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Synthetic ventures inspired by biosynthetic hypotheses: the evolution of a method for the oxidative amidation of phenols

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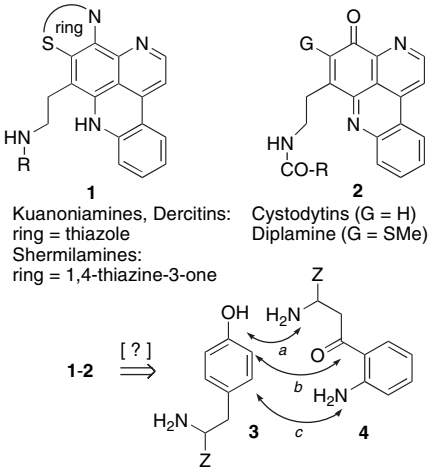
Abstract—We describe the development of a technique for the oxidative conversion of 4-alkyl phenols to derivatives of the corresponding 4-alkyl-4-amino-2,5-cyclohexanediones. This transformation, which was inspired by biogenetic considerations, constitutes a key step in the total syntheses of FR-901483, TAN-1251C, and cylindricine C.

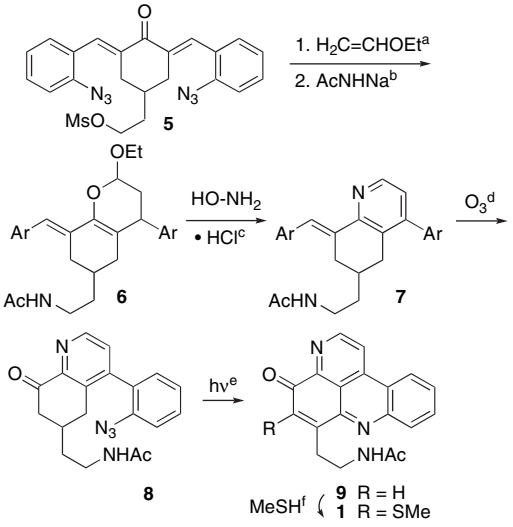
1. Introduction

The senior author of this article discovered the fascinating world of biosynthesis through an elective course in bioorganic chemistry that he attended as a graduate student.[1] Since then, almost as a reflex, he has routinely engaged in the exercise of imagining how an organism's biosynthetic machinery could possibly assemble the structure of an architecturally appealing natural product, even though he is not involved in the study of biosynthesis per se.

Such an exercise does not constitute mere intellectual overkill. Indeed, biogenetic considerations often suggest interesting strategies for the synthesis of structurally novel natural products, and may even lead to the development of valuable new methodology. For instance, our work on pyridoacridine alkaloids[2] was inspired by the supposition that the ring system of these substances, which are exemplified by structural types **1**–**2** in Scheme 1, may result through oxidative condensation of a molecule of tyramine (**3**, Z=H, a product of degradation of tyrosine, Z=COOH) with one of kynurenin or kynuramine (**4**, Z=COOH or Z=H), as outlined in Scheme 1. This surmise, details of which may have been misconstrued as embodying claims,[3] led to the development of techniques that accomplish the equivalent of bond-forming processes *a*–*c* through a new pyridine-forming reaction (*a*–*b*)[4] and a Meth-Cohn nitrene insertion into a C–H bond (*c*). Scheme 2



Scheme 1.



Scheme 2. (a) cat. $Yb(fod)_3$, $(CH_2Cl)_2$, reflux, 99%; (b) NaH, DMF, 97%; (c) MeCN, reflux, 62%; (d) O_3, CH_2Cl_2/MeOH, −78 °C, then Me_2S, 67%; (e) 250 W sunlamp, PhCl, 110 °C, then titration with DDQ, 30%; (f) 4:1 CH_2Cl_2/AcOH, then removal of volatiles and titration with DDQ in CH_2Cl_2, 94%.

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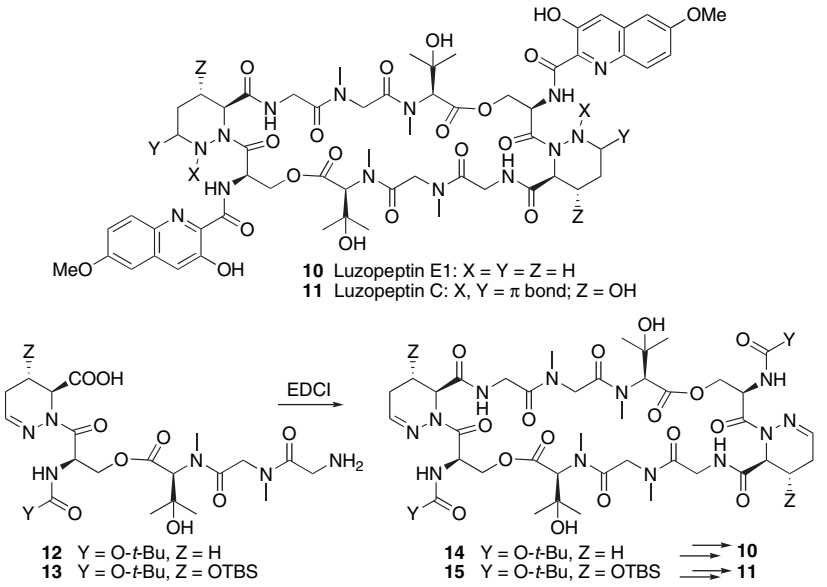


Scheme 3.

highlights these methods (**5**→**7** and **8**→**9**, respectively) in the context of the total synthesis of diplamine.[5]

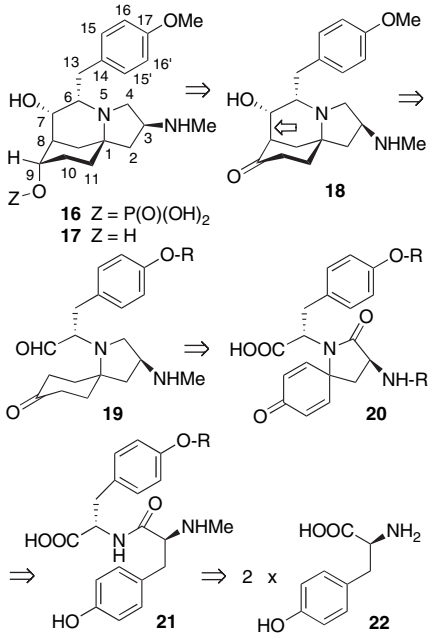
Other times, the pursuit of a 'biomimetic' approach to a target molecule may reveal unexpected chemical properties of an advanced intermediate that greatly facilitate endgame planning. This is what happened during our synthesis of luzopeptins (Scheme 3). Our strategy was influenced by the hypothesis that the macrocyclic portion of **10**–**11** is likely to emerge upon enzymatic cyclodimerization of a pentapeptide of the type **12**–**13**. It was ultimately discovered that C-terminus activation of **12**–**13** themselves triggers spontaneous assembly of macrocycles **14**–**15**. Yields are moderate (25% and 26%, respectively), but comparable to those observed in a stepwise sequence relying on preparation and cyclization of a discrete linear decapeptide.[6] Substances **14**–**15** were elaborated to luzopeptins E1 and C, respectively.[7]

2. FR-901483 and TAN-1251: development of a novel oxidative amidation of phenols

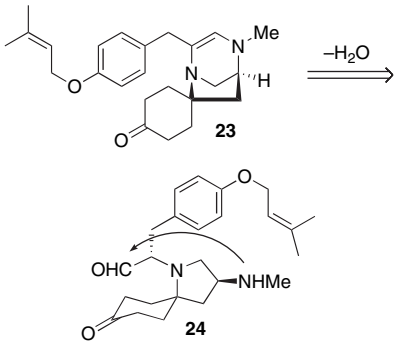
Unique opportunities for the development of methodology materialized in the mid-1990s with the discovery of a fungal metabolite termed FR-901483, **16** (Scheme 4).[8,9] This remarkable compound displays potent immunosuppressive activity, which is intimately associated with the presence of the labile C-9 phosphate ester. Unfortunately, phosphatases rapidly convert **16** to the corresponding diol **17**, which is inactive. Prospects for further development of **16** as a drug, therefore, seem modest.

Regardless, the structural novelty of **16** provided an irresistible opportunity for biogenetic speculation, and the fact that many nitrogenous natural products derive from aminoacids led to the conclusion that FR-901483 must be a dimer of tyrosine. Indeed, if the oxygen atom anchoring the phosphate ester were at some point part of a keto group, then the C-7–C-8 bond in the hypothetical intermediate **18** could be created through a regio- and diastereoselective intramolecular aldol cyclization of ketoaldehyde **19**, R=Me. The latter aldehyde might well emanate from biosynthetic precursor **20**, which is the product of oxidative spirolactamization of tyrosinyltyrosine **21**. If one could duplicate the conversion of **21** to **20** in the laboratory, then the synthesis of **16** would become relatively straightforward, and it could be carried out using enantiopure, inexpensive tyrosine, **22**, as the starting material.

An analogous reaction might also facilitate the synthesis of a group of fungal metabolites discovered at the Takeda Pharmaceutical Co. in Japan, and christened the TAN-1251 family of compounds.[10] These substances appear to share a common biogenetic precursor with **16** in the form of a variant of aldehyde **19** wherein R=prenyl. This material, described in Scheme 5 as compound **24**, may advance to TAN-1251C, **23**, via intramolecular enamine formation.

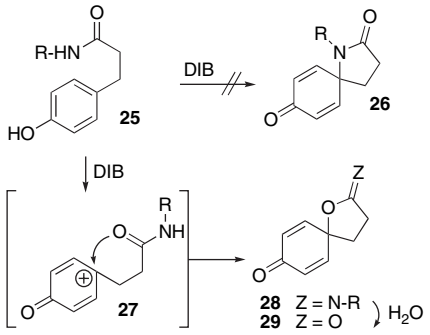


Scheme 4.



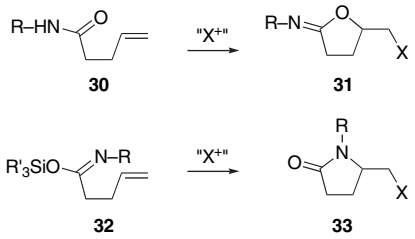
Scheme 5.

A search of the literature revealed that the oxidative cyclization of phenolic amides such as **21** to spirolactams of the type **20** was unknown,[11] even though the interest (and the synthetic potential!) of this transformation had obviously been recognized years earlier. For instance, in 1987 Kita described the reaction of **25** with $PhI(OAc)_2$ ('DIB'), or $PhI(OCOCF_3)_2$ ('PIFA').[12] Perhaps the intent was to reach spirolactams of the type **26**. However, oxidative attack of **25** furnished only lactone **29**, arguably through capture of an electrophilic intermediate arising from the phenol, and naively represented in Scheme 6 as **27**, by the carbonyl oxygen of the amide group. Hydrolysis of the intervening iminolactone **28** during workup then produces **29**.



Scheme 6.

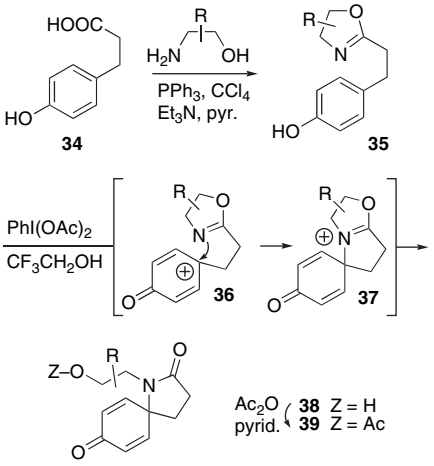
Knapp encountered analogous difficulties during work on the iodo-amidation of olefins.[13] Thus, reaction of **30** with I_2 resulted in the formation of **31** instead of the desired **33** (Scheme 7). These observations, and Kita's, are consistent with the notion that resonance interactions between the N atom and the carbonyl system in an amide promote accumulation of electronic density on the oxygen atom, which therefore becomes nucleophilic at the expenses of the N atom. Knapp circumvented such difficulties by the use of iminoethers **32** as substrates for iodolactamization. Resonance



Scheme 7.

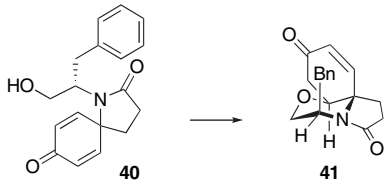
interactions in **32** now promote accumulation of electronic density on the nitrogen atom, which therefore becomes capable of expressing the desired nucleophilic reactivity.

It seemed to us that the same logic could be put to profit in our case, provided that an iminoether-type functionality resistant to the action of oxidants (e.g., DIB) could be identified. Oxazolines ultimately emerged as suitable amide equivalents in these transformations.[14] Such heterocycles are prepared by condensation of a phenolic carboxylic acid with a suitable 1,2-aminoalcohol. The Vorbrüggen oxazoline synthesis[15] proved to be especially effective for this purpose because, contrary to other methods for oxazoline formation,[16] it required no protection of the phenol. This removed the need for a supplementary protection/deprotection sequence. An initial version of the (formal) oxidative spirolactamization of phenolic amides thus emerged as indicated in Scheme 8 for the conversion of **35** to **38**[17] under Kita-type[18] conditions.



Scheme 8.

Compounds of general structure **38** are prone to undergo spontaneous Michael cyclization to morpholine derivatives. The proclivity to cyclize appears to depend on structural details, but the resulting morpholines always form in a highly diastereoselective manner. For instance, compound **40** cyclized to give **41** exclusively (Scheme 9; structure ascertained by X-ray crystallography). The stereoselective formation of **41** is attributable to the strong preference for the axial orientation on the part of alkyl substituents flanking the nitrogen atom in *N*-acyl piperidines and related six-membered heterocycles.[19]

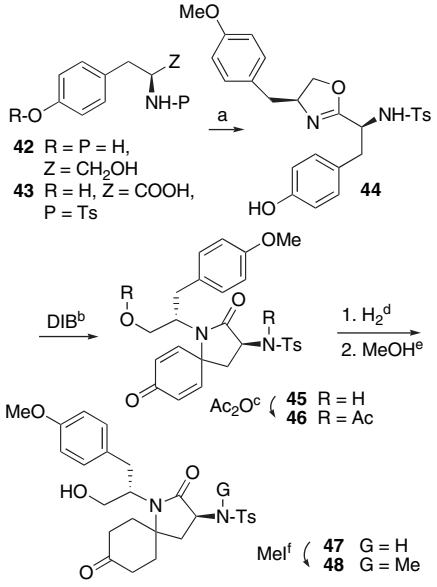


Scheme 9.

Morpholine formation is helpful in certain cases, because it leads to fully stereocontrolled desymmetrization of the 'locally symmetrical' dienone segment of the primary products, in a manner that secures a specific configuration of the now stereogenic spirocenter. This principle constitutes a

pivotal point in the synthesis of cylindricines (vide infra). In other instances, cyclization is problematic and must be suppressed. Acetylation of the OH group in **38** prior to purification readily accomplishes this objective. Overall yields of acetates **39** are typically between 45–50%. Such moderate yields must be weighed against the fact that the reaction rapidly converts inexpensive aminoacid-derived substances to valuable enantiopure intermediates.

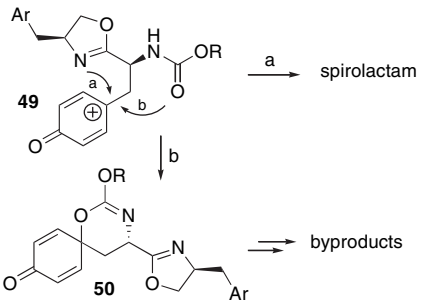
The opening moves of our syntheses of FR-901483 and TAN-1251C appear in Scheme 10. The key oxazoline **44** was prepared through the union of aminoalcohol **42** with acid **43**, both of which are readily available from L-tyrosine. Oxidative spirocyclization and acetylation of the primary product **45**, which was prone to Michael cyclization, provided **46**. The latter intermediate was uneventfully elaborated to **48**, at which stage the routes to TAN-1251C and FR-901483 diverged.



Scheme 10. (a) PPh_3, CCl_4, MeCN, pyridine, 25 °C, Et_3N, 73%; (b) CF_3CH_2OH, 25 °C; (c) pyridine, 4-DMAP, 25 °C, 41% b–c; (d) PtO_2, EtOAc, 25 °C, 96%; (e) K_2CO_3, 25 °C, 79%; (f) K_2CO_3, Me_2CO/DMF, 25 °C, 97%.

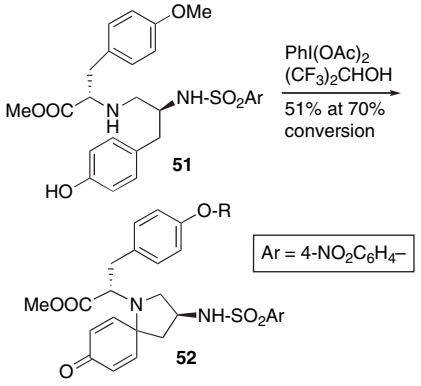
A comment is in order regarding our choice of an *N*-tosyl protecting group for **44**. Initial experiments carried out with variants of **44** displaying carbonyl-type *N*-protection furnished complex mixtures containing only some of the desired spirolactams. Byproducts were detected, the genesis of which is consistent with the following mechanistic picture. Oxidative activation of the phenol leads to an electrophilic intermediate represented in Scheme 11 as cation **49**. Capture by the oxazoline (pathway a) leads to the desired spirolactam. However, interception by the carbonyl group (pathway b) competes effectively, causing formation of iminocarbamate **50**, which then evolves to a variety of secondary products. It was necessary to subdue the nucleophilic aptitude of the *N*-blocking group in order to maximize formation of **45**. The use of an *N*-sulfonamido group emerged as an eminently effective solution.

A brief digression is appropriate at this juncture. The landmark Sorensen synthesis of **16** relied on an unprecedented



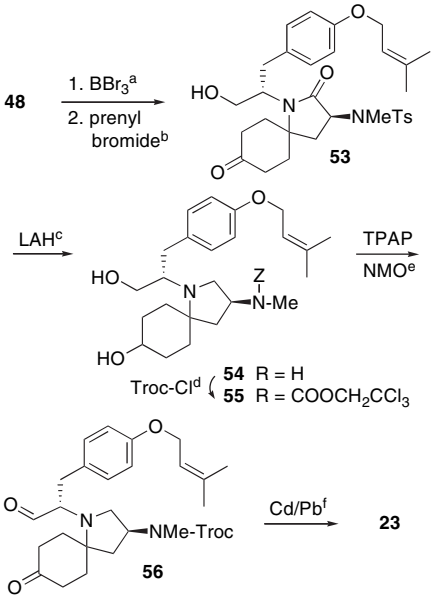
Scheme 11.

oxidative cyclization of phenolic amine **51** to spiropyrrolidine **52** (Scheme 12).[9b,20] Significantly, a sulfonamido protecting group was present on the spectator amino functionality in **51**. We presume that this choice was dictated by the difficulties adumbrated in Scheme 12.



Scheme 12.

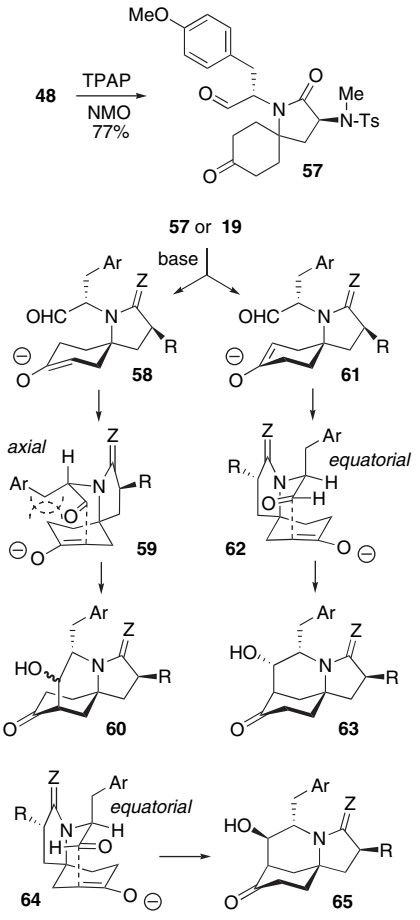
The operations leading from **48** to fully synthetic TAN-1251C[21] are depicted in Scheme 13. Phenolic ether exchange and vigorous LAH reduction provided **54**, which



Scheme 13. (a) CH_2Cl_2, −60 °C, 87%; (b) Cs_2CO_3, Me_2CO, 25 °C, 98%; (c) THF, 0 °C to reflux, 48 h, 88%; (d) aq THF, $NaHCO_3$, 25 °C, 62%; (e) CH_2Cl_2, 25 °C, 1 h, 63%; (f) THF, NH_4OAc buffer, 25 °C, 79%.

for ease of processing was *N*-blocked as the Troc derivative. Subsequent Ley oxidation[22] furnished ketoaldehyde **55**. Release of the free amino function with Cd/Pb couple[23] precipitated instant enamine formation leading to **23**. The yield of **23** from tyrosine was 4% over 16 steps.[24]

The synthesis of FR-901483 presented the complex issue of the aldol cyclization of ketoaldehyde **57**, prepared from **48** as detailed in Scheme 14, or of one of the type **19**. The success of this step is subordinate to the occurrence of the following sequence of events: the substrate must undergo chemoselective enolization of the cyclohexanone segment, leading to regioselective formation of enolate **61** (Z=H, H or O; P=prot. group), which must add diastereoselectively to the *Si*-face of the aldehyde to yield **65**. Superficially, any hope to entice **57**/**19** to behave as required may seem overly optimistic. A careful analysis leads to a more favorable prognosis.



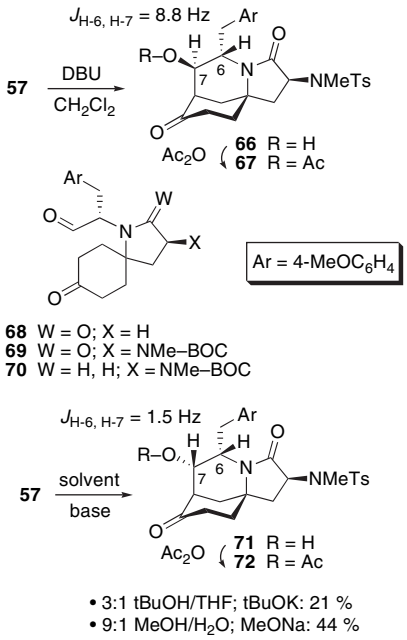
Scheme 14.

Important work by Myers indicates that the kinetics of enolization of protected α-amino aldehydes are not as rapid as one might expect.[25] This principle has been incorporated in a number of brilliant syntheses.[26] If this were true for **57**/**19**, then selective enolization of the cyclohexanone may be possible under gently basic conditions. Exposure to mild bases would promote reversible, non-regioselective formation of the ketone enolate and prime the molecule for aldol cyclization via isomeric chair-like transition states.[27] Scheme 14 illustrates that for a fixed (*S*)-configuration of the stereogenic center at the α-position of the aldehyde, aldol cyclization from the incorrect regioisomer of the cyclohexanone enolate, **58**, forces the 4-methoxybenzyl substituent into an axial orientation in transition states such as **59**. This generates severe compression against a methylene group of the enolate ring (dashed semicircles). No such problems subsist in regioisomeric transition state **62**, wherein the substituent in question is pseudoequatorial in the developing ring. This should favor selective formation of the correct regioisomer of the aldol product, both on kinetic and on thermodynamic grounds. However, a potential complication loomed if substituent Z were a carbonyl group. The ring system emerging from the aldol reaction is now an *N*-acyl piperidine. As mentioned earlier, substituents at the α-position of the nitrogen atom in such structures prefer the *axial* orientation.[18] The incorrect aldol regioisomer would then be favored under thermodynamic conditions, and possibly even under kinetic conditions, if the transition state for the aldol cyclization were product-like. Avoiding entanglement with these complications entailed execution of the aldol step with substrates in which substituent Z is a pair of H atoms; i.e., with a variant of **19**. This is the pathway that Sorensen chose.[9b] On the other hand, a sequence proceeding through direct aldol closure of **57** would be shorter than the one requiring prior elaboration to a protected form of **19**.

A computational simulation (MM+) carried out with simplified variants of transition state structures **59** and **62**, in which R=H, Z=O, and the distance between enolate and formyl carbons (dashed bonds) was arbitrarily fixed at 2.3 Å, suggested that **62** would still be less energetic than **59** by about 0.8 kcal/mol. This value is below the confidence level of the calculation; still, it engendered measured optimism concerning the feasibility of the aldol step in the desired *regiochemical* mode. The question of *diastereoselectivity* constituted a more delicate issue. Indeed, MM+ revealed that transition state models **62** and **64**, which reflect the desired (cf. **63**) and undesired (cf. **65**) epimers of the aldol product, are essentially isoenergetic, as are **63** and **65** themselves. This intimated that no substrate-directed diasterocontrol could be exerted during the aldol step in the absence of external influences.

In an attempt to reach a tricyclic intermediate, compound **57** was treated with DBU in CH_2Cl_2 (Scheme 15). This led to the stereoselective formation of a compound (accompanied by diastereomeric products) that was ultimately shown to be **66** by comparison with analogs of secure constitution. The sole structural parameter initially available to us was the magnitude of the vicinal coupling constant, $^3J_{H\text{-}6,H\text{-}7}$= 8.8 Hz (FR-901483 numbering), for acetate ester **67**. This suggested a trans-diaxial arrangement of the H's in question, i.e., formation of the incorrect aldol diastereomer. Still, it was apparent that the use of a weak base indeed promotes kinetically faster enolization of the cyclohexanone.

It did not escape our attention that the formation of **66** was consistent with the so-called Seebach rule.[28] This reactivity model holds for nonprotic solvents and it may break down in protic ones, leading to an erosion, or even a reversal, of diastereoselectivity, that may be ascribed to solvation of reactive species through H-bonding. One might hope that conduct of the reaction in a protic medium could afford reasonable



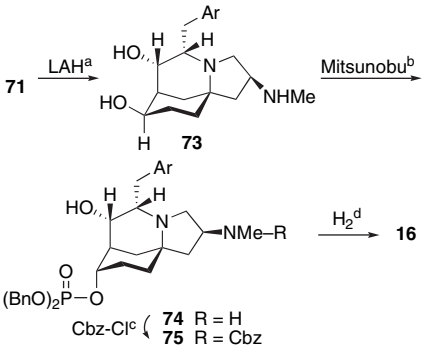
Scheme 15.

quantities of the desired aldol diastereomer. Indeed, pioneering work by Snider appearing in the literature at this juncture proved that model system **68**[9g] as well as 'real' substrate **69**,[9a] which differs from **57** only at the level of the *N*-protecting group (BOC in lieu of a tosylamide), cyclize diastereoselectively to the correct aldol isomer upon reaction with *t*-BuOK in *t*-BuOH. The same outcome obtained upon treatment of **70** with MeONa/MeOH, as reported shortly thereafter by Sorensen.[9b] Interestingly, Snider had determined that the aldol cyclization of **69** proceed with slightly lower diastereoselectivity in MeOH/NaOMe,[9a] suggesting that optimal conditions for this step are intimately dependent on structural details.

Ketoaldehyde **57** did not perform well under Snider-type conditions. First, the compound was poorly soluble in plain *t*-BuOH, necessitating the use of a 3:1 mixture of *t*-BuOH/THF to effect aldol cyclization (*t*-BuOK). This reaction furnished **71** as a significant component of a mixture of diastereomeric aldol products in 21% chromatographed yield: unacceptable in terms of both yield and diastereoselectivity. The structural assignment of **71** initially rested on the coupling constant, $^3J_{H\text{-}6\text{–}H\text{-}7}$=1.5 Hz, measured for acetate **72**, implying a cis relative configuration, and it was ultimately confirmed by an X-ray study of a derivative. Efforts to improve this step led us to examine alternative alcohol/alkoxide combinations. The reaction became increasingly more efficient as we switched to EtOH/EtONa and then to MeOH/MeONa. This again contrasted with the behavior of the Snider substrate, but it was consonant with Sorensen's choice of conditions.

The fact that **57** produced more of the desired **71** in media of higher polarity[29] and/or of higher hydrogen bonding ability[30] crystallized an interesting question: how could one render methanol even more polar and more apt to establish strong hydrogen bonds? A plausible answer was to add some water to the methanolic medium. We rapidly determined that a methanolic solution of **57** remained homogeneous upon dilution with up to 10 vol % of water. Addition of solid NaOMe triggered rapid aldol cyclization and diastereoselective formation of **71** in 44% chromatographed yield. It is tempting to speculate that if the biosynthetic pathway leading to **16** indeed involves aldol cyclization of a species akin to **19**, then the occurrence of this event within an enzyme with a hydrophilic active site hosting numerous water molecules could facilitate formation of the 'good' diastereomer.

With a reliable avenue to **71** in hand, the synthesis was completed rapidly and without incident (Scheme 16). Vigorous LAH reduction of **71** produced **73** (82%) plus a small amount of what appeared to be the epimeric alcohol. Compound **73** may also be obtained with complete diastereoselectivity (within the limits of 500 MHz ^{1}H NMR) by reduction of **71** with L-Selectride® and converted to fully synthetic **16**[31] by the Snider method.[9a] A more rapid endgame relied on regioselective Mitsunobu reaction of **73** with dibenzylphosphate à la Sorensen.[9b] The emerging **74** was extremely polar and difficult to purify. To palliate such difficulties, we installed an *N*-CBZ group prior to purification. Hydrogenolysis of pure **75** yielded totally synthetic FR-901483, the bis-hydrochloride salt of which was found to be identical to that of natural **16**.[24,32] The longest linear sequence in this synthesis is 17 steps from tyrosine, and the overall yield approaches 1.5%.

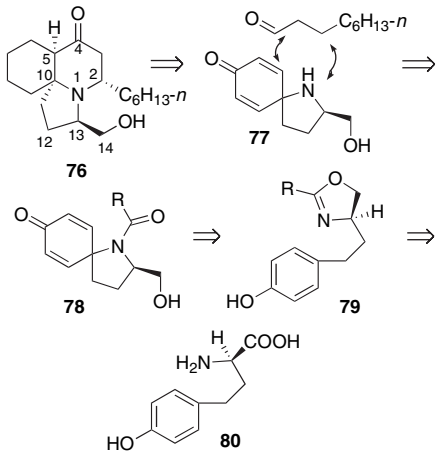


Scheme 16. (a) THF, −78 °C to reflux, 12 h, 91%; (b) DIAD, $(BnO)_2P(O)OH$, $(4\text{-}ClC_6H_4)_3P$; (c) Cbz/Cl, aq THF, $NaHCO_3$, 25 °C, 26% a–c; (d) Pd(C), MeOH, HCl, 25 °C, 3 h, 94%.

3. Second-generation methodology: oxidative cyclization of phenolic sulfonamides

We rapidly realized that a generic oxidative amidation of phenols holds considerable potential in the chemical synthesis of nitrogenous spirocycles. The biosynthetically inspired hypotheses that led to the chemistry of Scheme 8 thus stimulated the evolution of the methodology in a direction that no longer paralleled biomimetic pathways. A case in point is that of the cylindricines,[33] exemplified in Scheme 17 by (−)-cylindricine C, **76**.[34] These moderately cytotoxic, but structurally unique, secondary metabolites of the ascidian, *Clavelina cylindrica*, have engendered considerable interest in the synthetic community.[35] An approach to **76** based on oxazoline technology envisions annulation of the piperidinone ring onto spirodienone **77** (Scheme 17) with concomitant differentiation of the pair of diastereotopic olefins present in the substrate. Compound **77** is available through

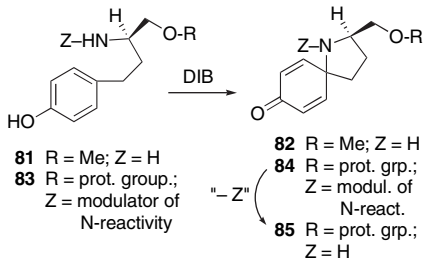
oxidative cyclization of oxazoline **79**, which in turn derives from homotyrosine, **80**.[36]



Scheme 17.

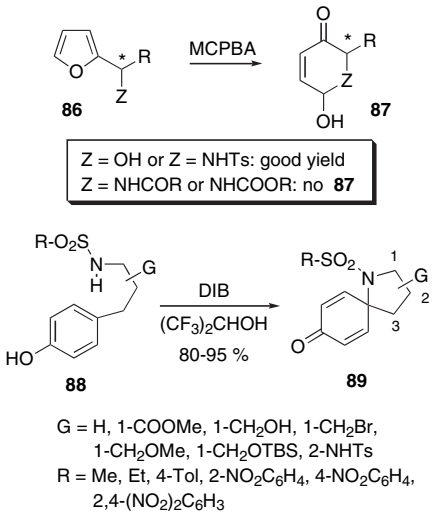
A number of technical difficulties conspired to render the above strategy entirely impractical. First of all, and contrary to previous cases, oxazoline **79** was difficult to purify due to its propensity to retain debris of reagents used in its preparation. Second, oxidative cyclization to **78** was low yielding (25–30%). Third, deacylation of the pyrrolidine nitrogen at the stage of **78**, in preparation for piperidone ring assemblage, was problematic and low yielding. Finally, free aminodienone **77** was prone to polymerization, presumably through cascade Michael-type reactions.

Some of the foregoing obstacles could have been circumvented through direct oxidative cyclization of an *N*-unprotected homoalaninol derivative. Such reactions proceed reasonably well with phenolic *secondary* amines[9b,19] but not so with *primary* ones. Thus, in our hands **81** never afforded the desired **82** in more than 6% yield (Scheme 18). A corrective measure for this unpleasant behavior could involve derivatization of the primary amine with a suitable group Z that modulates the reactivity of the nitrogen center (cf. **83**). Unit Z could then be removed at an opportune post-oxidation stage (cf. **84**→**85**). Kita had established that phenolic 3-arylpropanols cyclize efficiently to spirotetrahydrofurans upon oxidative attack with DIB.[11,17] If group Z in **83** imparted alcohol-like reactivity to the primary amino function, i.e., moderate nucleophilicity and low basicity, then conversion to **84** might become efficient.



Scheme 18.

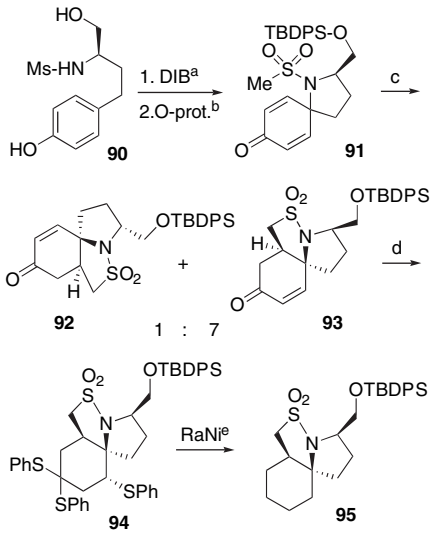
Recent literature precedents indicate that the reactivity of sulfonamides is comparable to that of alcohols. Especially significant in this regard is the work of Zhou,[37] who observed that furylsulfonamides (**86**, Z=NHTs; Scheme 19) undergo aza-Achmatowicz reaction[38] as efficiently as furylcarbinols (the original substrates for Achmatowicz reactions; **86**, Z=OH). This stands in sharp contrast to furylamides and furylcarbamates, which are poor substrates for this transformation. Sulfonamides **88** might well be competent substrates for the desired transformation.



Scheme 19.

It was most pleasing to discover that contrary to the case of oxazolines, which rarely afford yields of spirocycles greater than 50%, the oxidative cyclization of sulfonamides is nearly quantitative. The reaction tolerates a wide range of functional groups and it proceeds very cleanly: in most cases, there is no need for subsequent purification of products **89**.[39] Application of Fukuyama nitrobenzenesulfonamide technology[40] in this reaction yields materials that may be *N*-deblocked under gentle conditions. The resulting *N*-unprotected spirodienones are formal products of cyclization of primary amines. We have already alluded to the poor stability of such educts, which we prefer to avoid. Fortunately, an appropriate sulfonamide can function not only as a modulator of the reactivity of the nitrogen atom during oxidative spirocyclization, but also as a potential nucleophilic handle for elaboration of products **89** to advanced intermediates. This adds an interesting new dimension to the newly devised methodology.

In the context of the synthesis of **76** (Scheme 20),[41] a methanesulfonamide, was effectively employed as a carbonyl anion equivalent. To illustrate, oxidative cyclization of homotyrosine-derived **90** proceeded with no interference from the free alcohol. The highly polar spirodienone thus obtained was *O*-protected with a sterically demanding silyl ether, which directed a subsequent Michael-type cyclization regioselectively to the pro-*S* double bond of **91** (dr=7),[42] thereby exerting stereocontrol at the emerging spiro-stereogenic center through desymmetrization of the dienone. This technique for stereoselective spirocenter formation was inspired by the results of Scheme 9. Unusual in the realm of synthetic endeavoring, compound **93** contained surplus functionality relative to the required cylindricine intermediate **95**. Conversion to **95**, therefore, continued with

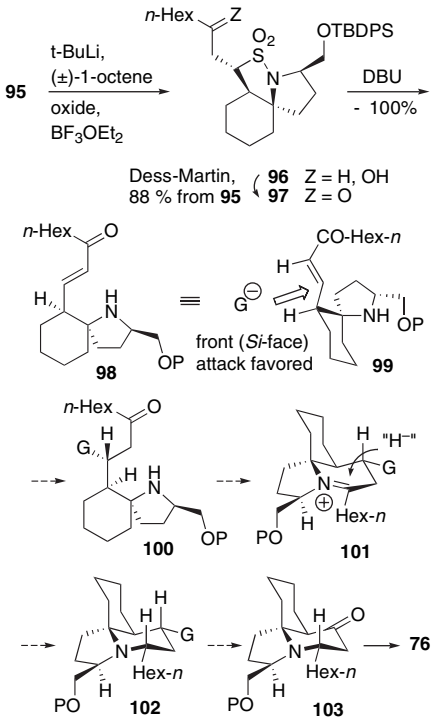


Scheme 20. (a) $(CF_3)_2CHOH$, 25 °C, 30 min; (b) DMF, imidazole, *t*-$BuPh_2$-SiCl, 3 h, 87% a–b; (c) KHMDS/toluene, THF, −100 °C, 3 h, 89%; (d) PhSH, BF_3OEt_2, CH_2Cl_2, 25 °C, 12 h, 77%; (e) 2:1 EtOAc/EtOH, 25 °C, 3 h, 77%.

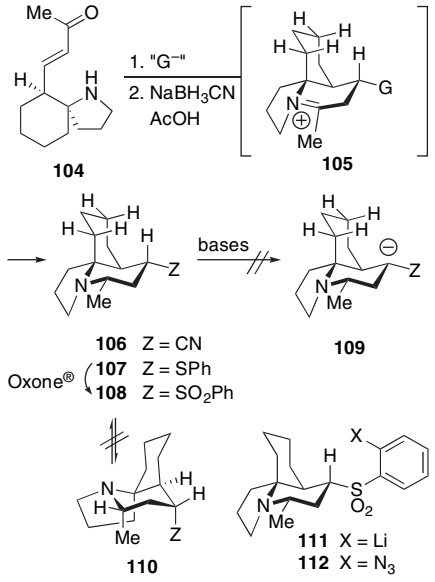
elaboration to trisulfide **94** and RaNi desulfurization.[43] It is worthy of note that the desilylated analog of **94** was crystalline and it was characterized by X-ray diffractometry. This confirmed the regiochemical outcome of the sulfonamide Michael cyclization, as well as the *R*-configuration of the sulfenylated stereogenic carbon. This configuration was expected based on an *anti*-selective conjugate addition of thiophenol directed by the spirosulfonamide nitrogen through a Felkin–Anh-type effect.[44]

Extensive model work aiming to define the best approach for the installation of the piperidinone ring on compound **95** revealed an optimal endgame strategy in the form of an intramolecular reductive amination of ketone **100** (Scheme 21). Group G in **100** stands for an appropriate precursor to the keto function of cylindricine C (cf. **102**→**76**). The steric demand of G must be sufficiently large to enforce a significant preference for conformer **101** of the iminium ion involved in the reductive amination step. Nucleophilic addition to such species tends to occur under stereoelectronic control in the axial mode;[45] therefore, reduction of **101** was expected to produce the correct (*S*)-configuration at C-2 in **102** (cylindricine numbering). Substituent G could be introduced by diastereoselective conjugate addition to enone **98**, which may be anticipated to react in the correct stereochemical sense on the basis of well documented conformational properties of a $C(sp^2)$–$C(sp^3)$ junction. Minimization of $A^{1,3}$-interactions would strongly favor conformer **99**. Consequently, a nucleophilic form of G should selectively add to the more exposed *Si*-face of the enone π bond.

The conversion of **95** to **98** again relied on transformations orchestrated by the sulfonamide unit, which therefore played a triple role during the synthesis: modulator of N-atom reactivity, agent for the desymmetrization of the 'locally symmetrical' dienone, and now implement for the annulation of the piperidinone segment. Deprotonation of **95** with *t*-BuLi[46] and reaction with (±)-1-octene oxide activated by BF_3OEt_2[47] resulted in fully diastereoselective (300 MHz ^{1}H NMR) α-face alkylation to yield **96**. Of course, this product was a 1:1 mixture of alcohol epimers, due to the racemic nature of the epoxide. However, Dess–Martin oxidation[48] of this mixture afforded stereochemically homogeneous ketone **97** (88% from **95**), which upon exposure to DBU experienced retro-Michael extrusion of SO_2 to furnish **98**. Unpleasant difficulties could be anticipated with the 1,4-addition of an actual oxygen nucleophile to **98**. Besides, one may foresee mediocre levels of conformational control if group G in **100** were an alcohol or a derivative thereof. Exploratory work aiming to reach ketones of the type **103**, therefore, relied on intermediates derived from racemic model enone **104** (Scheme 22) through conjugate addition



Scheme 21.



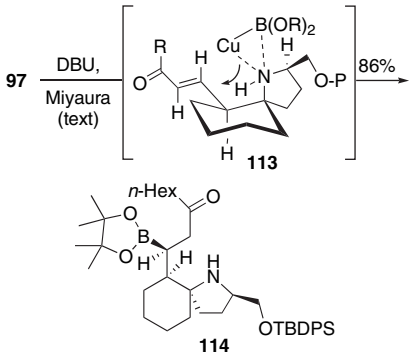
Scheme 22.

of a cyano or a phenylsulfenyl group, either one of which can function as a precursor to a carbonyl.

Nagata cyanation[49] of **104** took place in the anticipated sense, but with a modest 4:1 facial selectivity. The subsequent reductive amination likewise proceeded with moderate diastereocontrol. Conjugate addition of thiophenoxide ion fared much better, occurring with essentially complete stereoselectivity. The bulkier phenylsulfenyl substituent also performed exceptionally well as an element of stereocontrol during the subsequent reductive amination. However, to our utter dismay, the emerging tricyclic intermediates **106**–**108** resisted conversion to the corresponding ketone. Thus, failure was the result of attempted α-chlorination (PCl_5) of nitrile **106**, or deprotonation (cf. anion **109**, Z=CN)/oxidation, e.g., with the Davis oxaziridine. The same fate awaited attempts to induce Pummerer-type reactions of **107**, via the corresponding sulfoxide or through an *S*-halosulfonium ion, or to deprotonate sulfone **108**[50] as a prelude to oxygenation of anion **109** (Z=SO_2Ph). We imputed this string of failures to the conformational rigidity of structures **106**–**108**, which exist exclusively as the depicted conformers (NMR). The proton that must be abstracted in the course of the foregoing, unsuccessful reactions is inaccessible to external bases, situated as it is at an axial position *and* between the pair of axial protons on the second cyclohexane ring of the *cis*-decaline-type system. Interconversion of **106**–**108** with conformer **110**, in which the proton in question, being equatorial, would be more readily accessible, might facilitate deprotonation. However, a triad of problematic 1,3-diaxial interactions, especially severe if Z=SO_2Ph, all but precludes access to **110**. Even *intramolecular* reactions requiring abstraction of the recalcitrant proton were unfruitful. For instance, treatment of **108** with *t*-BuLi promoted *ortho*-lithiation to **111**. A solution of **111** was warmed to just above rt, in the hope to induce intramolecular proton transfer from the aliphatic C–H bond, and formation of a more stable anion. This only resulted in decomposition. Interception of **111** with trisyl azide furnished **112** (90%). Photochemical activation of the azido group was expected to form a triplet nitrenoid that might undergo insertion into the aliphatic C–H bond à la Meth-Cohn:[51] hydrolytic cleavage of the resultant would produce the target ketone. None of the desired product was obtained upon any form of azide activation.

At this juncture, we turned our attention to a bulky boronic ester as an alternative for group G in **100**, and we were not to regret this choice. The recently developed Miyaura conjugate borylation of enones[52] allowed us to subject **97** to an unprecedented transformation involving treatment with DBU, CuCl, KOAc, and bis-pinacolyldiboronate, leading directly to **114** in 86% yield (Scheme 23). Isolable enone **98** forms transiently through the action of DBU on **97**, the other reagents convert it to **114** in situ.

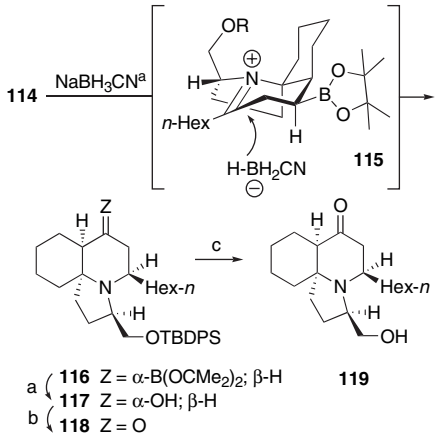
This second step, the Miyaura borylation proper, took place at an unusually fast rate (10 min instead of the normal 15 h or longer) and it occurred with complete reversal of facial selectivity at the level of **98**. Experiment determined that kinetic and stereochemical aspects of the reaction may be ascribed to the directing effect of the nitrogen atom: coordination of the Miyaura borylcopper complex (at the Cu atom,



Scheme 23.

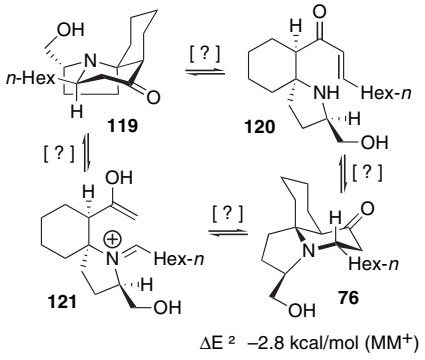
at the B atom, or at both) promotes directed delivery to the *Re* face of the alkene (cf. **113**).[53]

The stereochemical outcome of the Miyaura borylation created an interesting problem at the stage of the subsequent reductive amination step. As shown in Scheme 24, the boronic ester segment favors conformer **115** of the intermediate iminium ion. Axial delivery of hydride[44] upon $NaBH_3CN$/AcOH reduction produced the unnatural 2-(*R*)-configuration of tricyclic intermediate **116**. The latter was not isolated, but it was converted in situ to alcohol **117**, which was uneventfully elaborated to (−)-2-*epi*-cylindricine, **119**. Our synthetic material $[\alpha]_D^{25}$ −39 (*c* 0.5, CH_2Cl_2), was thus obtained in 15 steps and 18% overall yield from homotyrosine, and it was spectrally identical to the racemic **119** described by Weinreb.[35h]



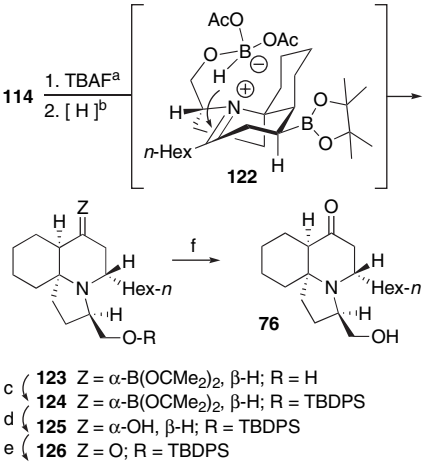
Scheme 24. (a) MeOH, cat. AcOH, 0 °C, 3 h, then aq NaOH, 30% H_2O_2, 0 °C, 30 min, 80%; (b) Dess–Martin periodinane, CH_2Cl_2, 1 h, 94%; (c) TBAF, THF, 25 °C, 3 h, 96%.

A computational simulation revealed that natural cylindricine contains at least 2.8 kcal/mol less steric energy than 2-*epi*-cylindricine. Furthermore, aspects of recorded syntheses of cylindricines may lead one to infer that it should be possible to induce isomerization of **119** to **76** through reversible opening of the piperidinone ring, either in a *retro*-Michael mode (cf. **120**, Scheme 25) or in a *retro*-Mannich sense (cf. **121**)—with a caveat. Observations recorded by Weinreb[35h] cast doubt on this surmise. We must go with Weinreb on this issue: extensive experimentation aiming to promote the desired isomerization, in the interest of reaching the natural product, was entirely unfruitful.



Scheme 25.

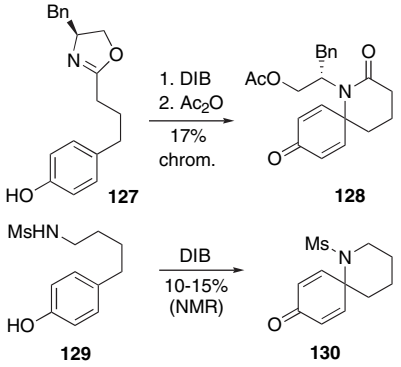
A felicitous development allowed us to exert complete reversal of facial selectivity in the reductive amination step, permitting access to intermediates displaying the natural C-2-(*S*)-configuration. Thus, ketone **114** was desilylated and treated with $NaBH(OAc)_3$ and AcOH. Analogy with the presumed course of the Evans directed carbonyl reduction[54] crystallized the idea that the reductant should rapidly anchor itself to the now free hydroxymethyl group of the substrate. Intramolecular hydride transfer from the resultant complex **122** (Scheme 26) would secure the correct C-2 configuration. The fact that such a hydride transfer must occur through a seven-centered cyclic transition state was a potential obstacle, but inspection of a molecular model of **122** allayed our concerns. Indeed, the borohydride agent is perfectly positioned to deliver H^- to the iminium ion with the correct orientation. Experiment vindicated this hypothesis: compound **123** emerged from the reaction as essentially the sole product. We are not aware of literature precedent for this type of directed *iminium ion* reduction. The synthesis of (−)-cylindricine C was thus completed as shown in Scheme 26.[55]



Scheme 26. (a) THF, 25 °C, 3 h, 95%; (b) $NaBH(OAc)_3$, cat. AcOH, CH_2Cl_2, −78° to 25 °C, 12 h, 73%; (c) *t*-$BuPh_2SiCl$, imidazole, DMF, 25 °C, 95%; (d) aq NaOH, 30% H_2O_2, 0 °C, 30 min, 97%; (e) Dess–Martin periodinane, CH_2Cl_2, 1 h, 94%; (f) TBAF, THF, 25 °C, 3 h, 96%.

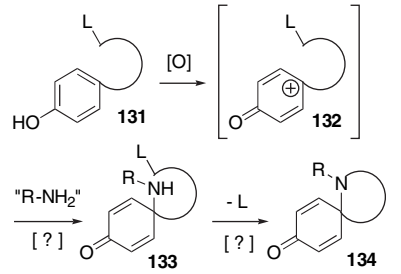
4. Third generation oxidative amidation of phenols: the bimolecular reaction

Oxazoline- and sulfonamide-based techniques of oxidative amidation of phenols suffer from a major limitation: formation of six-membered rings is problematic.[56] To illustrate, oxidative cyclization of **127** or **129** (Scheme 27) produced spiropiperidines **128** and **130** in a disheartening 10–15% yield. Spiranes **128–130** are synthetically valuable building blocks for many alkaloids: a more efficient avenue to these materials seemed highly desirable.



Scheme 27.

Efforts to correct the problem led to a 'third generation' method of oxidative amidation of phenols in the *bimolecular* regime. The genesis of the new process is rooted in the hypothesis sketched in Scheme 28. Oxidative activation of a 4-substituted phenol **131** (L=leaving group) and capture of the electrophilic intermediate, perhaps **132**, with the equivalent of a primary amine would surrender **133**, which upon nucleophilic displacement of L should produce the desired **134**.

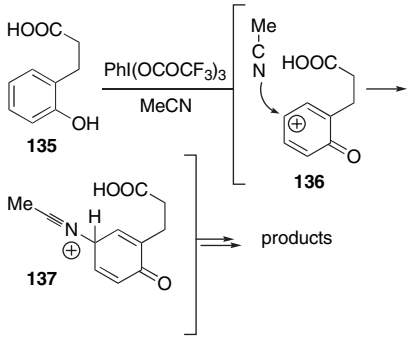


Scheme 28.

It must be stressed that a bimolecular variant of the oxidative amidation of phenols is problematic for several reasons. First of all, it is difficult to identify a competent nitrogen nucleophile that is also resistant to the action of oxidants such as DIB. Second, the kinetics of capture of the electrophilic resultant of phenol activation (cf. hypothetical cation **132**) by an external nitrogen nucleophile are generally unfavorable. Thus, all attempts to intercept the electrophilic agent produced through DIB activation of the phenol with amines (primary or secondary), pyridine, imidazole, and primary sulfonamides,[57] were entirely unsuccessful. Indeed, phenols **131** are customarily converted to products **133** through reaction with electrophilic nitrogen species,[58] but until recently, consensus had it that it was not possible to effect the same transformation with a nucleophilic nitrogenous agent.

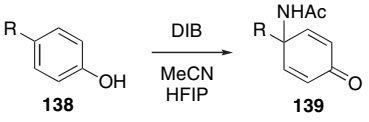
An interesting result disclosed by Wood (Scheme 29)[59] suggested a possible way to attain our objective. Thus, phenol **135** reacted with PIFA in MeCN to furnish products presumed to originate from nitrilium ion **137**, which forms

upon Ritter-type addition of MeCN to **136**. This induced us to study the oxidative amidation of 4-substituted phenols in the presence of nitriles, with the expectation that these might play the role of agent 'R–NH_2' of Scheme 28.



Scheme 29.

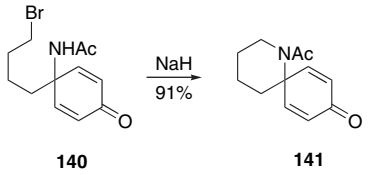
Oxidative attack of several 4-substituted phenols with PIFA in MeCN resulted in the formation of complex mixtures of products, whereas treatment of the same substrates with DIB in MeCN induced no reaction. However, acetamides **139** were obtained in fair to good yield upon DIB oxidation of phenols **138** in a mixture of MeCN and HFIP (Scheme 30).[60] Nitrile solvents other than MeCN may be used in the reaction, which also tolerate a range of useful functionality on the side chain of the substrates. Halogenated substrates performed quite well and afforded the expected products without incident. This is especially relevant to the present discussion: as seen in Scheme 31, exposure of, e.g., **140**, to NaH triggered cyclization to **141** in excellent yield, thereby circumventing the limitation alluded to earlier.



R	yield[a] %	R	yield[a] %
Me	56	$(CH_2)_nCN$	67 (n=2)
Pr-*n*	54		71 (n=3)
Pr-*i*	62		71 (n=4)
CH_2COOMe	58	$(CH_2)_nN_3$	42 (n=3)
$(CH_2)_2NHTs$	53		49 (n=4)
$(CH_2)_3OPiv$	67	$(CH_2)_nBr$	65 (n=3)
$(CH_2)_3CO_2TFE$	57		72 (n=4)

[a]chromatographed

Scheme 30.



Scheme 31.

The bimolecular oxidative amidation of phenols is the centerpiece of a number of ongoing synthetic efforts, disclosure of which is premature at this point. We find it interesting that a hypothesis formulated in connection with our effort toward **16** and **23**, and that falls squarely under the rubric of 'biomimetic chemistry,' ultimately spawned research that retains little of the original 'biomimetic' flavor. Venturing into the *terra incognita* of the reactions of Schemes 19 and 30, however, produced a great deal of new chemistry. Biosynthetic considerations are undeniably a major source of inspiration: the marriage thereof with the élan toward ever shorter avenues to molecular architectures that only synthesis can engender is a powerful motor to drive the progress of organic chemical technology.

5. Experimental

5.1. Experimental protocols

Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shift (δ) are in parts per million, and coupling constants (J) are in Hertz. Multiplicities are reported as: 's' (singlet), 'd' (doublet), 'dd' (doublet of doublets), 't' (triplet), 'q' (quartet), 'm' (multiplet), 'c' (complex), 'br' broad. IR spectra (cm^{-1}) were measured on a Perkin Elmer 1720-X FTIR from $CHCl_3$ solutions. Low- and high-resolution mass spectra (*m/e*) were obtained in the CI (isobutane), EI (70 eV), LSIMS (Cs^+), or ESI mode, as specified. Optical rotations were measured in $CHCl_3$, with concentrations (*c*) expressed in g/100 mL. All reactions were run under argon, and monitored by TLC. Reagents and solvents were commercial products and were used as received, including trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP), except THF (freshly distd Na/benzophenone); CH_2Cl_2, Et_3N (distd CaH_2). Ground 4 Å molecular sieves used for TPAP–NMO oxidations were activated at 120 °C under vacuum.

5.2. General procedure for the oxidative cyclization of phenolic oxazoline

A solution of DIB (0.4 g, 1.2 mmol) in TFE (5 mL) was added dropwise at rt over 5 min to a solution of a phenolic oxazoline (1.0 mmol) in TFE (5 mL), and the mixture was stirred for 30 min (argon). Solid $NaHCO_3$ (0.3 g) was added and after brief stirring the resulting suspension was filtered over glass wool and concentrated. The crude product was immediately taken up in anhydrous pyridine (0.8 g, 10.0 mmol) and treated with Ac_2O (1.0 g, 10.0 mmol) and DMAP (6.1 mg, 50 μmol) at rt for 12 h with good stirring. Finally, the mixture was evaporated and the residue was purified by chromatography and/or recrystallization.

5.2.1. Oxazoline 44. A solution of PPh_3 (8 g, 30 mmol) in 1:1 acetonitrile/pyridine (20 mL, warming necessary to completely dissolve PPh_3) was added dropwise at rt over 3 h to a solution of **42** (1.81 g, 10 mmol), **43** (3.35 g, 10 mmol), NEt_3 (3.05 g, 30 mmol), and CCl_4 (6.22 g, 40 mmol) in 1:1 MeCN/pyridine (20 mL) at 30 °C. Stirring was continued for 24 h at 30 °C (thermostat). Aqueous 0.5 M NaOH (200 mL) was added with good stirring and the organic layer was discarded. The aqueous layer was successively washed with Et_2O (2×50 mL) and CH_2Cl_2 (2×50 mL). These extracts were also discarded, then EtOAc (50 mL) was added to the aqueous layer and the mixture was carefully acidified to pH 6 with solid NH_4Cl. The layers were separated and the aqueous phase was extracted with

more EtOAc (4×50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to yield 3.5 g (73%) of **44**, orange foam, $[\alpha]_D^{25}$ +13.3 (*c* 1.00, EtOH). ^{1}H: 7.73 (2H, d, *J*=8.5), 7.26 (2H, d, *J*=8.5), 6.92 (2H, d, *J*=8.5), 6.83 (2H, d, *J*=8.5), 6.76 (2H, d, *J*=8.5), 6.44 (2H, d, *J*=8.5), 5.51 (1H, d, *J*=9.6, NH), 4.40–4.25 (1H, m), 4.15–4.00 (2H, m), 3.87–3.80 (1H, m), 3.73 (3H, s), 2.93 (2H, d, *J*=5.5), 2.60 (1H, dd, *J*=13.8, 5.5), 2.39 (3H, s), 2.10 (1H, dd, *J*=13.8, 7.7). ^{13}C: 166.2, 158.4, 155.5, 143.4, 137.3, 130.5, 129.9, 129.5, 129.1, 127.4, 125.7, 115.4, 114.0, 72.5, 66.7, 55.2, 52.2, 40.2, 38.9, 21.5. IR: 3260, 1515, 1445, 1340, 1305. MS (CI): 481 (MH^+). HRMS (CI): calcd for $C_{26}H_{28}N_2O_5S$ (MH^+) 481.1797; found: 481.1770.

5.2.2. Spirolactam 46. A solution of DIB (0.74 g, 2.3 mmol) in TFE (10 mL) was added dropwise over 5 min to a solution of oxazoline **44** (0.96 g, 2 mmol) in TFE (10 mL). The mixture was stirred for 30 min at rt; then solid $NaHCO_3$ (0.50 g, 6 mmol) was added. The suspension was filtered through glass wool and evaporated under reduced pressure. Crude **45** thus obtained was redissolved in pyridine (1.58 g, 20 mmol) and treated with Ac_2O (2.03 g, 20 mmol) and DMAP (24.4 mg, 0.2 mmol) at rt. After stirring overnight, the solution was diluted with EtOAc and washed with satd aq NH_4Cl (3×15 mL). The organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residue (10%→60% EtOAc/hexane) afforded 0.48 g (41%) of **46**, yellow foam, $[\alpha]_D^{25}$ −22.7 (*c* 1.21). ^{1}H: 8.04 (2H, d, *J*=8.1), 7.42 (2H, d, *J*=8.1), 7.10 (2H, d, *J*=8.5), 6.83 (3H, m), 6.24 (1H, dd, *J*=9.9, 1.8), 6.17 (1H, dd, *J*=10.3, 2.8), 6.07 (1H, dd, *J*=10.3, 1.8), 5.24 (1H, t, *J*=8.8), 4.57 (1H, dd, *J*=11.3, 8.3), 4.28 (1H, dd, *J*=11.3, 4.4), 3.78 (3H, s), 3.18 (1H, dd, *J*=12.1, 7.0), 3.23–3.05 (1H, m), 3.00 (1H, dd, *J*=12.1, 5.5), 2.54 (1H, dd, *J*=13.2, 5.5), 2.47 (3H, s), 2.42 (1H, dd, *J*=13.2, 5.2), 2.28 (3H, s), 2.03 (3H, s). ^{13}C: 184.1, 170.3, 169.8, 169.6, 158.6, 149.0, 148.6, 145.5, 136.2, 130.8, 130.2, 130.1, 129.6, 128.9, 127.6, 113.9, 62.5, 60.0, 57.5, 55.2, 34.7, 34.4, 25.1, 21. 7, 20.9. IR: 1745, 1705, 1675. MS (EI): 580 (M^+), 375, 323, 206 (100), 163, 147, 121, 91, 43. HRMS (EI): calcd for $C_{26}H_{28}N_2O_5S$ (M^+) 580.1879; found: 580.1884.

5.2.3. Cyclohexanone 47. A solution of **46** (0.548 g, 0.95 mmol) and PtO_2 (22 mg) in EtOAc (5 mL) was stirred at rt under 1 atm of H_2 overnight. Filtration (Celite) and concentration afforded 0.530 g (96%) of the corresponding saturated ketone, white foam, $[\alpha]_D^{25}$ −53.2 (*c* 1.25). ^{1}H: 8.07 (2H, d, *J*=8.1), 7.42 (2H, d, *J*=8.1), 7.15 (2H, d, *J*=8.5), 6.82 (2H, d, *J*=8.5), 5.20–5.06 (1H, m), 4.66 (1H, dd, *J*=11.0, 8.1), 4.31 (1H, dd, *J*=11.0, 5.5), 3.77 (3H, s), 3.41–3.28 (1H, m), 3.14 (2H, dd, *J*=7.0, 3.3), 2.79 (1H, dd, *J*=12.3, 10.1), 2.56–2.20 (5H, m), 2.46 (3H, s), 2.27 (3H, s), 2.18–2.07 (1H, m), 1.99 (3H, s), 1.89–1.54 (3H, m). ^{13}C: 208.3, 169.7, 169.6, 158.4, 145.3, 130.6, 130.4, 130.2, 127.6, 127.3, 114.0, 62.9, 60.2, 57.4, 55.4, 55.2, 38.0, 37.2, 35.2, 35.0, 33.9, 33.7, 25.2, 21.7, 20.9. IR: 3377, 1715, 1695. MS (CI): 585 (MH^+). HRMS (CI): calcd for $C_{30}H_{36}N_2O_8S$ (MH^+) 585.2271; found: 585.2285. A mixture of this material (0.530 g, 0.91 mmol) and K_2CO_3 (0.025 g, 0.18 mmol) in MeOH (18 mL) was stirred overnight, and then it was concentrated. The residue was taken up with EtOAc (30 mL) and acidified with 1 M HCl (20 mL). The layers were separated and the aqueous layer was extracted with more EtOAc (2×30 mL). The combined EtOAc extracts were washed with brine (30 mL) and dried ($MgSO_4$). Concentration afforded 0.360 g (79%) of **47**, yellow foam, $[\alpha]_D^{25}$ +2.7 (*c* 1.1). ^{1}H: 7.80 (2H, d, *J*=8.5), 7.32 (2H, d, *J*=8.5), 7.02 (2H, d, *J*=8.5), 6.79 (2H, d, *J*=8.5), 5.84 (1H, s, NH), 3.98 (1H, dd, *J*=11.1, 7.0), 3.87–3.72 (1H, m), 3.75 (3H, s), 3.69 (1H, dd, *J*=11.1, 3.3), 3.28–3.16 (1H, m), 3.11 (1H, dd, *J*=14.0, 8.1), 2.98 (1H, dd, *J*=14.0, 6.6), 2.88 (1H, dd, *J*=13.2, 8.1), 2.53–2.15 (4H, m), 2.43 (3H, s), 2.13–1.91 (1H, m), 1.90–1.56 (3H, m), 0.81–0.65 (1H, m). ^{13}C: 208.1, 171.8, 158.5, 144.0, 135.9, 130.4, 130.0, 129.9, 127.2, 114.0, 62.8, 61.5, 58.3, 55.2, 52.4, 38.0, 37.6, 37.1, 35.1, 33.8, 32.9, 21.5. IR: 3261, 1715, 1682. MS (CI): 501 (MH^+). HRMS (CI): calcd for $C_{26}H_{32}N_2O_6S$ (MH^+) 501.2059; found: 501.2058.

5.2.4. Compound 48. Iodomethane (caution: suspect carcinogen, corrosive, poison; 0.68 g, 4.8 mmol;) was added to a solution of **47** (0.785 g, 1.60 mmol) in acetone/DMF (14 mL/2 mL) containing K_2CO_3 (0.261 g, 1.92 mmol). After stirring for 12 h, the solution was concentrated and the residue was diluted with EtOAc (40 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield 0.780 g (97%) of **48**, yellow foam, $[\alpha]_D^{25}$ −76.0 (*c* 1.0). ^{1}H: 7.84 (2H, d, *J*=8.5), 7.31 (2H, d, *J*=8.5), 7.02 (2H, d, *J*=8.5), 6.75 (2H, d, *J*=8.5), 5.03 (1H, dd, *J*=10.7, 9.2), 4.12 (1H, dd, *J*=11.2, 7.2), 3.74 (3H, s), 3.72 (1H, dd, *J*=11.2, 3.3), 3.31–3.19 (1H, m), 3.13 (1H, dd, *J*=13.6, 8.8), 2.98 (1H, dd, *J*=13.6, 5.9), 2.76 (3H, s), 2.57 (1H, dd, *J*=12.7, 9.2); 2.45–2.35 (2H, m), 2.42 (3H, s), 2.21–2.09 (2H, m), 2.02–1.91 (2H, m), 1.74–1.63 (1H, m), 1.56 (1H, dd, *J*=12.7, 10.7), 0.68–0.57 (1H, m). ^{13}C: 208.4, 171.4, 158.5, 143.8, 136.1, 130.6, 130.4, 129.8, 127.6, 113.8, 63.1, 60.2, 58.5, 57.2, 55.3, 38.2, 37.2, 35.7, 34.1, 32.9, 31.8, 29.8, 21.6. IR: 3415, 1703. MS (CI): 515 (MH^+). HRMS (CI): calcd for $C_{27}H_{34}N_2O_6S$ (MH^+) 515.2216; found: 515.2215.

5.2.5. Prenyl ether 53. Commercial 1 M BBr_3 in CH_2Cl_2 (2.45 mL, 2.45 mmol) was added dropwise to a cold (−60 °C) solution of **48** (0.360 g, 0.7 mmol) in CH_2Cl_2 (2.3 mL). The mixture was stirred for 30 min, then it was warmed to 0 °C and stirring was continued for another 30 min. Aqueous 10% HCl solution (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2×5 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane: 70:30→90:10) afforded 0.306 g (87%) of the free phenol, yellow foam, $[\alpha]_D^{25}$ −76.5 (*c* 0.65). ^{1}H: 8.26 (1H, s), 7.86 (2H, d, *J*=8.3), 7.40 (2H, d, *J*=8.3), 7.02 (2H, d, *J*=8.7), 6.73 (2H, d, *J*=8.7), 4.99 (1H, dd, *J*=10.7, 9.0), 3.99 (1H, dd, *J*=11.3, 6.9), 3.72 (1H, dd, *J*=11.3, 5.1), 3.48–3.35 (1H, m), 3.11 (1H, dd, *J*=13.4, 9.0), 2.97 (1H, dd, *J*=13.4, 6.0), 2.78 (3H, s), 2.69 (1H, dd, *J*=13.0, 9.0), 2.68–2.53 (1H, m), 2.41 (3H, s), 2.32 (1H, dd, *J*=14.7, 9.0), 2.31–2.16 (1H, m), 2.11–1.92 (3H, m), 1.81 (1H, ddd, *J*=17.8, 14, 4.4), 1.70 (1H, t, *J*=11.7), 0.79–0.69 (1H, m). ^{13}C: 208.9, 171.8, 157.3, 144.5, 138.4, 131.9, 131.1, 130.8, 128.8, 116.3, 63.0, 61.1, 59.7, 58.5, 39.0, 38.1, 36.6, 35.2, 33.9, 32.5, 30.6, 21.9. IR: 3372, 1681. MS (CI): 501 (MH^+). HRMS (CI): calcd for $C_{26}H_{32}N_2O_6S$ (MH^+) 501.2059; found: 501.2049. A solution of this compound (0.354 g,

708 μmol), Cs_2CO_3 (0.346 g, 106 μmol), and 1-bromo-3-methyl-but-2-ene (122 μL, 106 μmol) in acetone (10 mL) was stirred at 50 °C for 2 h. After cooling to 25 °C, the mixture was filtered through Celite with additional CH_2Cl_2 (2×10 mL). The filtrates were concentrated and the residue was purified by column chromatography (silica gel, EtOAc/hexane: 60:40) to yield 0.394 g (98%) of **53**, colorless foam, $[\alpha]_D^{25}$ −75.0 (*c* 1.00). ^{1}H: 7.81 (2H, d, *J*=8.3), 7.32 (2H, d, *J*=8.3), 7.02 (2H, d, *J*=8.5), 6.77 (2H, d, *J*=8.5), 5.44 (1H, br t, *J*=6.7), 5.03 (1H, dd, *J*=10.6, 9.1), 4.44 (2H, d, *J*=7.0), 4.12 (1H, dd, *J*=11.8, 7.0), 3.73 (1H, dd, *J*=11.8, 3.2), 3.30–3.19 (1H, m), 3.13 (1H, dd, *J*=13.5, 9.7), 2.98 (1H, dd, *J*=13.5, 6.0), 2.77 (3H, s), 2.57 (1H, dd, *J*=12.7, 8.9), 2.45–2.35 (2H, m), 2.42 (3H, s), 2.25–2.09 (2H, m), 2.03–1.92 (2H, m), 1.77 (3H, s), 1.71 (3H, s), 1.70–1.59 (1H, m), 1.56 (1H, t, *J*=12.0), 0.60 (1H, d, *J*=12.8). ^{13}C: 209.3, 171.6, 158.0, 144.1, 138.6, 136.4, 130.9, 130.8, 130.2, 127.9, 119.9, 114.9, 65.2, 62.9, 60.5, 58.9, 57.5, 38.6, 37.6, 36.0, 34.3, 33.2, 31.4, 30.2, 26.3, 21.9, 18.6. IR: 3434, 1716, 1686. MS (CI): 569 (MH^+). HRMS (CI): calcd for $C_{31}H_{40}N_2O_6S$ (MH^+) 569.2685; found: 569.2682.

5.2.6. Compound 54. Commercial 1 M $LiAlH_4$ in THF (1.8 mL, 1.76 mmol) was added dropwise to a cold (−78 °C) solution of **53** (0.20 g, 352 μmol) in THF (3.5 mL). The mixture was warmed to 0 °C, stirred for an additional 15 min and then heated at reflux for 2 days. After cooling to 0 °C EtOAc was added (caution: vigorous reaction) followed by H_2O (30 μL), 15% NaOH (30 μL), and H_2O (90 μL). The precipitate was filtered through Celite and rinsed with EtOAc. The filtrates were concentrated to yield 0.124 g of crude **54**, colorless foam. ^{1}H: 7.00 (2H, d, *J*=8.6), 6.81 (2H, d, *J*=8.6), 5.47 (1H, t, *J*=6.7), 4.46 (2H, *J*=6.8), 3.57–3.46 (1H, m), 3.29 (1H, dd, *J*=9.8, 4.9), 3.19–3.05 (3H, m), 3.04–2.80 (2H, m), 2.62 (1H, br t, *J*=7.9), 2.43 (3H, s), 2.47–2.38 (1H, m), 2.2 (1H, ddd, *J*=14.3, 10.9, 2.9), 1.98–1.85 (3H, m), 1.77 (3H, s), 1.72 (3H, s), 1.67–1.19 (5H, m). ^{13}C: 157.8, 138.5, 131.2, 130.0, 120.1, 115.1, 70.2, 65.2, 62.9, 60.9, 57.8, 56.7, 49.4, 43.0, 36.6 (two resonances), 35.3, 34.1, 32.9 (two resonances), 26.2, 18.6. IR: 3379. MS (LSI): 403 (MH^+). HRMS (LSI): calcd for $C_{24}H_{38}N_2O_3$ (MH^+) 403.2961; found: 403.2959.

5.2.7. Carbamate 55. Trichloroethyl chloroformate (0.142 g, 0.67 mmol) was added to a solution of **54** (0.245 g, 0.61 mmol) and $NaHCO_3$ (0.154 g, 1.83 mmol) in THF/H_2O (3 mL/3 mL). After stirring at rt overnight the mixture was extracted with EtOAc (2×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Filtration of the residue through silica gel (EtOAc/hexane: 70:30) afforded 0.22 g (62%) of **55**, white foam, $[\alpha]_D^{25}$ −8.8 (*c* 1.05). ^{1}H: 7.01 (2H, d, *J*=8.4), 6.82 (2H, d, *J*=8.4), 5.47 (1H, t, *J*=6.7), 4.75 (2H, s), 4.66–4.54 (1H, m), 4.47 (2H, *J*=6.7), 3.64–3.52 (1H, m), 3.33 (1H, dd, *J*=10.1, 4.4); 3.16 (1H, t, *J*=10.1), 3.05–2.92 (3H, m), 2.95 (3H, s), 2.88 (1H, dd, *J*=13.5, 2.9), 2.44 (1H, t, *J*=13.5), 1.99–1.91 (2H, m), 1.78 (3H, s), 1.73 (3H, s), 1.76–1.54 (6H, m), 1.44–1.27 (2H, m). ^{13}C: 157.8, 155.0, 138.6, 130.9, 130.0, 120.1, 115.2, 96.0, 75.6, 70.1, 65.2, 62.7, 61.1, 57.1, 54.3, 45.0, 36.6, 36.1, 34.0, 33.3, 33.1, 32.7, 30.6, 26.2, 18.6. IR: 3410, 1712. MS (CI): 583 (w), 581, 579, 577 (MH^+, Cl cluster). HRMS (CI): calcd for $C_{27}H_{39}N_2O_5^{35}Cl_3$ (MH^+) 577.2003; found: 577.2006.

5.2.8. Aldehyde 56. A solution of **55** (65 mg, 112 μmol), 4-methylmorpholine-*N*-oxide (52 mg, 448 μmol), and Pr_4NRuO_4 (4 mg, 11.2 μmol) in CH_2Cl_2 (2.2 mL) containing suspended powdered 4 Å molecular sieves (56 mg, 0.5 g/mmol) was stirred at rt for 1 h. Filtration over silica gel (EtOAc) and concentration afforded 40 mg (63%) of **56**, colorless foam, $[\alpha]_D^{25}$ −38.6 (*c* 0.95). ^{1}H: 9.66 (1H, s), 7.06 (2H, d, *J*=8.6), 6.81 (2H, d, *J*=8.6), 5.52–4.41 (1H, m), 4.92–4.70 (3H, m), 4.47 (2H, *J*=6.7), 3.84 (1H, t, *J*=8.8), 3.44–3.39 (2H, m), 3.00 (3H, s), 2.67–2.57 (3H, m), 2.43–2.29 (2H, m), 2.26–2.18 (2H, m), 1.93–1.67 (3H, m), 1.78 (3H, s), 1.73 (3H, s), 1.51–1.40 (2H, m). ^{13}C: 210.6, 201.4, 157.9, 154.9, 138.5, 131.3, 130.8, 120.1, 114.9, 96.0, 75.7, 71.2, 65.2, 62.4, 59.6, 59.1, 41.3, 36.6, 39.1, 38.4, 30.4, 26.2, 18.6. IR: 3411, 1716. MS (CI): 579 (weak), 577, 575, 573 (MH^+, Cl cluster). HRMS (CI): calcd for $C_{27}H_{34}N_2O_5^{35}Cl_3$ (MH^+) 573.1690; found: 573.1690.

5.2.9. Synthetic TAN-1251C, 23. A mixture of **56** (50 mg, 87 μmol), THF (0.4 mL), aq 1 M NH_4OAc solution (0.4 mL), and 10% Cd/Pb couple (435 μmol of Cd) was vigorously stirred at rt for 1 h. The solid was filtered off and rinsed with EtOAc. The filtrate was basified (aq NaOH) and the product was extracted with EtOAc. Concentration and purification of the residue by preparative TLC (100% EtOAc) afforded 26 mg (79%) of TAN-1251C, pale yellow oil, $[\alpha]_D^{25}$ +23.4 (*c* 0.48, MeOH) (lit. $[\alpha]_D^{25}$ +24 (*c* 0.44, MeOH), Refs. 10 and 21b). ^{1}H: 7.08 (2H, d, *J*=8.7), 6.82 (2H, d, *J*=8.7), 5.53–5.46 (1H, m), 5.22 (1H, d, *J*=1.1), 4.47 (2H, d, *J*=6.7), 3.42–3.37 (1H, m), 3.22 (2H, s), 3.21 (1H, dd, *J*=11.5, 2.8), 2.80 (1H, dd, *J*=11.5, 1.9), 2.61–2.56 (1H, m), 2.51 (3H, s), 2.50–2.44 (1H, m), 2.41–2.17 (4H, m), 2.00 (1H, ddd, *J*=13.6, 10.7, 5.4), 1.89 (1H, *J*=13.6, 5.4), 1.86–1.81 (2H, m), 1.79 (3H, s, CH3); 1.73 (3H, s, CH3). ^{13}C: 212.0, 157.5, 138.4, 132.2, 130.2, 128.5, 128.2, 120.2, 114.8, 71.9, 65.1, 59.4, 52.5, 43.2, 41.8, 40.7, 39.9, 38.2, 37.6, 35.0, 26.2, 18.6. IR: 3393, 1716. MS (CI): 381 (MH^+). HRMS (CI): calcd for $C_{24}H_{33}N_2O_2$ (MH^+) 381.2542; found: 381.2543.

5.2.10. Aldehyde 57. A solution of **48** (0.340g, 0.66 mmol), 4-methylmorpholine-*N*-oxide (0.154 g, 1.32 mmol), and Pr_4NRuO_4 (23 mg, 66 μmol) in CH_2Cl_2 (13.2 mL) containing suspended powdered 4 Å molecular sieves (330 mg, 0.5 g/mmol), was stirred at rt for 15 min, then it was filtered over silica gel (EtOAc) and concentrated to afford 0.263 g (77%) of **57**, colorless foam, $[\alpha]_D^{25}$ −56.6 (*c* 1.25). ^{1}H: 9.57 (1H, s), 7.84 (2H, d, *J*=8.1), 7.32 (2H, d, *J*=8.1); 7.01 (2H, d, *J*=8.6), 6.75 (2H, d, *J*=8.6), 5.01 (1H, dd, *J*=11.0, 9.2), 3.76 (3H, s), 3.56–3.45 (1H, m), 3.36 (1H, d, *J*=7.7), 2.77 (3H, s), 2.75–3.70 (1H, m), 2.47–2.37 (2H, m), 2.42 (3H, s), 2.31–1.65 (5H, m), 1.47–1.33 (1H, m), 0.60–0.46 (1H, m). ^{13}C: 207.6, 197.6, 170.4, 158.8, 143.8, 136.0, 132.3, 130.6, 129.8, 127.7, 114.1, 63.2, 59.2, 57.0, 55.4, 37.9, 37.1, 35.6, 32.9, 32.9, 32.7, 29.9, 21.7. IR: 1736, 1717, 1698. MS (CI): 513 (MH^+). HRMS (CI): calcd for $C_{27}H_{32}N_2O_6S$ (MH^+) 513.2059; found: 513.2054.

5.2.11. Tricyclic intermediate 71. Commercial sodium methoxide (42 mg, 780 μmol) was added to a solution of **57** (200 mg, 390 μmol) in MeOH/H_2O (7.2 mL/0.8 mL), and the mixture was stirred at rt for 30 min. The solution was concentrated and the residue was diluted with EtOAc

(40 mL). This organic phase was sequentially washed with 1 M HCl (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated, and the residue was purified by preparative TLC (EtOAc/hexane: 60:40) to afford 90 mg (44%) of **71**, colorless foam, $[\alpha]_D^{25}$ −10.6 (*c* 1.41, EtOH). ^{1}H: 7.86 (2H, d, *J*=8.1), 7.31 (2H, d, *J*=8.1), 7.10 (2H, d, *J*=8.8), 6.76 (2H, d, *J*=8.8), 5.00 (1H, dd, *J*=11.0, 8.8), 3.81–3.69 (2H, m), 3.75 (3H, s), 3.38 (1H, dd, *J*=14.0, 8.8), 3.32–3.25 (1H, m), 2.82–2.76 (1H, m), 2.65–2.37 (3H, m), 2.61 (3H, s), 2.41 (3H, s), 2.29 (1H, dd, *J*=12.9, 8.8), 2.25–1.90 (2H, m), 1.80 (1H, dd, *J*=13.6, 3.3), 1.72 (1H, dd, *J*=12.9, 11.0). ^{13}C: 211.8, 171.5, 158.1, 143.5, 136.3, 130.7, 129.9, 129.8, 127.6, 113.9, 68.5, 59.8, 58.4, 57.2, 55.2, 50.7, 36.9, 35.61, 33.1, 32.3, 29.6, 28.3, 21.6. IR: 3428, 1702. MS (CI): 513 (MH^+). HRMS (CI): calcd for $C_{27}H_{32}N_2O_6S$ (MH^+) 513.2059; found: 513.2061.

5.2.12. Acetate 72. A solution of **71** (0.140 g, 0.27 mmol), pyridine (0.064 g, 0.81 mmol), acetic anhydride (0.033 g, 0.33 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (2.7 mL) was stirred at rt for 3 h. The mixture was concentrated and the residue was purified by preparative TLC (EtOAc/hexane: 60:40) to afford 0.140 g (93%) of **72**, colorless foam, $[\alpha]_D^{25}$ −27.8 (*c* 1.41). ^{1}H: 7.82 (2H, d, *J*=8.1), 7.30 (2H, d, *J*=8.1), 7.02 (2H, d, *J*=8.8), 6.74 (2H, d, *J*=8.8), 4.94–4.85 (2H, m), 3.80 (1H, dd, *J*=14.0, 7.4), 3.73 (3H, s), 3.41–3.32 (1H, m), 3.05 (1H, dd, *J*=14.0, 7.4), 2.92–2.86 (1H, m), 2.65–2.97 (2H, m), 2.57 (3H, s), 2.41 (3H, s), 2.30 (1H, dd, *J*=12.8, 8.8), 2.19 (3H, s), 2.04–1.84 (2H, m), 1.77 (1H, dd, *J*=12.8, 11.0). ^{13}C: 209.5, 170.4, 169.7, 158.3, 143.5, 136.3, 130.1, 129.7, 127.6, 113.9, 68.9, 58.3, 58.1, 56.6, 55.2, 47.5, 36.9, 35.2, 33.2, 32.1, 29.5, 28.9, 21.6, 21.0. IR: 3405, 1742, 1708. MS (CI): 555 (MH^+). HRMS (CI): calcd for $C_{29}H_{34}N_2O_7S$ (MH^+) 555.2165; found: 555.2163.

5.2.13. Diol 73. Commercial 1 M LAH in THF (0.96 mL, 0.96 mmol) was added dropwise to a cold (−78 °C) solution of compound **71** (98 mg, 191 μmol) in THF (2 mL). The mixture was warmed to 0 °C and stirred for 15 min, then it was refluxed overnight. The reaction was cooled to 0 °C and quenched with EtOAc (caution: vigorous reaction), followed by H_2O (30 μL), 15% NaOH (30 μL), and H_2O (50 μL). The precipitate was filtered through Celite and rinsed with EtOAc. The filtrate was concentrated to yield 60 mg of **73** (contaminated with some of its diastereomer) as a yellow foam. The two isomers were not separated at this point. ^{1}H: 7.17 (2H, d, *J*=8.6), 6.77 (2H, d, *J*=8.6), 3.93–3.81 (1H, m), 3.73 (3H, s), 3.65–3.39 (3H, m), 3.16–3.05 (1H, m), 2.77 (2H, d, *J*=5.0), 2.50 (1H, dd, *J*=9.4, 5.0), 2.29 (3H, s), 2.23–2.07 (2H, m), 2.01–1.87 (2H, m), 1.82 (1H, dd, *J*=12.7, 9.0), 1.73–1.64 (1H, m), 1.34 (1H, dd, *J*=12.7, 5.6), 1.29–1.19 (2H, m). ^{13}C: 156.7, 130.2, 129.3, 112.6, 68.8, 63.2, 60.2, 57.8, 55.3, 54.2, 53.6, 45.0, 43.1, 34.8, 33.7, 30.4, 29.8, 29.0. IR: 3384. MS (CI): 347 (MH^+). HRMS (CI): calcd for $C_{20}H_{30}N_2O_3$ (MH^+) 347.2335; found: 347.2338.

5.2.14. Synthetic FR-901483 bis-hydrochloride: 16·2HCl. Dibenzylphosphate (145 mg, 520 μmol), tris(4-chlorophenyl)phosphine (98 mg, 270 μmol), DIAD (54 μL, 270 μmol), and Et_3N (0.121 mL, 0.87 mmol) were added to a solution of **73** (30 mg, 86.7 μmol) in THF (1.7 mL). The mixture was stirred at rt for 1 h then it was concentrated. The residue was taken up with EtOAc, and the solution was washed (H_2O, then brine), dried ($MgSO_4$), and concentrated. The highly polar, crude Mitsunobu product was converted, taken up in CH_2Cl_2 (1 mL) and treated with NEt_3 (30 μL, 208 μmol), and benzyl chloroformate (20 μL, 135 μmol). After stirring at rt until TLC showed complete conversion, the solution was concentrated and the residue was purified by preparative TLC (10% MeOH in CH_2Cl_2) to afford **75** in an overall 26% yield from compound **73**. Aqueous 3 M HCl (6 μL) was added to a solution of **75** (13 mg, 17.5 μmol) in MeOH (1 mL). The mixture was concentrated and the residue was redissolved in MeOH (0.2 mL), treated with 10% Pd/C (5 mg) and stirred at rt under 1 atm of H_2 (balloon) for 3 h. Filtration through Celite and concentration yielded 7.6 mg (94%) of FR-901483 bis-hydrochloride, $[\alpha]_D^{25}$ +4.0 (*c* 0.35, MeOH, lit. [Ref. 9a] +5, rotation very sensitive to the amount of water and of residual HCl). ^{1}H (500 MHz, CD_3OD): 7.35 (2H, d, *J*=8.6), 6.92 (2H, d, *J*=8.6), 4.52 (1H, dd, *J*=13.6, 9.9), 4.36 (1H, br d, *J*=7.7), 4.33–4.26 (1H, m), 3.97 (1H, dd, *J*=13.6, 2.9), 3.93–3.88 (1H, m), 3.80 (3H, s), 3.67 (1H, br s), 3.34 (1H, m), 3.10 (1H, dd, *J*=12.4, 3.6), 2.81 (3H, s), 2.65 (1H, dd, *J*=14.0, 8.9), 2.48 (1H, br s), 2.35–2.07 (6H, m), 1.93 (1H, br d, *J*=14.2). ^{13}C (125 MHz, CD_3OD): 159.5, 130.7, 127.4, 114.3, 71.4, 67.9, 63.9, 61.0, 54.7, 54.1, 50.9, 41.8, 40.7, 33.0, 31.4, 27.2, 26.6, 21.7. MS (LSI): 427 (MH^+). HRMS (LSI): calcd for $C_{31}H_{38}N_2O_8S$ (MH^+) 427.1998; found: 427.2000.

5.3. General procedure for oxidative cyclization of phenolic sulfonamides 88

A solution of DIB (2.2 mmol) in HFIP (3.5 mL) was added to a solution of a phenolic sulfonamide (2 mmol) in HFIP (5 mL) during 5 min. After 30–60 min, a color change from yellow to green occurred and TLC showed complete conversion. The mixture was concentrated in vacuo and the residue was chromatographed (silica gel, typically 60:40 EtOAc/cyclohexane) to furnish the product, which is often obtained as a foam.

5.3.1. Spirodienone 91. A 1 M solution of $PhI(OAc)_2$ ('DIB') in hexafluoroisopropanol ('HFIP', 4.05 mL, 1.05 equiv of DIB) was added dropwise to a well stirred solution of (D)-(−)-*N*-methanesulfonyl-homotyrosinol (1.0 g, 3.86 mmol) in HFIP (15 mL) at rt. A color change from yellow to green occurred and no starting material was apparent (TLC) after 30 min. The volatiles were removed and the highly polar, crude product, tan foam, was used directly in the next step. $[\alpha]_D^{25}$ +10 (*c* 0.5, acetone) ^{1}H (acetone-d_6): 7.26 (1H, dd, *J*=9.8, 3.0), 7.03 (1H, dd, *J*=10.2, 3.0), 6.16 (1H, dd, *J*=10.2, 2.3), 6.10 (1H, dd, *J*=10.2, 2.3), 4.07 (1H, m), 3.76 (2H, m), 3.01 (3H, s), 2.52 (1H, m), 2.48 (1H, m), 2.18 (1H, m), 1.92 (1H, m). ^{13}C (acetone-d_6): 185.4, 153.7, 149.6, 128.6, 128.2, 65.2, 64.8, 63.9, 40.2, 38.6, 27.3. IR: 3414, 1666. HRMS (CI): calcd for $C_{11}H_{15}NO_4S$ (MH^+): 258.0800; found 258.0801. A solution of this material (0.9 g), imidazole (1 g, 4 equiv), and TBDPSCl (1.10 g, 1.1 equiv) in DMF (15 mL) was stirred at rt for 3 h, then it was diluted with EtOAc (20 mL) and washed with brine (15 mL). The organic phase was separated and the aqueous layer was extracted with more EtOAc (10 mL). The combined extracts were washed

with brine (4×15 mL), and then they were concentrated. Silica gel chromatography of the residue (1:1:0.1, EtOAc/hexanes/NEt3) afforded pure **91** (pale yellow foam, 1.56 g, 3.17 mmol, 82% from homotyrosinol mesylamide). $[\alpha]_D^{25}$ +8 (*c* 0.5, acetone). ^{1}H (acetone-d_6): 7.74 (m, 4H), 7.47 (m, 6H), 7.27 (1H, dd, *J*=10.2, 3.0), 6.94 (1H, dd, *J*=9.8, 3.0), 6.20 (1H, dd, *J*=10.2, 1.9), 6.09 (1H, dd, *J*=10.2, 2.3), 4.17 (1H, m), 4.03 (1H, dd, *J*=10.2, 3.8), 3.93 (1H, dd, *J*=10.2, 7.5), 2.95 (3H, s), 2.48 (2H, m), 2.30 (1H, m), 1.93 (1H, m), 1.10 (9H, s). ^{13}C (acetone-d_6): 185.2, 153.7, 148.7, 136.4, 134.0, 130.8, 129.1, 128.7, 128.2, 66.7, 65.3, 63.3, 39.6, 38.3, 27.3, 27.1, 19.8. IR: 1668. HRMS (CI): calcd for $C_{27}H_{33}NO_4SSi$ (MH^+): 496.1978; found: 496.1972.

5.3.2. Compounds 92 and 93. A 0.5 M solution of KHMDS in toluene (8 mL, 4 mmol, 1.3 equiv) was added to a cold (−100 °C), stirred solution of **91** (1.5 g, 3.00 mmol) in dry THF (100 mL), under argon. The reaction was allowed to warm up to 0 °C during 3 h, then it was quenched with aq satd NH_4Cl (50 mL) and diluted with EtOAc (50 mL). The aqueous phase was discarded and the organic layer was washed with brine (50 mL) and concentrated. A proton NMR spectrum of the crude product revealed that **93** was the major product of a 7:1 mixture of regioisomers (de=75%). Silica gel chromatography (3:7:0.1, EtOAc/hexanes/NEt3) afforded an inseparable mixture of **93** and its regioisomer (1.33 g, 2.70 mmol, 89%). Separation was effected at the stage of compound **95**. $[\alpha]_D^{25}$ +30 (*c* 0.5, CH_2Cl_2). ^{1}H: 7.67 (4H, m), 7.40 (6H, m), 6.62 (1H, dd, *J*=10.2, 1.9), 6.03 (1H, d, 10.2), 4.27 (1H, m), 3.67 (1H, dd, *J*=10.5, 4.9), 3.62 (1H, dd, *J*=7.6, 2.3), 3.43 (1H, dd, *J*=13.2, 7.9), 3.25 (1H, t, 12.4), 3.00 (1H, m), 2.70 (1H, dd, *J*=17.3, 5.3), 2.63 (1H, dd, *J*=16.2, 2.3), 2.14 (4H, m), 1.07 (9H, s). ^{13}C: 194.5, 150.2, 135.5, 134.7, 132.8, 129.8, 127.7, 71.1, 66.3, 61.1, 53.3, 40.6, 36.7, 34.8, 27.2, 26.8, 19.1. IR: 1682. HRMS (CI): calcd for $C_{27}H_{33}NO_4SSi$ (MH^+): 496.1978; found: 496.1975.

5.3.3. Thiophenol adduct 94 and regioisomer. A cold (0 °C) solution of the 7:1 mixture of regioisomers **92** and **93** (1.30 g, 2.62 mmol,), BF_3Et_2O (20 mol %, 70 mg), and thiophenol (1.8 g, 6 equiv) in CH_2Cl_2 (40 mL) was stirred overnight, during which time it was allowed to warm to rt. The reaction was quenched with aq satd K_2CO_3 (40 mL) and diluted with EtOAc (80 mL). The aqueous layer was separated and extracted with more EtOAc (30 mL). The combined extracts were washed with brine (50 mL) and concentrated. Silica gel chromatography (15:85, EtOAc/hexanes) of the residue provided **94** (1.63 g, 2.02 mmol, 77%, 7:1 mixture of regioisomers) as a foam. $[\alpha]_D^{25}$ +12 (*c* 0.5 CH_2Cl_2) ^{1}H: 7.80–7.00 (15H, m), 4.41 (1H, t, *J*=12.8), 4.25 (1H, m), 3.90 (2H, m), 3.65 (1H, t, *J*=8.3), 3.31 (1H, dd, *J*=13.2, 8.3), 2.59 (1H, m), 2.32 (1H, d, *J*=14.7), 2.24–1.23 (7H, m), 1.06 (9H, s). ^{13}C: 137.1, 136.3, 135.6, 134.6, 133.5, 133.4, 133.1, 130.8, 129.7, 129.5, 129.4, 129.0, 128.9, 128.7, 127.5, 127.4, 76.2, 65.5, 62.0, 61.0, 53.5, 51.9, 42.9, 42.2, 35.0, 30.9, 27.2, 26.7, 19.2. IR: 1474, 1436, 1307. MS (LSI): 808 (MH^+) for $C_{45}H_{45}NO_4S_4Si$.

5.3.4. Sulfonamide 95. A solution of **94** (1.35 g, 1.67 mmol, 7:1 mixture of regioisomers) in a 1:3 mixture of EtOAc/EtOH (100 mL) containing suspended activated Raney nickel (50% slurry in water, Acros, decanted and added as a wet metallic powder, 15 g) was stirred at rt for 4 h, then it was carefully filtered over Celite (caution: RaNi is pyrophoric when dry). The metallic residue was washed with more EtOAc (3×30 mL), and the combined organic phases were concentrated. Silica gel chromatography (1:9 EtOAc/hexanes) of the residue afforded pure **95** (pale yellow foam, 623 mg, 1.29 mmol, 77%), uncontaminated by the regioisomer formed during cyclization of **91**. $[\alpha]_D^{25}$ −13 (*c* 0.5, CH_2Cl_2) ^{1}H: 7.69 (4H, m), 7.39 (6H, m), 4.13 (1H, m), 3.65 (1H, dd, *J*=10.2, 4.9), 3.53 (1H, dd, *J*=10.2, 6.8), 3.48 (3H, t, *J*=13.2), 3.25 (1H, dd, *J*=13.2, 7.5), 2.50 (1H, m), 2.10–1.00 (12H, m), 1.08 (9H, s). ^{13}C: 135.6, 133.2, 129.6, 127.6, 73.8, 66.3, 59.5, 53.1, 40.8, 35.5, 35.1, 27.9, 26.8, 24.6, 23.4, 19.6, 19.2. IR: 1307. HRMS (CI): calcd for $C_{27}H_{37}NO_3SSi$ (MH^+): 484.2342; found: 484.2349.

5.3.5. Compounds 96. A 1.5 M pentane solution of *t*-BuLi (0.5 mL, 0.75 mmol, 1.1 equiv) was added to a cold (−78 °C), stirred solution of **95** (345 mg, 0.71 mmol) in THF (5 mL) under argon. After 15 min, $BF_3\cdot Et_2O$ (100 mg, 1.1 equiv) was added, followed 5 min later by (±)-octene oxide (120 mg, 1.3 equiv). The mixture was stirred for 3 h, during which time it was allowed to warm to 0 °C, then it was quenched with aq satd NH_4Cl (10 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with brine (10 mL), and concentrated. Crude **97**, foam, mixture of diastereomers, was advanced to the next step without further purification. IR: 3479, 1428, 1301. HRMS (CI): calcd for $C_{35}H_{53}NO_4SSi$ (MH^+): 612.3543; found: 612.3547.

5.3.6. Ketone 97. A 0.5 M solution of Dess–Martin periodinane in CH_2Cl_2 (Acros, 2.1 mL, 1.5 equiv) was added at rt to a solution of crude **96** (430 mg) in CH_2Cl_2 (4 mL) and the mixture was stirred for 2 h. The solution was diluted with EtOAc (15 mL) and washed with a 1:1 mixture of aq satd K_2CO_3 and aq satd $Na_2S_2O_3$ (3×10 mL), and then it was concentrated. Crude **97** (yellow foam, 381 mg, 0.62 mmol, 88% from **95**) required no further purification. $[\alpha]_D^{25}$ +3 (*c* 0.5, CH_2Cl_2). ^{1}H: 7.69 (4H, m), 7.39 (6H, m), 4.13 (2H, m), 3.69 (1H, dd, *J*=10.2, 4.9), 3.51 (1H, dd, *J*=10.2, 3.0), 3.12 (1H, dd, *J*=18.5, 5.7), 2.60 (1H, dd, *J*=18.5, 6.4), 2.50 (2H, m), 2.38 (3H, t, 7.5), 2.07–1.49 (11H, m), 1.28 (8H, m), 1.09 (9H, s), 0.90 (3H, t, *J*=5.4). ^{13}C: 206.2, 135.6, 134.7, 129.6, 127.6, 71.8, 66.2, 59.6, 56.9, 54.8, 47.5, 45.0, 42.9, 40.8, 35.9, 34.9, 31.4, 30.2, 28.7, 27.7, 26.6, 23.6, 22.4, 19.1, 13.9. IR: 1720, 1462, 1428, 1305. HRMS (CI): calcd for $C_{35}H_{51}NO_4SSi$ (MH^+): 610.3386; found: 610.3386.

5.3.7. Borylketone 114. A stirred solution of **97** (370 mg, 0.61 mmol) in dry DMF (5 mL) under argon was treated with DBU (100 mg, 1.05 equiv), followed, after 10 min, by bis(pinacolyl)diboronate (175 mg, 1.1 equiv), CuCl (70 mg, 1.1 equiv), and KOAc (70 mg, 1.1 equiv). Stirring was continued for 20 min, then the mixture was diluted with EtOAc (10 mL), sequentially washed with aq concd NH_4OH (2×5 mL) and brine (3×10 mL), and concentrated. Silica gel chromatography (1:9:0.1, EtOAc/hexanes/NEt_3) of the residue afforded pure **144** (pale yellow oil, 352 mg, 0.52 mmol, 86%). $[\alpha]_D^{25}$ +10 (*c* 0.5, CH_2Cl_2). ^{1}H: 7.59 (4H, m), 7.39 (6H, m), 4.01 (1H, dd, *J*=10.5, 2.6), 3.68 (1H, d, *J*=10.5), 3.51 (2H, br m), 2.62 (1H, dd, *J*=15.8, 3.0), 2.40 (2H, m), 2.30 (1H, dd, *J*=13.9, 3.4), 2.12–1.12 (15H, m),

1.09 (21H, s), 0.90 (3H, t, J=6.4). ^{13}C: 214.9, 135.6, 130.0, 127.7, 127.6, 72.1, 63.9, 58.0, 47.5, 45.1, 42.1, 34.5, 32.7, 31.5, 28.9, 26.9, 26.7, 24.5, 24.0, 23.7, 22.4, 19.5, 19.0, 13.9. HRMS (ESI): calcd for $C_{41}H_{64}NO_4BSi$ (MH^+): 674.4784; found: 674.4792.

5.3.8. Tricyclic intermediate 117. A cold (0 °C) solution of **114** (35 mg, 0.052 mmol), AcOH (1 drop), and $NaBH_3CN$ (10 mg, 3 equiv) in dry MeOH (3 mL) was stirred under argon for 4 h, then it was treated with aq 2 N NaOH (0.3 mL) and aq 35% H_2O_2 (0.2 mL) and stirred at 0 °C for another 30 min. The mixture was diluted with EtOAc (10 mL). The aqueous layer was separated and washed with more EtOAc (5 mL), and the combined organic phases were washed with brine (10 mL) and concentrated. Silica gel chromatography (1:9:0.1, EtOAc/hexanes/NEt_3) of the residue yielded pure **117** (pale yellow oil, 23 mg, 0.042 mmol, 80%). $[\alpha]_D^{25}$ +6 (c 0.5, CH_2Cl_2). ^{1}H: 7.69 (4H, m), 7.39 (6H, m), 4.14 (1H, m), 3.65 (1H, br), 3.41 (1H, br), 3.0 (1H, br), 2.48 (1H, br), 2.15–1.10 (25H, m), 1.08 (9H, s), 0.86 (3H, t, J=6.8). ^{13}C: 135.6, 129.5, 127.6, 127.5, 71.3, 66.9, 68.6, 63.8, 57.0, 39.7, 38.6, 37.4, 36.2, 33.6, 31.9, 31.8, 29.4, 26.9, 26.8, 26.5, 25.6, 23.7, 22.6, 19.2, 14.1. IR: 3417. HRMS (CI): calcd for $C_{35}H_{53}NO_2Si$ (MH^+): 548.3929; found: 548.3928.

5.3.9. Piperidinone 118. A 0.5 M solution of Dess–Martin periodinane in CH_2Cl_2 (Acros, 0.15 mL, 2.0 equiv) was added to a solution of **117** (20 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) at rt. The mixture was stirred for 2 h, then it was diluted with EtOAc (5 mL), washed with a 1:1 mixture of aq satd K_2CO_3 and aq satd $Na_2S_2O_3$ (3×5 mL), and concentrated. Silica gel chromatography of the residue (1:9:0.1, EtOAc/hexane/NEt3) delivered pure **118** (pale yellow oil, 19 mg, 0.034 mmol, 94%). $[\alpha]_D^{25}$ +3 (c 0.5, CH_2Cl_2). ^{1}H: 7.69 (4H, m), 7.39 (6H, m), 3.60 (1H, dd, J=10.2, 4.5), 3.40 (1H, t, J=8.7), 3.13 (1H, m), 3.00 (1H, m), 2.51 (1H, dd, J=15.4, 5.3), 2.44 (1H, br), 2.24 (1H, d, J=10.5), 2.10 (1H, dd, J=15.8, 7.2), 2.05–1.00 (16H, m), 1.08 (9H, s), 0.85 (3H, t, J=7.2). ^{13}C: 212.6, 135.6, 134.8, 129.6, 127.7, 127.6, 68.1, 68.0, 66.2, 58.5, 50.9, 43.0, 40.5, 36.9, 36.2, 31.8, 29.2, 26.9, 26.5, 26.0, 24.3, 23.1, 22.6, 21.6, 19.2, 14.1. IR: 1707. HRMS (CI): calcd for $C_{35}H_{51}NO_2Si$ (MH^+): 546.3767; found: 546.3768.

5.3.10. Synthetic (−)-2-epicylindricine C, 119. A solution of **118** (18 mg, 33 μmol) and TBAF (32 mg, 3 equiv) in THF (1 mL) was stirred at rt for 4 h. Concentration and chromatography of the residue (1:9:0.1, EtOAc/hexanes/NEt_3) afforded pure (−)-**119** (pale yellow oil, 10 mg, 0.032 mmol, 96%), whose ^{1}H NMR spectra were superimposable to those published by Weinreb (Ref. 35h). $[\alpha]_D^{25}$ −39 (c 0.5, CH_2Cl_2). ^{1}H: 3.53 (1H, dd, J=10.5, 4.1), 3.40–3.20 (3H, m), 2.63 (1H, dd, J=15.3, 5.7), 2.52 (1H, br), 2.27 (1H, m), 2.19 (1H, dd, J=15.4, 6.0), 2.03 (2H, m), 1.83 (2H, m), 1.70–1.20 (19H, m), 0.87 (3H, t, J=6.5). ^{13}C: 211.5, 68.9, 64.6, 63.7, 57.9, 50.9, 42.7, 39.4, 36.9, 36.7, 31.7, 29.7, 29.2, 26.6, 26.2, 24.3, 22.6, 22.6, 14.1. IR: 3445, 1707. HRMS (CI): calcd for $C_{19}H_{33}NO_2$ (MH^+): 308.2589; found: 308.2587.

5.3.11. Boronic ester 123. A solution of **114** (122 mg, 0.18 mmol) and TBAF (175 mg, 3 equiv) in THF (4 mL) was stirred at rt for 5 h, and then it was concentrated. The residue was quickly chromatographed (silica gel) by sequential elution with 1:9:0.1 EtOAc/hexanes/NEt_3 (silicon-containing byproducts) and 95:5 EtOAc/NEt_3 (elution of desilylated **123**). The spectra of the product (pale yellow oil, 75 mg, 0.17 mmol, 95%) suggest that it exists largely as the open-chain, instead of the hemiaminal, tautomer. $[\alpha]_D^{25}$ +11 (c 0.5, CH_2Cl_2). ^{1}H: 3.90 (1H, d, J=9.4), 3.61 (2H, m), 3.04 (1H, d, J=8.7), 2.71 (1H, dd, J=16.2, 3.8), 2.40 (2H, m), 2.31 (1H, dd, J=13.2, 3.8), 2.20–1.20 (21H, m), 1.15 (12H, d, J=12.4), 0.87 (3H, t, J=6.5). ^{13}C: 214.9, 79.3, 72.9, 63.3, 59.5, 47.2, 46.3, 42.3, 34.0, 32.7, 31.5, 28.9, 27.4, 26.8, 26.0, 24.9, 24.4, 24.0, 23.6, 22.4, 19.5, 14.0. IR: 3253, 1704. MS (ESI): 436 (MH^+) for $C_{25}H_{46}NO_4B$. A cold (−78 °C) solution of this material (70 mg, 0.16 mmol), AcOH (two drops), and $NaBH(OAc)_3$ (50 mg, 1.5 equiv) in CH_2Cl_2 (4 mL) was stirred under argon overnight, during which time it was allowed to warm up to rt. The mixture was diluted with EtOAc (10 mL) and washed with aq satd K_2CO_3 (10 mL). The organic phase was further washed with brine (10 mL) and concentrated. Silica gel chromatography of the residue (2:8:0.1 EtOAc/hexanes/NEt3) provided pure **123** (49 mg, 0.12 mmol, 73%) as a pale yellow oil, $[\alpha]_D^{25}$ −22 (c 0.5, CH_2Cl_2). ^{1}H: 3.44–3.22 (4H, m), 2.28 (1H, dt, J=12.8; 4.1), 2.22–1.90 (3H, m), 1.80–1.20 (22H, m), 1.25 (12H, s), 0.87 (3H, t, J=6.5). ^{13}C: 82.7, 66.3, 66.2, 56.1, 51.0, 37.0, 36.7, 35.4, 34.0, 31.9, 30.0, 29.7, 29.4, 28.9, 27.1, 24.9, 24.0, 22.7, 21.7, 19.0, 14.1. IR: 3409. MS (ESI): 420 (MH^+) for $C_{25}H_{46}NO_3B$.

5.3.12. Compound 124. A solution of **123** (42 mg, 0.10 mmol), imidazole (25 mg, 4 equiv), and TBDPSCl (28 mg, 1.1 equiv) in DMF (2 mL) was stirred at rt for 3 h, then it was diluted with EtOAc (5 mL) and brine (5 mL). The aqueous layer was removed and washed with more EtOAc (5 mL). The combined organic phases were washed with brine (4×15 mL) and concentrated. Silica gel chromatography of the residue (1:9:0.1 EtOAc/hexanes/NEt3) yielded pure **22** (pale yellow oil, 0.63 mg, 0.095 mmol, 95%). $[\alpha]_D^{25}$ +9 (c 0.5, CH_2Cl_2). ^{1}H: 7.70 (4H, m), 7.39 (6H, m), 3.52 (1H, br), 3.15 (3H, br), 2.20–1.00 (25H, m), 1.25 (12H, s), 1.06 (9H, s), 0.87 (3H, t, J=6.5). ^{13}C: 135.6, 129.4, 127.5, 82.6, 69.3, 65.3, 57.8, 50.7, 37.3, 35.6, 35.3, 34.2, 31.9, 29.7, 29.3, 27.1, 26.9, 26.4, 24.9, 24.8, 24.2, 22.6, 21.6, 19.2, 14.1. MS (ESI): 658 (MH^+) for $C_{41}H_{64}NO_3SiB$.

5.3.13. Alcohol 125. A cold (0 °C) solution of **124** (56 mg, 0.085 mmol), 2 N aq NaOH (0.5 mL), and aq 35% H_2O_2 (0.3 mL) in THF (2 mL) was stirred for 30 min, and then it was diluted with EtOAc (5 mL). The aqueous layer was discarded and the organic phase was washed with brine (3×3 mL) and concentrated. Crude **125** (45 mg, 0.083 mmol, 97%), pale yellow oil, was used without further purification. $[\alpha]_D^{25}$ +6 (c 0.5, CH_2Cl_2). ^{1}H: 7.66 (4H, m), 7.37 (6H, m), 4.14, (1H, br), 3.57 (1H, br), 3.16 (3H, br), 2.15–1.00 (25H, m), 1.08 (9H, s), 0.84 (3H, t, J=6.5). ^{13}C: 135.6, 134.3, 134.0, 129.4, 127.5, 73.6, 68.9, 65.1, 57.5, 46.9, 37.8, 36.2, 35.1, 35.0, 33.8, 31.8, 29.3, 27.2, 26.9, 26.2, 24.4, 23.1, 22.6, 19.2, 14.0. IR: 3417. HRMS (CI): calcd for $C_{35}H_{53}NO_2Si$ (MH^+): 548.3929; found: 548.3929.

5.3.14. Protected cylindricine C, 126. A 0.5 M CH_2Cl_2 solution of Dess–Martin periodinane (Acros, 0.5 mL,

1.5 equiv) was added to a solution of **125** (41 mg, 0.075 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 2 h, then it was diluted with EtOAc (5 mL), washed with a 1:1 mixture of aq satd K_2CO_3 and aq satd $Na_2S_2O_3$ (3×5 mL), and concentrated. Silica gel chromatography of the residue (1:9:0.1 EtOAc/hexanes/NEt3) afforded pure **126** (38 mg, 0.070 mmol, 94%) as a (pale yellow oil, $[\alpha]_D^{25}$ −6 (*c* 0.5, CH_2Cl_2). ^{1}H: 7.68 (4H, m), 7.39 (6H, m), 3.63, (1H, dd, *J*=6.4, 1.9), 3.32 (1H, m), 3.29 (1H, t, *J*=9.0), 3.09 (1H, m), 2.30–2.00 (7H, m), 1.70–1.00 (18H, m), 1.08 (9H, s), 0.84 (3H, t, *J*=7.2). ^{13}C: 211.4, 135.6, 134.0, 133.8, 129.6, 127.6, 70.2, 68.4, 57.7, 55.3, 50.1, 42.9, 35.8, 34.9, 34.8, 31.7, 29.7, 29.0, 26.9, 25.9, 24.4, 22.9, 22.5, 21.9, 19.2, 14.0. IR: 1707. HRMS (CI): calcd for $C_{35}H_{51}NO_2Si$ (MH^+): 546.3767; found: 546.3768.

5.3.15. Synthetic (−)-cylindricine C, 76. A solution of **126** (29 mg, 0.053 mmol) and TBAF (50 mg, 3 equiv) in THF (1 mL) was stirred at rt for 4 h, and then it was concentrated. Silica gel chromatography of the residue (1:9:0.1 EtOAc/hexanes/NEt3) provided pure (−)-**76** (pale yellow oil, 16 mg, 0.051 mmol, 96%), whose ^{1}H NMR spectra were superimposable to those published by Molander (Ref. 35a). The optical rotation measured for **3**, $[\alpha]_D^{25}$ −66 (*c* 0.5, CH_2Cl_2), matched that reported by Molander for (−)-cylindricine C, $[\alpha]_D^{25}$ −64 (*c* 0.2, CH_2Cl_2), and, in absolute value, that reported by Trost (Ref. 35b) for (+)-cylindricine C, $[\alpha]_D^{25}$ +61 (*c* 0.4, CH_2Cl_2). ^{1}H: 3.52, (2H, m), 3.44 (1H, m), 3.29 (1H, m), 2.86 (1H, br m), 2.30–2.07 (5H, m), 1.83 (1H, m), 1.77–1.20 (19H, m), 0.88 (3H, t, *J*=7.2). ^{13}C: 210.4, 70.6, 66.3, 56.5, 55.3, 50.2, 42.5, 36.4, 35.9, 35.2, 31.7, 29.2, 28.7, 27.1, 24.2, 22.7, 22.5, 21.8, 14.0. IR: 3445, 1707. HRMS (CI): calcd for $C_{19}H_{33}NO_2$ (MH^+): 308.2589; found: 308.2589.

5.4. General procedure for bimolecular oxidative amidation of phenols

A solution of $PhI(OAc)_2$ ('DIB', 232.0 mg, 0.7 mmol, 1.2 equiv) in $(CF_3)_2CHOH$ ('HFIP', 0.5 mL) was added dropwise over 30 s to a vigorously stirred solution of a phenol (0.6 mmol, 1 equiv) in MeCN (2.0 mL) and HFIP (1.5 mL) kept at 15 °C (bath temperature). The mixture was stirred for 20 min, and then it was concentrated. Silica gel chromatography of the residue, first with 1:1 AcOEt/Hexanes (removal of gross contaminants), and then with 5–10% MeOH in CH_2Cl_2, provided the pure product.

5.4.1. Amidodienones 139. *R=CH₃*. Yield=56%. ^{1}H: 6.82 (2H, d, *J*=10.2), 6.31 (1H, br s), 6.19 (2H, d, *J*=10.2), 1.91 (3H, s), 1.43 (3H, s). ^{13}C: 185.5, 170.3, 152.5, 127.6, 52.5, 26.1, 23.1. HRMS (CI): calcd for $C_9H_{12}O_2N_1$ (MH^+): 166.0868; found:166.0871.

R=(CH₂)₂CH₃. Yield=54%. ^{1}H: 6.77 (2H, d, *J*=10.2), 6.67 (1H, br s), 6.24 (2H, d, *J*=10.2), 1.96 (3H, s), 1.69 (2H, m), 1.22 (2H, m), 0.84 (3H, t, *J*=7.2). ^{13}C: 185.8, 170.0, 151.3, 128.6, 55.9, 40.4, 23.2, 16.4, 13.9. HRMS (CI): calcd for $C_{11}H_{16}O_2N_1$ (MH^+): 194.1181; found: 194.1182.

R=CH(CH₃)₂. Yield=62%. ^{1}H: 6.81 (2H, d, *J*=10.2), 6.31 (1H, br s), 6.26 (2H, d, *J*=10.2), 2.21 (1H, h, *J*=7.0), 1.91 (3H, s), 0.89 (6H, d, *J*=7.0). ^{13}C: 185.8, 170.1, 149.8, 129.3, 58.9, 34.7, 23.3, 16.9. HRMS (CI): calcd for $C_{11}H_{16}O_2N_1$ (MH^+): 194.1181; found: 194.1181.

R=CH₂COOMe. Yield=58%. ^{1}H: 6.95 (2H, d, *J*=10.2), 6.80 (1H, br s), 6.29 (2H, d, *J*=10.2), 3.72 (3H, s), 2.76 (2H, s), 1.97 (3H, s). ^{13}C: 184.7, 170.2, 170.1, 148.4, 128.8, 53.2, 52.3, 42.2, 23.5.

R=(CH₂)₂NHTs. Yield=53%. ^{1}H: 7.62 (2H, d, *J*=7.9), 7.24 (2H, d, *J*=7.9), 6.98 (1H, br s), 6.84 (2H, d, *J*=9.8), 6.21 (2H, d, *J*=9.8), 5.83 (1H, br s), 2.83 (2H, br m), 2.38 (3H, s), 2.03 (2H, br m), 1.91 (3H, s). ^{13}C: 185.6, 170.8, 150.4, 143.8, 136.1, 129.8, 128.9, 126.9, 54.8, 38.2, 37.7, 23.3, 21.5.

R=(CH₂)₃OPiv. Yield=67%. ^{1}H: 6.80 (2H, d, *J*=10.2), 6.30 (2H, d, *J*=10.2), 6.21 (1H, br s), 3.99 (2H, t, *J*=6.0), 1.95 (3H, s), 1.88 (2H, m), 1.53 (2H, m), 1.16 (9H, s). ^{13}C: 185.4, 178.4, 169.9, 150.1, 129.1, 63.3, 55.5, 38.6, 34.2, 27.0, 23.3, 22.6. HRMS (CI): calcd for $C_{16}H_{24}O_4N_1$ (MH^+): 294.1705; found 294.1705.

R=(CH₂)₃CO₂TFE. Yield=57%. ^{1}H: 6.84 (2H, d, *J*=10.2), 6.43 (1H, br s), 6.28 (2H, d, *J*=10.2), 4.47 (2H, q, *J*=8.3), 2.41 (2H, t, *J*=6.8), 1.94 (3H, s), 1.83 (2H, m), 1.62 (2H, m). ^{13}C: 185.4, 171.4, 170.0, 150.0, 129.2, 60.5 (q), 55.6, 37.2, 32.7, 23.4, 18.4.

R=(CH₂)₂CN. Yield=67%. ^{1}H: 6.89 (2H, d, *J*=10.2), 6.70 (1H, br s), 6.31 (2H, d, *J*=10.2), 2.26 (4H, br), 1.91 (3H, s). ^{13}C: 184.7, 170.5, 148.0, 130.0, 118.7, 55.0, 32.4, 23.4, 11.9.

R=(CH₂)₃CN. Yield=71%. ^{1}H: 6.91 (1H, br s), 6.82 (2H, d, *J*=10.2), 6.26 (2H, d, *J*=10.2), 2.31 (2H, t, *J*=6.8), 1.97 (2H, m), 1.89 (3H, s), 1.52 (2H, m). ^{13}C: 185.3, 170.2, 149.9, 129.1, 118.8, 55.3, 36.1, 23.2, 19.2, 16.8.

R=(CH₂)₄CN. Yield=71%. ^{1}H: 6.86 (2H, d, *J*=10.2), 6.60 (1H, br s), 6.26 (2H, d, *J*=10.2), 2.31 (2H, t, *J*=7.2), 1.92 (3H, s), 1.87 (2H, m), 1.60 (2H, q, *J*=7.2), 1.35 (2H, m). ^{13}C: 185.4, 170.1, 150.2, 129.0, 119.2, 55.7, 36.9, 25.0, 23.4, 22.4, 16.8.

R=(CH₂)₃N₃. Yield=42%. ^{1}H: 6.82 (2H, d, *J*=10.2), 6.29 (2H, d, *J*=10.2), 5.89. (1H, br s), 3.31 (2H, t, *J*=6.4), 1.98 (2H, m, 3H, overlapping a s), 1.47 (2H, m). ^{13}C: 185.4, 170.1, 150.0, 129.2, 55.6, 50.9, 34.9, 23.4, 22.9.

R=(CH₂)₄N₃. Yield=49%. ^{1}H: 6.79 (2H, d, *J*=10.2), 6.25 (1H, br s), 6.24 (2H, d, *J*=10.2), 3.20 (2H, t, *J*=7.0), 1.91 (3H, s), 1.78 (2H, m), 1.47 (2H, quintuplet, *J*=7.0), 1.25 (2H, m). ^{13}C: 185.6, 170.2, 150.7, 128.8, 55.8, 50.8, 37.4, 28.4, 23.2, 20.4.

R=(CH₂)₃Br. Yield=65%. ^{1}H: 6.81 (2H, d, *J*=10.2), 6.37 (1H, br s), 6.30 (2H, d, *J*=10.2), 3.35 (2H, t, *J*=6.0), 2.01 (2H, m), 1.96 (3H, s), 1.73 (2H, m). ^{13}C 185.3, 170.0, 149.9, 129.4, 55.5, 36.4, 32.8, 26.3, 23.5.

R=(CH₂)₄Br. Yield=72%. ^{1}H: 6.84 (2H, d, *J*=10.2), 6.68 (1H, br s), 6.26 (2H, d, *J*=10.2), 3.32 (2H, t, *J*=6.8), 1.91 (3H, s), 1.80 (4H, m), 1.37 (2H, m). ^{13}C: 185.6, 170.1, 150.6, 128.9, 55.8, 37.0, 32.9, 32.1, 23.3, 21.7.

5.4.2. Spirane 141. A solution of **140** (0.2 mmol) in dry THF (2.0 mL) was treated with solid NaH (1.1 equiv) and stirred at rt (Ar). After 1 h, TLC showed complete conversion. Satd aq NH_4Cl solution (two drops) was added and the mixture was concentrated. The residue was taken up with $CHCl_3$ (3×2 mL). Filtration and concentration provided essentially pure **141** (91%) as a slightly yellow oil. ^1H: 7.01 (2H, d, J=10.2), 6.19 (2H, d, J=10.2), 3.58 (2H, app t, J=5.7), 2.08 (3H, s), 1.80 (2H, m), 1.63 (4H, m). ^{13}C: 185.3, 171.8, 152.0, 125.9, 56.8, 38.2, 23.9, 23.2 (two overlapping signals), 19.5.

Note added in proof

A noteworthy synthesis of (−)-cylindricine has recently been disclosed by Swidorski, J. J.; Wang, J.; Sung, R. P. *Org. Lett.* **2006**, *8*, 777.

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