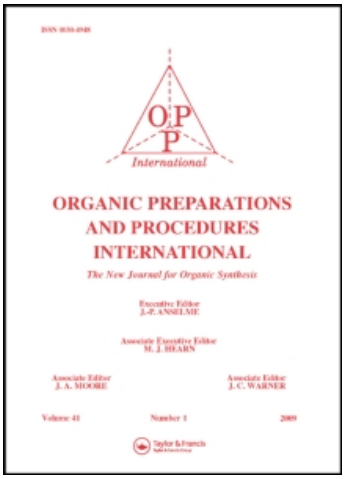

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AN ALTERNATIVE STRATEGY FOR THE PURIFICATION OF *meso*-2,4-PENTANEDIOL

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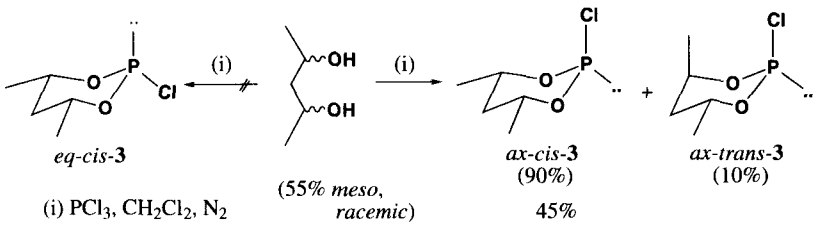
meso-2,4-Pentanediol is a useful reagent for the synthesis of conformationally locked organic heterocycles.[1] It has also been used as a model system for spectroscopic and chemical studies relating to polymers.[2] Its conversion to dihalides[3] led to the development of new organometallic compounds[4] and to new insights on the stereochemistry of substitution reactions.[5]

Among several routes available for its synthesis[6] the most efficient method[7] is that reported by Pritchard and Vollmer,[8] who separated a mixture of *racemic* and *meso* isomers (*ca.* 50:50), obtained by reduction of 2,4-pentanedione with sodium borohydride, through the formation of cyclic sulfite esters. Although the conversion of the isomeric pentanediols (**1**) to the cyclic sulfites (**2**) with thionyl chloride is straightforward,[8,9] the fractionational distillation is not simple, since the boiling points of the isomers are close (*cis*-**2**: lit.[8] bp. 72°/12 mmHg, lit.[1a] bp. 74°/12 mmHg; *trans*-**2**: lit.[8] bp. 82°/12 mmHg, lit.[1a] 80-82°/12 mmHg), making separation of the sulfite *cis*-**2** from the mixture tedious when using a spinning band column and difficult to achieve even with a column packed with glass helices.[10] We now report an alternative route for purification of *meso*-2,4-pentanediol from a *racemic*- and *meso*-mixture based on the stereoselective formation of phosphorochloridite *ax-cis*-**3** (Scheme 1) followed by its saponification. The reaction conditions were systematically varied in order to determine the highest ratio of *ax-cis*-**3**:*ax-trans*-**3**.



Scheme 1

The reaction between pure *meso*-pentanediol or racemic pentanediols with phosphorus trichloride has been reported by Verkade[11] and Mikolajczyk,[12] respectively. Both procedures include

the use of a base such as pyridine or triethylamine (TEA) to favor the reaction. However, the presence of a base is not neccesary in order to obtain the phosphorochloridites.[13] The reaction of the mixture of *meso*-and *rac*-pentanediols **1** (55:45) with phosphorus trichloride, showed (by ^{31}P NMR analysis of the crude material) that the process was stereoselective, inasmuch as the phosphorochloridite *ax-cis*-**3** was obtained in 90% yield and the phosphorochloridite *ax-trans*-**3** in only 10% yield; *eq-cis*-**3** was not detected, being thermodynamically less stable than *ax-cis*-**3**, presumably due to stereoelectronic effects. Therefore, the equatorial isomers are normally not observed in the reaction of conformationally locked diols with phosphorus trichloride.[14]

Based upon the successful preparation of *ax-trans*-**3** from *rac*-2,4-pentanediol and phosphorus trichloride in the presence of TEA,[12] one might expect that the reaction of the *meso*- and racemic-mixture of diols with phosphorus trichloride to be non-stereoselective. Thus, our results are both surprising and gratifying since this approach led to a reliable method for the purification of the *meso*-2,4-pentanediol after saponification of the phosphorochloridite *ax-cis*-**3** (90%) so formed.

The phosphorochloridites *ax-cis*-**3** and *ax-trans*-**3**, the bp. of which differ only slightly [*ax-cis*-**3**: lit.[11] bp. 72-73°/12 mmHg, *ax-cis*-**3**:*ax-trans*-**3** (50:50 mixture): lit.[11] bp. 77-79°/12 mmHg; this work: *ax-cis*-**3**:*ax-trans*-**3** (90:10 mixture) 30-32°/0.3 mmHg], form a constant boiling mixture which prevents further separation by distillation.[15]

The reaction between the mixture of *meso*- and *rac*-pentanediols **1** and phosphorus trichloride was carried out at several temperatures and reaction times. The ratios of the phosphorochloridites *ax-cis*-**3** and *ax-trans*-**3** determined by ^{31}P NMR analyses of the crude material are summarized in Table 1. In general, the stereoselectivity changed with temperature, so that an increase in the formation of the *ax-cis*-**3** stereoisomer was observed as the temperature was increased. On the other hand, the ratio of *cis*:*trans* of the phosphorochloridites remained nearly unchanged over longer periods.

The phosphorochloridites are sensitive to acidic conditions and also to moisture so that, in the experiments conducted at 0° or 30° for 3 hrs (Table 1), only the isomeric 2-hydro-2-oxo-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinanes **4**[16] were obtained as products. Remarkably, it was observed that the stereoselectivity *cis*/*trans* of the phosphorochloridites-**3** was increased with the increment of the by-products **4** suggesting that it is the selective decomposition of the phosphorochloridite *ax-trans*-**3** in the acidic medium[17] which is an important factor contributing to the diastereoselectivity in this reaction.

Finally, in order to assess the reproducibility of the method, several experiments were conducted at 0° for 5 min. The results suggest that the phosphorochloridite *ax-cis*-**3** is formed with a stereoselectivity of 90% ±2.

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR spectra at 270 and 67.5 MHz, respectively were recorded on a Jeol GSX-270 spectrometer and were obtained for $CDCl_3$ solutions. Chemical shifts (δ) are referenced to internal $(CH_3)_4Si$. ^{31}P NMR spectra were recorded at 109.25 MHz in $CDCl_3$ on the Jeol GSX-270 spectrom-

eter and are reported in ppm downfield (+) from external 85% H_3PO_4. The mass spectrometry analysis was obtained on a Hewlett Packard 5989A spectrometer.

Table 1. Effect of the Temperature and Time on the Ratio of *ax-cis*-**3**:*ax-trans*-**3** from Addition of 2,4-pentanediol to PCl_3

Temp. (°C)	Time (hrs)	Diol-1[a] *meso/rac* (1.2/1)	PCl_3[a]	CH_2Cl_2[a]	*ax-cis*-**3**[b]	*ax-trans*-**3**[b]
-78	0.08	1.0	1.0	1.7	71	29
-78	0.5	1.0	1.0	2.8	73	27
-78	12.0	1.0	1.0	2.8	70	30
-78	15.0	1.0	1.0	2.8	73	27
-78	20.0	1.0	1.0	2.0	74	26
-20	0.08	1.0	1.0	2.0	78	22
0	0.08	1.0	1.0	3.5	93	7
0	0.33	1.0	1.0	2.0	84	16
0	3.0	1.0	1.0	2.0	c	c
30	0.33	1.0	1.0	2.0	81	19
30	3.0	1.0	1.0	2.0	c	c

a) In equivalents. b) The percentages were determined by ^{31}P NMR spectroscopy of the crude material. c) Only compounds **4** were observed (see text).

***meso*- and *rac*-2,4-Pentanediols** obtained as a mixture (55:45)[18] from acetylacetone and sodium borohydride.

2-Chloro-4,6-dimethyl-1,3,2-λ^3-dioxaphosphorinanes (3).- In a three-necked 250-mL flask, fitted with a dropping funnel, a drying tube connected to an open flask containing an aqueous sodium hydroxide (75%) solution and a magnetic stirrer, were placed 16 mL of dry methylene chloride under nitrogen and 7.1 mL of phosphorus trichloride (81.6 mmol). The solution was stirred at 0° and 8.5 g (81.6 mmol) of a mixture of *meso*- and *rac*-pentanediols (55:45) was added dropwise over 5 min. The hydrogen chloride, which was evolved copiously, was allowed to bubble into the sodium hydroxide solution. The solution was concentrated at 65° on a rotary evaporator to afford an oil in a quantitative yield. The product was distilled under vacuum at bp. 30-32°/0.3 mm Hg to give 7.3 g (87%, based on the amount of *meso* diol) of a mixture of isomers *axial-cis*/*ax-trans* of around 90:10 composition. *Axial-cis*-**3**: ^1H NMR: δ 1.29 (d, J = 5.9 Hz, 6 H), 1.78 (m, J = 14.5 Hz, 1 H) 1.8 (m, 1 H), 4.76 (m, J = 5.9, 2 H); ^{13}C NMR: δ 22.21 (d, J_{CP} = 2.2 Hz, 2 C), 42.28 (d, J_{CP} = 3.3 Hz), 69.36 (d, J_{CP} = 3.3 Hz); ^{31}P NMR: δ 148.68 (s). *ax-trans*-**3**: ^{31}P NMR: δ 150.37 (s).

Saponification of 1,3,2-λ^3-dioxaphosphorinanes (3).- A 250 mL round-bottomed flask, equipped with a magnetic stirrer was charged with 7.26 g (43 mmol) of the distilled phosphorochloridites **3** obtained as described above. The flask was cooled to 0° in an ice-water bath and 10 mL of a solution of sodium hydroxide (12.9 M) was added cautiously (vigorous reaction) by syringe over a period of 5

min. to the stirred solution. The reaction mixture was stirred overnight at ambient temperature and the water was removed by vacuum distillation (20°/2.0 mmHg). Then, 40 mL of dichloromethane were added to the residue. The solution was dried over anhydrous sodium sulfate, filtered and concentrated by use of a rotary evaporator to give 3.77 g (84%, based on *ax-cis*-**3** compound) of *meso*/*rac*-pentanediols [*ca.* 90:10 composition after distillation in the kugelrohr (63°/3.5 mmHg)].

***meso*-2,4-Pentanediol (1)**.- The cyclic phosphorochloridite-saponification protocol was repeated on 4 g (38.4 mmol) of the diastereomerically enriched mixture (90:10) of *meso*- and *rac*-pentanediols obtained as described above. A sample of 0.86 g (23% overall yield based on the *meso* diol) of *meso*-2,4-pentanediol in high diastereomeric purity (98%) was obtained by distillation. ^{1}H NMR: δ 1.13 (d, J = 6.2 Hz, 6 H), 1.41 (dd, J= 14.5 , 9.2 Hz, 1 H) 1.5 (dd, J = 14.5, 9.2 Hz, 1 H), 3.98 (m, 2 H); ^{13}C NMR: δ 24.04 (s), 46.28 (s), 68.84 (s); MS: *m/z* 105 (M^+ + 1), 87 (M^+ - 17), 71 (M^+ - 33), 45 (M^+ - 59), 15 (M^+ - 89).

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