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1,4-DIENE AND 1,4-ENYNE SYNTHESIS VIA DICHLORONORCARENOL CLEAVAGE. SYNTHESIS OF CREPENYNIC ACID.

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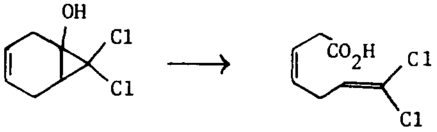
1,4-Diene and 1,4-enyne containing chains are exhibited in a wide variety of natural structures including fatty acids, insect pheremones and abnormal acyclic terpenes. Recently, the synthesis of such unsaturated systems has elicted considerable attention.[1] We wish to disclose a new route to these unsaturated chains which possesses preparative specificity in olefin geometry and flexibility in 1,4-diene or 1,4-enyne generation.

The procedure employs ring fragmentation of dichloronorcarenols[14] to produce acyclic olefins of Z-configuration. Thus, cleavage of 7,7-dichloro-1-noraren-3-enol 1 with lead (IV) acetate[12] generated the ring opened dienic carboxylic acid 2 (85%) in a fashion analogous to the work of Rubotton and co-workers[3] in less functionalized cyclopropanol systems.[13]



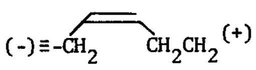
1 2

The norcarenol ring cleavage appears to be general (Table 1). Substrates with alkyl substitution on the dichloronorcarenol skeleton produce tri-substituted olefins of specific Z-configuration (4 and 6) and tetra-substituted olefins having predominant Z-configuration 8. In addition, the norcaranol oxides (10 and 12) undergo smooth conversion to the ring opened olefinic carboxylic acids (11 and 13).

In the cleavage of tetrasubstituted olefinic norcarenol 7, the unexpected formation of E-olefinic carboxylic acid 9 was observed, although the olefin isomer ratio (E/Z + E) was variable (5-23% E) for different runs under (ostensibly) identical conditions. However, the agent responsible for isomerization could not be readily determined, since the separate isomers 8 and 9 maintained geometric integrity under the reaction conditions containing lead (IV) acetate or lead (II) acetate $[Pb(OAc)_2\cdot 3H_2O]$ or their combination in acetic acid for at least two reaction periods.

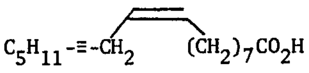
This lead (IV mediated dichloronorcarenol cleavage generates a 3,6-dienic carboxylic acid which possesses considerable synthetic versatility and potential. The preparation of homoallylically oxygenated Z-di- and Z-trisubstituted olefins is noteworthy.[4] Although numerous natural products incorporate Z-olefinic systems with homoallylic oxygenation, most substituted olefin synthesis produce predominantly E-isomers.[5] In addition, the structural diversity available via transformation of the 1,1-dichloro olefin moiety greatly expands the synthetic potential of these intermediates. Routine manipulation of the 2-substituted-1,1-dichloro olefin can afford terminal (or disubstituted) acetylene[6], 2-substituted-1-chloroalkyne,[6a] -1-chloro olefin[7] and -1,1-dimethyl olefin (isopropenyl) structures.[8] Finally, since phenols are the synthetic precursors of the dienic carboxylic acids (four steps)[14], through appropriate phenol substitution or functionalization a wide diversity in dienic acid progeny are available.

Using this cleavage transform for the preparation of a novel, central synthon 14, we have synthesized crepenynic acid 15, a key intermediate in plant and fungal biosynthesis of polyacetylenic fatty acids.[9] The synthetic route is outlined below (Scheme 1). Salient features of the synthesis include generation of the alcohol-protected lithium acetylide from the alcohol-protected dichloroolefin and in situ alkylation with pentyl bromide (eg. 16c → 16d).[6a] The corresponding dilithium alkoxide acetylide generated upon alkyl lithium treatment (3.3 equivalents) of the parent alcohol 17 competitively alkylated the alkoxide function (relative to the acetylide moiety) both in the presence and absence of HMPA. In addition, for the conversion of 18 to 19 dilithium tetrachloro cuprate[10] is the copper species most effective in catalysis of tosylate displacement relative to tosylate S-O bond scission (67%/25%) by the Grignard reagent.[15]



$(-)\equiv\text{-}CH_2\quad CH_2CH_2^{(+)}$

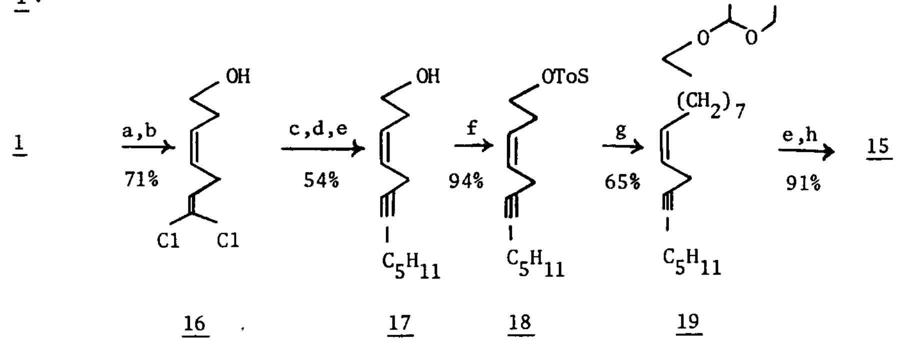
14



$C_5H_{11}\text{-}\equiv\text{-}CH_2\quad (CH_2)_7CO_2H$

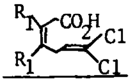
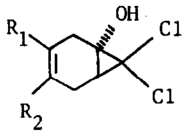
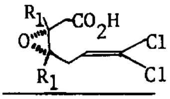
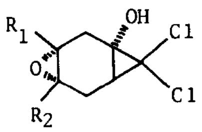
15

Scheme 1^{i}:



Reagents: a) AcOH/Pb$(OAc)_4$; b) Dibal-H, THF; R. T.; c) ethyl vinyl ether, HCl, 0°; d) THF, n-BuLi, -70° then C_5H_{11}-Br, HMPA; e) MeOH/H_2O/HCl; f) TsCl, pyr; g) THF, ClMg-$(CH_2)_6$OEVE, Li_2CuCl_4; h) Jones reagent, acetone; i) Yields refer to the isolated intermediates shown.

Table 1^{11}

		Substitution	Product 	Isolated Yield
	1	$R_1=R_2=H$	2	85%
	3	$R_1=H, R_2=$i-Pro	4	79%
	5	$R_1=$i-Pro, $R_2=H$	6	65%
	7	$R_1=R_2=Me$	8	72%
			9=(E-8)	12%
				
	10	$R_1=$i-Pro, $R_2=H$	11	59%
	12	$R_1=H$, $R_2=$i-Pro	13	69%

References

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4. Stereoselective olefin synthesis. Reviews: D. J. Faulkner, Synthesis, 175 (1971); J. Rencroft and P. G. Sammes, Quart. Rev. Chem. Soc., 25, 135 (1971).
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9. J. Bu'Lock and G. N. Smith, J. Chem. Soc. C., 332 (1967).
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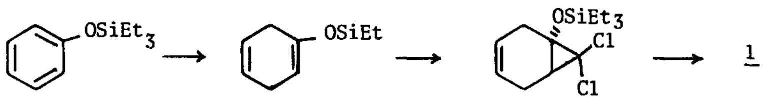
11. All compounds have ir, NMR and mass spectral properties consistent with the proposed structures. All products and intermediates listed (except 11, 13 and 19) have acceptable C and H analysis (±0.3% of theoretical).
12. These cleavage reactions were performed according to the procedure of Rubottom et al.[3] The only notable difference is a pronounced exotherm upon substrate alcohol addition and a shorter reaction period (always <2.5 hours).
13. For a related cleavage of 1-alkoxy-dichloronorcaranols via anodic oxidation see: M. Klehr and H. J. Shäfer, Ang. Chem. Int. Ed., 14, 247 (1975).
14. Dichloronorcarenols (e.g. 1, 3, 5, 7) are available in good yield via the sequence illustrated below:[2]



15. We wish to acknowledge the University Research Council of Vanderbilt University for support of this work and Professor D. F. Taber for his informative comments.

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