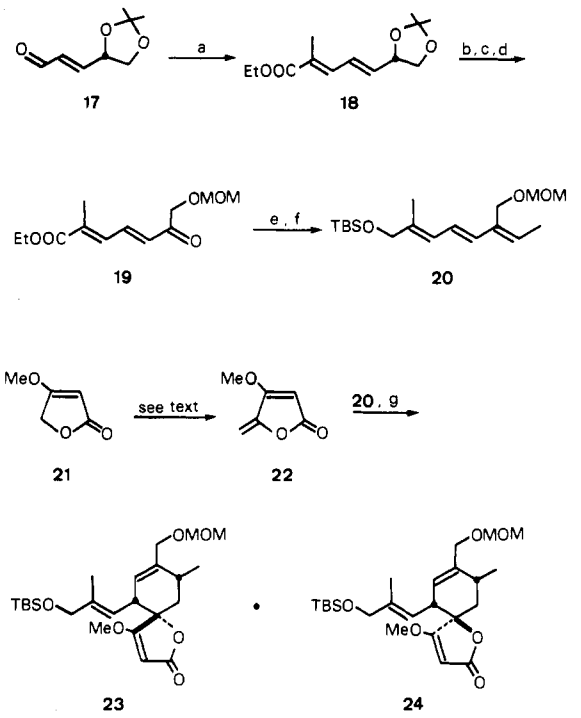
Scheme III[a,8]



[a] (a) $Ph_3P{=}C(Me)COOEt$, PhH, room temperature (96%, 2E/2Z = ca. 7:3); (b) p-TsOH, MeCN, H_2O, reflux (92%); (c) CH_3OCH_2Cl, i-Pr_2NEt, CH_2Cl_2, -50 °C to -20 °C (52%); (d) Swern oxidation (77%, 2E/2Z = ca. 9:1); (e) $Ph_3P{=}CHCH_3$, THF, -70 °C to room temperature (70%); (f) i-Bu_2AlH, Et_2O, 0 °C, then t-Bu(Me)$_2$SiCl, imidazole, DMF, room temperature (98%, ca. 90% purity); (g) o-$C_6H_4(Cl)_2$, 180 °C, (43%).

produced the acetylenic carbinol **13** as a single adduct in 63% yield. The stereochemistry at the carbinol center was determined at the next stage. The equatorial attack of the acetylide presumably derives from the nonbonded interaction associated with the pseudoaxial methyl substituent[13] and, to some extent, from the bulkiness of the Ce metal.[14] Transformation of **13** into spirotetronate **15** was cleanly achieved in 57% yield by heating with methanolic MeOK,[15] followed by O-silylation. The stereostructure of **15** was determined on the basis of ^1H NMR spectral analysis of the derived di-MOM ether **16**. As shown in Table I, compound **16** and di-*O*-methylkijanolide[1c] are very similar in the chemical shifts and coupling constants for the protons on the cyclohexene rings.

The second route to the upper fragment of **1** we envisaged was direct construction of the functionalized spiro ring by Diels-Alder cyclization of 5-methylenetetronate **22** with an appropriate triene. The dienophile **22** was prepared from methyl tetronate (**21**) by three steps: (1) (dimethylamino)methylenation at C(5) with $(Me_2N)_2CHOMe$;[16] (2) $NaBH_3CN$ reduction; (3) quaternization of the resulting 5-[(dimethylamino)methyl]tetronate with MeI followed by treatment with aqueous $NaHCO_3$ (72% overall yield, without purification of intermediates). The requisite triene **20** was prepared by the route shown in Scheme III.

Cycloaddition of **20** and **22** proceeded sluggishly, in contrast to a facile intramolecular version that we had employed in the total synthesis[17] of (±)-ircinianin, a marine sponge sesterterpene. After heating in *o*-dichlorobenzene at 180 °C for 7 h, there was obtained a mixture of diastereomeric adducts **23** and **24** (ratio, 1:3; separable by HPLC) in a combined yield of 43%. The ^1H NMR spectrum of the minor isomer **23** was quite similar to that of **16** in terms of chemical shifts and coupling constants. On the other hand, the major isomer **24** was significantly different from **23** in H-6$_\beta$ and H-10$_\beta$ resonances, upfield shifts of 0.31 and 0.44 ppm, respectively, which could be attributable to a shielding effect of the tetronate carbonyl in vicinity. The stereostructure of **23** was confirmed by the identity of the derived di-MOM ether with **16** in ^1H NMR.

In conclusion, of the two approaches described above, the first one (Scheme II) is evidently advantageous in terms of selectivity and yield in the crucial Diels-Alder cyclization. Synthesis of the top-half of **3** using the same strategy is in progress in this laboratory.

Note Added in Proof. The unfavorable product ratio of **9**/**10** (1:1.4-1.7) (Scheme II) could have been greatly improved to 7.2:1 (48% yield) by conducting the Diels-Alder reaction in trichloroethylene (ca. 80 °C, 14 h) and in the presence of Yb(fod)$_3$ (4 mol %).

Supplementary Material Available: Experimental details and spectral data of compounds used (12 pages). Ordering information is given on any current masthead page.

(12) (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904-3912. (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233-4236.

(13) For preferential axial attack of lithiopropiolate to unhindered cyclohexanone systems, see: Caine, D.; Smith, T. L., Jr. *Synth. Commun.* **1980**, *10*, 751-759; *J. Am. Chem. Soc.* **1980**, *102*, 7568-7570.

(14) With 2-methylcyclohexanone we observed the following ratios of axial to equatorial attack in THF: LiC≡CCOOMe, 67/33; $Cl_2CeC{\equiv}$CCOOMe, 43/57.

(15) Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1949**, 1423-1430.

(16) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717-742.

(17) Takeda, K.; Sato, M.-A.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903-3906.

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Seeking the Ideal Dehydrating Reagent

Summary: A set of "phosphonium anhydride" reagents is shown to have virtually ideal properties as selective oxygen extractors for net dehydration reactions in a series of illustrative examples.

Sir: A reaction central to synthesis is the bonding of an electrophile to oxygen to activate its release as a leaving group via elimination or substitution reactions, the overall result a net loss of water. Many electrophiles have been used for this purpose,[1] and all have drawbacks. In a project calling for formation of 2-arylbenzimidazoles from an aryl carboxylic acid and a substituted *o*-phenylenediamine, we found that the standard procedures were quite inadequate, as were many common phosphorus reagents. We focused on phosphorus electrophiles because of the unusual strength of the P-O bond. This implies avid first attack on oxygen and a very favorable second step releasing the oxygen as a phosphoryl group, the net effect an overall dehydration. We sought a reagent easy to prepare, se-

(1) Castro, B. R. *Org. React. (N.Y.)* **1983**, *29*, 1.

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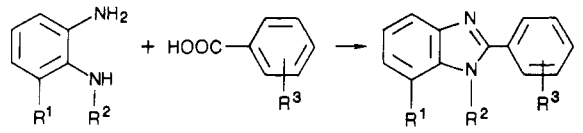
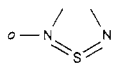
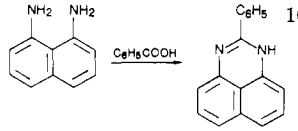
Table I. Dehydration to 2-Arylbenzimidazoles



	R^1	R^2	R^3	conditions[a]	yield,[b] %	product mp, °C (ref)[5]
1	H	H	H	30 min/RT	85 (95)	287 (6)
2	H	C_6H_5	H	60 min/RT	94 (93)	109 (7)
3	H	H	*o*-CH_3	30 min/RT	95	215 (5)
4	H	C_6H_5	*o*-CH_3	10 min/RT	90	100 (5)
5	COOEt	H	*p*-CH_3	30 min/0 °C	80	77 (5)
6	COOEt	H		20 min/RT	86 (95)	173 (5)
7				100 min/83 °C	71	172 (8)

lective for attack on oxygen, without any intrinsic nucleophiles (such as halide or phosphate ions) to form unwanted byproducts, reactive enough to proceed rapidly at moderate temperatures and capable of operating in a reasonable range of common solvents.

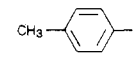
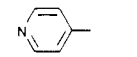
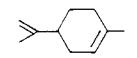
Our earlier formulation[2] of $Ph_3PO + Tf_2O \rightarrow Ph_3P(OTf)_2$ seemed ideal since Tf_2O provides strong activation (Tf = SO_2CF_3), and the only nucleophiles during reaction are the released phosphine oxide and triflate ion; but the yields were disappointing. The actual reagent was subsequently shown[3] to be $(Ph_3P^+)_2O,2OTf^-$, i.e., 2:1 stoichiometry, so that our prior preparations at 1:1 stoichiometry contained excess triflic anhydride, an often indiscriminate electrophile.

We now report that the correct reagent, formed instantly at 0 °C in CH_2Cl_2 from $2Ph_3PO + Tf_2O$, is a very satisfactory reagent for selective abstractions of oxygen. It is commonly used with Et_3N to neutralize the triflic acid formed, and the reactions are often complete in a few minutes at room temperature; alternatively, the reagent can be made in 1,2-dichloroethane and the reacton briefly refluxed (83 °C). For our model cases, the standard monoacylation of *o*-phenylenediamines with aroyl chlorides was plagued with diamide byproducts, but the cyclodehydration of those monoamides with the reagent was excellent. However, using 2 mol of reagent afforded the same 2-arylbenzimidazoles directly from the acid and diamine in comparably high yields as summarized in Table I. The formation of 2-phenylperimidine from *peri*-naphthalenediamine and benzoic acid proceeded similarly.

In another brief survey of the efficacy of the reagent, we found the dehydration of aldoximes to nitriles to be very facile, as summarized in Table II. Furthermore, reexamination of the reactions previously reported (with 1:1 stoichiometry)[2] now consistently showed yields over 90%, i.e., amide dehydration to nitrile, menthol dehydration, and one-step amide formation from acid and amine. Since no other active nucleophiles are present, nucleophiles of choice can presumably be added to afford one-step substitution of alcohols: $ROH \rightarrow [ROP^+R_3] + Nu^- \rightarrow RNu + R_3PO$. This has indeed been shown to be very effective in several cases by Rosen.[4] Our studies of

Table II. Oxime Dehydrations to Nitrile[5]

$RCH{=}NOH \rightarrow RCN$

	R	conditions[a]	yield, %
1		5 min/RT	94
2		5 min/RT	93
3	$(C_6H_2)_2CH$	5 min/RT	98
4		5 min/83 °C	95

the generality of this substitution will be reported in a subsequent paper.

The reagent may be precipitated as a white crystalline solid (mp 74–75 °C)[2] by addition of ether and dry filtration (Schlenck or syringe decantation), and this allows it to be dissolved in pyridine or THF for other applications. However, it is commonly used directly as prepared in CH_2Cl_2, without isolation.

At a practical level, a serious drawback to the reagent is the difficulty in separating the product from Ph_3PO. Our solution has been to use $Ph_2PON(CH_2CH_2)_2NCH_3$, mp 109 °C, made from diphenylphosphinic chloride (Ph_2POCl) and *N*-methylpiperazine. Used in place of Ph_3PO to make the reagent in the same way, this reagent functions eqully fast and well, and the returned phosphinamide (as its triflate salt) extracts completely into aqueous phase after reaction. (The reagent from hexamethylphosphoramide, however, is much less reactive.[3])

In summary, we believe this reagent meets the criteria advanced above for an ideal extractor of oxygens from organic molecules. Preliminary investigations into a variety of other new applications so far bear out this promise and will be communicated in due course.

Representative Experimental Procedure: Preparation of *N*-Diphenylphosphinyl-*N'*-methylpiperazine. A solution of 1.12 mL (10 mmol) of *N*-methylpiperazine in 10 mL of methylene chloride was added dropwise to a solution of 1.90 mL (10 mmol) of diphenylphosphinic chloride in 10 mL of methylene chloride at 0 °C. After 10 min the solution was washed with water (5×), dried ($MgSO_4$), and evaporated to 2.86 g (95%) solid, recrystallized from toluene to mp 108–109 °C.

Illustrative Dehydration: *o*-Phenylenediamine and Benzoic Acid. A solution of 1.57 mL (10 mmol) of triflic anhydride[9] in 30 mL of methylene chloride was added to a solution of 5.56 g (20 mmol) of triphenylphosphine oxide (or equivalent phosphinamide above) in 30 mL of ethylene dichloride at 0 °C. When precipitate appeared (≤15 min), a solution containing 0.44 g (4 mmol) of *o*-phenylenediamine and 0.61 g (5 mmol) of benzoic acid in 10 mL of ethylene dichloride was added dropwise. After being stirred for half an hour, the solution was washed (3×) with 5% sodium bicarbonate and water, dried ($MgSO_4$), and

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(3) Aaberg, A.; Gramstad, T.; Husebye, S. *Tetrahedron Lett.* **1979**, 2263.
(4) Ramos, S.; Rosen, W. *Tetrahedron Lett.* **1981**, 35; *J. Org. Chem.* **1981**, *46*, 3530.
(5) All products were isolated and satisfactorily identified by NMR, IR, and mass spectra.
(6) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427.
(7) Martsokha, B. K.; Pozharskii, A. F.; Simonov, A. M. *Zh. Obshch. Khim.* **1964**, *34*, 1317.
(8) Morita, N.; Dickstein, J. I.; Miller, S. I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2103.
(9) Triflic anhydride was prepared from triflic acid,[10] supplied from 3M Company, and maintained in a still over phosphorus pentoxide, under nitrogen, and distilled fresh as needed.
(10) Hendrickson, J. B.; Judelson, D. A.; Chancellor, T. *Synthesis* **1984**, 320.

evaporated. The residue was passed through a short column of silica in hexane–ethyl acetate (3:1) to remove phosphine oxide. Evaporation yielded 0.66 g (85%) of 2-phenylbenzimidazole, mp 287 °C.[6] When the phosphinamide reagent is used, washing with water is sufficient to remove the (recoverable) phosphinamide.

The same procedure suffices to prepare simple amides, by using only a 1:1:1 stoichiometry (acid/amine/reagent) and affording similar or higher yields.

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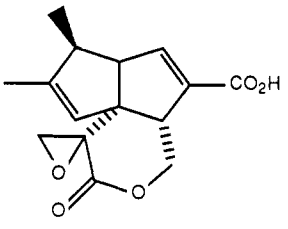
A Total Synthesis of Pentalenolactone E Methyl Ester via a [3 + 2] Annulation Strategy

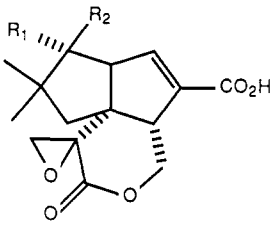
Summary: An efficient total synthesis of the methyl ester of pentalenolactone E is accomplished via a [3 + 2] annulation process.

Sir: We have recently reported an efficient and general route to annulated cyclopentanones utilizing a stepwise [3 + 2] process.[2] This new strategy for the construction of five-membered rings relies on the in situ generation of a γ-oxo ester enolate **2** from β-(silyloxy)cyclopropyl esters **1**. The 1,3-bifunctional system (**2**), when combined with a two-carbon acceptor such as [α-(phenylthio)vinyl]-phosphonium salt **3**, leads to a cyclopentene which is readily converted to its cyclopentanone analogue.

In this report we describe the application of this methodology to the total synthesis of the methyl ester of pentalenolactone E,[3] **8**. This latter compound is a member

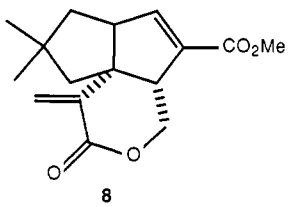


5



6 $R_1,R_2 = O$

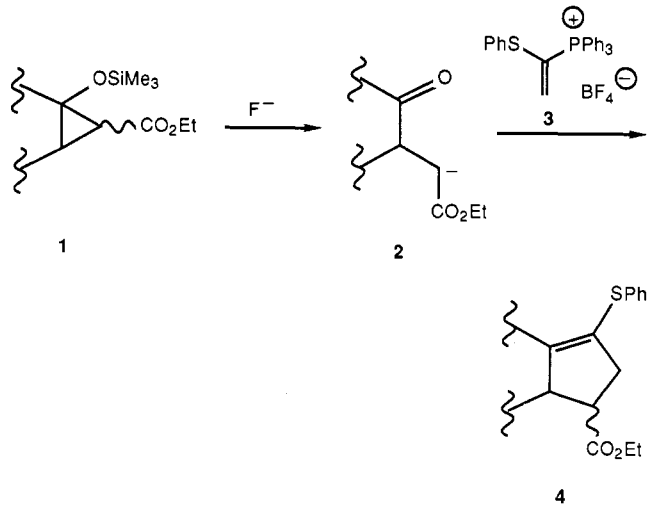
7 $R_2 = OH, R_1 = H$



8

of a class of lipophilic antibiotics isolated from culture broths of *Streptomyces* that also includes pentalenolactone **5** and the pentalenolactones G, **6**, and H, **7**. While several syntheses have been reported[4] for pentalenolactone E, **8**, the route described herein features an efficient one-pot cyclopentannulation process, ester differentiation leading to the γ-lactone, and a new sequence to the α,β-unsaturated methyl ester from the cyclopentanone.

Scheme I



1 **2** **4**

Our syntheses begins with the known[5] 4,4-dimethylcyclopentenone (**9**) which is reductively converted to its enol silyl ether regiospecifically.[6] Addition of *tert*-butyl diazoacetate[7] to the enol ether followed by ring-opening of the (silyloxy)cyclopropane with fluoride produces the α-alkylated cyclopentanone[8] **10** in 70% yield. We have found that the cyclopropanation route is far superior to the alkylation of the appropriate enolate with an α-halo *tert*-butyl ester in terms of yield and regiospecificity. Conversion of ketone **10** to its trimethylsilyl enol ether under thermodynamic control and cyclopropanation with ethyl diazoacetate produces the requisite (silyloxy)cyclopropane **11** in a yield of 65%.

The stage is set for the key cyclopentannulation reaction in which intermediate **11** is treated with potassium fluoride and 18-crown-6 in the presence of [α-(phenylthio)vinyl]-triphenylphosphonium tetrafluoroborate (**3**). The bicyclo [3.3.0]octene system[9] **12** is isolated in 95% yield as a 1:1 mixture of cis/trans stereoisomers. Chemoselective hydrolysis of the ethyl ester in methanolic hydroxide yields an enriched cis/trans (1.5/1) mixture of the carboxylic acid. It appears that during the basic hydrolysis there is some epimerization of the ester prior to hydrolysis. Attempts to directly epimerize the ester **12** with sodium ethoxide did not result in any changes in the 1:1 ratio of stereoisomers. The cis carboxylic acid could easily be separated from its trans isomer and was isolated in 57% yield. Reduction of the cis acid was affected with sodium

(1) Visiting Research Scholar from Universidade São Paulo, São Paulo, Brasil.
(2) Marino, J. P.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 1.
(3) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973.
(4) For previous syntheses of (±)-pentalenolactone E methyl ester, see: (a) Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289. (b) Cane, D. E.; Thomas, P. J. *J. Am. chem. Soc.* **1984**, *106*, 5295. (c) Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 3851. (d) Paquette, L. A.; Annis, G. D.; Schostarez, H. *J. Am. Chem. Soc.* **1982**, *104*, 6646.
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(6) Magnus, P. D.; Nobbs, M.; Exon, C. *Tetrahedron* **1981**, *37*, 4515.
(7) Liedhegener, A.; Regitz, M.; Hocker, J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 179.
(8) All new compounds gave correct elemental analyses or high resolution mass spectra and were fully characterized by 300-MHz ^{1}H NMR and ^{13}C NMR.
(9) 300-MHz ^{1}H NMR of pure cis methyl ester ($CDCl_3$): δ 1.03 (s, 3 H), 1.16 (s, 3 H), 1.43 (s, 9 H), 1.72 (d, 1 H, J = 14.2 Hz), 1.91 (d, 1 H, J = 14.2 Hz), 2.05 (dd, 1 H, J = 14.7, 3.8 Hz), 2.16 (d, 1 H, J = 14.7 Hz), 2.48 (AB, 2 H, J_{AB} = 15.0 Hz), 2.45–2.60 (m, 1 H), 2.96–3.14 (m, 2 H), 3.64 (s, 3 H), 7.16–7.31 (m, 5 H); mp 67–68 °C.

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