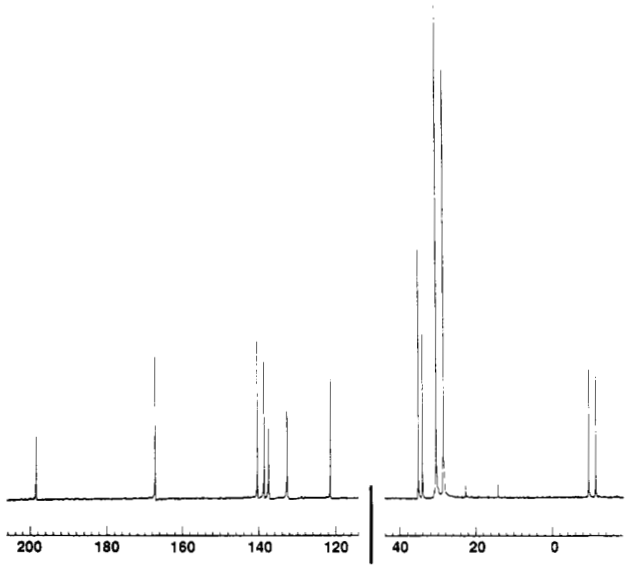

Figure 1. Proton-decoupled ^{13}C NMR spectrum of a 0.10 M solution of aluminum phenoxide **3a** in CD_2Cl_2 at −85 °C.

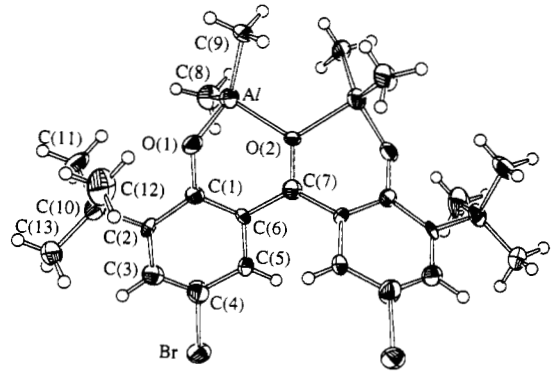

Figure 2. ORTEP drawing of the C_2-symmetric structure of aluminum phenoxide **3b**. Hydrogen atoms are shown as spheres of arbitrary size, and other atoms are represented by ellipsoids corresponding to 50% probability. Important interatomic distances (Å) and angles (deg) include O(2)–C(7) = 1.34 (2), Al–O(2) = 1.96 (1), Al–O(1) = 1.78 (1), O(1)–C(1) = 1.32 (2), C(1)–C(6) = 1.44 (3), C(6)–C(7) = 1.44 (2), O(1)–Al–O(2) = 92 (1), O(1)–Al–C(8) = 112 (1), O(1)–Al–C(9) = 110 (1), C(8)–Al–C(9) = 124 (1), and C(1)–O(1)–Al = 122 (1).

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

Acknowledgment. This work was funded by the Natural Sciences and Engineering Research Council of Canada, the Ministère de l'Éducation du Québec, and Merck Frosst. In addition, we are grateful to Dr. M. T. Phan Viet and Sylvie Bilodeau of the Regional High-Field NMR Laboratory for helping us record our ^{27}Al and variable-temperature ^{13}C NMR spectra. We also thank Professors Andrew R. Barron and Dieter Seebach for providing useful unpublished information.

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.

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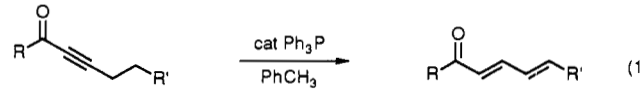
Internal Redox Catalyzed by Triphenylphosphine

Barry M. Trost* and Uli Kazmaier

Department of Chemistry, Stanford University
Stanford, California 94305-5080
Received April 20, 1992

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.[1-3] We wish to record a new type of catalysis by triphenylphosphine[4] that effects a remarkably facile isomerization of yne–carbonyl compounds to conjugated diene–carbonyl compounds,[5] which are common flavor constituents as well as important building blocks for complex targets.[6]

Warming a toluene solution of an ynone to 80–110 °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).



(1)

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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(8) The facility of the R_3P-induced isomerization raises the question of its involvement in those isomerizations supposedly catalyzed by transition metal complexes containing such ligands; see ref 5.

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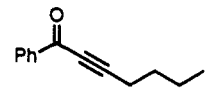
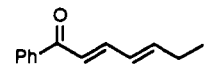
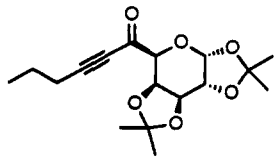
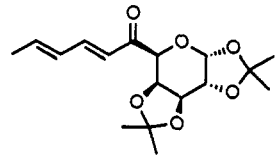
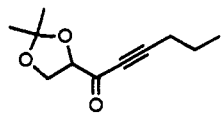
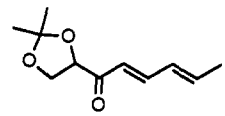
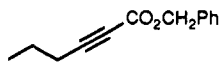
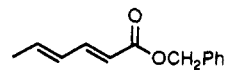
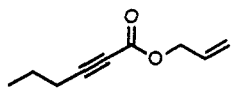
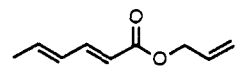
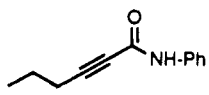
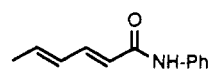
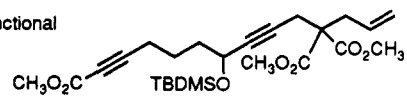
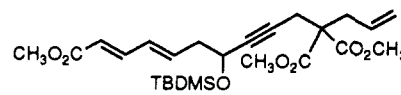
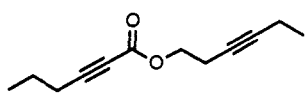
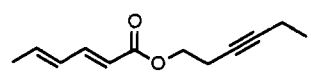
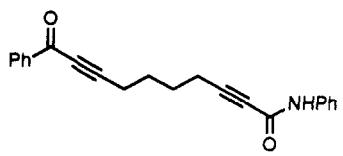
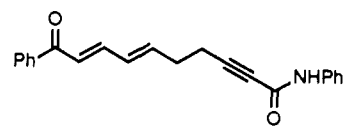
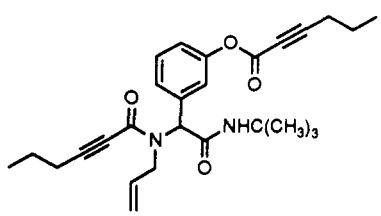
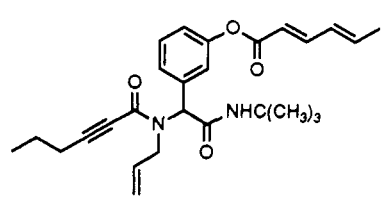
Table I. Isomerization of Yne–Carbonyl to Diene–Carbonyl[a]

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

[a] All reactions were performed at 0.5–1 M in toluene with 10–40 mol % Ph_3P. [b] 50 mol % of acetic acid added. [c] Reaction performed in xylene. [d] Reaction performed in C_6D_6 at 100 °C. [e] All new compounds have been satisfactorily characterized. [f] See ref 5.

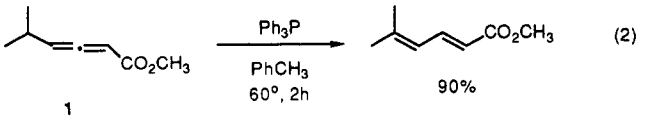
higher temperatures as well as the presence of acetic acid. Thus, the reactivity order with respect to the electron-withdrawing group (EWG) is ketone > ester > amide.

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.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. U.K. thanks the Alexander von Humboldt Foundation for a fellowship. Mass spectra were generously provided by the University of California—San Francisco Mass Spectrometry Center sponsored by the NIH Division of Research Resources.

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

K. C. Nicolaou,* K. Raja Reddy, Golfo Skokotas, Fuminori Sato,† and Xiao-Yi Xiao

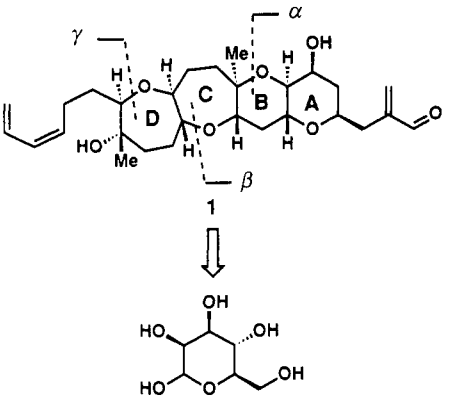
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037
Department of Chemistry, 9500 Gilman Drive
University of California at San Diego
La Jolla, California 92093

Received June 3, 1992

Hemibrevetoxin B (**1**), isolated from *Gymnodinium breve*, is a member of the "red tide" associated class of marine neurotoxins.[1] 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.[2]

Scheme I. Structure and Retrosynthetic Disconnections of Hemibrevetoxin B (**1**). Cyclization Sequence: α, β, γ



The total synthesis of hemibrevetoxin B (**1**) was executed as outlined in Scheme II. The mannose-derived[3] starting material **3** was converted to intermediate **4** by desilylation–benzylation, followed by removal of the acetonide and selective elaboration of the liberated diol using $^nBu_2SnO$–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_3Py oxidation, and a second Wittig olefination. Regio- and stereospecific ring closure of **5** under acidic conditions[4] 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[5] furnished lactone **8**. Elaboration of lactone **8** using our previously developed technology[6,7] 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[8] gave **9** in 75% overall yield from **8**. Regio- and stereoselective hydroboration of **10** as previously developed[7] 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 $PhSe(CH_2)_3Ph_3P^+I^-$–^{n}BuLi, and oxidation–syn-elimination of the resulting selenide. Finally, reduction of the ester group followed by Swern oxidation and in situ treatment[9]

* Author to whom correspondence should be addressed at The Scripps Research Institute.
† Visiting scientist from Dainippon Pharmaceutical Company, 1990–1992.

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