HETEROCYCLES, Vol. 14, No. 10 1980

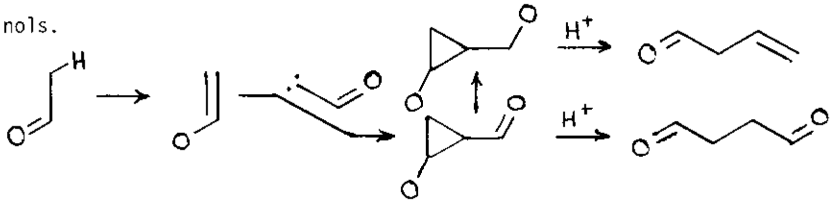
FURAN SYNTHESIS

Ernest Wenkert
Department of Chemistry, Rice University, Houston, Texas 77001, U.S.A.

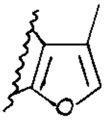
The use of dimethyl diazomalonate in copper-catalyzed cyclopropanations of enol ethers led to intermediates readily convertible into β-methylfuran, α-methylene-γ-lactone and β-methylene-γ-lactone units common among terpene structures and to a synthesis of menthofuran. The copper-induced interaction of enol ethers with ethyl diazopyruvate yielded oxydihydrofuroic esters from which α-furoic acids, furans and the common α-isopropylfuran terpene structure could be constructed. A similar reaction of diazopyruvic ester with acetylenes produced α-furoates directly. The Fétizon oxidation of β-oxycyclopropyl carbinols has been shown to give oxydihydrofurans, an observation on which another menthofuran synthesis was based. The copper-assisted decomposition of diazobiacetyl monoketal in n-butyl vinyl ether afforded a cyclopropane whose treatment with methanolic acid afforded veratrole. This unusual benzene ring construction was utilized in a new synthesis of hydrourushiol.

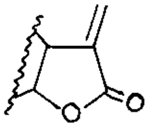
Oxygenated cyclopropanes have been used for some time as building blocks for terpene synthesis and one of several, generally applicable procedures has been that illustrated by scheme A.[1] Even though the 1,4-diketo products of the reaction sequence were utilized mostly for base-catalyzed cyclization and thence for the construction of cyclopentano-terpenes, it was understood that acid-induced transformation of the γ-diketo systems into furans could serve as the basis of future syntheses of furanoid terpenes. This possible reaction path has not been pursued, but furans have emanated from new chemistry of the α-diazocarbonyl reagents involved in the cyclopropanation (represented by the acylcarbene in scheme A) and of the intermediate β-oxycyclopropyl carbinols.

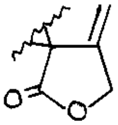
(A)

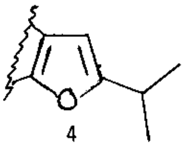


Whereas heretofore the cyclopropanation step had involved thermal, copper-assisted decompositions of exclusively diazoacetic ester or diazomethyl ketones[1], it now was decided to broaden the scope of the reaction by the imposition of an extra keto unit on the diazocarbon or the carbonyl group of the α-diazoketo reagent. Hence the chemistry of dimethyl diazomalonate (I), ethyl diazopyruvate (II) and diazobiacetyl or its equivalent (III) came under scrutiny and the furano-terpene types 1-4 became goals of synthesis.


1

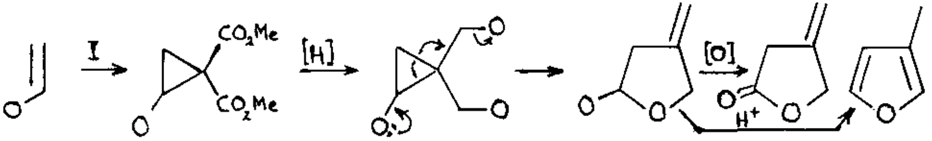

2


3


4

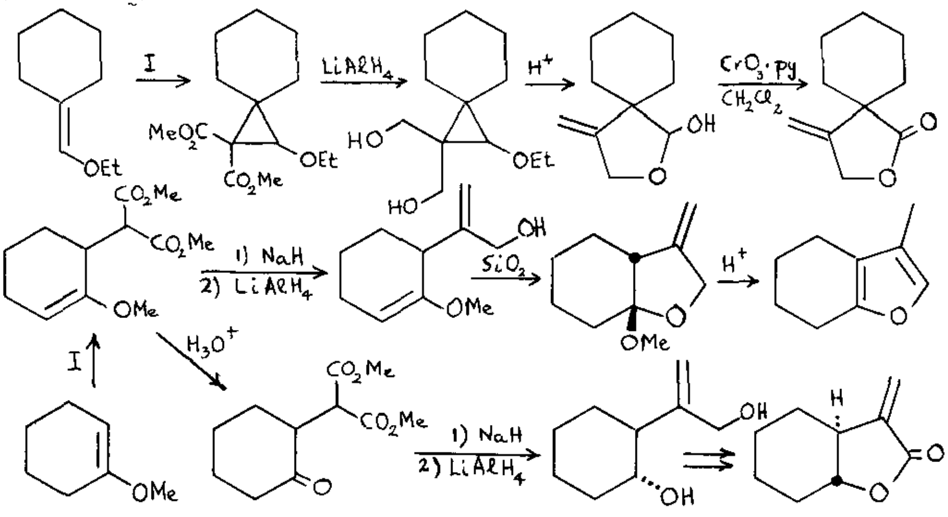
The following hypothetical synthesis route (scheme B) suggested that diazomalonic ester was suited ideally for the construction of two of the desired furano-terpene species.

(B)



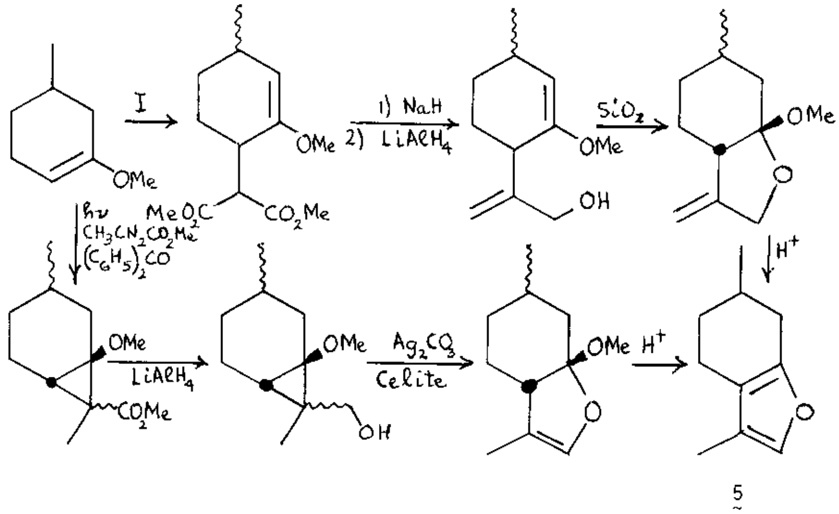
As scheme C[2] illustrates, the synthesis of a β-methylene-γ-lactone (3) from an aldehyde enol ether followed prediction, but the interaction of diazomalonic ester with a ketone enol ether failed to yield a cyclopropane, producing an olefin isomer instead. Nevertheless the general concept of a β-methylfuran (1) synthesis was preserved, when it was recognized that reduction of the olefinic malonic ester intermediate by the Dreiding-Marshall conversion of β-dicarbonyl compounds into allyl alcohols[3] would yield a substance in the same oxidation level as the desired β-oxycyclopropyl dicarbinol. Finally, the reaction scheme permitted also the construction of an α-methylene-γ-lactone (2).

(C)



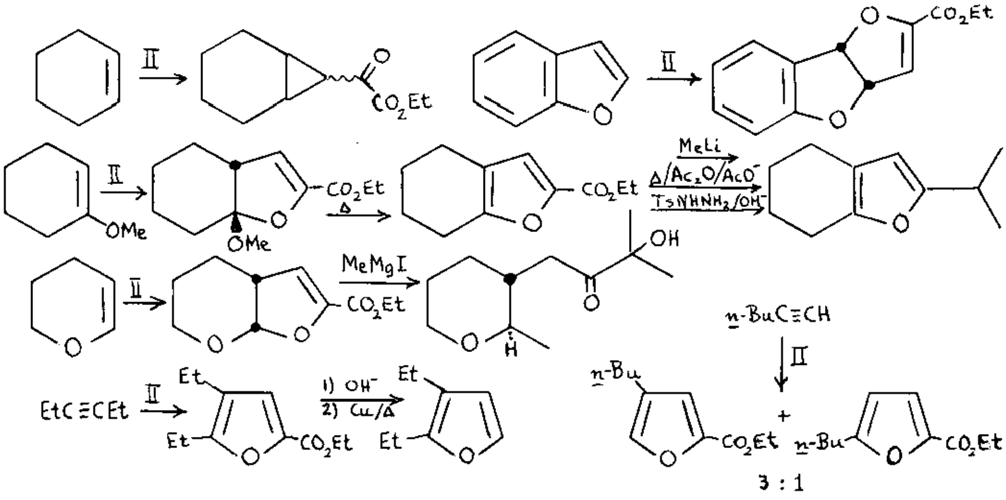
Scheme D depicts a synthesis of menthofuran (5) along lines of the above general β-methylfuran formation and an alternate procedure incorporating a new method of transformation of β-oxycyclopropyl carbinols into oxydihydrofurans (vide infra)[2].

(D)



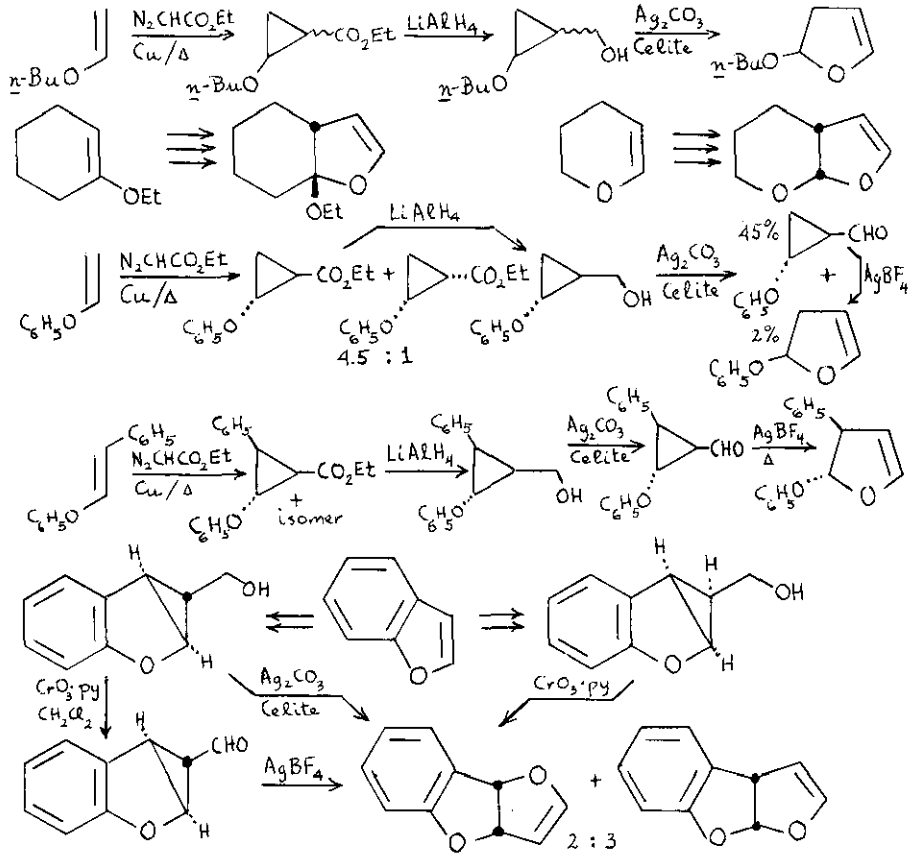
The interaction of ethyl diazopyruvate (II) with cyclohexene in a copper-catalyzed thermolysis yielded the expected cyclopropyl ketoester.[4,5] Contrastingly, reactions of the diazo compound with enol ethers led to dihydrofuroic esters (scheme E[4]). On exposure to polarized olefins the intermediate acylcarbenoid species thus behaved as a dipolarophile. Since the adduct (in the 1-methoxycyclohexene case) could be induced to eliminate alcohol, a two-step synthesis of α-furoic esters was on hand. The scheme became a one-step procedure on the replacement of the enol ethers by acetylenes. Simple manipulations on the carboethoxy group substituted it by an isopropyl function, thus completing the synthesis of the fourth type (4) of furano-terpenes, and by a hydrogen, hence making the reaction scheme a short furan synthesis.

(E)

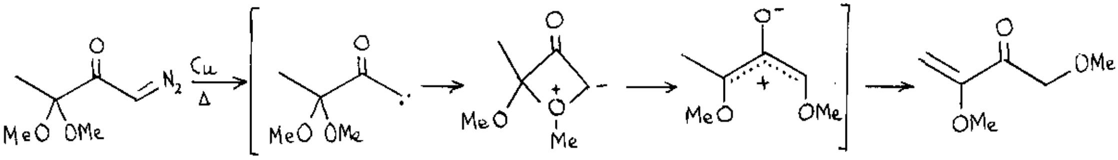


An early attempt to prepare a β-oxycyclopropyl carboxaldehyde by the Fétizon oxidation of a precursor alcohol led unexpectedly to a dihydrofuran isomer. Since elimination of alcohol from the latter would liberate a furan, thus producing yet one more facile furan synthesis, the generality of the oxidation result was investigated. As scheme F[4] suggests, the reaction appeared universal for all carbinols whose β-oxy units were reasonable electron donors. The study showed further, that β-oxycyclopropyl carboxaldehydes could be isomerized into oxydihydrofurans under silver ion catalysis, a reaction which, however, differed in rate and product yield from the Fétizon oxidation process.

(F)

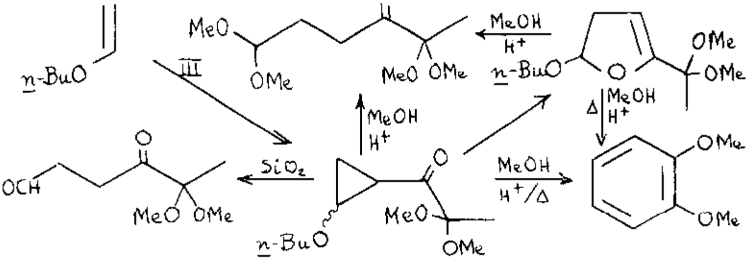


Diazobiacetyl proved to be an elusive reagent in view of the difficulty associated with preventing decarbonylation during the conversion of pyruvic acid into its acid chloride and the complex reaction behavior of the latter toward diazomethane.[6] As a consequence a masked form of diazobiacetyl was chosen as the starting material for the next series of reactions. It was prepared by exposure of biacetyl dimethyl ketal[7] to the Yates-Regitz method of diazo group transfer,[8] i.e. base-induced ketone formylation followed by treatment of the resultant β-ketoaldehyde monoenolate with tosyl azide. Whereas 1-diazo-3,3-dimethoxy-2-butanone (III) proved to be on the borderline of stability under the desired cyclopropanation reaction conditions, as revealed by its copper-catalyzed conversion into 1,3-dimethoxy-3-buten-2-one, it could be used in a subsequent cyclopropanation.



Copper-induced decomposition of the new diazo compound (III) in n-butyl vinyl ether yielded a cyclopropyl ketone, which isomerized into a dihydrofuran on being kept at ambient temperature or exposed to acid or the copper catalyst. Hydrolysis of the ketone yielded a diketoaldehyde monoketal, while methanolysis of the ketone or its isomer at ambient temperature afforded a diketoaldehyde acetal ketal. However, acid-catalyzed methanolysis at higher temperature led to the formation of veratrole (scheme G [4]).

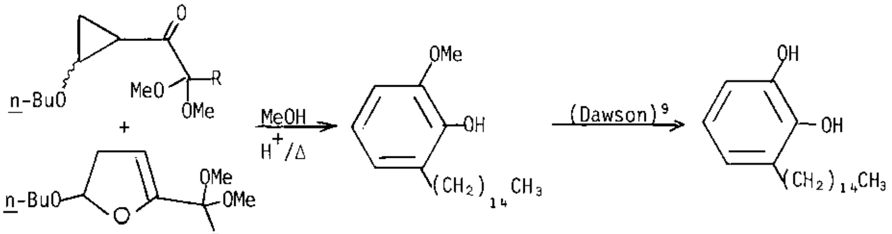
(G)



This most unusual construction of a vicinally oxygenated benzene ring was utilized in the synthesis of hydrourushiol (3-pentadecylcatechol),[9] one of the dermatologically active constituents of poison ivy. Scheme H delineates the preparation of the natural substance from another one, — stearic acid.[4]

$$RCH_2CO_2H \xrightarrow[Br_2]{PBr_3} \xrightarrow{H_2O} RCHBrCO_2H \xrightarrow[\Delta]{OH^-} \xrightarrow{CH_2N_2} \xrightarrow[HOAc]{CrO_3} RCOCO_2Me \xrightarrow[MeOH/H^+]{HC(OMe)_3}$$

$$RC(OMe)_2CO_2Me \xrightarrow{MeLi} RC(OMe)_2COMe \xrightarrow[EtO^-]{HCO_2Et} \xrightarrow{TsN_3} RC(OMe)_2COCHN_2 \xrightarrow[Cu/\Delta]{n\text{-}BuOCH=CH_2}$$



R = n-$C_{16}H_{33}$

Acknowledgment. E. W. acknowledges gratefully the devoted research efforts of his collaborators, cited in the references, and partial support by the Robert A. Welch Foundation.

References and Notes

1. E. Wenkert, *Acct. Chem. Res.*, 1980, **13**, 27.
2. E. Wenkert, M. E. Alonso, B. L. Buckwalter, and K. J. Chou, *J. Am. Chem. Soc.*, 1977, **99**, 4778.
3. J. A. Marshall, N. H. Anderson, and A. R. Hochstettler, *J. Org. Chem.*, 1967, **32**, 113, and references cited therein.
4. E. Wenkert and M. E. Alonso, unpublished observations; M. E. Alonso, Ph.D. dissertation, Indiana University, 1974.
5. *Cf.* also S. Bien and Y. Segal, *J. Org. Chem.*, 1977, **42**, 1685.
6. E. Wenkert and P. D. Woodgate, unpublished observations.
7. E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 1953, 3131.
8. M. Regitz and R. Meinz, *Chem. Ber.*, 1968, **101**, 2622 and references cited therein.
9. P. J. Vithayathil and C. R. Dawson, *J. Org. Chem.*, 1958, **23**, 1443.