g of compound **5**, mp 121–122 °C. The filtrate was evaporated, and the residue was separated by silica gel chromatography in CH_2Cl_2–EtOAc (10:1) to give 5.4 g of **5** and small amounts of isomeric 3-methoxy-6-methyl-1,2,4-triazine 2-oxide (~300 mg) and 3-methoxy-6-methyl-1,2,4-triazine 4-oxide (~400 mg). Mass spectra showed the following: for **5**, molecular ion at *m/e* 141 and major peaks at M – 16 and M – 17 (more abundant than M – 16); for **6**, molecular ion at *m/e* 141; for 3-methoxy-6-methyl-1,2,4-triazine 2-oxide, molecular peak at *m/e* 141; for 3-methoxy-6-methyl-1,2,4-triazine 4-oxide, molecular peak at *m/e* 141. Anal. Calcd for $C_5H_7N_3O_2$ (**5**): C, 42.55; H, 4.99; N, 29.77. Found: C, 42.60; H, 5.10; N, 29.83. Calcd for $C_5H_7N_3O_2$ (**6**): C, 42.55; H, 4.99,; N, 29.77. Found: C, 42.46; N, 5.15; N, 29.61.

6-Methyl-1,2,4-triazin-3(4*H*)-one 1-Oxide (7). A mixture of **5** (5.65 g, 0.04 mol) and Na_2CO_3 (0.7 g) in methanol–water (200 mL, 1:1 v/v) was stirred at 70–75 °C in a closed flask for 24 h. The solution was diluted with water (200 mL) and neutralized with Dowex 50 [H^+]. The mixture was heated to dissolve the precipitated **7** and filtered, and the resin was washed with hot water (~50 mL). The filtrates were cooled to 5 °C and the crystalline product collected by filtration (3.90 g). The filtrate was evaporated to yield an additional 1.0 g of **7**: yield 4.90 g (96.3%); mp 221–222 °C dec. The mass spectrum showed a molecular ion at *m/e* 127 and major peaks at M – 16 and M – 17. Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.96; N, 33.06. Found: C, 37.61; H, 3.98, N, 32.91.

4-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-1,2,4-triazin-3(4*H*)-one 1-Oxide (8) and Its α Anomer 9. A mixture of compound **7** (4.5 g, 0.035 mol), trimethylchlorosilane (1 mL), and hexamethyldisilazane (30 mL) was stirred at 100–110 °C until the **7** dissolved (approximately 1 h). Dry toluene (100 mL) was added, and the solution was evaporated. This step was repeated two more times, and the residue was dissolved in dry CH_2Cl_2 (100 mL). A dry mixture of HgO (6.5 g) and $HgBr_2$ (10.5 g) was added, and the mixture was cooled in ice under nitrogen. 2-Deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuransyl chloride (19 g) in CH_2Cl_2 (150 mL) was added with stirring. The mixture was stirred at 5 °C for 0.5 h and at room temperature for 0.5 h. It was then filtered, and the solids were washed with CH_2Cl_2 (200 mL). The combined filtrates were washed with 20% KI solution (2 × 150 mL) and H_2O (2 × 100 mL) and dried (Na_2SO_4). The solution was evaporated to a crystalline residue which was separated by chromatography on silica gel in CH_2Cl_2–petroleum ether–ether (5:2:1 v/v/v). Evaporation of the appropriate fractions gave 6.05 g of **8**, 4.77 g of **9**, and a mixture (2:3, 2.2 g) of **8** and **9**: compound **8**, mp 191–192 °C; compound **9**, mp 178–179 °C.

4-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-1,2,4-triazin-3(4*H*)-one 1-Oxide (10). A mixture of compound **8** (4.8 g, 0.01 mol) and KOH (400 mg) in methanol was stirred at room temperature for 20 h. The solution was neutralized with a weakly acidic cation exchanger (Amberlite CG-50, H^+) and filtered, and the resin was washed with methanol. The combined filtrates were evaporated to a syrup which was dissolved in ethanol for crystallization: yield 2.23 g; mp 193–194 °C. Anal. Calcd for $C_9H_3N_3O_5$: C, 44.44; H, 5.38; N, 17.27. Found: C, 44.31; H, 5.41; N, 17.17.

4-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-6-methyl-1,2,4-triazin-3(4*H*)-one 1-Oxide (11). Compound **9** (4.8 g, 0.01 mol) was deblocked by following the procedure for preparation of **10**: yield 1.94 g; mp 180–181 °C. Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.38; N, 17.27. Found: C, 44.24; H, 5.27; N, 17.16

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Registry No. **1**, 80083-14-3; **3**, 42836-95-3; **4**, 61178-10-7; **5**, 80083-15-4; **6**, 57537-20-9; **7**, 80083-16-5; **8**, 80083-17-6; **9**, 80083-18-7; **10**, 80083-19-8; **11**, 80105-71-1; 1,1-dimethoxyacetone, 6342-56-9; thiosemicarbazide, 79-19-6; 2-deoxy-3,5-di-D-*p*-toluoyl-D-*erythro*-pentofuransyl chloride, 3601-89-6.

Supplementary Material Available: Tables of UV spectral data for compounds **1**, **3–7**, **10**, and **11** and ^1H NMR spectral data for some 1,2,4-triazines (3 pages). Ordering information is given on any current masthead page.

New Synthesis of Spiro Phosphorane by Using Diphenyl Disulfide. A Facile Route to Cyclic Acyloxyphosphoranes from α-Hydroxy Acids

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Five-membered 1,3,2-dioxaphospholanes were subjected to reaction with 1,2- and 1,3-glycols, with 2-(methylamino)ethanol, and with α-hydroxy acids in the presence of diphenyl disulfide to produce various derivatives of spiro oxyphosphoranes **3** and **5**. The reactions were carried out at 0 °C with phosphonite **1a** and at 80 °C with phosphites **1b** and **1c**. Two moles of benzenethiol was isolated from the system by distillation in vacuo. The course of reaction of these ternary systems has reasonably been explained by invoking the intermediacy of a phosphonium benzenethiolate **7**.

Recently, a number of interesting reactions for the syntheses of pentacovalent oxyphosphoranes and their analogues from the corresponding trivalent phosphorus compounds have been reported.[1-4] However, most of these reactions involve some inconveniences, e.g., the employment of dangerous or expensive reagents and the necessity of eliminating concomitant byproducts. In this paper, we describe a new synthetic method for preparation of spiro

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Table I. Spiro Phosphoranes Prepared by Use of Diphenyl Disulfide as a Condensing Agent[a]

1[a]	2[a]	HX^1-R^3-X^2H	3	yields, %	^{31}P NMR,[b] ppm
1a	2a	$HOCH_2CH_2OH$	3a	95	−19
1a	2b		3b	85	−14
1a	2c		3c	72	−35
1a	2d		3d	56	−35
1b	2a	$HOCH_2CH_2OH$	3e	84[c]	−28

[a] An equimolar amount in diethyl ether. [b] The spectra were recorded at 24.3 MHz in methylene dichloride. All shifts are of upfield relative to 85% H_3PO_4. [c] Reacted at 80 °C for 4 h in acetonitrile.

Table II. Syntheses of Cyclic Acyloxyphosphoranes Using Diphenyl Disulfide[a]

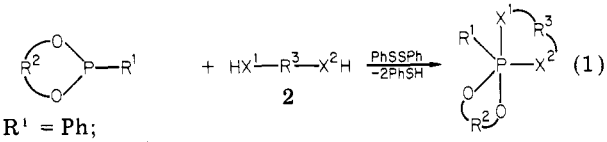
1[a]	4[a]	$HOC(R^4)(R^5)CO_2H$	5	yields,[b] %	^{31}P NMR,[c] ppm
1a	4a	$R^4 = R^5 = H$	5a	77	−22[d]
1a	4b[e]	$R^4 = H$; $R^5 = Me$	5b	66	−24
1a	4c[e]	$R^4 = H$; $R^5 = Ph$	5c	66	−24
1a	4d	$R^4 = R^5 = Me$	5d	76	−27
1a	4e[f]	$R^4 = H$; $R^5 = CH_2CO_2H$	5e	82	−24[g]
1c	4a	$R^4 = R^5 = H$	5f	65[h]	−38

[a] Three millimoles each in 6 mL of diethyl ether. [b] Not optimized. [c] The spectra were recorded at 24.3 MHz in dichloromethane unless noted otherwise. All shifts are observed upfield of 85% H_3PO_4 external standard. [d] In diethyl ether. [e] Racemic. [f] L isomer. [g] In dimethylformamide. [h] Three millimoles each in 4 mL of acetonitrile at room temperature for 24 h.

phosphoranes using the readily available and inexpensive reagent diphenyl disulfide, which is also suited for large-scale synthesis. The reaction involves combination of a cyclic phosphorus(III) compound with a glycol or with an α-hydroxy acid in the presence of diphenyl disulfide. The former combination produces spiro oxyphosphoranes, while the latter one affords spiroacyloxyphosphoranes.[5]

Results and Discussion

Preparation of Oxyphosphoranes. Trivalent phosphorus compounds containing a five-membered ring, **1a** and **1b**, were allowed to react with hydroxy acid, diol, and amino alcohol **2** in the presence of diphenyl disulfide to give spiro oxyphosphoranes **3** in good yields (eq 1). Di-



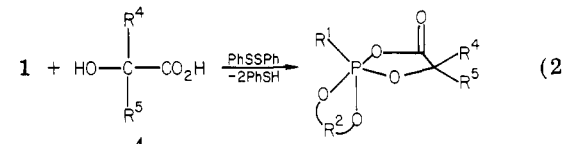
(1)

1a, R^1 = Ph; R^2 = $-(CH_2)_2-$
b, R^1 = OEt; R^2 = $-(CH_2)_2-$
c, R^1 = OMe; R^2 = $-(CMe_2)_2-$

2 **3**

phenyl disulfide acted as a hydrogen-accepting agent, and, thus, 2 mol of benzenethiol were isolated by distillation in vacuo (vide infra). In Table I are summarized some of the typical results. Both 1,2- and 1,3-glycols successfully reacted with **1a**, and the yields of **3a–c** were satisfactory. A β-amino alcohol, **2d**, also reacted to produce an aza-oxyphosphorane **3d**. However, neither 2-mercaptoethanol nor 1,2-diaminoethane gave the corresponding phosphoranes, yielding unknown polymeric products. With **1b** as the P(III) component, the reaction should be carried out at 80 °C in acetonitrile, probably because **1b** is less nucleophilic than **1a**. This type of reaction could not be applied to acyclic derivatives of phosphorus(III), e.g., triethyl phosphite.

Preparation of Spiro Acyloxyphosphoranes. When α-hydroxy acids **4** were allowed to react in the three-component system, various spiro acyloxyphosphoranes **5** were prepared (eq 2). Table II shows some results. Both un-



(2)

4 **5**

substituted (**5a**) and dimethyl-substituted (**5d**) ones were isolated for the first time. An interesting phosphorane, **5e**, having a carboxyl group was also prepared successfully from **1** and L-(−)-malic acid **4e**. The product had the five-membered ring of a 4-oxo-1,3,2-dioxaphospholane instead of the alternative six-membered-ring structure. Syntheses with benzilic acid and with tartronic acid were unsuccessful; polymeric materials of unidentified structures were produced. This method also worked well for the conbination between cyclic phosphite **1c** and **4a** in acetonitrile to give an acylpentaoxyphosphorane **5f**.

Previously, we reported a synthetic method for spiro acyloxyphosphoranes in which a cyclic P(III) compound was reacted with an α-keto acid[5b] or with acrylic acid.[5a] The reaction in the present study provides another synthetic method for spiro acyloxyphosphoranes, which affords a wider variety of products.

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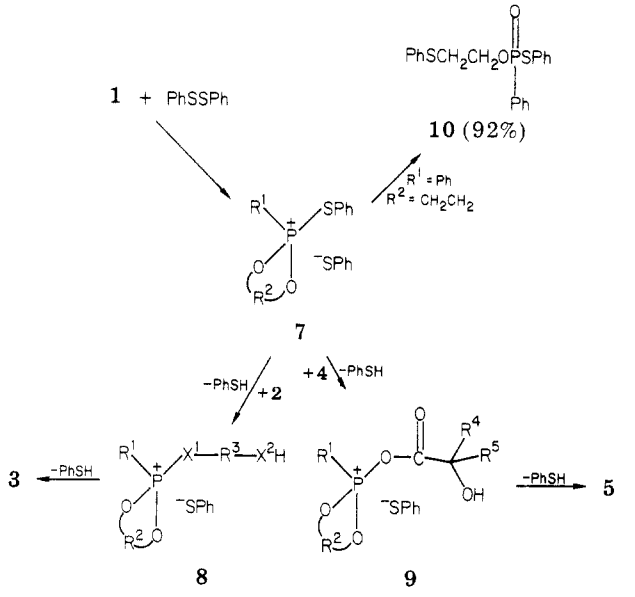
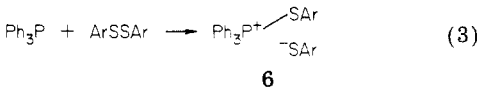
Scheme I



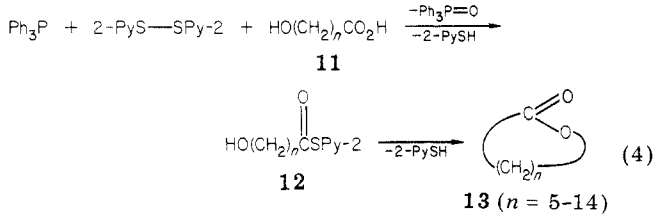
Reaction Course. The series of reactions leading to spiro phosphoranes **3** and **5** in the present study may be related to the condensation reactions with the Ph_3P–diaryl disulfide system as the condensation reagent,[6-8] in which a phosphonium thiolate **6** (eq 3) is the active species for



(3)

the reaction. The course of reactions of the spiro phosphorane synthesis is schematized as in Scheme I. Cyclic phosphonium benzenethiolate **7** is first formed, which then reacts with **2** or with **4** by the substitution of a PhS group to produce, respectively, **8** and **9**. On cyclization with the elimination of benzenethiol, **8** and **9** give, respectively, **3** and **5**. In total, 2 mol of benzenethiol is produced as the result of accepting two hydrogen atoms from **2** or **4**. The intermediacy of **7** is supported by the two-component reaction of **1a** with diphenyl disulfide, which produced phosphonothiolate **10** via **7**.

The formation of acyloxyphosphorane **5** is interesting when compared with the one-step macrolide synthesis by Corey et al.,[7a] who obtained 2-pyridinethiol esters **12** from ω-hydroxy carboxylic acid **11** by the following reaction (eq 4). When ω-hydroxy acids with $n \geq 2$ were used as a



(4)

difunctional nucleophile, **4**, in our synthesis of phosphoranes no corresponding acyloxyphosphorane was produced.

Experimental Section

Materials. 2-Phenyl- (**1a**[9]), 2-ethoxy- (**1b**[10]), and 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaphospholanes (**1c**)[10] were prepared as previously reported. Compounds **2a,c,d**, as well as 2-mercaptoethanol and 1,2-diaminoethane, were purified by distillation under nitrogen before use. Diphenyl disulfide, 2-hydroxyphenol (**2b**), and α-hydroxy acids (i.e., **4a-e** and benzilic and tartronic acids) were used after purified by recrystallization.

5-Phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (3a). Into 60 mL of diethyl ether containing both 6.56 g (30 mmol) of diphenyl disufide and 1.86 g (30 mmol) of ethylene glycol (**2a**) was added 5.04 g (30 mmol) of **1a** at 0° C under nitrogen, and the mixture was stirred at 0 °C for 1 h and at room temperature for another hour. After the reaction, ether was removed at a slightly reduced pressure, and then benzenethiol was distilled off at room temperature in vacuo. The amount of benzenethiol recovered was almost quantitative. On recrystallization of the solid residue from a 1:1 mixture of diethyl ether and dichloromethane, 6.52 g (95% yield) of a white crystalline solids was obtained (**3a**), mp 129–130 °C (lit.[1f,g] mp 123 °C).

The preparations of the following products were also carried out in a manner similar to that above.

2,3-Benzo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]-non-2-ene (3b): white crystals; mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 3.5–4.3 (m, 4), 6.5–8.0 (m, 9); IR (KBr) 1230 ($\nu_{P-O-aryl}$), 1060 ($\nu_{P-O-alkyl}$) cm^{-1}. Anal. Calcd for $C_{14}H_{13}O_4P$: C, 60.88; H, 4.74; P, 11.21. Found: C, 61.18; H, 4.81; P, 11.11.

8,8-Dimethyl-5-phenyl-1,4,6,10-tetraoxa-5-phospha[4.5]-decane (3c). This was isolated by distillation after removal of benzenethiol: colorless liquid; bp 121 °C (0.2 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3), 1.10 (s, 3), 3.1–4.2 (m, 4), 3.60 (d, J_{P-H} = 17.3 Hz, 2), 3.63 (d, J_{P-H} = 12.7 Hz, 2), 7.0–7.8 (m, 5); IR (KBr) 1050 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{13}H_{19}O_4P$: C, 57.79; H, 7.09; P, 11.46. Found: C, 57.84; H, 6.86; P, 11.61.

4-Methyl-5-phenyl-4-aza-1,6,9-trioxa-5-phosphaspiro-[4.4]nonane (3d): hygroscopic white crystals; mp 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 2.93 (d, J_{P-H} = 9 Hz, 3), 2.7–3.4 (m, 2), 3.2–4.1 (m, 6), 7.0–7.7 (m, 5); IR (KBr) 1047 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{11}H_{16}NO_3P$: C, 54.77; H, 6.69; N, 5.81; P, 12.84. Found (very hygroscopic): C, 54.26; H, 6.79; N, 5.43; P, 12.56.

5-Ethoxy-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (3e). An equimolar (3 mmol) mixture of **1b**, **2a**, and diphenyl disulfide in acetonitrile (4.0 mL) was maintained at 80 °C for 4 h under nitrogen. After removal of both acetonitrile and benzenethiol in vacuo, the product was isolated as described as above: white crystals; mp 34–36 °C (lit.[1e,f] mp 36–38 °C).

2-Oxo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5a). Equimolar (3 mmol) amounts of **1a**, diphenyl disulfide, and glycolic acid (**4a**) were dissolved in diethyl ether (6 mL), and the mixture was maintained at 0 °C for 3 h. Then, the reaction mixture was dried up in vacuo to remove benzenethiol. The white solid residue was subjected to recrystallization from a 1:1 mixture of diethdyl ether and dichloromethane to give **5a**: mp 128–129 °C; ^{1}H NMR ($CDCl_3$ δ 3.2–4.7 (m, 4), 4.18 (d, J_{P-H} = 13 Hz, 1), 4.26 (d, J_{P-H} = 13 Hz, 1), 7.2–8.0 (m, 5); IR (KBr) 1740 ($\nu_{C=O}$), 1040 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{10}H_{11}O_5P$: C, 49.60; H, 4.58; P, 12.79. Found: C, 49.72; H, 4.95; P, 12.80. The preparations of the other acyloxyphosphoranes were carried out likewise.

3-Methyl-2-oxo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro-[4.4]nonane (5b): while crystals; mp 56–57 °C (lit.[5b] mp 56–58 °C).

3,5-Diphenyl-2-oxo-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]-nonane (5c): white crystals; mp 108–109 °C (lit.[5b] mp 103–105 °C).

3,3-Dimethyl-2-oxo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5d): white crystals; mp 161–162 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3), 1.59 (s, 3), 3.3–4.4 (m, 4), 7.1–8.1 (m, 5); IR

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(KBr) 1750 ($\nu_{C=O}$), 1040 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_5P$: C, 53.34; H, 5.60; P, 11.46. Found: C, 52.94; H, 5.61; P, 11.47.

3-(Carboxymethyl)-2-oxo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5e): white crystals; mp 118–121 °C; ^1H NMR ($CDCl_3$) δ 2.4–3.0 (m, 2), 3.3–4.6 (m, 5), 6.9–7.9 (m, 5), 9.85 (s, 1); IR (KBr) 3400, 1730 ($\nu_{C=O}$) 1640 ($\nu_{C=O}$), 1035 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_7P$: C, 48.01; H, 4.36; P, 10.32. Found: C, 47.65; H, 4.80; P, 10.60.

5-Methoxy-2-oxo-7,7,8,8-tetramethyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5f). An equimolar (3 mmol) mixture of **1c**, **4a**, and diphenyl disulfide in acetonitrile (4 mL) was kept at room temperature with stirring under nitrogen. After 24 h, acetonitrile and benzenethiol were removed completly in vacuo, and the residue was subjected to the recrystallization as above: white crystals; mp 87–89 °C; ^1H NMR ($CDCl_3$) δ 1.3 (m, 12), 3.63 (d, J_{P-H} = 14 Hz, 3) 4.19 (d, J_{P-H} = 14 Hz, 2); IR (Nujol) 1755 ($\delta_{C=O}$), 1060 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_9H_{17}O_6P$: C, 42.86; H, 6.80; P, 12.28. Found: C, 42.54; H, 7.12; P, 12.32.

***S*-Phenyl *O*-[2-(Phenylthio)ethyl] Phenylphosphonothioate (10).** Equimolar (3 mmol) amounts of **1a** and diphenyl disulfide were dissolved in diethyl ether (6 mL), and the mixture was kept at room temperature under a nitrogen atmosphere for 3 h. On removing diethyl ether in vacuo a colorless viscous oil was given. It was then purified by the preparative TLC (silica gel–chloroform, R_f 0.4–0.5) to yield **10**: 92%; ^1H NMR ($CDCl_3$) δ 3.10 (t, J_H = 7 Hz, 2), 4.3 (m, 2), 7.0–7.8 (m, 15); ^{31}P NMR ($CDCl_3$ from 85% H_3PO_4) 41 ppm; IR (film) 1230 ($\nu_{P=O}$), 1060 (ν_{P-O-C}), 1000 cm^{-1} Anal. Calcd for $C_{20}H_{19}O_2PS_2$: C, 62.16; H, 4.96; P, 8.01. Found: C, 61.94; H, 4.94; P. 8.05.

Registry No. **1a**, 1006-83-3; **1b**, 695-11-4; **1c**, 14812-60-3; **2a**, 107-21-1; **2b**, 120-80-9; **2c**, 126-30-7; **2d**, 109-83-1; **3a**, 34736-73-7; **3b**, 71559-31-4; **3c**, 80317-87-9; **3d**, 80317-88-0; **3e**, 34736-72-6; **4a**, 79-14-1; (±)-**4b**, 598-82-3; (±)-**4c**, 90-64-2; **4d**, 594-61-6; (*S*)-**4e**, 97-67-6; **5a**, 75631-05-9; (±)-**5b**, 80317-89-1; (±)-**5c**, 80317-90-4; **5d**, 75631-06-0; (*S*)-**5e**, 80317-91-5; **5f**, 80317-92-6; **10**, 80317-93-7; diphenyl disulfide, 882-33-7.

Synthetic Studies in the Ajmaline Series[1]

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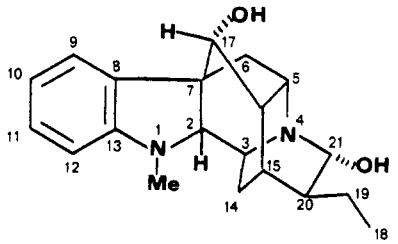
An approach to the Rauwolfia alkaloid ajmaline (1) is described. The bicyclic indole system **13a** was prepared by Fischer indole synthesis from either of the 9-azabicyclo[3.3.1]nonan-2-one derivatives **8** and **10**. Differentiation of a symetrically functionalized diol **6** by using poly(vinylpyridinium chlorochromate) (PVPCC) is described. The preparation of the indole system **13a** is discussed with appropriate reference to the stereochemical aspects involved. Further elaboration of **13a** to the tricyclic compounds **31** and **32** is presented.

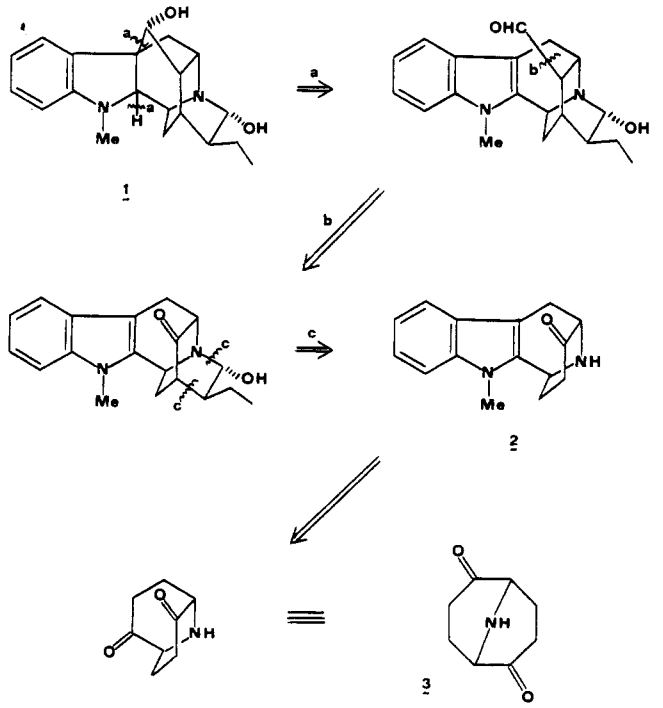
The appeal of the antiarrhythmic[3] Rauwolfia alkaloid ajmaline (1) to synthetic chemists has been the inherent



1 Ajmaline

challenge of preparing such a highly fused ring system. Previous syntheses of ajmaline,[4] isoajmaline,[5] and an elegant partial synthesis[6] have employed quite different approaches to control of stereochemistry and ring formation; however, all of these syntheses have shared the common feature of the Pictet–Spengler reaction in linking carbons 2 and 3. Because of this common feature, all of these previous syntheses[4–6] have utilized preformed indolic starting materials such as *N*-methyltryptophan and *N*-methylindole acetic acid.

Scheme I. Retrosynthetic Analysis of Ajmaline



In examining a number of alternative approaches to ajmaline, we were attracted to the possibility of constructing the indole moiety de novo. In particular, as shown in Scheme I, the series of retrosynthetic disconnections a–c gave the attractive intermediate **2**, which,

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