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Oxidative Spirocyclization of Phenolic Sulfonamides: Scope and Applications

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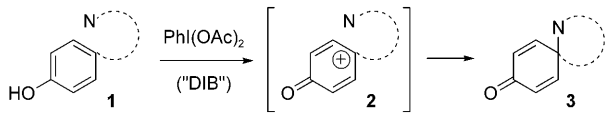
Abstract: A full account of the oxidative dearomatization of *para*- and *ortho*-phenolic sulfonamides is provided together with an overview of the chemistry of the products and their elaboration to building blocks for spirocyclic alkaloids. A concise total synthesis of putative lepadiformine complements the discussion.

Keywords: alkaloids · dearomatization · lepadiformine · phenols · sulfonamides

Introduction

The oxidative amidation of phenols achieves the conversion of substrates of type **1** into dienones **3** (Scheme 1).[1] The



Scheme 1. The oxidative amidation of phenols. DIB = $PhI(OAc)_2$.

process entails oxidative activation of the phenol with a hypervalent iodine reagent[2] such as $PhI(OAc)_2$ (DIB) or occasionally $PhI(OCOCF_3)_2$ (PIFA), followed by the capture of the putative reactive intermediate **2** by an appropriate nitrogen nucleophile.[3] Intramolecular and bimolecular variants of the reaction are known. In the intramolecular regime, an oxazoline[4] or sulfonamide[5] serve to intercept **2**.[6] In the bimolecular mode, acetonitrile discharges this function.[7] In its original form, oxidative amidation chemistry necessitated the use of fluoro alcohol solvents, for example, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). These non-nucleophilic, polar solvents are indeed the media of choice for many DIB- or PIFA-mediated transformations, as determined by Kita and coworkers.[8] Unfortunately, the high cost of TFE and, especially, of HFIP overshadows the usefulness of oxidative amidation chemistry. Therefore, we have researched alternative protocols that eschew the use of such media.

Initial success in this domain was recorded recently in the form of an improved procedure for the bimolecular oxidative amidation of phenols in acetonitrile containing 1.3–1.5 equivalents (relative to the substrate) of trifluoroacetic acid (TFA).[9] This development encouraged us to explore similar conditions for the oxidative cyclization of phenolic sulfonamides, a technology that is central to some ongoing efforts in our laboratory and that has resulted in the past in what has been described as a "unique approach"[10] to cylindricine alkaloids.[11] Herein, we disclose a solution to the foregoing problem, illustrate the scope of the reaction, discuss aspects of the reactivity of the products thus obtained, and demonstrate an application of the updated methodology in the synthesis of the originally proposed,[12] and later corrected,[13] structure of lepadiformine.[14,15]

Results and Discussion

An HFIP-free procedure for the oxidative cyclization of sulfonamides: The results that emanate from studies on bimolecular reactions[9] induced us to examine the DIB-promoted oxidative cyclization of test substrate **4a** to spiropyrrolidine **5a** in MeCN, CH_2Cl_2, or toluene containing TFA, or neat TFA in the temperature range −78 to 25 °C (Table 1). Reactions run at ambient temperature gave the best results. Thus, portionwise addition of DIB (1.1 equiv) to a dilute solution (10 mM) of **4a** in an appropriate solvent containing TFA (1.5 equiv) resulted in essentially quantitative conversion into **5a**. The reaction worked equally well in polar (MeCN), moderately polar (CH_2Cl_2), and nonpolar (PhMe) solvents. Only products of oxidative cyclization were detected in re-

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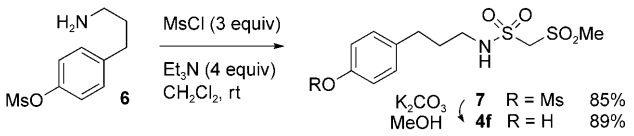
Table 1. Oxidative cyclization of model substrate **4a**.

Conditions[a]	Solvent	Yield [%][b]
A	MeCN	95
A	CH_2Cl_2	95
A	toluene	95
B	TFA	95

[a] Conditions A: A solution of DIB (1.1 equiv) and TFA (1.5 equiv) in the indicated solvent were added at room temperature by syringe pump to a solution of **4a** (1 equiv) in the same volume of solvent (the final formal concentration of **4a** was 10 mM). Conditions B: A solution of DIB (1.1 equiv) in TFA was added slowly at room temperature to a solution of **4a** in the same volume of TFA (the final formal concentration of **4a** was 0.3 M). [b] After chromatography. TFA = trifluoroacetic acid.

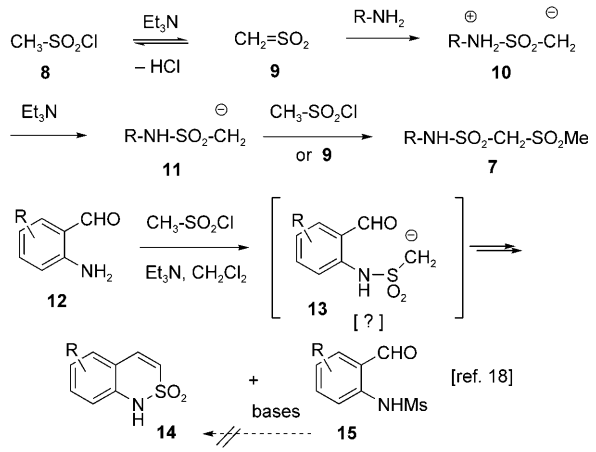
actions carried out in MeCN: the bimolecular amidation[7] did not compete. However, it transpired that the reaction could be more conveniently carried out in neat TFA, a solvent in which one could comfortably operate at a substrate concentration of 0.3 M (Table 1). Yields as high as those obtained in more dilute reactions were thus achieved; furthermore, TFA did not seem to promote the dienone/phenol rearrangement[16] of **5a**. The new protocol eliminated the need for HFIP and other cosolvents.

Scope of the *para*-oxidative cyclization of sulfonamides: The scope of the reaction with respect to the sulfonamide was explored with a number of substrates, including the unusual compound **4f** (Scheme 2). This substance was pre-



Scheme 2. Preparation of **4f**. MsCl = methanesulfonyl chloride.

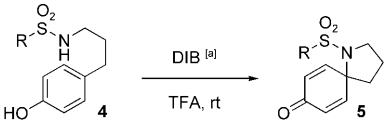
pared by *O*-deblocking of **7**, which emerged fortuitously, and in high yield when the mesylation of **6** was carried out with excess MsCl and Et_3N (3 and 4 equivalents, respectively) in CH_2Cl_2 at room temperature. Essentially none of the expected mesylamide was formed under these conditions. The pathway that leads to **7** is likely to involve a reaction of the amine with sulfene **9**, thus arising through Et_3N-promoted elimination of HCl from MsCl.[17] *N*-Deprotonation of zwitterion **10** yields **11**, which probably undergoes *C*-mesylation by reaction with more MsCl, or possibly with a second molecule of **9**. The presumed intervention of the reactive species **11** finds support in an observation recorded earlier in our laboratory. Thus, the treatment of 2-aminobenzaldehydes **12** with MsCl and Et_3N produced variable amounts of heterocycle **14** in addition to the expected **15** (Scheme 3).[18] Treatment of the latter with a base (Et_3N, *t*BuOK, NaH, NaHMDS) failed to promote cyclization to **14**, which therefore must ensue from an intermediate such as **13**.



Scheme 3. Presumed mechanism for the formation of **7** and **14**.

Alkylsulfonamides **4b–f** underwent oxidative cyclization in uniformly good-to-excellent yields upon exposure to DIB in TFA, and the resulting products were easily purified (Table 2). The *tert*-butyl[19] and benzylsulfonamides (Table 2, entries 2 and 4) afforded slightly lower yields relative to methyl, trifluoromethyl, cyclopropyl, and CH_2Ms sulfonamides. This outcome is presumably due to steric effects.

Table 2. Oxidative cyclization of phenolic alkylsulfonamides **4b–f**.



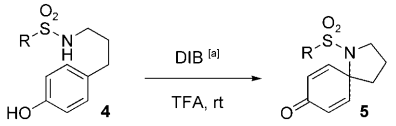
Entry	R	Product	Yield [%][b]
1	CF_3	**5b**	94
2	*tert*-butyl	**5c**	85
3	cyclopropyl	**5d**	90
4	benzyl	**5e**	89
5	$CH_3SO_2CH_2-$	**5f**	92

[a] These reactions were run under conditions B given in Table 1. [b] After chromatography.

All arylsulfonamides reacted efficiently. The yields were largely insensitive to the nature of the arylsulfonyl group (Table 3). Sterically hindered sulfonamides (i.e., triisopropylsulfonamide; Table 3, entry 8) or those incorporating electron-donating substituents on the aromatic ring (i.e., 4-methoxysulfonamide; Table 3, entry 7) reacted less efficiently, but still in more than 80% yield. All positional isomers of nitrophenyl (nosyl) sulfonamides cyclized efficiently (Table 3, entries 2–4).[20] The *ortho*- and *para*-nosyl products are significant because the sulfonamide group can be released under mild conditions,[21] as detailed by Kan and Fukuyama.[22]

Excellent results were also obtained with amino acid-derived substrates. Derivatives **16** of L-homotyrosinol,[23] in

Table 3. Oxidative cyclization of phenolic arylsulfonamides **4g–o**.

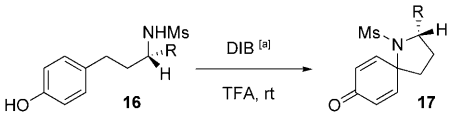


Entry	R	Product	Yield [%][b]
1	4-Me-C_6H_4	**5g**	94
2	2-O_2N-C_6H_4	**5h**	95
3	3-O_2N-C_6H_4	**5i**	95
4	4-O_2N-C_6H_4	**5j**	96
5	4-Br-C_6H_4	**5k**	93
6	4-MeC(O)C_6H_4	**5l**	93
7	4-MeO-C_6H_4	**5m**	85
8	2,4,6-triisopropylphenyl	**5n**	83
9	2-thienyl	**5o**	91

[a] These reactions were run under conditions B given in Table 1. [b] After chromatography.

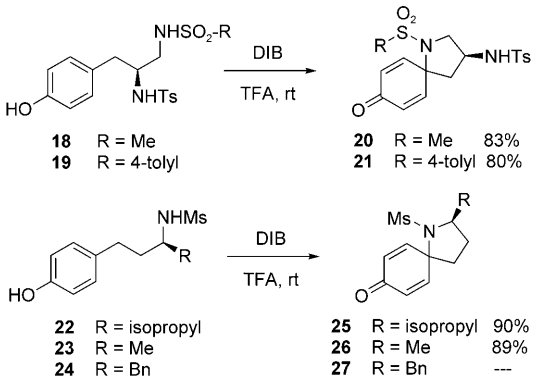
which the primary OH group was either free or protected with a group of modest steric demand (e.g, Me), cyclized in nearly quantitative yield (Table 4). The free OH group in **16a** did not compete with the sulfonamide moiety during oxidative cyclization; that is, no spiropyran product was observed. This result reaffirms that formation of a five-membered ring is kinetically much more favorable than a 6-membered ring. Indeed, the formation of spiropyrans and especially spiropiperidines under these conditions tends to be unsatisfactory. Furthermore, the emerging **17a**[20] was configurationally homogeneous, as apparent from ^{19}F NMR spectroscopic analysis of the corresponding Mosher derivative. Even the homotyrosinal methanesulfonamide **16c** cyclized in excellent yield, thus indicating that a sensitive formyl group is well tolerated during the reaction. On the other hand, derivatives of **16a** in which the OH group was blocked with a sterically demanding protecting group, such as TBDPS or trityl (Table 4, entries 4 and 5), failed to undergo oxidative amidation and provided an intractable mixture of products instead. Tyrosine derivatives **18** and **19** underwent cyclization in diminished, but still good, yield (about 80%; Scheme 4).[20] At this time, we can not account

Table 4. Oxidative cyclization of amino acid-derived phenolic methanesulfonamides **16a–e**.



Entry	R	Product	Yield [%][b]
1	CH_2OH	**17a**	95
2	CH_2OMe	**17b**	95
3	CHO	**17c**	94
4	$CH_2OTBDPS$	**17d**	–
5	CH_2OCPh_3	**17e**	–

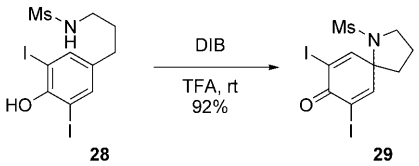
[a] These reactions were run under conditions B given in Table 1. [b] After chromatography. TBDPS = *tert*-butyldiphenylsilyl.



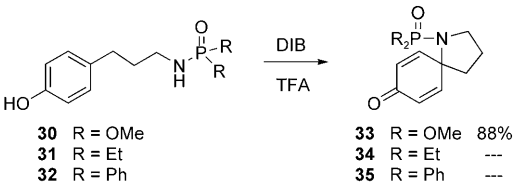
Scheme 4. Oxidative cyclization of amino acid-derived sulfonamides. Ts = 4-toluenesulfonyl.

for such a decrease. Valine and alanine derivatives **22** and **23** cyclized in high yield, but the reaction failed with phenylalanine-derived **24** (a complex mixture formed; no **27** was detected).

The effect of substitution on the phenolic ring has yet to be addressed in detail. One such example appears in Scheme 5. Compound **28**, obtained in high yield by iodination of **4a** with bis(pyridine)iodonium tetrafluoroborate,[24] cyclized in over 90% yield. The oxidative cyclization of phosphoramides[25] was also efficient; for example, **30** advanced to **33** in 88% yield (Scheme 6). However, phosphinamides **31** and **32** produced no **34** or **35**.



Scheme 5. Oxidative cyclization of iodophenol substrates.



Scheme 6. Behavior of phosphoramides and congeners in oxidative cyclization.

The *ortho*-oxidative cyclization of sulfonamides: All the examples seen thus far involve what may be termed the *para*-oxidative amidation of a phenol. However, an *ortho*-variant of the reaction (i.e., **36** and **37**; Table 5)[25] may provide interesting opportunities because the resulting dienones display rich chemistry that can be harnessed meaningfully in a synthetic context.[26] A study of the cyclization of **36** again

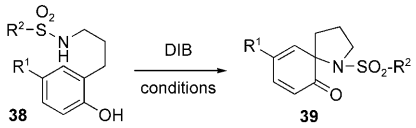
Table 5. Oxidative *ortho*-cyclization of phenolic methanesulfonamide **36**.

Conditions[a]	Solvent	Temperature	Yield [%][b]
A	CH_2Cl_2	−78 °C→rt	50
A	THF	−78 °C→rt	45
A	toluene	−78 °C→rt	51
A	toluene/MeCN (10:1)	−78 °C→rt	59
A	toluene/MeCN (10:1)	−30 °C→rt	52
A	toluene/MeCN (10:1)	0 °C→rt	50
A	toluene/MeCN (10:1)	rt	50
A	toluene/MeCN (10:1)	60 °C	45
A	toluene/MeCN (10:1)	reflux	45
B	TFA	rt	60

[a] Conditions A: A solution of **36** in the stated solvent was added slowly (syringe pump) at room temperature to a solution of DIB (1.1 equiv) and TFA (1.5 equiv) in the same solvent (the final formal concentration of **36** was 10.0 mM). Conditions B: A solution of DIB (1.1 equiv) in TFA was added at room temperature to a solution of **36** in the same volume of TFA (the final formal concentration of **36** was 0.3 M). [b] After chromatography.

revealed that the reaction was best carried out in neat TFA at room temperature and at a substrate concentration of 0.3 M. However, the *ortho*-oxidative amidation was generally less efficient than the *para* mode (Table 6). Substituents at the phenolic *para* position, regardless of electronic character (i.e., an electron-withdrawing Br atom in **38a** versus an electron-donating Me group in **38b**), resulted in lower yields. The reaction failed altogether with 2-nosyl substrate **38c** (a mixture of products and no **39c** were formed).

Table 6. Oxidative *ortho*-cyclization of various phenolic sulfonamides **38**.

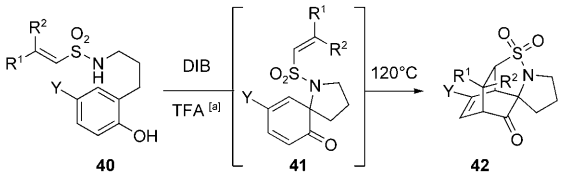


Entry	R^1	R^2	Conditions[a]	Product	Yield [%][b]
1	Br	Me	A	**39a**	30
2	Br	Me	B	**39a**	29
3	Me	Me	A	**39b**	51
4	Me	Me	B	**39b**	47
5	H	2-O_2N–C_6H_4	A or B	**39c**	–

[a] Conditions A and B are the same as in Table 5. [b] After chromatography.

The fact that *ortho*-dienones such as **39** readily undergo the Diels–Alder reaction[27] induced us to investigate a tandem *ortho*-oxidative amidation/IMDA reaction[28] of vinylsulfonamides **40** (Table 7).[25] Compounds **40a–c** emerged directly upon reaction of the corresponding free amines with commercially available 2-chloroethylsulfonyl chloride. Dienic substrates **40d** and **40e** were prepared by reaction of the free amine with the *trans* and *cis* isomers of 1-(1,3-butadien)ylsulfonyl chloride, respectively. The reported method for the synthesis of this material[29] involves *n*BuLi-promoted eliminative ring-opening of 3-sulfolene and trapping of the intermediate sulfinate with *N*-chlorosuccinimide (NCS). This affords a mixture of the two geometric isomers of the product, which are, remarkably, separable by column chromatography, albeit in moderate overall yield. Oxidative cyclization of **40** proceeded normally, but the primary products **41** resisted Diels–Alder cyclization at or near room temperature. Furthermore, although **41** was readily detectable by NMR spectroscopic analysis as the major component of the crude reaction mixture, chromatographic purification proceeded with major loss of material. It proved expedient to dilute the crude reaction mixture with toluene and heat the resulting solution to 120 °C to effect IMDA cyclization. Tetracyclic products **42** were thus isolated in 30–40 % yield.[20] Note that the diene moiety of **41d** and **41e** behaved exclusively as the dienophilic component of the IMDA step.[30]

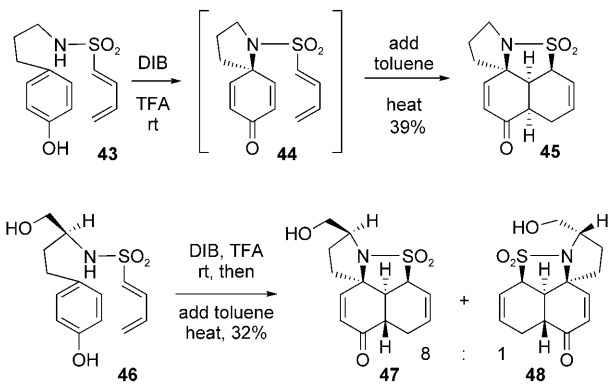
Table 7. Tandem oxidative *ortho*-cyclization IMDA reaction of sulfonamides **41**.



Entry	R^1	R^2	Y	Product	Yield [%][b]
1	H	H	H	**42a**	40
2	H	H	Br	**42b**	31
3	H	H	Me	**42c**	43
4	CH_2=CH−	H	H	**42d**	34
5	H	CH_2=CH−	H	**42e**	27

[a] The oxidative cyclization step was carried out under conditions B given in Table 5. Upon complete conversion of **40** into **41** (TLC), the mixture was diluted with toluene (2 volumes) and heated to 120 °C (oil-bath temperature) until completion of the IMDA step. [b] After chromatography.

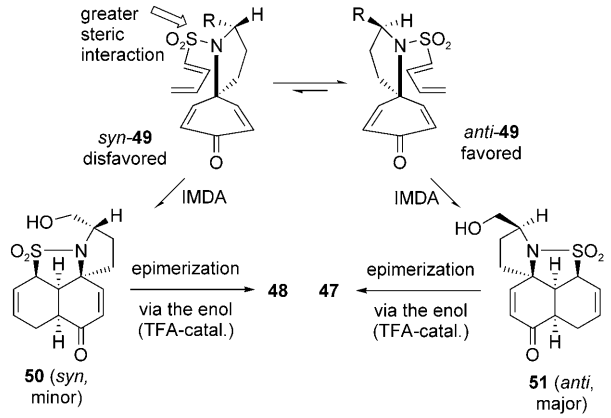
Related tandem processes initiated by *para*-oxidative cyclization of dienic sulfonamides have also been demonstrated.[30] To wit, treatment of **43** with DIB in TFA, followed by dilution with toluene and heating produced **45** in 39 % yield (Scheme 7). More importantly, the same reaction of **46** fur-



Scheme 7. Tandem *para*-oxidative amidation, that is, an IMDA reaction. IMDA = intramolecular Diels–Alder reaction.

nished an 8:1 mixture of **47** and **48** (major and minor products, respectively), but in moderate yield. Note that the latter compounds possess the *trans*-ring fusion of the decaline system.

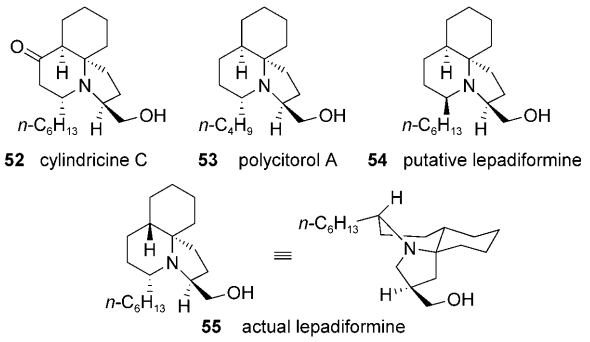
The stereochemical outcome of the reaction that led to **47** may be rationalized as delineated in Scheme 8. The action of DIB on the substrate initially yields azaspirane **49**



Scheme 8. Mechanistic hypothesis for the oxidative amidation, that is, an IMDA reaction of **43**.

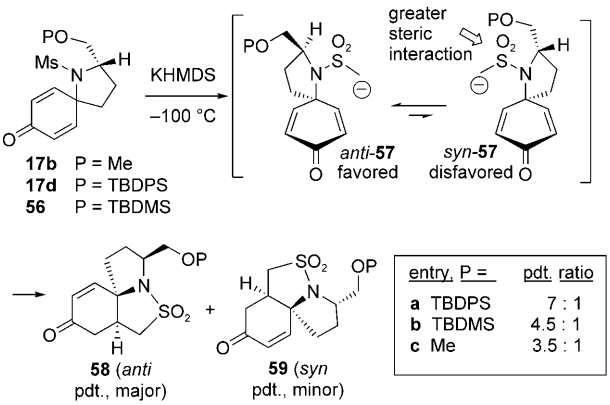
(Scheme 8; R = CH_2OH), which can undergo IMDA cyclization either from conformer *anti*-**49** or *syn*-**49** (*syn* and *anti* refer to the relative orientation of the sulfonyl and R groups). Clearly, *anti*-**49** is energetically preferred relative to *syn*-**49**, which suffers from a greater degree of steric compression between the SO_2 and R moieties. The primary IMDA adducts are undoubtedly the *cis*-decaline products **50** (minor) and **51**. The TFA still present in the medium may facilitate equilibration of the ketone with the corresponding enol, thus leading to epimerization of *cis*-decaline to the *trans* isomer.[31]

Desymmetrization of dienones obtained by *para*-oxidative amidation of sulfonamides: It is recognized that the spiro carbon atom in the transient **49** is not stereogenic, whereas it is becomes stereogenic in **47**. The IMDA step occurs selectively at the *pro*-S double bond of **49**, thereby desymmetrizing the "locally symmetrical" dienone and selectively inducing the *S* configuration of the spiro center in **47**. The stereocontrolled creation of stereogenic spirocenters through a dienone desymmetrization strategy is central to a number of our past and present synthetic endeavors. A recent review highlights this principle and illustrates some key applications in total synthesis.[32] It is also apparent from the above discussion that the sulfonyl segment, far from being merely a modulator of the reactivity of the nitrogen atom (i.e., a protecting group), does indeed function as an integral component of the target molecular architecture. Such a notion was first explored during our synthesis of cylindricine C,[11] in which a key step was the base-promoted stereoselective Michael cyclization of dienones of type **17** (see below). The advent of an improved procedure for the oxidative cyclization of sulfonamides provided an opportunity to revisit this transformation and other aspects of the chemistry of spirocyclic products that we had explored only briefly in the past. These studies would lay the groundwork for future investigations toward alkaloids such as polycitorol A (**53**)[33] and lepadiformine (**55**)[12–15] (Scheme 9).



Scheme 9. Azaspirocyclic natural products of current interest.

Foremost on our agenda was the optimization of the Michael cyclization of substrates **17**, thus leading to compounds **58** (Scheme 10), which are key building blocks for the alka-



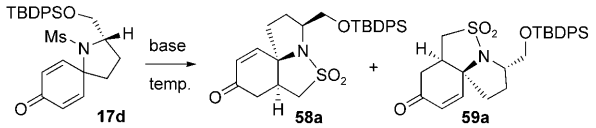
Scheme 10. Dienone desymmetrization through the Michael cyclization of methanesulfonamides.

loids in Scheme 9. This step establishes the configuration of the spiro center through a selective 1,4-addition of the anion of the sulfonamide to one of the diastereotopic double bonds of the enone, thereby desymmetrizing that "locally symmetrical" moiety. In its original form,[11] this operation was carried out by treatment of protected variants of **17a** (i.e., **17b**, **17d**, and **56**) with KHMDS at −100 °C. It will be recalled that **17d** is unavailable by direct cyclization of **16d** (Table 4). Indeed, **17d** and substrate **56** were prepared by protection of the OH group in **17a** with the appropriate silyl chloride. The diastereoselectivity observed in the cyclization step seemed to correlate with the steric demand of the *O*-

protecting group, thus attaining a maximal level with substrate **17d** (7:1 in favor of the desired **58a**). This outcome is consistent with a preferential reaction from conformer *anti*-**57** of the metalated sulfonamide, which experiences a lesser degree of steric compression relative to *syn*-**57**.

A more detailed study of the reaction was undertaken to improve the diastereoselectivity further. It soon transpired that the temperature and mode of addition are the primary determinants of stereocontrol (Table 8). Thus, highest selectivity was observed when the base was added to the substrate at −100 °C. On the other hand, no set of conditions improved the diastereomeric ratio beyond 7:1 in favor of **58a**.

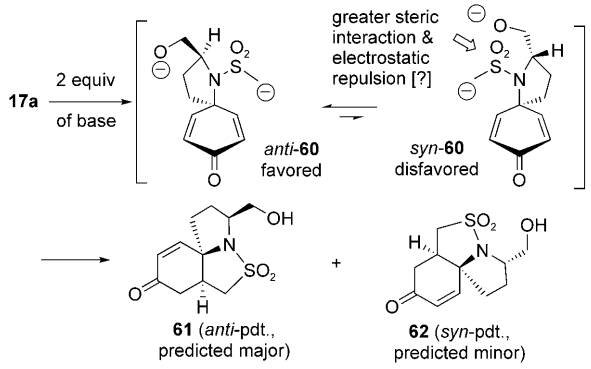
Table 8. Effect of bases and temperature on the Michael cyclization of **17d**.



Entry	Mode of addition[a]	*T* [°C]	Base	Yield [%][b]	**58a/59a**
1	A	−78	KHMDS	72	3:1
2	A	−100	KHMDS	81	7:1
3	A	−100	NaHMDS	77	7:1
4	A	−100	LiHMDS	80	7:1
5	A	−100	LiHMDS + CuCN	79	7:1
6	B	−100	LiHMDS	58	1.5:1

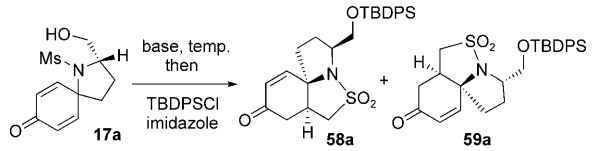
[a] A: Base was added to the substrate. B: Substrate was added to the base. [b] After chromatography. HMDS = bis(trimethylsilyl)amide.

A search for alternative factors that could influence product distribution led to the appealing surmise that electrostatic forces might amplify the steric repulsion between the sulfonyl and hydroxymethyl groups if the cyclization were carried out with the dianion of **17a** (Scheme 11). Experiments designed to probe this hypothesis revealed that it was convenient to *O*-protect the primary product of the Michael cyclization step, that is, the mixture of **61** and **62**, as the TBDPS derivative prior to purification. Yields and selectivities were easier to determine at the stage in which **58a** and **59a** resulted (a summary appears in Table 9). A higher level of stereocontrol was indeed achieved; however, contrary to



Scheme 11. Mechanistic hypothesis for the cyclization of the dianion of **17a**.

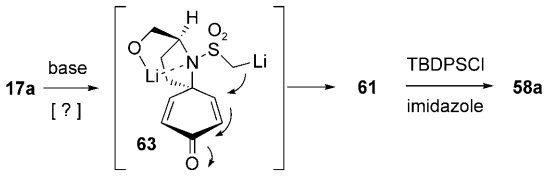
Table 9. Effect of bases and temperature on the Michael cyclization of **17a**.



Entry[a]	Base	*T* [°C]	Yield [%][b]	**58a/59a**
1	LiHMDS	−78	67	6:1
2	LiHMDS	−100	78	14:1
3	LiHMDS + CuCN	−100	78	14:1
4	NaHMDS	−100	77	8:1
5	KHMDS	−100	79	7:1

[a] Base was added to a solution of the substrate. [b] Overall yield of **58a** from **17a** over two steps and after chromatography.

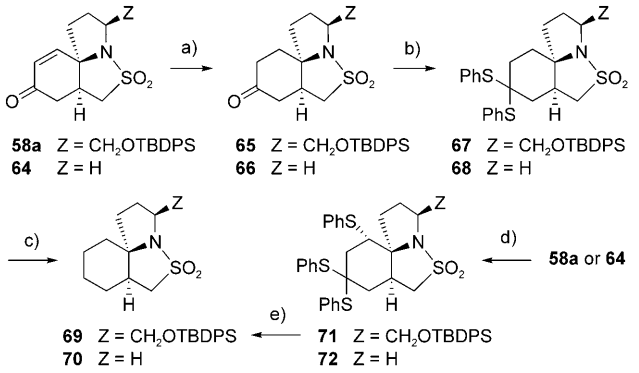
what would be predicted based on the model of Scheme 11, the selectivity increased with the Lewis acidity of the metal counterion. Thus, the best results (14:1 in favor of **58a**) were attained with LiHMDS, whereas Na and K bases afforded the same selectivity as with the *O*-TBDPS substrate. We rationalize this result by invoking cyclization through a rigid chelate of the initially formed lithium alkoxide with the sulfonamido nitrogen atom (refer to **63**; Scheme 12).



Scheme 12. Mechanistic hypothesis for the cyclization of the dilithio derivative of **17a**.

The justification for this hypothesis rests upon the observation that the NH group in a secondary sulfonamide displays reactivity similar to that of an alcohol.[5] It segues that the nitrogen atom of a tertiary sulfonamide is likely to be ether-like in character and consequently capable of ligating suitably Lewis acidic metal ions.

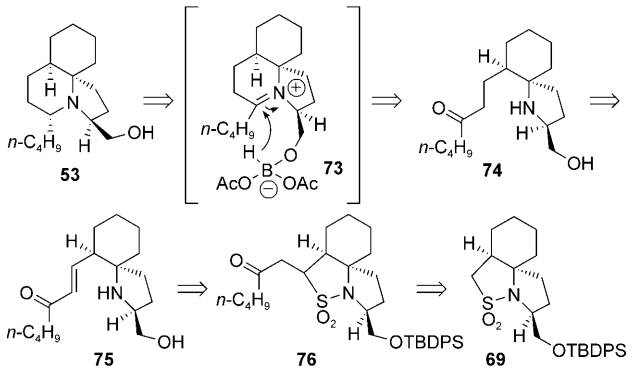
Reductive chemistry of ketones of the type 58a: A second aspect of this study pertained to the reductive chemistry of ketones of the type **58a** (Scheme 13). The synthesis of cylindricine alkaloids involves the reduction of **58a** to **69**. In the past, we had reached **69** from **71**, the triple thiophenol adduct of **56**, through desulfurization by using RaNi.[11] When this reaction was carried out on multigram scales, the desired **69** was accompanied by an unidentified byproduct that was difficult to separate. Fortunately, desulfurization of thioketals **67** and **68** with the $NiCl_2/NaBH_4$ system in a mix-



Scheme 13. Reductive chemistry of ketones **58a** and **64**. a) Pd(C), H_2 (1 atm), EtOH (**65**: 87, **66**: 85%); b) PhSH, BF_3OEt_2, CH_2Cl_2 (**67**: 84, **68**: 86%); c) $NiCl_2$, $NaBH_4$, MeOH/EtOH (**69**: 71, **70**: 70%); d) the same as (b) but with PhSH (20 equiv; **71**: 77, **72**: 75%); e) RaNi, EtOH (**71**→**69**: 77%).[11] TBDPS = *tert*-butyldiphenylsilyl.

ture of MeOH and EtOH[34] proceeded without byproduct formation. It should be noted that anhydrous $NiCl_2$ gave superior results in this step relative to hydrated $NiCl_2$. The thioketals were prepared in the customary fashion from ketones **65** and **66** obtained by hydrogenation over Pd(C) of **58a** and **64** (the latter was made in racemic form by the base-promoted cyclization of **5a**).

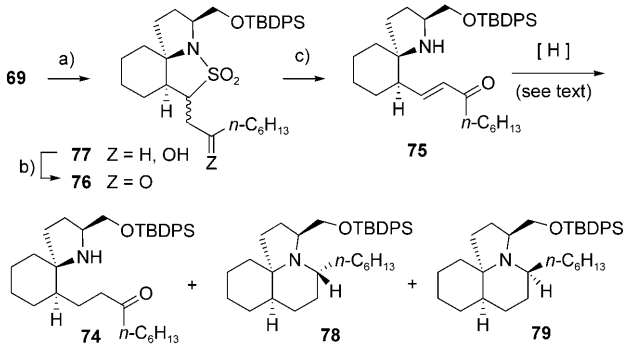
A final objective was to achieve the chemoselective reduction of *N*-unprotected enones of the type **75** to **74** (Scheme 14), without concomitant intramolecular reductive



Scheme 14. Strategy for polycitorol-type natural products.

amination. This goal was perceived as an important step toward to a possible total synthesis of polycitorol-type[32] natural products. Such an effort would rest on principles developed earlier during the synthesis of **52**,[11] a key step in which the directed reduction of an iminium species with $NaBH(OAc)_3$ (i.e., **73**) ensued upon cyclization of a ketone akin to **74**. In contrast, premature reductive cyclization of the nascent **74** during reduction of **75** would lead to tricyclic intermediates that displayed the incorrect configuration of the butyl side chain. By retracing the logic of the synthesis of **52**, we envisioned that **75** would derive from **69** by elaboration into **76** and desulfonylative fragmentation of the latter.

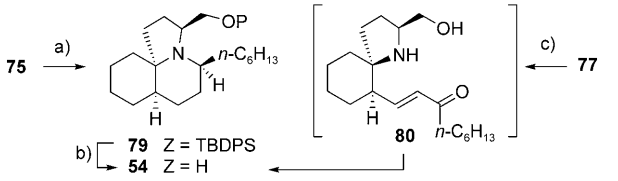
The sequence that led to **75** appears in Scheme 15. Alkylation of the anion of **69** with 1-octene oxide followed by Dess–Martin oxidation yielded **76**, which upon treatment



Scheme 15. Elaboration of **69** into **75** and reductive chemistry thereof. a) *t*BuLi, −78°C, 1-octene oxide, BF_3OEt_2; b) Dess–Martin periodinane (89% from **69**); c) DBU, DMF, 10 min (93%). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

with DBU in DMF provided **75** in 93% yield. Other amine bases (Et_3N, iPr_2NEt) were less satisfactory. The crucial reduction of **75** to **74** proved to be difficult. Thus, hydrogenation over Pd(C) or reaction with Et_3SiH in the presence of the Wilkinson catalyst, CuH (Stryker reagent)[35] with or without TMSCl, NaTeH,[36] and other agents[37] gave mixtures of desired **74** accompanied by the tricyclic product of intramolecular reductive amination. The latter consisted of an inseparable mixture of **78** and **79**. Substance **79** is recognized as the *O*-TBDPS derivative of putative lepadiformine **54**.

A more efficient transformation was the conversion of **75** into **79** by hydrogenation over the Adams catalyst (Scheme 16). Product **79** emerged as a single diastereomer within the limits of 300 MHz ^1H NMR spectroscopic analysis. Subsequent deprotection furnished **54**, namely, the originally proposed – but incorrect – structure of lepadiformine (Scheme 9). A more efficient conversion of **77** into **54** was achieved by TBAF-induced desilylation/SO_2 extrusion followed by hydrogenation of the transient **80** over the Adams catalyst. In this manner, **54** emerged in 31% yield from **17a** over eight steps.[38] The structure of **54** was confirmed by an X-ray crystallographic study of its HCl salt.[20]



Scheme 16. Synthesis of putative lepadiformine. a) H_2, PtO_2, EtOAc (80%); b) TBAF (96%); c) TBAF, THF, then H_2, PtO_2 (92%). TBAF = tetrabutylammonium fluoride.

Conclusion

This report has provided an overview of the *para*- and *ortho*-oxidative cyclization of phenolic sulfonamides and of aspects of the chemistry of the resulting products. The latter are essentially unavailable by any other means. Furthermore, they are demonstrably useful building blocks for the synthesis of nitrogenous compounds, including spirocyclic alkaloids and possibly also substances of interest in medicinal chemistry. Applications of the findings described herein are actively being pursued and additional results in this area shall be reported in due course.

Experimental Section

Representative procedure for the *para*-oxidative cyclization of phenolic sulfonamides (preparation of 17a): A solution of DIB (354 mg, 1.1 mmol) in TFA (1.7 mL) was added slowly at room temperature to a stirred solution of **16a** (212 mg, 1.0 mmol) in TFA (1.7 mL). The final formal substrate concentration was 0.3 M. Upon completion of the reaction (10 min, TLC), the mixture was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (1% MeOH in EtOAc) to afford the spirocyclic product **17a** as a light yellow foam (245 mg, 95%). Small crystals formed over time, thus enabling an X-ray crystallographic study to be conducted. $[\alpha]_D^{22} = -20.3°$ ($c = 1.1$ in acetone); ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C, TMS): $\delta =$ 7.26 (dd, $^3J_1$(H,H) = 9.8, $^3J_2$(H,H) = 3.0 Hz, 1H), 7.04 (dd, $^3J_1$(H,H) = 9.9, $^3J_2$(H,H) = 3.0 Hz, 1H), 6.16 (dd, $^3J_1$(H,H) = 9.9, $^3J_2$(H,H) = 2.3 Hz, 1H), 6.10 (dd, $^3J_1$(H,H) = 10.1, $^3J_2$(H,H) = 2.1 Hz, 1H), 4.15 (br, 1H), 4.12–4.04 (m, 1H), 3.82–3.72 (m, 2H), 3.00 (s, 3H), 2.61–2.33 (m, 2H), 2.24–2.13 (m, 1H), 1.99–1.89 ppm (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C, TMS): $\delta =$ 184.4, 152.7, 148.7, 127.7, 127.3, 64.2, 63.9, 63.1, 39.3, 37.7, 26.5 ppm; IR (film): $\tilde{\nu} =$ 3417 (OH), 2929, 1667 (C=O), 1328 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{15}NO_4SNa$: 280.0619 $[M+Na]^+$; found 280.0619.

Representative procedure for the oxidative cyclization of phenolic phosphoramides (preparation of 33): A solution of DIB (425 mg, 1.3 mmol) in TFA (2.1 mL) was added slowly at room temperature to a stirred solution of **30** (310 mg, 1.2 mmol) in TFA (2.1 mL). The final formal substrate concentration was 0.3 M. Upon completion of the reaction (10 min, TLC), the mixture was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (6% MeOH in EtOAc) to afford the spirocyclic product **33** as a light yellow oil (270 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 6.84 (d, $^3J =$ 10.1 Hz, 2H), 6.16 (d, $^3J =$ 10.1 Hz, 2H), 3.66 (s, 3H), 3.62 (s, 3H), 3.54–3.47 (m, 2H), 2.09–2.01 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 185.3, 151.5, 127.1, 61.99 (61.93), 53.43 (53.36), 48.94 (48.87), 40.39 (40.25), 25.14 (25.01) ppm; IR (film): $\tilde{\nu} =$ 1662 (C=O), 1251, 1016 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{11}H_{16}NO_4P$: 257.0817; found 257.0821.

Representative procedure for the *ortho*-oxidative cyclization of phenolic sulfonamides (preparation of 37): A solution of DIB (354 mg, 1.1 mmol) in TFA (1.7 mL) was added slowly at room temperature to a stirred solution of **36** (230 mg, 1.0 mmol) in TFA (1.7 mL). The final formal substrate concentration was 0.3 M. Upon completion of the reaction (10 min, TLC), the mixture was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 2:1) to afford the spirocyclic product **37** as a light-yellow oil (136 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 7.01 (ddd, $^3J_1 =$ 9.8, $^3J_2 =$ 5.8, $^4J =$ 0.7 Hz, 1H), 6.55 (dd, $^3J =$ 9.6, $^4J =$ 0.8 Hz, 1H), 6.16 (ddd, $^3J_1 =$ 9.6, $^3J_2 =$ 5.8, $^4J =$ 0.9 Hz, 1H), 6.05 (dd, $^3J_1 =$ 9.8, $^4J =$ 0.8 Hz, 1H), 3.78–3.57 (m, 2H), 2.96 (s, 3H), 2.27–1.97 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 201.6, 146.1, 142.0, 124.9, 119.8, 73.2, 49.4, 39.7, 39.5, 22.8 ppm; IR (film): $\tilde{\nu} =$ 1655 (C=O); 1318, 1147 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{10}H_{13}NO_3S$: 250.0514 $[M+Na]^+$; found 250.0512.

General procedure for the tandem *ortho*-cyclization/intramolecular Diels–Alder reaction of phenolic vinylsulfonamides (preparation of 42c): A solution of DIB (177 mg, 0.55 mmol) in TFA (0.5 mL) was added slowly at room temperature to a stirred solution of **40c** (128 mg, 0.5 mmol) in TFA (0.5 mL). The final formal substrate concentration was 0.3 M. Upon consumption of the starting material (15 min, TLC), the mixture was diluted with twice the volume of toluene (2 mL) and heated to reflux. Upon completion of the reaction (5 h, TLC), the mixture was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:2) to afford the spirocyclic product **42c** as a colorless foam (54 mg, 43% yield). Small crystals formed over time, thus enabling an X-ray crystallographic study to be conducted. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 6.09 (dt, $^3J_1 = {}^3J_2 =$ 6.9, $^4J =$ 1.6 Hz, 1H), 3.76–3.66 (m, 1H), 3.47–3.40 (m, 2H), 3.37–3.30 (m, 1H), 3.02–2.91 (m, 1H), 2.83 (dt, $^2J =$ 14.5, $^3J_1 = {}^3J_2 =$ 2.3 Hz, 1H), 2.31–2.18 (m, 1H), 2.17–2.05 (m, 1H), 2.05–1.92 (m, 2H), 1.94 (d, $^3J =$ 1.6 Hz, 3H), 1.63–1.54 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 202.4, 139.8, 125.8, 71.3, 56.6, 48.8, 45.7, 44.7, 29.6, 27.3, 27.1, 21.7 ppm; IR (film): $\tilde{\nu} =$ 1731 (C=O) cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{15}NO_3S$: 276.0670 $[M+Na]^+$; found 276.0664.

Acknowledgements

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