A Highly Enantioselective Synthesis of Phosphate Triesters

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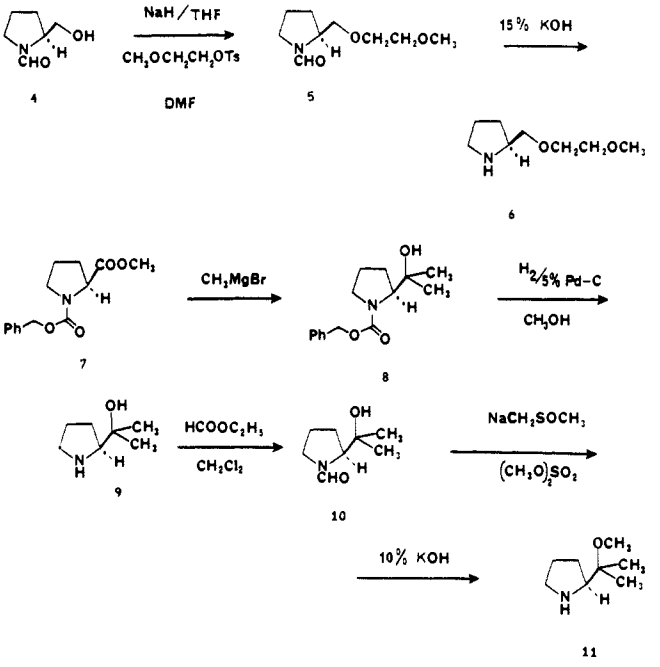
Abstract: A general methodology for the preparation of both enantiomers of a variety of trialkyl phosphates with enantiomeric excesses ranging from 87 to 92% is described. Bis(2,4-dichlorophenyl) phosphoramidates bearing a 2-substituted pyrrolidine moiety as the chiral auxiliary are prepared and examined for their stereoselectivity. Considerations based on both the absolute configuration of the product phosphates as well as the X-ray structural determination of one of the bis(2,4-dichlorophenyl) phosphoramidates suggest these substitutions occur with preponderant inversion of configuration at phosphorus.

The first successful attempts to prepare optically active compounds with asymmetric phosphorus atoms were reported early in this century by Meisenheimer and Lichtenstadt who partially resolved ethylmethylphenylphosphine oxide.[2] Aside from the classical methods of resolution,[3,4] the modern techniques of separation of covalently bonded diastereomers have emerged more recently to provide a variety of chiral organophosphorus compounds.[5,6]

While synthetic methods for asymmetric induction at phosphorus are virtually unknown, the biological significance of chirality at phosphorus is clearly no less important than chirality at carbon. It has been established, for example, that acetylcholinesterase is inhibited in vitro by the (-)-(*S*) enantiomer of the agent Sarin approximately 4200 times faster than by the (+)-(*R*) enantiomer.[7] The (-) enantiomer of the antitumor agent cyclophosphamide is known to be more effective against ADJ/PC6 plasma cell tumors in mice and less readily metabolized in humans than the (+) antipode.[8]

While optically active organophosphorus compounds have been employed in asymmetric Wittig reagents,[9] Horner-Emmons reagents,[10] enantioselective catalytic hydrogenations,[11] and derivatizing agents for the determination of enantiomeric purity by ^{31}P NMR,[12] the lesser known chiral phosphate triesters have only recently been investigated as biological models and probes. Synthetic oligodeoxyribonucleotide (DNA) triesters are resistant to nucleases but are readily absorbed by cells, thus making them potential antiviral drugs and drug carriers.[13,14]

Scheme I



We report here a general and highly enantioselective method for the synthesis of chiral trialkyl phosphate (**1a**) and dialkyl 2,4-dichlorophenyl phosphate (**1b**) involving asymmetric induction at prochiral phosphorus. Our strategy employs as a key design element chiral auxiliary reagents derived from L-proline.[15] Unlike the known methods for chiral phosphate triester synthesis which utilizes chiral auxiliaries derived from L-proline,[16] D-glucose,[17] and (-)-ephedrine,[18] the method is direct and does not require any physical separation of diastereomers. As depicted in the Newman projection of **2**, it was thought that chelation of a metal ion by the phosphoryl and ether oxygen atoms could act both to facilitate

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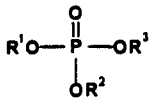
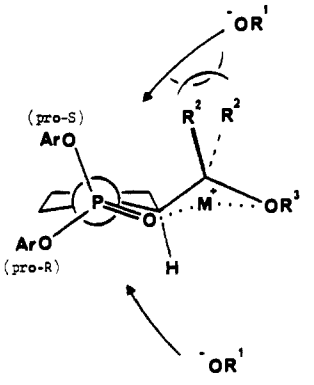
nucleophilic substitution at the phosphorus atom and create a rigid intermediate wherein approach of the alkoxide along the $S_N2(P)$ displacement axis colinear to the *pro-S* aryloxy–phosphorus bond[19] would be favored by steric factors.



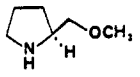
1a: $R^1 = R^2 = R^3 = alkyl$
1b: $R^1 = R^2 = alkyl$, $R^3 = 2,4\text{-dichlorophenyl}$



2: $R^1 = alkyl$, $R^2 = H, CH_3$, $R^3 = CH_3, CH_2CH_2OCH_3$
Ar = 2,4-dichlorophenyl

Results and Discussion

Synthesis of the Chiral Auxiliaries and Phosphoramidates. The 2-substituted pyrrolidines **3**, **6**, and **11** we chose as chiral auxiliaries were prepared from L-proline either according to the method reported by Seebach and co-workers[20] or a variation as shown in order to incorporate the desired substituent (Scheme I). Al-



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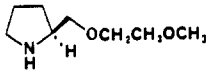

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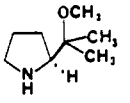
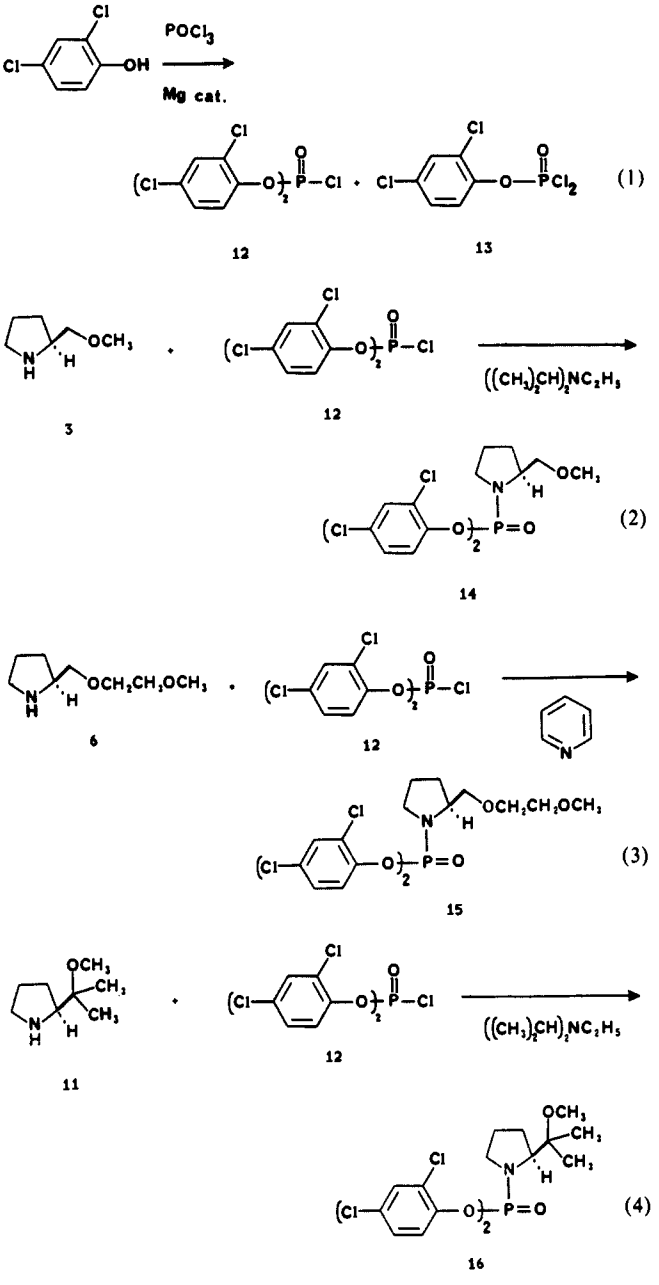


11

kylation of *N*-formyl-L-prolinol (**4**) with 2-methoxyethyl *p*-toluenesulfonate followed by saponification gave the 2-methoxyethyl ether of L-prolinol (**6**) in 75% yield after evaporative distillation (Kugelrohr). For the synthesis of the chiral auxiliary **11**, we found it most convenient to utilize *N*-carbobenzyloxy-L-proline methyl ester (**7**). Addition of methylmagnesium bromide followed by deprotection of the carbobenzyloxy (Cbz) group gave the amino alcohol **9** in good yields. Alkylation of the *N*-formyl derivative **10** gave, after saponification, the desired amino methyl ether **11** in 69% overall yield.

The 2,4-dichlorophenoxy ligand was chosen for the initial investigation on the basis of potential crystallinity, isolability, and ability to function as an excellent leaving group. When 2,4-dichlorophenol and phosphorus oxychloride were heated in the presence of magnesium according to the Rosenmund–Vogt method of diarylphosphoryl chloride synthesis,[21] a 45% yield of bis-[(2,4-dichlorophenyl)oxy]phosphoryl chloride (**12**) was obtained (eq 1). Virtually complete separation of the [(2,4-dichlorophenyl)oxy]phosphoryl dichloride (**13**) was possible by direct evaporative distillation of the reaction mixture. Reaction of the crystalline bis(diaryloxy)phosphoryl chloride **12** with chiral pyrrolidines **3**, **6**, or **11** in the presence of tertiary amine base gave the chiral bis(2,4-dichlorophenyl) phosphoramidates **14**, **15**, and **16** (eqs 2–4) in 65–77% yields. While the diaryl phosphoramidates **15** and **16** were isolated as viscous oils, we were rewarded to find that the solid **14** crystallized from ether–hexane in the form of single prismatic crystals. This presented us with the opportunity to determine the preferred conformation along the P–N bond of a diaryl phosphoramidate in the crystalline state through an X-ray diffraction study.



The single crystal X-ray diffraction analysis of **14** revealed that the P=O was essentially coplanar and syn with respect to the N–C(2) bond of the pyrrolidine ring system. The X-ray analysis also confirmed the prediction on the basis of comparison of experimentally obtained ^{15}N–^{31}P coupling constants of pyrrolidine phosphoramidates[22] with values calculated by using the finite perturbation method,[23] that the nitrogen geometry would be essentially trigonal. It also became clear from an examination of the ORTEP drawings (Figures 1 and 2) of the crystal structure viewed along the $S_N2(P)$ approach axis from directions opposite to the *pro-S* (Figure 1) and *pro-R* (Figure 2) ligands that the displacement of the *pro-S*-(2,4-dichlorophenyl)oxy group was indeed sterically preferred.

Optically Active Alkyl 2,4-Dichlorophenyl Methyl Phosphates. The predictions mentioned above regarding the expected con-

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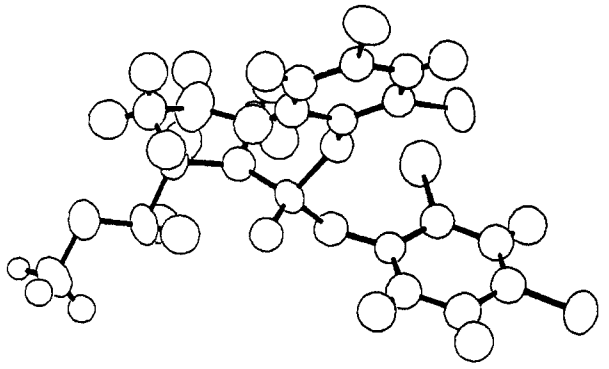


Figure 1. ORTEP drawing of the single crystal X-ray structure of **14** viewed along the $S_N2(P)$ approach axis from the direction opposite to the *pro-S*-(2,4-dichlorophenyl)oxy ligand.

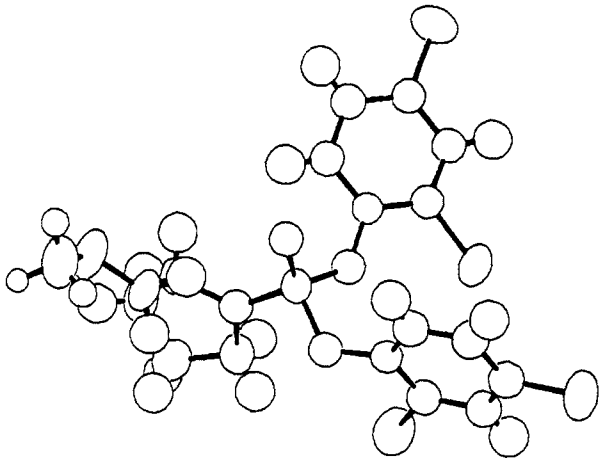


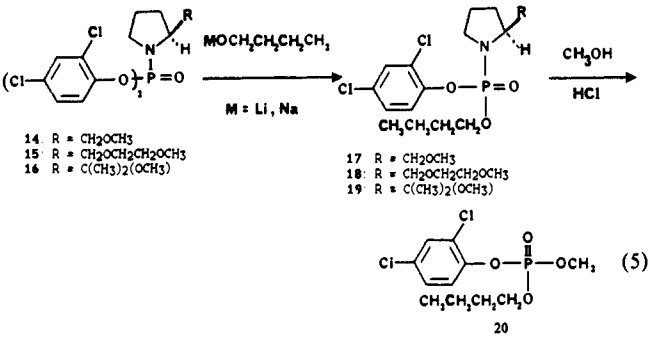
Figure 2. ORTEP drawing of the single crystal X-ray structure of **14** viewed along the $S_N2(P)$ approach axis from the direction opposite to the *pro-R*-(2,4-dichlorophenyl)oxy ligand.

formational preferences upon the stereoselectivity of displacement reactions occurring at phosphorus were borne out experimentally when it was found that the reaction of phosphoramidates **14**, **15**, and **16** with a slight excess of lithium or sodium *n*-butoxide followed by protic acid–methanolysis gave the chiral *n*-butyl 2,4-dichlorophenyl methyl phosphate (**20**) (eq 5) with 78% to >95% enantiomeric excess (ee) (Table I). The optical purity was determined by integration of the methoxyl doublets (^{1}H NMR) in the presence of the chiral lanthanide-shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]-europium(III) (Eu(hfc$_3$)).[24,25] Recovery of the chiral auxiliaries **3**, **6**, or **11** could be effected in moderate yield by basification and extraction of the acidic aqueous layer during the workup of the methanolysis step.

Substituent Effects in the Chiral Auxiliary and the Nucleophile. A comparison of the % ee as a function of the L-prolinol ether side chain reveals that steric bulk adjacent to the ether oxygen was indeed exerting a favorable effect on the stereochemical outcome in the manner predicted by the model. Introduction of two methyl groups at C-1 of the ether bearing carbon (**16**) resulted in a highly stereoselective (>95% ee) synthesis of chiral phosphate **20**. Increasing the number of ether oxygens available for chelation only served to facilitate the conversion to monoalkyl phosphoramidate **18** and actually lead to a decreased stereochemical yield of the chiral phosphate **20** (Table I).

While the *n*-butyl phosphoramidates **17–19** could easily be isolated in 71–90% yields, we were unable to separate the diastereomers by chromatography or induce crystallization.[26] Since protic acid alcoholysis of chiral phosphoramidates has been established to proceed stereospecifically with inversion of configuration at phosphorus,[27] the assumption is made here that the %

Table I. Metal *n*-Butoxide Displacement Reactions of Amidates **14–16** and Acid-Catalyzed Methanolysis of the Resulting Amidates **17–19**[a]



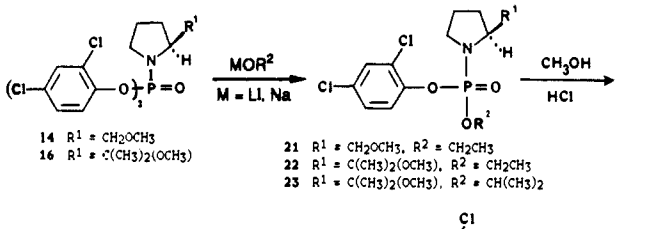
(5)

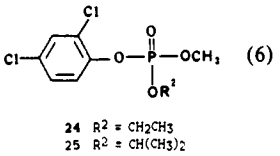
20

		n-butoxide displacement		protic acid-catalyzed methanolysis	
entry	M	butyl aryl amidate	yield,%	yield **20**,%	% ee[b,c]
1	Li	**17**	65	74	83[d]
2	Na	**17**	71	64	92
3	Li	**18**	90	73	78[e]
4	Li	**19**	63	73	>95
5	Na	**19**	72	74	>95[f]

[a] Metal *n*-butoxide displacement reaction in entry 3 was carried out at −78 °C. All other *n*-butoxide displacement reactions were conducted at 0 °C. [b] Determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$. [c] The major enantiomer possessed the *S* configuration in all cases. [d] $[\alpha]^{22}_D$ −3.07° (*c* 2.18, CHCl$_3$). [e] $[\alpha]^{20}_D$ −2.6° (*c* 2.5, CHCl$_3$). [f] $[\alpha]^{22}_D$ −3.6° (*c* 4.1, CHCl$_3$).

Table II. Sodium Alkoxide Displacement Reactions of Amidates **14** and **16** and the Acid-Catalyzed Methanolysis of the Resulting Amidates **21–23**





(6)

24 R2 = CH2CH3
25 R2 = CH(CH3)2

			sodium alkoxide displacement		acid-catalyzed methanolysis		
entry	M	R^2	alkyl aryl amidate	yield,%	alkyl aryl methyl phosphate	yield,%	% ee[a]
1	Li	C_2H_5	**21**	60	**24**	31	88
2	Na	C_2H_5	**22**	67	**24**	67	<95[b]
3	Na	*i*-C_3H_7	**23**	71	**25**	61	90[c]

[a] Determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$. [b] $[\alpha]^{22}_D$ −1.9°(*c* 3.1, CHCl$_3$). [c] $[\alpha]^{22}_D$ −1.1°(*c* 5.7, CHCl$_3$).

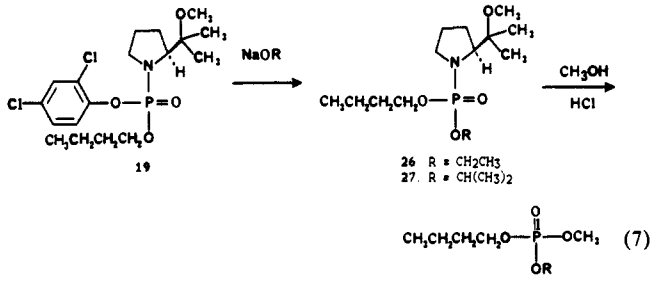
(24) The stoichiometry of chiral lanthanide-shift reagent required for quantitative measurement of enantiomeric excess was determined by using racemic phosphate triesters prepared by sequential displacement of chloride then 2,4-dichlorophenol from bis[(2,4-dichlorophenyl)oxy]phosphoryl chloride **12** with the appropriate alcohol or alkoxide (see supplemental material).
(25) References 17b and 17c.

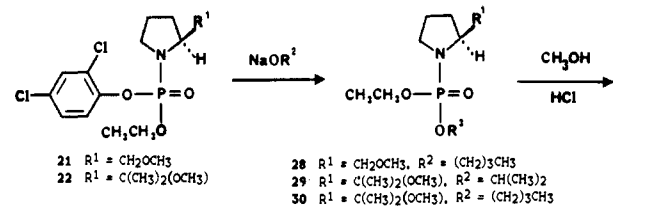
(26) The presence of epimers at phosphorus was not detectable by TLC or ^{1}H NMR. This is in sharp contrast to the diastereomeric phosphoramidates derived from L-proline methyl ester which are readily separated by column chromatography (ref 16).
(27) (a) Kobayashi, Y.; Koizumi, T.; Yoshii, E. *Chem. Pharm. Bull.* **1979**, *27*, 1641. (b) Garrison, A. W.; Boozer, C. E. *J. Am. Chem. Soc.* **1968**, *90*, 3486.

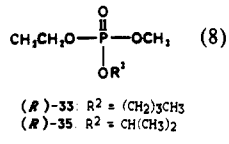
ee directly reflects the degree of asymmetric induction obtained in the first step.

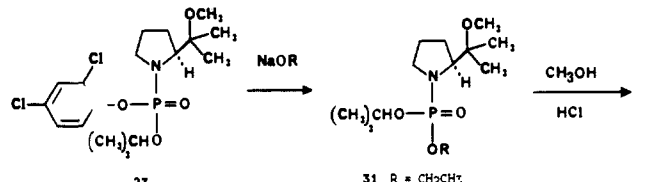
Displacement studies with the alkoxides of ethanol and 2-propanol (eq 6) revealed that the reaction time and temperature were strongly dependent on the nature of the nucleophile (Table II). While the yield and % ee[24] could be optimized for the less reactive ethoxide to about the same extent as *n*-butoxide (Tables I and II), it became apparent that the sterically more demanding nucleophile 2-propoxide gave decreased degree of asymmetric induction under the same reaction conditions. Therefore, the nature of the nucleophilic alkoxide must be considered when choosing the appropriate chiral auxiliary and the reaction conditions optimized in each case to achieve efficient optical yields.

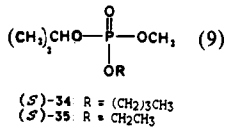
Synthesis of Optically Active Trialkyl Phosphates. Continuing toward the development of a general procedure for the preparation of optically active trialkyl phosphates, we focused our attention on the reaction of alkyl 2,4-dichlorophenyl phosphoramidates with alkoxides. The phosphoramidates **19**, **21–23** were selected for this study since they had been obtained in a state of very high diastereomeric purity. Displacement with excess sodium alkoxide followed by methanolysis in the presence of protic acid afforded the chiral phosphate triesters **33–35** (eqs 7–9) in 42–54% overall yields with % ee's ranging from 66 to 92% (Table III).[24] The lower chemical yields of these dialkyl methyl phosphates compared to the dialkyl 2,4-dichlorophenyl phosphates (Table I) reflects the greater water solubility of the trialkyl phosphates and therefore loss on workup. While the reaction conditions were carefully controlled in each of these experiments, it is likely that the optical yields are also not optimized.











It was then found that increased optical yields of the trialkyl phosphates could be obtained by reversing the order of the methanolysis and alkoxide displacement steps. When solutions of (−)-**20**, (−)-**24**, and (−)-**25** were treated with excess sodium alkoxide at room temperature, the chiral dialkyl methyl phosphates **33** and **35** were formed (eq 10–12) in 87–91% ee (Table IV). Taking into account the optical purities of the starting materials, these substitution reactions proceeded with 93–99% stereoselectivity.

Table III. Sodium Alkoxide Displacement Reactions of Amidates **19**, **21–23** and Acid-Catalyzed Methanolysis of the Resulting Amidates **26–32**

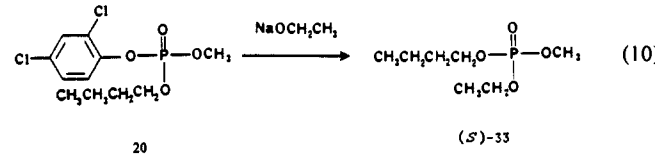
entry	alkyl aryl amidate	dialkyl amidate (yield,%)	dialkyl methyl phosphate	
			phosphate (yield,%)	% ee[a]
1	**19**	**26** (90)	(*S*)-**33** (53)	71
2	**19**	**27** (87)	(*R*)-**34** (63)	92
3	**21**	**28** (84)	(*R*)-**33** (59)	88
4	**22**	**29** (73)	(*R*)-**35** (52)	66
5	**22**	**30** (90)	(*R*)-**33** (47)	71
6	**23**	**31** (90)	(*S*)-**35** (41)	81
7	**23**	**32** (90)	(*S*)-**34** (54)	92

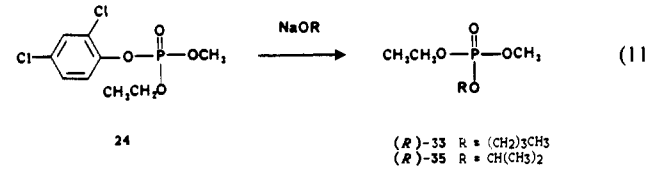
[a] Determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$.

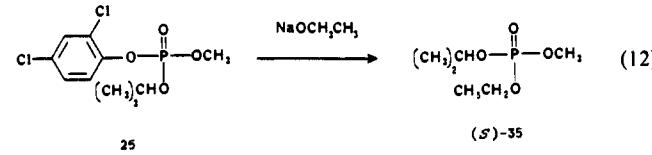
Table IV. Sodium Alkoxide Displacement Reactions of Phosphates **20**, **24**, and **25**

entry	(*S*)-alkyl aryl methyl phosphate (% ee)[a]	dialkyl methyl phosphate		
		phosphate	yield,%	% ee[a]
1	**20** (>95)	(*S*)-**33**	73	88
2	**24** (94)	(*R*)-**35**	42	91
3	**24** (94)	(*R*)-**33**	55	87
4	**25** (90)	(*S*)-**35**	62	89

[a] Determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$.







Assignment of Absolute Configuration at Phosphorus. While it was tempting to assign stereochemistry at phosphorus in the phosphoramidates **17–19**, **21–23** the *S* configuration from steric considerations during the displacement step, we sought a more rigorous proof by correlation to a known chiral phosphate triester. Fortunately, Hall and Inch have described the correlation of optically pure (−)-(*R*)- and (+)-(*S*)-ethyl isopropyl methyl phosphate with the relative change in chemical shift of the methoxyl doublet in the presence of Eu(hfc)$_3$.[17b,18b] The ethyl isopropyl methyl phosphate (**35**) obtained from the protic acid-methanolysis of phosphoramidate **31** was indeed found to be dextrorotatory and enriched in the "low-field" enantiomer in the presence of Eu(hfc)$_3$, in agreement with the observations of Hall and Inch. Assuming that the methanolysis step proceeded stereospecifically with inversion of configuration,[27] then the penultimate phosphoramidate **31** must also be of the *S* configuration

at phosphorus. If we further assume that the previous ethoxide displacement on phosphoramidate **23** proceeded with configurational inversion, then the absolute stereochemistry of **23** at phosphorus must also be *S*.

These assignments are further supported by the observation of enrichment of the lower field methoxy doublets in each of the alkyl 2,4-dichlorophenyl methyl phosphates **20**, **24**, and **25**. While no direct correlation to a known triester was available in these examples, (+)-(*R*)-ethyl methyl phenyl phosphate had been correlated with the "high-field" methoxyl doublet in the presence of $Eu(hfc)_3$.[17c] Since the 2,4-dichlorophenyl ethyl methyl phosphate **23** should coordinate to the cationic europium atom in the same fashion as methyl ethyl phenyl phosphate, the magnetic environment experienced by the enantiomeric methoxyl protons would be nearly identical. Regardless of the chiral auxiliary employed, all of the alkyl 2,4-dichlorophenyl methyl phosphates prepared in this investigation were determined to be low-field enantiomers and levorotatory and are therefore assigned as (−)-(*S*) configuration. Since the ethyl isopropyl methyl phosphate ((−)-**35**) obtained from treatment of 2,4-dichlorophenyl isopropyl methyl phosphate (**25**) with ethoxide was also found to be the low-field isomer in the presence of $Eu(hfc)_3$, it must also be of the *S* configuration. Thus, the alkoxide displacement of the 2,4-dichlorophenoxy group from the (*S*)-alkyl aryl methyl phosphates **20**, **24**, and **25** must be proceeding with stereochemical inversion at phosphorus in 93–99% stereoselectivity.

On the basis of stereochemical correlations, an $S_N2(P)$ mechanism[28] with preferential displacement of the *pro*-(*S*)-2,4-dichlorophenoxy ligand of phosphoramidates **2** is proposed. These results serve to demonstrate that a high degree of enantioselectivity can be obtained through asymmetric displacement at prochiral phosphorus.

Experimental Section

(*S*)-2-[(Methoxyethoxy)methyl]pyrrolidine (6). A solution of *N*-formyl-L-prolinol[20] (**4**) (6.46 g, 50.0 mmol) in 100 mL of dry THF was added dropwise to a stirred suspension of sodium hydride (1.44 g, 60.0 mmol) in 100 mL of dry THF at 0 °C under N_2. After the mixture was allowed to stir for 10 min at 0 °C, a solution of 2-methoxyethyl *p*-toluenesulfonate[29] (14.0 g, 60.8 mmol) in 25 mL of dry DMF was added and the stirring continued at room temperature for 30 min. Then the reaction was gradually brought to reflux and allowed to react at that temperature for 2 h. After the reaction mixture was cooled, it was filtered, and the solid was washed with ether (100 mL). The combined eluents were then concentrated at reduced pressure and dried in vacuo overnight. The crude *N*-formyl ether **5** was then taken up in 45 mL of 15% KOH and heated to reflux for 2 h. After cooling the reaction mixture, it was extracted with ether (5 × 60 mL), dried over $MgSO_4$, and concentrated at reduced pressure. This concentrate was evaporatively distilled (160 °C/25 mm) to afford 6.00 g (75%, from *N*-formyl-L-prolinol (**4**)) of analytically pure pyrrolidine **6** as a colorless oil: $[\alpha]^{22}_D$ +6.40° (*c* 5.00, CH_2Cl_2); 60-MHz ^1H NMR (CCl_4) δ 1.23–2.10 (m, 5 H, $HNCH_2CH_2CH_2$), 1.72–3.83 (m, 9 H, NCH_2, $NCHCH_2OCH_2CH_2OCH_3$), 3.37 (s, 3 H, OCH_3); IR (CCl_4) 2880 (s), 1456 (w), 1205 (m), 1112 (s) cm^{-1}. Anal. Calcd for $C_8H_{17}NO_2$ C, 60.35; H, 10.76; N, 8.80. Found: C, 58.75; H, 10.45; N, 8.45.

***N*-(Benzyloxycarbonyl)-L-proline Methyl Ester (7).** To anhydrous methanol (1.25 L) cooled to −10 °C (isopropyl alcohol–dry ice bath) was added dropwise thionyl chloride (8.03 mL, 1.10 mmol) with stirring. To this solution was then added *N*-(benzyloxycarbonyl)-L-proline[30] (124.0 g, 500 mmol) in dry dichloromethane (60 mL). After the mixture was allowed to stir at −10 °C for 2 h, the solution was brought to room temperature and stirred overnight. Solid sodium bicarbonate was added in small portions to the vigorously stirring reaction mixture until neutral pH was reached, the mixture filtered, and the filtrate was concentrated and partitioned between ether (300 mL) and water (100 mL). After separation of the ether phase, the aqueous layer was extracted with ether (2 × 100 mL), and the combined ether extract washed with brine (1 × 50 mL), dried with sodium sulfate, concentrated in vacuo, and distilled (bp 190 °C/0.01 mm) to give 129.7 g (99%) of **7** as a clear colorless oil: $[\alpha]^{22}_D$ −56.5° (*c* 1.94, CH_3OH) [lit.[31] $[\alpha]^{20}_D$ −57.3° (*c* 1.0, CH_3OH)]; R_f 0.18 (ethyl acetate–hexanes 1:3); ^1H NMR ($CDCl_3$) δ 1.76–2.36 (m, 4 H, $NCH_2CH_2CH_2$), 3.34–3.75 (m, 2 H, NCH_2), 3.58 and 3.75 (rotamers) (s, 3 H total, OCH_3), 4.30–4.44 (m, 1 H, $NCH(CO_2CH_3)$), 5.01, 5.07, 5.14, 5.17, and 5.22 (rotamers) (s, 2 H total, OCH_2Ph), 7.22–7.43 (m, 5 H, PhH); IR (neat) 3035 (w), 2980 (m), 2955 (m), 1740 (vs), 1702 (vs), 1497 (w), 1412 (vs), 1353 (vs), 1280 (s), 1202 (vs), 1172 (vs), 1120 (s), 1090 (s), 1030 (m), 1002 (m), 771 (m), 745 (m), 700 (m) cm^{-1}.

(*S*)-*N*-(Benzyloxycarbonyl)-2-(1-hydroxy-1-methylethyl)pyrrolidine (8). To a rapidly stirring solution of *N*-(benzyloxycarbonyl)-L-proline methyl ester (**7**) (10.53 g, 40.0 mmol) in 60 mL dry THF cooled to −20 °C was added dropwise 40 mL of methylmagnesium bromide in diethyl ether (3.0 M, 120 mmol). After stirring at −20 °C for 0.5 h, the cooling bath was changed to one of ice–water and stirring continued for a further 1 h. The reaction was quenched by slowly pouring into a saturated NH_4Cl solution containing some ice and after separation of the organic layer, the aqueous phase was extracted with ether (4 × 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, concentrated, and the resulting yellow oil evaporatively distilled. After a minor forerun (130–140 °C/0.03 mm) was collected and discarded, 9.36 g (89%) of tertiary alcohol **8** (bp 160 °C/0.03 mm) was obtained as a slightly yellow oil: $[\alpha]^{22}_D$ −69.4° (*c* 1.38, $CHCl_3$); R_f 0.27 (ethyl acetate–petroleum ether 1:2); ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H, CCH_3), 1.19 (s, 3 H, CCH_3), 1.50–2.22 (m, 4 H, $NCH_2CH_2CH_2$), 3.19–3.35 (m, 1 H, $NCHH$), 3.70–3.86 (m, 1 H, $NCHH$), 3.90–4.01 (t, J = 7.33 Hz, 1 H, $NCHC(OH)(CH_3)_2$), 5.16 (s, 2 H, OCH_2Ph), 5.62 (br s, 1 H, OH), 7.30–7.54 (s, 5 H, PhH); IR (neat) 3380 (br), 2965 (m), 1670 (vs), 1447 (s), 1410 (vs), 1355 (s), 1210 (m), 1110 (m), 948 (w) cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.37; H, 8.11; N, 5.34.

(*S*)-1-Methyl-1-(2-pyrrolidinyl)ethanol (9). (*S*)-*N*-(Benzyloxycarbonyl)-2-(1-hydroxy-1-methylethyl)pyrrolidine (**8**) (26.33 g, 100 mmol) in 190 mL of anhydrous methanol was hydrogenated at room temperature over 5% palladium–charcoal (1.70 g) until the presence of starting material was not detected by TLC (typically requiring about 2–3 h). The mixture was then filtered through Celite, the Celite washed with ether (300 mL), and the combined organic phase evaporated in vacuo and evaporatively distilled (bp 110 °C/10 mm) to afford 11.15 g (86%) of **9** as a colorless oil which slowly crystallized to a highly hygroscopic, low melting solid: $[\alpha]^{25}_D$ −32.3° (*c* 1.84, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.19 (s, 3 H, CCH_3), 1.30 (s, 3 H, CCH_3), 1.65–2.00 (m, 4 H, $HNCH_2CH_2CH_2$), 3.00–3.30 (m, 3 H, $HNCH_2$ and $HNCHC(OH)(CH_3)_2$), 4.5 (br s, 2 H, NH and OH); ^{13}C NMR (Me_2SO-d_6) δ 25.7, 26.0, 26.4, 27.4, 46.5, 67.1, 70.0; IR (neat) 3300 (br), 2960 (vs), 2867 (s), 1640 (w), 1538 (w), 1460 (w), 1378 (m), 1335 (w), 1226 (w), 1148 (m), 1080 (w), 945 (w) cm^{-1}. Anal. Calcd for $C_7H_{15}NO$: C, 64.74; H, 11.04; N, 10.78. Found: C, 64.11; H, 11.88; N, 10.49.

(*S*)-*N*-Formyl-2-(1-hydroxy-1-methylethyl)pyrrolidine (10). A solution of amino alcohol **9** (8.82 g, 68.3 mmol) and ethyl formate (33.5 mL, 415 mmol) in 42 mL of dry CH_2Cl_2 was allowed to stir for 2 days at room temperature under N_2. The reaction mixture was concentrated in vacuo to a yellow oil and passed through 3 in. of silica with the aid of ethyl acetate to give, after concentration of eluents, an oil. Evaporative distillation (140 °C/0.03 mm) of this material afforded 9.68 g (90%) of **10** as a colorless oil. A small portion was purified by flash chromatography using ethyl acetate as the eluent for elemental analysis: $[\alpha]^{21.5}_D$ −132.8° (*c* 1.16, $CHCl_3$); R_f 0.41 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.09 (major rotamer) and 1.17 (minor rotamer) (s, 3 H total, CH_3), 1.18 (major rotamer) and 1.24 (minor rotamer) (s, 3 H total, CH_3), 1.47–2.31 (m, 5 H, $NCH_2CH_2CH_2$ and OH), 3.10–3.20 (minor rotamer) and 3.25–3.44 (major rotamer) (m, 1 H total, $NCHH$), 3.68–4.05 (m, 2 H, $NCHH$ and $NCHC(OH)(CH_3)_2$), 8.30 (major rotamer) and 8.40 (minor rotamer) (s, 1 H total, CHO); IR (neat) 3380 (br), 2975 (s), 2880 (m), 1647 (vs), 1467 (w), 1416 (m), 1385 (s), 1337 (w), 1170 (m), 1140 (w) cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.75; H, 9.69, N, 8.82.

(*S*)-2-(1-Methoxy-1-methylethyl)pyrrolidine (11). A solution of sodium methylsulfinyl carbanion was prepared from sodium hydride (3.46 g, 144 mmol) and 56 mL of dry DMSO according to the procedure of Sjöberg.[32] To a stirred solution of hydroxyamide **10** (10.69 g, 68.0 mmol) in 20 mL of dry DMSO containing a trace of triphenylmethane under N_2 kept at ambient temperature by a room-temperature water bath was added sodium methylsulfinyl carbanion until a bright red solution persisted. This mixture was treated with dimethyl sulfate (7.1 mL, 75 mmol) and stirring with cooling continued for 10 min. The reaction mixture was then treated with 20 mL of H_2O and 200 mL of CH_2Cl_2 and

(28) Benschop, H. P.; Van der Berg, G. R.; Boter, H. L. *Recl. Trav. Chim. Pays-Bas.* **1968**, *87*, 387.
(29) This sulfonate was prepared in quantitative yield by treatment of 2-methoxyethanol in pyridine with TsCl.
(30) Bodanszky, M.; du Vigreud, V. *J. Am. Chem. Soc.* **1959**, *81*, 5688.
(31) Ito, A.; Takashishi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.
(32) Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand. Ser. B* **1972**, *26*, 275.

the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic phase dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting crude product was evaporatively distilled (115 °C/0.03 mm) to afford 10.38 g (89%) of (*S*)-*N*-formyl-2-(1-methoxy-1-methylethyl)pyrrolidine as a colorless oil. A small portion was further purified by flash chromatography using ethyl acetate as the eluent for elemental analysis: $[\alpha]^{22}_D$ −45.2° (*c* 1.76, $CHCl_3$); R_f 0.35 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.07 (major rotamer) and 1.17 (minor rotamer) (s, 3 H total, $C(OCH_3)(CH_3)CH_3$), 1.13 (major rotamer) and 1.18 (minor rotamer) (s, 3 H total, $C(OCH_3)(CH_3)CH_3$), 1.63–2.17 (m, 4 H, $NCH_2CH_2CH_2$), 3.00–3.20 (m, 1 H, NCHH), 3.18 (minor rotamer) and 3.20 (major rotamer) (s, 3 H total, OCH_3), 3.50–3.60 (minor rotamer), 3.68–4.00 (major rotamer) and 4.09–4.21 (minor rotamer) (m, 2 H total, NCH*H* and $NCHC(OCH_3)(CH_3)_2$), 8.23 (minor rotamer) and 8.36 (major rotamer) (s, 1 H total, CHO); IR (neat) 2970 (s), 2935 (s), 2885 (m), 2825 (m), 1650 (vs), 1465 (m), 1458 (m), 1407 (s), 1382 (vs), 1177 (m), 1146 (m), 1088 (m), 1065 (m) cm^{-1}. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.14; H, 10.22; N, 8.16.

A mixture of (*S*)-*N*-formyl-2-(1-methoxy-1-methylethyl)pyrrolidine (2.88 g, 16.8 mmol) in 36 mL of 10% KOH was heated at refluxing temperature for 1.5 h. The cooled reaction mixture was extracted with ether (5 × 60 mL), and the ethereal layer dried over Na_2SO_4, filtered, and concentrated in vacuo. Evaporative distillation (95 °C/10 mm) of this concentrate afforded 2.08 g (86%) of amino ether **11** as a colorless liquid: $[\alpha]^{24}_D$ −24.5° (*c* 2.36, CH_3OH); R_f 0.08 (methanol–dichloromethane 3:1); ^1H NMR ($CDCl_3$) δ 1.13 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.18 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.44–1.80 (m, 4 H, $HNCH_2CH_2CH_2$), 2.12 (br, 1 H, NH), 2.75–2.90 (m, 1 H, HNCHH), 2.94–3.08 (m, 2 H, HNCH*H* and $HNCHC(OCH_3)(CH_3)_2$), 3.22 (s, 3 H, OCH_3); ^{13}C NMR (Me_2SO-d_6) δ 20.8, 21.5, 25.7, 26.2, 46.7, 48.6, 65.4, 76.4; IR (neat) 3310 (br), 2965 (s), 2820 (m), 1630 (w), 1460 (w), 1377 (w), 1365 (w), 1246 (w), 1180 (w), 1145 (w), 1080 (m), 920 (w) cm^{-1}. Anal. Calcd for $C_8H_{17}NO$: C, 74.37; H, 13.26; N, 10.84. Found: C, 66.23; H, 12.23; N, 9.61.

Bis(2,4-dichlorophenyl) Phosphorochloridate (12). A mixture of freshly distilled phosphoryl chloride (17.5 mL, 188 mmol), magnesium turnings (0.16 g, 6.6 mmol), and 2,4-dichlorophenol (48.9 g, 300 mmol) was gradually heated to an oil bath temperature of 120 °C under a reflux condenser connected to a trap for neutralization of acidic fumes (a vigorous release of HCl gas takes place at approximately 110 °C). After heating at 120 °C for 3 h, the bath temperature was raised to 160 °C and heating was continued for a further 3 h. The resulting viscous orange oil was evaporatively distilled directly to first give 14.20 g of 2,4-dichlorophenyl phosphorodichloridate (**13**) (bp 180 °C/0.02 mm) as a colorless liquid. Further distillation of the reaction mixture afforded the bis(2,4-dichlorophenyl) phosphorochloridate (**12**) as a colorless oil which when taken up in a minimum volume of hexanes and placed in the freezer provided 27.70 g (45%) of the title compound as analytically pure white crystals.

Meanwhile, a mixture of the recovered 2,4-dichlorophenyl phosphorodichloridate (**13**) (14.2 g, 50.7 mmol), magnesium turnings (23 mg, 0.96 mmol), and 2,4-dichlorophenol (7.44 g, 45.6 mmol) was heated at 150 °C oil-bath temperature for 5 h and the resulting oil evaporatively distilled to give a further 7.53 g of **12** for a combined yield of 58%: mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 7.29 (dd, *J* = 2.0, 8.8 Hz, 2 H, ArH), 7.39–7.56 (m, 4 H, ArH); IR ($CHCl_3$) 3100 (w), 3020 (w), 1580 (w), 1473 (vs), 1388 (w), 1310 (s), 1252 (s), 1225 (s), 1146 (m), 1102 (vs), 1058 (s), 971 (vs), 872 (m), 830 (vs) cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_5O_3P$: C, 35.46; H, 1.49. Found: C, 35.61; H, 1.40.

Bis(2,4-dichlorophenyl) 1-[(2*S*)-2-(Methoxymethyl)pyrrolidinyl]-phosphonate (14). Representative Procedure. To a stirred mixture of bis(2,4-dichlorophenyl) phosphorochloridate (**12**) (8.12 g, 20.0 mmol) in 20 mL of dry CH_2Cl_2 cooled to 0 °C under N_2 was added dropwise a solution of (*S*)-2-(methoxymethyl)pyrrolidine[19] (**3**) (2.30 g, 20.0 mmol) and diisopropylethylamine (3.90 mL, 22.0 mmol) in 20 mL of dry CH_2Cl_2. After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stir overnight. The mixture was diluted with CH_2Cl_2, washed with 10% HCl (1 × 30 mL) and saturated $NaHCO_3$ (1 × 30 mL), and dried over Na_2SO_4. Filtration and removal of solvent under reduced pressure gave a yellow solid which was purified by flash chromatography using 20% ethyl acetate in hexanes as the eluent. There was obtained 6.33 g (65%) of **14** as white crystals: mp 76–77 °C (diethyl ether–hexanes); $[\alpha]^{22}_D$ −33.0° (*c* 3.10, $CHCl_3$), R_f 0.22 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 1.75–2.06 (m, 4 H, $NCH_2CH_2CH_2$), 3.26 (s, 3 H, OCH_3), 3.26–3.64 (m, 4 H, CH_2OCH_3, NCH_2), 3.96–4.12 (m, 1 H, $NCHCH_2OCH_3$), 7.14–7.25 (m, 2 H, ArH), 7.41 (apparent d, *J* = 2.4 Hz, 2 H ArH), 7.49 (ddd, *J* = 1.5, 5.9, 8.8 Hz, 2 H, ArH); IR ($CHCl_3$) 3005 (w), 1585 (w), 1575 (w), 1478 (vs), 1390 (w), 1290 (m), 1255 (m), 1230 (m), 1215 (m), 1100 (s), 1063 (m), 930 (m), 870 (w), 828 (m) cm^{-1}. Anal. Calcd for $C_{18}H_{18}Cl_4NO_4P$: C, 44.57; H, 3.74; N, 2.89. Found: C, 44.57; H, 3.69; N, 2.86.

(*S*)-Butyl 2,4-Dichlorophenyl 1-[(2*S*)-2-(Methoxymethyl)-pyrrolidinyl]phosphonate (17). A stirred solution of bis(2,4-dichlorophenyl) phosphoramidate **14** (2.00 g, 4.12 mmol) in 20 mL of dry THF was cooled to 0 °C under N_2. Meanwhile, a 0.11 M solution of lithium butoxide was prepared in a separate flask from 1-butanol (1.34 mL, 14.6 mmol) and *n*-butyllithium (7.65 mL of 1.62 M solution in hexanes, 12.4 mmol) in 100 mL dry THF under N_2 at 0 °C. To the ice bath cooled solution of phosphoramidate **14** was then added lithium butoxide (57 mL, 6.3 mmol) dropwise over 3 h. After allowing to stir for an additional 1 h, the reaction mixture was quenched by partitioning between 60 mL of CH_2Cl_2 and 50 mL of saturated $NaHCO_3$. The organic layer was then separated, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Purification of the organic layer concentrate by flash chromatography using 40% ethyl acetate in hexanes as the eluent afforded 1.054 g (65%) of **17** as a colorless oil. A small portion was evaportively distilled (190 °C/0.05 mm) for elemental analysis: $[\alpha]^{20}_D$ −28.9° (*c* 3.06, $CHCl_3$); R_f 0.32 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.29–1.49 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.53–1.99 (m, 6 H, $OCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2$), 3.11–30.49 (m, 4 H, NCH_2, CH_2OCH_3), 3.28 (s, 3 H, OCH_3), 3.83–3.99 (m, 1 H, $NCHCH_2OCH_3$), 4.12 (dq, *J* = 2.4, 6.7 Hz, 2 H, $OCH_2CH_2CH_2CH_3$), 7.13–7.24 (7, 1 H, ArH), 7.40 (dd, *J* = 1.2, 2.4 Hz, 1 H, ArH), 7.52 (dd, *J* = 1.2, 8.5 Hz, 1 H, ArH); IR ($CHCl_3$) 3005 (m), 2965 (m), 2935 (m), 2880 (m), 1480 (vs), 1263 (s), 1235 (m), 1210 (m), 1100 (s), 1062 (s), 1030 (s), 927 (m), 810 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{24}Cl_2NO_4P$: C, 48.50; H, 6.10; N, 3.53. Found: C, 48.73; H, 6.17; N, 3.54.

(*S*)-Butyl 2,4-Dichlorophenyl Methyl Phosphate (20). Representative Procedure. A stirred solution of phosphoramidate **19** (614 mg, 1.45 mmol) in 45 mL of dry MeOH was cooled to 0 °C under N_2. Then, dry hydrogen chloride was bubbled into the cooled solution for ca. 1.5–2 min and the reaction mixture allowed to react overnight at room temperature. The mixture was concentrated at reduced pressure to a yellowish oil to which 50 mL of ether was added, followed by 10 mL of H_2O. The organic phase was separated and the aqueous layer extracted with ether (5 × 50 mL). The combined ethereal phase was then throughly dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the crude phosphate **20**. This material was purified by flash chromatography using 35% ethyl acetate in hexanes as the eluent and evaporatively distilled (170 °C/0.06 mm) to afford 334 mg (74%) of **20** as a colorless oil. ^1H NMR spectral analysis in the presence of $Eu(hfc)_3$ indicated >95% ee, the low-field enantiomer being in excess: $[\alpha]^{22}_D$ −3.61° (*c* 4.10, $CHCl_3$); R_f 0.38 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.31–1.54 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.61–1.80 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 3.90 (d, *J* = 11.2 Hz, 3 H, OCH_3), 4.20 (q, *J* = 6.8 Hz, 2 H, $OCH_2CH_2CH_2CH_3$), 7.2 (dd, *J* = 2.4, 8.8 Hz, 1 H, ArH), 7.34–7.47 (m, 2 H, ArH); IR (neat) 2880 (s), 1475 (vs), 1292 (s), 1260 (s), 1235 (s), 1100 (w), 1040 (vs), 935 (vs), 828 (s) cm^{-1}. Anal. Calcd for $C_{11}H_{15}Cl_2O_4P$: C, 42.20; H, 4.83. Found: C, 42.37; H, 4.90.

(*S*)-2,4-Dichlorophenyl ethyl 1-[(2*S*)-2-(methoxymethyl)-pyrrolidinyl]phosphonate (21) was prepared from phosphoramidate **14** (1.50 g, 3.09 mmol) and lithium ethoxide by the method described for the preparation of phosphoramide **17**. Purification by flash chromatography using 40% ethyl acetate in hexanes as the eluent provided 685 mg (60%) of **21** as a slightly yellow oil. A small portion was evaporatively distilled (160 °C/0.02 mm) for elemental analysis: $[\alpha]^{22}_D$ −33.2° (*c* 1.43, $CHCl_3$); R_f 0.22 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 1.30–1.42 (m, line spacing = 6.7, 7.9 Hz, 3 H, OCH_2CH_3), 1.70–2.00 (m, 4 H, $NCH_2CH_2CH_2$), 3.08–3.48 (m, 4 H, NCH_2, CH_2OCH_3), 3.28 (s, 3 H, OCH_3), 3.83–3.97 (m, 1 H, $NCHCH_2OCH_3$), 4.10–4.29 (m, 2 H, OCH_2CH_3), 7.14–7.24 (m, 1 H, ArH), 7.37–7.43 (m, 1 H, ArH), 7.53 (dd, *J* = 1.8, 8.5 Hz, 1 H, ArH); IR (neat) 2980 (s), 1477 (vs), 1390 (m), 1275 (s), 1250 (s), 1240 (s), 1100 (vs), 1060 (vs), 1040 (vs), 968 (s), 925 (s), 812 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{20}Cl_2NO_4P$: C, 45.67; H, 5.48; N, 3.80. Found: C, 45.81; H, 5.58; N, 3.78.

(*S*)-Butyl Ethyl 1-[(2*S*)-2-(1-Methoxy-1-methylethyl)pyrrolidinyl]-phosphonate (26). Representative Procedure. To a stirred solution of phosphoramidate **19** (1.20 g, 2.83 mmol) in 15 mL of dry THF at room temperature under N_2 was added sodium ethoxide (8.25 mmol, prepared from 198 mg of sodium hydride and 0.52 mL of EtOH in 20 mL of dry THF). After allowing the mixture to stir for 3 days, it was quenched by partitioning between 20 mL of saturated $NaHCO_3$ and 50 mL of CH_2Cl_2. After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layer was thoroughly dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the resulting crude product by flash chromatography using 70% ethyl acetate in hexanes as the eluent afforded 779 mg (90%) of **26**.

A small portion was evaporatively distilled (120 °C/0.02 mm) for elemental analysis: $[\alpha]^{23}_D$ -23.2° (c 1.16, $CHCl_3$); R_f 0.27 (70% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.16 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.18 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.23-1.53 (m, line spacing = 7.1, 7.1, 4.4, 7.3, 7.8, 7.3, 6.8 Hz, 5 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$), 1.53-2.06 (m, 6 H, $OCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2$), 2.83-3.08 (m, 1 H, NCHH), 3.19 (s, 3 H, OCH_3), 3.26-3.47 (m, 1 H, NCHH), 3.66-3.85 (m, 1 H, $NCHC(OCH_3)(CH_3)_2$), 3.89-4.11 (m, 4 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$); IR (neat) 2960 (s), 1268 (s), 1245 (s), 1062 (vs), 1024 (vs), 980 (m), 957 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{30}NO_4P$: C, 54.71; H, 9.84; N, 4.56. Found: C, 54.99; H, 10.11; N, 4.47.

(*R*)-Butyl Ethyl Methyl Phosphate [(*R*)-33] via Protic Acid Catalyzed Methanolysis of 30. Representative Procedure. Phosphate (*R*)-**33** was prepared from phosphoramidate **30** (459 mg, 1.48 mmol) by the method described for the preparation of phosphate **20**. Purification by flash chromatography using 50% ethyl acetate in hexanes as the eluent followed by evaporative distillation (95 °C/0.8 mm) afforded 136 mg (47%) of (*R*)-**33** as a colorless liquid. ^1H NMR spectral analysis in the presence of $Eu(hfc)_3$ indicated 71% ee, the high-field enantiomer being in excess: $[\alpha]^{23}_D$ -0.07° (c 9.84, acetone); R_f 0.12 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.28-1.52 (m, 5 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$), 1.58-1.75 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 3.76 (d, J = 11.2 Hz, OCH_3), 3.97-4.21 (m, 4 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 13.58, 16.12, 16.18, 18.69, 32.29, 32.34, 54.06, 54.11, 63.83, 63.88, 67.57, 67.62; IR (neat) 2960 (s), 1463 (w), 1270 (vs), 1030 (vs), 836 (s) cm^{-1}; MS (CI, CH_4) *m/z* (relative intensity) 197 (MH^+, 20.8), 169 (12.9), 141 (100), 113 (35). Anal. Calcd for $C_7H_{17}O_4P$: C, 42.86; H, 8.73. Found: C, 41.85; H, 8.97.

(*R*)-33 via Sodium *n*-Butoxide Displacement of Phosphate 24. Representative Procedure. A 0.34 M solution of sodium butoxide was prepared from 1-butanol (0.20 mL, 2.2 mmol) and sodium hydride (50.8 mg, 2.12 mmol) in 6 mL of dry THF under N_2 at room temperature. To a stirred solution of phosphate **24** (115 mg, 0.405 mmol) in 3 mL of dry THF at room temperature under N_2 was then added sodium butoxide (2.4 mL, 8.2 mmol) over 30 min. After allowing the reaction mixture to stir for 2.5 h, it was quenched by partitioning between 10 mL of saturated $NaHCO_3$ and 30 mL of CH_2Cl_2. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 layer was thoroughly dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography using 45% ethyl acetate in hexanes as the eluent followed by evaporative distillation afforded 27.4 mg (55%) of a colorless liquid possessing identical ^1H NMR, IR, and TLC characteristics with that of **33** prepared from **30**. ^1H NMR spectral analysis in the presence of $Eu(hfc)_3$ indicated 87% ee, the high-field enantiomers being in excess.

Recovery of Chiral Auxiliary 11. Representative Procedure. Aqueous HCl layers from several phosphoramidate methanolysis reactions were combined and basified with 20% NaOH. This aqueous solution was extracted with ether (5 × 100 mL), and the ethereal layer dried over N_2SO_4, filtered, and concentrated to a yellow liquid. This material was evaporatively distilled to afford 1.32 g (60% recovery) of aminoether **11**, identical in bp, NMR and IR characteristics with those of freshly prepared sample: $[\alpha]^{23}_D$ -24.8° (c 2.94, MeOH).

Recovery of chiral auxiliary reagents **3** and **6** were carried out in analogous fashion to also provide unchanged materials in satisfactory yields.

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Supplementary Material Available: General experimental details, method of preparation, and spectral data for compounds not included in the Experimental Section; tables of data for X-ray diffraction study, bond angles, interatomic distances, positional parameters, isotropic temperature factors, and anisotropic temperature factors of compound **14** (32 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Isolobophytolide and (±)-Crassin by Titanium-Induced Carbonyl Coupling

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Abstract: Syntheses of the antitumor cembrane lactones (±)-crassin (**1**) and (±)-isolobophytolide (**2**) are reported. The key steps are the titanium-induced pinacol coupling of lactone keto aldehydes **3c** and **3t** to yield macrocyclic diols without harming the lactone rings also present in the molecules. Compound **3t** yields a diol (**18a**) that is converted into isolobophytolide by epoxide formation and methylenation. Compound **3c** yields a diol (**21a**) that is converted into crassin by double stereochemical inversion of the hydroxyl groups, translactonization, and methylenation. The syntheses demonstrate an important extension of the titanium-induced carbonyl-coupling reaction by showing that complex, polyoxygenated macrocycles can be produced.

The cembrene diterpenes are a large and varied class of natural products characterized by the presence of a 14-membered carbocyclic ring.[1] Cembranes have been detected in plants, insects, and animals and have been found in terrestrial as well as marine environments. The majority of known cembranes have come from pine trees and tobacco plants,[2] but many others have come from marine organisms.[3] Simple marine invertebrates, particularly the Caribbean gorgonians (sea fans and sea whips, order *Gorgonacea*) and the Pacific soft corals (true soft corals, order *Alcyonacea*) have provided a rich selection of highly oxygenated

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