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Diastereoselective oxyselenylation of 1,*n*-diolefins utilizing PET generated [PhSeSePh]$^{+\bullet}$ as an electrophilic species: An efficient and general strategy for the synthesis of α,α'-*trans*-dialkyl cyclic ethers†

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Abstract

PET-generated electrophilic selenium species [PhSeSePh]$^{+\bullet}$ are found to effect stereoselective oxyselenylation of 1,*n*-diolefins (**1**) leading to a novel methodology to the synthesis of α,α'-*trans*-dialkyl cyclic ethers (**8**).

Keywords: Photosensitized electron transfer (PET), episelenonium radical cation, oxyselenylation, α,α'-*trans*-dialkyl cyclic ethers.

1. Introduction

Stereoselective synthesis of α,α'-dialkyl cyclic ethers has attracted considerable attention recently owing to their unique structural features and presence in a large number of polyether antibiotics and other biologically active natural products.[1] In the majority of these natural products, cyclic ether units display α-α'-*trans*-dialkyl substituents. For example, majority of *Annonaceous acetogenins* marine natural products possess *trans*-2,5-dialkyl tetrahydrofurans[2] while swinholides,[3] the potent cytotoxic agents,[4] and laurapinnacins[5] display *trans*-2,6-dialkyl tetrahydropyran and *trans*–2,7-dialkyl oxepans moieties, respectively. Among the various strategies reported[6] for the synthesis of these structural units, bis addition of an oxygen nucleophile across the 1,*n*-diolefins (dienes) moiety represents an attractive approach.[7] However, these strategies afford a mixture of diastereomers. Oxyselenylation of diolefins (**1**), reported[8] by using PhSeCN-$CuCl_2$ or PhSeCl as reagents in aqueous acetonitrile, is known to produce α,α'-dialkyl cyclic ethers. However, the process uses very toxic and unstable reagent that is also not stereoselective. The nonstereoselectivity of these reagents could be due to possible lack of steric restriction for face selection from the transition state structure (**2**) (Scheme 1) during the intramolecular selenoetherification step.

We had earlier reported[9, 10] an *in situ* activation of PhSeSePh to an electrophilic selenium species [PhSeSePh]$^{+\bullet}$ employing 1,4-dicyanonaphthalene (DCN) as light-harvesting electron acceptor through the photosystem (Fig. 1). The utility of this transient species was also suggested for efficient selenoetherification[9] and enyne cyclization[10] reactions. Intrigued by the possible utilization of [PhSeSePh]$^{+\bullet}$ for the *trans* selective oxyselenylation of **1**, owing to the

†Dedicated to Prof. S. C. Bhattacharyya.
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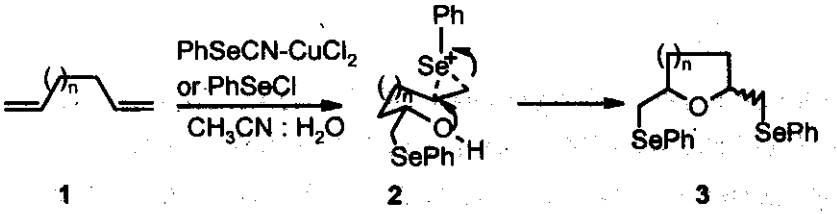


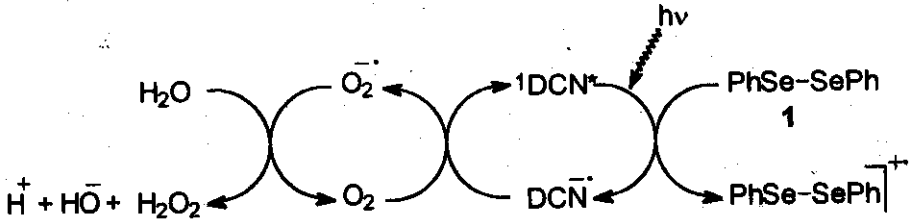
Scheme 1.

envisaged *syn* addition[11] of the hydroxyl group to the episelenonium radical cation[12] moiety from the expected transition state structure **4** (Scheme 2), we have initiated this study. We report here the full details[13] of the concept for the synthesis of various α,α'-*trans*-dialkyl-substituted tetrahydrofurans, tetrahydropyrans and oxepanes.

2. Results and discussion

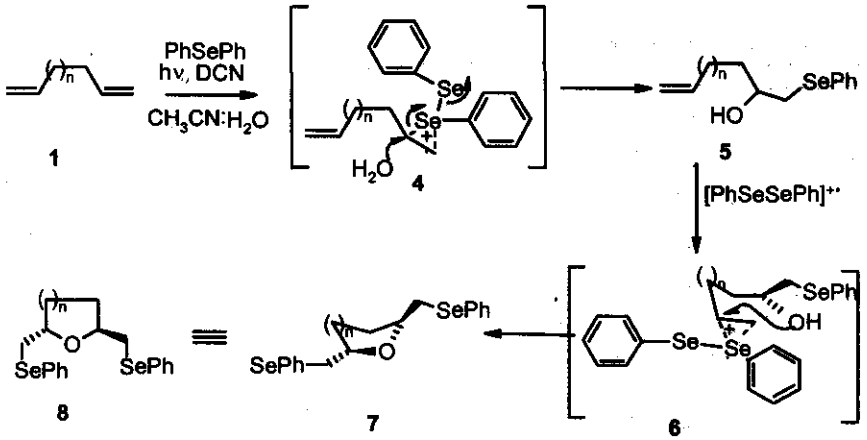
To evaluate the utility of PET-generated PhSeSePh]$^{+\cdot}$ in the stereoselective oxyselenylation of 1,*n*-dienes, oxyselenylation of 1,5-hexadiene (**1**, $n = 0$) was initiated first by irradiating a dilute solution of **1** (6.0 mmol) in the presence of PhSeSePh (6.0 mmol) and DCN (0.60 mmol) in CH_3CN:H_2O (4:1) using a Pyrex filtered light (>280 nm) emanating from a 450 W Hanovia medium pressure lamp. Dissolved oxygen present in the solvent was not removed during irradiation. The progress of the reaction was monitored by TLC as well as by GC. After 8 h, when almost 60% of **1** was consumed, irradiation was discontinued. Removal of the solvent followed by column chromatographic purification of the crude mixture afforded **8** ($n = 0$) in 80% yield. The yield of **8** was calculated on the basis of the starting material utilized. DCN was recovered almost quantitatively (>98%) at the end. ^{1}H and ^{13}C NMR, and mass spectral details characterized oxyselenylated product **8**. 2,5-*trans*-Stereochemistry in **8** was assigned on the basis of the observance of two independent signals for both H-2 (multiplet, δ 4.31) and H-5 (multiplet, δ 4.17) and also for C-2 (δ 79.18) and C-5 (δ 78.70), respectively. This assignment is also found to be in agreement with the reported[14] parameters for *trans*-cyclic ethers. Diastereomeric purity of **8** (>97%) was established by comparing the HPLC analysis (reverse phase, C_{18} bonda pack, 0.5 μm) with the authentic mixture prepared by following the reported procedure.[14]

Mechanistically, these results can be rationalized in the contexts of Scheme 2. It is probable that electrophilic selenium species [PhSeSePh]$^+$, formed by the PET oxidation of PhSeSePh,



DCN=1,4-dicyanonaphthalene

FIG. 1.



Scheme 2.

react first with one of the double bonds of **1** followed by the opening of the resultant episelenonium radical cation (**4**) under the influence of moisture to provide **5**. Subsequent formation of another episelenonium radical cation intermediate (**6**) followed by intramolecular *syn* addition of the –OH moiety leads to the formation of **8** stereoselectively.

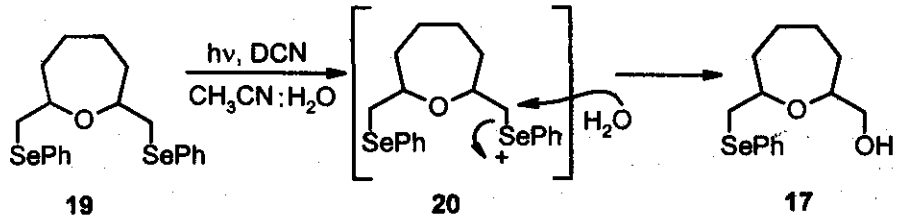
The α,α′-*trans*-dialkyl stereochemistry in each major product was established by detailed spectral analyses. In all the cases, the products were isolated in the diselenylated form except in the case of **12** where monodeselenylted product (**17**) was formed by further oxidative PET cleavage of –C-Se- bond (Scheme 3), a process already reported by us earlier.[14] This result encouraged us to explore the generality of such stereoselective oxyselenylation reaction involving substrates **9–13** (Table I).

In conclusion, a novel method has been developed for the synthesis of α,α′-*trans* cyclic ethers via oxyselenylation of dienes utilizing an *in situ*-generated electrophilic selenium species.

3. Experimental

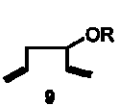
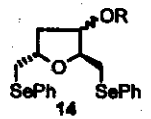
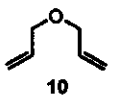
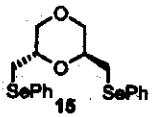
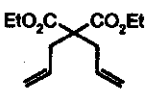
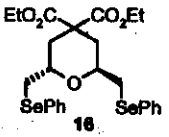
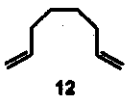
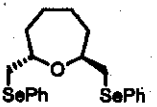
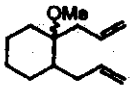
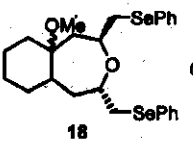
3.1. *General methods*

DCN (1,4-dicyanonaphthalene)[15] and PhSeSePh[16] were synthesized and purified following the literature procedures. Organic solvents such as acetonitrile, petroleum ether (60–80°C), ethyl



Scheme 3.

Table I
***trans*-Selective oxyselenylation of 1,n-diolefins**

Substrate	Irradiation time (h)	Products[a]	Yields[b]	Diastereomeric purity
 **9**	15	 **14**	60	(1:1)[c]
 **10**	14	 **15**	80	
 **11**	15	 **16**	65	(1.7:1)[c]
 **12**	16	 **17**	50	
 **13**	16	 **18**	60	(1:1)[c]

a) Characterized by ^{1}H and ^{13}C NMR and mass spectral data. b) isolated yields calculated on the basis of starting material utilized.

acetate and THF were purified and dried before use. All nuclear magnetic resonance spectra were recorded on either Bruker AC200 or Bruker MSL300 NMR spectrometers using $CDCl_3$ as solvent. Chemical shifts are reported in ppm (δ) relative to internal standard chemical shift of Me_4Si. Coupling constants are given in Hertz. IR spectra were taken in $CHCl_3$ on a Perkin–Elmer model 2830 spectrometer. Mass spectra were obtained at a voltage of 70 eV on a Finnigan MAT-1020B instrument. HPLC analysis was performed on a Perkin–Elmer (model 250 binary LC pump along with LC135, diode array detector) liquid chromatography using reverse-phase C_{18} (bondapack 0.5 μm) column, eluting with CH_3CN/H_2O solvent mixture. Column chromatography was carried out on silica gel (60–120 mesh). Dienes used were obtained from either commercial source or prepared by following reported literature procedure.

Diene **9** was prepared by the alkylation of free hydroxy group of commercially available 1,5-hexadien-3-ol with octyl bromide, whereas **11** was prepared by the sequential double alkylation of diethyl malonate with allyl bromide. Substrates **10** and **13** were prepared by following the literature procedure.[17, 18]

Progress of the reaction was monitored by TLC and GC (capillary column, methyl silicone 30%) analysis.

3.2. *General procedure for oxyselenylation reaction of dienes*

A mixture of **1** (0.5 g, 6.09 mmol), diphenyldiselenide [PhSeSePh] (1.9 g, 6.0 mmol) and DCN (0.108 g, 0.60 mmol) was dissolved in a 500 ml acetonitrile water solution (4:1). The resultant solution was irradiated at room temperature with 450 W Hanovia medium pressure mercury vapor lamp housed in a Pyrex jacketed immersion well without removing the dissolved oxygen. The progress of the reaction was monitored by TLC and GC (capillary column, methyl silicone 30%) analyses. Photolysis was discontinued after 8 h, when 60% of **1** was consumed. Solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel using pet ether:ethyl acetate mixture (20:1) to give 2.1 g (80%) of oxyselenylated product (**8**). Yield of **8** was calculated based on the consumption of respective dienes. DCN was isolated almost quantitatively. IR ($CHCl_3$): 2940, 1590, 1480, 1200, 1030, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (4H, m), 7.33 (6H, m), 4.31 (1H, m), 4.17 (1H, m), 3.16 (2H, m), 3.01 (2H, m), 2.15 (2H, m) and 1.76 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 132.58, 132.49, 130.92, 129.43, 129.09, 126.65, 79.18, 78.70, 33.20, 32.13, and 31.26. Mass (*m/z*): 412(M^+, 3%), 255(19), 213(14), 171(25), 157(55), 91(72), 83(100) and 55(65).

14: Yield 60%, IR ($CHCl_3$): 2900, 1460, 1100, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (4H, m), 7.25 (6H, m), 4.25 (1H, m), 4.05 (1H, m), 3.85 (1H, m), 3.35–2.90 (6H, m), 2.35 (2H, m), 1.54 (2H, m), 1.30 (12H, bs), 0.90 (3H, t, $J = 5.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): (Major): δ 132.29, 130.22, 128.99, 126.64, 83.18, 82.73, 82.09, 69.63, 37.71, 36.93, 33.11, 33.03, 29.36, 29.22, 22.61 and 14.04. (Minor): δ 132.57, 127.71, 127.40, 125.97, 82.09, 78.41, 78.28, 69.41, 37.95, 36.66, 31.80, 29.81, 26.52, 26.16 and 14.04. Mass (*m/z*): 538(M^+, 45%), 383(40), 253(53), 183(52), 157(62), 113(51), 71(79) and 57(100).

15: Yield 80%, IR ($CHCl_3$): 3019, 1215, 753 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): 7.60 (4H, m), 7.25 (6H, m), 3.90 (1H, m), 3.75 (3H, m), 3.55 (1H, dd, $J = 5.3$ and 11.2 Hz), 3.05 (4H, m), and 2.73 (1H, dd, $J = 5.3$ and 11.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.32, 133.15, 129.50, 127.48, 75.54, 70.61, 70.38, 69.50, 28.68 and 28.32. Mass (*m/z*): 428(M^+ 20%), 314(14), 271(29), 197(45), 178(65), 171(72), 157(100), 117(38), and 91(50).

16: Yield 65%, IR ($CHCl_3$) 2940, 1730, 1200, 1080, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.60 (4H, m), 7.25 (6H, m), 4.65 (1H, m), 4.35 (1H, m), 4.20 (2H, m), 3.75 (2H, m), 3.25 (2H, m), 3.15 (2H, m), 2.67 (2H, m), 2.15 (1H, m), 1.75 (1H, m) and 1.20 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$): (Major): δ 171.32, 133.09, 132.89, 129.24, 127.26, 80.47, 77.68, 61.57, 61.36, 59.59, 42.53, 41.77, 32.84, 31.14, 15.49 and 14.24, (Minor): δ 77.42, 61.43, 58.93, 42.33, 41.18, 32.03, and 29.82, Mass (*m/z*): 570(M^+ 4%), 399(36), 307(18), 241(15), 167(35), 157(75), 91(100), and 77(67).

17: Yield 50%, IR ($CHCl_3$) 3401, 2822, 1212, 1059 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 7.50 (2H, m), 7.24 (3H, m), 4.08 (1H, m), 3.88 (1H, m), 3.71 (1H, m), 3.08 (1H, dd, $J = 7.2$ and 12.9 Hz), 2.95 (1H, dd, $J = 7.2$ and 12.9 Hz), 2.05 (2H, m), 1.95–1.87 (2H, m), 1.65–1.54 (2H, m), and 1.27 (3H, bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 132.77, 130.56, 129.24, 127.03, 78.55, 68.56, 33.26, 31.75 and 26.17.

18: Yield 60%, IR ($CHCl_3$): 2900, 1430, 1270, 1120, 1070, 735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.50 (4H, m), 7.27 (6H, m), 4.00 (2H, m), 3.10 (5H, m), 2.84 (2H, m), 1.24–1.58 (13H, m). ^{13}C NMR (75 MHz, $CDCl_3$): (Major): δ 137.41, 133.51, 131.93, 129.54, 127.30, 76.82, 76.60, 74.41, 47.70, 43.32, 36.10, 34.98, 34.71, 33.01, 30.93, 29.27, 26.13, and 21.13. (Minor): δ 133.80, 132.56, 132.21, 132.02, 130.98, 72.25, 70.92, 47.90, 39.65, 33.42, 32.11, 30.09, 29.97, 28.70, 24.20, and 22.31. Mass (*m/z*): 524(M^+, 1%), 352(15), 295(60), 221(100), 203(35), 137(25) and 71(65).

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