of *N*-fluoropyridinium salts. Thus, contrary to unsubstituted salt **1**, 2,4,6-trimethyl salt **2** failed to produce any 9α-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 6α- and 6β-isomeric steroids, and bulky **2** or **7** almost exclusively gave the 6β-isomer, possibly as a result of the fluorination at the less hindered β-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 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_3OF[45] or $FClO_3$.[46] 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.

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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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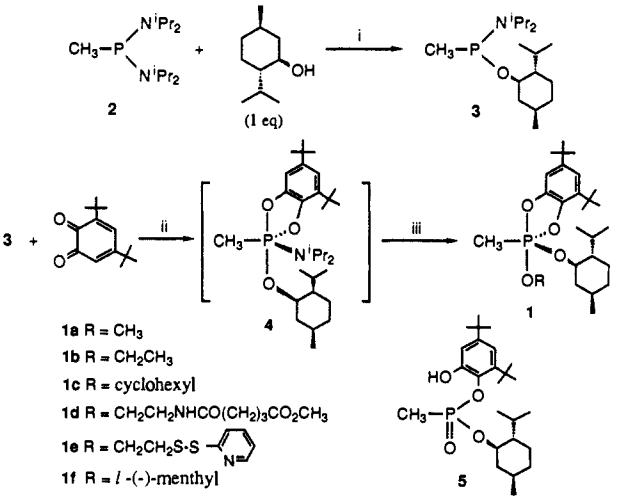
Pentacoordinated phosphorus (phosphoranes) are of interest as models for the intermediate or transition state for phosphoryl transfer occurring in the hydrolysis of phosphates and phosphonates.[1a-d] Such intermediates have been proposed for an increasing number of reactions catalyzed by phosphoryl- and nucleotidyl-transfer enzymes.[1c,2] 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 phosphoryl-transfer reactions frequently involve "unsymmetric" oxyphosphoranes possessing five different substituents bound to phosphorus. No general synthetic method for such unsymmetric phosphoranes has been reported.

Scheme I[a]



[a] Reagents and conditions: (i) 1*H*-tetrazole (5 mol %), dry CH_2Cl_2, 25 °C, 40 h; (ii) dry CH_2Cl_2, 0 °C, 2 h; (iii) ROH (1 equiv), dry CH_2Cl_2, 25 °C, overnight.

We now describe a novel synthetic route to the unsymmetric methylphosphoranes **1a-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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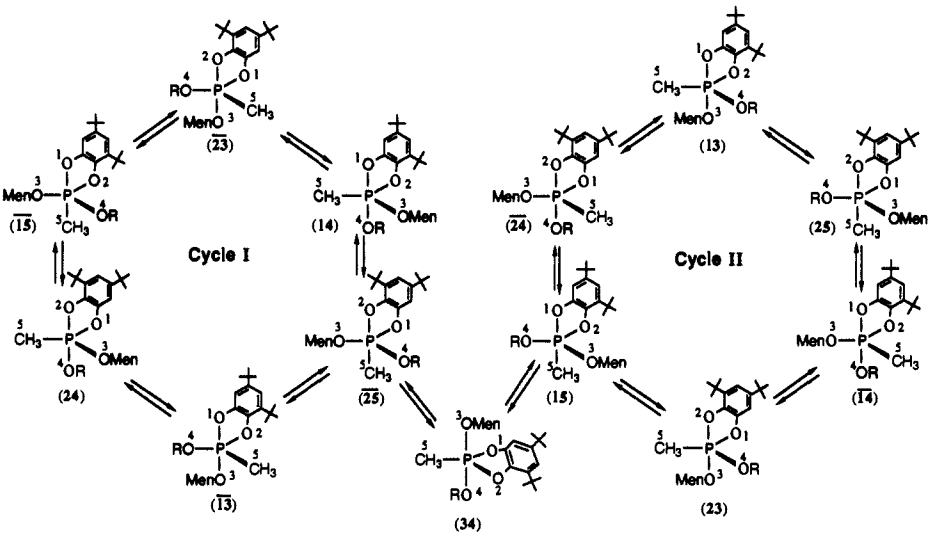
Table I. Isolated Yield and ^{31}P, ^{1}H, and ^{13}C NMR Spectral Data of Phosphoranes **1**

phos-phoranes	yield,[a] %	$\delta(^{31}P)$,[b] ppm	$\delta(^{1}H)$ for CH_3–P,[c] ppm (coupling const, $J_{HCP\ (Hz)}$)	$\delta(^{13}C)$ for CH_3–P,[c] 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)
1b	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[d]	−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)
1f	95	−20.21	1.84 (d, 17.8)	22.8 (d, 199)

[a] Phosphoranes **1** were purified by flash column chromatography on silica gel (hexane–NEt_3, 9:1) unless otherwise specified. [b] Solvent is $CDCl_3$. Chemical shifts downfield of the reference (85% H_3PO_4 as an external standard) are indicated as positive. [c] Methyl group bound to phosphorus atom. Solvent is $CDCl_3$. [d] Hexane–AcOEt–NEt_3 (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[6] to afford the key intermediate aminophosphorane **4**. The formation of diastereomeric **4** was monitored by ^{1}H and ^{31}P NMR;[7] 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.[9]

Unsymmetric phosphoranes **1a–e** displayed two signals of approximately equal intensity in ^{31}P NMR; two doublets were also observed in both ^{1}H and ^{13}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 ^{31}P NMR and one doublet for the corresponding methyl in ^{1}H and ^{13}C NMR (Table I). Variable-temperature ^{31}P NMR showed that the two signals persisted for **1a** at 119 °C ($CDCl_2CDCl_2$) 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 $CDCl_3$ 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

(3) 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%. ^{31}P NMR of **3** gave two signals (δ +112.4 and +121.6 ppm relative to 85% H_3PO_4 as an external standard), indicating that **3** exists as a mixture of two diastereomers.

(4) Diaminophosphine **2** was synthesized by methylation of bis(*N*,*N*-diisopropylamino)chlorophosphine[5] with CH_3Li (Et_2O, −78 to 25 °C, 16 h): bp 70–74 °C at 0.07 mmHg, 87%; ^{31}P NMR δ +40.9 ppm.

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(7) Two signals were observed in the ^{31}P NMR spectrum (δ −15.4 and −15.7 ppm), and two doublets were observed for CH_3–P in the ^{1}H NMR spectrum (δ 1.74 and 1.84 ppm, J_{HP} = 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; ^{31}P NMR +32.2 (48%) and +32.9 (52%) ppm.

(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.

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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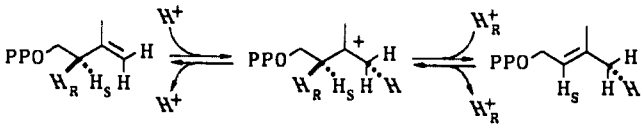
Isopentenyl diphosphate:dimethylallyl diphosphate isomerase (EC 5.3.3.2) catalyzes the interconversion of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) by allylic rearrangement of a hydrogen.[1,2] This is an essential activation step in isoprene biosynthesis which provides the electrophilic allylic diphosphate needed as a primer for all of the subsequent prenyl transfer reactions in the pathway.[3] 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]



In an elegant series of experiments, Cornforth and co-workers[6-8] 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.[9] 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.[10-22] Croteau and Loomis[19] and Shibuya et al.[22] suggested that isomerization of IPP to DMAPP was a likely step for scrambling to occur in the systems studied. Koyama et al.[23,24] 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

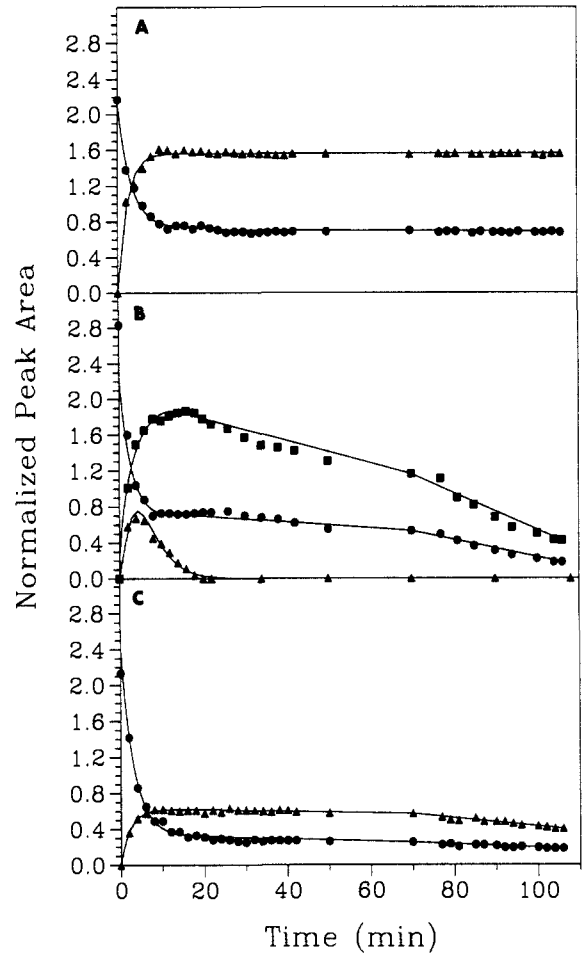


Figure 1. Exchange of hydrogens in IPP and DMAPP with D_2O. Spectra were recorded at 2-min intervals (16 transients/spectrum at 500 MHz) in 0.5 mL of buffer containing 50 mM K_2HPO_4, 200 mM KCl, 10 mM $MgCl_2$, and 0.5 mM dithiothreitol, pH 7.0. Samples were equilibrated at 24 °C before addition of 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 (▲). Part B: methyl hydrogens in IPP (●), (*E*)-DMAPP (▲), and (*Z*)-DMAPP (■). Part C: hydrogens at C(2) in IPP (●) and DMAPP (▲).

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