

Figure 1.

the catalytic activity of this Rh/Cu system. Such a broad range of chemoselectivity in hydrogenation reactions is remarkable.<sup>3-5</sup>

The functionalities that cannot be tolerated under the reaction conditions are (1) aryl iodides because they deactivate the catalyst toward reaction with an alkyne, (2) terminal alkynes which also deactivate the catalyst, (3) 1-(trimethylsilyl)-1-alkynes which do not reduce cleanly to the alkene, and (4) terminal alkenes or propargylic alcohols because they undergo regioisomerization.

Several reaction conditions were studied to see the effect of using silanes in the absence of water so that no silicon sol or gel formation would occur. When the triethoxysilane reaction was executed on 7-tetradecyne (1 mol % RhCl<sub>3</sub>, and 15 mol %  $Cu(NO_3)_2$  in THF) in the absence of water, approximately 50% of the alkyne was hydrosilylated and 35% was converted to 7-tetradecene (4.8:1 Z/E ratio) after 24 h. Then, addition of water to the reaction mixture caused protodesilylation of the alkenyltriethoxysilane to afford a total of 71% yield of 7-tetradecene (3.5:1 Z/Eratio). If we used triethylsilane in place of triethoxysilane (1 mol % RhCl<sub>3</sub>, and 15 mol %  $Cu(NO_3)_2$  in THF) in the absence of water, approximately 50% of the alkyne was hydrosilylated and 30% was converted to 7-tetradecene (3.8:1 Z/E ratio) after 24 h. Then, addition of water to the reaction mixture caused protodesilylation of the alkenvitriethylsilane to afford a total of 60% yield of 7-tetradecene (3.6:1 Z/E ratio). In the absence of triethoxysilane, a mixture of  $RhCl_3$  and  $Cu(NO_3)_2$  in THF and water does not respond as a hydrogenation catalyst with exogenous  $H_2$ ; thus, the silane is essential and the use of triethoxysilane under our standard reaction conditions proved to afford the highest yields and stereoselectivities.

We also screened other metal salts  $[Al(NO_3)_3, Ti(OEt)_4, Zr(OEt)_4, Zr(O)(NO_3)_2, Ni(NO_3)_2, Cu(OAc)_2, Cu(SO_4)_2]$ with RhCl<sub>3</sub> and noted that all of these metal salts dramatically changed the activity and the stereoselectivity of the reduction process; however, the RhCl<sub>3</sub>/Cu(NO<sub>3</sub>)<sub>2</sub> combination was optimal.

It is clear from powder X-ray diffraction (XRD) analysis of the xerogel (solvent free gel) that Cu(0) is present in the material. However, we were not able to detect any Rh(0)species even with more concentrated Rh samples; thus, we cannot presently determine whether this catalyst system is homo- or heterogeneous.<sup>5a,13</sup> A bimetallic system is indeed necessary since the reduction does not occur in the absence of either one of the two metals. Scanning electron micrographs (SEM) of the xerogel show only amorphous material. It was intriguing that while the Pd-containing xerogel<sup>1</sup> had an unusually large surface area (BET using  $N_2$  adsorption at 77 K) of 852 m<sup>2</sup>/g and a specific pore volume (N<sub>2</sub> pore volume filling) of 3.33 cc/g, the Rh/Cu material had a very small surface area of only  $2.8 \text{ m}^2/\text{g}$  and an undetectably low specific pore volume. Moreover, when resuspended in an aqueous THF solvent, the Rh/Cu xerogel was not an active hydrogenation catalyst in the presence of  $H_2$ .

Acknowledgment. This research was funded by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Department of the Navy, Office of the Chief of Naval Research, Young Investigator Award Program (1989–92), the National Science Foundation (RII-8922165, DMR-9158315, DMR-9101539), and generous industrial contributors to the NSF Presidential Young Investigator Award (1991–96) for J.M.T.: Hercules Incorporated, IBM Corporation, Ethyl Corporation, and the Shell Development Co. The SEM was purchased with a grant from the National Science Foundation (BIR-8805143). We thank Molecular Design Ltd. for the use of their synthetic database.

Supplementary Material Available: Detailed reduction procedures and spectroscopic data for the compounds listed in Table I (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

## Rearrangements of 4-Alkynyl-, 4-Alkenyl-, and 4-Alkyl-4-hydroxy-3-methylenecyclobutenes

John E. Ezcurra, Christine Pham, and Harold W. Moore\* Department of Chemistry, University of California, Irvine, California 92717 Received May 4, 1992 (Revised Manuscript Received June 21, 1992)

Summary: Reported here are the thermal rearrangements of the 4-alkynyl- (1), 4-alkenyl- (7), and 4-alkyl-4hydroxy-2-methyl-1-phenyl-3-benzylidenecyclobutene (11) to, respectively, the phenol 5, derived from the *p*quinonemethide 4, the benzylidenecyclohexenone 10, and the acyclic dienone 14.

Generation of quinonemethides from methylenecyclobutenes, as represented by the transformation of 1 to 4, is unprecedented. However, a number of related transformations have appeared that suggest this to be a reasonable process. For example, many simple acyclic (Z)-1,2,4-heptatrien-6-ynes (enynylallenes) have been shown to undergo facile cycloaromatization to produce products formally derived from  $\alpha$ ,3-dehydrotoluene biradical intermediates.<sup>1</sup> Similar allene and biradical intermediates are envisaged to be involved in the rearrangement presented here. Another related analogy is the facile ring

0022-3263/92/1957-4787\$03.00/0 © 1992 American Chemical Society

<sup>(13)</sup> For some work on distinguishing between heterogeneous and homogeneous reactions, see: (a) Crabtree, R. H.; Mellea, M. F.; Mihelcic, J. M.; Quirk, J. M. J. Am. Chem. Soc. 1982, 104, 107. (b) Lyon, D. K.; Finke, R. G. Inorg. Chem. 1990, 29, 1784, 1789.



expansion of 4-alkynyl-4-hydroxycyclobutenones to 1,4benzoquinones.<sup>2</sup> This reaction has also been explained in terms of cycloaromatization of an enynylketene to a biradical intermediate. Collapse of the biradical to the quinone would be akin to the quinonemethide-forming step.

Generation of the quinonemethide 4 was accomplished upon thermolysis of 1 (*E* isomer) in methanol (0.1 M) at 140-145 °C for 38 h (Scheme I). This is envisaged to involve electrocyclic ring opening of 1 to the corresponding (*Z*)-1,2,4-heptatrien-6-yne 2. Cycloaromatization to the biradical 3 followed by H atom migration then leads to the reactive *p*-quinonemethide 4 which was trapped by the solvent to give the phenol 5 (42%).<sup>3</sup>

Evidence for the biradical intermediate was obtained from a study of the thermolysis of a solution of 1 in 1,4cyclohexadiene (0.005 M) at 140 °C for 49 h. This resulted in the phenol 6 (65%), a product viewed as arising from H atom abstraction from the solvent by the biradical 3.

In previously reported and related studies 4-alkenyl(and aryl)-4-hydroxycyclobutenones were shown to rearrange to hydroquinones via the corresponding dienylketene intermediates.<sup>4</sup> More recently, a synthesis of 5methylene-1,3-cyclohexadienes (o-isotoluenes) from 1,2,4,6-heptatetraenes (dienylallenes) has appeared.<sup>5</sup> Thus, it was of interest to see if analogous dienylallenes could be generated from 4-alkenyl-4-hydroxy-3methylenecyclobutenes and if they too would lead to Scheme II



ring-closed carbocyclic products. To this end, the E isomer of 7 was subjected to thermolysis in refluxing p-xylene. After 30 min, the reaction was complete and a mixture of the E and Z isomers (1:2.2) of 4-benzylidene-3-methyl-2phenylcyclohex-2-en-1-one (10) was realized in 65-81%isolated yield (Scheme II). This transformation is envisaged to involve ring opening of 7 to the conjugated allene intermediate 8 which undergoes electrocyclic ring closure to 9 followed by tautomerization to the cyclohexenones 10. It is of interest that the product is isolated as the benzylidenecyclohexenone rather than the tautomeric phenol. Further studies are needed in order to reveal the generality of this unusual transformation.

Finally, it was observed that the E isomer of 11 gives 3(Z),5(E)-4-methyl-3,6-diphenylhexa-3,5-dien-2-one (14) in 38% isolated yield when subjected to thermolysis in refluxing *p*-xylene for 38 h. This product presumably arises from the penultimate conjugated allene precursor, 12, which suffers a 1,5-hydrogen shift (ene reaction) to give 13, the ultimate precursor to 14 (Scheme III).

The *E* stereochemistry of the 5-alkene moiety in 14 was disclosed by the coupling constant of the alkene protons (J = 16.2 Hz). The stereochemistry of the 3-alkene was not established but assigned as *Z* based upon the assumption that this site did not suffer stereochemical change during the thermolysis.

The required alkylidenecyclobutenes 1, 7, and 11 were synthesized from 3-methoxy-4-phenylcyclobutenedione (15) as outlined in Scheme IV.<sup>6</sup> As a representative case, 3-methoxy-4-phenylcyclobutenedione (15)<sup>7</sup> was converted to the 4-benzylidenecyclobutenones 16a and 16b (60–85%, 1:1.7 mixture of the *E* and *Z* isomers) upon treatment with the ylide derived from benzyltriphenylphosphonium chloride in anhydrous ether at ambient temperature.<sup>8,9</sup> These benzylidenecyclobutenones were further function-

Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. J. Org. Chem. 1992, 57, 794. Myers, A. G.; Proteau, P. J. J. Am. Chem. Soc. 1989, 111, 1146. Myers, A. G.; Kuo, E. Y.; Finney, N. S. J. Am. Chem. Soc. 1989, 111, 8057.
Myers, A. G.; Dragovich, P. S. J. Am. Chem. Soc. 1989, 111, 9130. Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. Tetrahedron Lett. 1989, 30, 4995.
Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. Tetrahedron Lett. 1990, 31, 2907. Fujiwara, K.; Kurisaki, A.; Hirama, M. Tetrahedron Lett. 1990, 31, 4329. Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. J. Am. Chem. Soc. 1989, 111, 4120. Nakatani, K.; Arai, K.; Hirayama, N.; Matsuda, F.; Terashima, S. Tetrahedron Lett. 1990, 31, 2323. Nicolaou, K. C.; Dai, W. M. Angew. Chem., Int. Ed. Engl. 1991, 30, 1387. Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. J. Am. Chem. Soc. 1920, 112, 7825.

Chem. Soc. 1990, 112, 7825.
(2) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.;
Patil, S.; Moore, H. W. J. Am. Chem. Soc. 1989, 111, 975. Xia, H.; Moore,
H. W. J. Am. Chem. Soc. 1992, submitted.

<sup>(3)</sup> The assigned structures of all new compounds are in agreement with their spectral and analytical data.

 <sup>(4)</sup> Perri, S. T.; Moore, H. W. J. Am. Chem. Soc. 1990, 112, 1897.
(5) Andemichael, Y. W.; Wang, K. K. J. Org. Chem. 1992, 57, 796.

<sup>(6)</sup> For the syntheses of related cyclobutenediones see the following selected references: Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. J. Org. Chem. 1988, 53, 2477. Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. J. Org. Chem. 1988, 53, 2482. Liebeskind, L. S.; Wang, J. Tetrahedron Lett. 1990, 31, 4293. Liebeskind, L. S.; Fengl, R. W. J. Org. Chem. 1990, 55, 5350. Liebeskind, L. S.; Wirtz, K. R. J. Org. Chem. 1990, 55, 5350. Xu, S.; Verxa, B. R.; Sullivan, R. W.; Moore, H. W. Tetrahedron Lett. 1991, 32, 1129.

<sup>(7)</sup> This was obtained in 80% overall yield upon treatment of 2,3-dimethoxycyclobutenedione (dimethyl squarate) with phenyllithium followed by trifluoroacetic anhydride.

<sup>(8)</sup> The product of ylide attack on the vinylogous ester carbonyl group to give the regioisomer of 16 was previously reported. This product (17%) was not detected in our reaction. Its reported spectral data (<sup>1</sup>H NMR and IR) are slightly different than those observed for either 16a or 16b. See: Knorr, H.; Ried, W.; Knorr, U.; Pustoslemsek, P.; Oremek, G. *Liebigs Ann. Chem.* 1977, 545. Ried, W.; Knorr, H.; Knorr, U. *Chem. Ber.* 1976, 109, 1506.

Communications



alized by addition of methyllithium (THF, -78 °C) followed by hydrolysis (trifluoroacetic anhydride) to produce a diastereomeric mixture (1.5:1) of 17 (75-91%). This mixture served as the precursors to the isomeric mixtures of 1 (43%), 7 (61-66%), and 11 (70%) upon addition of hexynyllithium, vinyllithium, and methyllithium, respectively. It was noticed that the Z isomers of 1, 7, and 11 were much less thermally stable than their E counterparts, and thus the E isomers were employed for the thermolysis studies reported here.

Scheme IV



In conclusion, the syntheses of 4-alkynyl-, 4-alkenyl- and 4-alkyl-4-hydroxybenzylidenecyclobutenes have been accomplished in an efficient manner starting from commercially available dimethyl squarate. These cyclobutenols undergo electrocyclic ring opening to conjugated allene intermediates which react further to give products arising from, respectively, biradical intermediates, electrocyclic ring closure and 1,5-hydrogen shifts. In view of the plethora of methods available for the synthesis of substituted cyclobutenediones, the ring expansions presented here represent potentially useful synthetic transformations.<sup>6</sup>

Acknowledgment. The authors thank the National Institutes of Health (GM-36312) for financial support of this work. We are also grateful to Catherine A. Moore for technical assistance in obtaining high resolution mass spectral data.

Supplementary Material Available: Experimental procedures and data for all compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

## A New Strategy for the Synthesis of Nucleoside Analogues Based on Enzyme-Catalyzed Aldol Reactions

Kevin K.-C. Liu and Chi-Huey Wong\*

Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037 Received March 17, 1992

Summary: A new synthetic approach to nucleoside analogs based on enzyme-catalyzed aldol condensations has been demonstrated in the synthesis of 6-adenyl-6-deoxy-Dfructose and 6-adenyl-6-deoxy-L-sorbose.

Nucleoside analogues with modifications at the carbohydrate or base portion have been used extensively as antibiotics and as biological probes.<sup>1-7</sup> Nucleosides are

## Scheme I OH 0: a) FDP aldolase :C HO R b) acid phosphatase OH OH R 1

traditionally synthesized by chemical methods.<sup>3</sup> Enzymatic synthesis of nucleosides based on nucleoside phos-

<sup>(9)</sup> The stereochemical assignments of 16a, 16b, and 17 are based upon the deshielding anisotropic effects of the carbonyl group on the vinyl proton in the E isomer (16a). The resonance of the vinyl proton in this isomer appears at 6.48 ppm while that of the Z isomer 16b came at 6.38 ppm. This downfield shift was also observed for the E isomer of 17. The assignments were confirmed by a 7% NOE enhancement of the vinyl proton of the Z isomer of 17 on irradiation of the methyl group. The stereochemistry of the respective isomers of 1, 7 and 11 was similarly established by NOE experiments.

<sup>(1)</sup> Suhadolnik, R. J. Nucleoside Antibiotics; J. Wiley: New York, 1970.

<sup>(2)</sup> Suhadolnik, R. J. Nucleoside as Biological Probes; J. Wiley: New York, 1979.

<sup>(3)</sup> Nucleoside Analogues; Chemistry, Biology and Medicinal Applications; Walk, R. T., DeClerq, E., Eckstein, F., Eds.; NATO Advanced Study Institute Series; Plenum: New York, 1979; Vol. 26.

<sup>(4) (</sup>a) Thiers, B. H. Dermatol. Clin. 1990, 8, 583-587. (b) O'Brien, J. J.; Campolir, D. M. Drugs 1989, 37, 233-309.

<sup>(5)</sup> Shimada, N.; Saito, S.; Hasegawa, S.; Takahashi, K.; Fuji, A.; Takita, T.; Seki, J.; Hoshino, H.; Nishiyama, Y.; Nagahata, T.; Matsubara, K. 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, CA 1988; Abstract 1008. (6) Norbeck, D.; Sparton, S.; Broder, S.; Mitsuya, H. Tetrahedron

Lett. 1989, 6263.