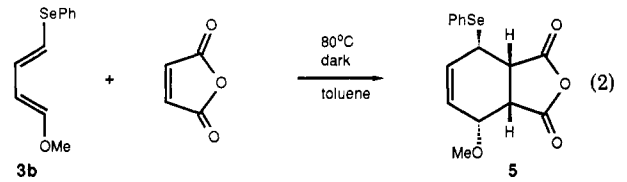
Preliminary mechanistic studies have so far been limited to the use of free radical inhibitors. Varying concentrations of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or tetramethylpiperidinyloxy radical (TEMPONE) have no apparent effect on the photochemical isomerization process. However, the presence of 2 equiv of BHT does appear to retard the thermal isomerization of **3b** and **3c**. That the isomerization process may involve cyclobutene intermediates, via conrotatory electrocyclic reactions, is suggested by analogy to observations made by Trost et al.[9] in their attempt to prepare (*E,E*)-1-(phenylsulfinyl)-4-methoxy-1,3-butadiene. Such a mechanism can account for the stereochemical stability of **3d**.

Although this facile geometric isomerization process of 1-phenylseleno 1,3-dienes might be expected to reduce their usefulness in Diels–Alder-type chemistry, this is not the case. For example, heating an equilibrium mixture of all four possible stereoisomers of **3b** with maleic anhydride, at 80 °C in the dark, leads to a *single stereoisomeric product* **5** in good yield (greater than 80% by $^1$H NMR). The stereochemistry was confirmed by $^1$H NMR and NOEDIFF experiments. Thus the *E,E* stereoisomer is kinetically "milked" from the equilibrium. Compound **5** is also obtained in good yield by reaction of isomerically pure **3b** with maleic anhydride (eq 2).




Further studies on the mechanisms of both the photoinduced and thermally driven isomerization will be reported along with a more comprehensive study of the Diels–Alder reactivity of these new 1-phenylseleno 1,3-dienes.

**Acknowledgment.** Financial support was provided by NSERC of Canada in the form of operating grants (M.D.F. and G.S.B) and by the Alfred P. Sloan Foundation (M. D.F.).

**Supplementary Material Available:** Experimental details, $^1$H NMR spectra, and analytical data on compounds **3** and $^1$H NMR and $^1$H NMR NOEDIFF data on **5** (9 pages). Ordering information is given on any current masthead page.

(9) Trost, B. M.; Godleski, S. A.; Ippen, J. *J. Org. Chem.* **1978**, *43*, 4559.
(10) Fellow of the Alfred P. Sloan Foundation (1984–1987).

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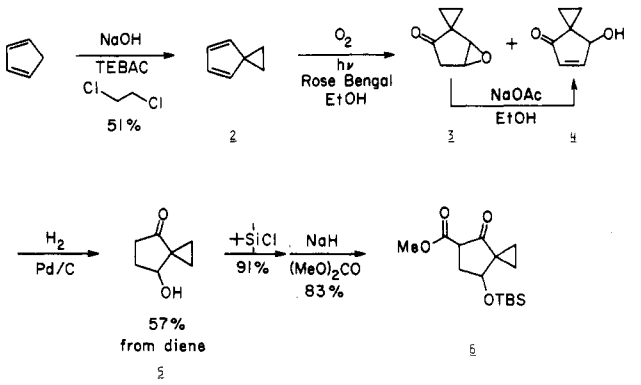
## Synthesis of Pederol

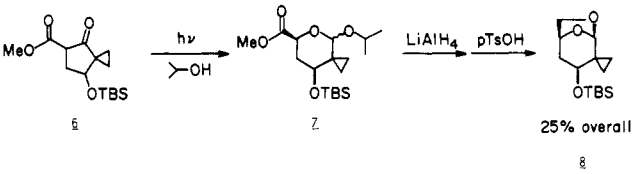
*Summary:* The synthesis of pederol, the "right half" of pederin, has been accomplished by using an oxacarbene intermediate to construct its pyran unit.

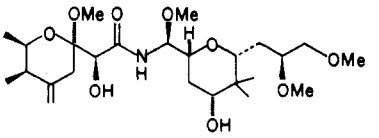
*Sir:* Despite considerable mechanistic study of the photochemical ring expansion of cycloalkanones to oxacarbenes,[3] its unique possibilities for selective organic synthesis have heretofore been unexploited. Reports have appeared only recently concerning cyclobutanone ring expansions that provide entries into tetrahydrofuran structures.[4] Tetrahydropyrans can also be produced by using this methodology.[5] We have undertaken the total synthesis of the naturally occurring compound pederin[6] (**1**) utilizing the photochemical generation of a 2-tetrahydropyranylidene as a key step. This initial report describes the preparation of the "right half" of pederin, pederol.

**Scheme I**




**Scheme II**




Pederin

1

The synthesis of the substrate for the photoreaction is summarized in Scheme I. It begins with cyclopentadiene, which is cycloalkylated with dichloroethane under improved conditions using phase-transfer catalysis.[7] This gives spiro[2.4]heptadiene (**2**) in 51% yield. Lots of 40 g

(1) Research Fellow of the Alfred P. Sloan Foundation, 1986–1988.
(2) Merck Postdoctoral Fellow.
(3) Yates, P.; Loutfy, R. *Acc. Chem. Res.* **1975** *8*, 209.
(4) Pirrung, M. C. *Angew. Chem., Int. Ed. Engl.* **1985** *24*, 1043. Davies, H.; Roberts, S.; Wakefield, B.; Winders, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1166. Pirrung, M. C.; DeAmicis, C. V. *Heterocycles* **1987**, *25*, 189. Crossland, N. M.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1978**, 661.
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(6) Structure: Furusaki, A.; Watanabe, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedon Lett.* **1968**, 6301. Previous synthetic approaches: Tsuzuki, K.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 4745. Adams, M.; Duggan, A., Smolanoff, J., Meinwald, J. *J. Am. Chem. Soc.* **1979**, *101*, 5364. Isaac, K.; Kocienski, P.; Campbell, S. *J. Chem. Soc., Chem. Commun.* **1983**, 249. Sternbach, D. Abstracts *of Papers*, 187th National Meeting of the American Chemical Society, St. Louis, MO; American Chemical Society: Washington, DC, 1984; ORGN 159. Meinwald, J. *Pure Appl. Chem.* **1977** *49*, 1275. Yanagiya, M.; Matsudo, F.; Hasegawa, K.; Matsumoto, T. *Tetrahedron Lett.* **1982**, 4039; *Tetrahedron* **1984**, *40*, 2337. Isaac, K.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1982**, 460. Kocienski, P.; Willson, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1011. Matsuda, R.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1982**, 4043. Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1983**, 1277.
(7) Makosza, M. Pol. Pat. 55 571, 1968; *Chem. Abstr.* **1968**, *70*, 106047f.

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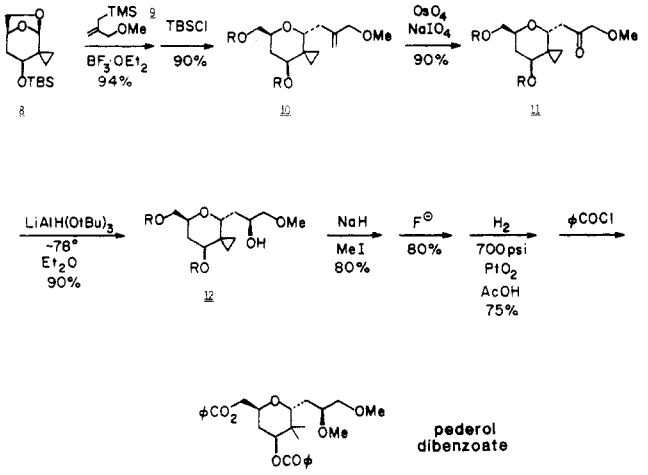
**Scheme III**




of **2** are thereby easily prepared in an afternoon. Singlet oxygenation in ethanol (sun lamp, Rose Bengal, up to 25 g/L) provides directly a 70:30 mixture of epoxy ketone **3** and the desired hydroxy enone **4**.[8] Without purification, this mixture is subjected to in situ elimination with sodium acetate and hydrogenation using palladium on carbon. There is thus obtained the desired hydroxy ketone **5** in 57% overall yield from the diene. Protection of the hydroxyl (*t*-$BuMe_2SiCl$, imidazole, DMF, 48 h) and carboxylation (2.7 equiv NaH, 2.7 equiv of dimethyl carbonate, benzene, reflux, 8 h) set the stage for the ring expansion reaction.

The cyclopropyl group in **6** is a crucial element of the synthetic design. Based on precedent,[5cd] it was expected to direct the C–C bond cleavage in the desired sense. It has an augmenting effect on the n,$\pi^*$ absorption of the cyclopentanone. It stabilizes the oxacarbene through spiroconjugation, and likely has a similar effect on the oxacarbonium ion used subsequently. Finally, it performs a structural function as the precursor to the geminal methyl groups. On the basis of a number of model studies, the oxygen protecting group and the precursor to the carbinolamine–ether carbon were chosen to maximize the yield of ring-expansion product.[9]

The irradiation of **6** is conducted in isopropyl alcohol (20g/L, 4 h, room temperature) with a Hanovia medium-pressure mercury lamp (Scheme II). Two substances are obtained in comparable amounts and in good material balance. The less polar photoproduct proves to be the desired pyran **7**.[10] It is isolated by filtration through silica (30:1 hexane/ethyl acetate) and subjected to a two-step protocol ($LiAlH_4$, $Et_2O$, 0 °C; 3 mol % *p*-TsOH, benzene, $Na_2SO_4$, 3 days). This yields the key intermediate bicyclic acetal **8** in 25–27% overall yield. Formation of this acetal obviates a multitude of potential problems. Being much less polar than any hydroxyl-containing byproducts of the sequence, **8** is easily separated from them, again on silica. It also ensures the desired stereochemistry, since an acetal in the epimeric series must either adopt a boat form or place the bulky siloxy group in an axial position.[11] Finally, based on the work of Kishi,[12] it was thought that the cyclic acetal would permit stereocontrol at the 2- and 6-positions of the tetrahydropyran. This proved to be the case, as shown in Scheme III.

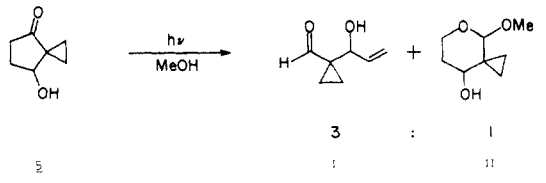
A synthon for the dimethoxypropyl side chain was available in the methyl ether **9** formed from Trost's allylic silane.[13] Condensation with **8** (3.9 equiv of **9**, 2.4 equiv of $BF_3$·$OEt_2$, 0 °C, $CH_2Cl_2$, 1 h) produces an alcohol mixture in 94% yield. Silylation permits a simple separation (30:1 hexane/ether, silica) into **10** (80%) and an isomer (10%). Lemieux–Johnson oxidation (catalytic $OsO_4$, 13 equiv of $NaIO_4$, 3:1 acetone/$H_2O$, 48 h, 90%) gives ketone **11**. Stereocontrolled reduction occurs at −78 °C in ether to produce a single alcohol in 87% yield. Methylation (2NaH, 2MeI, THF, 97%) and deprotection ($Bu_4NF$, THF, 48 h, 90%) give dehydropederol. Cyclopropane cleavage is conducted in acetic acid with Adams' catalyst at 700 psi of hydrogen (20 h, room temperature), producing pederol in 80% yield. Its stereochemistry and constitution were demonstrated by conversion to the dibenzoate and spectral comparison with authentic material and its stereoisomers.

In summary, the total synthesis of pederol has been achieved in 2% overall yield and in 15 chemical steps. The synthesis is noteworthy for its high stereocontrol, made possible by the use of intermediate **8**, and it constitutes an initial demonstration of the utility of oxacarbenes in natural products synthesis.

**Acknowledgment.** Financial support was provided by the NSF Presidential Young Investigator program (to M.C.P., CHE 8451324), the NIH (GM 38226), and Merck, Sharp, & Dohme Research Laboratories (fellowship to P.M.K.). NMR spectra were obtained on instruments provided by NSF equipment grants (CHE 8109064 and CHE 8414329). We thank Prof. Kocienski for comparison spectra.

(8) The formation of **3** was unexpected for a singlet oxygen reaction of a diene, though it is synthetically equivalent to **4**. It has been observed before: Adam, W.; Erden, I. *J. Org. Chem.* **1978**, *43*, 2737. Takeshita, H.; Kanamori, H.; Hatsui, T. *Tetrahedron Lett.* **1973**, 3139.

(9) Model studies were conducted on **5** and derivatives protected with silyl and acyl groups. For example, irradiation of **5** in MeOH provides I and II. This type of product is also precedented in Wakefield's studies




of similar reactions.[5d] Silyl is the most convenient protecting group in this synthetic sequence. Examination of spiro[2.4]heptanone substituted with cyano, 2-(1,3-dioxolanyl), and methoxycarbonyl groups reveals the latter is far superior. Less polar solvents have in our experience[4ac] proved more effective, which may explain superior yields in isopropyl alcohol as compared to methanol or ethanol. The foregoing will be discussed in detail in the full paper.

(10) Considerable effort has been expended to identify this other product. All attempted manipulations have returned the diastereomeric mixture **6**.

(11) Partial NMR ($CDCl_3$): δ 4.63 (s, 1 H), 4.59 (m, 1 h), 4.24 (dd, *J* = 10, 6 Hz, 1 H), 3.86 (d, *J* = 7, Hz, 1 h), 3.74 (m, *J* = 7 Hz, 1 H), 1.88 (dd, *J* = 13, 6 Hz, 1 H), 1.60 (dd, *J* = 13, 10 Hz, 1 H).

(12) Lewis, M.; Cha, J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(13) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org.* Synth. **1984**, *62*, 58. **9**: 1.8 equiv of NaH, THF, 0 °C; 1.2 equiv of MeI, room temperature, overnight; bp 60 °C (0.4 torr). NMR ($CDCl_3$) δ 4.90 (s, 1 H), 4.74 (s, 1 H), 3.81 (s, 2 H), 3.35 (s, 3 H), 1.57 (s, 2 H), 0.04 (s, 9 H).

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