synthetic route to **3** is essentially the same as the one employed for the synthesis of 2'-deoxymugineic acid.[6]

The left-half fragment of **1** was constructed from (*S*)-azetidine-2-carboxylic acid[11] (**6**), outlined in Scheme III.[10] Esterification of **6** was carried out by refluxing azeotropically with benzyl alcohol (4.8 equiv) and *p*-toluenesulfonic acid (1.2 equiv) in benzene (4 h). The crude product was directly N-alkylated with *tert*-butyl bromoacetate (1.5 equiv) in the presence of diisopropylethylamine (2.5 equiv) in tetrahydrofuran–benzene (1:1) (room temperature, 4 h), giving the diester **7** as a colorless oil, $[\alpha]^{21}_D$ −36.6° (*c* 1, MeOH), in 83% yield. Removal of the *tert*-butyl function of **7** with an excess of trifluoroacetic acid (room temperature, 2 h) afforded the amino acid **8**. Direct C-acylation[7,8] of benzyl isocyanoacetate (2 equiv) with the amino acid **8** smoothly proceeded by the use of DPPA (1.2 equiv) and potassium carbonate sesquihydrate (4 molar equiv) in dimethylformamide (0 °C, 2 h; room temperature, 40 h) to give the key intermediate oxazole **9** as a slightly yellow oil, $[\alpha]^{21}_D$ −56.1° (*c* 1, MeOH), in 80% yield from **7**.

Conversion of the oxazole function to the β-hydroxy-α-amino acid was achieved analogously to our prumycin synthesis.[8a] Treatment of **9** with methanesulfonic acid (10 equiv) in benzyl alcohol–water (10:1) (room temperature, 16 h) afforded the methanesulfonate of the α-amino ketone **10**, which was isolated by addition of diethyl ether followed by decantation. The crude product dissolved in ethanol was adjusted to pH 2 with 1 M sodium hydroxide in aqueous ethanol at −30 °C, cooled to −70 °C, and treated with sodium borohydride (1.5 molar equiv) in ethanol at −70 °C for 40 min. Quenching with 1 M hydrochloric acid followed by extractive workup afforded a diastereomeric mixture of the amino alcohols. Treatment of the mixture with di-*tert*-butyl dicarbonate (1.25 equiv) in chloroform (room temperature, 5 h) afforded a mixture of N-protected β-hydroxy-α-amino acid esters (**11a**, **12a**, and the other isomers), which were separated by column chromatography on silica gel with hexane–diethyl ether (1:2) to give two oily fractions, the less polar and the more polar isomers, in 19 and 44% yields, respectively. Although the major fraction was a mixture of two diastereomers and inseparable at this stage, the corresponding *tert*-butyldimethylsilyl derivatives obtained by treatment with *tert*-butyldimethylchlorosilane (2 equiv) and imidazole (6 equiv) in dimethylformamide (room temperature, 18 h) were separable by column chromatography on silica gel with hexane–diethyl ether (4:1), giving the more polar isomer as a colorless oil, $[\alpha]^{23}_D$ −11.9° (*c* 1, CH_2Cl_2), in 54% yield and the less polar isomer, $[\alpha]^{23}_D$ −15.9° (*c* 1, CH_2Cl_2), in 28% yield. From our result[8a] and the other[12] concerning reduction of α-acylamino acids, we assumed that the major isomer was (2'*S*, 3'*S*)-**11b** or (2'*R*, 3'*R*)-**12b** with erythro configuration. The ultimate proof for the structure **11b** assigned to the major isomer was obtained by converting to mugineic acid in three steps.

Thus, the *tert*-butyloxycarbonyl (Boc) group of the major isomer **11b** was first deprotected with trimethylsilyl trifluoromethanesulfonate[13] (3 equiv) in methylene chloride (0 °C, 1 h) under argon. The crude product **11c** was directly coupled with the right-half fragment **3** (1.1 equiv) by the use of sodium cyanoborohydride (1.45 equiv) in the presence of trifluoroacetic acid in isopropyl alcohol–tetrahydrofuran (5.6:3, pH 5) (room temperature, 17 h). The fully protected mugineic acid **13** was obtained in 75% yield as a colorless oil, $[\alpha]^{23}_D$ −17.1° (*c* 1, CH_2Cl_2). Final deprotection was achieved with methanesulfonic acid–anisole (10:1) (room temperature, 4 h), giving mugineic acid (**1**), mp 209–212 °C dec, $[\alpha]^{22}_D$ −62.5° (*c* 1, H_2O), in 71% yield. The synthetic material **1** was identical with the natural mugineic acid,[4] mp 210–212 °C dec, $[\alpha]_D$ −70.7° (*c* 0.97, H_2O), by IR, ^1H and ^{13}C NMR spectral, and chromatographic comparisons and exerted a parallel activity to that of natural one on inhibitory effect against angiotensin-converting enzyme.[5]

The above reaction sequence comprises a facile synthesis of mugineic acid in 11 steps from known and readily available (*S*)-azetidine-2-carboxylic acid (**6**) with an overall yield of 8.4%. Stereochemistry of the other isomers obtained by reduction of the α-acylamino acid ester **10** is now under investigation.

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Bis(neopentyloxy)triphenylphosphorane: A Versatile, Nonalkylating Cyclodehydration Reagent

Summary: Bis(neopentyloxy)triphenylphosphorane (BNTP; ^{31}P δ −58.3) is prepared in 48% yield by reaction of 2 equiv of lithium neopentoxide with dibromotriphenylphosphorane in anhydrous dichloromethane from −78 to 25 °C. BNTP smoothly converts a variety of diols, 2-aminoethanol, and 4-mercaptobutanol to the corresponding heterocycles in excellent yields (>95%) by ^{13}C and ^{31}P NMR analysis.

Sir: Quite recently, new emphasis has been placed on the synthetic potential of dioxytriphenylphosphoranes as mild, regioselective cyclodehydrating reagents for preparing a wide selection of oxygen,[1] nitrogen,[2] and sulfur[3] heterocycles. However, despite the relative ease of preparation of some dioxyphosphoranes [e.g., $Ph_3P(OEt)_2$ and $Ph_3P(OHex)_2$][1] by oxidative addition of alkyl peroxides to Ph_3P, the potential hazards associated with the preparation and use of peroxides (particularly, in large quantities)[4] serve

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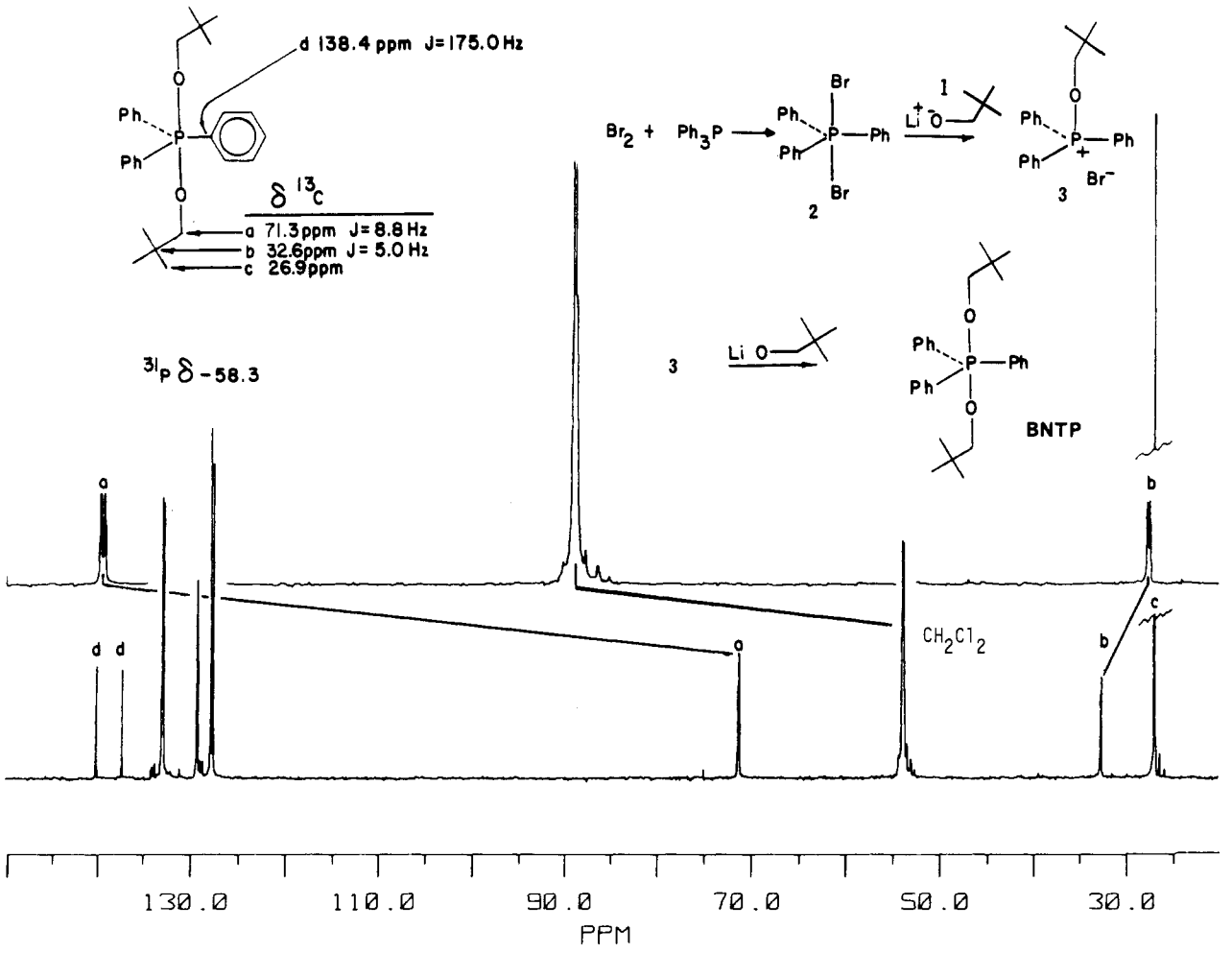
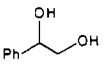
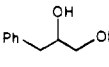
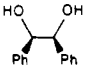
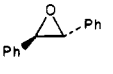
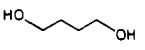
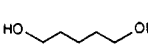
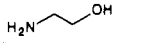
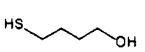
Chart I. Reaction Scheme and ^{13}C NMR Spectrum Characterizing BNTP



to restrain extensive use of this methodology. In an effort to circumvent this concern, we envisioned a nonperoxidic approach to bis(neopentyloxy)triphenylphosphorane (BNTP) which should possess "cyclodehydrative potential" equivalent to that observed for $Ph_3P(OEt)_2$.[1] This report details our most recent findings on this subject.

Lithium neopentoxide (1)[5,6] reacts rapidly with dibromotriphenylphosphorane (2)[6] at −78 °C (dry ice–acetone bath) to afford (neopentyloxy)triphenylphosphonium bromide (3; ^{31}P δ 61.7).[11] Phosphonium

Table I. Cyclodehydration of Active Hydrogen Compounds with Bis(neopentyloxy)triphenylphosphorane

entry	substrate	product	yield (%)[a]
1			95
2			94
3			95
4			99
5			95
6			98
7			93

[a] Yields are determined by GLC and/or ^{13}C NMR analyses of the reaction mixtures with comparison with retention times and NMR spectra of authentic samples.

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(5) Neopentyl alcohol was prepared according to the procedures developed by Summer et al. [Summer, L. H. Blankman, H. D.; Miller, P. C. *J. Am. Chem. Soc.* **1954**, *76*, 803].

(6) **Synthetic Procedure.** Lithium neopentoxide (1) was prepared by adding *n*-butyllithium (9.6 mL of 2.5 M solution, 0.024 mol) via syringe to a vigorously stirred solution of neopentyl alcohol (2.1 g, 0.024 mol) at 0 °C in 80.0 mL of anhydrous toluene solvent[7] under an argon atmosphere. In a separate three-necked flask, bromine (0.616 mL, 0.024 mol) in 20.0 mL of anhydrous dichloromethane was added slowly to triphenylphosphine (3.14 g, 0.012 mol) in anhydrous dichloromethane (60.0 mL) at −78 °C (dry ice–acetone) to afford dibromotriphenylphosphorane (2) in situ. Freshly prepared 1 (ca. 0.024 mol from above) was added dropwise (ca. 15 min) to phosphorane 2 (ca. 0.0121 mol) at −78 °C to afford initially (neopentyloxy)triphenylphosphonium bromide (3; ^{31}P δ 61.7). At 25 °C, additional lithium neopentoxide reacts with 3 to afford crude BNTP (65%) as determined by an inverse gated-decoupled ^{31}P NMR experiment (δ −58.3). The BNTP solution was removed from lithium bromide by syringe and placed in a dry flask under an argon atmosphere. The dichloromethane/toluene solvent mixture was removed under vacuum affording colorless crystals.[8] The flask was back-filled with argon[9] and BNTP was subsequently extracted from the remaining impurities[8] with anhydrous hexanes (70 mL).[10] BNTP in hexanes solvent was transferred by syringe to a tared, argon-filled flask and the hexanes solvent was removed under high vacuum to afford colorless, crystalline BNTP (0.1 mmHg for 1 h). The flask was back-filled with argon to afford 2.55 g (48%) of homogenous BNTP. Calcd for $C_{28}H_{37}O_2P$: C, 77.03; H, 8.54. Found: C, 77.23; H, 8.48.

(7) Toluene was distilled from benzophenone ketyl under an argon atmosphere. See: Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley-Interscience; New York, 1972; p 439.

bromide **3** consumes an additional equivalent of **1** at 25 °C to afford bis(neopentyloxy)triphenylphosphorane (BNTP; 48%; ^{31}P δ −58.3).[6] The ^{13}C (Chart I) and ^{31}P NMR parameters exhibited by BNTP are consistent with the trigonal-bipyramidal conformation with diapical neopentyloxy ligands.[1] The observable couplings, $^{2}J_{POC}$ = 8.8 Hz and $^{3}J_{POCC}$ = 5.0 Hz, are analogous to those observed for $Ph_3P(OEt)_2$ and $Ph_3P(OHex)_2$.[1]

In a typical cyclodehydration reaction (Table I; entry 3), *meso*-1,2-diphenylethane-1,2-diol (642 mg, 3 mmol) was treated with a solution of BNTP (0.5 M, 3 mmol) in dichloromethane solvent (40 °C, 24 h) to afford *trans*-stilbene oxide (>95% by GLC and ^{13}C NMR analyses). The solvent was removed and the sample redissolved in $CDCl_3$: ^{1}H NMR ($CDCl_3$) δ 3.83 (*s*, 2 H, CHOC) and 7.40 (*m*, 10 H, Ar H's); ^{13}C NMR (CH_2Cl_2) δ 62.7 (Ph*C*CPh) with noise decoupling. This result is consistent with the ring closure predictions of Baldwin[12] where the 3-exo-tet cyclization with inversion at the displacement terminus is expected. Tetrahydrofuran and tetrahydropyran are also formed from the respective diols in excellent yields by employing this methodology (Table I, entries 4 and 5).

Previously, we had noted that $Ph_3P(OEt)_2$ mediated conversions of several 1,2-amino alcohols to the corresponding aziridines are excellent if an equivalent of reactant and substrate is maintained. Additional $Ph_3P(OEt)_2$ initiates *N*-ethylation of the aziridinyl nitrogen affording the tertiary amine.[2] However, reaction of 1,2-ethanolamine with 2 equiv of BNTP gives aziridine in >98% with no spectroscopic evidence for N-neopentylation of the parent aziridine. Undoubtedly, the methylene group of $Ph_3P^+OCH_2C(CH_3)_3$ is sufficiently sterically hindered to diminish the effectiveness of aziridinyl nitrogen Arbuzov attack.[2]

Finally, S-ethylation is particularly problematic in the synthesis of cyclic sulfides from reactions of mercapto alcohols with $Ph_3P(OEt)_2$. For example, the cyclodehydration of 4-mercaptobutanol with $Ph_3P(OEt)_2$ gives tetrahydrothiophene (65%) and 4-(ethylthio)butanol (35%).[3] However, BNTP cyclodehydrates 4-mercaptobutanol to tetrahydrothiophene in >98% by ^{13}C NMR and GLC analyses. Competitive thiolate attack on the α methylene carbon is apparently suppressed when the neopentyl group constitutes part of the oxo ligand.

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(8) The composition of this material is largely BNTP, lithium bromide,and triphenylphosphine oxide.
(9) Nitrogen gas would be an acceptable substitute.
(10) Reagent-grade hexanes are distilled from calcium hydride under argon.
(11) The ^{31}P chemical shift assigned to **3** (δ 61.7) is similar to that (δ 62) reported for ethoxytriphenylphopshonium tetrafluoroborate [Ph_3P^+OEt,BF_4^-]. See: Denney, D. B.; Denney, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85–89. The ^{13}C shifts of the neopentoxy ligand and the ^{13}C–^{31}P coupling constants are also indicative of the alkoxyphosphonium structure.
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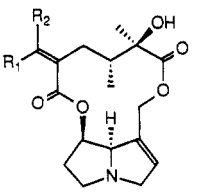
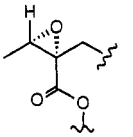
Synthesis of the Macrolactone Pyrrolizidine Alkaloid Integerrimine

Summary: Synthesis of the natural enantiomer of the 12-membered dilactone integerrimine was accomplished by coupling retronecine with a masked version of integerrinecic acid. The latter was acquired in homochiral form from (*R*)-(−)-3-hydroxy-2-methylpropionate.

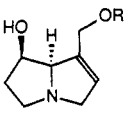
Sir: The powerful hepatotoxic, carcinogenic, and other physiological properties associated with alkaloids of the pyrrolizidine family have brought these substances to high prominence in recent years.[1] Conspicuous among this group of structures is a set of 12-membered dilactones that includes integerrimine (**1**), its geometrical isomer seneci-



1, R_1 = H, R_2 = CH_3
2, R_1 = CH_3, R_2 = H



3



4, R = H
23, R = SitBuMe$_2$

onine (**2**), and the epoxide jacobine (**3**), each of which consists of a dicarboxylic (necic) acid spanning the C-7,C-9 hydroxy functions of retronecine (**4**). Although numerous routes to **4** have been published,[2] less success has attended synthetic efforts directed at the complex macrolactones. However, a recent synthesis of (±)-**1**[3] provides encouraging precedent for a plan that connects the fully functionalized necic acid to its pyrrolizidine base,[4] and we now describe a stereocontrolled synthesis of the natural enantiomer of **1** that assembles the macrolactone from a protected homochiral form of integerrinecic acid and naturally derived (+)-**4**.

The [(trimethylsilyl)ethoxy]methyl (SEM)[5] ether **6** of methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (**5**) was converted to aldehyde **8** via alcohol **7**.[6] Treatment of **8** with methylmagnesium bromide, followed by Swern oxidation,[6] afforded **9** which, in a chelation-controlled Grignard reaction[7] with vinylmagnesium bromide, yielded a 4:1 mixture of the desired alcohol **10** and its diastereomer **11**. These were easily separated (HPLC, μ-Porasil) as their cyclic carbonates, prepared from the mixture of diols with carbonyldiimidazole, and the major carbonate **12**, after hydrolysis to **13**, was transformed to iodo acetate **15** via the primary tosylate **14**.

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