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METHODOLOGY FOR THE SYNTHESIS OF PYRIDINES AND PYRIDONES: DEVELOPMENT AND APPLICATIONS

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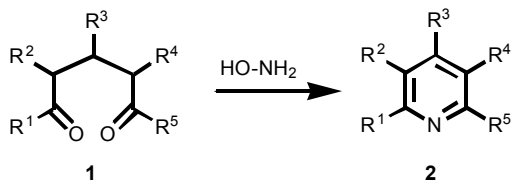
Abstract – We review some reactions devised in our laboratory for the rapid assembly of pyridines and pyridones. Applications of the new methods in the total synthesis of lavendamycin, pyridoacridine and phenanthroizidine alkaloids (pyridine chemistry), and of camptothecin, nothapodytine B and streptonigrone (pyridone-forming reactions) are described.

INTRODUCTION

Heterocyclic chemistry provides substantial opportunity for development of new synthetic methods. Indeed, the bioactivity of many heterocycles and the noteworthy architecture of numerous heterocyclic natural products often translate into interesting challenges in the chemical domain. Over the years, we have devised a number of new reactions to deal with such issues. Herein we review methodology developed in our laboratory in connection with the synthesis of pyridine and pyridone natural products.

DEVELOPMENT OF A PYRIDINE-FORMING REACTION

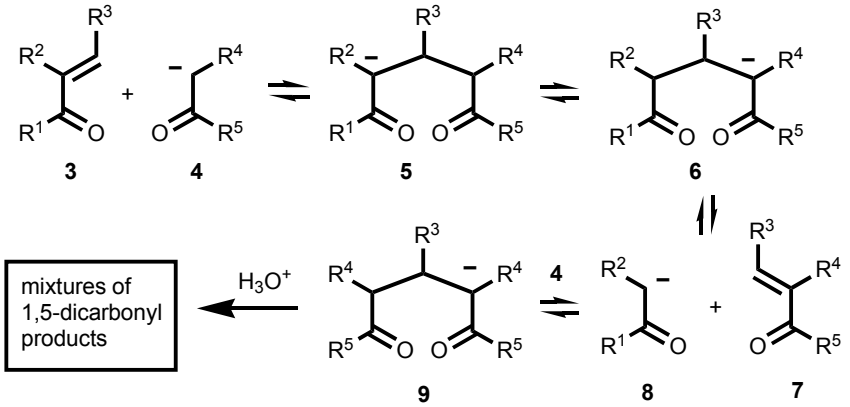
The Knoevenagel-Stobbe pyridine synthesis[1] proceeds through the interaction of a 1,5-dicarbonyl compound with hydroxylamine (Scheme 1). Two problems are often observed during the reaction. First, yields of pyridines are moderate, and sometimes low,[2] possibly due to competing aldol-type reactions of the substrate. These are probably triggered by the intervention of enol forms of the substrate. Second, the



1 2

Scheme 1

This paper is dedicatd to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

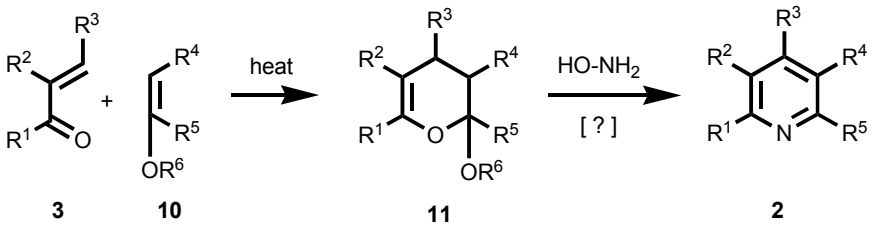


Scheme 2

preparation of 1,5-dicarbonyl compounds such as **1** generally involves Michael-type chemistry (Scheme 2), which can afford mixtures of products with certain permutations of components **3** and **4**, due to competing retro-Michael fragmentation of the primary adduct, **5**.[3]

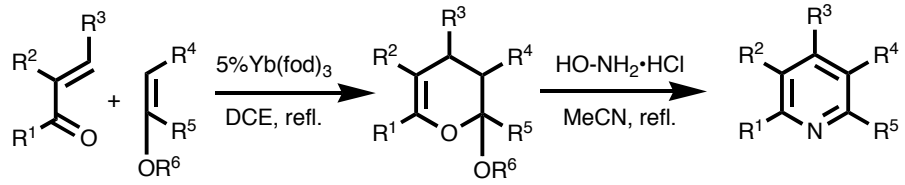
Retrosynthetic analysis of various heterocyclic targets of interest to us unveiled the desirability of an efficient variant of Knoevenagel-Stobbe pyridine synthesis. An appealing solution was to engage dihydropyrans **11**, in lieu of **1**, in a reaction with hydroxylamine. Compounds **11** are "protected" variants of **1**, which cannot tautomerize to reactive enol derivatives, therefore they are unable to undergo aldol-type condensation. This should diminish their propensity to undergo side reactions during pyridine formation. Moreover, they may be made by the formal cycloaddition[4] of an enecarbonyl compound with a vinyl ether. This circumvents the problems delineated in Scheme 2 and it enables the use of ethyl vinyl ether, 1-methoxy propene, and the like, as synthetic equivalents of ill-behaved aldehyde enolates.

The uncatalyzed cycloaddition of enecarbonyl compounds with vinyl ethers normally requires forcing conditions.[5] Fortunately, lanthanide complexes such as $Yb(fod)_3$[6] were found to accelerate the reaction of enones possessing at least one aryl or heteroaryl substituent[7] in conjugation with the carbonyl group.[8] Pyran formation then occurs readily in refluxing 1,2-dichloroethane ("DCE"). More importantly, the action of hydroxylamine hydrochloride in refluxing MeCN[9] efficiently converted **11** into pyridines. Representative examples of the new reaction appear in Tables 1-2.[10]



Scheme 3

Table 1. Representative pyridines obtained by the new process - I



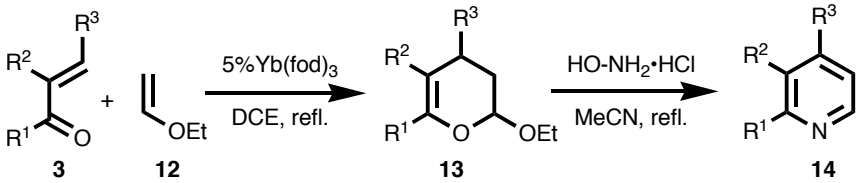
3 **10** **11** **2**

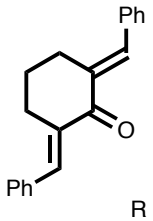
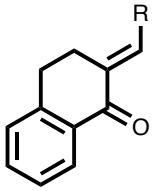
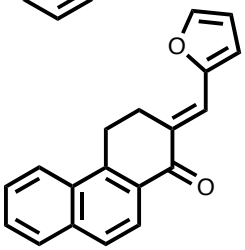
entry	R^1	R^2	R^3	R^4	R^5	R^6	% yield of pyran	% yield pyridine
a	Ph	H	Ph	H	H	Et	99	95
b	Ph	H	Ph	H	Me	Me	99	93
c	Ph	H	Ph	Me	H	Et	97	89
d	Ph	H	Ph	Me	Me	Et	93	88
e	Ph	H	Ph	H	Et	Et		
f	Ph	H	Ph	$-(CH_2)_4-$		Me	78	76
g	(*E*) Ph-CH=CH	H	Ph	H	H	Et	98	90
h	Ph	H	*c*-C_6H_{11}	H	H	Et	87	72
i	Ph	H	*n*-C_9H_{19}	H	H	Et	89	89
j	2-quinolyl	H	2,3,4-$(MeO)_3$Ph	H	Me	Me	88	85

As seen from the data of Table 1, the cycloaddition step succeeds with a range of vinyl ethers. Regio- and stereoisomers of vinyl ethers tend to equilibrate in the presence of $Yb(fod)_3$, and the ether isomer with the highest HOMO energy combines selectively with the enone. This is exemplified in the behavior of 2-ethoxy-1-butene (entry e), which isomerized to 2-ethoxy-2-butene faster than it combined with chalcone. Vinyl ethers derived from cycloalkanones participate in the new reaction to give useful pyridocycloalkanes (entry f), the synthesis of which is not always straightforward.[11] Methoxyallene[12] and (*Z*)-1-methoxy-3-trialkylsilyl-1-propenes[13] add readily to enones under catalysis by $Yb(fod)_3$, but the adducts do not necessarily yield pyridines upon reaction with HO-NH_2•HCl in MeCN.[14] Alkynyl ethers, dihydropyran, and dihydrofuran, failed altogether in the cycloaddition step.

The new process converts dienones to alkenylpyridines (Table 1, entry **g**; Table 2, entry **k**). Un–

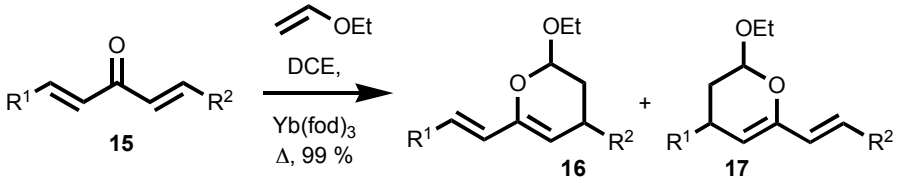
Table 2. Representative pyridines obtained by the new process - II



enone		entry	% yield of pyran	% yield pyridine
		**k**	100	86
	R = H	**l**	87	72
	R = Ph	**m**	89	89
	R = 2-furyl	**n**	100	85
		**o**	84	72

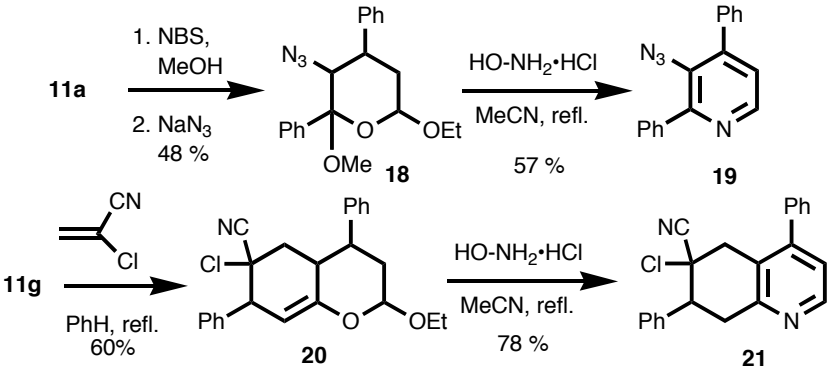
symmetrical dienones in which the two π systems are sterically different tend to combine with vinyl ethers selectively at the less encumbered double bond (cf. **15a**, Scheme 4). By contrast, electronic differences between the two π systems promote insignificant regioselectivity (cf. **15b)**.

It is possible to modify the electron-rich pyran nucleus in cycloadducts **11** prior to pyridine formation, thereby expanding the scope the reaction. For instance, methoxybromination of **11a** and subsequent reaction with NaN_3 yielded **18**, which ultimately furnished azidopyridine **19** (Scheme 5). In a like vein,



a	R^1 = 2-NO_2-C_6H_4; R^2 = H	**100**	:	**0**
b	R^1 = 4-NO_2-C_6H_4; R^2 = 2-Furyl	**1**	:	**1**

Scheme 4

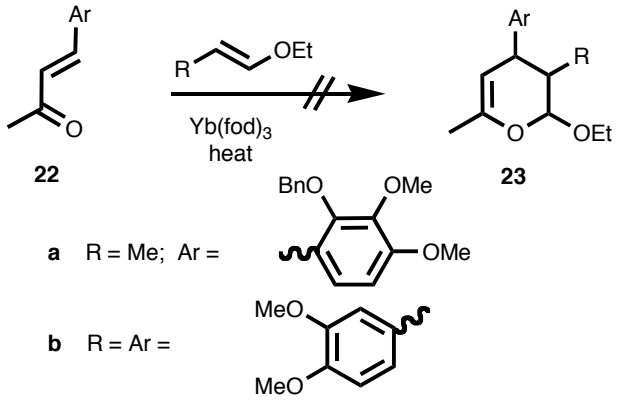


Scheme 5

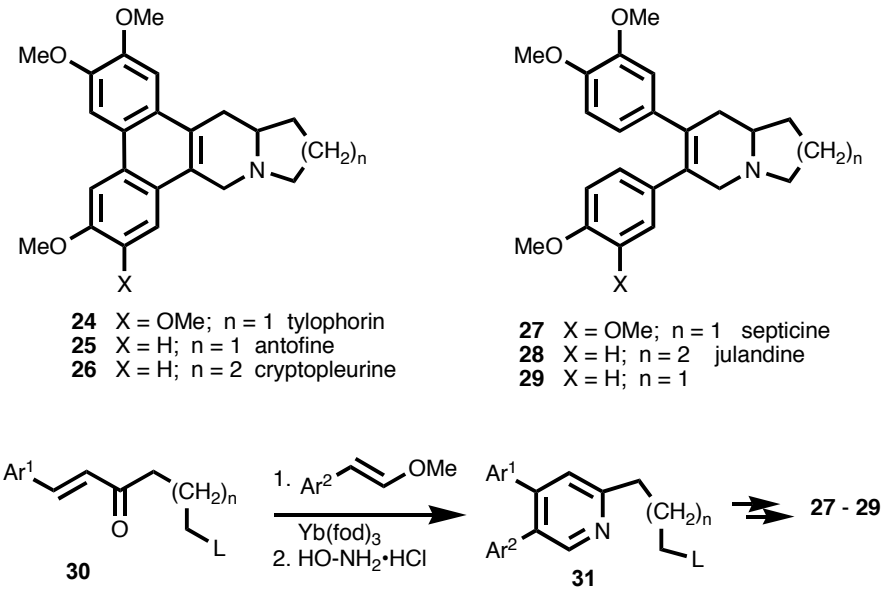
pyrans obtained from dienones contain an the electron-rich diene system that can participate in Diels-Alder reactions before pyridine formation. For instance, **11g** combined with chloroacrylonitrile to provide **20**, which was then advanced to pyridine **21**. The sequence leading to intermediates such as **20** may be conducted in one pot by refluxing a dienone, e.g. **11g**, a vinyl ether, $Yb(fod)_3$, and an electron-deficient dienophile in DCE.

STERICALLY CONGESTED PYRIDINES: SYNTHESIS OF PHENANTHROIZIDINE ALKALOIDS

Steric and/or electronic effects may oppose the union of particular enone / vinyl ether pairs. For instance the reaction leading to **23a** fails because of unfavorable electronics, while that leading to **23b** fails on steric grounds (Scheme 6).[15] This bars access to the intermediate cycloadducts, and consequently to the ultimate pyridines, which nonetheless could be useful platforms for the synthesis of various nitrogenous substances. The phenanthroizidine alkaloids,[16] **24**-**26**, and their seco precursors, **27**-**29**, constitute a case in point. Synthetic and medicinal chemistry[17] interest in these natural products is motivated by their multifaceted bioactivity (antitumor activity,[18] inhibition of protein synthesis,[16] nerve growth stimulation, cardiovascular and immunological effects, antiinflammatory action[19]) and by their unusual structure. Given that *seco*-alkaloids **27**-**29** may be oxidatively cyclized to **24**-**26**, a plausible route to phenanthro-



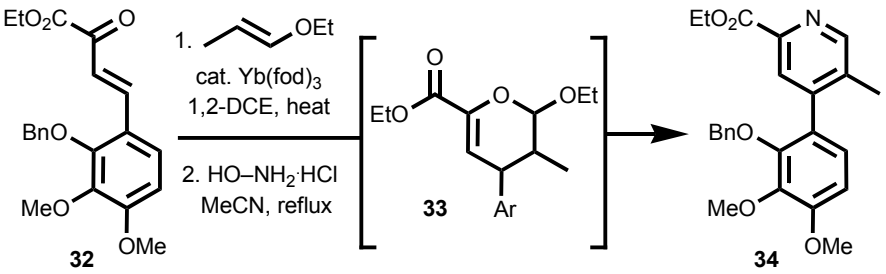
Scheme 6



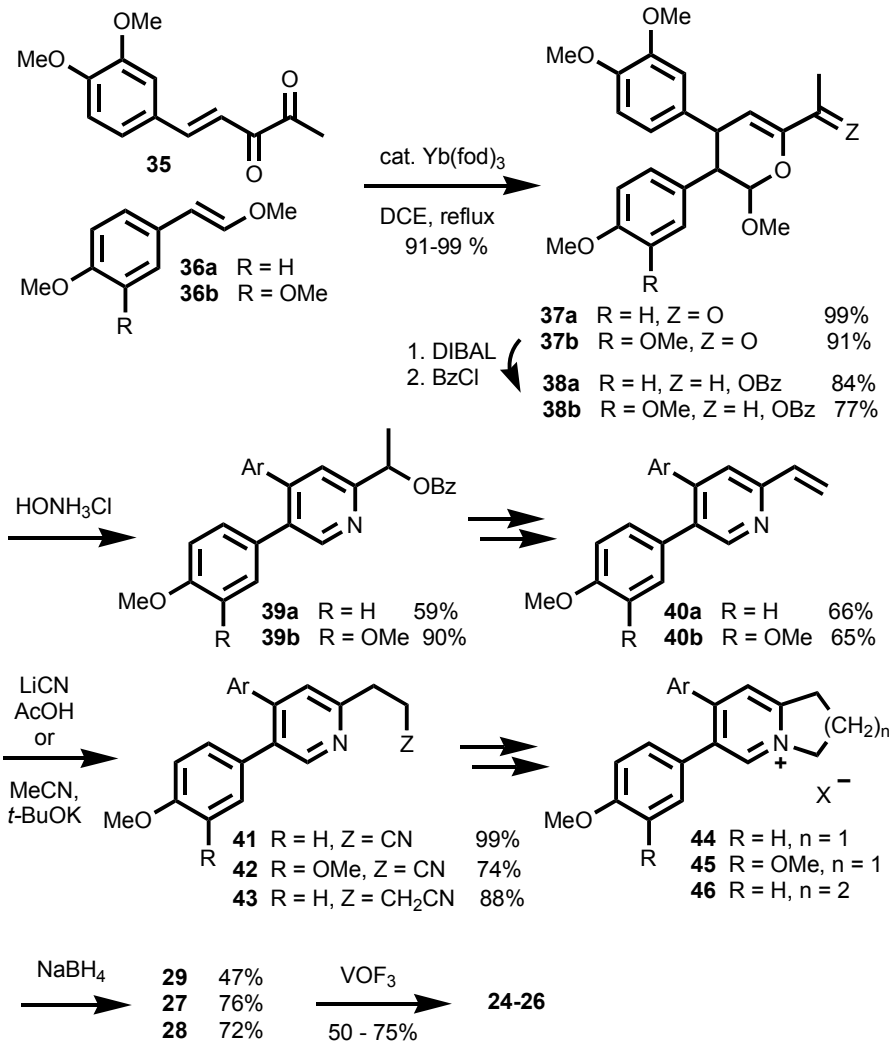
Scheme 7

izidine natural products proceeds through pyridines **31** (Scheme 7). Unfortunately, the initial cycloaddition reaction of enones **30** failed, thwarting the implementation of the overall strategy.

Sterically congested pyridines **31** ultimately became accessible through the agency of α-dicarbonyl analogs of the original enones. The new substrates are much more reactive than the parent compounds. For example, **32** combined smoothly with 1-ethoxypropene to form **33** and thence pyridine **34** in good yield (Scheme 8), even though **22a** had failed in the same reaction (Scheme 6). More relevant to the phenanthroizidine effort was the successful reaction of **35** with **36** (Scheme 9). Cycloadducts **37** were then elaborated to vinylpyridines **40**, which reacted readily with HCN or with the anion of MeCN to give **41**-**43**. The latter were elaborated to pyridinium salts **44**-**46**, which upon reduction produced (±)-septicine, **27**, (±)-julandine, **28**, and (±)-seco-antofine, **29**.[20] Known oxidative cyclization techniques finally converted such *seco*-compounds to fully-fledged phenanthroizidines.[21]



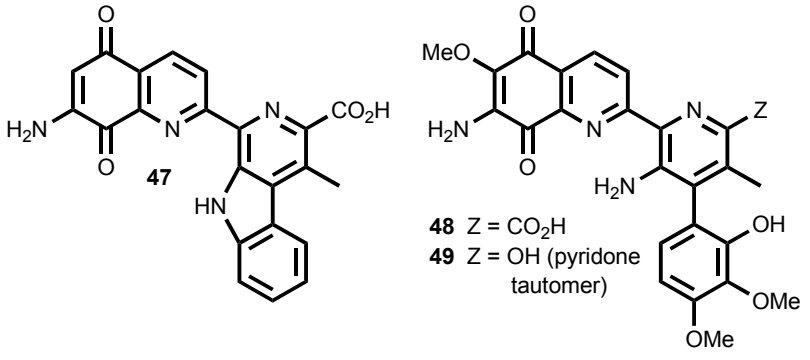
Scheme 8



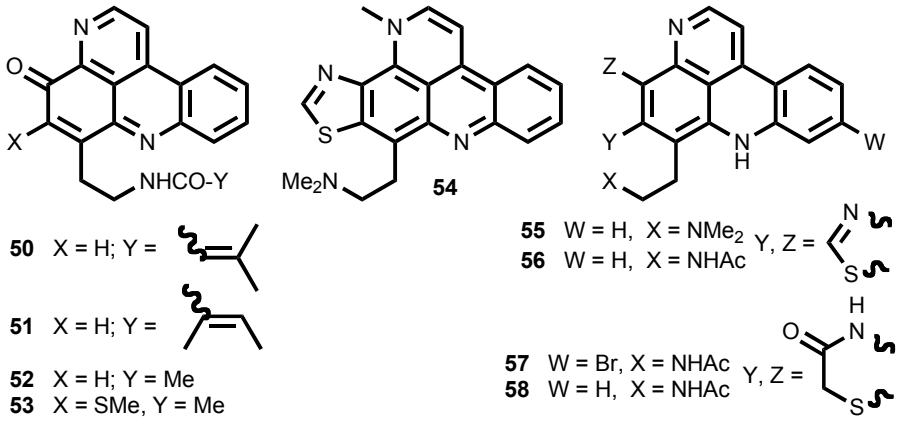
Scheme 9

HARNESSING THE REACTIVITY OF NITRENES ON THE WAY TO LAVENDAMYCIN AND TO PYRIDOACRIDINE ALKALOIDS

Lavendamycin, **47**,[22] is the biosynthetic precursor[23] of streptonigrin, **48**, streptonigrone, **49**, and related molecules ("streptonigrinoids", Scheme 10).[24] These substances elicit a remarkable spectrum of biological



Scheme 10

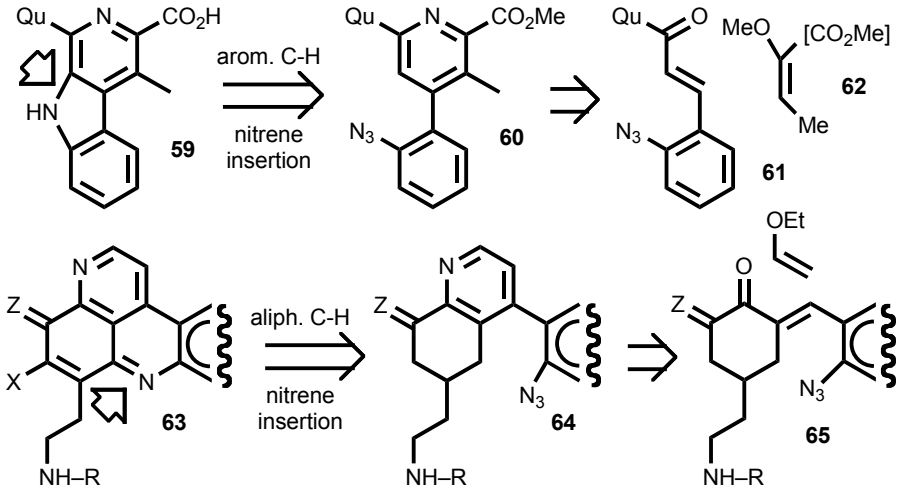


Scheme 11

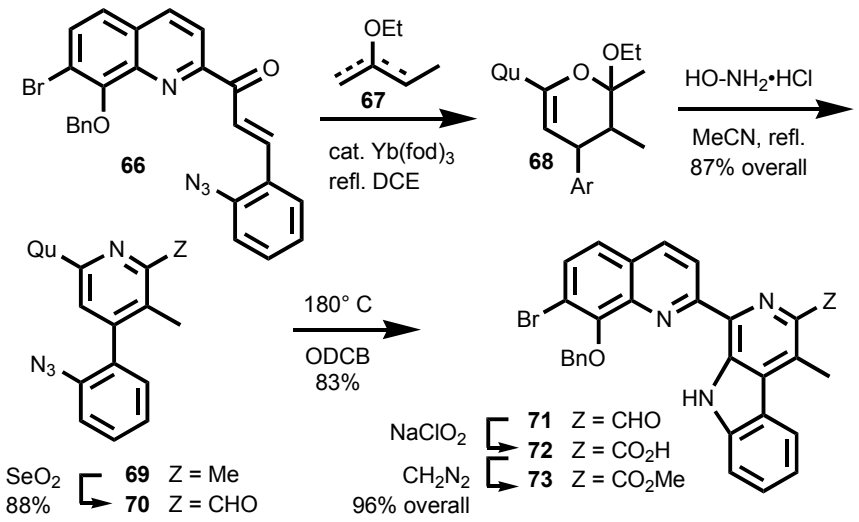
responses.[25] In particular, **47** and **48** are highly cytotoxic. This has provided an impetus for a great deal of synthetic and medicinal chemistry research.[26] Appreciable cytotoxicity is also found in pyridoacridine alkaloids,[27] representatives of which are cystodytins A, **50**, B, **51**, and J, **52**, diplamine, **53**, dercitin, **54**, nordercitin, **55**, kuanoniamine, **56**, and shermilamines A, **57**, and B, **58** (Scheme 11).

Release of the C–N bonds indicated with stubby arrows in Scheme 12 simplifies the retrosynthetic analysis of **47** and of **50**-**58** and permits the application of the pyridine-forming reaction to the synthesis of precursors **60** and **64**. The linkage in question could be re-established through the insertion of a nitrene into a C–H bond. The work of Meth-Cohn[28] suggested that formation of a singlet nitrene from of the azido group in **60** should promote selective insertion into the neighboring aromatic C–H bond (at least in a formal sense)[29] to yield β-carboline **59**, while the pyridoacridine framework **63** should emerge upon preferential insertion of a triplet nitrene derived from azide **64** into an aliphatic C–H bond.[30]

A formal synthesis of lavendamycin methyl ester was thus executed as delineated in Scheme 13. A key aspect of the sequence is the cycloaddition of enone **66** with a mixture of isomers of vinyl ether **67**. As seen earlier (Table 1, entry **e**, and relative discussion), the isomers of the ether equilibrate rapidly during



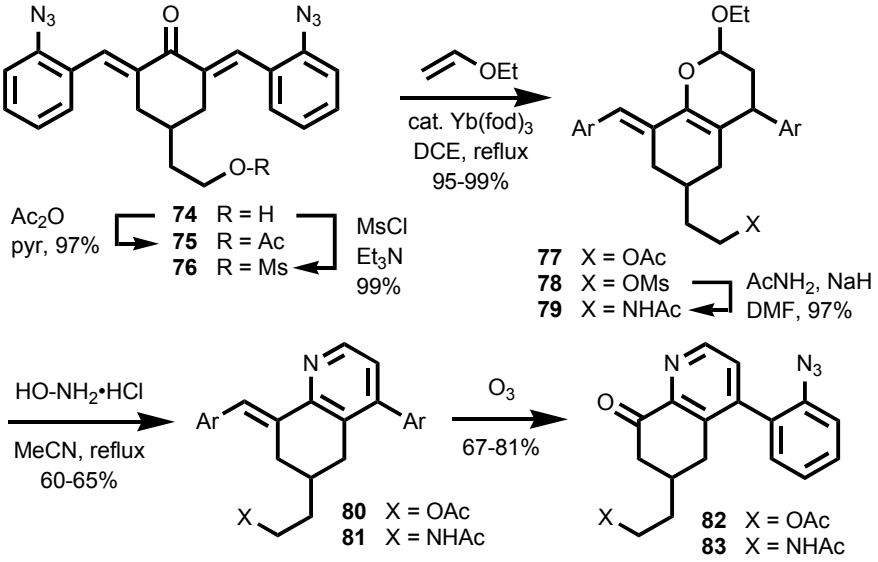
Scheme 12



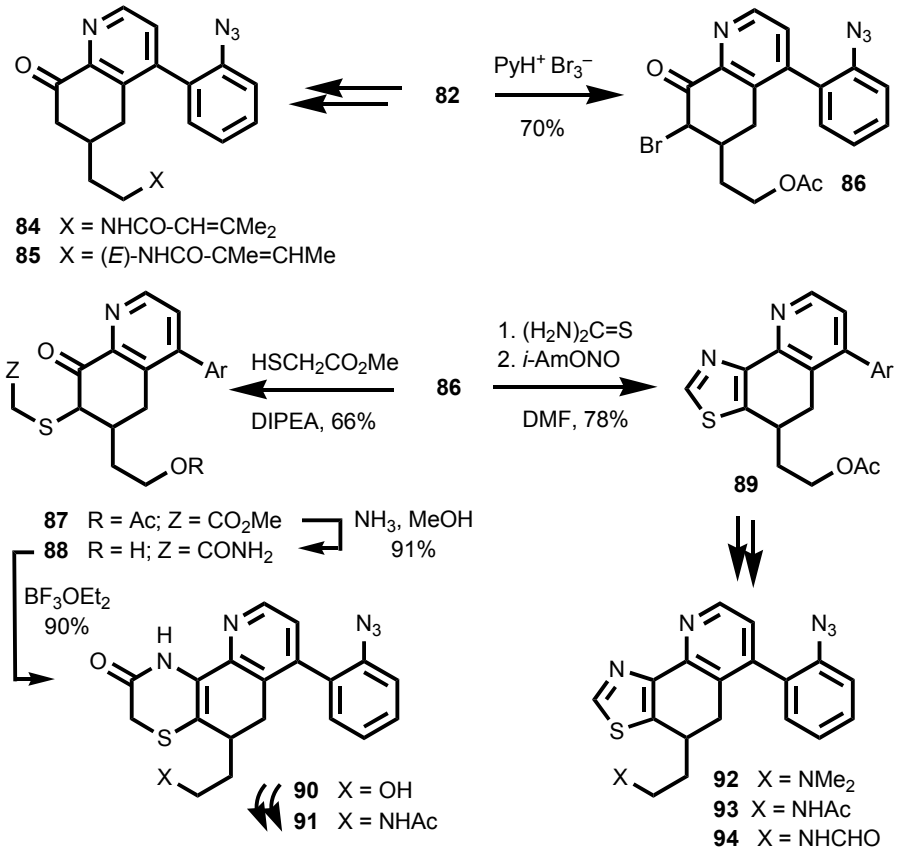
Scheme 13

the cycloaddition step. Selective reaction of the more electron-rich isomer resulted in exclusive formation of **68**, which was then converted to pyridine **69**. Oxidation to **70** set the stage for thermolysis of the azide in refluxing ortho-dichlorobenzene, a treatment that indeed furnished carboline **71** in high yield.[31] Further elaboration of **71** to the known intermediate **73**[32] completed the formal synthesis of **47**.[33]

Our approach to **50**-**58** rested on the perception that group Z in **64** should be an oxygen atom. A carbonyl version of **64** seemed to be most readily available through the ozonolysis of an alkylidene intermediate. Considering the structural requirements for the cycloaddition step, we started with symmetrical bis-benzylidene ketone **74**, from which **82** and **83** were readily fashioned as adumbrated in Scheme 14. While ketone **83** is the direct forerunner of **52** and **53**, compound **82** was further modified as shown in Scheme 15 to reach precursors **84**-**85** and **91**-**94** of the other pyridoacridine alkaloids.

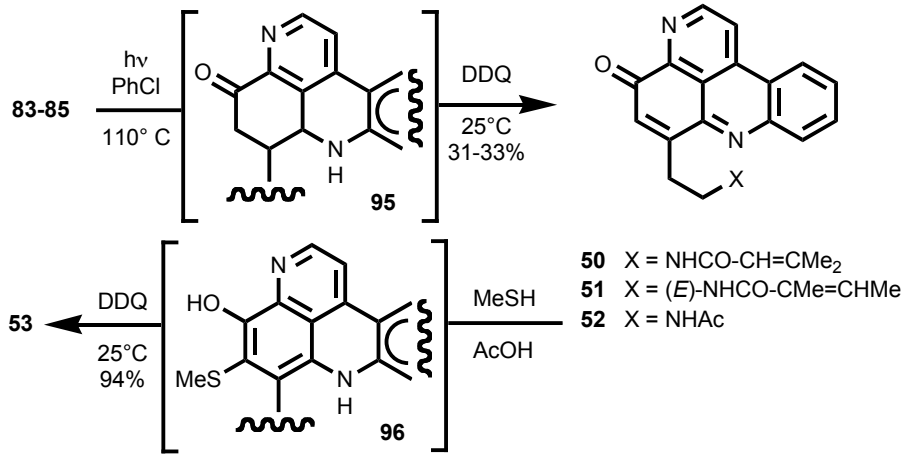


Scheme 14



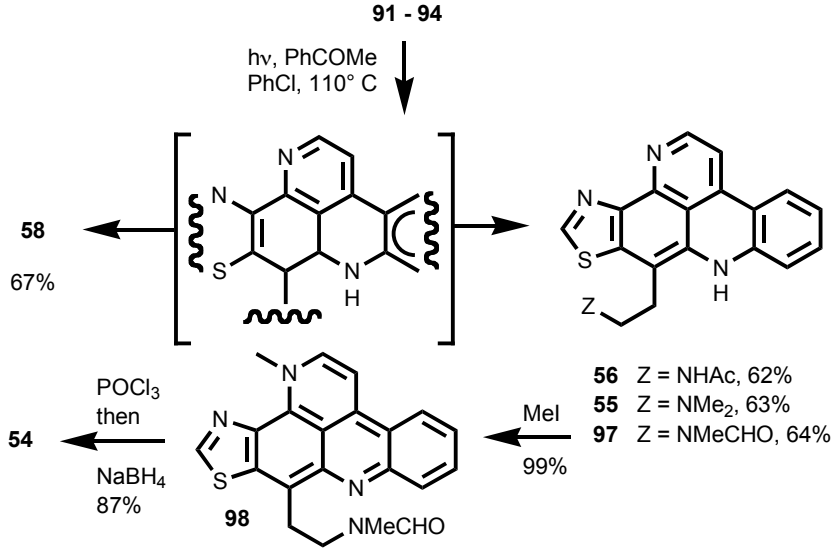
Scheme 15

The synthesis of cystodytins and diplamine continued with a Meth-Cohn triplet sensitized photolysis of **83**-**85** (Scheme 16). The pyridyl ketone present in these intermediates acted as an internal triplet sensitizer, eliminating the need for an external one. Irradiation thus induced cyclization to isolable lumiproducts **95**. These were best oxidized *in situ* (DDQ) to cystodytins A (**50**) - B (**51**),[34] and J (**52**). The overall yield for this two-step sequence was 30-33%. Sequential treatment of **52** with MeSH (addition to the quinonimine) and DDQ (oxidation of the adduct **96**) surrendered diplamine, **53**, in 94% yield.[35]



Scheme 16

The photochemical cyclization of intermediates **91**-**94** required an external triplet sensitizer, since the substrates lack an aromatic keto group, but it proceeded much more efficiently (60-65% yield). The sensitizer here was an excess of acetophenone. Under these conditions, the primary lumiproducts, which are isolable, underwent *in situ* oxidation directly to shermilamine B, **58**, kuanoniamine, **56**, nordercitine **55**, and compound **97** (not a known natural product).[36] It is likely that the oxidant in these reactions is photoexcited MeCOPh, which may act as a hydrogen atom acceptor. Especially bioactive dercitin, **54**, was reached from **97** as seen in Scheme 17.[37]

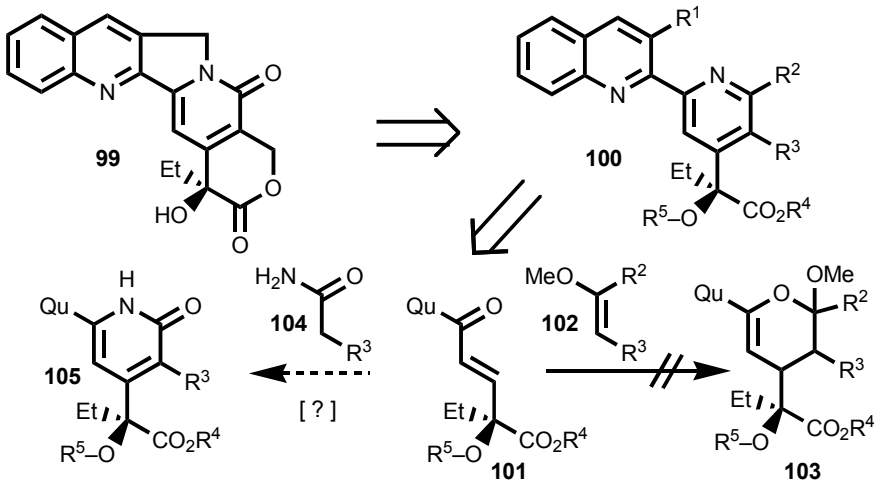


Scheme 17

CAMPTOTHECIN: FAILURE OF THE PYRIDINE CHEMISTRY AND DEVELOPMENT OF A PYRIDONE-FORMING REACTION

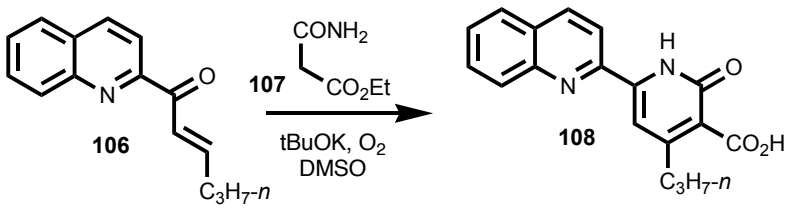
The discovery of the potent antitumor agent, camptothecin ("CPT" **99**)[38] in the 1960's[39] stimulated enormous interest both in the biomedical and the chemical arenas. This excitement abated as a result of flawed early clinical trials, but later fundamental developments[40] again catapulted **99** to the forefront of cancer research in the final decade of the XX century. Today, a number of CPT-based drugs are well established as valuable antineoplastic resources.[41]

Renewed interest in **99** and congeners induced us to conceive an approach based on the pyridine forming reaction (Scheme 18), only to discover that a plethora of unforeseen difficulties made this plan of attack entirely unworkable. Briefly, we failed to identify a permutation of groups R^2 and R^3 in **102** that would permit the assembly of a congener of pyridine **100** suitable for advancement to **99**. It transpired from these efforts that the construction of a pyridone such as **105** through the union of enone **101** with amide **104** would nullify the foregoing obstacles. Of course, the synthesis of pyridones by the merger of active methylene amides (cf. **104**, R^3 = carbonyl, cyano, or other electron-withdrawing group) with enones is well documented, but such a pyridone construction may require as many as three steps, and overall yields



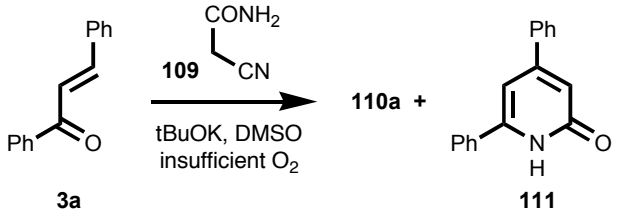
Scheme 18

may be mediocre.[42] Experiment revealed that an enecarbonyl compound and an active methylene amide combine efficiently under the influence of tBuOK in DMSO, and under an O_2 atmosphere (no cooling), to give functionalized pyridones in one step.[43] Cyanoacetamide, **109**, affords superior results in this reaction (Table 3), thanks to the resistance of a CN group to the basic agents utilized therein. Malonic monoamides, e.g. **107**, are less useful, due to the propensity of ester groups to undergo cleavage during the process (Scheme 19).



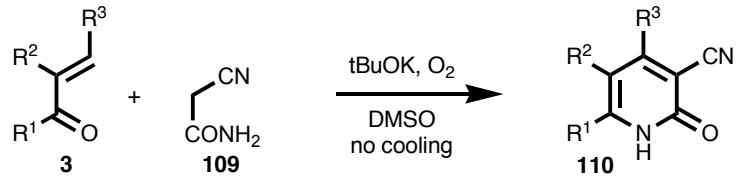
Scheme 19

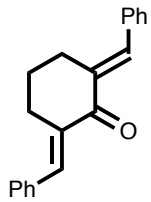
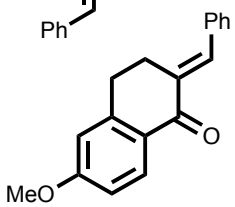
Scale-up of the reaction may favor the formation of 3-unsubstituted pyridones **111** as byproducts (Scheme 20). Experiment ascertained that compounds **111** arise as a result of an inadequate rate of O_2 diffusion into the reaction medium. The problem may be corrected by operating in a reactor that permits continuous bubbling of O_2 in the reaction mixture (Figure 1). On the other hand, pyridones of structural type **111** are normally prepared by cyclization of acyclic precursors: their assembly in the [3+3] format of Scheme 20 is quite unusual, but potentially valuable. This encouraged us to seek a way to maximize the formation of such "descyano" pyridones. In that connection, it was observed that compounds **111** become the exclusive



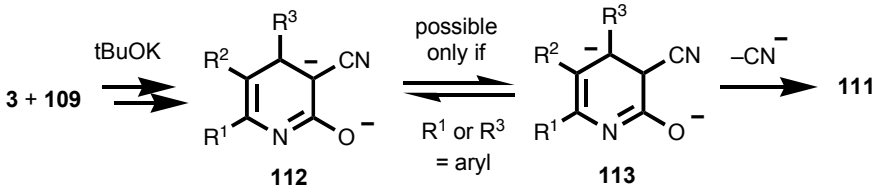
Scheme 20

Table 3. Representative 3-cyano-2-pyridones obtained by the new process

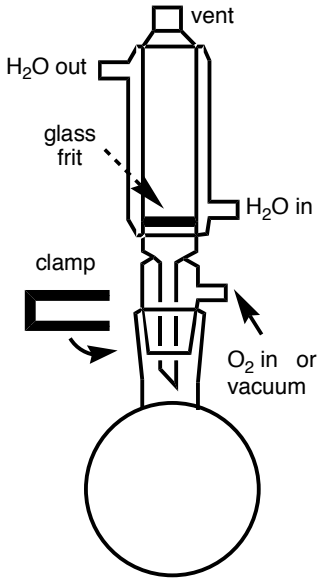


entry	R^1	R^2	R^3	% yield
a	Ph	H	Ph	88
b	Me	H	4-MeO-C_6H_4	83
c	Me	H	*i*-Pr	64
d	Me	H	*cyclo*-C_6H_{11}	63
e	H	H	Ph	65
f	H	H	2-MeO-C_6H_4	61
g				89
h				81

products of reactions run under O_2-free conditions, provided that the substrate possesses at least one aromatic ring in conjugation with the C=O group (Table 4).[44] Such an aryl group appears to promote equilibration of an initially formed dianionic intermediates **112** with one of the type **113**, which then aromatizes through elimination of cyanide ion (Scheme 21). The latter step is greatly facilitated by heating to 100-140° C.



Scheme 21

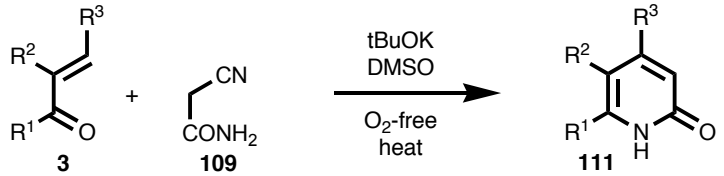


The device is securely clamped to a flask of appropriate size. The upper chamber is charged with a DMSO solution of an enone (or enal) and cyanoacetamide, then O_2 flow is started. Gas flow and the viscosity of DMSO keep the solution from percolating through the frit. Addition of t-BuOK induces an exothermic reaction that may be moderated, if necessary, by passing cold water through the outer jacket of the device. When the reaction is complete, gas flow is halted and vacuum is applied. The reaction mixture passes through the frit (removal of suspended matter) into the flask. The pyridone precipitates upon acidification of the filtrate and it is recovered by filtration.

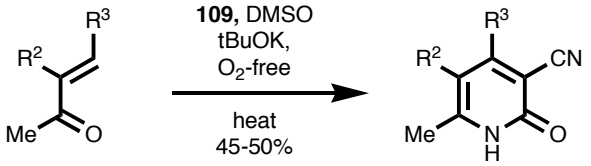
Figure 1. Reactor for 3-cyanopyridone synthesis

In support of the above mechanistic picture, aliphatic enones **114** and **115** reacted with **109** to give 3-cyano-2-pyridones **116** and **117** even in the anoxic regime, albeit in moderate yield (Scheme 22). We believe that **114**-**115** again combine with **109** to form transient dianions of the type **112**, which now can no longer isomerize to **113**. Instead, they react with DMSO as described by Massiot[45] to yield **116**-**117**.

Table 4. Representative 3-unsubstituted-2-pyridones prepared by the new procedure



entry	R^1	R^2	R^3	% yield
a	Me	H	4-Me-C_6H_4	60
b	Me	H	4-MeO-C_6H_4	55
c	Me	H	3-CF_3-C_6H_4	84
d	Ph	H	Ph	99
h	Me	H	Ph	89
i	H	H	Ph	69
j	H	H	4-MeO-C_6H_4	80

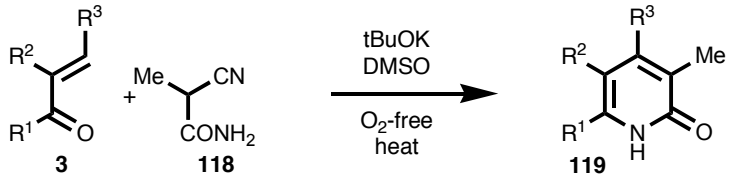


114 $R^2 = H$, $R^3 = C_5H_{11}$-n
115 $R^2 = R^3 = Me$
116 $R^2 = H$, $R^3 = C_5H_{11}$-n
117 $R^2 = R^3 = Me$

Scheme 22

The use of a 2-alkyl homolog of **109** in the chemistry of Table 4 provides a convenient route to 3-alkyl-2-pyridones. Table 5 outlines the preparation of representative 3-methyl-2-pyridones, **119**, by this method.[46] A modification of the technique permits the construction of synthetically valuable 4-pyridonyl

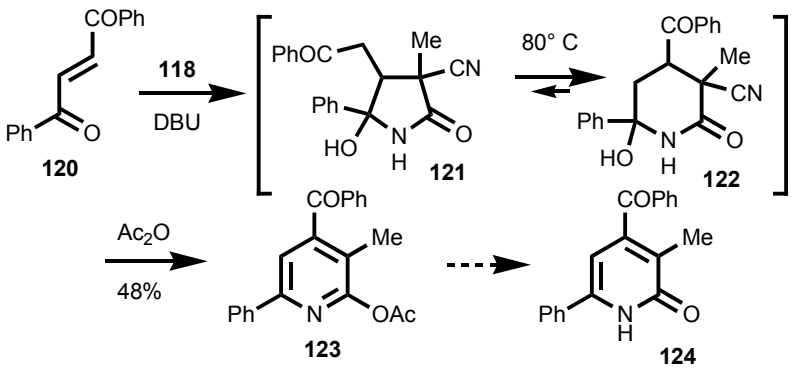
Table 5. Some 3-methyl-2-pyridones obtained by the new procedure



3 **118** **119**

entry	R^1	R^2	R^3	% yield
a	Ph	H	Ph	88
b	Me	H	Ph	70
c	2-quinolyl	H	Ph	99

ketones from 1,2-diacylethylene substrates. As exemplified in Scheme 23, the cyanoamide component, e.g., **118**, is first added in a 1,4-sense to the carbonyl compound (catalytic DBU), resulting in formation of a mixture of amidal isomers **121** and **122**. Thermal equilibration of this mixture (80 °C) promotes the

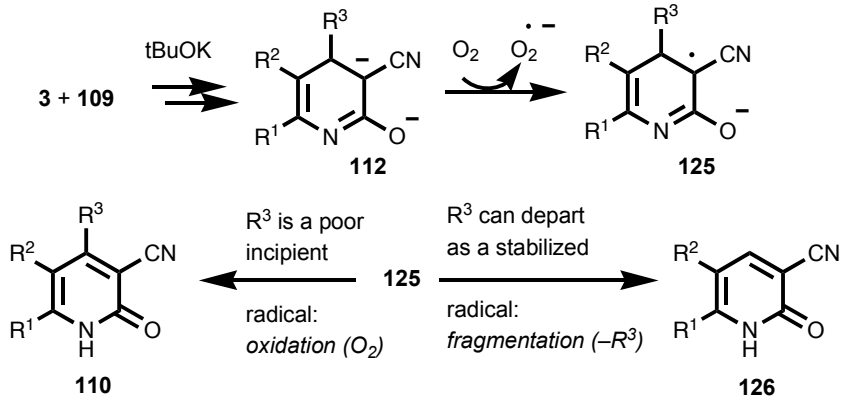


120 **121** **122** **123** **124**

Scheme 23

accumulation of isomer **122**.[44] A final treatment with Ac_2O finally triggers formation of acetoxy pyridine **123**, which is hydrolyzed to **124** during workup of the reaction.[47]

A troublesome limitation of the pyridone chemistry of Table 3 manifests itself when group R^3 in **3** is apt to depart as a stabilized radical. This encourages the formation of variable quantities of abnormal pyridones **126** (Scheme 24). Relative to "normal" products **110**, compounds **125** have suffered excision of the R^3 substituent, and as consequence we refer to them as "eunuch pyridones." Their genesis is attributable to fragmentation of a presumed radical intermediate of structure **125**, which we believe to arise from dianion **112** through SET reaction with O_2. Radical **125** may partition between an oxidative pathway leading to the anticipated **110**, and a fragmentation one that yields **126**. Controlling the formation of such eunuch pyridones proved to be generally difficult.[14]

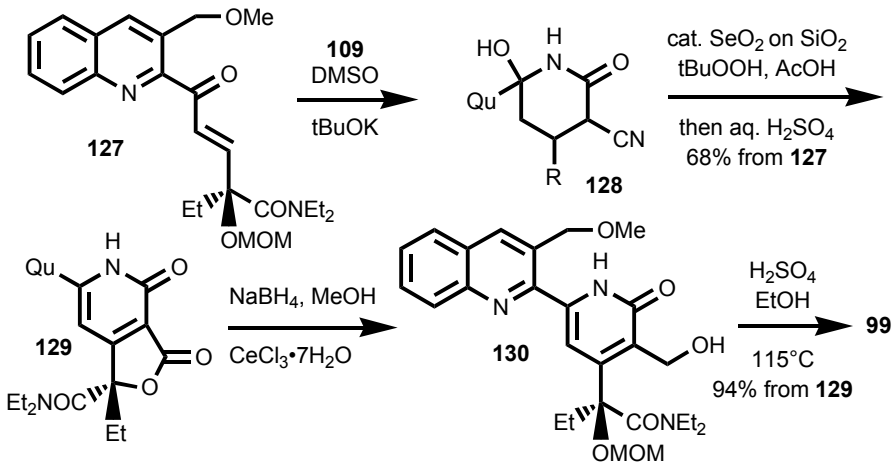


R^3	ratio of **110** to **126**
aryl	100 : 0
n-alkyl	100 : 0
cycloalkyl	97-99 : 1-3
1,1-diethoxyethyl	95 : 5
3-hydroxy-1-penten-3-yl	0 : 100

Scheme 24

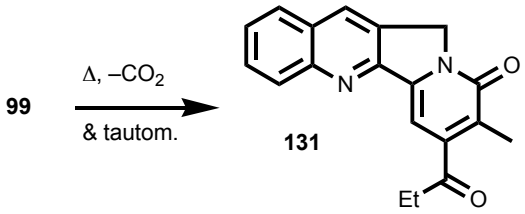
SYNTHESIS OF (+)-CAMPTOTHECIN, NOTHAPODYTINE B, AND STREPTONIGRONE.

The pyridone chemistry forms the centerpiece of our syntheses of (+)-camptothecin, nothapodytine B, and streptonigrone. Salient aspects of the synthesis of **99** are highlighted in Scheme 25. Our initial intent was to reach an advanced pyridone intermediate through the union of **127** with **109** as per Table 3. However, we discovered that **127** and related enecarbonyl compounds were exceedingly prone to form the eunuch pyridones under standard conditions (tBuOK, DMSO, O_2). All efforts to moderate such a proclivity proved fruitless. Fortunately, a two-step sequence that involved 1,4-addition of **109** to **127** and oxidation of the resultant **128** with tBuOOH and catalytic SeO_2 on silica gel[48] permitted efficient access to pyridone **129**, which is recognized as a variant of the so-called Stork lactone.[49] Luche-type reduction of **129** proceeded quantitatively to afford **130**, vigorous acidic treatment of which provided (+)-**99**.[50]



Scheme 25

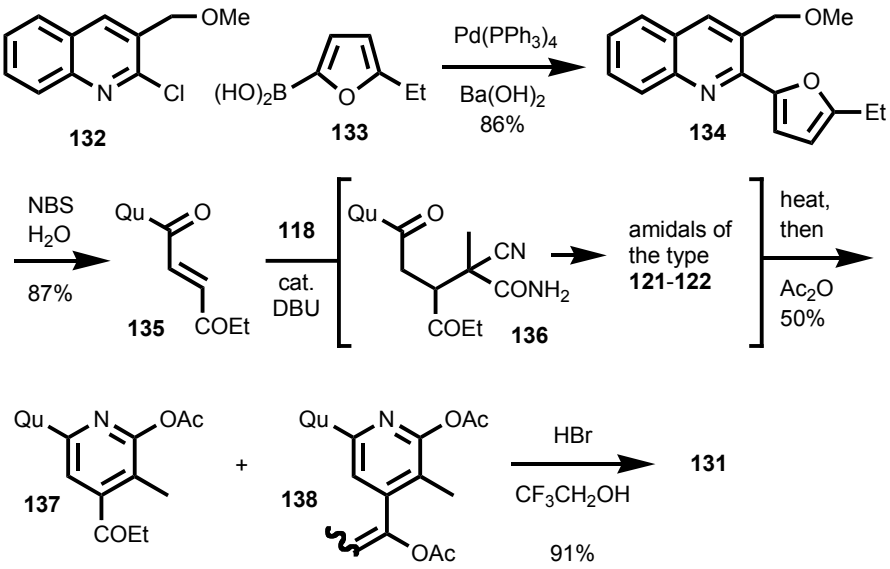
Better luck awaited the application of the methodology for 3-alkylpyridone construction to the total synthesis of nothapodytine B, **131**, and of streptonigrone, **49**. Alkaloid **131** bears an obvious resemblance to camptothecin, and indeed it is a product of thermolysis thereof (Scheme 26).[51] It is not cytotoxic, but it possesses useful antiviral activity.[52] The compound has been the focus of a number of synthetic studies that reflect noteworthy advances in heterocyclic chemistry.[53] Our own synthesis of **131**[44] proceeded in 4



Scheme 26

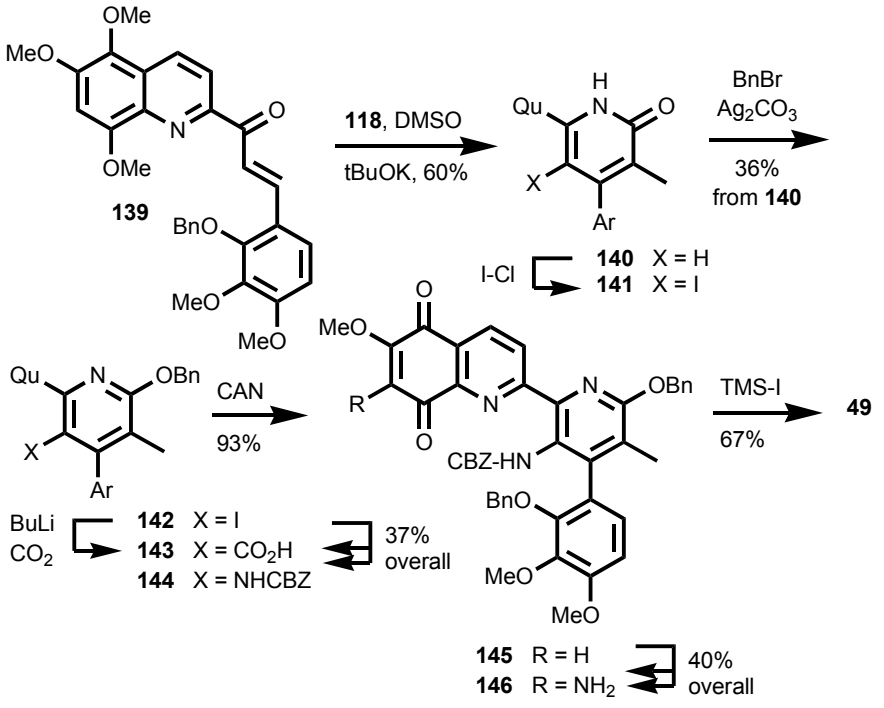
steps starting with Suzuki coupling of chloroquinoline **132** with **133** (Scheme 27).[54] Oxidative cleavage of the furan ring in the ensuing **134** (aqueous NBS)[55] surrendered **135**. This diacylethylene compound served as the enone component of a 3-methylpyridone construction under the conditions of Scheme 23. The electron-withdrawing character of quinoline ring renders the C-2 quinolyl carbonyl group particularly electrophilic. As a consequence, that C=O group completely controls the electrophilic reactivity of the olefinic linkage. Conjugate addition of **118** thus occurred with exclusive formation of amidals of the type **121** and **122** arising from regioisomer **136** of the Michael product. Thermal equilibration of such amidals and Ac_2O treatment afforded a mixture of **137** and **138**. Treatment of such a mixture with HBr in trifluoroethanol[56] produced the target alkaloid in 34% overall yield for the 4-step sequence.

The key phases of our synthesis of streptonigrone appear in Scheme 28. The condensation of enone **139** with **118** was carried out under standard conditions to afford **140** in 60% yield. Exposure of the latter to I–Cl resulted in a highly selective iodination at the pyridone C-5 position (pyridone numbering). The resultant **141** is a sensitive compound that was best converted immediately, and without purification, to



Scheme 27

pyridine **142**. Installation of the requisite amino functionality proceeded by a two-step sequence involving halogen-metal exchange (n-BuLi) and carboxylation (dry CO_2 gas), followed by a time-honored Yamada-Curtius reaction.[57] The synthesis continued with CAN oxidation of the electron-rich quinoline in **144** to the corresponding quinone **145**, which underwent amination to **146** by a modification of a sequence originally described by Weinreb.[58] The synthesis culminated with a global deprotection of **146** using TMS-I.[59]



Scheme 28

CONCLUSION

The reactions described herein facilitate the construction of substituted pyridines and pyridones of interest in both natural products and in medicinal chemistry. We believe that in many cases the above techniques are superior to known alternatives for the synthesis of the heterocycles of interest. It is our hope that practitioners of synthetic heterocyclic chemistry in both industry and academia will make increasingly greater use of these useful methods.

ACKNOWLEDGMENT

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REFERENCES (AND NOTES)

1. (a) N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.,* 1952, **74**, 4923; H. Stobbe and C. Striegler, *J. Prakt. Chem.,* 1912, **86**, 241; E. Knoevenagel and R. Weissgerber, *Ber.,* 1893, **26**, 436.
2. Cf. K. Haffner, *Tetrahedon Lett.,* 1994, **35**, 1349 (31% yield); R. Paul and S. Tschelitscheff, *Bull. Soc. Chim. Fr.,* 1954, 1139; C. H. Heathcock, E. F. Kleinmn, and E. S. Binkley, *J. Am. Chem. Soc.,* 1982, **104**, 1054, and refs. cited therein.
3. Kametani's pioneering studies on streptonigrin are especially informative: T. Kametani, A. Kozuka, and S. Tanaka, *Yakugaku Zasshi,* 1970, **90**, 1574; T. Kametani, S. Tanaka, and A. Kozuka, *Yakugaku Zasshi,* 1971, **91**, 1068.
4. The term “cycloaddition” as used in this paper is only meant to describe the outcome of the reaction of a conjugated carbonyl compound with a vinyl ether, and it should not be construed as implying any particular mechanism for the process.
5. R. I. Longley, W. S. Emerson, and A. J. Blardinelli, *Org. Synth. Coll. Vol. IV*, 1963, 311. See especially Note 6 therein.
6. S. Danishefsky and M. Bednarski, *Tetrahedron Lett.* 1984, **25**, 721.
7. The major frontier orbital interaction involved in this process occurs between the HOMO of the vinyl ether and the LUMO of the enone. Conjugation of the enecarbonyl system with an aryl group lowers the LUMO energy (EHMO calculations), diminishing the HOMO-LUMO gap and accelerating the reaction.

8. Interestingy, lanthanide complexes are poor catalysts for the analogous reaction of simple aliphatic enones. For an exceptional case see: Y. Chapleur and M.-N. Euvrard, *J. Chem. Soc., Chem. Commun.,* 1987, 884.
9. Ethanol was initially employed as the solvent in this step (see ref. 10), but MeCN was later found to be superior. In many cases, the use of MeCN is essential to achieve an efficient conversion.
10. M. A. Ciufolini and N. E. Byrne, *J. Chem. Soc., Chem. Commun.*, 1988, 1230; N. E. Byrne, *Dissertation*, Rice University, 1991; M. A. Ciufolini, 'Advances in Heterocyclic Natural Product Synthesis,' ed. by W. H. Pearson, JAI Press, Greenwich, CT, 1996; Vol. 3, p. 1. For additional examples of this useful reaction see: J. G. Cordaro, J. K. McCusker, and R. G. Bergman, *Chem. Commun.*, 2002, 1496.
11. H. Beschke, *Aldrichimica Acta,* 1978, **11**, 13.
12. S. Hoff, L. Brandsma, and J. F. Arens, *Rec. Trav. Chim. Pays-Bas,* 1968, **87**, 916.
13. A. Hosomi, H. Hashimoto, and H. Sakurai, *J. Org. Chem.,* 1978, **43**, 2551.
14. M. A. Ciufolini and F. Roschangar, *Tetrahedron*, 1997, **53**, 11049.
15. That such failures are due primarily to steric or to electronic problems is borne out of computational investigations (EHMO and MM+ methods).
16. Leading reviews: Z. Li, Z. Jin, and R. Huang, *Synthesis* 2001, 2365; E. Gellert, 'Alkaloids: Chemical and Biological Perspectives,' Vol 5., ed. by S. W. Pelletier, John Wiley & Sons, New York, 1987, p. 55; M. Suffness and G. A. Cordell, 'The Alkaloids,' Vol. 25, ed. by A. Brossi, Academic Press, Inc, Orlando, 1985, p. 156; R. C. Bick and W. Sinchai, 'The Alkaloids,' Vol 19, ed by R. G. A. Rodrigo, Academic Press, New York, 1981, p. 193; T. R. Govindachari and N. Viswanathan, *Heterocycles,* 1978, **11**, 587.
17. Recent work: L. Wei, Q. Shi, K. F. Bastow, A. Brossi, S. L. Morris-Natschke, K. Nakagawa-Goto, T.-S. Wu, S. L. Pan, C.-M. Teng, and K.-S. Lee, *J. Med. Chem.*, 2007, **50**, 3674; C.-W. Yang, T.-H. Chuang, P.-L. Wu, W.-H. Huang, and S.-J. Lee, *Biochem. Biophys. Res. Commun.*, 2007, **354**, 942; L. Wei, A. Brossi, R. Kendall, K. F. Bastow, S. L. Morris-Natschke, Q. Shi, and K.-H. Lee, *Bioorg. Med. Chem.*, 2006, *14*, 6560.
18. W. Gao, W. Lam, S. Zhong, C. Kaczmarek, D. C. Baker, and Y.-C. Cheng, *Cancer Res.*, **2004**, *64*, 678, as well as ref. 16.
19. C.-W. Yang, W.-L. Chen, P.-L. Wu, H.-Y. Tseng, and S.-J. Lee, *Mol. Pharmacol.*, 2006, **69**, 749, and refs. cited therein.
20. This compound was not a known natural product at that time, but it was subsequently isolated from *Cynanchum vincetoxicum*: D. Strk, A. K. Lykkeberg, J. Christensen, B. A. Budnik, F. Abe, and J. W. Jaroszewski, *J. Nat. Prod.*, 2002, **65**, 1299.

21. M. A. Ciufolini and F. Roschangar, *J. Am. Chem. Soc.,* 1996, **118**, 12082.
22. D. M. Balitz, J. A. Bush; W. T. Bradner, T. W. Doyle, F. A. O'Herron, and D. E. Nettleton, *J. Antibiot.*, 1982, **35**, 259.
23. S. J. Gould and C. C. Chang, *J. Am. Chem. Soc.*, 1980, **102**, 1702; S. J. Gould, C. C. Chang, D. S. Darling, J. D. Roberts, and M. Squillacote, *J. Am. Chem. Soc.*, 1980, **102**, 1707.
24. Reviews: G. Bringmann, Y. Reichert, and V. V. Kane, *Tetrahedron*, 2004, 60, 3539; D. L. Boger, *Strategies Tactics Org. Synth.*, 1989, **2**, 1. S. J. Gould and S. M. Weinreb, *Prog. Chem. Org. Nat. Prod.*, 1982, **41**, 77.
25. For instance: (a) inhibition of NO-dependent activation of soluble guanylyl cyclase: I. S. Severina, N. V. Pyatakova, A. B. Postnikov, M. N. Preobrazhenskaya, and Y. V. Khropov, *Eur. J. Pharmacol.*, 2004, **483**, 127. (b) inhibition of *ras* farnesylation: W. C. Liu, M. Barbacid, M. Bulgar, J. M. Clark, A. R. Crosswell, L. Dean, T. W. Doyle, P. B. Fernandes, S. Huang, V. Manne, D. M. Pirnik, J. S. Wells, and E. Meyers, *J. Antibiot.*, 1992, **45**, 454. (c) inhibition of reverse transcriptase: H. Okada, H. Mukai, Y. Inouye, and S. Nakamura, *J. Antibiot.*, 1986, **39**, 306. (d) induction of topoisomerase II-dependent DNA cleavage: Y. Yamashita, S. Kawada, N. Fujii, and H. Nakano, *Cancer Res.*, 1990, **50**, 5841.
26. Recent work: T. Fryatt, H. I. Pettersson, W. T. Gardipee, S. J. Green, A. M. Z. Slawin, H. D. Beall, and C. J. Moody, *Bioorg. Med. Chem.* 2004, **12**, 1667; W. T. McElroy and P. DeShong, *Tetrahedron* 2006, **62**, 6945, and references cited therein.
27. Leading reviews: E. Delfourne and J. Bastide, *Med. Res. Rev.* 2003, **23**, 234; D. Skyler and C. H. Heathcock, *J. Nat. Prod.* 2002, **65**, 1573; Q. Ding, K. Chichak, and J. W. Lown, *Curr. Med. Chem.* 1999, **6**, 1; T. F. Molinski, *Chem Rev.* 1993, **93**, 1825.
28. I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Research,* 1977, 17; J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, and H. Suschitzsky, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2194.
29. We presume that the reaction actually proceeds through a 4-electron electrocyclization of the singlet nitrene, followed by a [1,5]-sigmatropic H shift.
30. Controversy persists regarding the precise mechanism of such reactions, especially with regard to the spin state of the nitrene: G. Smolinsky, *J. Am. Chem. Soc.,* 1961, **83**, 2489; J. S. Swenton, *Tetrahedron Lett.*, 1968, 3421; J. S. Swenton, I. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.*, 1970, **92**, 3103; Smith, P. A. S. 'Azides and Nitrenes: Reactivity and Utility,' ed. by E. F. V. Scriven, Academic Press, Inc., Orlando, FL, 1984, Chapter 3.
31. Thermolysis of **69** also proceeded smoothly; however, the ensuing carboline resisted oxidation of the pyridine C-6 methyl group, arguably due to the presence of the electron-donating N-substituent on the pyridine ring: P. J. Wittek, T. K. Liao, and C. C. Cheng, *J. Org. Chem.*, 1979, **44**, 870.

32. D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, 1985, **50**, 5790.
33. M. A. Ciufolini and M. J. Bishop, *J. Chem. Soc., Chem. Commun.*, 1993, 1463.
34. M. A. Ciufolini and N. E. Byrne, *J. Am. Chem. Soc.*, 1991, **113**, 8016.
35. M. A. Ciufolini and Y.-C. Shen, *Tetrahedron Lett.*, 1995, **36**, 4709.
36. M. A. Ciufolini, Y.-C. Shen, and M. J. Bishop, *J. Am. Chem. Soc.*, 1995, **117**, 12460.
37. M. J. Bishop and M. A. Ciufolini, *J. Am. Chem. Soc.*, 1992, **114**, 10081.
38. Leading references - chemistry: M. E. Wall, and M. C. Wani, '*The Alkaloids*,' ed. by G. A. Cordell, Academic Press, Inc., San Diego, CA, 1998; vol 50, ch. 13; Y. Kawato and H. Terasawa, *Progr. Med. Chem.*, 1997, **34**, 69, W. Du, *Tetrahedron*, 2003, **59**, 8649. Pharmacology: L. M. Randall-Whitis and B. J. Monk, *Exp. Opinion Pharmacother.*, 2007, **8**, 227; Q. Y. Li, Y. G. Zu, R.-Z. Shi, and L. P. Yao, *Curr. Med. Chem.*, 2006, **13**, 2021.
39. M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, 1966, **88**, 3888.
40. Y. H. Hsiang, R. Herzberg, S. Hecht, and L. F. Liu, *J. Biol. Chem.*, 1985, **260**, 14873; P. Philippart, L. Harper, C. Chaboteaux, C. Decaestecker, K. Bronckart, L. Gordover L. Lesueur-Ginot, H. Malonne, O. Lavergne, D. C. H. Bigg, P. M. da Costa, and R. Kiss, R. *Clin. Cancer Res.*, 2000, **6**,1557; C. F. Stewart, *Cancer Chemother. Biol. Resp. Modif.*, 2001, **19**, 85; B. Arun and E. P. Frenkel, *Exp. Opin. Pharmacother.*, 2001, **2**, 491.
41. Review: M. Kreditor, M. Fink, and H. S. Hochster, *Cancer Chemother. Biol. Resp. Modif.*, 2005, **22**, 100. For emerging drugs derived from CPT see: F. Zunino and G. Pratesi, *Exp. Opin. Invest. Drugs*, 2004, **13**, 269; R. W. Versace, *Exp. Opin. Ther. Patents*, 2003, **13**, 751.
42. Discussion: H. Meislich, 'Pyridine and its Derivatives,' ed. by E. Klingsberg, Interscience, Inc., New York, 1962; Vol. 3, p 509; P. R. Ruby, 'Pyridine and its Derivatives,' ed. by E. Klingsberg, Interscience, Inc., New York, 1960; Vol. 1, p. 99 (see especially p. 286); H. H. Otto and O. Rinus, *Arch. Pharm.* 1979, *312*, 548; G. Jones, 'Comprehensive Heterocyclic Chemistry,' ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, UK, 1984; Vol. 2A, p 395.
43. R. Jain, F. Roschangar, and M. A. Ciufolini, *Tetrahedron Lett.*, 1995, **19**, 3307.
44. L. Carles, K. Narkunan, S. Penlou, L. Rousset, D. Bouchu, and M. A. Ciufolini, *J. Org. Chem.*, 2002, **66**, 4304.
45. G. Massiot, F. Sousa Oliveira, and J. Levy, *Tetrahedron Lett.*, 1982, **23**, 177.
46. Additional example of 3-alkylpyridone synthesis by a similar [3+3] construction: A. R. Katritzky, S. A. Belyakov, A. E. Sorochinsky, S. A. Henderson, and J. Chen, *J. Org. Chem.*, 1997, **62**, 6210.
47. The sensitivity of diacylethylenes to the basic conditions of Table 5 mandated such experimental modifications.

48. T. Ohtsuka, H. Shirahama, and T. Matsumoto, *Chem. Lett.*, 1981, 1703.
49. G. Stork and A. G. Schultz, *J. Am. Chem. Soc.*, 1971, **16**, 4074.
50. Ref. 14 as well as: M. A. Ciufolini and F. Roschangar, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1692; M. A. Ciufolini, and F. Roschangar, 'Targets in Heterocyclic Chemistry,' Vol. 3, ed. by O. A. Attanasi and D. Spinelli, Italian Society of Chemistry, Rome, 2000.
51. J. M. D. Fortunak, A. R. Mastrocola, M. Mellinger, and J. L. Wood, *Tetrahedron Lett.*, 1994, **35**, 5763.
52. E.g.: D. P. Curran, M. A. Parniak, and A. Gabarda, PCT Int. Appl. 2003, WO 2003103610.
53. For synthetic activity prior to 2002 see refs. 44 and 56. Recent efforts: W. R. Bowman, M. O. Cloonan, A. J. Fletcher, and T. Stein, *Org. Biomol. Chem.*, 2005, **3**, 1460; S. P. Chavan and S. Rasapalli, *Tetrahedron Lett.*, 2004, **45**, 3941; G. B. Raolji, S. Garçon, A. E. Greene, and A. Kanazawa, *Angew. Chem. Int. Ed.*, 2003, **42**, 5059; K. E. Henegar, and T. A. Baughman, *J. Heterocycl. Chem.*, 2003, **40**, 601; I. Kato, M. Higashimoto, O. Tamura, and H. Ishibashi, *J. Org. Chem.*, 2003, **68**, 7983.
54. For similar Pd-mediated reactions of 2-chloroquinolines see: M. A. Ciufolini, J. W. Mitchell, and F. Roschangar, *Tetrahedron Lett.*, 1996, **37**, 8281.
55. Y. Kobayashi, M. Nakano, G. B. Kumar, and K. Kishihara, *J. Org. Chem.*, 1998, **63**, 7505.
56. J. Hong and D. L. Boger, *J. Am. Chem. Soc.* 1998, **120**, 1218.
57. T. Shioiri, T., K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203; K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, 1974, **30**, 2151.
58. S. M. Weinreb, F. Z. Basha, S. Hibino, N. A. Khatri, D. Kim, W. E. Pye, and T.-T. Wu, *J. Am. Chem. Soc.*, 1982, **104**, 536; D. Kim and S. M. Weinreb, *J. Org. Chem.* , 1978, **43**, 125; S. Hibino and S. M. Weinreb, *J. Org. Chem.*, 1977, **42**, 232.
59. B. K. Chan and M. A. Ciufolini, *J. Org. Chem.*, 2007, **72**, 8489.

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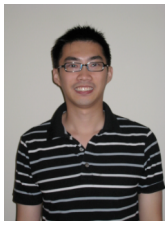

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