditions: (i) 1H-tetrazole (5 mol %), dry CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 40 h; (ii) dry CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h; (iii) ROH (1 equiv), dry CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, overnight.

phosphoranes possessing five different substituents bound to phosphorus. No general synthetic method for such unsymmetric phosphoranes has been reported.

We now describe a novel synthetic route to the unsymmetric methylphosphoranes la-e having one l-menthoxy group and various other alkoxy groups bound to phosphorus. The key synthetic step in this process is the direct displacement of the N,N-diisopropylamino group in the intermediate 4 by alcohols (Scheme I). Methylphosphoranes **1a**-e were obtained in high yield after purification via column chromatography under basic conditions (Table I).

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Table I. Iso	olated Yield	and <sup>31</sup> P, <sup>1</sup>	H, and	<sup>13</sup> C NMR S	Spectral	Data of	Phosphoranes	1
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phos- phoranes	yield," %	δ( <sup>31</sup> P), <sup>b</sup> ppm	$\delta({}^{1}\text{H})$ for CH <sub>3</sub> -P, <sup>c</sup> ppm (coupling const, $J_{\text{HCP (Hz)}}$ )	$\delta(^{13}C)$ for CH <sub>3</sub> -P, <sup>c</sup> ppm (coupling const, $J_{CP}$ (Hz))	
1a	88	-20.24	1.81 (d, 17.7)	20.8 (d, 193)	
		-21.56	1.87 (d, 17.6)	21.8 (d, 192)	
16	94	-20.21	1.82 (d, 17.7)	21.1 (d, 193)	
		-21.43	1.87 (d, 17.6)	22.1 (d, 192)	
1c	86	-19.66	1.81 (d, 17.8)	21.7 (d, 194)	
		-20.78	1.87 (d, 17.7)	22.5 (d, 193)	
1d	90 <sup>4</sup>	-20.53	1.84 (d, 17.8)	21.0 (d, 193)	
		-21.95	1.89 (d, 17.7)	22.0 (d, 192)	
1e	100	-20.48	1.82 (d, 17.8)	20.9 (d, 193)	
		-21.91	1.88 (d, 17.7)	21.9 (d. 192)	
lf	95	-20.21	1.84 (d, 17.8)	22.8 (d. 199)	

<sup>a</sup> Phosphoranes 1 were purified by flash column chromatography on silica gel (hexane-NEt<sub>3</sub>, 9:1) unless otherwise specified. <sup>b</sup>Solvent is CDCl<sub>3</sub>. Chemical shifts downfield of the reference (85% H<sub>3</sub>PO<sub>4</sub> as an external standard) are indicated as positive. <sup>c</sup>Methyl group bound to phosphorus atom. Solvent is CDCl<sub>3</sub>. <sup>d</sup>Hexane-AcOEt-NEt<sub>3</sub> (5:1:0.6) was used as solvent for chromatagraphy.

Scheme II. Pseudorotational Process of 1a-e





The diastereomeric monosubstituted aminophosphine  $3^3$  was allowed to react with 3,5-di-*tert*-butyl-1,2-benzoquinone<sup>6</sup> to afford the key intermediate aminophosphorane 4. The formation of diastereomeric 4 was monitored by <sup>1</sup>H and <sup>31</sup>P NMR;<sup>7</sup> without isolation, 4 was allowed to react directly with the appropriate alcohol at room temperature to yield  $1a-f.^8$  Importantly, no substitution of the *l*-menthoxy group in 4 was observed under these conditions.<sup>9</sup>

(7) Two signals were observed in the <sup>31</sup>P NMR spectrum ( $\delta$  -15.4 and -15.7 ppm), and two doublets were observed for CH<sub>3</sub>-P in the <sup>1</sup>H NMR spectrum ( $\delta$  1.74 and 1.84 ppm, J<sub>HP</sub> = 16.2 and 16.4 Hz, respectively), indicating that 4 was composed of two diastereomers.

(8) The aminophosphorane 4 reacted rapidly with water to give N,N-diisopropylamine and the diastereomeric phosphonate 5 quantitatively; <sup>31</sup>P NMR +32.2 (48%) and +32.9 (52%) ppm.
(9) In our alternative approach to 1 from 3 via unsymmetrical alkoxy(*l*-

(9) In our alternative approach to 1 from 3 via unsymmetrical alkoxy(*l*-menthoxy)(methyl)phosphines, substitution of both the *l*-menthoxy group and the N,N-diisopropylamino group of 3 by an alcohol (i.e., cyclohexanol) was observed to give a mixture (1:2:1) of the three possible dialkoxy(methyl)-phosphines.

Unsymmetric phosphoranes 1a-e displayed two signals of approximately equal intensity in <sup>31</sup>P NMR; two doublets were also observed in both <sup>1</sup>H and <sup>13</sup>C NMR for the methyl bound to phosphorus. On the other hand, the symmetric phosphorane 1f prepared by the same method gave only one signal in <sup>31</sup>P NMR and one doublet for the corresponding methyl in  $^1\mathrm{H}$  and  $^{13}\mathrm{C}$  NMR (Table I). Variable-temperature <sup>31</sup>P NMR showed that the two signals persisted for 1a at 119 °C (CDCl<sub>2</sub>CDCl<sub>2</sub>) and the signal of 1f remained a single peak even at -93 °C (acetone- $d_6$ ). These spectral data may be understood in terms of Scheme II, which depicts two sets of trigonal-bipyramidal pseudorotatomers. Structures within cycle I are mutually diastereomeric and rapidly interconverting. They are insulated from the diastereomerically related set in cycle II because the linkage between the two is the strained diequatorial (34) stereoisomer. Furthermore, 1f is a structurally symmetrical (but not a stereochemically symmetrical) analogue. Accordingly each pseudorotatomer of one cycle for 1f becomes identical with the corresponding rotamer of the second cycle, with the result that only one pseudorotatomer cycle exists.

Surprisingly, 1a-f are hydrolytically stable in the absence of acid; phosphorane 1b, for example, remained unchanged in CDCl<sub>3</sub> for at least 2 weeks even in the presence of water or 0.1 N NaOH at room temperature. However, 1a-f are extremely labile to aqueous acids; compound 1a or 1b reacted with 0.1 N HCl immediately to give a 1:1 mixture of diastereomeric phosphonate 5 quantitatively (Scheme I).

Finally this work represents a first step toward the development of stable transition-state analogues for phosphoryl-transfer reactions. Analogues 1d and 1e possess the requisite stability and

<sup>(3)</sup> Compound 3 was prepared from diaminophosphine  $2^4$  by using 5 mol % of 1*H*-tetrazole as a catalyst: bp 96-100 °C at 0.08 mmHg, 88%. <sup>31</sup>P NMR of 3 gave two signals ( $\delta$  +112.4 and +121.6 ppm relative to 85% H<sub>3</sub>PO<sub>4</sub> as an external standard), indicating that 3 exists as a mixture of two diastereomers.

<sup>(4)</sup> Diaminophosphine 2 was synthesized by methylation of bis(N,N-diisopropylamino)chlorophosphine<sup>5</sup> with CH<sub>3</sub>Li (Et<sub>2</sub>O, -78 to 25 °C, 16 h): bp 70-74 °C at 0.07 mmHg, 87%; <sup>31</sup>P NMR  $\delta$  +40.9 ppm.

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necessary linker group required of a hapten for antibody production, and this aspect of the work will be reported separately.

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Supplementary Material Available: Experimental details for the preparation of 1a, 2, 3, and 5 and spectral data for these compounds and 1b-f as well as details of a stability test for 1b (9 pages). Ordering information is given on any current masthead page.

## Hydrogen Exchange during the Enzyme-Catalyzed **Isomerization of Isopentenyl Diphosphate and Dimethylallyl Diphosphate**

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Isopentenyl diphosphate:dimethylallyl diphosphate isomerase (EC 5.3.3.2) catalyzes the interconversion of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) by allylic rearrangement of a hydrogen.<sup>1,2</sup> This is an essential activation step in isoprene biosynthesis which provides the electrophilic allylic diphosphate needed as a primer for all of the subsequent prenyl transfer reactions in the pathway.<sup>3</sup> Studies with electronically deactivated alternate substrates and transition-state/reactive-intermediate analogues indicate that the reaction proceeds by addition and elimination of a proton through a carbocationic intermediate or a transition state with considerable carbocationic character.4,5

$$PPO \xrightarrow{H_{R}} H_{S} H \xrightarrow{H^{+}} PPO \xrightarrow{H_{R}} H_{S} H \xrightarrow{H^{+}} H \xrightarrow{H^{+}_{R}} PPO \xrightarrow{H^{+}_{R}} H \xrightarrow{H^{+}_{R}} H$$

In an elegant series of experiments, Cornforth and co-workers6-8 determined that isomerization of IPP to DMAPP is antarafacial, with a proton added to the re face of the C(3)-C(4) double bond and the pro- $R(H_R)$  hydrogen removed from C(2). Thus, the new methyl in DMAPP is in the E position. As a consequence of the isomerization, the hydrogens of the (E)-methyl group in DMAPP and those at C(4) and the *pro-R* locus of C(2) in IPP exchange with protons from water.<sup>9</sup> However, there are several examples in the literature where label from C(2) of mevalonate is not stereospecifically incorporated into the (E)-methyl of the dimethylallyl unit in isoprenoids.<sup>10-22</sup> Croteau and Loomis<sup>19</sup> and

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Figure 1. Exchange of hydrogens in IPP and DMAPP with D<sub>2</sub>O. Spectra were recorded at 2-min intervals (16 transients/spectrum at 500 MHz) in 0.5 mL of buffer containing 50 mM K<sub>2</sub>HPO<sub>4</sub>, 200 mM KCl, 10 mM MgCl<sub>2</sub>, and 0.5 mM dithiothreitol, pH 7.0. Samples were equilibrated at 24 °C before addition of enzyme, and the probe temperature was maintained at 24 °C. Chemical shifts were referenced to internal tert-butyl alcohol (1 mM), and integrals for each resonance were normalized to the tert-butyl alcohol standard. Part A: hydrogens at C(1) in IPP (•) and DMAPP (A). Part B: methyl hydrogens in IPP (•), (E)-DMAPP (▲), and (Z)-DMAPP (■). Part C: hydrogens at C(2) in IPP ( $\bullet$ ) and DMAPP ( $\blacktriangle$ ).

Shibuya et al.<sup>22</sup> suggested that isomerization of IPP to DMAPP was a likely step for scrambling to occur in the systems studied. Koyama et al.<sup>23,24</sup> discovered that there was a substantial loss of stereoselectivity for pig liver isomerase when ethyl and ethylidene derivatives of IPP and DMAPP were used as alternate substrates. With an ample supply of IPP isomerase available from our efforts

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