must open in a disrotatory manner. As this happens, the back lobes of the σ-bonding orbital swing into a much more favorable orientation for bonding with a radical center of the other ring. The distinguishing factor then becomes whether the C1–C4 bond cleaves all the way to **1** or whether an intramolecular backside trapping occurs.[17] Alternatively, the sequence **3c** → **10**-T could be quite stereospecific, but interconversion of **10**-T and **10**-C via **1** ($k_{t'}$) is competitive with conversion of **10**-T to products.[19]

In summary, our anticipation that the unusual structural features of azoalkane **2** would give rise to new chemistry was confirmed. The conventional C1–C5 cleavage process (k_c) is operative in **3**, but it alone cannot explain the deuterium scrambling results. Our current model requires one of two unprecedented processes: frontside radical attack on a C–C bond or formation of an organic tetraradical (**1**). Studies to differentiate these alternatives and to further characterize the interesting C_9H_{12} potential energy surface are underway.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corp., the Camille and Henry Dreyfus Foundation, and the National Science Foundation (Grant No. CHE-8024664) for support of this work and the use of the Southern California Regional NMR Facility (NSF Grant 7916324A1). We also thank Dr. William R. Croasmun for assistance in obtaining high-field NMR data.

Registry No. 1, 82482-44-8; **2a**, 82482-45-9; **2b**, 82482-46-0; **2c**, 82482-47-1; **4**, 82482-48-2; **5**, 3641-77-8; **5**-C, 82482-49-3; **5**-T, 82534-92-7; **5**-V, 82482-50-6; **9**, 82494-76-6; 5-diazo-1,3-cyclopentadiene, 1192-27-4; spiro[bicyclo[2.1.0]pentane]-5,1′-cyclopenta-2′,4′-diene, 82494-77-7; 2,3-bis[ethoxycarbonyl]-2,3-diazabicyclo[2.2.1]hept-5-ene-7,5′-spirobicyclo[2.1.0]pentane, 82482-51-7; cyclobutene, 822-35-5; PTAD, 4233-33-4; $EtO_2CN{=}NCO_2Et$, 1972-28-7.

(17) The conversion of **1** to **5** could occur by a sequence such as **1** → **10** → **8** → **5** or by a more direct **1** → **8** → **5** path. The latter sequence involves a reaction of **1** that is directly analogous to the unusually facile 1,5-vinyl migration of 1,3,6,8-spiro[4.4]nonatetraene.[18]

(18) Semmelhack, M. F.; Weller, H. N.; Foos, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 292-4.

(19) Our model assumes that the conversion of **3** to **10** is irreversible. Given the high strain of a bicyclo[2.1.0]pentane moiety, **3** → **10** appears highly exothermic. In the free radical analogue,[15b] bicyclo[3.1.0]hex-2-yl rearranges very rapidly to 3-cyclopentenylmethyl and 3-cyclohexenyl (both reactions are analogues to **10** → **8**), but it has never been observed to rearrange to 5-bicyclo[2.1.0]pentylmethyl (the analogue to **10** → **3**). Note also that sequences such as **3c** → **10** → **3b** → **5** would have to produce a 1:1 mixture of **5**-C and **5**-T and thus cannot explain the scrambling result from **2c**.

α-Lithiomethylenetriphenylphosphorane, a Highly Reactive Ylide Equivalent

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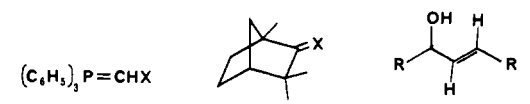
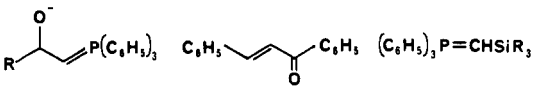
Methylenetriphenylphosphorane (**1**),[1] the simplest Wittig reagent, has been used in countless syntheses of terminal olefins since its introduction almost 2 decades ago. Despite its widespread utility, this reagent is known to be inapplicable with unreactive substrates such as epoxides or hindered ketones.[2] We describe herein a simple method for ylide activation that enlarges the range of application of **1** and suggests a variety of new synthetic possibilities.



(1) Wittig, G.; Schoellkopf, U. *Chem. Ber.* **1954**, *87*, 1318.

Although **1** is commonly prepared by deprotonation of methyltriphenylphosphonium ion with alkyllithium reagents, the literature contains no indication of the possibility of further deprotonation. However, it has been discovered that the reaction of **1** with *tert*-butyllithium in tetrahydrofuran (THF) solution[3] (−78 to −40 °C over 1 h and −40 °C for 1 h) produces a red to red-orange solution of the lithiated ylide **2** at concentrations up to 0.2 M. The lithiated ylide **2** can also be produced as an orange suspension in ether by the reaction of methyltriphenylphosphonium bromide with 2 equiv of *sec*-butyllithium (−78 to −40 °C for 1 h and 20 °C for 3 h) or from **1** with 1 equiv of *tert*-butyllithium (−78 to 20 °C over 2 h and 20 °C for 3 h) in ether. Although fenchone (**3**) is unaffected by treatment with **1** at temperatures up to 50 °C in a variety of solvents (e.g., THF, THF–hexamethylphosphoric triamide (HMPA), or dimethyl sulfoxide), it reacts with the lithiated ylide **2** in the presence of 20 equiv of HMPA (−50 to 20 °C for 1 h) to form an adduct that decomposes to the exo-methylene derivative **4** (87% yield) in the presence of excess *tert*-butyl alcohol at 20 °C for 12 h.[4]

Reaction of **2** in ether with 2 equiv of benzaldehyde or 2 equiv of hexanal (−78 to 20 °C for 2 h and 20 °C for 14 h) results in formation of the trans-allylic alcohol **5** (60%) or **6** (54%), respectively. Nucleophilic addition of **2** to the formyl group of an aldehyde is expected to give a 1:1 adduct, the β-oxido ylide **7**,[5]



7 **8** **9**

which has been shown previously[5] to react with a second equivalent of aldehyde to yield a trans-allylic alcohol (**5** or **6**). In these reactions of aldehydes and the above described reaction with fenchone, the crude reaction product was found by thin-layer chromatographic analysis not to contain significant quantities of the alcohol that would result from addition of the alkyllithium reagent used to generate **2** (*t*-BuLi or *sec*-BuLi) and the carbonyl compound. This fact shows that a full equivalent of the alkyllithium reagent is consumed in the reaction with **1** and adds further evidence for formulating the reagent as **2**. Still more evidence comes from the formation of **8** from the reaction of **2** (−78 °C, THF) with 1 equiv of benzoyl chloride followed by 1 equiv of benzaldehyde and from the formation of silylated ylides **9**[6] by reaction of **2** with 1 equiv of various trialkylchlorosilanes at −78 °C in THF.

The utility of **2** as a synthetic reagent is also demonstrated by the reaction with epoxides. Treatment of **2** in ether with cyclopentene oxide (0 °C for 2 h and 20 °C for 20 h) generates the γ-oxido ylide **10**, which reacts with benzaldehyde (−78 °C for 1.5 h and 20 °C for 8 h) to form the trans,trans-homoallylic alcohol

(2) See, for example: (a) McMurry, J. E.; Choy, W. *Tetrahedron Lett.* **1980**, *21*, 2477. (b) Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758. (c) McMurry, J. E. *Ibid.* **1968**, *90*, 6821. (d) Boeckman, R. K., Jr.; Silver, S. M. *Tetrahedron Lett.* **1973**, 3497.

(3) All organometallic reactions were conducted under an atmosphere of dry argon. Solutions of **1** were prepared from methyltriphenylphosphonium bromide and *n*-butyllithium (1 equiv) in THF at 0 °C for 10 min and 20–25 °C for 20 min.

(4) All products were purified chromatographically and characterized by infrared, proton magnetic resonance, and mass spectroscopy.

(5) (a) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226, 3523. (b) Corey, E. J.; Yamamoto, H. *Ibid.* **1970**, *92*, 6636, 6637. (c) Corey, E. J.; Ulrich, P.; Venkateswarlu, A. *Tetrahedron Lett.* **1977**, 3231.

(6) See: (a) Schmidbaur, H.; Stühler, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 231. (b) Plenat, F. *Tetrahedron Lett.* **1981**, *22*, 4705.

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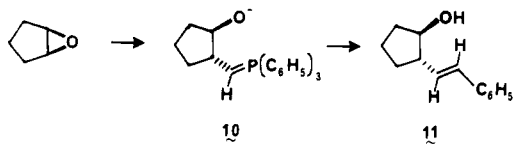
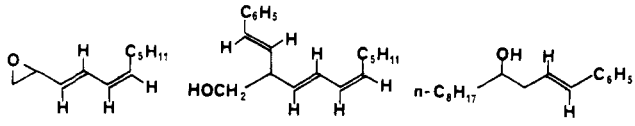


10 11

11 in 65% yield. The selective formation of the trans double bond in 11 is due to the presence of the basic γ-oxido group in 10 and was expected on the basis of previously described reactions of γ-oxido ylides with aldehydes.[7] In contrast to these results with 2, coupling of cyclopentene oxide and methylenetriphenylphosphorane was unsuccessful even under forcing conditions (50 °C, THF). The conversion of cyclopentene oxide to 11 represents a powerful synthetic construction in that two carbon–carbon bonds, and also three stereocenters are formed in the process. Such a method is potentially well suited for the synthesis of complex trans-homoallylic alcohols, for instance, the macrodiylide asplasmomycin.[8]

Two other examples of the coupling of an epoxide, lithio ylide 2, and an aldehyde were also investigated. Reaction of the epoxide 12[9] with 2 (−78 to 25 °C over 2 h and 25 °C for 18 h) followed



12 13 14

by treatment with benzaldehyde (25 °C for 4 h) furnished the triene 13 as major product. In a similar way, the homoallylic alcohol 14 was obtained from 1-decene oxide, lithio ylide 2, and benzaldehyde in good yield.

A number of other applications of α-lithiated alkylidenetriphenylphosphoranes are now under investigation in our laboratories with special emphasis on new methods for the joining of three components with the formation of two carbon–carbon linkages in one operation. Our work on lithiated ylides complements recent studies on various dicarbanionic species including doubly deprotonated nitro compounds[10] and carbonyl compounds.[11-19] These classes of enhanced carbon nucleophiles provide synthetic capabilities going far beyond those available from conventional reagents.[20]

Registry No. 1, 3487-44-3; 2, 82537-28-8; 3, 1195-79-5; 4, 13567-57-2; 5, 62668-02-4; 6, 82537-29-9; 8, 614-47-1; 10, 82537-30-2; 11, 82537-31-3; 12, 82537-32-4; 13, 82537-33-5; 14, 82537-34-6; benzaldehyde, 100-52-7; hexanal, 66-25-1; cyclopentene oxide, 285-67-6; methyltriphenylphosphonium bromide, 1779-49-3; 1-decene oxide, 2404-44-6.

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(20) This research was assisted financially by a grant from the National Science Foundation.

An Intramolecular Diels–Alder Reaction of an Isobenzofuran: A Convergent Synthesis of Resistomycin

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The gram-positive antibiotic Resistomycin, first isolated[1] from *Streptomyces resistomycificus* by Brockman and Schmidt-Kastner in 1951, was assigned[2,3] the pentacyclic phenalenone structure 1 (Chart I) in 1968. Despite sporadic synthetic forays[4,5] in the intervening years, Resistomycin has not yet been synthesized. Our experience[6] with the use of isobenzofurans as dienes in natural product synthesis led us to explore their applicability in the intramolecular Diels–Alder reaction.[7] A synthesis of Resistomycin is a particularly rigorous test of this idea, for if the complex, highly functionalized isobenzofuran 2 can be elaborated and employed in such a manner, the technique will not only provide a facile route to the antibiotic but also have wider implications for easy synthetic access to a variety of condensed aromatics and hydroaromatic systems. We now report the successful execution of this plan and the first synthesis of Resistomycin.

Our methods of in situ isobenzofuran generation, previously defined,[8] demanded that the precursors of 2 be the two aldehydes 3 and 4, the former corresponding to carbon atoms 6–10 and the C_9-methyl group and the latter comprising the rest of the Resistomycin molecule. A brief synthesis of 3 was developed[9] from 3,4-dimethylphenol (5). Methoxymethylation of 5 was followed by regiospecific deprotonation[10] with *tert*-butyl-lithium and treatment with diethylcarbamoyl chloride to provide 6 exclusively. Hydrolysis and methylation produced 7, which was oxidized with complete regiospecificity[11] at the C_4-methyl group by ceric ammonium nitrate to 3. The overall yield for the transformation of 5 to 3 was 72%.

A convergent synthesis of the acetylenic aldehyde 4 was un-

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(7) Intramolecular Diels–Alder reactions of isobenzofurans have not been recorded in the literature. The first report of such a reaction with an isoindole has recently appeared. Ciganek, E. *J. Org. Chem.* **1980**, *45*, 1512.
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(9) An existing synthesis of the carboxylic acid corresponding to 3 was not efficient enough for our purposes. Meldrum, A. N.; Alimchandani, R. I. *J. Indian Chem. Soc.* **1929**, *6*, 253. 3: bp 169–172 °C (1 mmHg); ν_{max} 1695, 1635 cm^{-1}; NMR ($CDCl_3$) δ 10.13 (s, 1 H), 7.67 (s, 1 H), 6.77 (s, 1 H), 3.9 (s, 3 H), 3.57 and 3.15 (q, 2 H each), 2.69 (s, 3 H), 1.25 and 1.05 (t, 3 H each, J = 7.0 Hz); M^+ 249 (11), 248 (9), 177 (100).
(10) Christensen, H.; *Synth. Commun.* **1975**, *5*, 65. Ronald, R. C. *Tetrahedron Lett.* **1975**, 3973.
(11) Oxidation of 7 to 3 was accomplished with 4 equiv of ceric ammonium nitrate in aqueous acetic acid at 0 °C for 1 h. The oxidation of aryl methyl groups to aryl aldehydes is believed to occur in four stages, each requiring 1 equiv of Ce^{IV} ion (Richardson, W. H. "Oxidation in Organic Chemistry"; Wiberg, K. B., Ed.; Academic Press: New York, 1965; part A, p 271). Our choice of this reagent was prompted by the expectation that a *p*-methoxy substituent would favor oxidation at the C-4 methyl group by stabilizing radical or cationic intermediates in the usual manner.

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