methylimidazo[1,5-a]-1,3,5-triazin-4-one (**1g**), mp 192 °C dec.

The analogy between C8 substitution in **1d** and **1e**, as examples, and N9 substitution on hypoxanthine and guanine, respectively, suggests further applications of the intriguing cyclization–rearrangement sequence.

Acknowledgment. This work was supported by Research Grant CHE 76-23543 from the National Science Foundation. B.G. was on leave from the Institute of Organic Chemistry, Polish Academy of Sciences, Poznań, Poland. J.B.H. and B.N.H. held Eli Lilly and Company Fellowships in Chemistry.

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(9) $R = \Sigma\|F_{obsd}| - |F_{calcd}\|/\Sigma|F_{obsd}|$; $R\omega = [\Sigma\omega\|F_{obsd}| - |F_{calcd}\|^2/\Sigma\omega|F_{obsd}|^2]^{1/2}$.
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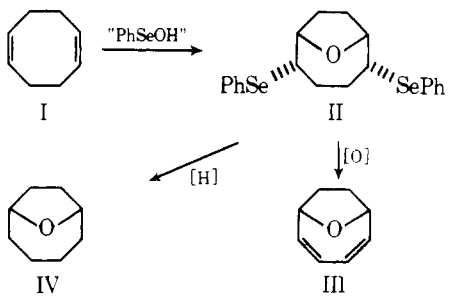
Organoselenium-Induced Ring Closures: Cyclization of Dienes with "PhSeOH" to Form Cyclic Ethers

Summary: "PhSeOH" converts dienes to cyclic ethers; use of the reaction in the synthesis of eucalyptole, (±)-linalool, *cis*-terpin, a "cage" ether, and a prostacyclin analogue is described.

Sir: In connection with our continuing programs[1-4] directed at developing new synthetic methodology employing novel selenium reagents, we have observed that a variety of simple and structurally complex dienes afford cyclic ethers in good to excellent yield when subjected to treatment with "PhSeOH", a new reagent recently independently introduced by Sharpless[5] and Reich.[6,7] This reaction represents a novel and simple procedure for the construction of complex oxygen-containing heterocyclic systems with simultaneous introduction of two phenylseleno (PhSe) groups. The high frequency in which oxygen heterocycles occur in nature and the synthetic potential of the phenylseleno group[8] should make this new cyclization process an extremely powerful synthetic method.

This novel selenium-induced cyclization of dienes is illustrated in Scheme I. Specifically, treatment of 1,5-cyclooctadiene (I) with "PhSeOH"[5] in CH_2Cl_2 at 25 °C afforded the bis(phenylseleno)oxabicyclo[4.2.1]nonane derivative II[9] in

Scheme I

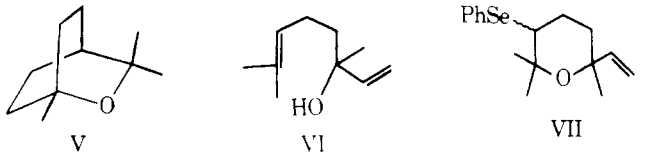


90% yield.[10,11] Subsequent oxidation (O_3, CH_2Cl_2, −78 °C) followed by syn elimination[12] of the derived selenoxide furnished the known bicyclic diene III[13] (73% yield[10]), thus confirming the skeletal structure assigned to II. The stereochemistry of II follows both from mechanistic considerations (vide infra) and the observation of a single resonance in the ^{77}Se NMR spectrum.[14] Finally, reduction of II with *tri*-n-butyltin hydride [$PhCH_3$, 110 °C, traces of azobis(isobutyronitrile)] led to the known saturated tetrahydrofuran derivative IV[15] in 80% yield.

To explore both the generality and utility of this new methodology, a series of dienes was subjected to the cyclization process. As indicated in Table I, good yields of cyclic products were obtained from a wide variety of dienes, thereby clearly demonstrating the potential of this method as a ring-forming reaction.[16] In general, highly substituted dienes and those conformationally fixed enter into this reaction with increased rates and yields, the final products depending on the precise diene substitution as well as the relative stability of the derived products. Such characteristics are beneficial in that selectivity is often observed (see Table I).

The reported cyclization process is presumed to proceed via initial Markownikoff's addition of "PhSeOH" across the more highly substituted olefinic bond to generate a β-hydroxyselenide which subsequently undergoes cyclization with participation of a second molecule of "PhSeOH". The latter reaction is quite reminiscent of the cyclization of unsaturated ethers induced by phenylselenenyl chloride.[1b] In cases where cyclization is not favored, good to excellent yields of mono and/or bis(hydroxyselenides) are obtained.[7]

To demonstrate the utility of this selenium-based methodology for construction of natural and other complex structures, we report here a number of facile approaches to such systems. Thus, reductive removal of the phenylseleno groups (Raney Ni, THF) from **10a**[19] furnished eucalyptole (V) in 80%

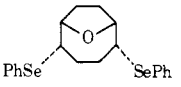
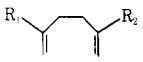
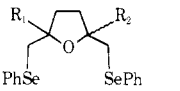
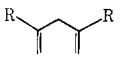
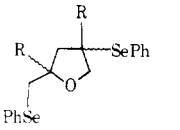
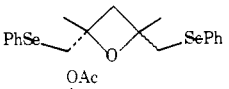
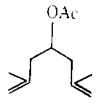
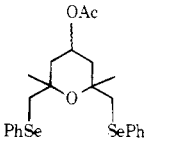
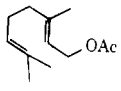
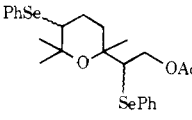
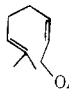
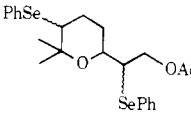
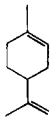
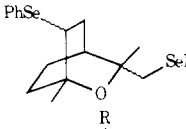
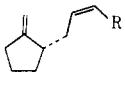
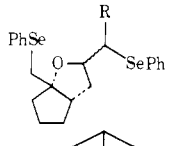
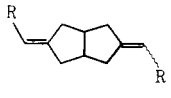
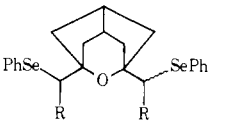


V VI VII

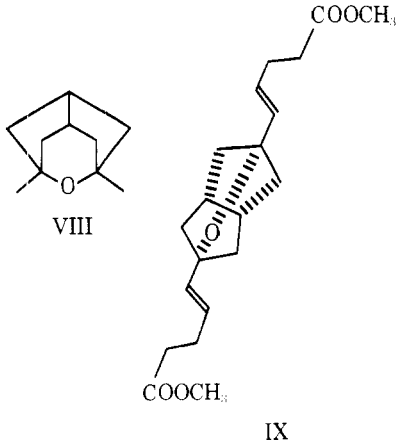
yield, which was identical in all respects with an authentic sample. (±)-Linalool (VI) on the other hand was obtained in 45% overall yield from either **8a** or **9a** by: (i) cleavage of the acetate ($LiAlH_4$, THF, 2 h); (ii) elimination of the β-hydroxyphenylselenide functionality (MsCl, Et_3N, CH_2Cl_2);[21] and (iii) reductive cleavage of the derived cyclic ether (VII) (Na–liquid NH_3, 10 min).[22] Facile formation of complex cage-type systems is illustrated by the preparation of VIII in 85% yield via treatment of **12a** with *n*-Bu_3SnH in toluene (110 °C, 2 h) in the presence of trace amounts of azobis(isobutyronitrile).[23] Finally, oxidative (*m*-CPBA, CH_2Cl_2) removal of the phenylseleno groups from **13a** afforded the interesting cage prostacyclin analogue IX[2b,24] in 96% yield.

The ability of "PhSeOH" to functionalize readily available starting materials such as dienes to form cyclic ethers ac-

Table I. Cyclization of Dienes with "PhSeOH"[a]

diene	reaction time, h	cyclic product[9]	yield, %[10]
1 	24	 **1a**	90
2, $R_1 = R_2 = H$ 	24	 **2a**[17]	64
3, $R_1 = R_2 = CH_3$	24	**3a**[17]	59
4, $R_1 = CH_3$; $R_2 = H$	36	**4a**	44
5, R = H 	144	 **5a**	42
6, $R = CH_3$	48	**6a** (24%)[17]	60
		 **6b** (34%)[17]	
7 	72	 **7a**[18]	56.5
8 	48	 **8a**	58
9 	48	 **9a**	49
10 	24	 **10a**[19]	47
11, $R = (CH_2)_3COOCH_3$ 	72	 **11a**	30
12, R = H 	144	 **12a**	34
13, $R = (CH_2)_3COOCH_3$	72	**13a**	18

[a] Reactions were carried out on 0.1–1.0 mmol scale and products isolated by column or preparative layer chromatography on silica gel.



VIII IX

companied by the simultaneous introduction of two phenylseleno groups into the organic substrate adds considerably, we believe, to the synthetic scope of organoselenium chemistry.[25] The syntheses reported here are the first examples of the simplification this powerful cyclization reaction brings to the construction of relatively complex frameworks. Ongoing research in our laboratories is directed toward future applications of this novel process to the synthesis of highly oxygenated natural products as well as to the construction of theoretically interesting molecules.[26]

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(2) (a) K. C. Nicolaou and W. E. Barnette, *J. Chem. Soc., Chem. Commun.*, 331 (1977). (b) For a review see: K. C. Nicolaou, G. P. Gasic, W. E. Barnette, *Angew. Chem., Int. Ed. Engl.*, **17**, 293 (1978).

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(9) The structure assigned to each new compound was in accord with its infrared, mass, and 220 or 360 MHz NMR spectra. Analytical samples obtained by recrystallization or chromatography (TLC or LC) gave satisfactory C and H combustion analyses within 0.4% and/or appropriate parent ion

identification by high-resolution mass spectrometry.
(10) All yields recorded here were based on isolated material which was >95% pure.
(11) The following experimental procedure for the cyclization of 1,5-cyclooctadiene is representative of the reactions indicated in Table I. To a magnetically stirred, ice-cooled solution of diphenyl diselenide (312.1 mg, 1.0 mmol) in dry methylene chloride (7 mL) under argon was added dropwise chilled 30% hydrogen peroxide (110 μL, 1.0 mmol). After stirring vigorously at 0 °C for 30 min (white crystalls deposit), powdered anhydrous magnesium sulfate (200 mg) was added and the mixture was stirred for an additional 30 min at ice-bath temperature. The ice bath was removed, 1,5-cyclooctadiene (81.1 mg, 0.75 mmol) was added, and the mixture was stirred vigorously for 24 h at 25 °C. The reaction mixture was poured in ether (125 mL) and washed with 5% auqeous sodium carbonate (2 × 25 mL), water (10 mL), and brine (10 mL) successively. The dried ($MgSO_4$) solvents were removed and the residue was subjected to preparative layer chromatography, (E. Merck silica methylene chloride, R_f 0.45) to afford bis(phenylseleno)oxabicyclo[4.2.1]nonane (II) (294.5 mg, 90%) as colorless crystals recrystallized from petroleum ether; mp 95.5–96 °C; ^1H NMR (220 MHz, CCl_4) δ 1.88–2.16 (m, 8 H), 3.56 (m, 2 H, CH-Se), 4.48 (m, 2 H, CHO), 7.13 (m, 6 H), 7.35 (m, 4 H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 28.5, 30.3, 49.2, (CSe), 80.9 (CO), 127.1, 129.1, 133.8. Anal. Calcd for $C_{20}H_{22}OSe_2$: C, 55.05; H, 5.08. Found: C, 55.28; H, 5.18.
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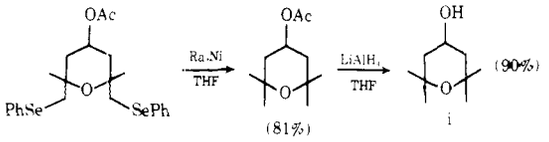
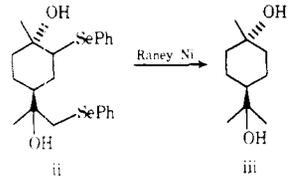
(14) We are greatful to Dr. Ralph H. Obenauf and JEOL Analytical Instruments, Inc. for providing us with the ^{77}Se NMR spectrum of II; δ 7.57 relative to Et_2Se.
(15) F. G. Bordwell and M. L. Douglass, *J. Am. Chem. Soc.*, **88**, 993 (1966).
(16) Formation of cyclic ethers as reported here should be contrasted with the carbon–carbon bond formation reaction recently reported to occur upon treatment of 1,6-cyclononadiene with $PhSeO_2CCH_3$; see D. L. J. Clive, G. Chittattu, and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 441 (1978).
(17) Carbon skeletons were established rigorously by: (a) reductive removal (Raney Ni) of the phenylseleno groups to afford the known cyclic ethers; or (b) reductive fragmentation with *n*-Bu_3SnH to afford 2,4-dimethyl-4-penten-2-ol.
(18) The carbon skeleton of **7a** was established as illustrated below by conversion to the known alcohol (i); N. Nemeroff, M. M. Joullié and G. Preti, *J. Org. Chem.*, **43**, 331 (1978).



(19) Along with the cyclic product **10a**, the cyclization of limonene (**10**) produced considerable amounts (28%) of the dihydroxy diselenide ii as well as some monohydroxy selenide. The diselenide ii was efficiently converted to *cis*-terpin[20] (iii), a naturally occurring substance by Raney Ni reduction (70%).



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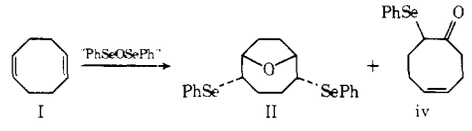
(22) K. C. Nicolaou, W. J. Sipio, R. L. Magolda, and D. A. Claremon, *J. Chem. Soc., Chem. Commun.*, 83 (1979).
(23) D. L. J. Clive, G. Chittattu, and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 41, (1978).
(24) Biological studies with this compound are currently in progress.
(25) **Note Added in Proof:** The recent introduction of "PhSeOSePh" as a useful synthetic reagent [see Shimizu, Takeda, and Kuwajima, *Tetrahedron Lett.*, 419 (1979)] prompted us to explore its reactivity with a 1,5-diene. To this end, reaction of 1,5-cyclooctadiene (I) with "PhSeOSePh" prepared according to Kuwajima afforded II and iv in 16 and 56% yield,[10] respectively. This experiment demonstrated not only that there is a difference in the reactivity of the two reagents, but also lends support to the proposed nature of the electrophilic species involved in our selenium-induced cyclizations as well as the reactions reported by Sharpless,[5] Reich,[6] and Kuwajima.



(26) We gratefully acknowledge financial support of this work from the National Institutes of Health [National Cancer Institute, CA-22807 (A.B.S.); Heart, Lung and Blood Institute, HV-E2931 (K.C.N.)] and the Donors of the Petroleum Research Fund, administered by the American Chemical Society (A.B.S. and K.C.N.). In addition we thank Mr. S. T. Bella of the Rockefeller University for the microanalysis and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220 and 360 MHz NMR spectra were obtained.
(27) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983.
(28) Alfred P. Sloan Fellow, 1979–1981.

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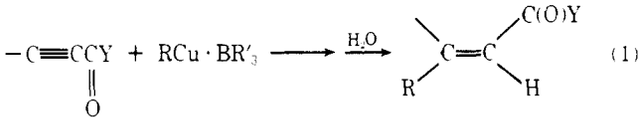
Stereocontrolled Cis Addition of Organocopper Reagents RCu·BR′$_3$ to α,β-Acetylenic Carbonyl Compounds

Summary: The reagent RCu·BR′$_3$ adds to α,β-acetylenic carbonyl compounds with a high stereospecificity at reasonably low temperatures (−70 to −20 °C), which cannot be achieved with reagents previously available.

Sir: Conjugate addition of organocopper reagents to α,β-acetylenic esters and acids is one of the most ubiquitous and useful methods to prepare various tri- and tetrasubstituted olefins[1] and is frequently employed for the natural product synthesis.[2] Since the reaction presumably proceeds through the carbon–copper enolate, the yield and the geometry of the products highly depend on temperature and duration of reaction before quenching.[2,3] No attempts have yet been made to control the stereochemistry of this reaction by developing a new reagent with wide applicability. We now wish to report that the use of organocopper–organoborane complexes (RCu·BR′$_3$) solves some of the inherent problems associated with these highly useful bond construction reactions (eq 1).



(1)

Y = OR″, OH, C, H

Previously, we reported that the alkenylborane–alkylcopper complexes underwent facile thermal dimerization to give the corresponding (*E,E*)-1,3-dienes with high stereospecificity.[4] The dimerization proceeded with greater stereospecificity than that of the free alkenylcoppers or the tri-*n*-butylphosphine complexes.[5] This observation suggested that the vinyl carbon–copper bond of the organocopper–organoborane complexes[6] might be more configurationally stable than that of normal organocopper reagents.[7] To test this idea and to develop a new methodology to influence the stereochemistry of the conjugate addition, we examined the reaction of various RCu·BR′$_3$ complexes with α,β-acetylenic esters, acids, ketones, and aldehyde. The results are summarized in Table I.

Completely stereospecific addition to α,β-acetylenic esters and acids can be realized by using RCu·BR′$_3$ (entries 1–3 and 10–14). Such a high specificity at the reasonably low temperatures cannot be achieved with reagents previously available. *Since the stereospecificity via methylcopper reagents is generally greater than that via n-butylcopper re-*

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