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BOROHYDRIDE INDUCED CLEAVAGE OF AZO DERIVATIVES OF β-KETOESTERS. A USEFUL VARIANT OF THE JAPP-KLINGEMANN REACTION FOR C-NUCLEOSIDE SYNTHESIS.

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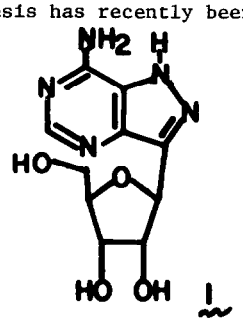
The C-nucleosides, a group of molecules containing ribose bound to the carbon atom of a heterocyclic aglycone, exhibit significant antibacterial, antiviral and antitumor activity.[1] Our efforts to develop new routes to members of this group, such as the pyrazolopyrimidine nucleoside formycin (1), without recourse to natural ribose are based on the oxabicycloheptanone 2, an intermediate whose synthesis has recently been disclosed.[2]



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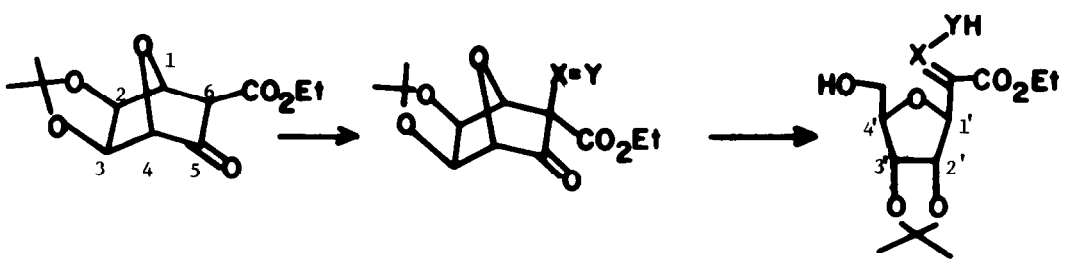
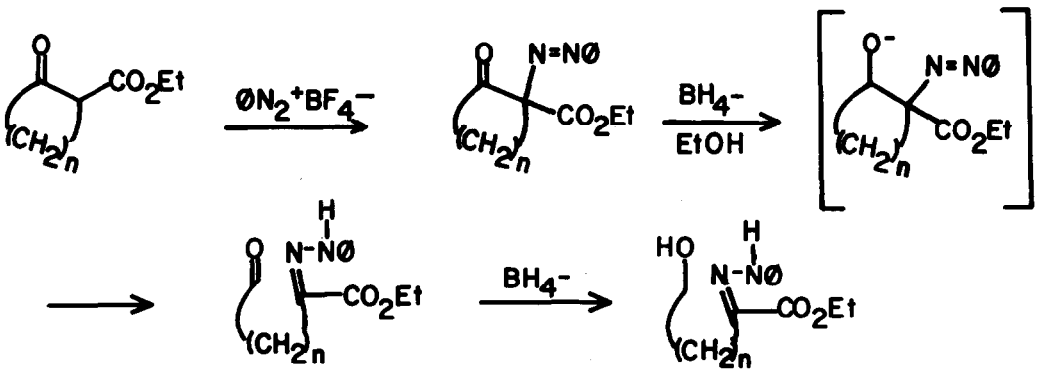
The transformation of 2 to a suitably functionalized derivative 3, followed by a hydride promoted scission of the C(5)-C(6) bond was envisioned to yield a tetrasubstituted tetrahydrofuran 4. Such a reduction-cleavage process, if available, would permit the direct obtention of the requisite C-4' hydroxymethyl group as well as insure the stereochemical integrity of the product. The appropriate choice of the elements X and Y would also facilitate elaboration of the C-1' appendage to heterocycle.



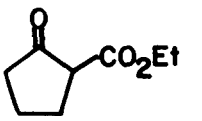
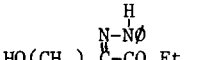
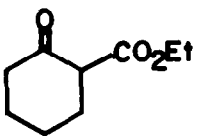
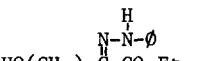
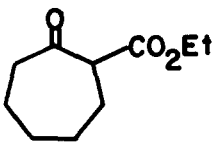
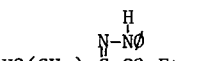
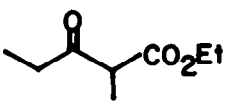
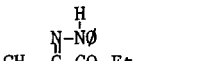
2 3 4

In pursuit of a general method for the reduction-cleavage reaction of substituted β-ketoesters we were led to investigate a novel variant of the Japp-Klingemann reaction. The relatively unstable azo compounds generated from substituted β-ketoesters have previously been shown to undergo cleavage by nucleophiles such as ethanol, phenol, aniline, etc. to yield hydrazones of α-ketoesters.[3] The relative ease with which these fragmentation reactions proceed suggested that borohydride should likewise promote such reactions to furnish the corresponding alcohols as depicted in the following scheme.



This concept was tested on several cyclic β-ketoesters and one acyclic example. The phenylazo derivative was conveniently generated from the active methinyl compound by reaction with freshly prepared benzenediazonium fluoroborate[4] in a mixture of pyridine and water. Further purification of this intermediate was accomplished by silica gel chromatography (20% ethyl acetate-hexane). The azo compound was then dissolved in absolute ethanol and treated at room temperature with 2.2 equivalents of $NaBH_4$. After a period of 10-20 min, the reaction mixture was quenched with 5% HCl, a saturated solution of sodium chloride added, and the product extracted with ether. The yellow oil obtained was chromatographed on silica gel (20% ethyl acetate-hexane) to afford the desired phenylhydrazone in good yield (Table).

Table. Borohydride Cleavage of Azo Derivatives

β-Ketoester [a]	Product [b]	Yield [c]
 [d]		62
		97
		88
		96

a. The β-ketoesters were prepared by the method of A. P. Krapcho, J. Diamanti, C. Cayen and R. Bingham, Org. Syn., 47, 20 (1967).

b. Isolated as a mixture of the syn and anti isomers. Satisfactory spectral and physical data were obtained for all new compounds.

c. These represent optimized values.

d. The corresponding azo compound was found to readily decompose on attempted chromatography and is therefore best used without further purification.

Finally, the application of this methodology to the oxabicycloheptanone 2 was carried out. The α-phenylazo compound 3 (X=Y = N=NØ) was prepared by sequential treatment of 2 with lithium diisopropyamide and benzenediazonium fluoroborate.[5] The borohydride cleavage proceeded in good yield to afford the highly functionalized C-β-ribofuranosyl derivative 4.

The reduction-cleavage process has important implications for synthesis design, and studies are currently underway to examine other functional groups (e.g., -N=O;  ; ) useful for the conversion of 2 to modified C-nucleosides.

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4. D. T. Flood, Org. Syn., Coll. Vol., 2, 295 (1943).

5. Generation of this azo compound by use of pyridine and water as in the previous examples was precluded, for 2 underwent facile cleavage to afford the corresponding acid-ester.