

Figure 1. Proton-decoupled  $^{13}\text{C}$  NMR spectrum of a 0.10 M solution of aluminum phenoxide **3a** in  $\text{CD}_2\text{Cl}_2$  at  $-85^\circ\text{C}$ .

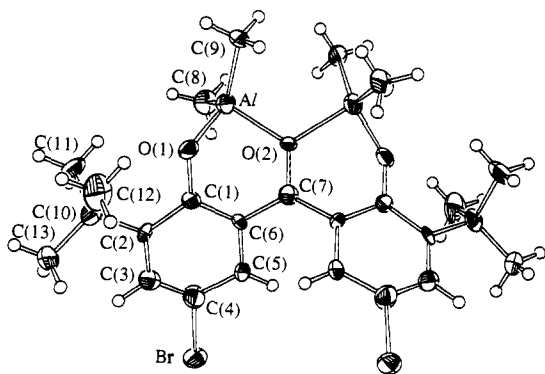


Figure 2. ORTEP drawing of the  $\text{C}_2$ -symmetric structure of aluminum phenoxide **3b**. Hydrogen atoms are shown as spheres of arbitrary size, and other atoms are represented by ellipsoids corresponding to 50% probability. Important interatomic distances (Å) and angles (deg) include  $\text{O}(2)\text{-C}(7) = 1.34$  (2),  $\text{Al-O}(2) = 1.96$  (1),  $\text{Al-O}(1) = 1.78$  (1),  $\text{O}(1)\text{-C}(1) = 1.32$  (2),  $\text{C}(1)\text{-C}(6) = 1.44$  (3),  $\text{C}(6)\text{-C}(7) = 1.44$  (2),  $\text{O}(1)\text{-Al-O}(2) = 92$  (1),  $\text{O}(1)\text{-Al-C}(8) = 112$  (1),  $\text{O}(1)\text{-Al-C}(9) = 110$  (1),  $\text{C}(8)\text{-Al-C}(9) = 124$  (1), and  $\text{C}(1)\text{-O}(1)\text{-Al} = 122$  (1).

and may have useful chemical consequences, including enhanced reactivity of the carbonyl group.

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**Supplementary Material Available:** Spectroscopic and analytical data for compounds **3a** and **3b** and intermediates involved in their synthesis and description of the structure determination and tables of X-ray crystallographic data for compound **3b**, including atomic coordinates, interatomic distances and angles, anisotropic thermal parameters, and fixed hydrogen atom coordinates (10 pages); listing of observed and calculated structure factors for compound **3b** (6 pages). Ordering information is given on any current masthead page.

(26) For a theoretical study of the 1:2 complex of formaldehyde with  $\text{BH}_3$ , see: LePage, T. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 6642.

## Internal Redox Catalyzed by Triphenylphosphine

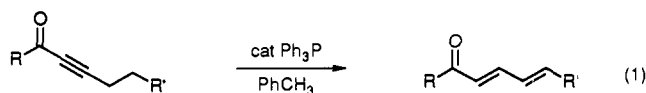
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Redox reactions constitute one of the fundamental types of transformations in a synthetic sequence. Adjustment of oxidation level by internal hydrogen reorganization is more atom economical than external sequential reduction-oxidation (or vice versa) processes. Such reactions have fallen almost exclusively into the domain of transition metal catalysts.<sup>1-3</sup> We wish to record a new type of catalysis by triphenylphosphine<sup>4</sup> that effects a remarkably facile isomerization of yne-carbonyl compounds to conjugated diene-carbonyl compounds,<sup>5</sup> which are common flavor constituents as well as important building blocks for complex targets.<sup>6</sup>

Warming a toluene solution of an ynone to  $80\text{--}110^\circ\text{C}$  with 5-10 mol % of triphenylphosphine leads smoothly to the corresponding conjugated dienone (eq 1 and Table I). Both aromatic and aliphatic ketones successfully participate, but the latter require slightly higher temperatures (entry 1 vs 2 or 3).



Switching from a ketone to an ester as the acetylenic activating group allows the reaction to proceed but is best done in the presence of a weak acid such as acetic acid. The compatibility of both a benzyl ester (entry 4) and especially an allyl ester (entry 5), groups which may not survive transition metal catalyzed reactions, highlights the virtues of this unusual catalyst system. The less electron withdrawing amide (entry 6) requires somewhat

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(2) For a few examples of Pd-catalyzed internal redox of olefinic systems, see: Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395. Carless, H. A.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980. Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558. Sakaki, S.; Kanai, H.; Tarama, K. *Can. J. Chem.* **1974**, *52*, 2857. Bingham, O.; Hudson, B.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton Trans.* **1974**, 1521. Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870. Cruikshank, B. I.; Davies, N. R. *Aust. J. Chem.* **1973**, *26*, 2635. Cesinger, F.; Fell, B.; Krings, P. *Tetrahedron Lett.* **1966**, 633. Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1966**, *88*, 3491. Cramer, R.; Lindsey, R. V. *J. Am. Chem. Soc.* **1966**, *88*, 3534. Sparke, M. B.; Turner, L.; Wenham, A. J. M. *J. Catal.* **1965**, *4*, 1.

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(8) The facility of the  $\text{R}_3\text{P}$ -induced isomerization raises the question of its involvement in those isomerizations supposedly catalyzed by transition metal complexes containing such ligands; see ref 5.

Table I. Isomerization of Yne-Carbonyl to Diene-Carbonyl<sup>a</sup>

Entry	Substrate	Temp/Time(h)	Product <sup>e</sup>	Isolated Yield
A. Ketones				
1		80°/4		83%
2		110°/16		83%
3		110°/2		88%
B. Ester				
4 <sup>b</sup>		110°/6		75%
5 <sup>b</sup>		110°/14		83%
C. Amide				
6 <sup>b,c</sup>		140°/14		84%
D. Polyfunctional				
7 <sup>b</sup>		110°/14		69%
8 <sup>b,c</sup>		60°/5		79%
9		110°/14		82%
10 <sup>d</sup>		100°		71%

<sup>a</sup>All reactions were performed at 0.5–1 M in toluene with 10–40 mol % Ph<sub>3</sub>P. <sup>b</sup>50 mol % of acetic acid added. <sup>c</sup>Reaction performed in xylene. <sup>d</sup>Reaction performed in C<sub>6</sub>D<sub>6</sub> at 100 °C. <sup>e</sup>All new compounds have been satisfactorily characterized. <sup>f</sup>See ref 5.

higher temperatures as well as the presence of acetic acid. Thus, the reactivity order with respect to the electron-withdrawing group (EWG) is ketone > ester > amide.

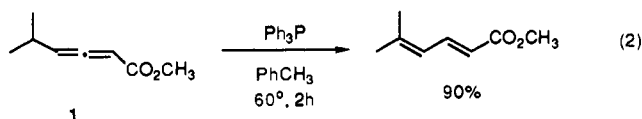
The requirement of an electron-withdrawing group is clearly established by the competitions illustrated by the examples of entries 7 and 8. Smooth isomerization of the ynoate to the corresponding dienoate occurred with no effect whatsoever on the nonconjugated acetylene (nor isolated olefin).

Given the reactivity order established, we examined the internal competition among acetylenic ketones, esters, and amides. The ynone of entry 9 isomerizes even at 60 °C to the dienone with

the acetylenic amide unperturbed when exposed to a catalytic amount of triphenylphosphine. More dramatically, the polyfunctional dipeptide of entry 10 exhibits exclusive isomerization of ynoate with the mixed catalyst system of triphenylphosphine and acetic acid.

Attempts to detect allenic intermediates by following the reaction by NMR spectroscopy or VPC failed. To determine the viability of such intermediates, we subjected the allene ester 1 to triphenylphosphine (eq 2). Isomerization occurs even at 60 °C in the absence of any acetic acid rather than the 110 °C required for the ynoate. The high reactivity of this allene would make it

rather unlikely to be able to detect such a species in the acetylene isomerization even if it were an intermediate.



The isomerization of eq 2 was explored as a function of the phosphine to probe the mechanism of the reaction. Poorer donor trivalent phosphorus compounds like phosphites are almost unreactive as catalysts. On the other hand, more nucleophilic phosphines like hexamethylphosphorus triamide or, better, tri-*n*-butylphosphine lead to faster consumption of allene but considerable production of oligomeric products. To differentiate between nucleophilicity and basicity as the more important factor, tertiary amines were examined. *No reaction was observed!* While space limitations preclude further mechanistic speculation, the current observations support the concept of a series of prototropic shifts triggered by nucleophilic addition of the phosphine. The simplicity and extraordinary selectivity of the procedure make it a very practical approach for the synthesis of the very useful polyene carbonyl systems. Its extraordinary chemoselectivity enhances the utility of this new type of catalysis for internal redox compared to typical transition metal catalyzed processes.

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**Supplementary Material Available:** Characterization data for the products of Table I and eq 1 as well as the substrate of entry 10 of Table I (4 pages). Ordering information is given on any current masthead page.

## Total Synthesis of Hemibrevetoxin B

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Hemibrevetoxin B (1), isolated from *Gymnodinium breve*, is a member of the "red tide" associated class of marine neurotoxins.<sup>1</sup> Herein we report the first total synthesis of this structurally novel molecule in its naturally occurring form.

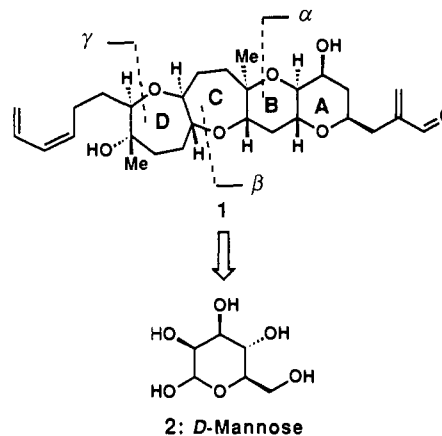
After several abortive attempts to construct the hemibrevetoxin B polycyclic skeleton by a convergent approach, we chose a linear route in which each ring was constructed sequentially starting from ring A and moving toward ring D (Scheme I). This, one ring at a time, sequential approach may also be Nature's way of forming the brevetoxins.<sup>2</sup>

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**Scheme I.** Structure and Retrosynthetic Disconnections of Hemibrevetoxin B (1). Cyclization Sequence:  $\alpha$ ,  $\beta$ ,  $\gamma$



The total synthesis of hemibrevetoxin B (1) was executed as outlined in Scheme II. The mannose-derived<sup>3</sup> starting material 3 was converted to intermediate 4 by desilylation-benzoylation, followed by removal of the acetonide and selective elaboration of the liberated diol using <sup>n</sup>Bu<sub>2</sub>SnO-BnBr and TBSOTf. Extension of the side chain of 4 to reach the allylic epoxide 5 was achieved by ozonolysis, followed by Wittig reaction, Dibal reduction, Sharpless epoxidation, SO<sub>3</sub>Py oxidation, and a second Wittig olefination. Regio- and stereospecific ring closure of 5 under acidic conditions<sup>4</sup> led to the bicyclic intermediate 6 in 90% yield. Stitching the third ring required the intermediacy of compound 7, which was derived from 6 by silylation, followed by hydroboration, aldehyde generation, conjugated ester formation, and hydrogenation. Sequential ester hydrolysis and desilylation of 7 followed by lactonization using the Yamaguchi protocol<sup>5</sup> furnished lactone 8. Elaboration of lactone 8 using our previously developed technology<sup>6,7</sup> of thionolactone formation followed by organometallic reagent addition and a sulfur elimination sequence proceeded smoothly, furnishing the enol ether 9 in 70% overall yield. The alternative procedure via the enol triflate and side chain addition developed by Murai<sup>8</sup> gave 9 in 75% overall yield from 8. Regio- and stereoselective hydroboration of 10 as previously developed<sup>7</sup> led to 10 (separated from a ca. 4:1 mixture of C-14 epimers), which was elaborated to tetracycle 11 by standard chemistry. Repeat of the side chain attachment as described above for 8 → 10 followed by Swern oxidation led to a mixture of epimeric ketones (C-19, hemibrevetoxin B numbering). Equilibration of this position with DBU in refluxing toluene followed by MeMgI addition led to a 3:2 epimeric mixture (at C-18, isomer 12 is the major product) of alcohols from which 12 was isolated by chromatography. Removal of both benzyl groups from 12 followed by differentiation of the generated hydroxyls and elaboration of the primary position led to methyl ester 13. Introduction of the diene system was accomplished by selective desilylation followed by Swern oxidation, a Wittig reaction with the ylide derived from PhSe(CH<sub>2</sub>)<sub>3</sub>Ph<sub>3</sub>P<sup>+</sup>I<sup>-n</sup>BuLi, and oxidation-syn-elimination of the resulting selenide. Finally, reduction of the ester group followed by Swern oxidation and in situ treatment<sup>9</sup>

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