Tetrahedron Letters,Vol.27,No.13,pp 1485-1488,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

INTRAMOLECULAR CYCLOADDITIONS USING VINYL SULFIDE DIENOPHILES

D.R. Williams*[1] and R.D. Gaston
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

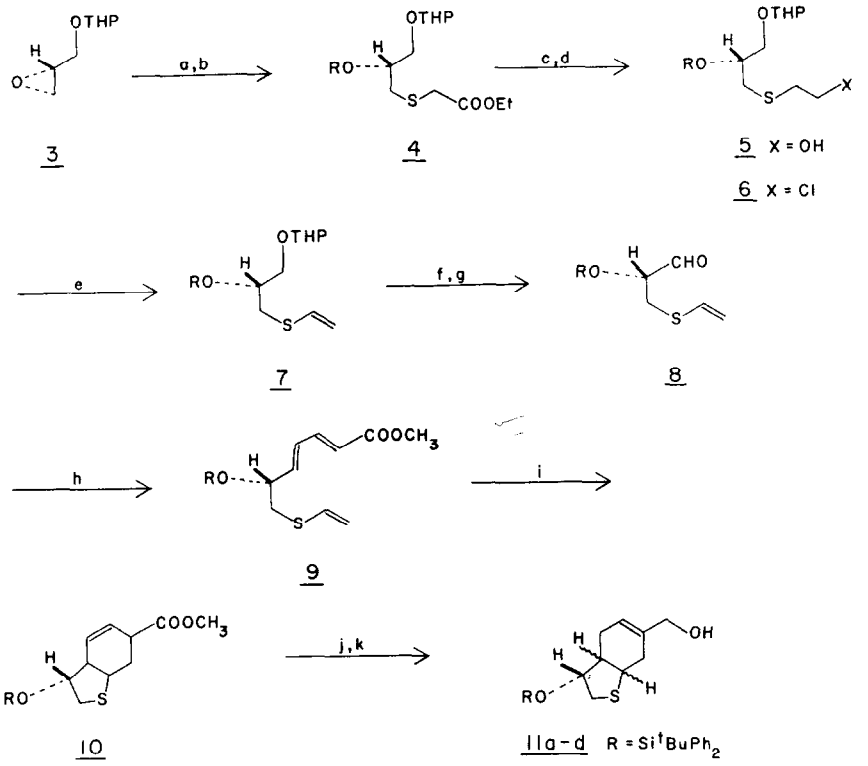
Summary: The formation of hexahydrobenzo(b)thiophenes have been examined by a Diels-Alder route featuring a vinylic sulfide as the dienophilic component. Unique aspects of the observed stereoselectivity and further stereochemical transformations are presented.

In the course of investigations of natural product synthesis, we have undertaken studies of the intramolecular Diels-Alder reaction for preparation of substituted hexahydrobenzo(b)-thiophenes (1). Reports have explored opportunities for intramolecular cycloadditions with substrates bearing nitrogen or oxygen, contained within imine, amine, amide, ether and ester functionalities.[2] An important feature of our study required use of a vinylic sulfide moiety as a dienophilic component. Although examples of vinyl sulfides as Diels-Alder dienophiles are unknown, our studies sought to utilize the electron deficient diene 2 (R_1=$COOCH_3$), initially suggesting an inverse electron demand cycloaddition affording the bicyclic products 1.

2 1

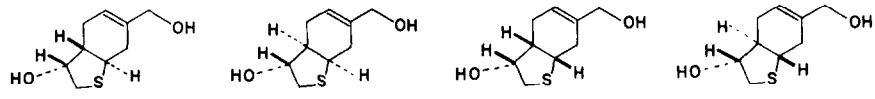
The preparation of the desired *E,E*-methyl ester 2, and our Diels-Alder results are illustrated in Scheme I.[3] Wittig reaction with methyl-4-triphenylphosphorane crotonate gave the Diels-Alder precursor 9 in 92% yield as a mixture of four olefin isomers.[4] Fortunately, the desired *E,E*-diene ester 9 was separated by flash chromatography as the major component (60% yield).[5] Heating 9 in *ortho*-dichlorobenzene at reflux (1.5h) under argon led to formation of Diels-Alder products 10 (98% yield) as two major and two minor diastereoisomers. Base-induced conjugation of the carbon double bond ($NaOCH_3$; MeOH; 22°C), and reduction (DIBAL; 3 equivs; CH_2Cl_2; -78°C) gave the primary alcohols 11a-d, having the four components in 40:45:11:4 ratio, respectively.[6] Although sufficient quantities were not available to allow complete characterization of the most minor product 11d, our three cycloadducts were purified and fully assigned by ^1H- and ^{13}C-NMR as their diols 12a-c.[7]

Scheme I

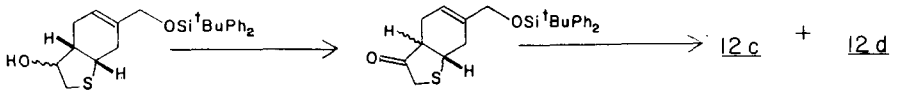


(a) $HSCH_2COOEt$, NaOEt (catalytic), ethanol, 22°C (99%); (b) Cl-Si^{t}BuPh$_2$, imidazole, DMF, 50°C, 24h (98%); (c) $LiAlH_4$, THF, 0°C, 3h (96%); (d) TsCl, LiCl, CH_2Cl_2, Et_3N, 22°C, 18h (72%); (e) DBU (4 equiv), toluene, reflux, 33h (85%); (f) 0.02 M methanol solution of 7, PPTs (1 equiv), 22°C, 24h (92%); (g) ClCOCOCl (1 equiv), DMSO, CH_2Cl_2, then Et_3N at -78°C (90%); (h) Ph_3P=CH-CH=CHCOOMe (1.1 equiv), THF, HMPA (1 equiv), 22°C, 4h (60%); (i) *ortho*-dichlorobenzene, reflux (98%); (j) NaOMe (catalytic), MeOH, 5h (63%); (k) DIBAL (3 equiv), CH_2Cl_2, -78°C (100%).

The structure of the highly crystalline, least polar diastereoisomer 12a (mp 117-118°C from acetone) was unambiguously established by X-ray diffraction studies.[8] However, samples of the minor *cis*-fused diol 12c were contaminated with the major stereoisomer 12b.

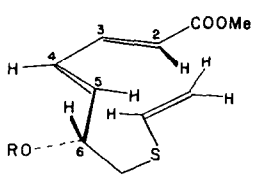


Fortunately pure 12c was obtained upon oxidation (oxalyl chloride; DMSO; Et_3N; -78°C) of a mixture of the *cis*-fused isomer 13, affording equal proportions of *cis*- and *trans*-fused ketones 14.[9] Reduction with L-selectride (THF; -78°C; 100% yield), and subsequent fluoride deprotection ($nBu_4N^+F^-$; THF; 22°C) led exclusively to the diols 12a and 12c, which were readily separated by preparative thin-layer chromatography.

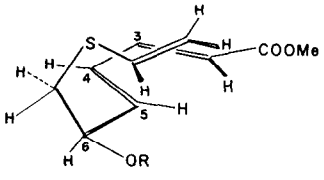


13 14

The stereoselectivity for our Diels-Alder process should be considered in light of the possibilities for two pairs of diastereotopic transition states. A pair of *exo*-bridging transition states lead to formation of the *trans*-fused products 12a and 12d (ratio 10:1), whereas *endo*-bridging situations provide the two *cis*-fused isomers 12b and 12c (ratio 4:1). Thus, the alkoxy substituent at C-6 has induced a preference for cycloadditions from the conformers A and B, giving rise to the observed major products 12a and 12b, respectively.



A



B

Interestingly, in each case the siloxy substituent is located in a plane defined by the diene component with eclipsing interactions to the vinylic hydrogens at C-4 and C-5, respectively. Our observations are in accord with the published results of Roush[10] and Weinreb[2b] for examples of intramolecular cycloadditions bearing similar siloxy substitution. Moreover, this stereoselectivity is reversed compared to examples in which the C_6-siloxy group has been replaced by alkyl.[11] The evidence would suggest that allylic ether substituents, located along the bridging elements of an intramolecular Diels-Alder substrate, will generate subtle electronic interactions which will have an important impact on the stereochemical outcome of the process.[12] Further efforts are underway.

Acknowledgement: We thank the American Heart Association (Indiana Affiliate, Inc.), the National Institutes of Health (AI17668) for generous support of our research, and acknowledge assistance of the National Science Foundation for purchase of high field NMR (CHE81-05004) and high-resolution mass spectrum instrumentation (CHE81-11957).

References:

1. Alfred P. Sloan Foundation Fellow (1983-1987).
2. (a) M.L. Bremmer and S.M. Weinreb, *Tetrahedron Letters*, *24*, 261 (1983); (b) R.A. Gobao, M.L. Bremmer and S.M. Weinreb, *J. Am. Chem. Soc.*, *104*, 7065 (1982); (c) S.F. Martin, S.A. Williamson, R.P. Gist and K.M. Smith, *J. Org. Chem.*, *48*, 5170 (1983); (d) M. Yoshioka, H. Nakai and M. Ohno, *J. Am. Chem. Soc.*, *104*, 1133 (1984); (e) T. Takebayashi, N. Iwasawa, T. Mukaiyama and T. Hata, *Bull. Chem. Soc. Japan*, *56*, 1669 (1983).
3. All compounds were purified and fully characterized by infrared, nuclear magnetic resonance (360 MHz), and high resolution mass spectral data and/or combustion elemental analyses. Complete details will be provided in the full account of this work.
4. Attempts to isomerize mixtures of the *2E,4Z*- and *2Z,4E*-diene esters with light or iodine failed to afford additional amounts of 9. Also condensations of 8 with the phosphonate anion of ethyl 4-(diethoxyphosphinyl)crotonate led to cleavage of the silyl ether and decomposition of aldehyde 8.
5. Small quantities of the corresponding *2E,4Z*-methyl ester (10-15%) often contaminated samples of 9. However, this isomer did not undergo the Diels-Alder reaction, and was recovered unchanged.
6. Ratios were determined by analytical HPLC (Microsorb Si column, 250 x 4.6mm, 25% $CHCl_3$ in hexanes) and were consistent with ratios obtained by ^{1}H-NMR (360 MHz) integrations of the vinyl hydrogen signals for the conjugated methyl esters from 10. Investigations of cycloaddition of the corresponding MEM-protected diene of 9 gave similar product ratios. Thus far, attempts to explore Lewis acid catalysis have led to decomposition of the vinyl sulfide moiety.
7. A partial listing of data for key compounds includes the following: For diol 12a: ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.77 (m, 1H), 4.48 (m, 1H), 4.07 (bs, 2H) 3.35 (dt, 1H, J=5.1, 11.3), 3.10 (AB of ABX, 2H, J=0.0, 4.0, 11.8, $\Delta\nu$=125.1), 2.55 (m, 1H), 2.27 (m, 3H), 1.75 (ddt, 1H, J=2.9, 5.6, 11.3), 1.62 (d, 1H, J=7.0), 1.38 (bs, 1H); ^{13}C-NMR (75.4 MHz, acetone-d_6) δ 138.43, 122.04, 74.64, 66.38, 52.13, 45.05, 40.13, 34.31, 26.00; Diol 12b: ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.73 (m, 1H), 4.31 (m, 1H), 4.03 (bs, 2H), 3.90 (m, 1H), 3.07 (AB of ABX, 2H, J=3.0, 5.3, 11.7, $\Delta\nu$=178.6), 2.60-2.10 (m, 4H), 1.95-1.75 (m, 2H), 1.42 (bs, 1H); ^{13}C-NMR (75.4 MHz, acetone-d_6) δ 136.31, 119.62, 77.94, 66.66, 47.11, 42.28, 37.69, ~30 (obscured by acetone), 24.70; Diol 12c: ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.83 (m, 1H), 4.55 (m, 1H), 4.03 (bs, 2H), 3.65 (m, 1H), 3.03 (AB of ABX, 2H, J=5.4, 6.2, 11.1, $\Delta\nu$=74.4), 2.53-2.18 (m, 5H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 135.88, 121.32, 78.17, 66.95, 43.16, 41.58, 36.58, 30.88, 21.57.
8. Structure 12a was determined by single crystal X-ray analysis (-159°C) of colorless, equidimensional plates. All atoms were located, including hydrogens, and refined by full-matrix techniques to final residuals of R(F)=0.026 and R_w(F)=0.033. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 85036.
9. Oxidation of the pure *trans*-fused secondary alcohol obtained from 12a also gave a 1:1 (*cis*:*trans*) mixture of bicyclic ketones 14, possibly suggesting a reversible Michael sequence.
10. W.R. Roush, H.R. Gillis and A.I. Ko, *J. Am. Chem. Soc.*, *104*, 2269 (1982), and references therein; S.E. Hall and W.R. Roush, *J. Org. Chem.*, *47*, 4611 (1982).
11. W.R. Roush and A.G. Myers, *J. Org. Chem.*, *46*, 1509 (1981); K.C. Nicolaou and R.L. Magolda, *Ibid.*, *46*, 1506 (1981). Also see, D.F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions," Springer-Verlag, New York (1984); and D.R. Williams, R.D. Gaston and I.B. Horton, *Tetrahedron Letters*, *26*, 1391 (1985), and references therein.
12. This stereoelectronic effect was first recognized by M. Hirama and M. Uei, *J. Am. Chem. Soc.*, *104*, 4251 (1982). For conformational effects of alkoxy groups located adjacent to the dienophile, see R.L. Funk and W.E. Zeller, *J. Org. Chem.*, *47*, 180 (1982).

(Received in USA 23 January 1986)