REGIOSELECTIVE PREPARATION OF TRICYCLIC TERPENE RING SYSTEMS BY CYCLOADDITION OF 1,3,3-TRIMETHYL-2-VINYLCYCLOHEXENE WITH UNSYMMETRICAL QUINONES

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Abstract: High pressure reactions of 1,3,3-trimethyl-2-vinylcyclohexene with unsymmetrical <u>p</u>-benzoquinones are accelerated by ZnBr_2 and regio- and stereoselectively produce substituted 4,4,10-trimethyl- and 4,4,8,10-tetramethyloctahydrophenanthrene ring systems.

We recently reported that the Diels-Alder reaction of 1,3,3-trimethyl-2-vinylcyclohexene, 1. with 1.4-benzoquinone, 2a, yielded 3a which gave 4 upon acid catalyzed enolization.^{1a},² The reactions provide a potentially rapid and efficient method for the synthesis of podocarpane and related diterpenes.³ We now report that high pressure 4+2 cycloadditions of 1 with unsymmetrical 1,4-benzoquinones 2b and 2c are regio- and stereoselective and present a direct and versatile synthetic approach to many classes of terpenes.^{1b},³ Of particular interest is that these high pressure reactions are accelerated by ZnBr₂. However, Lewis acid catalyzed reactions of 1 and 2b and 2d at atmospheric pressure do not furnish 4+2 adducts; rather, products resulting from alkylation of the quinone are found.

In the present investigation, reaction of 1 and 2b at 7 kbar in CH_2Cl_2 for 14 days gave exclusively <u>endo</u> adduct 3b in 80% yield.⁴ Some loss of stereoselectivity in reactions of 1 and 2b was found at higher pressures (10-12 kbar/5-14 days);⁵ small amounts (4-10%) of an as





- 2 a, R₁-R₄=H
 - **b**, $R_1 = OCH_3$, $R_2 R_4 = H$
 - c, $R_1 = OCH_3$, $R_2 = R_4 = H$, $R_3 = CH_3$ d, $R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = CH_3$



- 3 a, R₁-R₄=H
 - **b**, $R_1 = OCH_3$, $R_2 R_4 = H$
 - **c**, R₁=OCH₃, R₂=R₄=H, R₃=CH₃

yet unidentified isomer of 3bs were observed in the 300 MHz ¹H NMR spectrum of the crude reaction mixture. However, reaction of 1 and 2b at 12 kbar (CH_2Cl_2) for <u>15 hr</u> in the presence of ZnBr₂ (1 equiv) furnished only 3b in 52% yield; no reaction between 1 and 2b was apparent at 12 kbar for 15 hr in the absence of ZnBr₂. In a similar manner, 1 and 2c maintained at 12 kbar/14 days in CH_2Cl_2 with ZnBr₂ (1.1 equiv) gave exclusively 3c in >90% yield. No reaction between 1 and 2c was observed without ZnBr₂ present.

Adduct 3b results from <u>endo</u> addition of 1 and 2b and the stereochemistry of 3b is assigned by 300 MHz ¹H NMR. A J_{H8-H9} of 5 Hz indicates a <u>cis</u> BC ring fusion and the unusual downfield chemical shift of the C-1 axial proton (2.38 ppm, ddd, J=13, 13, 4 Hz) implies that H_1 is deshielded by the C-11 carbonyl group.⁷ Drieding models show that the C-11 carbonyl and H_1 in 3b are indeed very close. In a model of the <u>exo</u> 4+2 adduct of 1 and 2b, the C-11 carbonyl and H_1 are far apart. The position of the methoxy group in 3b was established by acid catalyzed enolization (aq HCl/THF, rt, 93%) and methylation (KO<u>t</u>-Bu/(MeO)₂SO₂/THF, rt, 41%) to afford 5 which has been reported previously.⁸

The structure of 3c was determined as follows. Reaction of 3c with KO<u>t</u>-Bu/<u>p</u>-bromobenzyl bromide in THF produced 6 (53%). Single crystal X-ray analysis of 6 confirmed its structure (Figure 1) and established a <u>cis</u> relationship between the C-8 and C-10 methyl groups. The configuration of the stereocenter at C-9 was determined by NOE experiments on 3c and on isomer 7 which was formed cleanly in 83% yield by treatment of 3c with KO<u>t</u>-Bu/THF (0°C, 40 min) followed by 5% aqueous formic acid. Irradiation of the methyl resonances at 1.37 and 1.24 ppm in 3c (CDCl₃) resulted in approximately a 25% and 16% enhancement, respectively, of the C-9 hydrogen resonance at 2.88 ppm. Sequential irradiation of all of the methyl resonances in 7 failed to produce any significant enhancement of the C-9 hydrogen signal at 2.78 ppm. These observations are consistent with a β C-H bond at C-9 in 3c and an α C-H bond at C-9 in 7.

Titanium(IV) catalyzed reactions of 1 and 2b at atmospheric pressure follow a different path. Addition of 1 to the complex formed between quinone 2b and a 2:3 mixture of $Ti(0\underline{i}-Pr)_4$ and $TiCl_4$ at -20°C in CH_2Cl_2 gave dihydrobenzofuran 8 in 54% yield (Scheme I). The structure of 8 was verified by X-ray crystallographic analysis (Figure 2). Similarly, reaction of 1 and 2d in the presence of $TiCl_4$ at -78°C in CH_2Cl_2 produced 9 in 41% yield. A mechanistic rationale which accounts for the formation of 8 and 9 (Scheme I) involves alkylation of the Lewis acid-quinone complex by diene 1 to form zwitterionic intermediate 10 followed by loss of a proton and carbon-oxygen bond formation which affords 8/9 on hydrolytic workup.

Several aspects of the research described above are noteworthy. First, the syntheses of 3b and 3c demonstrate that the combination of high pressure and Lewis acid is effective in promoting particularly recalcitrant Diels-Alder reactions. In the synthesis of 3c, the quaternary centers at C-8 and C-10 are formed stereoselectively in a single step with the relative configuration found in most naturally occurring terpenes possessing the 4,4,8,10-tetramethylperhydrophenanthrene moiety. Thus, the method holds considerable promise as a general synthetic approach to many classes of terpenes. Finally, the preparation of 8 and 9 described herein represents a potentially versatile and regioselective formal 3+2 synthetic approach to the furan ring of highly substituted dihydrobenzofurans from quinones and alkenes. Further studies on this unique approach to dihydrobenzofurans are in progress.⁹



5 R=CH₃, R₁=OCH₃





Scheme I



2d R≂CH₃







9, R=CH₃



Figure 1. ORTEP diagram of 6.



Figure 2. ORTEP diagram of 8.

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- 4. All new compounds were characterized by 300 MHz ¹H NMR, 75.3 MHz ¹³C NMR, IR, UV and mass spectroscopy, including exact mass, on chromatographically homogeneous material.
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