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AN ENANTIOCONTROLLED APPROACH FOR THE SYNTHESIS OF CHIRAL 3,5-DISUBSTITUTED 2(1*H*)-PYRIDINONES[†]

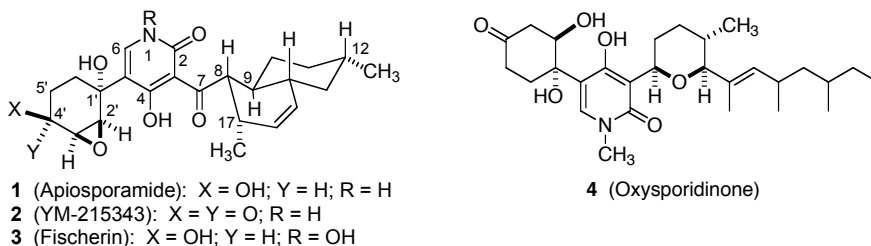
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Abstract – An enantioselective route for the convergent synthesis of chiral, nonracemic 5-substituted 3-acyl-2(1*H*)-pyridinones is reported. Claisen rearrangement provides direct access to the α -branched 2-[4-(*tert*-butyldimethylsilyloxy)cyclohex-2-enyl]-3-hydroxypropionaldehyde as a key intermediate. The application of mild oxidation conditions facilitates the preparation of a series of 3,5-disubstituted 2(1*H*)-pyridinones.

Our recent studies toward the synthesis of naturally occurring pyridinones, such as apiosporamide (**1**),¹ YM-215343 (**2**),² fischerin (**3**),³ and oxysporidinone (**4**)⁴ have focused on the development of a convergent, enantiocontrolled strategy which provides rapid access to C-1' deoxy derivatives of these novel 2(1*H*)-pyridinone systems. Significant antibacterial, antifungal and cytotoxic properties associated with the natural metabolites are difficult to assess owing to their relative instability.



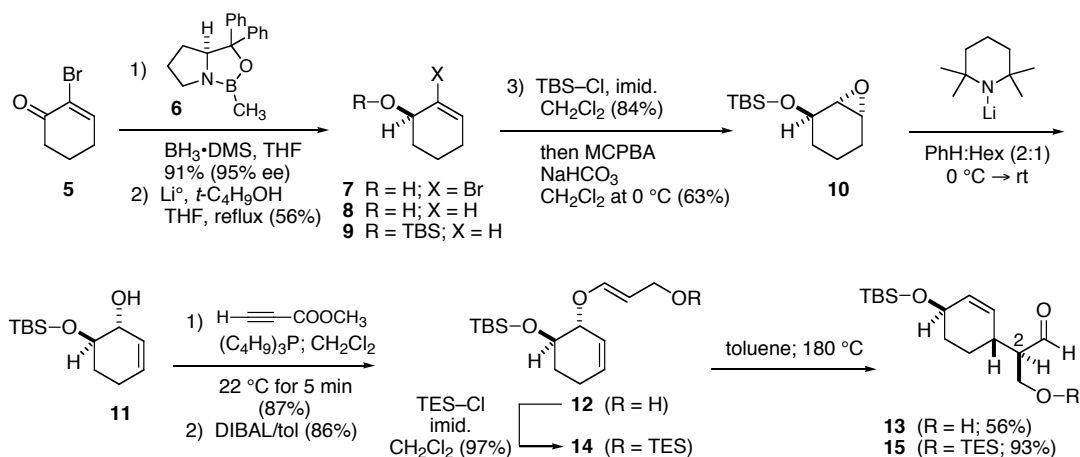
The presence of the C-1' tertiary hydroxyl group in these structures is postulated to contribute to the observed labile behavior. Facile synthesis of the corresponding deoxy compounds provides an opportunity for studies of biological activity as well as a platform for late-stage oxidation for introduction

[†] Dedicated to Professor Barry M. Trost in celebration of his 65th birthday.

of the C-1' hydroxyl moiety. We and others have previously reported studies of total syntheses of 5-aryl-2-pyridone representatives of this family, including tenellin,⁵ ilicicolin H,⁶ sambutoxin,⁷ and leporin A,⁸ and pyridovericin.⁹ However, the stereochemical complexities of structures (**1–4**) display two independent components, as exhibited by the cyclohexanediol and the *trans*-decalin unit which are joined by the planar pyridone ring in **1**. A convergent synthesis approach is required to address these concerns. Herein we describe an enantioselective route featuring a useful Claisen rearrangement for preparation of chiral, nonracemic 4-substituted 2-cyclohexen-1-ols and the highly efficient transformation to yield 5-substituted 2-pyridinones.

Preparation of the optically active cyclohexenyl component is summarized in Scheme 1. Beginning with 2-bromocyclohex-2-en-1-one, the Corey CBS asymmetric reduction¹⁰ with **6** results in 91% yield of **7** with high enantioselectivity (91–95% ee). Surprisingly, the reductive removal of the 2-bromo substituent proved more difficult than anticipated.¹¹ Reactions of **7** with excess lithium metal in a mixture of THF and *tert*-butanol (5:1 by volume) proceeded very slowly, requiring more than 24 h at reflux for complete consumption of starting material. While a number of other techniques proved to be less advantageous, this dissolving metal reduction consistently gave 56% yield of (*R*)-2-cyclohexen-1-ol (**8**) and some over-reduction to cyclohexanol (approximately 10%).

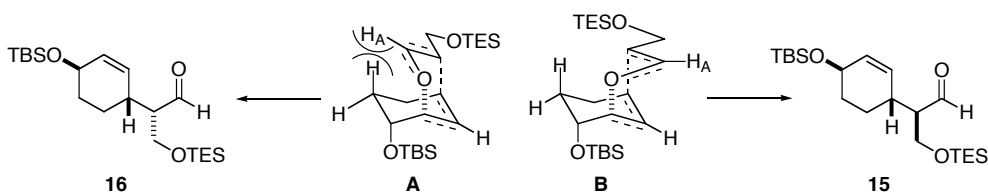
Scheme 1.



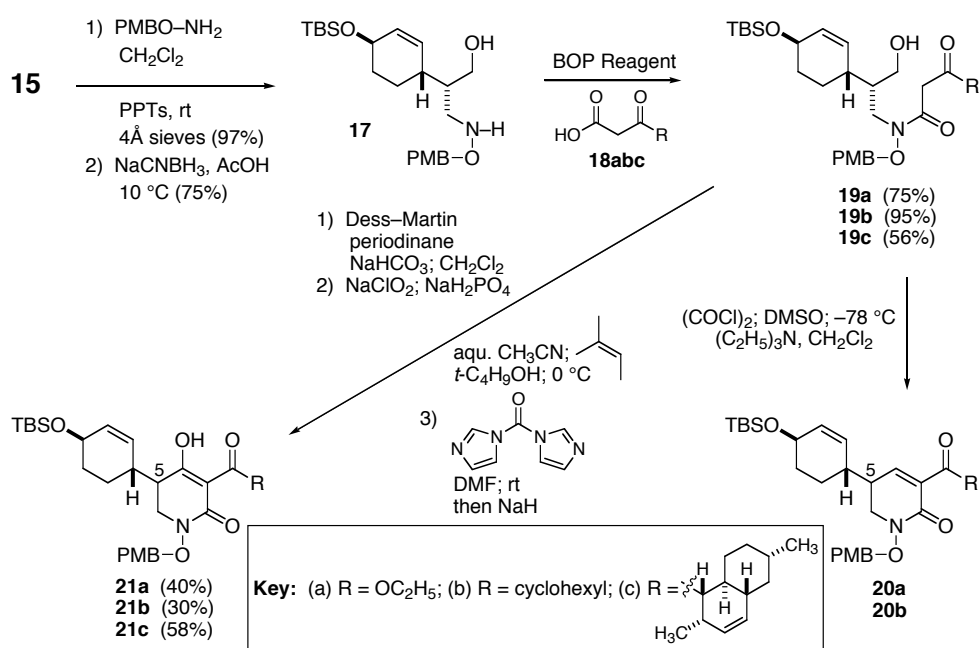
Silylation and subsequent epoxidation of **9** with buffered *meta*-chloroperbenzoic acid gave a 78% yield of a 4:1 mixture of epoxides which were readily separated by flash chromatography affording **10**. Base-induced isomerization¹² gave allylic alcohol (**11**), and facile conjugate addition with methyl propiolate, catalyzed by tri-*n*-butylphosphine, yielded the (*E*)- α,β -unsaturated ester (87%) for subsequent DIBAL reduction to provide allylic alcohol (**12**) (86%). Claisen rearrangement of **12** proceeded in a resealable Carius tube at 180 °C to give the β -hydroxy aldehyde (**13**) (56% yield) with high diastereoselectivity at C-2 (dr 13:1). However, the thermal rearrangement of the triethylsilyl ether (**14**) provided a superior yield of **15** (93%; dr 8:1 at C-2) as well as small amounts of the β -elimination product (2.5%). A rationale for the

observed stereoselectivity of the concerted [3,3]-process is illustrated by analysis of the chair-like and boat-like arrangements of **A** and **B** (Figure 1), respectively. The conformation in **A**, leading to the 2(*S*)-diastereomer (**16**), reveals a nonbonded steric interaction of the vinylic hydrogen H_A with remaining axial hydrogen of the cyclohexenyl ring. This destabilizing interaction is avoided in **B** which yields 2(*R*)-**15** as the major product.

Figure 1.



Convergent construction of the pyridone ring system is illustrated in Scheme 2. Amino alcohol (**17**) is readily produced in two steps from aldehyde (**15**) *via* reductive amination of the corresponding oximino ether derived from 4-methoxybenzylamine (70–75% yield for 2 steps). Acylation using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) for activation of β -ketocarboxylic acids (**18a**, **18b**, and **18c**) gave the expected amides (**19a**, **19b**, and **19c**) with minimal byproducts of *O*-acylation.¹³ Swern oxidation¹⁴ of the primary alcohol provides the expected aldehyde in high yield, however, attempted purification by silica gel chromatography effected an undesired cyclization to yield the 5,6-dihydropyridones (**20a** and **20b**). Alternatively, the use of Dess–Martin

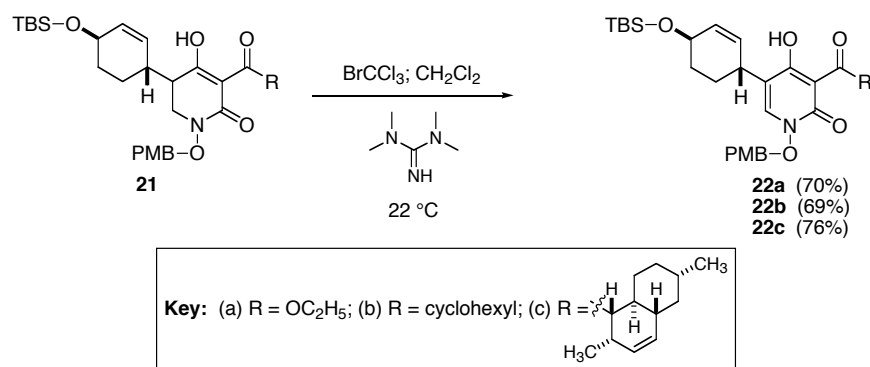


periodinane¹⁵ allows for isolation of crude aldehyde without the need for flash chromatography, and this material may be oxidized with sodium chlorite under buffered conditions¹⁶ to yield carboxylic acids. Treatment of the crude carboxylic acids with 1,1'-carbonyldiimidazole and sodium hydride gave the 5,6-

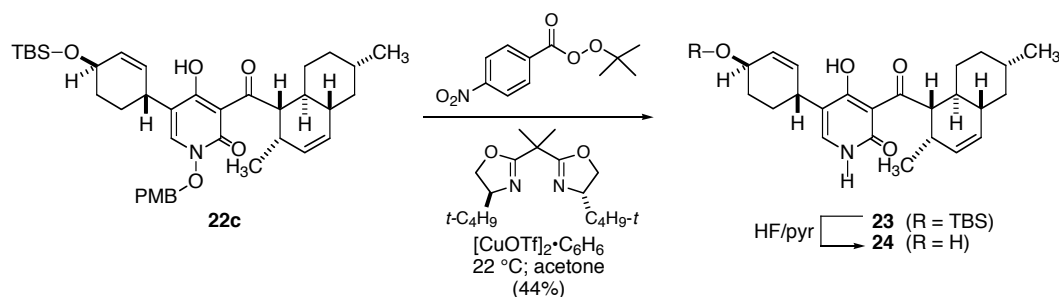
dihydro-4-hydroxy-2-pyridones (**21a**, **21b** and **21c**) in 30–58% overall yields (over 3 steps). Proton NMR spectroscopy provides evidence that pyridones (**20** and **21**) are mixtures of C-5 diastereomers. Furthermore, the examples of 5,6-dihydro-4-hydroxy-2-pyridones (**21**) have been shown to exist as mixtures of equilibrating enol and keto tautomers.

Finally, the parent heterocycles were obtained by mild oxidation of **21abc** with bromotrichloromethane, as based on previous studies from these laboratories,¹⁷ providing good yields of **22abc**. Similarly, treatment of **20ab** under these oxidation conditions also gave the analogous 2(1*H*)-pyridones (60%). Subsequent cleavage of the N–O bond is efficiently undertaken using SmI₂ at –78 °C (95%). However, we have recently observed an unexpected N–O cleavage of **22c** in our attempts to selectively provoke an asymmetric C-1' Karasch oxidation.¹⁸ Using *tert*-butylperoxy-4-nitrobenzoate in the presence of the

Scheme 3.



copper bis(oxazoline) complex derived from copper(I) triflate,¹⁹ pyridone (**23**) was immediately formed as the major product without evidence of the expected allylic oxidation.²⁰ Although additional efforts are necessary to generalize and optimize conditions for this transformation, this unusual N–O cleavage under oxidizing conditions has led to the isolation of desired 2(1*H*)-pyridone (**24**) for further studies.



In summary, we have established a convergent route for the enantioselective preparation of chiral, nonracemic 5-substituted 3-acyl-2(1*H*)-pyridinones. A novel Claisen rearrangement selectively affords a chiral 3-hydroxypropionaldehyde derivative as a key building block for pyridone synthesis. An unanticipated oxidative N–O bond cleavage reaction has been described.

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