apparatus for 1.9 h. Removal of the solvent in vacuo left a mixture of **28** and **29**.

Compounds **28** and **29** were separated by preparative GC (column f, 155 °C). Collection of the second peak afforded 0.11 g (19%) of **29**, whose spectral data were identical with those of an authentic sample.

An analytical photolysis of 10 mL of 0.015 M **28** in benzene, after 7.7 h of irradiation through quartz, showed, by GC analysis (column b, 120 °C) using naphthalene as an internal standard, a 65% conversion of **28**, yielding **29** (34%).

Sensitized Irradiation of 2-(3-Methylphenyl)-1,6-heptadiene (28). An analytical photolysis of 10 mL of 0.016 M **28** and 0.024 g of xanthone in benzene, after 7.7 h of irradiation through Pyrex, showed, by GC analysis (column b, 120 °C) using 2-methylnaphthalene as an internal standard, a 60% conversion of **28** to give **29** in 50% yield.

Direct Irradiation of 1-(2-Methylphenyl)-6-hepten-1-one (2). A solution of 5.0 g (0.025 mol) of **2** in 500 mL of benzene was irradiated through quartz in the preparative photochemical apparatus for 9.1 h. After the solvent had been removed in vacuo, the residue was distilled and 2.1 g (63%) of *o*-methylacetophenone was isolated from the fraction boiling at 56–57 °C (1.7 mmHg). Spectral comparison with an authentic sample confirmed the structural assignment.

Acknowledgment. We gratefully acknowledge support of this research by a grant from the National Science Foundation (CHE77-07881 A01). R.D.B. thanks the Marathon Oil Co. for summer support and the Boettcher Foundation for a fellowship.

Registry No. **1**, 81536-61-0; **2**, 83845-35-6; **3**, 83845-36-7; **4**, 83845-37-8; **5**, 83845-38-9; **6**, 70561-39-6; **14**, 502-44-3; **15**, 83845-39-0; **16**, 83861-69-2; *cis*-**17**, 83845-40-3; *trans*-**17**, 83845-59-4; **18**, 83845-41-4; **22**, 73357-80-9; **23**, 83845-42-5; **24** (isomer 1), 83845-43-6; **24** (isomer 1) tosyl hydrazone, 83845-44-7; **24** (isomer 2), 83845-60-7; **24** (isomer 2) tosyl hydrazone, 83845-61-8; **25**, 83845-45-8; **26**, 83845-46-9; **27**, 83845-47-0; **28**, 83845-48-1; **29**, 83845-49-2; **30**, 83845-50-5; **31**, 83845-51-6; **32**, 83845-52-7; **33**, 83845-53-8; **34**, 83845-54-9; **35**, 83845-55-0; **36**, 83845-56-1; **37**, 83845-57-2; **38**, 83845-58-3; **39**, 14918-24-2; Ph_3PCHCO_2Et, 1099-45-2; *o*-tolunitrile, 529-19-1; *o*-bromotoluene, 95-46-5; 2-cyclopentenone, 930-30-3; *o*-methylstyrene, 611-15-4; 5-hexenal, 764-59-0; methyltriphenylphosphonium bromide, 1779-49-3.

Asymmetric Synthesis of Enantiomeric Cyclophosphamides

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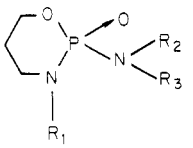
An efficient asymmetric synthesis of the enantiomers of cyclophosphamide was developed on the basis of three important steps: (1) a highly stereospecific synthesis of the 2-chloro-2-oxo-1,3,2-oxazaphosphorinane ring from an optically active amino alcohol and phosphoryl chloride (diastereomer ratio obtained is 10:1 to 12:1); (2) the use of the diethanolamine derivative as an intermediate for introduction of the mustard group; (3) a novel, simple, and effective method for cleaving an *N*-benzyl group by sulfuric acid in toluene, instead of hydrogenolysis.

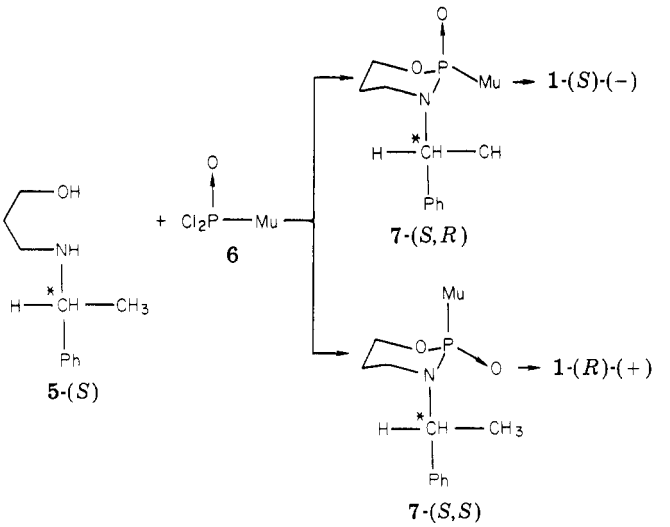
It is still an open question whether (−)-(*S*)-cyclophosphamide [2-[bis(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorinane, (*S*)-**1**] is a therapeutically more effective antineoplastic agent[2] than the racemic mixture. Since the first resolution[3,4] of cyclophosphamide **1**, a number of



1, R_1 = H; R_2 = CH_2CH_2Cl; R_3 = CH_2CH_2Cl
2, R_1 = CH_2CH_2Cl; R_2 = H; R_3 = CH_2CH_2Cl
3, R_1 = CH_2CH_2Cl; R_2 = CH_2CH_2Cl; R_3 = CH_2CH_2Cl
4, R_1 = CH_2CH_2Cl; R_2 = H; R_3 = $CH_2CH_2OSO_2CH_3$

synthetic methods have been developed leading to the optically active forms of **1** and the related compounds, iphosphamide (**2**), trophosphamide (**3**), and sulphosphamide (**4**). A stereospecific synthesis of the enantiomers of **2**[5] and of **3**[5] was reported recently. Resolution of **3** by a platinum complex was also reported.[6] Absolute configurations of the levorotatory form of **1** as *S*[7a] and of the

Scheme I[a]



[a] Mu = $N(CH_2CH_2Cl)_2$.

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(2) Cox, P. J.; Farmer, P. B.; Jarman, M.; Jones, M.; Stec, W. J. *Biochem. Pharmacol.* **1976**, *25*, 993.

(3) Kinas, R.; Pankiewicz, K.; Stec, W. J. *Bull. Acad. Pol. Sci., Ser. Sci. Chem.* **1975**, *23*, 981.

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dextrorotatory form as R[7b] were independently determined by X-ray analysis. Direct resolution of the racemic mixture of **1** was reported by using (*S*)-(−)- or (*R*)-(+)-[[(1-naphthyl)phenylmethyl]silyl chloride.[8] Most recently, we have reported[9] a direct resolution method for chiral phosphamides such as **1** using optically active *N*-acyloxyalkyl derivatives. There is a clear need, however, for an efficient asymmetric synthesis for **1**–**4**, as most of the above methods require special conditions and reagents and/or have low yields.

Here we report an efficient asymmetric synthesis of the enantiomers of **1** which is based on three important steps: (1) a highly stereospecific synthesis of the 2-chloro-2-oxo-1,3,2-oxazaphosphorinane ring; (2) the use of the diethanolamine derivative as an intermediate for introduction of the mustard group; (3) a novel, simple, effective method for cleaving an *N*-benzyl group by sulfuric acid in toluene, instead of hydrogenolysis.

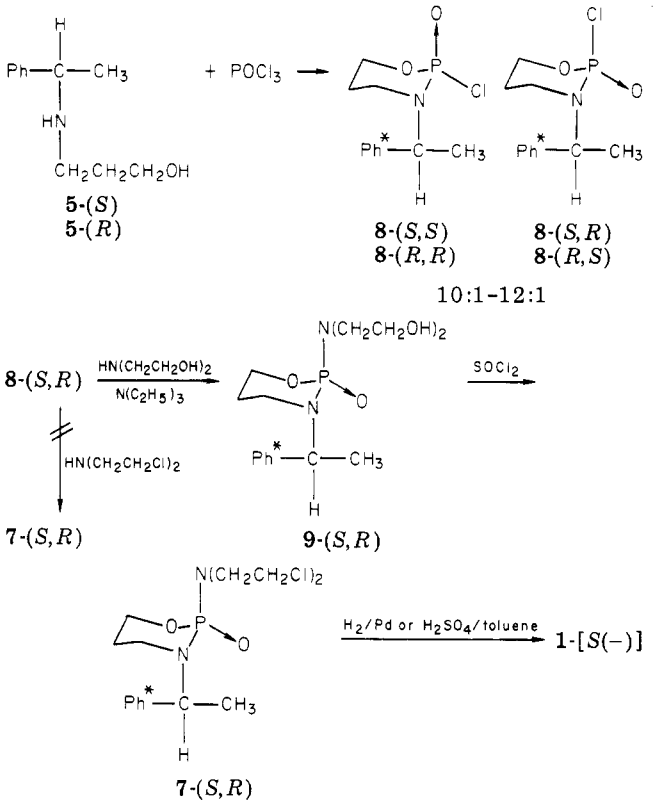
In the original Stec synthesis,[3] the optically active amino alcohol **5**-(*S*) was reacted with *N*,*N*-bis(2-chloroethyl)-phosphoramidodichloridate (**6**) to give a mixture of diastereomers of 2-[bis(2-chloroethyl)amino]-3-[(*S*)-α-methylbenzyl]-1,3,2-oxazophosphorinane 2-oxides, **7**-(*S*,*R*)[10] and **7**-(*S*,*S*), in a 1:1 ratio.

Separation of the diastereomers of **7** by chromatography followed by hydrogenolysis afforded the enantiomers **1**-(*S*)-(−) and **1**-(*R*)-(+). Contrary to the reaction between **5**-(*S*) or **5**-(*R*) with **6**, which leads to a 1:1 mixture of the diastereomers, we have found that the amino alcohol **5**-(*S*) reacts with phosphoryl chloride ($POCl_3$) in a highly stereoselective manner.[11] The same observation, but under different conditions and with lower stereoselectivity, was reported independently.[12] Thus, the diastereomers of 2-chloro-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane, **8**-(*S*,*S*) and **8**-(*S*,*R*) were obtained by us in a ratio of from 10:1 to 12:1 in an almost quantitative yield. Recrystallization from toluene–hexane yielded the major diastereomer **8**-(*S*,*S*) in pure form in about 78% yield. Chromatography of the mother liquors yielded 3–5% of the minor diastereomer **8**-(*S*,*R*) and further amounts of **8**-(*S*,*S*). Similarly, the antipodal amino alcohol **5**-(*R*) resulted in the diastereomers **8**-(*R*,*R*) and **8**-(*R*,*S*).

We have found that, in general, nonpolar solvents and low temperatures are necessary for high stereoselectivity and high yield. The decreasing stereoselectivity order observed is toluene > xylene ≈ diethyl ether ≈ tetrahydrofuran > dichloromethane > 1,2-dichloroethane. Temperatures of −20 to −30 °C result in good stereoselectivity. These findings explain the lower stereoselectivity (80:20) observed by Stec et al.[12] with dichloromethane. (The pure diastereomers were not isolated.[12])

Attempts to convert the pure isomers **8**-(*S*,*S*) and **8**-(*R*,*R*) directly into the precursors **7**-(*S*,*S*) and **7**-(*S*,*R*), respectively, have failed, clearly due to the reduced reactivity of **8**, combined with the low basicity and instability of the nor-nitrogen mustard, $HN(CH_2CH_2Cl)_2$. On reaction of the more basic and stable diethanolamine with **8**-(*S*,*S*), the crystalline 2(*S*)-[bis(2-hydroxethyl)amino]-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane [**9**-(*S*,*S*)] was obtained in high yields. The same reaction of the minor diastereomer **8**-(*S*,*R*) afforded the oily diastereomer **9**-(*S*,*R*). The other two diastereomeric diols, **9**-(*R*,*R*) and **9**-(*R*,*S*), respectively, were prepared from the corresponding **8**-(*R*,*R*) and **8**-(*R*,*S*). In the above nucleophilic displacement, the specific rotation has changed from a large plus value, **8**-(*S*,*S*), to a large minus value, **9**-(*S*,*S*). The opposite trend was observed in the case of the **8**-(*S*,*R*) → **9**-(*S*,*R*) transformation. The assumption that this result corresponds to an inversion of the configuration around the phosphorus was later confirmed. It is remarkable that the reaction is fully stereospecific. NMR studies indicated that no diastereomer **9**-(*S*,*R*) was formed in the reaction of **8**-(*S*,*S*) with diethanolamine, and no **9**-(*S*,*S*) could be detected from the **8**-(*S*,*R*) → **9**-(*S*,*R*) reaction.

Scheme II



Treatment of **9**-(*S*,*S*) with thionyl chloride gave 2(*S*)-[bis(2-chloroethyl)amino]-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane [**7**-(*S*,*S*)] in high yield. The other diastereomers **7**-(*S*,*R*), **7**-(*R*,*R*), and **7**-(*R*,*S*) were prepared similarly and identified fully with authentic samples prepared by the known synthetic method.[3] Hydrogenolysis of the α-methylbenzyl group by using the known method[3] yielded **1**-[*R*(+)] from **7**-(*S*,*S*) or **7**-(*R*,*S*) and **1**-[*S*(−)] from **7**-(*S*,*R*) or **7**-(*R*,*R*). On the other hand, a novel, simple and very efficient method for cleavage of the *N*-benzyl group was found which can effectively replace the hydrogenolysis. We have found that the benzyl group can be cleaved by a strong acid (e.g., H_2SO_4) in a nonpolar solvent, such as toluene. Thus, the overall stereoselective-stereospecific synthesis of the optically active enantiomers of cyclophosphamide (**1**) can be summarized by the example given in Scheme II.

During the novel acidic C–N bond cleavage of the benzylic type amide in **7** in toluene, it was found that the cleaved benzylic group reacted with the solvent to give *o*- and *p*-(α-methylbenzyl)toluene (**13**) as shown in Scheme

(7) (a) Adamiak, D. A.; Kinas, R.; Saenger, W.; Stec, W. J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 330. (b) Karle, I. L.; Karle, J. M.; Egan, W.; Zon, G.; Brandt, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 4803.

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(9) Bodor, N.; Knutson, K. B.; Sato, T. *J. Am. Chem. Soc.* **1980**, *102*, 3969.

(10) In this notation, the first letter in the parentheses denotes the carbon configuration, and the second letter refers to the phosphorus configuration. This notation is followed throughout the paper.

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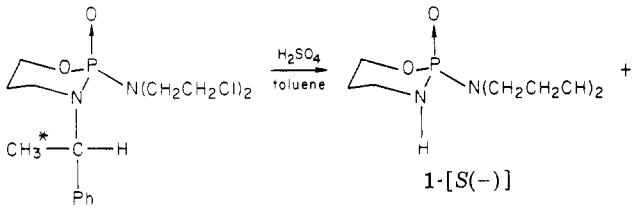
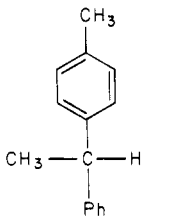
Scheme III

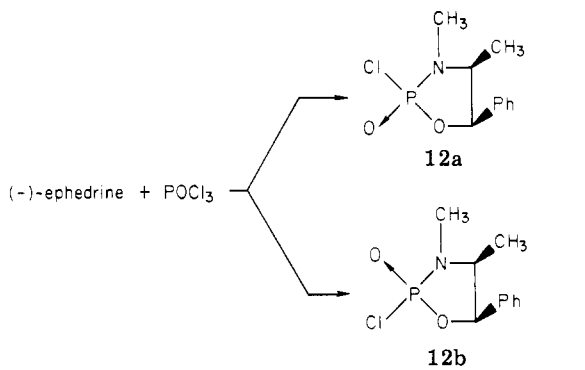


7-(*R*,*R*) 1-[*S*(−)]



13 (ortho and para)

Scheme IV



III. The structure of **13** was confirmed by NMR and mass spectra.

Similarly, the major diastereomer 8-(*S*,*S*) leads to 1-[*R*-(+)] via the diol **9**-(*S*,*S*). The assignments of the absolute configuration of phosphorus atoms in the diastereomers of **8** and **9** were based on the known absolute configuration of the enantiomeric cyclophosphamide[7a,b] [1-[*S*(−)] and 1-[*R*(+)]] and the corresponding precursors **7**-(*S*,*S*) and **7**-(*R*,*R*).

The overall result of the present studies is a highly stereospecific synthesis of cyclophosphamide enantiomers. The most important step is a high stereoselective reaction of the amino alcohol **5** with phosphoryl chloride.

Similar behavior has been observed in the rection of (−)-ephedrine with phosphoryl chloride,[13] where **12a** is the major (65%) and **12b** is the minor (6%) product (Scheme IV).

Similar asymmetric syntheses for other cyclic phosphamides should be feasible.

Experimental Section

All melting points are uncorrected. Commercial grade solvents and reagents were used without purification.

IR spectra were recorded on Hitachi 215 grating infrared spectrophotometer. ^{1}H NMR spectra were measured with a Varian EM 360 (60 MHz), a Varian EM 390 spectrometer (90 MHz), or a Bruker WH-200 spectrometer (200 MHz). Mass spectra were recorded on Shimazu LKB-9000 mass spectrometer at a 70-eV ionizing energy. Optical rotation measurements were made with a Union Giken PM-71 polarimeter. Silica gel 60 (F_{254}) was used for TLC. Solvent systems for TLC were (A) benzene–$CHCl_3$–acetone (8:2:1) and (B) $CHCl_3$–MeOH (8:1).

2(*S*)-Chloro-3-[(*S*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [8-(*S*,*S*)] and Its Diastereomer [8-(*S*,*R*)]. To a cooled solution of phosphoryl chloride (308 g, 2.01 mol) in toluene (1.5 L) was added a solution of *N*-[(*S*)-α-methylbenzyl]-3-aminopropan-1-ol [**5**-(*S*): 359 g (2 mol); $[\alpha]^{25}_D$ −40.5% (*c* 4.0, benzene)] and triethylamine (407 g, 4.02 mol) in toluene (1 L) under efficient stirring. The temperature was maintained at −40 to −20 °C during the addition and for an additional 30 min. After being allowed to warm to room temperature, the mixture was washed with 5% hydrochloric acid and water and dried over $MgSO_4$. Evaporation of the solvent at reduced pressure gave a colorless semicrystalline mixture (515 g). This was dissolved in toluene (0.8 L), hexane (2.2 L) was added portionwise, and the solution was chilled in an ice bath for several hours. Colorless needles of 8-(*S*,*S*) (78%); were obtained: 408 g mp 71–73 °C; $[\alpha]^{25}_D$ +51.5° (*c* 8.2, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.60 (3 H, d, *J* = 7 Hz), 2.30 (2 H, m), 2.5–3.4 (2 H, m), 4.30 (2 H, m), 4.83 (1 H, m), 7.33 (5 H, br s); MS, *m*/*e* (relative intensity) 259 (M^+, 25), 244 (100); R_f 0.48 (A). Anal. Calcd for $C_{11}H_{15}ClNO_2P$: C, 50.88; H, 5.82; N, 5.40. Found: C, 51.08; H, 5.80; N, 5.18.

The liquor was concentrated and the residue was chromatographed on silica gel [benzene–$CHCl_3$–acetone (8:2:1)]. The minor isomer was isolated and recrystallized from ether-hexane to afford the colorless pillars of 8-(*S*,*R*) (13 g); mp 69–71 °C; $[\alpha]^{25}_D$ −61.4° (*c* 3.1, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.57 (3 H, d, *J* = 7 Hz), 1.83 (2 H, m), 2.5–3.3 (2 H, m), 4.3 (2 H, m), 5.17 (1 H, m), 7.37 (5 H, m); MS, *m*/*e* (relative intensity) 259 (M^+, 22), 244 (100), 128 (40), 105 (90), 77 (52); R_f 0.57 (A). Anal. Calcd for $C_{11}H_{15}ClNO_2P$: C, 50.88; H, 5.82; N, 5.40. Found: C, 51.00; H, 5.72; N, 5.38.

2(*R*)-Chloro-3-[(*R*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [8-(*R*,*R*)] and Its Enantiomer [8-(*R*,*S*)]. From *N*-[(*R*)-α-methylbenzyl]-3-aminopropan-1-ol [**5**-(*R*)] were obtained colorless crystals of 8-(*R*,*R*) (75%) and 8-(*R*,*S*) (3%) as above. 8-(*R*,*R*): mp 71–73 °C; $[\alpha]^{25}_D$ −51.7° (*c* 6.8, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.60 (3 H, d, *J* = 7 Hz), 2.03 (2 H, m), 2.5–3.4 (2 H, m), 4.30 (2 H, m), 4.83 (1 H, m), 7.33 (5 H, br s); MS, *m*/*e* (relative intensity) 259 (M^+, 23), 244 (100), 128 (40), 77 (60); R_f 0.48 (A). Anal. Calcd for $C_{11}H_{15}ClNO_2P$: C, 50.88; H, 5.82; N, 5.40. Found: C, 50.98; H, 5.76; N, 5.40. 8-(*R*,*S*): mp 79–71 °C; $[\alpha]^{25}_D$ −61.3° (*c* 3.3, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.57 (2 H, d, *J* = 7 Hz), 1.83 (2 H, m), 2.5–3.3 (2 H, m), 4.3 (2 H, m), 5.17 (1 H, m), 7.37 (5 H, m); MS, *m*/*e* (relative intensity) 259 (M^+, 20), 244 (98), 128 (50), 105 (100); R_f 0.57 (A). Anal. Calcd for $C_{11}H_{15}ClNO_2P$: C, 50.88; H, 5.82; N, 5.40. Found: C, 51.01; H, 5.75; N, 5.36.

2(*S*)-[Bis(2-hydroxyethyl)amino]-3-[(*S*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [9-(*S*,*S*)]. A solution of 8-(*S*,*S*) (25.8 g), diethanolamine (26.5 g), and triethylamine (40 mL) in acetonitrile (200 mL) was refluxed for 3 h under stirring. The solvent and excess triethylamine were evaporated at reduced pressure. To the residue were added 10% hydrochloric acid (100 mL) and saturated NaCl solution (100 mL), and the mixture was extracted with $CHCl_3$ (2 × 200 mL). The $CHCl_3$ layer was dried (MgSO) and evaporated. The residue was recrystallized from acetone to afford colorless prisms of **9**-(*S*,*S*): 21 g (65%); mp 104–106 °C; $[\alpha]^{25}_D$ −65.1° (*c* 6.2, EtOH); R_f 0.30 (B); ^{1}H NMR ($CDCl_3$) δ 1.50 (3 H, d, *J* = 7 Hz), 1.70 (2 H, m), 3.20 (6 H, m), 3.7 (4 H, m), 4.1 (4 H, m), 4.76 (4 H, m), 7.23 (5 H, m); MS, *m*/*e* (relative intensity) 297 ($M^+ - CH_2OH$, 13), 146 (65), 105 (78), 104 (100), 77 (45). Anal. Calcd for $C_{15}H_{25}N_2O_4P$: C, 54.87, H, 7.67; N, 8.53. Found: C, 55.18; H, 7.53; N, 8.42.

2(*R*)-[Bis(2-hydroxyethyl)amino]-3-[(*S*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [9-(*S*,*R*)]. A solution of 8-(*S*,*R*) (5.2 g), diethanolamine (5.3 g), and triethylamine (10 mL) in acetonitrile (50 mL) was reacted and treated as above. The residue was chromatographed on silica gel (80 g). Elution with $CHCl_3$–MeOH (5%) gave a colorless thick oil of **9**-(*S*,*R*): 5.5 g (85%); R_f 0.30 (B); $[\alpha]^{25}_D$ −8.7° (*c* 5.2, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.65 (3 H, d, *J* = 7 Hz), 1.80 (2 H, m), 3.20 (6 H, m), 3.60 (4 H, m), 4.27 (4 H, m), 4.63 (1 H, m), 7.22 (5 H, m).

2(*R*)-[Bis(2-hydroxyethyl)amino]-3-[(*R*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [9-(*R*,*R*)] and Its Diastereomer [9-(*R*,*S*)]. The diastereomeric diols **9**-(*R*,*R*) and **9**-(*R*,*S*) were prepared as above by starting from 8-(*R*,*R*) and 8-(*R*,*S*). **9**-(*R*,*R*): mp 104–106 °C; R_f 0.30 (B); $[\alpha]^{25}_D$ +51.6° (*c*

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6.23, EtOH). **9**-(*R,S*): thick oil, R_f 0.30 (B); $[\alpha]^{25}_D$ -8.6° (*c* 6.1, EtOH).

2(*S*)-[Bis(2-chloroethyl)amino]-3-[(*S*)-α-methylbenzyl]-1,3,2-oxazaphosphorinane 2-Oxide [7-(*S,S*)] and Its Diastereomers 7-(*S,R*), 7-(*R,R*), and 7-(*R,S*). To a stirred solution of thionyl chloride (7.14 g, 60 mM) in dichloromethane (30 mL) was added dropwise a solution of **9**-(*S,S*) (6.57 g, 20 mM) and hexamethylphosphoric triamide (5.4 g, 30 mM) under cooling in an ice bath. The mixture was then refluxed for 30 min. After the mixture was cooled, the excess thionyl chloride was decomposed by the addition of a mixture of acetic acid (3 mL) and MeOH (15 mL). The solvent was evaporated, and water (200 mL) was added to the residue. The mixture was extracted with carbon tetrachloride. The organic layer was washed (10% HCl, water, 10% NaOH, water) and dried (Na_2SO_4). The solvent was removed by evaporation, and the residue was purified on a short silica gel column [benzene–$CHCl_3$–acetone (10:2:1)] to afford thick colorless oil of **7**-(*S,S*): 6.3 g (86%); $[\alpha]^{25}_D$ -70° (*c* 2.6, benzene). The other diastereomers were similarly prepared: **7**-(*S,R*), $[\alpha]^{25}_D$ -0.94° (*c* 1.28, benzene); **7**-(*R,R*), $[\alpha]^{25}_D$ +73.5° (*c* 8.3, benzene); **7**-(*R,S*), $[\alpha]^{25}_D$ +1.2° (*c* 2.6, benzene). These compounds were identified by the direct comparison with the authentic samples prepared by the Stec method[3] (IR, NMR, MS, and TLC).

(*R*)-(+)-Cyclophosphamide [1-*R*(+)] and (*S*)-(-)-Cyclophosphamide [1-*S*(-)]. (1) Hydrogenolysis of **7**-(*S,S*) or **7**-(*R,S*) according to the Stec method[3] afforded **1**-[*R*(+)]: 60–65% yield; mp 67–68 °C (AcOEt–*i*-Pr_2O); $[\alpha]^{25}_D$ +2.48° *c* 10, MeOH). Hydrogenolysis of **7**-(*R,R*) of **7**-(*S,R*) or **7**-(*S,R*) gave **1**-[*S*(-)]: 55–67% yield; mp 67–68 °C (AcOEt–*i*-Pr_2O); $[\alpha]^{25}_D$ -2.46° (*c* (AcOEt–*i*-Pr_2O); MeOH).

(2) 2-(*S*)-[Bis(2-chloroethyl)amino]-3-[(*S*)-α-methylbenzyl]-2-oxo-1,3,2-oxazaphosphorinane [**9**-(*S,S*), 37 g] was dissolved in toluene (300 mL) and cooled in an ice–salt bath. Under stirring with a mechanical stirrer, 37 g of concentrated sulfuric acid was added dropwise at a rate so that the temperature did not exceed 10 °C. After the completion of the addition, the mixture was stirred for 15 min. The mixture was then poured into ice–water (500 mL), hexane (300 mL) was added, and the organic layer was separated. The organic layer was extracted with water (2 × 200 mL). The combined water layer was extracted with chloroform (3 × 200 mL), and the chloroform layer was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give crude crystals of (*R*)-(+)-cyclophosphamide. Recrystallization of the crude material from ethyl acetate and isopropyl ether afforded pure (*R*)-(+)-cyclophosphamide: 21 g (81%); mp 67–68 °C; $[\alpha]^{25}_D$ +2.46° (*c* 9.3, MeOH).

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Registry No. (±)-(*R*)-**1**, 60030-72-0; (-)-(*S*)-**1**, 60007-96-7; (*S*)-**5**, 59198-54-8; (*R*)-**5**, 58028-69-6; (*S,S*)-**7**, 58028-73-2; (*S,R*)-**7**, 58028-72-1; (*R,R*)-**7**, 58028-71-0; (*R,S*)-**7**, 58028-70-9; (*S,S*)-**8**, 72578-63-3; (*S,R*)-**8**, 72578-62-2; (*R,R*)-**8**, 73834-61-4; (*R,S*)-**8**, 73834-62-5; (*S,S*)-**9**, 73837-99-7; (*S,R*)-**9**, 73834-60-3; (*R,R*)-**9**, 74457-85-5; (*R,S*)-**9**, 83862-09-3.

Preparation and Acetolysis of 7-Norbornadienylmethyl and (7-Methyl-7-norbornadienyl)methyl Brosylates. An Intramolecular Retro-Diels–Alder Reaction following Laticyclic Participation[1]

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The title compounds, **19**- and **20**-OBs, respectively, have been prepared and their acetolysis rates and products determined. At 99.2 °C the acetolysis of **19**-OBs ($k_t = 3.63 \times 10^{-6}$ s^{-1}) produces 40% unrearranged acetate, **19**-OAc, by direct displacement and 60% tetracyclo[3.3.0.0^{3,8}.0^{4,6}]oct-7-yl acetate. Under identical conditions **20**-OBs is 97 times as reactive ($k_t = 3.53 \times 10^{-4}$ s^{-1}) and yields 56% of approximately equal amounts of *syn*- and *anti*-1-methyltetracyclo[3.3.0.0^{3,8}.0^{4,6}]oct-7-yl acetates and a total of 44% of a mixture of *endo*-1-methyltricyclo-[3.3.0.0^{2,7}]oct-3-en-6-yl acetate (**28**-OAc) and its retro-Diels–Alder product, 3-(1-methyl-2,4-cyclopentadien-1-yl)-*trans*-1-propenyl acetate (**29**-OAc). Comparison of these results with those of other norbornenyl and norbornadienyl derivatives suggests that unsymmetrical ($2^0 + 2^0 + 1^+$) laticyclic stabilization is enhanced relative to ($2^0 + 1^+$) pericyclic stabilization in the acetolysis of **19**- and **20**-OBs. Such stabilization is appreciably greater in **20**-OBs than in **19**-OBs. The intramolecular retro-Diels–Alder reaction that converts **28**- to **29**-OAc under acetolytic conditions is discussed, and its comparative rarity is emphasized by citing other norbornadienyl derivatives known to behave in this manner.

An appropriately situated, remote double bond enhances solvolytic reactivity and therefore is usually presumed to stabilize the resulting carbocation.[2] The solvolytic reactivity of **2**-OTs is 10^{11} times that of **1**-OTs,[3] for example, while **5**-OBs is $10^{5.3}$ times as reactive as **4**-OBs[4] (Chart I). Whether a second, remote double bond provides additional stabilization is less clear. The doubly unsaturated **3**-Cl is 10^3 times more reactive than **2**-Cl,[5] but **6**-OBs and **5**-OBs react at comparable rates.[6]

In an attempt to understand and predict the overall effect of several such isolated "ribbons" of unsaturation within a molecule, Goldstein and Hoffmann have developed a symmetry-based, topological model for their ho-

(1) Portions of this work have been reported at: (a) The 30th Southeastern Regional Meeting of the American Chemical Society, Savannah, GA, Nov 8–10, 1978, Abstract No. 252; (b) The 178th National Meeting of the American Chemical Society, Washington, DC, Sept 9–14, 1979, Abstract ORGN 142; (c) The Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 24–29, 1980, Abstract ORGN 360.

(2) For a recent summary with leading references see: Lowery, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper & Row: New York, 1981; pp 396–436.

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