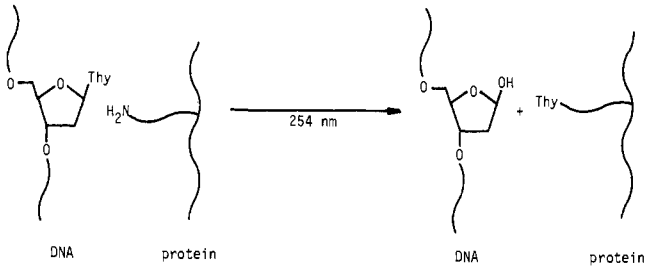
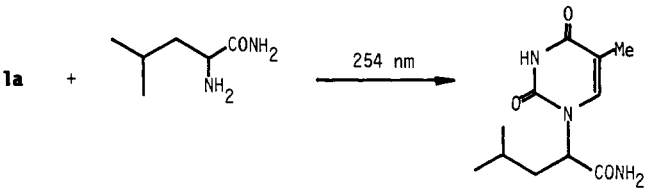
Scheme III



extruded from **1c** as *n*-heptylamine, with the incorporation of the nitrogen of *n*-butylamine into the N(1) position of the photoproduct **3a**. In contrast to the direct irradiations, acetone-sensitized irradiation of **1a** with *n*-butylamine in alkaline aqueous solution never produced **3a** but gave a mixture of thymidine photodimers exclusively,[16] nor was the formation of **3a** observed when **1a** was irradiated in acetonitrile containing *n*-butylamine.

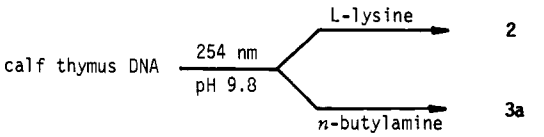
On the basis of these observations, the plausible mechanism shown in Scheme II is proposed. Nucleophilic attack of the amino group on C_6 of the photoexcited **1a**, probably the singlet state, would occur first to give 6-alkylamino-5,6-dihydrothymidine **4**.[4g,17] Ring opening of **4** under basic conditions followed by subsequent intramolecular cyclization would then furnish **5**.[18] An alternative mechanism involving a photohydrate of **1a** as the precursor of **4** might be ruled out by the fact that reaction of thymidine photohydrates, prepared by the known method,[19] with *n*-butylamine did not give **3a** under the basic conditions.

Under conditions where **1a** reacts smoothly with lysine, irradiation of other nucleosides such as adenosine, guanosine, cytidine, and uridine in the presence of lysine did not produce any ninhydrin positive photoproduct, whereas photoreaction of ribothymidine with lysine gave **2** (40%). These results indicate that the photoadduct formation with lysine is specific for thymidine. Irradiation of **1a** with other amino acids such as leucine, glycine, aspertic acid, and arginine did not give the corresponding photoadduct under the conditions. However, irradiation of **1a** with their amide derivatives provided the corresponding photoadducts. For example, photoreaction of **1a** (1 mM) with free L-leucine amide (3 mM) in water (pH 8.8) proceeded sluggishly to give **6**[9] (24%).



6

In order to ascertain whether this type of photoreaction occurs between DNA and lysine, we have examined the photoreaction of DNA with lysine. A solution (pH 9.8) of calf thymus DNA (5 mg, P-L Biochemicals) and free L-lysine (50 mg) in double-distilled water (20 mL) was irradiated with low-pressure mercury lamp (Vycor filter) at 10 °C under similar conditions. After passing through a membrane filter to remove DNA, the solution was concentrated and the residue was subjected to preparative TLC[7] as described above. High-performance LC[8] of the extract showed a peak corresponding to **2**. Collection of the high-performance LC peak gave a photoproduct whose chromatographic behaviors and UV spectrum are identical with those of **2**. Thus, we were able to confirm that the same photoproduct **2** is indeed formed in the photoreaction of DNA with lysine. The yield of **2** estimated by high-performance LC was ca. 1% on the basis of thymine contained in DNA. Likewise, irradiation of DNA (2 mg)



with *n*-butylamine (10 mg) in distilled water (10 mL, pH 9.8) followed by a similar workup provided **3a** (2.5% based on thymine), whereas irradiation of heat-denaturated single-strand DNA in the presence of *n*-butylamine produced **3a** (9%) more efficiently under the identical conditions.[20]

The foregoing photoreaction of DNA in the presence of lysine or alkylamines can induce a specific cleavage of thymine moieties from DNA chains without any acid hydrolysis, thus enabling utilization of this reaction as a new method for specific modification of DNA. It seems likely that a similar reaction can take place between photoexcited DNA and lysine residues in a protein. In such cases the thymine moiety in DNA might migrate to a neighboring lysine residue of the protein as illustrated in Scheme III. The present observations also suggest that this type of photoreaction may play an important role in UV-induced damage on nucleic acids in cells. We are continuing to explore the scope and mechanism of this novel photoreaction.[21]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan and the Yamada Science Foundation.

(16) (a) Fisher, G. F.; Johns, H. E. *Photochem. Photobiol. Nucleic Acids* **1975**, *1*, 169. (b) Ben-Hur, E.; Elad, D.; Ben-Ishai, R. *Biochim. Biophys. Acta* **1967**, *149*, 355.

(17) (a) Summers, W. A.; Enwall, C.; Burr, J. G.; Letsinger, R. L. *Photochem. Photobiol.* **1973**, *17*, 295. (b) Schetlar, M. D. *Ibid.* **1976**, *24*, 315 and references therein.

(18) For analogous reactions, see: ref 14 and (a) Broom, A. D.; Anderson, G. L. *J. Org. Chem.* **1977**, *42*, 4159. (b) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4423. (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865.

(19) Cadet, J.; Ducolomb, R.; Teoule, R. *Tetrahedron* **1977**, *33*, 1603.

(20) Control experiments showed that 254-nm light and *n*-butylamine are indispensable for the formation of **3a**.

(21) **Note Added in Proof.** An alternative pathway involving nucleophilic attack of the amino group on C_2 of the photoexcited **1a** cannot be ruled out at this time. Characterization of the intermediate formed at low-temperature irradiation will be reported in a forthcoming paper.

Tricyclo[4.2.2.2^{2,5}]dodeca-1,5-diene

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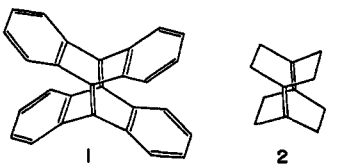
New Haven, Connecticut 06511

Received May 27, 1980

The properties of compounds such as **1**,[1] in which two nonconjugated double bonds are forced by their geometry to interact with each other, have been of considerable interest.[2] We wish to report a simple preparation for the parent hydrocarbon, tricyclo[4.2.2.2^{2,5}]dodeca-1,5-diene (**2**).



1 **2**

Deuterium-labeled $\Delta^{1(4)}$-bicyclo[2.2.0]hexene (**3**-d_4) was prepared by the elctrochemical reduction of 1-chloro-4-bromo-

(1) Viavattene, R. L.; Greene, F. D.; Cheung, L. D.; Majeste, R.; Trefonas, L. M. *J. Am. Chem. Soc.* **1974**, *96*, 4342.

(2) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1. Wittsel, K.; McGlynn, S. P. *Chem. Rev.* **1977**, *77*. 745. Bishof, P.; Hashmall, J. H.; Heilbronner, E.; Hornung, V. *Helv. Chim. Acta* **1969**, *52*, 1745.

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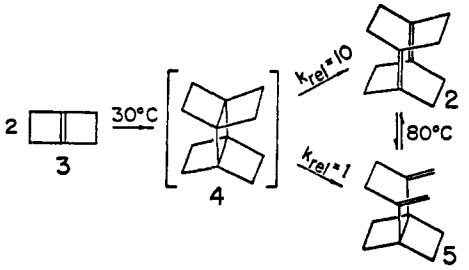
bicyclo[2.2.0]hexane-*2,2,3,3-d*$_4$ in dimethylformamide (DMF) solution.[3-5] The ^{2}H NMR spectrum could be observed in the reaction solvent and gave a singlet at δ 3.26.[6] At 55 °C, the signal due to **3**-*d*$_4$ diminished and was replaced by two singlets (with proton decoupling) at δ 2.13 and 2.92.[7] Knowing the conditions under which this new compound was formed, it was possible to repeat the experiment by using unlabeled **3**. The compound was isolated by extracting the cold DMF solution with pentane, washing with 1 N HCl at 0 °C, drying and removing the solvent under reduced pressure.

The ^{1}H NMR spectrum of the residue ($CDCl_3$ solution) consisted of an A2B2 pattern (two doublets) at δ 2.24 and 2.99. The ^{13}C NMR spectrum had two bands, at δ 35.6 and 139.2. The upfield band resulted from a carbon coupled to two hydrogens ($J_{^{13}C\text{-}H}$ = 133 Hz), whereas the downfield band was due to a quaternary carbon and had a chemical shift characteristic of olefinic carbons. If it is accepted that the compound is a dimer of **3**, these data clearly indicate that it is the diene, **2**. In view



of the reactivity of the [2.2.2]propellane,[8] it is reasonable to propose that the pentacyclic propellane (**4**) is an intermediate and undergoes ring opening under the conditions of its formation.

The thermal cleavage of **4** could lead to either **2** or **5**. The formation of **2** from **4** must be kinetically controlled since the initially obtained product at lower temperatures contains 90% **2** and only 10% **5**, whereas at higher temperatures (see below) **2** is converted to **5**. INDO[9] calculations for **4** and for the species formed by stretching one of the propellane bonds have shown that the symmetry inversion observed between the HOMO of normal and stretched [2.2.2]propellane[10] also occurs with **4**. The unoccupied orbital which has the larger coefficient for a 2,3 bond and the appropriate symmetry for interacting with the HOMO of the stretched species is that those for the other propellane bond, leading to the preferred cleavage path giving **2** rather than **5**.

When **2** was heated to 80 °C in DMF solution, it was converted to **5**.[11] The reaction did not proceed to completion but rather gave an equilibrium mixture of **2** and **5** (1:4 ratio at 90 °C). The Cope rearrangement of **2** → **5** is analogous to the rearrangment of bicyclo[4.2.2]deca-1,5-diene to 2,5-dimethylenebicyclo-[4.2.0]octane which was studied by Wiseman and Vanderbilt.[12] In this case, the absence of one bridge leads to a reduced interaction between the double bonds in the reactant and the reaction proceeds to completion. A study of the conversion of **2** → **5**

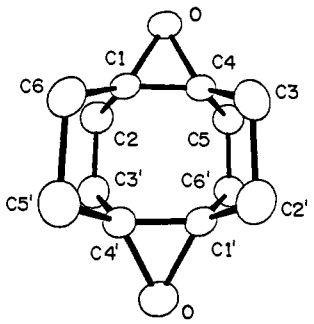


Figure 1. Structure of the diepoxide **7**.

Table I. Geometrical Parameters for Diepoxide **7**

bond lengths, Å		bond angles, deg	
C1-O	1.458	C1-O-C4	60.4
C1-C2	1.516	O-C1-C4	59.8
C2-C3'	1.562	O-C1-C2	120.1
		C1-C2-C3'	107.3
		C3-C4-C5	110.5

provides a unique opportunity to examine an essentially degenerate Cope rearrangement for which the less favored boat activated complex[13,14] is required and to obtain a measure of the interaction energy between the double bonds in **2**.

The conversion of **2** → **5** was studied in toluene-*d*$_8$ solution via NMR spectroscopy (270 MHz). It was a first-order process and gave the rate constants (2.4 ± 0.2) × 10^{-4} (76.2 °C), (8.3 ± 0.3) × 10^{-4} (87.1 °C), (1.87 ± 0.07) × 10^{-3} (94.5 °C), and (3.5 ± 0.2) × 10^{-3} s^{-1} (100.0 °C). These lead to $\Delta H^{\ddagger}$ = 28 ± 1.5 kcal/mol and $\Delta S^{\ddagger}$ = 5 ± 4 eu. The activation enthalpy is markedly less than that for the normal Cope rearrangement of 1,5-hexadiene which proceeds via the favored chair conformation (34 kcal/mol)[13] and the "high temperature Cope rearrangement" of 1,5-hexadiene which is believed to proceed via a boat activated complex (45 kcal/mol).[13] These results confirm the conclusion of Doering and Roth[13] that the boat activated complex was disfavored because of the repulsive interactions developed in forming this species. When the interaction is built into the reactant, as in the case of **2**, the activation energy is markedly reduced.

The strain energy of **5** cannot be less than that of bicyclo-[2.2.0]hexane, or 50 kcal/mol.[15] A study of the equilibrium between **2** and **5** as a function of temperature showed that the diene **2** had the lower enthalpy (ΔH = 3 ± 1 kcal/mol), but **5** is favored at equilibrium because of its higher entropy.[16] The strain energy in **2** must then be at least 47 kcal/mol. The major source of strain in **2** is the repulsive interaction between the two pairs of π orbitals, and thus each double bond is destabilized by about 20–23 kcal/mol.[17]

The diene **2** has remarkably high chemical reactivity. A chloroform solution of **2** reacts with atmospheric oxygen to give a new substance, **7**. The ^{1}H NMR spectrum again had an A2B2 pattern (two quartets) at δ 1.75 and 2.13. The ^{13}C NMR spectrum had two bands, at δ 27.1 and 62.1. The upfield carbon was coupled to two hydrogens, whereas the downfield carbon was not coupled to protons. The compound was found to have two oxygens, and the absence of carbonyl or hydroxy bands in the infrared spectrum suggested a diepoxide structure. This was confirmed by X-ray

(3) Wiberg, K. B.; Burgmaier, G. J.; Warner, P. *J. Am. Chem. Soc.* **1971**, *93*, 246. Wiberg, K. B.; Bailey, W. F.; Jason, M. E. *J. Org. Chem.* **1974**, *39*, 3803.

(4) Casanova, J.; Rogers, H. R. *J. Org. Chem.* **1974**, *39*, 3803.

(5) The chlorobromide was prepared by the previously described method (Scherer, K. V.; Meyers, T. J. "Abstracts of Papers", 155th National Meeting, American Chemical Society, San Francisco, CA, 1967; American Chemical Society: Washington, DC, 1967: *P*-1800) except that deuterium was substituted for hydrogen in the hydrogenation–hydrogenolysis step.

(6) The proton chemical shift was δ 3.24.[3]

(7) The dimerization of **3** has been reported to yield **5** as the product (Wiberg, K. B.; Jason, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3393). The formation of **2** was not observed at that time probably because of its high reactivity towards oxygen and its thermal conversion to **5**. The direct observation of **2** via ^{2}H NMR spectroscopy made it possible to design a procedure for its isolation.

(8) Eaton, P. E.; Temme, G. H., III *J. Am. Chem. Soc.* **1973**, *95*, 7508.

(9) Pople, J. A.; Beveridge, D. L. "Approximate Molecular Orbital Theory"; McGraw-Hill: New York, 1970.

(10) Stohrer, W.-D.; Hoffmann, R. *J. Am. Chem. Soc.*, **1972**, *94*, 779. Newton, M.D.; Schulman, J. M. *Ibid.* **1972**, *94*, 4391.

(11) The evidence for the structure of **5** has been presented.[7]

(12) Wiseman, J. R.; Vanderbilt, J. J. *J. Am. Chem. Soc.* **1978**, *100*, 7730.

(13) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. Goldstein, M. J.: Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7174. Shea, K. J.; Phillips, R. B. *Ibid.* **1978**, *100*, 654.

(14) Doering, W. v. E.; Toscano, V. G.; Beasley, G. J. *Tetrahedron* **1971**, *27*, 5299.

(15) Baas, J. M. A.; van de Graaf, B; van Rantwijk, F.; van Veen, A. *Tetrahedron* **1979**, *35*, 421.

(16) The diene **5** would be expected to have a greater entropy than **2** because of its lower symmetry (σ = 4 for **2**) and expected lower frequency vibrational modes.

(17) The destabilization of **2** probably results in large measure from pyramidalization at the double bonds as was found with **1**. For a discussion of the energy changes accompanying pyramidalization, see: Volland, W. V.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 533.

crystallography and is shown in Figure 1.[18] The bond lengths and angles are summarized in Table I.

The diene **2** also undergoes facile Diels-Alder reaction and reacts with bromine to form a dibromide with internal bridging to give another bicyclo[2.2.0]hexane derivative.[19] The details of these and other reactions will be presented subsequently.

Acknowledgment. This investigation was supported by NSF Grant CHE-78-27880 and, in part, by NSF Grant CHE-79-16210 (high-field NMR spectrometer).

Supplementary Material Available: Positional parameters, bond distances, and bond angles with their estimated standard deviations for **7** (2 pages). Ordering information is given on any current masthead page.

(18) Crystal data: space group *Pbca*; a = 9.580 (2), b = 9.258 (2), c = 11.012 (2) Å, Z = 4. Diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer: 932 reflections ($F^2 \geq 3.05\ F^2$) were used in the structure solution and refinement. The structure was solved by direct methods using the program MULTAN and 132 reflections having $E_{min} \geq 1.45$. All programs were those of the Enraf-Nonius SDP program library. Final values of the residuals were R = 0.043 and R_w = 0.045.

(19) The ^{13}C NMR spectrum indicates the absence of a C-C double bond in the product as well as a symmetry corresponding to that of **2**. The analysis indicates two bromines. In principle, bridging could occur in two ways, but models indicate that only bridging to form the bicyclo[2.2.0]hexane ring is possible.

Total Synthesis of Pretyrosine (Arogenate)

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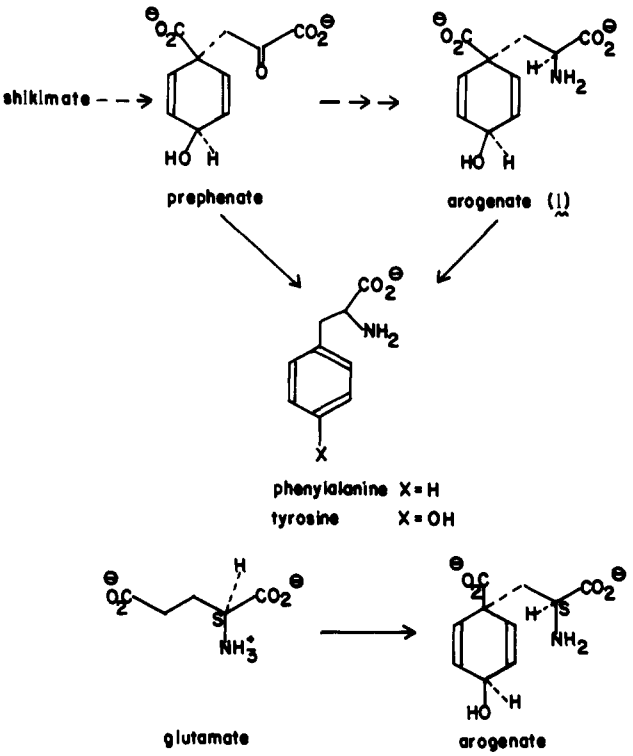
Received November 25, 1980

Since its discovery, it had been assumed that prephenic acid, biosynthetically derived from shikimate, was the last nonaromatic intermediate in the elaboration of the crucial amino acids phenylalanine and tyrosine and that these are exclusively derived from the corresponding aryl pyruvates.[1,2] More recently, largely as a consequence of the investigations of the Jensen group,[3,4] an alternative mode of L-tyrosine biosynthesis has been uncovered. The crucial variation is that the transamination of the keto group of prephenate can also occur prior to aromatization. This pathway has been established in a variety of bacterial and yeast organisms.[5,6] Interestingly, in pseudomonal bacteria and plants, both the "prephenate" and the "pretyrosine" routes to tyrosine appear to be cofunctional.[7]

Early investigations delineating the existence of this pathway pointed to the formation of intermediate **1**,[3,4] which was aptly named "pretyrosine". Given its involvement in phenylalanine biosynthesis,[8] the designation pretyrosine has given way[9] to the more general appelation, "arogenate" (**1**). The initial deductions of the structure of arogenate were based more on clever guesswork and intuition than on hard chemical or spectroscopic information. Rigorous investigations into the nature of this curious amino acid were hampered by its instability and extremely difficult accessibility. More recently, very convincing spectroscopic and chiroptical data were brought to bear in support of structure **1** by Zamir and co-workers.[9]



Given its important role in biosynthesis, difficult accessibility, extensive functionality, and precarious stability, a total synthesis of arogenate appeared to be a worthy objective. Particularly interesting to us was the possibility of obtaining the compound in optically pure form. The realization of these goals is the subject of this report. It will be recognized that in this enterprise we were drawing extensively on methodology which previous workers in our laboratory had developed pursuant to the total synthesis of prephenate,[10] as well as of γ-carboxyglutamate[11] and tazettine.[12] Our chiral source was the readily available amino acid, L-glutamic acid in the form of its pyroglutamate derivative **2**.

We have already described[11] the conversion of **2** → **3** in essentially quantitative yield through the agency of the Bredereck reagent, bis(dimethylamino)-*tert*-butoxymethane. Hydrolysis of the enamine linkage was readily accomplished through the action of aqueous 1 N HCl:THF at room temperature, affording **4** as a mixture of geometric isomers.

Reaction of **4** with diphenyl disulfide and tri-*n*-butylphosphine (THF, room temperature)[13] afforded a 68% yield of an E/Z mixture of vinyl sulfides **5**.[14] These were grouped together for the next step. Oxidation of **5** with *m*-chloroperoxybenzoic acid

(1) Haslam, E. "The Shikimate Pathway"; Wiley: New York, 1974.
(2) For a recent review, see: Ganem, B. *Tetrahedron* **1978**, *34*, 3353.
(3) Stenmark, S. L.; Pierson, D. L.; Glover, G. I.; Jensen, R. A. *Nature (London)* **1974**, *247*, 290.
(4) Fazel, A. M.; Bowen, J.; Jensen, R. A. *Proc. Natl. Acad. Sci. U.S.A* **1980**, *77*, 1270.
(5) (a) Jensen, R. A.; Pierson, D. L. *Nature (London)* **1975**, *254*, 667. (b) Fazel, A. M.; Jensen, R. A. *J. Bacteriol.* **1979**, *138*, 805. (c) *Ibid.* **1979**, *140*, 580.
(6) Bode, R.; Birnbaum, D. *Biochem. Physiol. Pflanzen.* **1978**, *173*, 44.
(7) (a) Patel, N.; Pierson, D. L.; Jensen, R. A. *J. Biol. Chem.* **1977**, *252*, 5839. (b) Patel, N.; Stenmark-Cox, S.; Jensen, R. A. *Ibid.* **1978**, *253*, 2972. (c) Rubin, J. L.; Jensen, R. A. *Plant Physiol.* **1979**, *64*, 727.
(8) See ref 9, footnote 13.
(9) Zamir, L. O.; Jensen, R. A.; Arison, B. H.; Douglas, A. W.; Alberg-Schönberg, G.; Bowen, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 4499.
(10) Danishefsky, S.; Hirama, M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7013.
(11) Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385.
(12) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838.
(13) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. For a comparable reaction to prepare selenides, see: Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(14) (a) Along with the desired vinyl sulfides **5**, there was isolated a 15.6% yield of the bis sulfide resulting from a 1,4 addition of thiophenol to **5**. (b) **5**: IR ($CHCl_3$) ν_{max} 3.28, 5.61, 5.73, 5.78, 6.18, 7.68 μm; ^1H NMR (250 MHz, $CDCl_3$) δ 2.57 (ddd, J = 2.4, 3.6, 18.0 Hz, 1), 2.98 (ddd, J = 3.0, 10.2, 18.0 Hz, 1), 4.76 (dd, J = 3.9, 10.2 Hz, 1), 5.12 and 5.17 (s, 2 parts of benzylic H, 2), 5.22 and 5.25 (s, 2 parts of benzylic H, 2), 7.3-7.6 (m, 15), 7.66 (dd, J = 2.4, 3.0 Hz, 1); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 23.7, 26.8, 47.5, 55.7; 56.8; 58.9; 67.4, 68.3. MS, m/e calcd for $C_{27}H_{23}NO_5S$, 473.1297; found, 473.1308.

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