Tetrahedron Letters,Vol.27,No.9,pp 1015-1018,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

AN EFFICIENT BENZOQUINONE BASED DIELS-ALDER APPROACH TO PODOCARPANE DITERPENES

Thomas A. Engler* and Sriram Naganathan

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Abstract: A short, convergent synthesis of (±)11,14-dimethoxypodocarpa-8,11,13-triene, **11**, is described based on successful high pressure and Lewis acid catalyzed Diels-Alder reactions for the construction of the 4,4,10-trimethyloctahydrophenanthrene ring system.

The podocarpane unit, **1**, is part of the basic carbocyclic framework of several classes of di-, sester-, and triterpenes.[1] Several methods for the preparation of this tricyclic network are known of which the most popular are successive Robinson annulation processes and biomimetic cation-olefin or cation-arene cyclization reactions.[2] This note reports a new, direct and highly versatile strategy for the construction of this ring system.

The method focuses on the 4+2 cycloaddition reaction of 1,4-benzoquinone, **2**, with 2,6,6-trimethyl-1-vinylcyclohexene, **3**, which is readily available in two steps from inexpensive β-ionone in ≥70% overall yield.[3] Diels-Alder reactions of the sterically hindered diene **3** with dimethyl acetylenedicarboxylate (DMAD)[3,4] and maleic anhydride[5] have been reported; however, the reproducibility of the latter reaction has been questioned.[3b] Methoxy- and pyrrolidino-derivatives of **3**, **4** and **5**, respectively, react with DMAD to give 4+2 cycloadducts **6**,[3b,6] but attempts to effect Diels-Alder reactions with other derivatives of **3** with various dienophiles have generally failed.[3] It was not apparent at the outset of this work that Diels-Alder reactions of **3** with dienophiles more sterically demanding than DMAD would succeed.[7]

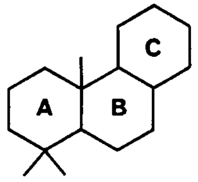
We now report that a Diels-Alder reaction of **2** and **3** can be effected under high pressure or by Lewis acid catalysis. Thus, a 1:2.8 mixture of **2** and **3**, respectively, in CH_2Cl_2 (0.76 M in **2**) subjected to 6 Kbar for 14 days affords, after silica gel chromatography (1:4 ethyl acetate:hexanes), *endo*-cyclohexendione **7** (32%, R_f 0.35, mp 92-93°C), hydroquinone **8** (16%, R_f 0.14, mp 174-176°Cd) and quinone **9** (14%, R_f 0.57, mp 81-82°C).[8] Identification of **7** as the *endo*-cycloadduct is based on its 300 MHz pmr spectrum which shows that H_1 is deshielded by the carbonyl oxygen at C-11 and appears as a ddd at 2.38 ppm. In **7**, large coupling constants to H_1 of 12 and 12 Hz (J_{gem} and $J_{\textit{trans}\text{-diaxial}}$) establish that H_1 occupies an axial position. Similar deshielding of C-1 protons in C-11 oxygenated diterpenes has been noted.[9] Dreiding models of the *exo*-4+2-cycloaddition adduct of **2** and **3** suggest that the C-11 oxygen would be too far from the C-1 axial hydrogen to have a noticeable effect on its chemical shift. A *cis* BC ring fusion is indicated by a $J_{H_8-H_9} = 5$ Hz.

Hydroquinone **8** apparently results from SiO_2 catalyzed enolization of **7**. In a separate experiment, **7** cleanly rearranges to **8** (84% isolated yield) upon treatment with a catalytic amount of aqueous HCl in THF. The source of quinone **9** may involve either a) a high pressure accelerated rearrangement of **7** to **8** which is then oxidized to **9** by **2**, or b) a high pressure promoted oxidation of **7** directly to **9** by **2**. In control experiments, addition of 1,4-benzoquinone to a solution of **8** in benzene effects complete conversion (tlc, pmr) to **9** with the formation of hydroquinone in ≤1 hr; no **9** is present in a CH_2Cl_2 solution of **7** and **2** open to the atmosphere for 4 hr.[10] Hydroquinone **8** is only slowly oxidized by oxygen and can be chromatographed and handled open to the atmosphere for more than a day without serious air oxidation, however, noticeable (tlc) amounts of **9** are present after 48 hr in solution. In addition, **9** is reduced to **8** in 97% yield with zinc dust in HOAc.

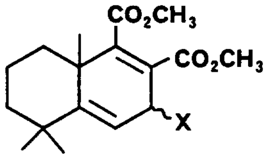
A more effective preparation of **7** is accomplished by a Lewis acid catalyzed cycloaddition reaction of **2** and **3**. Addition of diene **3** (1 equiv) to a solution of $SnCl_4$ (1 equiv) and 1,4-benzoquinone, **2** (3.4 equiv), in CH_2Cl_2 at -40°C and stirring for 3 hr followed by neutral quench (pH=7 buffer), extraction and chromatography on silica gel gives **7** in 69% yield as the only 1:1 cycloadduct. A 4:1 mixture of **7** and **9** is obtained in 69% yield with $BF_3 \cdot Et_2O$ as catalyst at 0°C in CH_2Cl_2 with a catalyst:quinone:diene ratio of 2:4:1. Efforts to obtain cycloaddition adducts from **2** and **3** without catalysis or high pressure produce **7**, **8**, and **9** in ≤10% combined yield after 12 hr at 120°C; at higher temperatures (140° or 160°C), extensive degradation occurs and complex reaction mixtures result.

Both **7** and **8** are methylated with NaO<u>t</u>-Bu/$(CH_3O)_2SO_2$/THF to give **10** (mp 103-104°C) in 65% and 78% yield, respectively, and **10** is hydrogenated in HOAc[11] (10% Pd/C, 50 psi, 12 hr) to afford **11** (84%, mp 133-134°C) with a <u>trans</u> AB ring juncture which is identical (300 MHz pmr, ms and tlc) to a sample of **11** prepared from natural podocarpic acid.[12] The ^1H nmr of the crude mixture from hydrogenation of **10** reveals the presence of a second minor product (≤8% yield) which we have tentatively identified as the <u>cis</u> isomer **12**;[13] the ratio of **11**:**12** is ≈11:1. Thus, the reaction of **2** and **3** to produce **7** and **8** should provide an expedient synthesis of podocarpa-8,11,13-triene derivatives having a <u>trans</u> AB ring fusion which is the most commonly naturally occuring configuration.[1,2a]

The chemistry presently described is notable in that 1) **10** and **11** are useful intermediates for the synthesis of diterpenes possessing ring B and/or C oxygenation,[14] especially at C-11[9a] where introduction of oxygen substituents at this carbon in previous strategies has been a difficult problem,[12] 2) **11** has also served as an intermediate in the preparation of labdane diterpenes and drimane sesquiterpenes, including the insect antifeedant warburganal, **13**, via oxidative cleavage of the C ring,[12a,15] and 3) the high pressure and Lewis acid promoted Diels-Alder reactions of **3** and 1,4-benzoquinone appear to be stereoselective; we have found no evidence for the formation of a second stereoisomer of **7**. We are currently investigating the reactions of **3** with other quinone dienophiles and the application of these reactions to the synthesis of diterpenes.

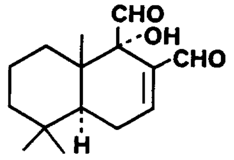


1

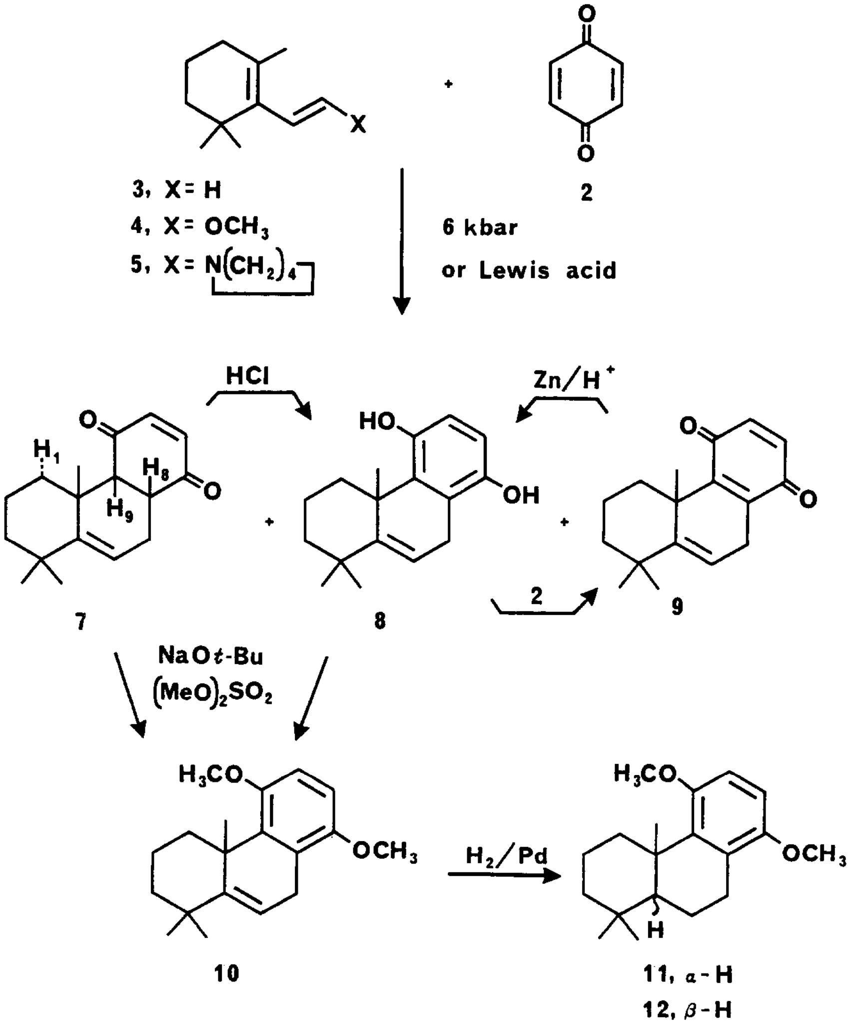


6, X= OCH_3

or $N(CH_2)_4$



13



Acknowledgements- We thank Professor Dale Boger and Daniel Yohannes for conducting some of the high pressure experiments, Professors Richard Givens, Robert Carlson and Albert Burgstahler for helpful discussions, Professor S.W. Pelletier for providing a sample of **11** for spectral comparison and Professor Dave Macomber for obtaining 400 MHz nmr spectra. This research was supported financially by the State of Kansas, the University of Kansas Graduate Research Fund and the Research Corporation.

References and Notes

1. T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring Compounds", Vol. 1, Academic Press: New York, 1972; pp. 185-186, 275 and 281-282.
2. (a) K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Noze, "Natural Products Chemistry", Vol. 1, Academic Press: New York, 1974; Chapter 4; (b) J.R. Hanson, "Terpenoids and Steroids - Specialist Periodical Report of the Royal Society of Chemistry", Vol. 1-12; The Royal Society of Chemistry: London, 1971-1983.
3. (a) S.V. Ley, D.M. Hollinshead, S.C. Howell, M. Mahon, N.M. Ratcliffe and P.A. Worthington J. Chem. Soc., Perkin I, **1983**, 1579; (b) J.H. Lallemand, M. Jalali-Naimi and D. Guillerm, Tetrahedron, **1983**, 39, 749.
4. (a) J.D. White and L.P.J. Burton, J. Org. Chem., **1985**, 50, 357; (b) S.P. Tanis and K. Nakanishi, J. Am. Chem. Soc., **1979**, 101, 4398 c) G. Brieger, Tetrahedron Lett., **1965**, 4429 and references cited in the above.
5. J.A. Campos and J.F. Garcia, Rev. Soc. Quim. Mex., **1975**, 19, 93.
6. R.L. Snowden, ibid, **1984**, 3835.
7. A recent report of a high pressure promoted hetero-Diels-Alder reaction of a complex derivative of **3** with diethylmesoxalate prompted us to report our results at this time in communication form, see J. Jurczak, W. Daniewski and E. Kubak, J. Org. Chem., **1985**, 50, 3963.
8. All new compounds were characterized by 300 MHz pmr, 75.3 MHz ^{13}C nmr, ir, uv and mass spectroscopy, including exact mass, on chromatographically homogeneous material.
9. (a) R.V. Stevens and G.S. Bisacchi, J. Org. Chem., **1982**, 47, 2396; (b) W. Nagata, T. Terasawa and K. Tori, J. Am. Chem. Soc, **1964**, 86, 3746.
10. Small amounts of **9** are apparent after 9 hr in a CH_2Cl_2 solution of **7** and **2** with silica gel present. Further experiments are in progress to firmly establish the origin of **9** and will be reported in a full paper.
11. For other examples of hydrogenation in acidic media of the 5,6-olefin unit in podocarpane diterpenes and related compounds to afford trans AB ring fusions , see (a) T. Matsumoto, S. Usui and T. Morimoto, Bull. Chem. Soc. Jpn., **1977**, 50, 1575; (b) Y. Tachibana, ibid., **1975**, 48, 298, and reference 3a.
12. (a) S.W. Pelletier, Y. Ohtsuka, Tetrahedron, **1977**, 33, 1021; (b) Y. Ohtsuka and A. Tahara, Chem. Pharm. Bull., **1978**, 26, 2007; (c) T. Matsumoto, Y. Ohsuga, S. Harada and K. Fukui, Bull. Chem. Soc. Jpn., **1977**, 50, 266, and references cited therein.
13. An unusually high field singlet at 0.67 ppm in the 300 MHz pmr of the crude reaction mixture is characteristic of an α C-4 methyl group in ring C aromatic podocarpane diterpenes with cis AB ring fusions due to shielding of this methyl group by the aromatic ring; see J.D. Martin, Tetrahedron, **1973**, 29, 2553 and reference 9b.
14. For examples, see (a) G.H. Eugster and P. Ruedi,Helv. Chim. Acta, **1984**, 67, 1523 and reference 12.
15. (a) H. Akita and T. Oishi, Chem. Pharm. Bull., **1981**, 29, 1580; (b) H. Akita, T. Oishi and A. Anazawa, ibid., **1981**, 29, 1588 and references cited therein.

(Received in USA 10 December 1985)