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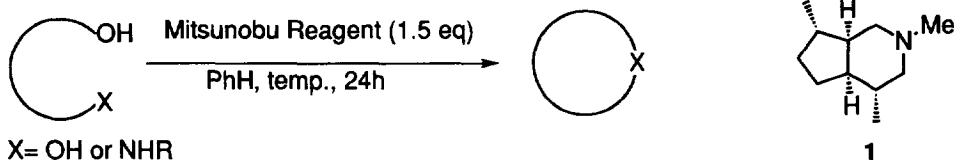
Formation of Heterocycles by the Mitsunobu Reaction. Stereoselective Synthesis of (+)- α -Skytanthine

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Abstract: Cyanomethylenetriethylphosphorane was shown to mediate the dehydrocyclization of diols and amino alcohols to give the corresponding 6-membered *O*- and *N*-heterocycles in 90% or better yields. Using the reaction as a key step, (+)- α -skytanthine, a unique mono terpene alkaloid, was synthesized stereoselectively.
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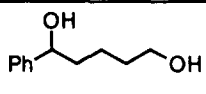
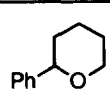
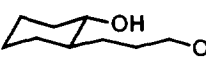

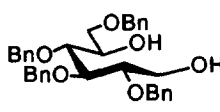
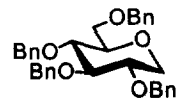
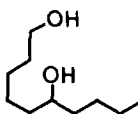
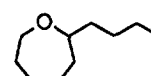
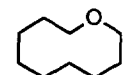
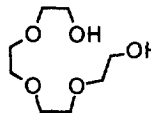
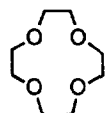
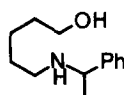
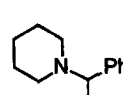
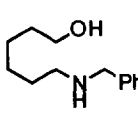
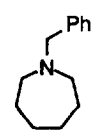
The Mitsunobu reaction is a unique alkylation reaction utilizing the redox system between diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP), and has been applied widely in organic synthesis for the condensation of alcohols and various nucleophiles.¹ We have recently introduced two types of new reagents applicable to the reaction of nucleophiles of larger pK_a . They are azodicarboxamides, e.g. *N, N, N', N'*-tetramethylazodicarboxamide (TMAD)² and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD)³ in combination with tributylphosphine (TBP), and phosphorane reagents, such as cyanomethylene-tributyl⁴ and -trimethylphosphorane⁵ (CMBP and CMMP). In the course of these studies, we found that CMBP, but not any of the azo reagents, was capable of forming dibenzyl ether (91 % yield) from benzyl alcohol at 100°C,^{6,7} and that CMBP successfully mediated the reaction of (methylthiomethyl)tolylsulfone (whose pK_a is as weak as 23.4 in DMSO⁸) with various alcohols.³ Anticipating that the phosphorane reagents would mediate intramolecular dehydrocyclization leading to the formation of cyclic ethers and amines, as the traditional DEAD-TPP reagent does in some cases,^{9,10} we have systematically studied on the reaction of these reagents on various diols and amino alcohols.¹¹ The results are presented herein along with an application to the stereoselective synthesis of (+)- α -skytanthine (**1**),¹² a unique monoterpene alkaloid.



The reaction was performed typically as follows. For the reactions with the azo reagent systems, a phosphine (TPP or TBP) (1.5 mmol) and an azo reagent (1.5 mmol) were added successively to a dry benzene (3 mL) solution of an alcohol (1 mmol) with stirring under argon atmosphere. Stirring was continued at room

temperature for 24 h. For those with phosphorane reagents, a reagent (1.5 mmol) was added to a dry benzene (5–10 mL) solution of an alcohol (1 mmol), and heated with stirring in a sealed vessel. The products were generally isolated by silica-gel column chromatography after evaporation of the solvent *in vacuo*. The results obtained are listed in the following Table.

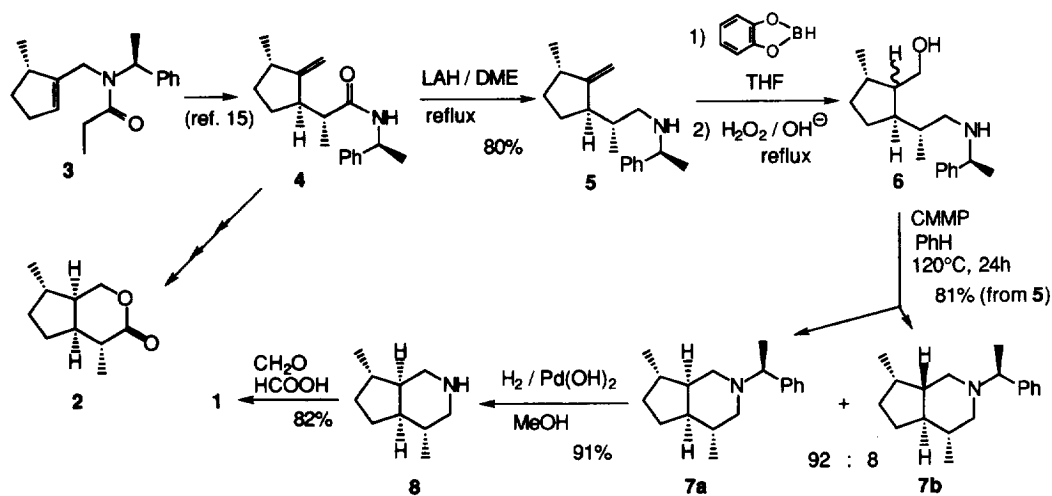
Table. Reaction of diols and amino alcohols.

Entry	Alcohol	Reagents (temp. (°C))	Product	% Yield
1		DEAD-PPh ₃ (r.t.)		7
		TMAD-PBu ₃ (r.t.)		72
		DHTD-PBu ₃ (r.t.)		55
		CMBP (60)		90
2		DEAD-PPh ₃ (r.t.)		57
		TMAD-PBu ₃ (r.t.)		73
		DHTD-PBu ₃ (r.t.)		45
		CMBP (100)		93
3		CMBP (80)		91
4		DEAD-PPh ₃ (r.t.)		0
		CMBP (120)		54
		CMMP (100)		16
5	HO(CH ₂) ₆ OH	CMBP (100)		0
6		DEAD-PPh ₃ (r.t.)		0
		TMAD-PBu ₃ (r.t.)		0
		CMBP (60)		30
7		DEAD-PPh ₃ (r.t.)		43
		TMAD-PBu ₃ (r.t.)		49
		DHTD-PBu ₃ (r.t.)		27
		CMBP (120)		83
		CMMP (120)		89
8		DEAD-PPh ₃ (r.t.)		0*
		TMAD-PBu ₃ (r.t.)		0
		CMBP (r.t.)		26
		CMBP (120)		18
		CMMP (120)		9

* : Reported by Bernotas and Cube (ref. 10b).

Table clearly shows that 1) both phosphorane reagents promote every reaction examined, while the combination of an azo compound and a phosphine mediates only a few reactions (entries 1, 2, 7), and 2) the yield is always better with the former in cases where both types of reagents work. The followings are also noted. 3) The best results are obtained with phosphorane reagents, especially CMBP, in all cases examined with one exception (entry 7). 4) Cyclization to a 6-membered ring proceeds in much better yield (entries 1–3, 7) than those to the 7-, 10- and 12-membered rings (entries 4–6, 8). 5) The phosphorane reagents, but not azo reagents are capable of cyclization to the medium rings (entries 4, 6, 8) except a 10 membered ring (entry 5). 6) The configuration of the products¹³ verifies that the cyclization proceeds through the initial activation of the primary hydroxyl group and subsequent nucleophilic attack of the secondary hydroxyl group, resulting in retention of configuration at the secondary carbinyl center of the reaction products (entries 2, 3). Thus, the use of CMBP for cyclization to 6-membered rings in 90% or better yields is a worthwhile and general method in organic synthesis.

In order to demonstrate the usefulness of the reaction, we applied it to a stereoselective short-step synthesis of (+)- α -skytanthine, the antipode of a unique monoterpene alkaloid first isolated from *Skytanthus acutus*¹² and synthesized twice.¹⁴ The synthesis started from the amide **4**, the product of the asymmetric aza-Claisen rearrangement of **3**, and an intermediate for our synthesis of (-)-isoiridomyrmecin (**2**).¹⁵ The amide **4** was reduced with LiAlH_4 to give the amine **5** (80% yield). The amine was subjected to hydroboration-oxidation affording an inseparable mixture of amino alcohols **6**, which was heated at 100°C in benzene for 24 h (*vide supra*) to afford a 92 : 8 mixture (determined by capillary GLC) of piperidines, **7a** and **7b**, (81% yield for 2 steps) which are easily separable by silica-gel column chromatography. After their structures were secured by 2D NMR spectra (the presence of an NOE between the methyl group on the cyclopentane ring and the newly-formed bridgehead methine proton in the major isomer **7a**, but not in **7b**), the major isomer **7a** was hydrogenolyzed to give a colorless oil which was identified as nor- α -skytanthine (**8**) (91% yield).^{14b} The final methylation of **8** under the reported conditions^{14b} completed the synthesis of (+)- α -skytanthine **1**, $[\alpha]_D^{25} +70$ (c 0.74, CH_2Cl_2), the antipode of natural product, $[\alpha]_D^{25} -75$ (c 1.9, CH_2Cl_2).^{14b}



Thus, the value of the reaction described in the present paper was demonstrated in the synthesis described above.

Acknowledgment: The authors are deeply indebted to Dr. E. Pombo-Villar, Sandoz Pharma Ltd., for the spectra of synthetic nor-a-skytanthine.

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(Received in Japan 24 January 1996; revised 9 February 1996; accepted 15 February 1996)