

FACILE CONSTRUCTION OF C<sub>10</sub> MODIFIED PROSTAGLANDIN PRECURSORS.  
DIYL TRAPPING REACTIONS USING PHENYL VINYL SULFOXIDE AND PHENYL VINYL SULFONE

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Summary. The application of 1,3-diyl trapping reactions to the synthesis of commonly used prostanoid precursors is described

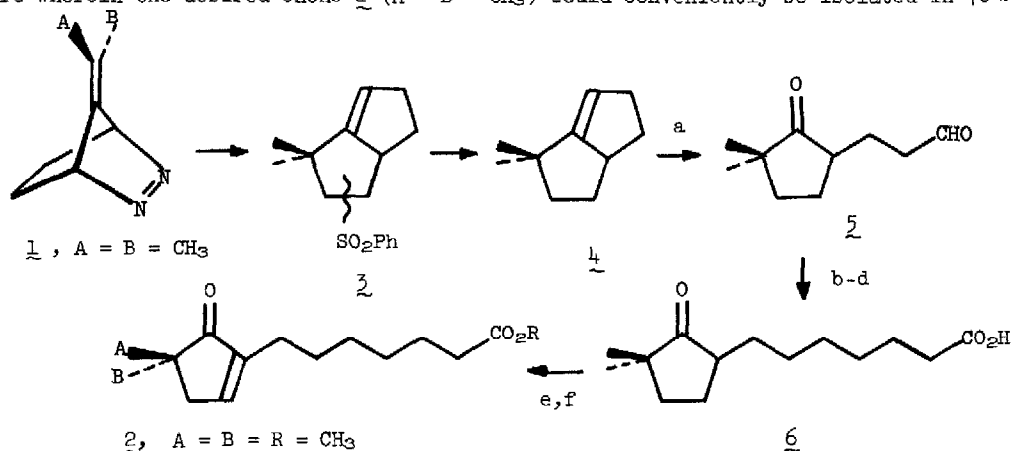
Previously, we have demonstrated that cyclopenta-1,3-diyls related to trimethylene-methane serve as useful intermediates in the synthesis of linearly fused tricyclopentanoids.<sup>2</sup> We report herein a simple and general scheme for the construction of C<sub>10</sub> modified prostaglandins in which a 1,3-diyl trapping reaction constitutes the key step. Recently, Pernet and colleagues have reported a means of synthesizing C<sub>10</sub> and C<sub>11</sub> modified prostanoids, they also reported that certain C<sub>10</sub> dimethyl prostaglandins act as highly potent gastric secretion inhibitors in dogs and as antihypertensives in rats and dogs.<sup>3</sup>

Some flexibility is built into the scheme described below in terms of the selection of C<sub>10</sub> substituent(s) in that they originate as substituents located at C<sub>8</sub> of the readily available bicyclic azo compound 1.<sup>4</sup> The target molecule is enone 2 (A = B = CH<sub>3</sub>) since a conjugate addition has been shown to provide a satisfactory means of adding the requisite C<sub>12</sub> side chain.<sup>5</sup> The basic plan calls for the construction of a bicyclo(3.3.0)octene ring system followed by oxidative cleavage of a bridgehead pi bond to generate the prostanoid C<sub>7</sub> carbonyl as well as three of the seven carbons of the C<sub>8</sub> side chain, and finally, elaboration of the rest of the C<sub>8</sub> side chain and introduction of the  $\Delta^{8,12}$  pi bond.

The bicyclo(3.3.0)octene ring system was conveniently prepared by refluxing an acetonitrile solution of azo compound 1 (A = B = CH<sub>3</sub>) in the presence of a four-fold excess of phenyl vinyl sulfone. Removal of the solvent and excess diylophile led to an 85 % chromatographed yield of sulfone 3 as a mixture of isomers. However, since the phenyl sulfonyl group is removed in the next step, the regio- and stereochemical outcome of the diyl trapping reaction was of no concern. Thus, treatment of 3 with an excess of 6 % Na(Hg) in methanol in the presence of 4 equiv of disodium hydrogen phosphate at 25°C for 2.5 h, produced hydrocarbon 4 in 82 % yield.<sup>6</sup> Overall, phenyl vinyl sulfone has served as the synthetic equivalent of ethylene. It should be noted that commercially available phenyl vinyl sulfoxide works just as well as the sulfone in the diyl trapping reaction.

Ozonolysis of 4, followed by reductive workup (Zn, AcOH) and conversion to the keto dimethyl acetal, provided a convenient point for purification of the somewhat unstable keto aldehyde 5. A Wittig reaction on 5 using the phosphonium ylid derived from methyl 4-bromo-

crotonate, followed by hydrogenation and saponification, served to fully elaborate the C<sub>8</sub> side chain (80 % from the keto dimethyl acetal of 5). Introduction of the  $\Delta^{8,12}$  pi bond was complicated somewhat by virtue of the fact that elimination of the selenoxide derived from the dianion of 6 afforded a 3:1 mixture of endo- to exocyclic enones. However, esterification followed by equilibration using rhodium(III) chloride in methanol provided an 8:1 mixture wherein the desired enone 2 (A = B = CH<sub>3</sub>) could conveniently be isolated in 70% yield.<sup>7</sup>



a, O<sub>3</sub>, pentane, -78°C, Zn, AcOH, 15°C, 30 min; CH<sub>3</sub>OH, H<sup>+</sup>; purification then acetone, Et<sub>2</sub>O, H<sub>3</sub>O<sup>+</sup>, 25°C, 2 h, b, Ph<sub>3</sub>P=CHCH=CHCO<sub>2</sub>CH<sub>3</sub>, DMSO, 25°C, 30 min, 60°C, 2 h; c, H<sub>2</sub>, 10% Pd-C, EtOAc, 24 h; d, NaOH, CH<sub>3</sub>OH-H<sub>2</sub>O (3:1), H<sup>+</sup>, e, 2.2 equiv LDA, THF -78°C, 1 h, 3 equiv PhSeCl, THF, 0°C, 15 min, H<sub>2</sub>O<sub>2</sub>, AcOH-H<sub>2</sub>O, 25°C, 45 min, f, (COCl)<sub>2</sub>, PhH, DMF (cat.) then CH<sub>3</sub>OH

Acknowledgements: This work was primarily supported by funds obtained from a President's Undergraduate Fellowship awarded to L.B., we greatly appreciate this assistance. We are also grateful to the National Cancer Institute, DHEW (Grant Number CA 21144-03) for partial support. We thank Dr. Robert Petty of UCSB for numerous gc-ms analyses.

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8. NOTE ADDED IN PROOF: Trost and Chan recently reported the cycloaddition of 2-acetoxymethyl-3-allyltrimethylsilane to electron deficient olefins, including a substituted phenyl vinyl sulfone, catalyzed by palladium(0) to afford methylenecyclopentanes. It was suggested that a trimethylenemethane-palladium complex served as an intermediate in the reaction. See Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.*, 1979, 101, 6429, 6432.

(Received in USA 4 February 1980)