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The Synthesis of Optically Active P-Heterocycles

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ABSTRACT: *Optically active 1-alkoxy- and 1-amino-3-phospholene oxides were synthesized by the reaction of the corresponding 1-chloro-3-phospholene oxides with (1R,2S,5R)-(–)menthol and (S)-(–)-α-phenylethylamine. The 3-methyl-3-phospholene oxides were subjected to dichlorocyclopropanation under liquid–liquid phase transfer catalytic conditions to afford the 3-phosphabicyclo[3.1.0]hexane 3-oxides as a mixture of four diastereomers. Thermolysis of the menthyl-phosphabicyclohexane oxides led to the corresponding 1,2-dihydrophosphinine oxide as a diastereomeric mixture of two double-bond isomers. As a result of additional steps, the dichlorocarbene addition reaction of the 1-menthyl-3,4-dimethyl-3-phospholene oxide resulted in eventually, the formation of a 4-dichloromethylene-1,4-dihydrophosphinine oxide.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:271–277, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20599

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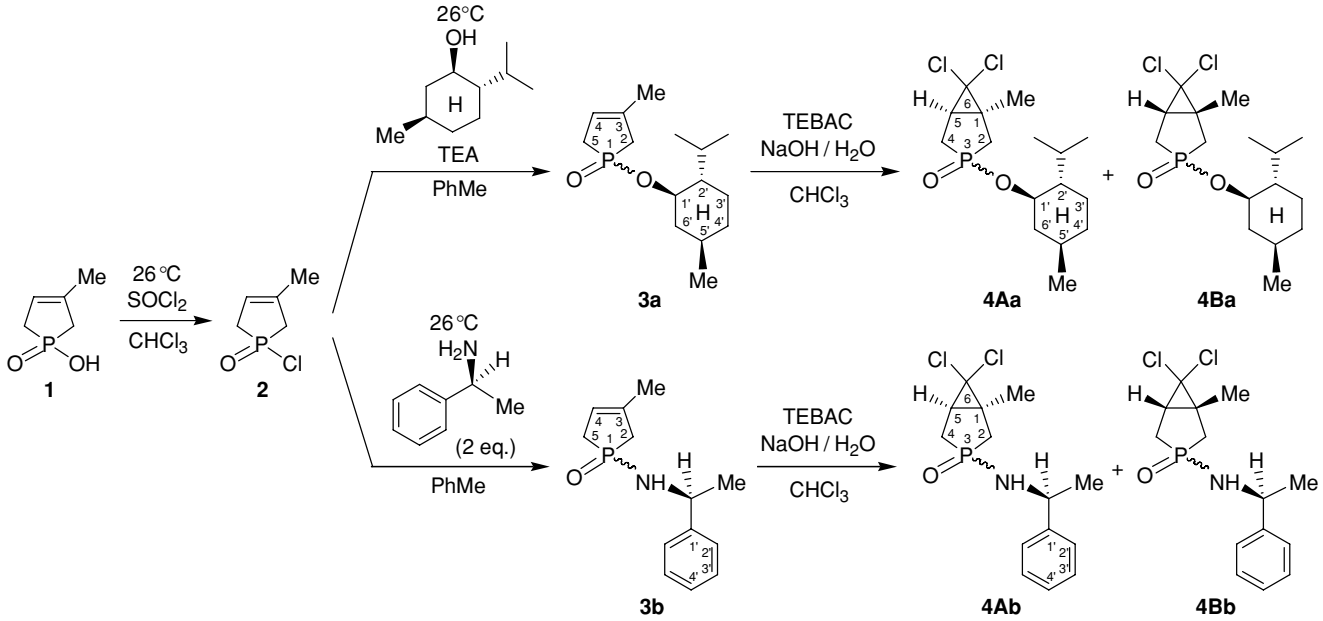
INTRODUCTION

These days the P-heterocyclic discipline is of increasing importance [1,2]. The P-heterocycles are used as building blocks in synthetic organic chemistry, as catalysts, as ligands in transition metal complexes, and as biologically active substrates [1–3]. The most easily available 3-phospholene oxides served well as starting materials for six-membered P-heterocycles [4,5]. A two-step ring enlargement including 3-phosphabicyclo[3.1.0]hexane 3-oxides as the intermediates made available 1,2-dihydro- and 1,2,3,6-tetrahydrophosphinine oxides [4,5]. Other derivatives including 1,4-dihydrophosphinine oxides were also synthesized [5]. All of the P-chiral heterocycles prepared were racemates [4,5]. Petrusiewicz and his co-workers were the first who developed methods for the synthesis of optically active P-heterocycles [6–13]. Fogassy et al. including one of the authors of this paper have recently elaborated the simple resolution of 3-phospholene oxides via molecule complexes and coordination complexes [14–17]. Ring enlargement of the antipodes of the 3-phospholene oxides may obviously lead to optically active 1,2-dihydrophosphinine oxides.

In this paper, we describe the preparation of optically active 3-phospholene oxides by substitution at the phosphorus atom and their conversion



SCHEME 1

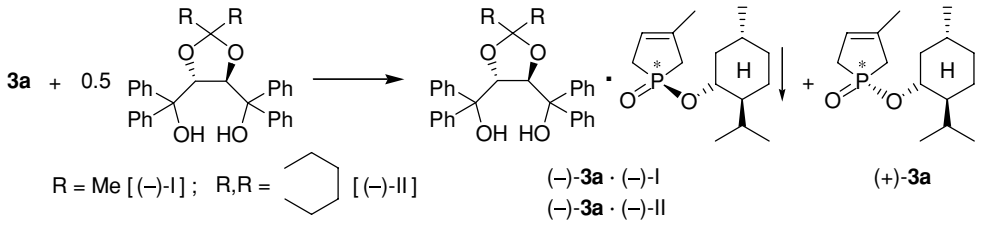
to 3-phosphabicyclo[3.1.0]hexane 3-oxides, as well as 1,2- and 1,4-dihydrophosphinine oxides.

RESULTS AND DISCUSSION

In our efforts to synthesize optically active P-heterocycles, we utilized (1*R*,2*S*,5*R*)-(–)-menthol and (*S*)-(–)-α-phenylethylamine as the chiral-building blocks. 1-Hydroxy-3-methyl-3-phospholene oxide **1** was converted to the corresponding phosphinic chloride (**2**) by reaction with thionyl chloride in chloroform. Intermediate **2** was then reacted with (1*R*,2*S*,5*R*)-(–)-menthol and (*S*)-(–)-α-phenylethylamine in toluene, using triehylamine or one more equivalent of the chiral amine itself as the base to give cycloalkyloxy- and aminophospholene oxides **3a** and **3b**, respectively (Scheme 1). The substituted phospholene oxides (**3a** and **3b**) were obtained as a 1:1 mixture of two diastereomers due to the *P*-chirality of chlorophospholene oxide **2** and the *C*-chiral center, or fixed *C*-chiral centers in the nucleophilic reactants.

Then 3-methyl-3-phospholene oxide **3a** was subjected to ring enlargement by the "dichlorocarbene" method [4]. According to this method, in the first step, dichlorocarbene, generated from chloroform by aqueous NaOH under phase transfer catalytic conditions, was added on the double bond of the phospholene oxide (**3a**). Both diastereomers of the phospholene oxide (**3a**) afforded the 3-phosphabicyclo[3.1.0]hexane 3-oxide (**4a**) as a mixture of **A** and **B** isomers; consequently, the dichlorocarbene adduct (**4a**) was obtained as a mixture of four isomers (Scheme 1). The assignment of the stereostructures to isomers **A** and **B** is tentative. Partial separation of the diastereomers was possible; column chromatography led to a fraction consisting of 50% of $\mathbf{4A_1a}$ and 50% of $\mathbf{4A_2a}$.

Dichlorocyclopropanation of phenylethylaminophospholene oxide **3b** was also accomplished

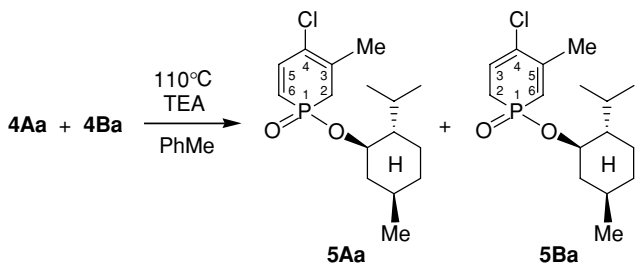


SCHEME 2

under liquid–liquid phase transfer catalytic conditions. In this case, the corresponding dichlorocarbene adduct (**4b**) was again formed as four isomers (Scheme 1), but probably due to hydrolytic side-reactions the yield was moderate. In the earlier described liquid–liquid phase dichlorocyclopropanation reaction of 1-diethylamino-3-methyl-3-phospholene oxide, the diastereomer containing the dichlorocyclopropane ring and the oxygen of the P=O moiety in the trans disposition was assumed to be the major isomer [18].

The diasteromers of racemic 1-[(1′*R*,2′*S*,5′*R*)-menthyloxy]-3-methyl-3-phospholene oxide **3a** were separated by the method elaborated by us for the resolution of 3-phospholene 1-oxide derivatives [14,15]. According to this method, 0.5 equiv of (–)-TADDOL derivative I or II was added to the ethyl acetate solution of menthyloxy-phospholene oxide **3a**. After the addition of hexane to the hot solution, the supramolecular formation (–)-**3a**·(–)-I or (–)-**3a**·(–)-II precipitated. After the first and second recrystallization, complex (–)-**3a**·(–)-I was obtained in a yield of 64% with an ee of 90% and in a yield of 25% with an ee of >99%, respectively. Recrystallization of complex (–)-**3a**·(–)-II led to a 45% yield and 90% ee. Hence, the use of TADDOL I was more efficient than "spiro TADDOL" II. The phospholene oxide (–)-**3a** was regenerated by flash column chromatography of the supramolecular complexes (–)-**3a**·(–)-I and (–)-**3a**·(–)-II.

In the next stage, we carried out the second step of the ring enlargement, that is the thermal opening of the dichlorocyclopropane ring. Thermolysis of the 3-phosphabicyclo[3.1.0]hexane 3-oxide **4a** was accomplished in boiling toluene in the presence of 1 equiv of triethylamine to furnish the 1,2-dihydrophosphinine oxide **5a** as a ca 3:1 mixture of double-bond isomers **A** and **B** (Scheme 3). It is worth mentioning that the diastereomeric composition of the starting material (**4a**) did not complicate the situation, as the dihydrophosphinine oxides of type **5** are in any case formed as a ca 3:1 mixture of two double-bond isomers [4,5].



SCHEME 3

Beside the optically active 3-methyl-3-phospholene oxides (**3a** and **3b**), the analogous 3,4-dimethyl-3-phospholene oxides (**8a** and **8b**) were also prepared. In this instance, however, the corresponding phosphinic chloride **7** was obtained from 1-ethoxy-3,4-dimethyl-3-phospholene oxide **6** by a reaction with phosphorus pentachloride. Reaction of intermediate **7** with (1*R*,2*S*,5*R*)-(–)-menthol and (*S*)-(–)-α-phenylethylamine provided phospholene oxides **8a** and **8b**, respectively, as single isomers (Scheme 4).

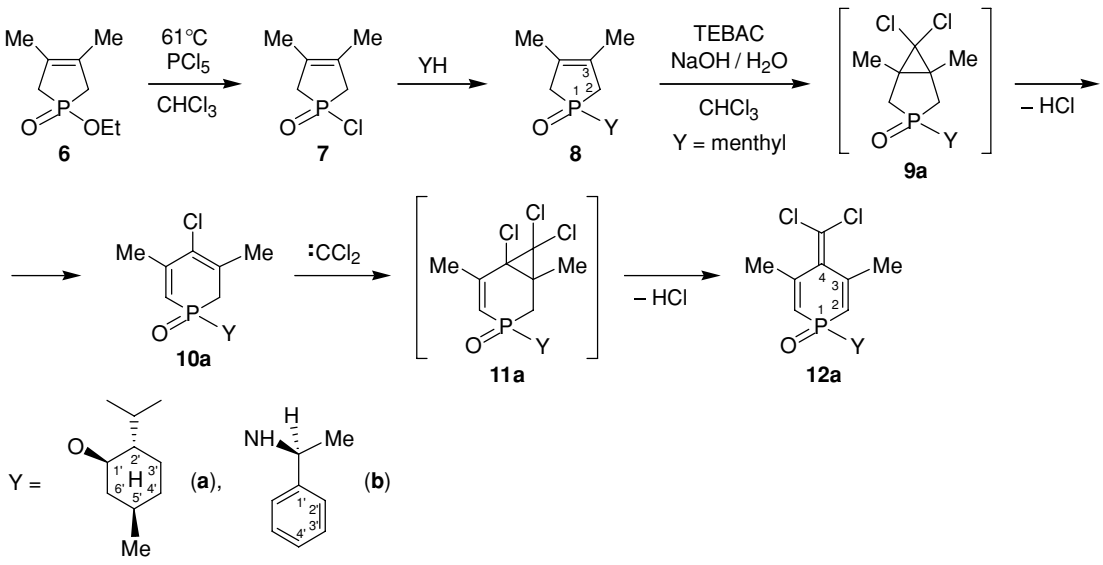
The treatment of phospholene oxide **8a** with $NaOH/H_2O$-chloroform under phase transfer catalytic conditions resulted, eventually 4-dichloromethylene-1,4-dihydrophosphinine oxide **12a** (Scheme 4). The reaction sequence followed an earlier protocol [4,19], according to which the primarily formed dichlorocarbene adduct (in the present case **9a**) is not stable under the conditions of the reaction and undergoes a spontaneous cyclopropane ring opening to afford and 1,4-dihydrophosphinine oxide (in this case **10a**). Then, the dihydrophosphinine oxide may be the subject of a second series of transformation with the excess of the reagents present to give a 1,4-dihydrophosphinine oxide (in this case **12a**) via the corresponding dichlorocarbene adduct (in this case **11a**) (Scheme 4). The difference in the stability of monomethyl-phosphabicyclohexane **4** and that of dimethyl derivative **9** is the consequence of the number of the methyl groups on the skeleton. The special opening of the cyclopropane ring in intermediate **11** to result in an exocyclic 4-dichloromethylene group is also the consequence of the additional methyl group. The novel mechanism is under evaluation by quantum chemical calculations [20].

The new 3-phospholene oxides **3a, 3b, 8a**, and **8b**, 3-phosphabicyclo[3.1.0]hexane oxides **4a** and **4b**, dihydrophosphinine oxides **5a** and **12a** were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectroscopical methods.

In conclusion, eight new optically active P-heterocycles comprising four 3-phospholene oxides, two 3-phosphabicyclo[3.1.0]hexane 3-oxides, a 1,2- and a 1,4-dihydrophosphinine oxide have been described that can be used as P-ligands after deoxygenation.

EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts



SCHEME 4

are downfield relative to 85% H_3PO_4 and TMS. The couplings are given in hertz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

*Synthesis of 1-[(1R,2S,5R)-Menthyloxy]-3-methyl-3-phospholene 1-oxide (**3a**)*

To 13.2 g (100.0 mmol) of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**) in 40 mL of chloroform, 9.0 mL (124.0 mmol) of thionyl chloride was added and the solution was stirred for 16 h. After evaporation of the volatiles, the residue was taken up in 300 mL of toluene. To the solution so obtained, 13 mL (102.0 mmol) of triethylamine and 15.6 g (100 mmol) of (1*R*,2*S*,5*R*)-(–)-menthol were added and the mixture was stirred at 26°C for 16 h. After filtration, the product was purified by column chromatography (silica gel, 2% methanol in chloroform) to give 13.5 g (50%) of **3a** as a 1:1 mixture of two diastereomers.

$[\alpha]_D^{25} = -44.4$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.6, 3H, $C_{5'}$—CH_3), 0.92 (d, J = 6.6, 6H, $CH(CH_3)_2$), 1.80 (s, 3H, C_3—CH_3), 2.30–2.60 (m, 4H, CH_2PCH_2), 4.15–4.35 (m, 2H, OCH), 5.52 (d, J = 35.4, 1H, C_4H); HRMS, $[M + H]^+_{found} = 271.1810$, $C_{15}H_{28}O_2P$ requires 271.1827.

Isomer **A**: ^{31}P NMR ($CDCl_3$) δ 73.28; ^{13}C NMR ($CDCl_3$) δ 15.9 ($C_{5'}$—CH_3),[a] 20.7 (J = 3.6, C_3—CH_3),[b] 21.0 ($CHCH_3$), 22.0 ($CHCH_3$), 23.1 ($C_{3'}$), 25.8 ($C_{5'}$), 31.4 (J = 88.9, C_5),[c] 31.5 ($CHMe_2$), 34.1 ($C_{4'}$), 35.3 (J = 92.0, C_2),[d] 43.5 ($C_{6'}$), 48.5 (J = 6.3, $C_{2'}$),[e] 76.7 (J = 7.5, $C_{1'}$), 120.2 (J = 11.1, C_4),[f] 136.4 (J = 16.8, C_3)[g].

Isomer **B**: ^{31}P NMR ($CDCl_3$) δ 73.33; ^{13}C NMR ($CDCl_3$) δ 16.0 ($C_{5'}$—CH_3),[a] 20.9 (J = 3.6, C_3—CH_3),[b] 21.0 ($CHCH_3$), 22.0 ($CHCH_3$), 23.1 ($C_{3'}$), 25.8 ($C_{5'}$), 31.5 ($CHMe_2$), 32.6 (J = 88.4, C_5),[c] 34.0 (J = 92.5, C_2),[d] 34.1 ($C_{4'}$), 43.5 ($C_{6'}$), 48.5 (J = 6.3, $C_{2'}$),[e] 76.7 (J = 7.5, $C_{1'}$), 120.5 (J = 10.7, C_4),[f] 136.4 (J = 16.8, C_3)[g].

[a–g]may be reversed

*Resolution of 1-[(1′R, 2′S, 5′R-Menthyloxy]-3-methyl-3-phospholene 1-oxide (**3a**) using (–)-TADDOL (I)*

To 0.21 g (0.77 mmol) of racemic 1-[(1′*R*,2′*S*,5′*R*)-menthyloxy]-3-methyl-3-phospholene oxide (**3a**) and 0.18 g (0.38 mmol) of (–)-TADDOL (I) in 0.2 mL of hot ethyl acetate, 2 mL of hexane was added. After the addition, colorless crystals of the complex started to appear immediately. After 2 h, the crystals were separated by filtration to give 0.20 g (71%) of complex [(–)-**3a**·(–)-I] with an ee of 71%. The complex was further purified by two recrystallizations from ethyl acetate–hexane (0.2 mL/1 mL) to afford complex (–)-**3a**·(–)-I in a yield of 64% with an ee of 90% and in a yield of 25% with an ee of >99%, respectively. Column chromatography (silica gel, chloroform-methanol) of the complex regenerated 18 mg (25%) of the enantiomerically pure (–)-1-[(1′*R*,2′*S*,5′*R*)-menthyl]-3-methyl-3-phospholene 1-oxide [(–)-(**3a**)]; ee >99%; $[\alpha]_D^{25} = -77.6$ (*c* 0.4, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ 73.2.

*Synthesis of 1-[(1S)-1-Phenylethylamino]-3-methyl-3-phospholene l-oxide (**3b**)*

To 6.6 g (50.0 mmol) of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**) in 20 mL of chloroform,

4.5 mL (62.0 mmol) of thionyl chloride was added and the solution was stirred for 16 h. After evaporation of the volatiles, the residue was taken up in 150 mL of toluene. To the solution so obtained, 13 mL (102.0 mmol) of (*S*)-α-phenylethylamine was added and the mixture was stirred for 16 h. After filtration, the product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 8.8 g (75%) of **3b** as a 1:1 mixture of two diastereomers.

$[\alpha]_D^{25} = -26.8$(*c* 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, *J* = 6.6, $CHCH_3$), 1.68 and 1.70 (s, 3H, C_3—CH_3, isomer **A** and **B**), 2.00–2.55 (m, 4H, CH_2PCH_2), 2.91 (bs, 1H, NH), 4.30–4.50 (m, 1H, CH), 5.44 (d, *J* = 33.6, 1H, C_4H), 7.20–7.39 (m, 5H, Ar); HRMS, $[M + H]^+_{found} = 236.1192$, $C_{13}H_{19}NOP$ requires 236.1204.

Isomer **A**: ^{31}P NMR ($CDCl_3$) δ 62.0; ^{13}C NMR ($CDCl_3$) δ 20.1 ($CHCH_3$),[a] 25.5 (*J* = 3.1, C_3—CH_3),[b] 31.9 (*J* = 81.4, C_2),[c] 34.6 (*J* = 85.2, C_5),[d] 50.2 (CHMe),[e] 120.2 (*J* = 9.5, C_3),[f] 125.6 ($C_{2'}$),*126.7 ($C_{4'}$), 128.1 ($C_{3'}$),* 136.3 (*J* = 11.1, C_4),[g] 145.0 ($C_{1'}$); *may be reversed.

Isomer **B**: ^{31}P NMR ($CDCl_3$) δ 62.5; ^{13}C NMR ($CDCl_3$) δ 20.3 ($CHCH_3$),[a] 25.6 (*J* = 3.3, C_3—CH_3),[b] 32.4 (*J* = 81.2, C_2),[c] 35.2 (*J* = 84.3, C_5),[d] 50.4 (CHMe),[e] 120.3 (*J* = 9.3, C_3),[f] 125.6 ($C_{2'}$),* 126.7 ($C_{4'}$), 128.1 ($C_{3'}$),* 136.1 (*J* = 11.2, C_4),[g] 145.0 ($C_{1'}$); *may be reversed.

[a–g]may be reversed.

*Synthesis of 1-[(1R,2S,5R)-Menthyloxy]-3,4-dimethyl-3-phospholene 1-oxide (**8a**)*

To 0.80 g (4.6 mmol) of 1-ethoxy-3,4-dimethoxy-3-phospholene 1-oxide (**6**) in 20 mL of chloroform, 1.0 g (4.9 mmol) of phosphorus pentachloride was added and the mixture was kept at reflux for 2.5 h. After filtration and evaporation of the volatiles, phosphinic chloride **7** was dissolved in 20 mL of toluene. To the solution so obtained, 0.65 mL (4.7 mmol) of triethylamine and 0.79 g (5.1 mmol) of (1*R*,2*S*,5*R*)-(–)-menthol were added and the mixture was stirred for 16 h. After filtration, the product was purified by column chromatography (silica gel, 2% methanol in chloroform) to give 1.3 g of **8a** as colorless oil. $[\alpha]_D^{25} = -104.0$ (*c* 0.4, CH_2Cl_2); ^{31}P NMR ($CDCl_3$) δ 66.6; ^{13}C NMR ($CDCl_3$) δ 15.7 ($C_{5'}$—CH_3), 16.2 (*J* = 4.2, CH_3), 16.4 (*J* = 4.0, CH_3), 20.6 ($CHCH_3$), 21.7 ($CHCH_3$), 22.8 ($C_{3'}$), 25.6 ($C_{5'}$), 31.2 ($CHMe_2$), 33.8 ($C_{4'}$), 36.1 (*J* = 91.4, C_5), 37.3 (*J* = 93.4, C_2), 43.2 ($C_{6'}$), 48.2 (*J* = 6.3, $C_{2'}$), 76.2 (*J* = 7.4, $C_{1'}$), 127.0 (*J* = 13.1, C_3), 127.3 (*J* = 12.7, C_4); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.8, 3H, $C_{5'}$—CH_3), 0.91 (d, *J* = 6.0, 6H, $CH(CH_3)_2$), 1.72 (s, 6H, C_3—CH_3), 2.32–2.60 (m, 4H, CH_2PCH_2), 4.15–4.35 (m, 2H, OCH); HRMS, $[M + H]^+_{found} = 285.1964$, $C_{16}H_{30}O_2P$ requires 285.1983.

*Synthesis of 1-[(1S)-1-Phenylethylamino)]-3,4-dimethyl-3-phospholene 1-oxide (**8b**)*

To 0.80 g (4.6 mmol) of l-ethoxy-3,4-dimethoxy-3-phospholene 1-oxide (**6**) in 20 mL of chloroform, 1.0 g (4.9 mmol) of phosphorus pentachloride was added and the mixture was kept at reflux for 6 h. After filtration and evaporation of the volatiles, phosphinic chloride **7** was dissolved in 20 mL of toluene. To the solution so obtained, 1.2 mL (9.2 mmol) of (*S*)-α-phenylethylamine was added and the mixture was stirred for 16 h. After filtration, the product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.93 g (81%) of **8b** as colorless oil. $[\alpha]_D^{25} = +103.0$ (*c* 0.4, CH_2Cl_2); ^{31}P NMR ($CDCl_3$) δ 55.3; ^{13}C NMR ($CDCl_3$) δ 16.1 ($CHCH_3$), 16.3 ($CHCH_3$), 25.8 (*J* = 6.2, C_3—CH_3), 36.9 (*J* = 83.5, C_5), 37.6 (*J* = 83.2, C_2), 50.6 (CHMe), 125.7 ($C_{2'}$),* 126.9 ($C_{4'}$), 127.4 (*J* = 11.6, C_3), 128.3 ($C_{3'}$),* 145.1 (*J* = 2.9, $C_{1'}$), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, *J* = 6.6, 3H, $CHCH_3$), 1.52 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.08–2.25 (m, 2H, CH_2), 2.30–2.52 (m, 2H, CH_2), 2.88 (bs, 1H, NH), 4.31–4.51 (m, 1H, CH), 7.20–7.39 (m, 5H, Ar). HRMS, $[M + H]^+_{found} = 250.1347$, $C_{14}H_{21}NOP$ requires 250.1361.

*Synthesis of 6,6-Dichloro-3-[(1R,2S,5R)-menthyloxy]-1-methyl-3-phosphabicyclo-[3.1.0]hexane 3-oxide (**4a**)*

To the mixture of 2.0 g (7.4 mmol) of 1-[(1*R*,2*S*,5*R*)-menthyloxy]-3-methyl-3-phospholene 1-oxide (**3a**) and 0.20 g (0.80 mmol) of TEBAC in 40 mL of chloroform, a solution of NaOH (5.5 g of NaOH in 7 mL of water) was added dropwise and the mixture was kept at reflux for 3 h. The mixture was cooled to 26°C, filtrated, the organic phase separated and made up to its original volume. To the solution, 0.10 g (0.40 mmol) of TEBAC and 5.5 g of NaOH in 7 mL of water were added and the mixture was kept at reflux for 3 h. The mixture was cooled and filtrated; the organic phase was separated and concentrated. The crude product so obtained was purified by column chromatography (silica gel, 2% methanol in chloroform) to give 0.50 g (19%) of **4a** consisting of isomers $\mathbf{A_1}$ (30%), $\mathbf{A_2}$ (29%), $\mathbf{B_1}$ (21%), and $\mathbf{B_2}$ (20%) as a colorless oil. Repeated chromatography led to a fraction containing only isomers $\mathbf{A_1}$ (50%) and $\mathbf{A_2}$ (50%). $[\alpha]_D^{25} = -46.0$ (*c* 1, $CHCl_3$); HRMS, $[M + H]^+_{found} = 353.1176$, $C_{16}H_{28}Cl_2O_2P$ requires 353.1204 for the ^{35}Cl isotopes.

Isomer $\mathbf{A_1}$: ^{31}P NMR ($CDCl_3$) δ 81.0; ^{13}C NMR ($CDCl_3$) δ 15.7 ($C_{5'}$—*C*H_3), 20.8 (CH*C*H_3), 21.7 (J = 7.8, C_1—CH_3),[A] 21.9 (CH*C*H_3), 22.9 ($C_{3'}$),[B] 25.9 ($C_{5'}$), 27.7 (J = 91.0, C_2),[C] 31.1 (J = 12.6, C_1), 31.4 ($CHMe_2$), 32.5 (J = 94.3, C_4),[E] 33.3 (J = 12.4, C_5),[D] 34.0 ($C_{4'}$), 42.9 ($C_{6'}$),[F] 48.3 (J = 5.9, $C_{2'}$), 72.2 (J = 14.1, C_6).

Isomer $\mathbf{A_2}$: ^{31}P NMR ($CDCl_3$) δ 81.1; ^{13}C NMR ($CDCl_3$) δ 15.7 ($C_{5'}$—*C*H_3), 20.8 (CH*C*H_3), 21.8 (J = 7.5, C_1—CH_3),[A] 21.9 (CH*C*H_3), 22.8 ($C_{3'}$),[B] 25.9 ($C_{5'}$), 26.7 (J = 92.2, C_2),[C] 31.1 (J = 12.6, C_1), 31.4 ($CHMe_2$), 32.6 (J = 12.6, C_5),[D] 33.5 (J = 91.0, C_4),[E] 34.0 ($C_{4'}$), 43.0 ($C_{6'}$),[F] 48.3 (J = 5.9, $C_{2'}$), 72.2 (J = 14.1, C_6).

[A–F]may be reversed.

Isomer $\mathbf{B_1}$: ^{31}P NMR ($CDCl_3$) δ 85.7; ^{13}C NMR ($CDCl_3$) δ 15.8 ($C_{5'}$—*C*H_3),[a] 21.0 (CH*C*H_3), 21.6 (J = 7.7, C_1—*C*H_3),[b] 21.9 (CH*C*H_3),[c] 22.9 ($C_{3'}$),[d] 25.8 ($C_{5'}$),[f] 27.0 (J = 88.9, C_2),[e] 31.1 (J = 12.7, C_1), 31.6 ($CHMe_2$),[g] 32.6 (J = 90.9, C_4),[h] 32.7 (J = 10.8, C_5),[i] 34.0 ($C_{4'}$), 43.6 ($C_{6'}$),[j] 48.7 (J = 6.0, $C_{2'}$),[k] 72.0 (J = 12.3, C_6)[l].

Isomer $\mathbf{B_2}$: ^{31}P NMR ($CDCl_3$) δ 86.2; ^{13}C NMR ($CDCl_3$) δ 15.9 ($C_{5'}$—*C*H_3),[a] 21.0 (CH*C*H_3), 21.5 (J = 7.9, C_1—CH_3),[b] 22.0 (CH*C*H_3),[c] 23.0 ($C_{3'}$),[d] 25.3 (J = 91.4, C_2),[e] 25.9 ($C_{5'}$),[f] 31.1 (J = 12.7, C_1), 31.5 ($CHMe_2$),[g] 31.8 (J = 92.8, C_4),[h] 32.4 (J = 11.2, C_5),[i] 34.0 ($C_{4'}$), 43.5 ($C_{6'}$),[j] 48.6 (J = 5.8, $C_{2'}$),[k] 72.1 (J = 12.1, C_6)[l].

[a–l]may be reversed.

*Synthesis of 6,6-Dichloro-3-[(1S)-l-phenylethylamino]-1-methyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (***4b***)*

To the mixture of 4.0 g (17.0 mmol) of 1-[(1*S*)-1-phenylethylamino]-3-methyl-3-phospholene 1-oxide (**3b**) and 1.36 g (6.0 mmol) of TEBAC in 80 mL of chloroform, a solution of 26.0 g of NaOH in 28 mL of water was added dropwise and the mixture was kept at reflux for 3 h. The mixture was cooled and filtrated; the organic phase was separated and concentrated. The crude product so obtained was purified by column chromatography (silica gel, 2% methanol in chloroform) to give 1.0 g (19%) of **4b**, consisting of isomers **A** (36%), **B** (26%), **C** (29%), and **D** (9%) as a colorless oil. Repeated chromatography led to a fraction containing only isomers A (60%) and B (40%). $[\alpha]_D^{25}$ = −8.3 (*c* 1.3, $CHCl_3$); HRMS, $[M + H]^+_{found}$ = 318.0586, $C_{14}H_{19}Cl_2NOP$ requires 318.0581 for the ^{35}Cl isotopes.

Isomer **A**: ^{31}P NMR ($CDCl_3$) δ 75.7; ^{13}C NMR ($CDCl_3$) δ 21.7 (J = 7.1, C_1—CH_3), 25.6 (J = 85.9, C_4), 26.2 (J = 5.3, CH—CH_3), 31.7 (J = 12.6, C_1), 32.8 (J = 84.9, C_2), 33.2 (J = 10.6, C_5), 50.3 (J = 1.4, CH—CH_3), 72.4 (J = 13.7, C_6), 125.7 (C_β), 127.3 (C_δ), 128.6 (C_γ), 144.9 (J = 3.2, C_α); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3H, C_1—CH_3), 1.55 (d, J = 6.9, 3H, CH—CH_3), 7.27—7.38 (m, 5H, Ar).

Isomer **B**: ^{31}P NMR ($CDCl_3$) δ 75.9; ^{13}C NMR ($CDCl_3$) δ 21.3 (J = 7.3, C_1—CH_3), 27.2 (J = 84.1, C_4), 26.0 (J = 5.4, CH—CH_3), 31.5 (J = 86.4, C_2), 31.9 (J = 12.3, C_1), 33.3 (J = 11.1, C_5), 50.4 (J = 1.3, CH—CH_3), 72.5 (J = 12.6, C_6), 126.0 (C_β), 127.4 (C_δ), 128.6 (C_γ), 144.8 (J = 3.4, C_α); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3H, C_1—CH_3), 1.55 (d, J = 6.9, 3H, CH—CH_3), 7.27–7.38 (m, 5H, Ar).

Isomer **C**: ^{31}P NMR ($CDCl_3$) δ 74.2.

Isomer **D**: ^{31}P NMR ($CDCl_3$) δ 74.9.

*Synthesis of 3- and 5-Methyl-4-chloro-1-[(1R,2S, 5R)-menthyloxy]-1,2-dihydrophosphinine 1-oxides (***5Aa** *and* **5Ba***)*

A mixture of 3.3 g (9.4 mmol) of dichlorcyclopropane derivative **4a** consisting of isomers $\mathbf{A_1}$ (30%), $\mathbf{A_2}$ (29%), $\mathbf{B_1}$ (21%), and $\mathbf{B_2}$ (20%) and 1.4 ml (10.0 mmol) of triethylamine in 50 mL of dry toluene was stirred at the boiling point for 10 h. Then the precipitated salt was filtered off and the filtrate concentrated in vacuum. The crude product so obtained was purified by repeated column chromatography ((1) 3% methanol in chloroform and (2) ethyl acetate–hexane 3:1, using silica gel as the absorbent) to give 1.8. g (61%) of the title product **5a** as a mixture of four isomers (**5Aa1**: 34%, **5Aa2**: 42%, **5Ba1**: 13%, and **5Ba2** 11%). $[\alpha]_D^{25}$ = −57.0 (*c* 1.0, $CHCl_3$); HRMS, $[M + H]^+_{found}$ = 317.1447, $C_{16}H_{27}ClO_2P$ requires 317.1437 for the ^{35}Cl isotope.

For major isomers $\mathbf{5Aa_1}$ and $\mathbf{5Aa_2}$: ^{31}P NMR ($CDCl_3$) δ 31.0 (34%) and 31.2 (42%); ^{13}C NMR ($CDCl_3$) δ 15.78, 15.85 ($C_{5'}$—CH_3), 20.8 (CH*C*H_3), 21.8 (CH*C*H_3), 22.8, 22.9 ($C_{3'}$),* 23.4 (J = 10.4) (C_3—*C*H_3), 25.5, 25.8 ($C_{5'}$), 31.5 ($CHMe_2$), 33.9 ($C_{4'}$),* 34.0 (J = 99.8), 34.9 (J = 100.2) (C_2), 43.67, 43.9 ($C_{6'}$), 48.3 (J = 7.1), 48.4 (J = 7.0) ($C_{2'}$), 76.8 (J = 7.2), 77.0 (J = 7.5) ($C_{1'}$), 119.6 (J = 121.2), 120.8 (J = 121.0) (C_6), 123.3, (J = 21.9) (C_3), 131.9 (J = 8.6), 132.2 (J = 8.9) (C_4), 143.9, 144.6 (C_5); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J = 6.0), 0.83 (d, J = 5.6, 3H) ($CHCH_3$), 0.92 (d, J = 5.5, $CH(CH_3)_2$), 2.03 (s, C_3—CH_3), 6.07 (t, $^2J_{PH}$ = $^3J_{HH}$ = 10.0, C_6H), 6.70 (dd, $^3J_{PH}$ = 39.6, $^3J_{HH}$ = 12.8, C_5H); *tentative assignment.

For minor isomers $\mathbf{5Ba_1}$ and $\mathbf{5Ba_2}$: ^{31}P NMR ($CDCl_3$) δ 30.1 (13%) and 30.2 (11%); ^{13}C NMR ($CDCl_3$) δ 15.6, 15.85 ($C_{5'}$—*C*H_3), 20.9 (CH*C*H_3), 21.9 (CH*C*H_3), 22.7, 22.8 ($C_{3'}$),* 24.6 (J = 5.6), 24.8 (J = 5.8) (C_5—CH_3), 25.4, 25.7 ($C_{5'}$), 28.4 (J = 99.0), 29.1 (J = 100.4) (C_2), 31.5 ($CHMe_2$), 33.9 ($C_{4'}$),* 43.71 ($C_{6'}$), 48.4 (J = 7.0), 48.5 (J = 10.8) ($C_{2'}$), 76.6

(J = 4.0), 76.7 (J = 4.0) ($C_{1'}$), 118.9 (J = 125.8), 120.0 (J = 126.1) (C_6), 123.4 (J = 8.0), 123.8 (J = 10.5) (C_3), 131.2 (J = 2.0), 131.5 (J = 2.0) (C_4), 149.8 (J = 1.6), 150.7 (J = 1.6) (C_5); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 5.5, $CH(CH_3)_2$), 2.12 (s, C_5—CH_3); *tentative assignment.

*Synthesis of 4-Dichloromethylene-3,5-dimethyl-1-[(1R,2S,5R)-menthyloxy]-1,4-dihydrophosphinine l-oxide (**12a**)*

To the mixture of 0.76 g (2.7 mmol) of 1-[(1*R*,2*S*,5*R*)-menthyloxy]-3,4-dimethyl-3-phospholene l-oxide (**8**) and 0.035 g (0.15 mmol) of TEBAC in 5 mL of chloroform, a solution of 4.0 g (0.10 mol) of NaOH in 4 mL of water was added dropwise and the mixture was kept at reflux for 3 h. The mixture was cooled to 26°C and filtrated; the organic phase was separated and concentrated. The crude product so obtained was purified by column chromatography (silica gel, 2% methanol in chloroform) to give 0.33 g (33%) of **12a** as a colorless oil.

$[\alpha]_D^{25} = -59.6$ (c 1.0, $CHCl)_3$; ^{31}P NMR ($CDCl_3$) δ 18.0; ^{13}C NMR ($CDCl_3$) δ 15.8 ($C_{5'}$—$CH_{3'}$), 20.8 ($CHCH_3$), 21.7 ($CHCH_3$)), 22.7 ($C_{3'}$), 23.4 (J = 16.3, C_3—CH_3), 23.6 (J = 16.0, C_5—CH_3), 25.1 ($C_{5'}$), 31.4 ($CHMe_2$), 33.8 ($C_{4'}$), 43.3 ($C_{6'}$), 48.5 (J = 6.5, $C_{2'}$), 77.3 (J = 7.5, $C_{1'}$), 122.7 (J = 128.0, C_2), 122.8 (J = 130.1, C_6), 123.8 (J = 4.2, CCl_2), 136.5 (J = 24.4, C_4), 154.3 (J = 15.2, C_3, C_5); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 6.9, $C_{5'}$—CH_3), 0.89 (d, 3H, J = 7.0, $CH(CH_3)_2$), 0.91 (d, 3H, J = 6.4, $CH(CH_3)_2$), 2.32 (s, 6H, C_3—CH_3), 4.02 (dq, J_1 = 9.8, J_2 = 4.5, 3H, OCH), 5.99 (d, J = 10.5, 1H, C_2H), 6.03 (d, J = 10.6, 1H, C_6H); HRMS, $[M + H]^+_{found}$ = 377.1214, $C_{18}H_{28}Cl_2O_2P$ requires 377.1204.

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