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ELECTROREDUCTIVE CYCLIZATION REACTIONS. STEREOSELECTION, CREATION OF QUATERNARY CENTERS IN BICYCLIC FRAMEWORKS, AND A FORMAL TOTAL SYNTHESIS OF QUADRONE.[1a]

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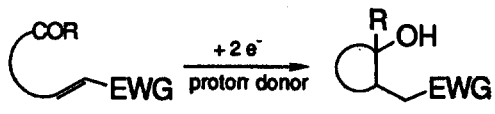
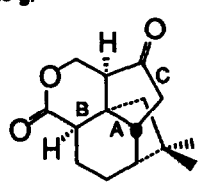
Abstract. The electroreductive cyclization reaction has been successfully applied to an efficient formal total synthesis of quadrone (1). Two of the four rings were created electrochemically, a third *via* a novel oxidative-decarboxylation and cyclization onto a remote nitrile functional group (22→24).

We are pleased to report that the electroreductive cyclization reaction has been successfully applied to a formal total synthesis of quadrone (1).[2] This reaction involves the electrochemical reduction of an alkene, activated by one or more electron withdrawing groups, and cyclization of the resulting radical anion onto an aldehyde or ketone tethered to the β-carbon of the alkene (eq 1).[3] We targeted the three sigma bonds labeled A, B, and C in the structure of quadrone (1) as strategic bonds, well-positioned for formation using redox chemistry. Highlights of the synthetic sequence include the stereoselective electroreductive cyclization of 6 to 7 and 8 (bond A), creation of the quaternary center and the bicyclo[3.2.1] ring system which is common to many natural products through the electroreductive conversion of 15 to 16 (bond B), and the oxidative-decarboxylation-cyclization of 22 to 24 which served to form bond C and create the third of the required four rings. Pragmatically, it is noteworthy that the electroreductive cyclization reactions were carried out routinely, reproducibly and in excellent yield on quantities ranging from 30 mg to 3.5 g.



(1)

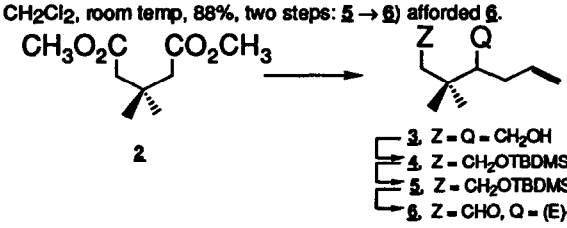
EWG = electron withdrawing group



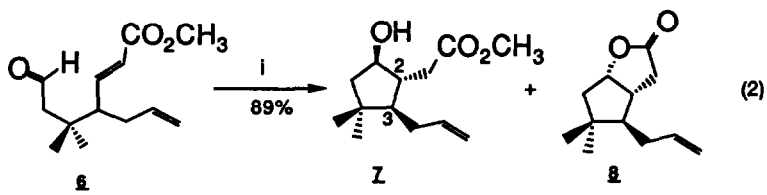
1, quadrone

Unsaturated ester 6 was prepared in a straightforward manner beginning with the allylation of dimethyl 3,3-dimethylglutarate (2) (LDA, THF, -78 °C; allyl bromide, THF room temp, 2 h, 85%). Reduction of the product (LAH, THF, 0°C, → 3, 96%), followed by selective monoprotection of the less hindered primary alcohol gave 4 (TBDMSiCl, imidazole, DMF, -30 °C, 96%); oxidation (PCC, CH_2Cl_2, room temp, 94%), Horner-Emmons-Wadsworth olefination

[$(MeO)_2POCH_2CO_2CH_3$, NaH, THF, 92%, two steps: 4 → 5)], desilylation (HF, CH_3CN, room temp), and a second oxidation (PCC, CH_2Cl_2, room temp, 88%, two steps: 5 → 6) afforded 6.

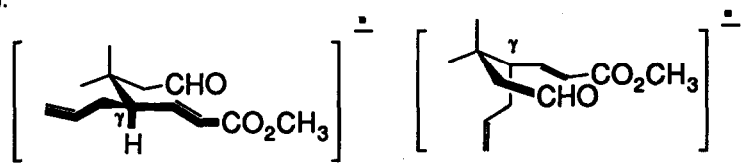


The electroreductive cyclization of 6 proceeded in excellent yield (89%; eq 2) to afford 7 and 8 and generate the first of the four rings of quadrone (1).



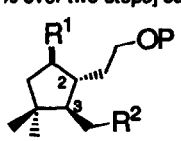
i, e- (Hg, SCE), $CH_2(CO_2CH_3)_2$, n-Bu_4NBr, CH_3CN

Of the four possible products, *only* those where the substituents located at C_2 and C_3 are *trans* to one another were produced. This stereoselectivity undoubtedly arises because of the preference for the allyl unit to occupy a pseudo-equatorial, rather than a pseudoaxial orientation in the transition state leading to ring formation. We intend to test the notion that any substituent located gamma to the electron withdrawing group would similarly lead to a stereocontrolled electroreductive cyclization, provided the substituent cannot function as a leaving group (gamma cleavage could occur prior to cyclization).



9 10

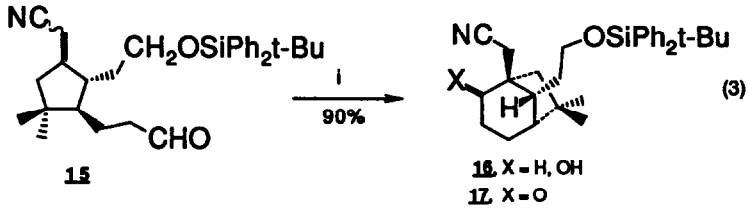
The lactone 8 and the γ-hydroxy ester 7 were reduced (LAH, THF, 0 °C, 7,8 → 11, 95%), the resulting diols, epimeric at C_1, were selectively monoprotected (TBDPSiCl, imidazole, CH_2Cl_2, 0 °C, 11 → 12, 96%), and the secondary alcohol oxidized (PCC, CH_2Cl_2, room temp, 12 → 13) to afford a single ketone. Horner-Emmons-Wadsworth olefination [$(EtO)_2POCH_2CN$, NaH, THF, room temp, 12 → 14, 76% over two steps] satisfactorily afforded an α,β-unsaturated nitrile;



7, 8 → 11, R^1 = H, OH, P = OH, R^2 = CH=CH_2
12, R^1 = H, OH, P = DPTBS, R^2 = CH=CH_2
13, R^1 = O, P = DPTBS, R^2 = CH=CH_2
14, R^1 = CHCN, P = DPTBS, R^2 = CH=CH_2
15, R^1 = CHCN, P = DPTBS, R^2 = CH_2CHO

surprisingly, the corresponding unsaturated ester could not be prepared in this manner.[4] The allyl appendage was elaborated next (9-BBN, THF, 0 °C to room temp; H_2O_2, NaOH 0 °C to room temp, then PCC, CH_2Cl_2, room temp, 14 → 15, 85%, two steps), setting the stage for formation of bond B (see 1) and the carbocyclic six-membered ring.

Electrochemically initiated cyclization of the nitrile-aldehyde 15 led in 90% yield to the requisite [3.2.1] framework 16 as well as a quaternary center bearing substituents suitable for elaboration. The mixture of diastereomeric alcohols was converted, *via* oxidation with PCC, to a single diastereomeric ketone 17. The result is of utility in conjunction with the present synthetic endeavor, and it significantly expands the scope of the electroreductive cyclization reaction.[3]

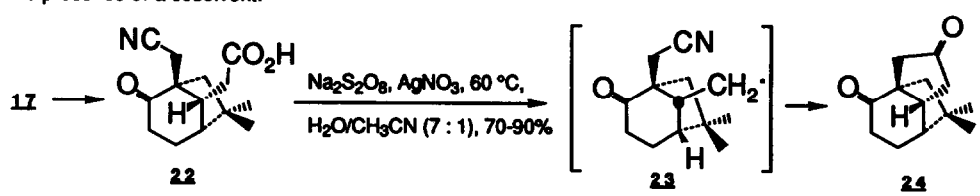


15 16, X = H, OH 17, X = O (3)

i, -2.4 V (Hg; SCE), $CH_2(CO_2CH_3)_2$, *n*-Bu_4NBr, CH_3CN, room temp

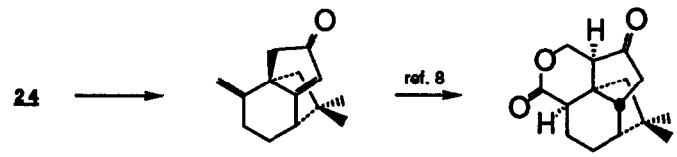
The steric demands placed upon the reaction (15 → 16) were relatively severe, considering the need to close onto the fully substituted β-carbon of the α,β-unsaturated unit. That it did not fail, suggests that the transition state for closure may occur prior to expression of the full steric requirements for bond formation.

Comparison of the material in hand (17) with the desired tricycle, 24, reveals the presence of an extra carbon. To set the stage for its removal, the silyl ether was cleaved (TBAF, THF, 0 °C, 92%), and the resulting primary alcohol was oxidized ($RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 1:1:1.5, 0 °C to room temp, 90%)[5] to a carboxylic acid 22. Treatment of 22 with sodium peroxydisulfate and silver nitrate, in a 7:1 mixture of water and acetonitrile as a cosolvent (60 °C), led to oxidative cleavage of the acid and generation of a radical; it closed onto the nitrile to afford an imine which was hydrolyzed *in situ* to provide diketone 24 in 70-90% yields. This reaction has received a reasonable amount of attention in the Soviet literature,[6] but to our knowledge, has not been widely used in synthesis. It is indeed a useful reaction, particularly when run in the presence of a cosolvent.[7]



22 23 24

The formal total synthesis was completed by converting diketone 24 to enone-olefin 25, a compound which Kende and coworkers previously converted to quadrone (1) in four steps.[2,8] Fortunately, it was possible to selectively form the enone in the five-, rather than the six-membered ring (LTMP, THF, -78 °C, 30 min) of 24, presumably because abstraction of a proton from the former was preferred kinetically. The enolate was trapped with PhSeCl (THF, -78 °C to room temp) and the resulting α-phenylseleno ketone converted to the corresponding enone with hydrogen peroxide (2.5 M H_2O_2, CH_2Cl_2, pyridine, 0 °C to room temp, 3 h, 93% based on recovered starting material). Methylenation ($Ph_3P{=}CH_2$, THF/hexanes, 0 °C, 5 min, 97%) provided our target structure 25, material whose spectral data nicely matched those reported for this compound by Kende.[2,8]



We believe that the success of this strategy argues effectively for the more widespread use of electrochemistry as a routine tool in organic synthesis.[9] The equipment necessary to conduct reactions electrochemically is commercially available and is modestly priced. The techniques are easy to learn, applicable to conducting reactions on a wide range of scales, and can be applied to the construction of reasonably complex molecules. Additional studies are underway in these laboratories to demonstrate and discover further, the virtues of this under-utilized methodology.

Acknowledgements. The authors are very grateful to the National Science Foundation for its support of our research. We also thank Professor Andrew Kende for a copy of the ^{1}H NMR spectrum of **25**.

References and Notes

1. (a) Dedicated to the memory of our colleague and friend, Manuel M. Baizer, whose pioneering spirit and zest for chemistry were an inspiration to all who knew him. (b) Taken, in part, from the Ph.D. Dissertation of Ronald L. Wolin, UCSB, 1988.

2. Recent and past synthetic efforts are summarized in: "Polyquinane Chemistry", Paquette, L. A. and Doherty, A. M., Eds., Springler-Verlag, New York, 1987, "Topics in Current Chemistry", Paquette, L. A., Ed., Springler-Verlag, New York, 1984. See also: (a) Magnus, P.; Principe, L. M.; Slater, M. *J. Org. Chem.*, **1987**, *52*, 1483; (b) Neary, A. P. and Parsons, P. J. *J. Chem. Soc, Chem. Commun.* **1989**, 1090 and (c) ref. 8, below.

3. (a) Little, R. D.; Nugent. S.; Baizer, M. M. *Tetrahedron Lett.*, **1982**, *23*, 1339. (b) Fox, D. P.; Little, R. D.; Baizer, M. M. *J. Org. Chem.*, **1985**, *50*, 2202. (c) Moëns, L.; Little, R. D.; Baizer, M. M. *J. Org. Chem.*, **1986**, *51*, 4497. (d) Little, R. D.; Fox, D. P.; Van Hijfte, L.; Dannecker, R.; Sowell, C. G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. *J. Org. Chem.*, **1988**, *53*, 2287.

4. The unsaturated ester was prepared using a Reformatsky reaction. Details can be found in reference 1b.

5. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

6. Ogibin, Y. N.; Troyanskii, E. I.; Nikishin, *Izvestiya, Akademii Nauk SSSR, Seriya Khimicheskaya*, **1975**, 1461. G. I. Nikishin, in "Organic Synthesis: Modern Trends", O. Chizhov, Ed., pp. 53-64, Blackwell Scientific Publications, Oxford, 1987.

7. We intend to explore the possibility of conducting this process electrochemically.

8. We are grateful to Professor Kende for Supplying us with this information. See: Kende, A. S.; Roth, B.; Sanfilippo, P. G. G.; Blacklock, T. J. *J. Am. Chem. Soc.*, **1982**, *104*, 5808.

9. (a) Gassman, P. G.; Lee, C. *Tetrahedron Lett.*, **1989**, *30*, 2175. (b) Becking, L. and Schäfer, H. J. *Tetrahedron Lett.* **1988**, *29*, 2801. (c) Stern, A. and Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763 and references therein. (d) Fry, A. J.; Susla, M.; Weltz, M. *J. Org. Chem.* **1987**, *52*, 2496. (e) Shizuri, Y.; Ohkubo, M.; Yamamura, S. *Chem. Lett.* **1989**, 113 and references therein.

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