Experimental Section

The ^1H NMR spectra were obtained on a Varian T-60 spectrometer using tetramethylsilane as an internal standard in deuteriochloroform. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Optical rotations were taken in ethanol using an ETL-NPL 143A automatic polarimeter. Elemental analysis was performed by Atlantic Microlab, Inc. Melting points were determined on a Fisher-Johns block and are uncorrected.

(+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane (1). To a 1000-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 250 mL of anhydrous ether and 12.6 g (0.33 mol) of lithium aluminum hydride. To this stirred mixture was added, dropwise, 20.0 g (0.10 mol) of (+)-camphoric acid in 300 mL of anhydrous THF. After the addition was completed, the reaction was refluxed for 4 h. Then, the reaction was cooled to room temperature and quenched by the dropwise addition of 12 mL of water, followed by 12 mL of 15% aqueous sodium hydroxide, and finally by 35 mL of water. The precipitate was filtered and washed with copious amounts of THF. The filtrate was dried quickly over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford 14.2 g (83%) of 1, mp 128–131 °C. An analytical sample was prepared by sublimation (70 °C, 0.1 torr): mp 133–134 °C; $[\alpha]^{25}_D$ + 60.8 (*c* 2.5, EtOH); IR (KBr) 3300, 1050, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, s), 1.00 (6 H, s), 1.25–2.10 (7 H, m), 3.20–3.75 (4 H, m). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 69.70; H, 11.70.

General Procedures for Acetophenone Reductions. To a 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 1.00 g (0.025 mol) of lithium aluminum hydride and 100 mL of anhydrous ether. To this stirred solution was added, dropwise, 4.3 g (0.025 mol) of 1 in 40 mL of THF. The reaction was heated to reflux for 1 h after the addition of 1 had been completed. Then, 0.025 mol of achiral alcohol (Table I) in 20 mL of ether was added, dropwise, to the reaction and heated to reflux for another 1.5 h. The reaction was then cooled to room temperature and 3.0 g (0.025 mol) of acetophenone in 20 mL of ether was added, dropwise. After 2 h of additional reflux, the reaction was cooled to room temperature and quenched by the dropwise addition of 1 mL of water, followed by 1 mL of 15% aqueous sodium hydroxide, and finally by 3 mL of water. The precipitate was filtered and washed with 25 mL of ether. The filtrate was dried quickly over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant residue was then purified as previously described.[2]

Acknowledgment. The authors would like to thank Professor R. N. McDonald for helpful discussions.

Registry No.—1, 68510-42-9; (+)-camphoric acid, 124-83-4; acetophenone, 98-86-2; lithium aluminum hydride, 16853-85-3.

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(6) Many of the chiral alcohols used in the literature contain amino and ether functions in addition to the hydroxy function(s). These have an apparent effect upon the reduction as well and their presence in this study would cloud the effects which this study is attempting to measure. For a dramatization of these secondary effects see ref 2 and references contained therein.
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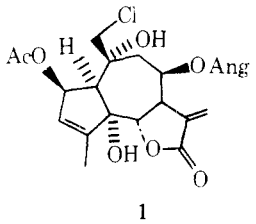
Communications

Three-Carbon Annelations. New Routes to the Nazarov Cyclization via Protected Cyanohydrins

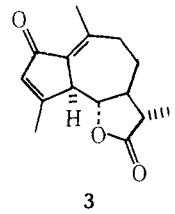
Summary: α'-Hydroxy vinyl ketones, prepared by the addition of anions of protected cyanohydrins to ketones, provide a useful entry to cyclopentenone annelation via the Nazarov cyclization.

Sir: We are currently investigating the synthesis of a number of sesquiterpene lactones which have been shown to possess cytotoxic, antitumor, and antifungal activity, e.g. eupachlorin acetate[1] (1), deacetylmatricarin[2] (2), and deacetoxymatricarin[3] (3). We envision a three-carbon annelation of a suitably functionalized cycloheptanone to obtain this end.

There are many interesting and elegant approaches to the formation of the cyclopentane ring; however, only a small fraction of these can be applied to schemes requiring a cyclopentane annelation.[4] The Nazarov cyclization,[5] despite potential utility, has found little use in this field. Ready availability of 3-keto-1,4-dienes or their equivalent would present a useful method for the annelative construction of the ring system we desire. We are pleased to report our initial findings hold promise as a general method for cyclopentenone annelation.



1



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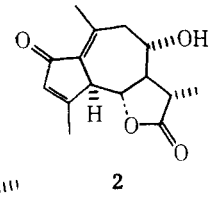
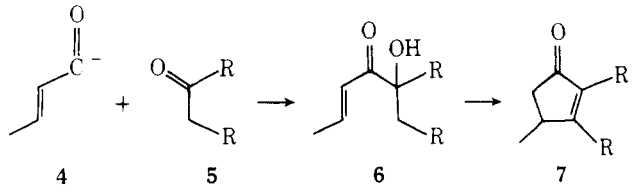


2

Our strategy to the cyclopentenones centers on the dehydration and subsequent Nazarov cyclization of α'-hydroxy enones such as 6. These are prepared by the addition of an acyl anion equivalent of crotonaldehyde 4 to the carbonyl compound 5, on which the annelation will take place.



4 5 6 7

We have found the use of the ethyl vinyl ether protected cyanohydrin[6] **8a** or the trimethylsilyl protected cyanohydrin[7] **8b** of crotonaldehyde to be effective acyl anion equivalents. Reaction of **8a** or **8b** with ketones proceeds as shown in Scheme I. Addition takes place exclusively at the α carbon[8] to give addition products of type **10** as is illustrated for cyclohexanone.

The Me_3SiCN adduct of crotonaldehyde is especially interesting in that intramolecular transfer of the trimethylsilyl group occurs with concomitant loss of cyanide, giving rise to addition products such as **12b** directly.[7a] The ethyl vinyl ether protected addition product, **10a**, requires acidic hydrolysis followed by treatment with base in order to unmask the requisite α-hydroxy enone **12c**.

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Table I

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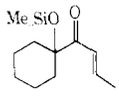
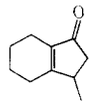
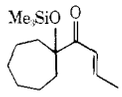
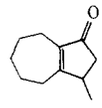
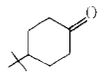
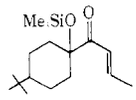
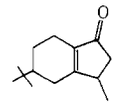
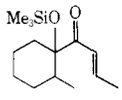
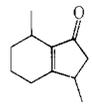
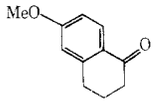
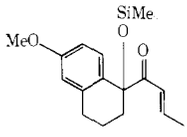
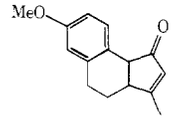
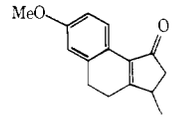
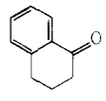
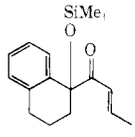
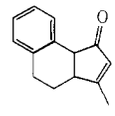
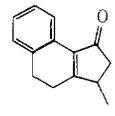
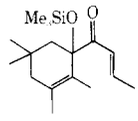
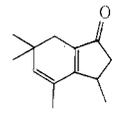
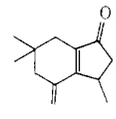
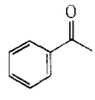
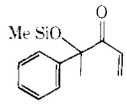
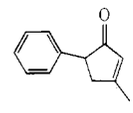
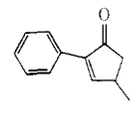
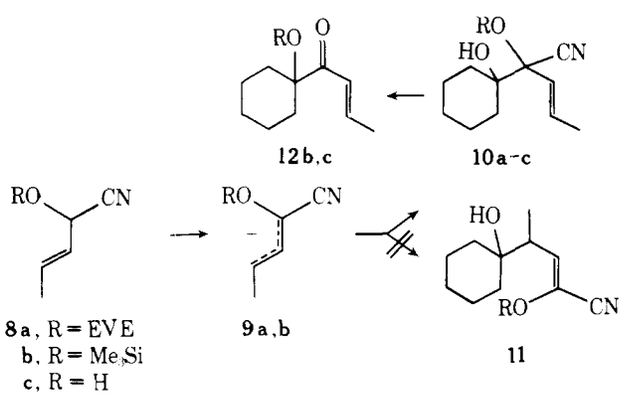
		64			48
		64			41
		70			81
		71			22
		89			99 (23:77)
		78			99 (50:50)
		53			80 (70:30)
		69			78 (48:52)

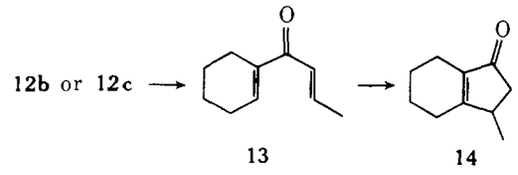
[a] All yields based on isolated material, chromatographed and distilled.

Scheme I



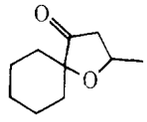
8a, R = EVE
b, R = Me_3Si
c, R = H

Either **12b** or **12c** may be dehydrated directly with TsOH in refluxing toluene. Compounds such as **12c** require catalytic amounts of acid, while compounds such as **12b** require 1.1 equiv of acid. Treatment of **12b** with 1 equiv of TsOH results in immediate loss of the trimethylsilyl group and the resultant α-hydroxy enones **12a** may be isolated in quantitative yield



if so desired. Under the reaction conditions of TsOH in toluene, the intermediate dienone, **13**, has never been observed and its presence can only be inferred by the isolation of the cyclopentenone **14**.

We have examined a variety of carbonyl compounds (Table I) and our preliminary findings are that those compounds which stabilize the intermediate carbonium ion provide for facile dehydration (reaction times of <1 min). The α-hydroxy enones which provide no π-conjugate stabilization of the intermediate carbonium ion dehydrate at a slower rate and also result in the formation of small amounts of furanones, such as **15**, via an acid-catalyzed intramolecular Michael addition.[10]



15

Preliminary results indicate that the formation of the furanones may be avoided by conversion of the α-hydroxy enones to the dienones **13** by use of the Burgess reagent, $Et_3N^+SO_2N^-CO_2CH_3$.[11] The cyclopentenone may then be prepared by acid-catalyzed cyclization of the dienone.

A typical procedure for this three-carbon annelation is illustrated for the case of cyclohexanone. To a solution of 2.0 mmol of lithium diisopropylamide in dry THF, under N_2, and cooled to −78 °C is added 0.40 mL (2.1 mmol) of the tri-

methylsilyl protected cyanohydrin of crotonaldehyde. After a period of 10 min, 0.15 mL (1.43 mmol) of cyclohexanone is added followed by additional stirring for 10 min and then quenching the reaction with 0.20 mL of glacial acetic acid. The mixture is partitioned between ether and water, extracted three times with ether, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel (20% Et_2O/hex) followed by Kugelrohr distillation [bp 100 °C (0.05 torr)] affords 220 mg (0.9 mmol, 64%) of α-trimethylsilyloxy enone **12b.**

The α-trimethylsilyloxy enone (123 mg, 0.51 mmol) and 116 mg of TsOH (0.61 mmol) are dissolved in 8 mL of toluene and refluxed through 4 Å molecular sieves for 4 h. Standard workup followed by chromatography on silica gel (20% Et_2O/hexane) and Kugelrohr distillation [bp 130 °C (10 torr)] affords 34 mg (48%) of the cyclopentenone.

Further development of this method of three-carbon annelation and its application to the total synthesis of a wide variety of natural products is under current investigation in our laboratories.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corporation for support of this work.

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(8) Hiyama[4g] and co-workers have taken a similar approach to cyclopentenone annelation using *gem*-dichloroallyllithium. However, the ratio of α to γ attack on the carbonyl is known to vary with substrate for this reagent,[9] possibly lessening its generality.
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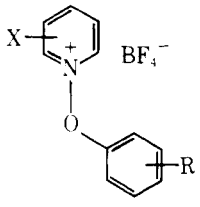
Azide-Catalyzed Rearrangement of *N*-(Aryloxy)pyridinium Salts. Facile Synthesis of 3-(*o*-Hydroxyphenyl)pyridines

Summary: *N*-(Aryloxy)pyridinium tetrafluoroborates react with azide (and other) ions in solution to give good yields of 3-(*o*-hydroxyphenyl)pyridines under mild conditions; the rearrangements may be rationalized by invoking either a 3,5 shift or a homolysis and radical recombination.

Sir: *N*-(Aryloxy)pyridinium tetrafluoroborates (**1**) are proving to be versatile compounds. They have been used to generate aryloxenium ions,[1] and undergo base-catalyzed rearrangement to give 2-(*o*-hydroxyphenyl)pyridines (**2**).[2] *N*-(Mesityloxy)- (**1**: R = 2,4,6-Me_3) and *N*-(duryloxy)pyridinium tetrafluoroborate (**1**: R = 2,3,5,6-Me_4) generated in situ undergo base-catalyzed rearrangement to *N*-(hydroxybenzyl)pyridinium salts, probably via quinone methide intermediates.[3] We now report a remarkably facile and convenient rearrangement of **1** to give good yields of 3-(*o*-hydroxyphenyl)pyridines (**3**), so that, depending on the conditions used, **1** can be converted into the 2- or the 3-*o*-hydroxyarylated pyridine derivative. All other rearrangements to C-3 or C-5 reported by us previously have involved a migrating group bound to both oxygen and C-2.



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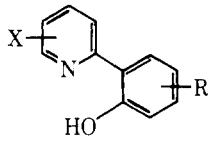

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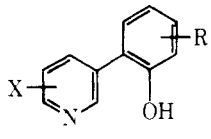

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Attack by a nucleophile on **1** might be anticipated to proceed by one of at least three pathways.[4] Reaction could take place at C-1 of the activated aryl nucleus leading to displacement of the pyridine 1-oxide; alternatively, attack could take place at C-2 (and possibly, but to a lesser extent, at C-4) of the pyridine ring to give a dihydro-1-(aryloxy)pyridine derivative.[5] In the latter case, at least two options are available: (i) loss of ArOH with formation of the 2-substituted pyridine,[5] or (ii) rearrangement to give a 3-substituted pyridine. Indeed, it was suggested[3] that a 1-(aryloxy)-2-chloro-1,2-dihydropyridine derivative might undergo a 3,5-shift to give a 3-(*o*-hydroxyaryl)pyridine.

Reaction of *N*-(*p*-nitrophenoxy)pyridinium tetrafluoroborate (**1**: R = 4-NO_2; X = H) with sodium azide in dry acetonitrile at room temperature gave a highly insoluble, initially amorphous material (M^+· 216) melting over a wide range. This could be recrystallized from DMF to give pale yellow crystals, mp 294–298 °C dec (70.3%), of 3-(2-hydroxy-4-nitrophenyl)-pyridine (**3**: R = 4-NO_2; X = H).[6] Acetylation of the crude product gave the pure *O*-acetate of **3** (75%), mp 133–134 °C (ethanol–hexane). The structure of the rearrangement product was confirmed by its authentic synthesis by nitration of 3-(2-hydroxyphenyl)pyridine.[7] The high melting point (and its lack of sharpness) as well as the relative insolubility of this product is to be contrasted with the properties of its *O*-acetate and of its hydrogen tetrafluoroborate salt [mp 205 °C (from ether–acetone)], and suggests that **3** (R = 4-NO_2) exists mostly in the zwitterionic form. Blocking either the phenolic oxygen or the pyridine nitrogen atoms then prevents formation of the zwitterion.

Other inorganic ions were also effective in achieving the transformation **1** → **3** (X = H; R = 4-NO_2). Thus cyanide, iodide, carbonate (needed 48 h for maximum yield), thiosulfate, and acetate gave **3** (crude yields reported) in 89, 68, 90, 42, and 47% yields, respectively. On the other hand, no rearrangement products could be obtained with nitrate, chloride, bromide, thiocyanate, sulfite, chlorate, perchlorate, nitrite, dihydrogen phosphate, or sulfide ions. The reaction with azide ion can be carried out at room temperature or in boiling acetonitrile; aqueous acetonitrile may also be used as can DMF. The reaction with azide also takes place in water but the yields are lower.

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