New Oxidative Transformations of Phenolic and Indolic Oxazolines: An Avenue to Useful Azaspirocyclic Building Blocks

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The oxidative cyclization of a phenolic amide to a spirolactam has long been regarded as an "impossible" reaction, because exposure of the substrates to a variety of oxidants results in formation of spirolactones with consequent loss of the amine segment. We recently communicated that this heretofore unknown transformation may be achieved by oxidation of oxazoline analogues of phenolic and indolic amides. Herein, we provide full details of our work.

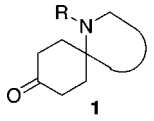
Introduction

A number of recently discovered natural products display novel architectures embodying variations on the theme of spiroheterocycle **1** (Scheme 1).[1] The assembly of this apparently simple structure, in a format consonant with the conditions imposed by the target molecules, may result in fairly elaborate routes if standard synthetic methodology is utilized.

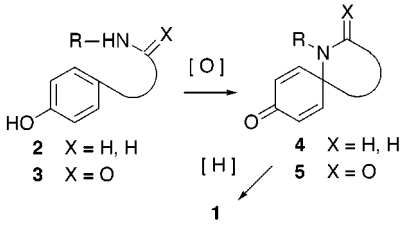
An especially direct avenue to subtarget **1** would materialize if a phenolic amine such as **2** could be induced to undergo oxidative cyclization to **4**, which could then be reduced to **1**. The oxidative cyclization of amide **3** to spirolactam **5** would also be serviceable as an entry to **5** (Scheme 2).

The desirability of the transformations of Scheme 2 was surely recognized as early as 1987, when Kita and collaborators disclosed a pioneering study of the oxidation of phenolic amides with iodobenzene diacetate ("DIB").[2] However, these workers observed that compounds **3** are converted to lactones **7** under oxidative conditions, and not to spirolactams **5**. Seemingly, it is the oxygen atom of the amide that intercepts the electrophilic intermediate arising through interaction of the phenol with DIB. The presumed primary product, iminolactone **6** (Scheme 3), is rapidly hydrolyzed during workup to yield **7**. The Kita results have been fully confirmed in the course of this study.

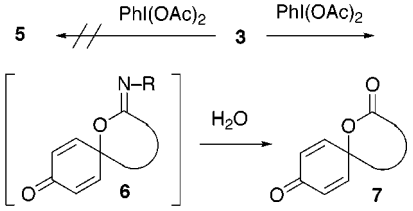
Scheme 1



Scheme 2



Scheme 3



The preferential formation of spirolactones over spirolactams in Kita-type oxidations is likely due to an electronic effect. Amide resonance causes accumulation of negative charge on the carbonyl oxygen, which becomes basic and nucleophilic, while the nitrogen atom is actually electron-deficient and thus unable to express nucleophilicity. Knapp encountered an analogous difficulty in his study of iodolactamization of olefins (cf. **8** → **9**, Scheme 4), but he was able to harness the effects responsible for the reactivity of the oxygen atom of an amide and cause them to operate in favor of the nitrogen atom, by engaging an imino analogue of the amide, such as an imidate, as the nucleophile in such reactions (cf.

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|| To whom correspondence regarding X-ray data should be addressed.

(1) E.g., FR901483: (a) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara M. *J. Antibiot.* **1996**, *49*, 37 (isolation). (b) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Am. Chem. Soc.* **1999**, *121*, 7778 (synthesis). TAN-1251: (c) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. World Patent WO 91/13887 (1991) to Takeda Chemical Industries, Ltd. (isolation). (d) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493 (synthesis). Cyclindricines: (e) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. H. *Tetrahedron* **1993**, *49*, 8645 (isolation). (f) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183 (synthesis).

(2) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 2, 3927.

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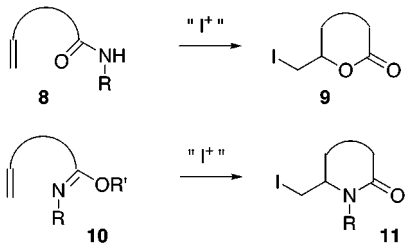
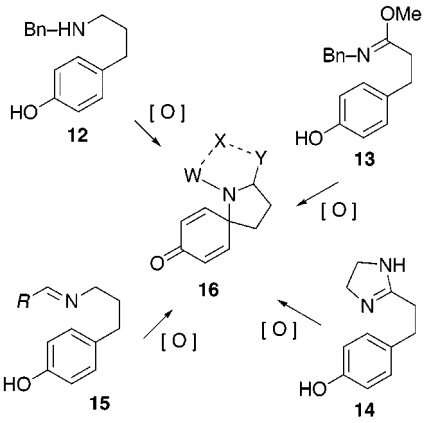
Published on Web 06/16/2000

Scheme 4



Scheme 5

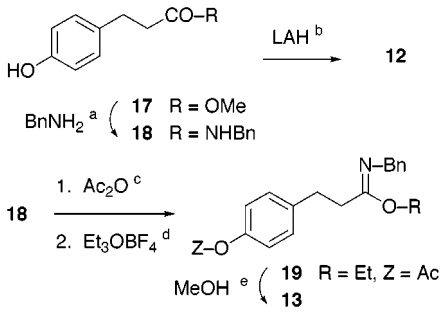


10 → **11**).[3] Application of similar logic ultimately allowed us to realize the transformation depicted in Scheme 2. In this paper, we provide a full account of studies directed toward the development of this chemistry.[4] The techniques developed in the course of this investigation also proved to be applicable to indolic (as opposed to phenolic) systems,[5] thereby permitting the creation of novel heterocyclic systems. The new transformations are likely to facilitate the synthesis of structures of the type **1** to a substantial extent.[6]

Background

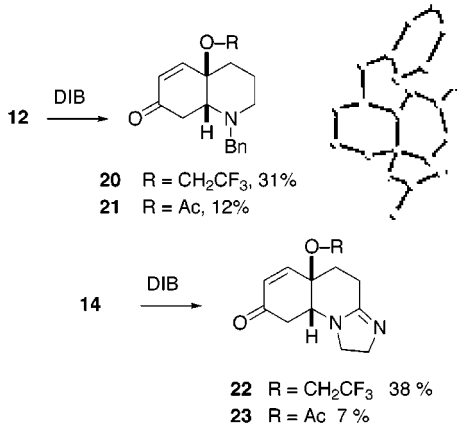
Plausible avenues to the desired subgoals were initially explored by studying the oxidative cyclization of amine **12**, imino ether **13**, and imidazoline **14**[7] to spirocycles of general structure **16** (Scheme 5). Phenolic imines **15** (R = aryl, alkyl) were also considered as interesting substrates for the new transformation; however, their preparation proved to be troublesome and they were not further investigated. By contrast, the synthesis of **12**–**13** was straightforward (Scheme 6). The only point of

Scheme 6[a]



[a] Reagents and conditions: (a) excess amine, no solvent, 150 °C, 95%; (b) THF, reflux, 94%; (c) pyridine, 96%; (d) CH_2Cl_2, rt, 78%; (e) K_2CO_3, MeOH, rt, 89%.

Scheme 7



interest here is that formation of **13** involved transetherification of intermediate imino ethyl ether **19** during deacetylative release of the phenol with K_2CO_3/MeOH.

Treatment of **12**–**14** with DIB in trifluoroethanol ("TFE") under Kita conditions[8] afforded none of the desired **16**. Compound **12** furnished a ca. 3:1 mixture of bicyclic amines **20** (major product, Scheme 7) and **21** (minor). The structure of **21**, a nicely crystalline material, was confirmed by X-ray crystallography.[9] By contrast, imidazoline **14** afforded a ca. 5:1 mixture of compounds **22** and **23**. These results are consistent with a mechanism in which trifluoroethanol or acetate ion/acetic acid released from DIB intercept an electrophilic intermediate produced through interaction of the phenol with the oxidant. This intermediate is naively represented in Scheme 8 as structure **24**. The presumed primary products thus obtained, dienones **25**–**26**, then undergo rapid Michael cyclization to **20**–**23**.

The reason nucleophilic capture of electrophile **24** by the nitrogen atom is not competitive with the pathways leading to presumed intermediates **25**–**26** remains unclear. Reactions involving DIB develop significant acidity: possibly, basic groups such as amine or amidine exist in protonated form during the reaction. This would suppress the nucleophilicity of the N atoms and it would not allow them to compete effectively with the solvent or acetate ion for **24**. Conduct of the reaction in the presence of basic agent or acid scavengers, a plausible

(3) (a) Knapp S. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 57. It is well recognized that imidates react preferentially at nitrogen with a variety of electrophiles; cf.: (b) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, UK, 1979; Vol. 2, Chapter 8, pp 385–590, see esp. pp 490 ff. (c) Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamnon Press: Oxford, UK, 1991; Vol. 6, Chapter 2.7, pp 485–599, see esp. pp 529 ff. and references cited in b–c.

(4) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667.

(5) Braun, N. A.; Bray, J.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985.

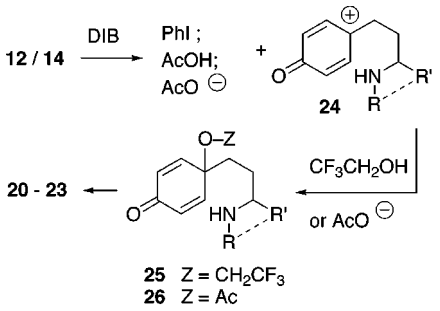
(6) Alternative methods for the preparation of related spiroheterocycles: (a) Bryce, M. R.; Gardiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res., Synop.* **1989**, 1. (b) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985. (c) Cossy, J.; Bouzide, A. *Tetrahedron* **1997**, *53*, 5775.

(7) McFarland, J. W.; Howes, H. L., Jr. *J. Med. Chem.* **1972**, *15*, 365.

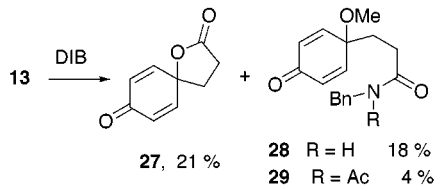
(8) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435.

(9) Peters, K.; Peters, E.-M.; Braun, N. A.; Ciufolini, M. A. *Z. Kristallogr. NCS* **1999**, *214*, 273.

Scheme 8



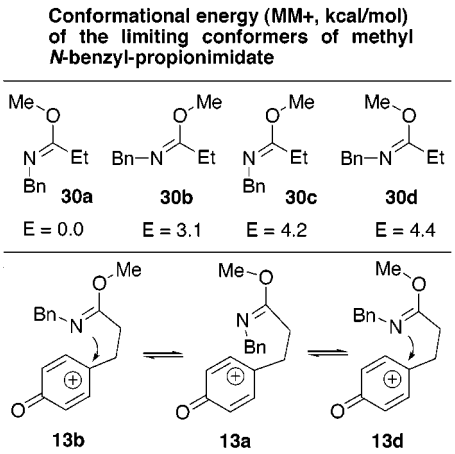
Scheme 9



remedy for the above difficulties, proved to be entirely inappropriate. Insoluble bases, such as $NaHCO_3$, had no effect on the reaction, probably because the rate at which they remove the acid present in solution it quite slow in a purely organic medium. Likewise, acid scavengers such as propylene oxide were ineffective. Soluble bases, such as triethylamine, promoted the formation of intractable mixtures. Numerous experiments, as well as evidence accumulated by other workers in the field, suggest that the acidity of the medium may be important for the success of DIB oxidations. Indeed, adjuvants such as TMSOTf have been utilized in other types of DIB-promoted processes.[10] It is noteworthy that in the above reactions a presumed electrophilic intermediate arising from the phenol is intercepted by TFE, an allegedly nonnucleophilic solvent. We have observed a number of similar events in the course of this study (vide infra). This is seemingly the first report describing the capture of reactive intermediates formed during oxidation of aromatic substrates with hypervalent iodine reagents by TFE. Use of hexafluoro-2-propanol, instead of TFE, as the solvent for the reactions of Scheme 7 delivered only acetate products to the complete exclusion of materials resulting from capture of electrophilic intermediates by the solvent. The use of hexafluoro-2-propanol for DIB reaction was first described by Kita.

The behavior of imino ether **13** differed significantly from that of **12**/**14**. Reaction with DIB afforded a nearly equimolar mixture of lactone **27** and amide **28**, accompanied by a small quantity of the noteworthy imide **29** (Scheme 9). No products of trifluoroethoxylation were apparent in this case. A superficial explanation for the formation of the observed products may invoke initial decomposition of the starting **13** through alcohol exchange with the solvent, so that methanol would be liberated in the reaction medium.[11] Methoxylated compounds **28**−**29** could then be accounted for by capture of intermediates of the type **24** by free MeOH, while lactone **27** would result through interception of **24** by the carbonyl oxygen of the amide, followed by hydrolysis during workup (cf. Scheme 3). However, the above scenario fails to account for formation of imide **29**. At this time, we believe that a conformational effect controls the genesis of **27**−**29**.

Scheme 10



Molecular mechanics calculations (MM+ force field)[12] indicate that the most stable conformer of iminoether **30**, a computationally better tractable mimic of **13**, is **30a** (Scheme 10). In this zero-energy conformation, the *N*-alkyl group is trans to the oxygen atom. Structure **30d** corresponds to the most energetic conformer of the iminoether, about 4.4 kcal/mol above **30a**, while **30b** is estimated to be about 3 kcal/mol more energetic than **30a**. Isomerization of **30a** to **30b**/**30d** may be problematic, because the rate of *E*−*Z* isomerization of imines, oximes, and related species in which the nitrogen atom is formally an sp^2 hybrid is notoriously slow.[13] Scheme 10 also shows that cyclization of **13** through N-capture of an electrophile of the type **24** is possible only from conformers **13b** or **13d**. The slow kinetics of iminoether isomerization, in combination with the significant energy demand of **13b**/**13d** relative to **13a**, may create such a small population of reactive conformers that the desired mode of cyclization of **13** is essentially suppressed. Under these conditions, reactive species **24** could be captured by the oxygen atom of the imidate to give oxonium ion **31**. This intermediate may react with acetate ion (path **a**, Scheme 11) to form iminolactone **32**, which would be rapidly hydrolyzed to **27** upon workup. Alternatively (path **b**), **31** could fragment to nitrilium ion **33**, which may be intercepted by the solvent or by acetate ion to yield **34** or **35**, respectively. Both the new iminoether **34** and iminoester **35** would be easily hydrolyzed to **28** upon workup; however, compound **35** could also undergo an N→O acetyl wanderung. This would account for formation of imide **29**, variable amounts of which could also suffer hydrolysis during workup to yield more **28**.

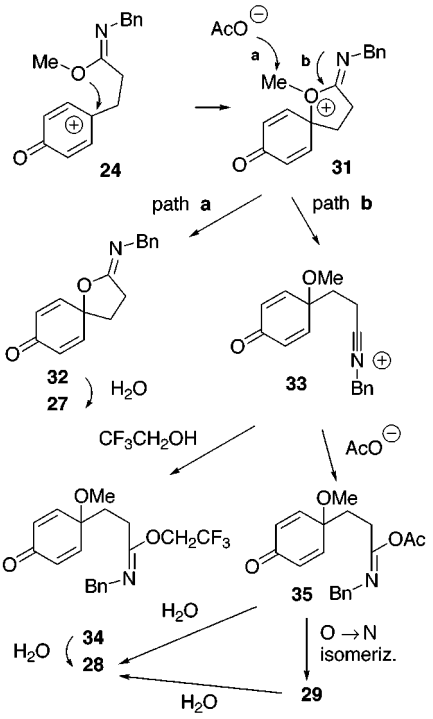
(10) Kita, Y.; Egi, M.; Okajima, A.; Ohtsubo, M.; Takada, T.; Tohma, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1491.

(11) It may also be surmised that adventitious moisture might have promoted hydolysis of the imino ether, resulting in liberation of MeOH. However, it is not likely that the reaction medium contained enough water to permit formation of **27**−**29** in the observed yields. In addition, products of *hydroxylation* of the substrate (cf. **25**/**26**, Z = H) would also have resulted if sufficient moisture were present in the system, as it happens indeed when similar phenols of the type are exposed to DIB in moist trifloroethanol.

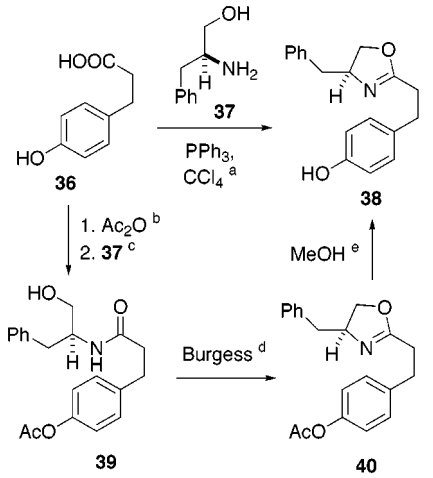
(12) All computational work described herein was carried out with the PC-based Hyperchem package, available from Hypercube, Inc., Ontario, Canada.

(13) Cf., e.g.: (a) Lambert, J. B.; Takeuchi, Y. *Cyclic Organonitrogen Stereodynamics*; VCH: New York, NY, 1992; pp 76 ff. (b) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, UK, 1979; Vol. 2 (Sutherland, I. O., Ed.), Chapter 8, pp 385−590. See especially pp 396−7 and references therein.

Scheme 11



Scheme 12[a]



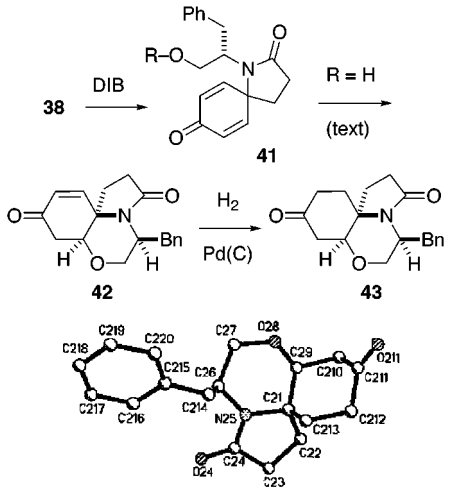
[a] Reagents and conditions: (a) MeCN/pyr, Et_3N, rt, 60−70%; (b) aq NaOH, 90−95%; (c) BOP-Cl, Et_3N, CH_2Cl_2, 0 °C to rt, 70−75%; (d) THF, 70 °C (tube), 65−75%; (e) K_2CO_3, rt, 1 h, 70−80%.

The above results suggested that a cyclic analogue of an imino ether, e.g., an oxazoline, may resolve the conformational difficulties presumed to be at the root of the behavior of **13**. This proved to be the case.

Oxidation of Phenolic Oxazolines

Oxazoline **38** (Scheme 12) was prepared in one step from commercial 3-(4-hydroxyphenyl)propionic acid and L-phenylalaninol, as detailed by Vorbrüggen.[14] A significant advantage of this method is that no protection of the phenol was necessary during the reaction. However, separation of the oxazolines from coproduced triphenylphosphine oxide is sometimes troublesome. The oxazoline may also be made by cyclization of a preformed *N*-hydroxyethyl amide **39** with the Burgess reagent,[15] as described by Wipf,[16a] but in this case the phenol must be blocked as the acetate ester; otherwise the yield of oxazoline drops to less than 10%. It appears that the free phenol reacts with the Burgess reagent to form water-soluble sulfate esters that are not readily cleaved back to desired **38**, that are easily lost upon workup, and from which retrieval of **38** is difficult. Compound **40** may be safely converted to **38** by treatment with methanolic K_2CO_3.

Scheme 13



Addition of **38** to a solution of DIB in trifluoroethanol at 25 °C (Kita conditions, Scheme 13) induced rapid conversion to spirolactam **41** in about 50% crude yield (NMR). The yield dropped when the reaction was run at higher (>25 °C) or lower (0 °C) temperatures, or when solid DIB was added to a solution of substrate. The balance of the starting oxazoline was converted to complex oligomeric materials. It must be noted that meticulous adherence to the workup technique prescribed by Kita is essential in order to obtain maximum yields of product. The reaction must thus be quenched with solid $NaHCO_3$, then filtered, and concentrated. A standard aqueous workup protocol results in much lower yields. As noted earlier, conduct of the reaction in the presence of (insoluble) $NaHCO_3$ or (soluble) propylene oxide had no effect on product yields, whereas complex, intractable mixtures resulted in the presence of triethylamine, and the yield of **41** dropped to less than 5% (NMR). It is noteworthy that oxidation of **38** with $PhI(OCOCF_3)_2$ ("PIFA") produced only small amounts of **41**, accompanied by much polymeric material. Once again, adjuvants such as $NaHCO_3$, propylene oxide, or triethylamine had no beneficial effect on yields or product distribution.

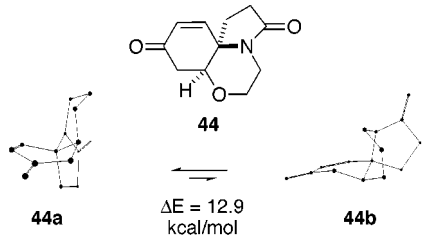
Spirolactam **41** thus obtained underwent spontaneous Michael cyclization to a single diastereomer of tricyclic compound **42** upon standing. The stereochemistry of this material was ultimately confirmed by X-ray diffractom-

(14) (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (b) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.

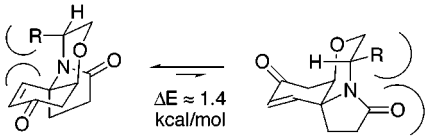
(15) (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 788.

(16) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576.

Scheme 14



Scheme 15

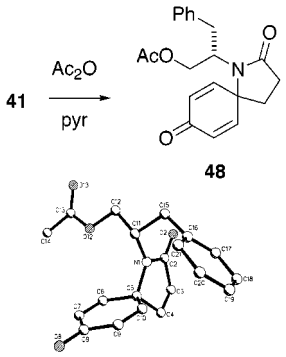


42 R = Bn
46 R = Me

45 R = Bn
47 R = Me

etry of the hydrogenated derivative of **42**, ketone **43**,[17] but it was anticipated to be as depicted in Scheme 13 on several grounds. First of all, a molecular mechanics study (MM+ force field)[12] of ring system **44** revealed an innate preference for conformer **44a** over **44b** (ΔE = 12.9 kcal/mol; Scheme 14, H atoms not shown for greater clarity). Although in **44b** the nitrogen atom is equatorial and the ethano branch of the γ-lactam is axial in the cyclohexenone unit, both morpholine and cyclohexenone rings may adopt a chair conformation. By contrast, placement of ethano segment at the equatorial position of the cyclohexenone and amide nitrogen at the axial position creates an extremely strained conformer **44b**, wherein the rigidity of the amide group forces the morpholine subunit into a boat form. Cyclization of **41** can produce diastereomeric compounds **42** (observed) and **45** (not observed, Scheme 15), which on the basis of the above calculations would be expected to exist largely, if not exclusively, as conformers of the type **44a**. The *N*-acylmorpholine subunit in these molecules is conformationally similar to an *N*-acylpiperidine. It is well-known that, in order to minimize severe nonbonding interactions with the amide carbonyl group,[18] substituents adjacent to the N atom of *N*-acylpiperidines strongly favor the axial position, even if a *syn*-pentane-like interaction with other axial substituents develops as consequence. The benzyl substituent occupies the axial position (favored in this case) in **42**, whereas it is forced to an equatorial position (unfavorable) in **45**. Compound **42** was thus anticipated to form as the major product. This conclusion was further supported by molecular mechanics calculations with **42** and with its methyl analogue **46**. In both cases, the best diastereomer ($\Delta E \approx$ 1.4 kcal/mol)[19a] is the one in which all substituents α to nitrogen, namely the methyl or benzyl group as well as the cyclohexenone ring branch, are axial in the morpholine ring; this despite the

Scheme 16



serious *syn*-pentane-like interaction between axial substituents.[16] Even a molecular mechanics simulation of the transition states for cyclization of **41** revealed a preference in favor of the structure shown ($\Delta E \approx$ 1.1 kcal/mol),[19a,b] which was thus predicted to be favored both on kinetic and on thermodynamic grounds.[20]

Contact with silica gel during chromatographic purification of **41** accelerated conversion to **42**. This propensity to cyclize was observed in all subsequent compounds of analogous structure, and while cyclization might be useful as a means to differentiate the diastereotopic π bonds of the dienone system, in our case this event was undesirable. Cyclization was readily suppressed by acetylation of **41** without prior purification. It should be noted that bases stronger than pyridine must be avoided during acetylation. Thus, exposure of **41** to triethylamine, used in conjunction with Ac_2O or AcCl, promoted rapid formation of **42**, while acetylation with Ac_2O/pyridine/DMAP proceeded without incident. The yield of **48** from **41** for the two step sequence, DIB oxidation/acetylation, was 47% after chromatography. The X-ray crystal structure of acetate **48** appears in Scheme 16.

The new reaction was explored with representative oxazolines **51**−**53** (Scheme 17), which were obtained either by the Vorbrüggen method from an appropriate carboxylic acid/1,2-amino alcohol pair (**51**, **53**), or by the Wipf procedure (**52**). Tyrosine-derived compounds **49**−**50** were stereochemically labile in the presence of acids. Even exposure to silica gel promoted erosion of optical integrity. This well-known propensity of oxazolines[16] ruled against extensive purification prior to oxidation. Oxidative cyclization of **51** and acetylation afforded **54** in 42% chromatographed yield. Thus, substitution on the oxazoline ring constitutes neither a requirement for, nor an obstacle in, oxidative cyclization. However, the substrate may not contain additional functionality capable of competing for an electrophilic species of the type **24** via a 5- or 6-centered transition state. For instance, oxazoline **52**, obtained from *N*-BOC-tyrosine, cyclized to afford **55** in only 22% yield. The low yield of this reaction is attributable, at least in part, to participation of the carbamate in the capture of electrophile **57** (Scheme 18). Workup of the resulting **58** and consequent hydrolytic cleavage of the oxazoline may then lead to a variety of byproducts. In sharp contrast, cyclization of tosylamide **53** proceeded in 41% yield, since the sulfonyl protecting group is insufficiently nucleophilic to interact with a positive species such as **57**.

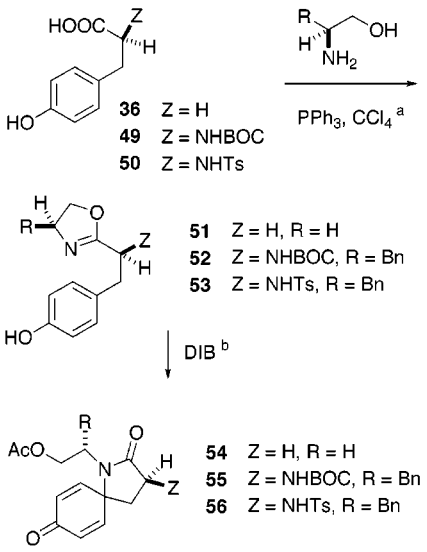
(17) Peters, K.; Peters, E.-M.; Braun, N. A.; Ciufolini, M. A. *Z. Kristallogr. NCS* **1999**, *214*, 555.

(18) Cf., e.g.: (a) Chow, Y. L.; Colón, C. J.; Tan, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821. (b) Lunazzi, L.; Cerioni, G.; Foresti, E.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 717. See also: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(19) (a) Calculated by molecular mechanics (MM+). This probably represent a lower limit for this value, since the MM+ force field tends to underestimate DE's for conformers of highly strained systems such as the ones discussed herein. (b) Approximate transition state structures were created by fixing the distance between the reacting atoms at 2.5 Å and by allowing the remainder of the molecular framework to relax in the MM+ force field.

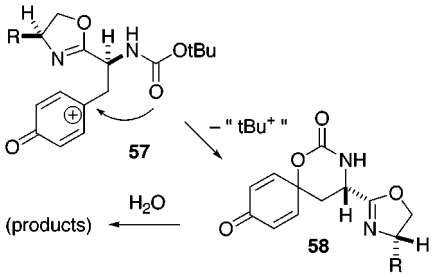
(20) Implicit in this surmise was the assumption that the reversibility of the conjugate addition of the OH group to the dienone would probably lead to a thermodynamic product.

Scheme 17[a]



[a] Reagents and conditions: (a) Et_3N, 1:1 pyridine−MeCN, rt, 69% for **51**, 44% for **53**; 36% for **52** over four steps through the Wipf procedure (see text); (b) TFE, rt, 42% for **54**, 22% for **55**, 41% for **56**.

Scheme 18

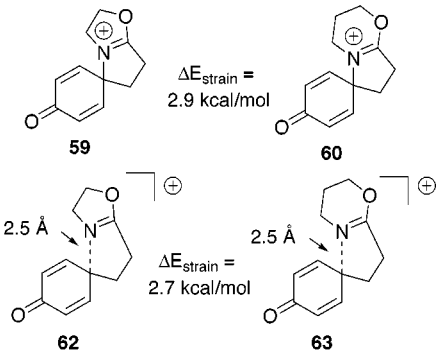


In an effort to improve the yields of these reactions, we briefly examined the effect of alternative solvents, of other oxidizing agents, and of structural variations in the substrates on overall efficiency. The substantial cost of TFE was a major incentive to explore other solvents to conduct the new transformation, but in complete accord with earlier observations by Kita, only hexafluoro-2-propanol (even more costly than TFE) emerged as an alternative. No reaction whatever occurred in CH_2Cl_2 or in polar, aprotic solvents such as acetonitrile, nitromethane, or DMF.

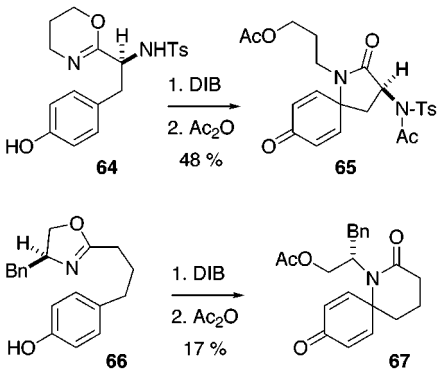
Experiments in which compound **53** was exposed to the Dess−Martin periodinane in MeCN returned largely unchanged[21] starting oxazoline, even after long contact time. A recent synthesis of discorhabdin C has shown that $CuCl_2$ induces oxidative phenolic coupling of sensitive intermediates more efficiently than DIB or PIFA.[22] However, reaction of **53** with $CuCl_2$ gave none of the desired spirocycle. It thus appears that oxidation of **38** to **41** is currently possible only with DIB.

A molecular mechanics study of presumed reaction intermediates in our oxidative processes indicated that oxazolinium species **59** (Scheme 19) contains 2.9 kcal/mol more strain energy than oxazinium ion **60**. A similar energy difference (ΔE = 2.7 kcal/mol) was estimated for

Scheme 19



Scheme 20



approximate transition-state structures **62** and **63**.[18,19] This suggested that, e.g., oxazine **64** may undergo oxidative cyclization more efficiently than oxazoline **51**. However, treatment of **64** as detailed earlier afforded **65** in only marginally better yield (48% instead of 42%, Scheme 20). One may thus conclude that the moderate efficiency of these processes is probably not attributable to difficulties hampering nucleophilic capture of the electrophilic intermediate. In addition, many DIB-promoted transformations of complex phenolic substrates reportedly proceed in about 50% yield,[8,16] signaling that innate limitations of DIB as an oxidant may be responsible for such moderate efficiencies.

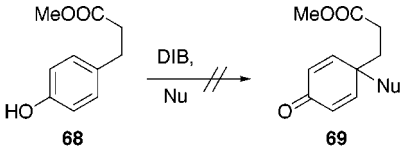
In all cases described so far, the newly formed spirolactam is a five-membered ring. The reactivity of substrate **66** was examined in order to establish whether six-membered spirocycles may also be obtained by the new reaction. Oxidative cyclization to **67** did occur upon exposure of **66** to DIB, but in a disappointing 17% chromatographed yield. Evidently, the kinetics of formation of the incipient six-membered ring is significantly slower than that of the five-membered ring, leaving the door open to myriads of side reactions. Finally, several experiments were conducted in an attempt to induce bimolecular capture of the electrophilic intermediate resulting from activation of the phenol with nucleophiles such as acetamidine, imidazole, sodium azide, lithium cyanide and phenylboronic acid (Scheme 21). These reactions were carried out with substrate **68** in the presence of excess external nucleophile under conditions otherwise identical to those detailed above. All such attempts resulted in complex mixtures containing none of the desired products **69**.

A useful transformation of the dienones obtained by the new reaction involves hydrogenation to cyclohexanone derivatives. Appearances notwithstanding, this

(21) Some degradation of the substrate became evident after 12 h of exposure to the Dess−Martin oxidant.

(22) Aubart, K. M.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 16.

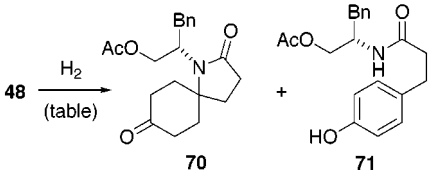
Scheme 21



68 **69**

Nu = acetamidine, imidazole, phenylboronic acid, sodium azide

Scheme 22



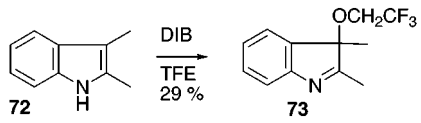
Catalyst	5 % Rh(C)	10 % Pd(C)	1 % Pt(C)
Reduction potential	0.600 V	0.951 V	1.118 V
Ratio **70** : **71**	0 : 100	60 : 40	100 : 0

operation is not trivial, due to the propensity of the substrates to undergo reductive aromatization under hydrogenolytic conditions. To illustrate (Scheme 22), hydrogenation (1 atm) of **48** at room temperature in ethyl acetate with 10% Pd(C) resulted in a product mixture composed of 60% of desired **70** and 40% of **71**. Reductive aromatization was the sole observed event when 5% Rh(C) was employed as the catalyst. By contrast, clean conversion of **48** to **70** occurred with 1% Pt(C) or PtO_2 (Adams catalyst). It seems likely that the sequence of events leading to aromatization involves either initial oxidative addition of zerovalent metal to the dienone C−N s bond or electron transfer from the zerovalent metal to the dienone, followed by hydrogenolysis of the intermediate organometallic complex. The ease of oxidative addition or electron transfer would be expected to be a function of the oxidation potential of the metal. Indeed, the extent of aromatization seems to correlate with the reduction potential of Rh (0.600 V), Pd (0.951 V), and Pt (1.118 V).[23] We also note that use of Pt(C) as a catalyst may promote variable degrees of reduction of the ketone to an alcohol. This process is slower than dienone hydrogenation and it is generally easy to control by monitoring of the course of the reduction (TLC) and avoiding prolonged reaction times. In any event, overreduction is all but suppressed by the use of PtO_2 as the catalysts.

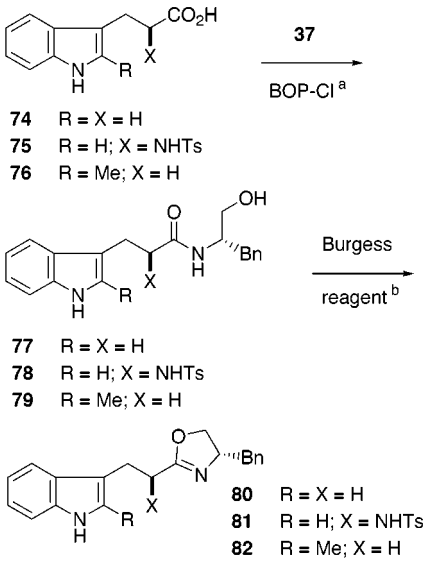
Oxidation of Indolic Oxazolines

It is well established that DIB and other hypervalent iodine reagents readily attack the indole nucleus.[24] Indeed, we found that exposure of **72** to DIB in TFE under Kita conditions affords **73** (Scheme 23), albeit in low yield. Once again, allegedly nonnucleophilic CF_3CH_2-OH had acted as a nucleophilic trap toward the electrophilically activated indole. This observation suggested that indolic oxazolines may undergo oxidative cyclization in the same manner as their phenolic counterparts.

Scheme 23



Scheme 24[a]



[a] Reagents and conditions: (a) CH_2Cl_2, Et_3N (95% for **77**, 51% for **78**, 88% for **79**); (b) THF, 70 °C, sealed tube (64% for **80**, 53% for **81**, 65% for **82**).

The Vorbrüggen protocol gave unsatisfactory results in the indole series, but the Wipf method afforded the desired oxazolines in fair yield. Accordingly, indolic acids **74**−**76** were coupled with (*S*)-phenylalaninol under the influence of BOP-Cl, and the resulting hydroxyethyl amides were cyclized to oxazolines with the Burgess reagent (Scheme 24).

The behavior of indolic substrates toward DIB proved to be quite sensitive to the nature of substituents present on the ring. To illustrate, oxidation of **80** with 1 equiv of DIB under Kita conditions indeed afforded a 1:1 mixture of diastereomers **84** and **85** of the expected product in 48% cumulative yield after chromatography. Compounds **84**−**85** probably resulted from initially formed spiro intermediates **83**, which subsequently underwent rapid intramolecular nucleophilic addition of the alcohol to the imino function (Scheme 25).[25] Heterocycle **84** was chromatographically faster moving than **85**, so that the two could be readily separated by preparative TLC (100% Et_2O). In a like manner, reaction of tryptophane-derived **81** furnished a 1:1 mixture of **86** (faster, 5:1 Et_2O−hexane) and **87** (slower) in 40% cumulative chromatographed yield. The stereochemistry of all products rests on NOE interactions (2D NOESY) observed as shown for example in Scheme 26 with **84** and **85**.

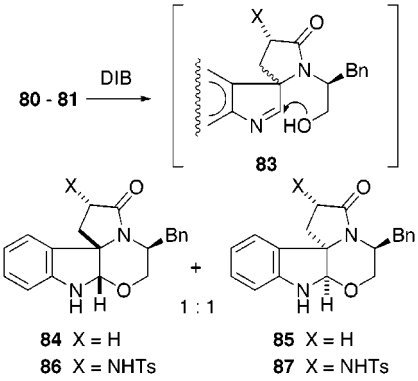
In contrast to the above substrates, reaction of 2-methyl indole derivative **82** with one molar equivalent of DIB under the same conditions produced quinonimine bis-(trifluoroethyl)monoketals **89** (faster, 100% Et_2O) and **90**

(23) Vanysek P. Electrochemical Series. In *Handbook of Chemistry and Physics*, 1st student version; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987; pp D91−D98.

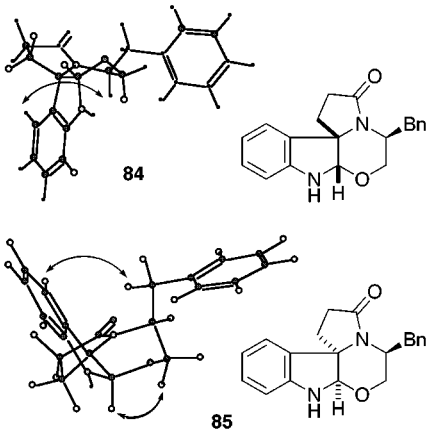
(24) E.g.: Awang, D. V. C, Vincent, A. *Can. J. Chem.* **1980**, *58*, 1589. Moriarty, R. M.; Sultana, M. *J. Am. Chem. Soc.* **1985**, *107*, 4559.

(25) Example of an analogous process: Pihko, P. M.; Koskinen, Ari M. P.; Nissinen, M. J.; Rissanen, K. *J. Org. Chem.* **1999**, *64*, 652.

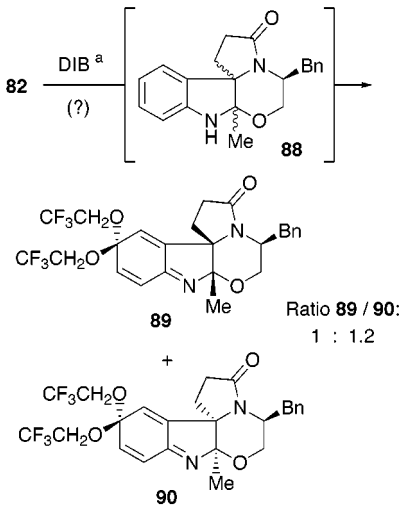
Scheme 25



Scheme 26

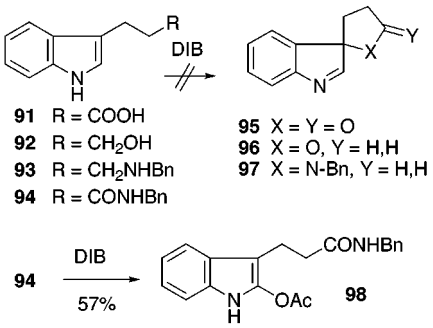


Scheme 27



(slower) in a 1:1.2 ratio and in a modest 23% chromatographed yield (Scheme 27).[26] The balance of starting **82** advanced to intractable polymeric materials. We presume that an initial reaction of **82** with DIB must have given rise to intermediate **88**, a formal aniline derivative that may have undergone further oxidation to a quinonimine monoketal. Regardless of the precise sequence of events involved in the genesis of **89**−**90**, it is interesting that long cherished beliefs regarding the nonnucleophilicity of TFE were once again clashing against experimental reality.

Scheme 28



It is also worthy of note that conversion of **82** to **89**−**90** corresponds to a six-electron oxidation, whereas only 1 equiv of DIB (a two-electron oxidant) had been used in this experiment. However, exposure of **82** to *3* equiv of DIB in an effort to improve yields had only a marginal effect on the outcome of the reaction: the yield of products increased to only about 30%. Similarly, control experiments in which only 0.8 equiv of DIB were used relative to **82** again produced **89**−**90** as the sole identifiable products and in about 20−25% yield. These results suggest that oxidation of the presumed primary products **88** to quinonimine monoketals probably occurs much faster than oxidative cyclization of the starting oxazoline **82**.

Additional variability was observed in the reaction of acid **91**, alcohol **92**, amine **93**, and amide **94** with DIB. Parallel with the behavior of phenolic analogues of these compounds led us to infer that heterocycles **95**−**97** should emerge from these reactions (Scheme 28). However, compounds **91**−**93** produced complex mixtures of oligomeric materials upon reaction with DIB, whereas amide **94** underwent clean acetoxylation at C-2 of the indole to give derivative **26** in 57% chromatographed yield (Scheme 28). No identifiable products arising through addition of TFE to the substrates were observed in these reactions. It is apparent that the variable reactivity of indolic substrates must be attributed to subtle electronic differences that defy a simplistic explanation.

In summary, a heretofore "impossible" reaction, the oxidative cyclization of phenolic ω-arylalkanoic carboxamides to spirolactams, may be achieved by the use of DIB via oxazoline intermediates. An "indolic" variant the new spirolactam synthesis is also possible, with the proviso that indolic substrates tend to show variable reactivity toward DIB. These new transformations embody a further aspect of the rapidly growing field of organic hypervalent iodine chemistry[27] and should be quite useful in the synthesis of a range of nitrogenous substances, including heterocyclic natural products and intermediates for medicinal chemistry research.

(26) For related quinonimine syntheses see ref 10 as well as: (a) Barret, R.; Daudon, M. *Tetrahedron Lett*. **1991**, *32*, 2133−2134. (b) Kita, Y.; Egi, M.; Okajima, A.; Ohtsubo, M.; Takada, T.; Tohma, H. *Chem. Commun*. **1996**, 1491−1492. (c) Related spirocycles formally derived from indoles: Rodriguez, J. G.; Urrutia, A.; de Diego, J. E.; Martinez-Alcazar, M. P.; Fonseca, I. *J. Org. Chem*. **1998**, *63*, 4332−4337.

(27) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem.. Int. Ed. Engl.* **2000**, *39*, 622, 625. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*, 1st ed.; Academic Press: San Diego, CA, 1996. (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179−1255. (d) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (d) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891, and references therein

Experimental Section

Experimental Protocols. Unless otherwise noted, NMR spectra (δ, ppm) were recorded in $CDCl_3$. Coupling constants *J* are in Hz. Multiplicities are reported as follows: "s" (singlet), "d", "dd" (doublet, doublet of doublets), "t" (triplet), "q" (quartet), "m" (multiplet), "c" (complex), "br" broad. IR spectra (cm^{-1}) were obtained from films deposited on NaCl plates. Low- and high-resolution mass spectra (*m/e*) were obtained in the EI (70 eV) mode or, alternatively, in CI (CH_4), or FAB (Cs^+) mode if so 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. The following compounds were prepared as described in the literature: *N*-(*tert*-butoxycarbonyl)-L-tyrosine;[28] *N*-tosyl-L-tyrosine;[29] 4-(4-hydroxy-phenyl)butyric acid;[30] 3-(4-acetoxyphenyl)propionic acid and 4-(4-acetoxyphenyl)butyric acid;[31] methyl 3-(4-hydroxyphenyl)propionate;[32] Na-tosyl-L-tryptophan;[33] 3-(2-methyl-indol-3-yl)propionic acid;[34] L-phenylalaninol;[35] Burgess reagent.[15b] All other reagents and solvents were commercial products used as received except: THF (freshly distilled Na/benzophenone), CH_2Cl_2, Et_3N (distilled CaH_2). The following abbreviations are used: BOP-Cl, *P*,*P*-bis(2-oxo-3-oxazolidinyl)-phosphinic chloride; DMAP, 4-(dimethylamino)pyridine; TFE, 2,2,2-trifluoroethanol.

Oxazolines by the Wipf Method. A degassed (argon) solution of a hydroxyethyl amide (2.0 mmol) of a *p*-acetoxyarylpropionic or *p*-acetoxyarylbutyric acid and Burgess reagent (0.6 g, 2.4 mmol) in THF (10 mL) was heated at 70 °C (oil bath temperature) in a pressure Pyrex tube for 2 h, and then it was allowed to cool to rt. Addition of Et_2O caused precipitation of triethylammonium salts. The suspension was filtered over silica gel (Et_2O), and the filtrate was evaporated. If necessary, the residue was purified by column chromatography.

(*S*)-2-[2-(4-Acetoxyphenyl)ethyl]-4-benzyl-2-oxazoline (40): 74% yield from *N*-[(*S*)-1-benzyl-2-hydroxyethyl]-3-(4-acetoxyphenyl)propionamide; colorless oil; $[\alpha]^{20}_D = -9.9°$ (*c* = 2.18); ^{1}H 2.28 (s, 3H), 2.53−2.66 (m, 3H), 2.91−2.99 (m, 2H), 3.07 (dd, 1H, *J* = 5.2, 13.6), 3.94 (dd, 1H, *J* = 7.2, 8.4), 4.16 (dd, 1H, $J_1 = J_2 = 8.4$), 4.35 (m, 1H), 7.01 (d, 2H, *J* = 8.5), 7.17−7.32 (m, 5H), 7.22 (d, 2H, *J* = 8.5); ^{13}C 20.2, 28.9, 30.7, 41.0, 66.4, 70.8, 120.8, 125.7, 127.7, 128.5, 128.6, 137.2, 137.5, 148.4, 166.2, 168.6; IR 1765, 1665; MS 323 $[M]^+$; HRMS calcd for $C_{20}H_{21}NO_3$ 323.1521, found 323.1520.

(*S*)-2-[(*S*)-2-(4-Acetoxyphenyl)-1-[*N*-(*tert*-butoxycarbonyl)amino]ethyl]-4-benzyl-2-oxazoline: 67% yield from (*S*)-*N*-[(*S*)-1-benzyl-2-hydroxyethyl]-3-(4-acetoxyphenyl)-2-[*N*-(*tert*-butoxycarbonyl)amino]propionamide; colorless oil; $[\alpha]^{20}_D = -28.0°$ (*c* = 0.25); ^{1}H 1.43 (s, 9H), 2.27 (s, 3H), 2.59 (dd, 1H, *J* = 8.1, 13.7), 2.89−3.11 (m, 3H), 4.01 (dd, 1H, *J* = 6.9, 8.2), 4.19 (dd, 1H, $J_1 = J_2 = 8.2$), 4.29 (m, 1H), 4.63 (m, 1H), 5.10 (d, 1H, *J* = 7.9, NH), 6.99 (d, 2H, *J* = 8.5), 7.14 (d, 2H, *J* = 8.5), 7.14−7.32 (m, 5H); ^{13}C 21.5, 28.7, 38.5, 41.9, 50.1, 67.4, 72.8, 80.2, 121.8, 127.0, 128.9, 129.6, 130.9, 134.3, 138.0, 150.0, 166.7, 169.9; IR 3420, 1770, 1715, 1670; MS 439 $[M + H]^+$, 438 $[M]^+$; HRMS calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2154.

(*S*)-2-[(*R*)-2-(4-Acetoxyphenyl)-1-[*N*-(*tert*-butoxycarbonyl)amino]ethyl]-4-benzyl-2-oxazoline. This material, $[\alpha]^{20}_D = -21.1°$ (*c* = 0.29), was separated from the major diastereomer above by preparative TLC (1:1 Et_2O/hexane): ^{1}H 1.42 (s, 9H), 2.28 (s, 3H), 2.46 (dd, 1H, *J* = 8.8, 13.2), 2.90−3.15 (m, 3H), 3.97 (dd, 1H, *J* = 7.4, 8.8), 4.23 (dd, 1H, $J_1 = J_2 = 8.8$), 4.32 (m, 1H), 4.63 (m, 1H), 5.21 (d, 1H, *J* = 7.4, NH), 7.02 (d, 2H, *J* = 8.8), 7.04−7.31 (m, 5H), 7.16 (d, 2H, *J* = 8.8); ^{13}C 21.6 (q), 28.7 (q), 38.5 (t), 42.1 (t), 50.0 (d), 67.4 (d), 73.0 (t), 80.2 (s), 121.7, 127.0, 128.9, 129.6 and 131.0 (all d), 134.3, 138.0 and 150.0 (all s), 166.7 (s), 169.83 (s).

(*S*)-2-[3-(4-Acetoxyphenyl)propyl]-4-benzyl-2-oxazoline: 68% yield from *N*-[(*S*)-1-benzyl-2-hydroxyethyl]-4-(4-acetoxyphenyl)butyramide; pale yellow oil; $[\alpha]^{20}_D = -11.5°$ (*c* = 1.02); ^{1}H 1.91−2.00 (m, 2H), 2.26−2.31 (m, 2H), 2.28 (s, 3H), 2.60−2.71 (m, 3H), 3.08 (dd, 1H, *J* = 5.1, 13.8), 3.92 (dd, 1H, *J* = 7.3, 8.4), 4.13 (dd, 1H, $J_1 = J_2 = 8.4$), 4.36 (m, 1H), 6.99 (d, 2H, *J* = 8.6), 7.18 (d, 2H, *J* = 8.6), 7.18−7.32 (m, 5H); ^{13}C 20.9, 27.2, 27.3, 34.3, 41.5, 66.9, 71.2, 121.2, 126.2, 128.3, 129.1, 129.2, 137.7, 138.9, 148.7, 167.5, 169.4; IR 1765, 1670; MS 337 $[M]^+$; HRMS calcd for $C_{21}H_{23}NO_3$ 337.1678, found 337.1684.

Deacetylation of the Protected Oxazolines. A mixture of acetylated oxazoline (2.0 mmol), K_2CO_3 (42 mg, 0.3 mmol), and MeOH (3 mL) was stirred at rt for 1 h and then it was filtered over silica gel (1 g; MeOH) and evaporated. If necessary, the residue was purified by column chromatography or recrystallization.

(*S*)-4-Benzyl-2-[2-(4-hydroxyphenyl)ethyl]-2-oxazoline (38): 73% yield from (*S*)-2-[2-(4-acetoxyphenyl)ethyl]-4-benzyl-2-oxazoline; colorless crystals; mp 141−143 °C (recrd MeOH/Et_2O); $[\alpha]^{20}_D = -26.8°$ (*c* = 1.16, MeOH); ^{1}H (DMSO-d_6) 2.36−2.41 (m, 2H), 2.59 (dd, 1H, *J* = 7.1, 13.6), 2.67−2.72 (m, 2H), 2.80 (dd, 1H, *J* = 6.1, 13.6), 3.83 (dd, 1H, *J* = 7.3, 8.1), 4.14 (dd, 1H, *J* = 8.1, 9.4), 4.25 (m, 1H), 6.64 (d, 2H, *J* = 8.5), 6.98 (d, 2H, *J* = 8.5), 7.18−7.29 (m, 5H); ^{13}C (DMSO-d_6) 29.7, 30.8, 41.4, 66.8, 71.1, 115.3, 126.3, 128.3, 129.3, 129.4, 130.6, 138.5, 156.1, 165.9; IR (KBr) 3420, 1665; MS 281 $[M]^+$; HRMS calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1416.

(*S*)-4-Benzyl-2-[(*S*)-1-[*N*-(*tert*. butoxycarbonyl)amino]-2-(4-hydroxyphenyl)ethyl]-2-oxazoline (52): 81% yield from (*S*)-2-[(*S*)-2-(4-acetoxyphenyl)-1-[*N*-(*tert*. butoxycarbonyl)-amino]ethyl]-4-benzyl-2-oxazoline; colorless, viscous oil. This material was used without purification because of facile epimerization: ^{1}H 1.43 (s), 2.60 (dd, 1H, *J* = 8.4, 13.6), 2.97−3.07 (m, 3H), 4.05 (dd, 1H, *J* = 7.0, 8.0), 4.23 (dd, 1H, $J_1 = J_2 = 8.0$), 4.33 (m, 1H), 4.61 (m, 1H), 5.14 (d, 1H, *J* = 8.0, NH), 6.64 (d, 2H, *J* = 8.3), 6.95 (d, 2H, *J* = 8.3), 7.14−7.32 (m, 5H); IR 3300, 1720, 1670; MS 396 $[M]^+$; HRMS calcd for $C_{23}H_{28}N_2O_4$ 396.2049, found 396.2044.

(*S*)-4-Benzyl-2-[3-(4-hydroxyphenyl)propyl]-2-oxazoline (66): 81% yield from (*S*)-2-[3-(4-acetoxyphenyl)propyl]-4-benzyl-2-oxazoline; yellow, viscous oil; $[\alpha]^{20}_D = -4.9°$ (*c* = 2.08); ^{1}H 1.88−1.98 (m, 2H), 2.26−2.32 (m, 2H), 2.57 (t, 2H, *J* = 7.4), 2.66 (dd, 1H, *J* = 8.4, 13.7), 3.13 (dd, 1H, *J* = 4.8, 13.7), 3.98 (dd, 1H, *J* = 7.3, 8.7), 4.17 (dd, 1H, $J_1 = J_2 = 8.7$), 4.41 (m, 1H), 6.71 (d, 2H, *J* = 8.3), 6.97 (d, 2H, *J* = 8.3), 7.17−7.31 (m, 5H); ^{13}C 27.2, 27.5, 34.2, 41.4, 66.3, 71.6, 115.3, 126.5, 128.5, 129.2, 129.4, 132.2, 137.3, 154.8, 169.4; IR 3320, 1655; MS 295 $[M]^+$; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572.

Oxazolines by the Vorbrüggen Procedure. A solution of Ph_3P (2.4 g, 9.0 mmol) in 1:1 MeCN/pyridine (5 mL; warming is necessary to dissolve the PPh_3) was added dropwise over 2 h to a solution of phenolic acid (3.0 mmol), amino alcohol (3.0 mmol), Et_3N (0.9 g, 9.0 mmol), and CCl_4 (1.8 g, 12.0 mmol) in 1:1 MeCN/pyridine (5 mL). The mixture was stirred at rt for 14 h, then it was evaporated and the residue was processed as follows. **Workup Procedure for 4-Unsubstituted Oxazolines and *N*-Tosyl Compounds.** The residue was partitioned between CH_2Cl_2 and 0.5 M aqueous NaOH. The organic phase was discarded, and the water layer was extracted with more CH_2Cl_2. The extracts were again discarded. The aqueous phase was layered with EtOAc and acidified (cooling, stirring) to pH 6 with solid NH_4Cl (6 g). Addition of some 0.2 M aqueous AcOH may be necessary to reach pH 6 (for C-2′ unsubstituted compounds, it is possible to acidify with 3 M HCl instead of NH_4Cl/AcOH). The layers were separated, and the aqueous was extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated. The product was purified by filtration over silica gel. **Workup Procedure for Other Oxazolines.** The residue was dissolved in Et_2O and basified to pH 8−9 with concentrated aqueous NH_4OH solution. The organic layer was separated, and the water phase was

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extracted with Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated. It may be necessary to redissolve the crude product in Et_2O and filter off the precipitated $Ph_3P{=}O$ prior to further purification.

2-[2-(4-Hydroxyphenyl)ethyl]-2-oxazoline (51): 68% yield from 3-(4-hydroxyphenyl)propionic acid and ethanolamine after purification by preparative TLC (100% EtOAc); $R_f = 0.26$; colorless crystals; mp 123−125 °C dec; ^{1}H (DMSO-d_6) 1.68 (s, OH), 2.39−2.44 (m, 2H), 2.70−2.75 (m, 2H), 3.64−3.70 (m, 2H), 4.12−4.18 (m, 2H), 6.66 (d, 2H, $J = 8.5$), 6.99 (d, 2H, $J = 8.5$); ^{13}C (DMSO-d_6) 29.7, 30.8, 54.0, 66.8, 115.3, 129.2, 130.8, 156.0, 166.4; IR (KBr) 3420, 1660; MS 191 $[M]^+$; HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0946.

(*S*)-4-Benzyl-2-[(*S*)-1-[*N*-(4-methylphenyl)sulfonylamino]-2-(4-hydroxyphenyl)ethyl]-2-oxazoline (53): 44% yield from *N*-tosyl-L-tyrosine and (*S*)-2-amino-3-phenyl-1-propanol after filtration through a short plug of silica (100% Et_2O), not extensively purified because of facile epimerization; pale yellow foam; $[\alpha]^{20}_D = -30.7°$ ($c = 0.87$); ^{1}H 2.16 (dd, 1H, $J = 8.5, 13.6$), 2.39 (s, 3H), 2.72 (dd, 1H, $J = 5.5, 13.6$), 2.93 (d, 2H, $J = 5.5$), 3.86 (dd, 1H, $J = 6.7, 7.8$), 4.04 (dd, 1H, $J_1 = J_2 = 7.8$), 4.07 (m, 1H), 4.33 (m, 1H), 5.78 (d, 1H, $J = 9.2$, NH), 6.52 (d, 1H, $J = 8.5$), 6.87 (d, 1H, $J = 8.5$), 7.03 (d, 2H, $J = 8.5$ Hz), 7.19−7.27 (m, 5H) 7.72 (d, 2H, $J = 8.5$); ^{13}C 21.5, 38.9, 41.1, 52.3, 66.2, 72.6, 115.4, 126.7, 127.3, 128.6, 128.9, 129.5, 130.5, 137.0, 137.2, 143.4, 155.4, 166.9; IR 3280, 1665; MS (CI) 451 $[M + H]^+$; HRMS calcd for $C_{25}H_{26}N_2O_4S$ 450.1613, found 450.1618

Oxidative Cyclization of Phenolic Oxazolines. A solution of DIB (0.4 g, 1.2 mmol) in TFE (5 mL) was added dropwise over 5 min to a solution of the oxazoline (1.0 mmol) in TFE (5 mL). The mixture was stirred for 30 min at room temperature (argon), and then it was treated with solid $NaHCO_3$ (0.3 g). 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 mmol)] at rt for 12 h with good stirring. Finally, the mixture was evaporated and the residue was purified by chromatography and/or recrystallization.

1-[(*S*)-2′-Acetoxy-1′-benzylethyl]-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (48): 47% yield from (*S*)-4-benzyl-2-[2-(4-hydroxyphenyl)ethyl]-2-oxazoline; chromatography 1:1 EtOAc/Et_2O, $R_f = 0.46$; colorless needles; mp 163−65 °C (recrd EtOAc/Et_2O); $[\alpha]^{20}_D = +31.4°$ ($c = 0.44$); ^{1}H 1.85−2.07 (m, 2H), 2.05 (s, 3H), 2.48−2.56 (m, 2H), 2.87 (dd, 1H, $J = 4.9, 13.2$), 3.12 (m, 1H), 3.47 (dd, 1H, $J = 10.6, 13.2$), 4.38 (dd, 1H, $J = 5.4, 11.3$), 4.53 (dd, 1H, $J = 8.1, 11.3$), 5.14 (dd, 1H, $J = 3.1, 10.1$), 5.85 (dd, 1H, $J = 2.1, 10.1$), 6.21 (dd, 1H, $J = 2.1, 10.1$), 6.78 (dd, 1H, $J = 3.1, 10.1$), 7.12−7.32 (m, 5H); ^{13}C 21.0, 30.0, 30.5, 34.5, 57.0, 62.8, 63.5, 127.1, 128.6, 129.2, 129.6, 129.9, 137.9, 148.6, 149.2, 170.2, 175.0, 184.2; IR 1735, 1690, 1670; MS 339 $[M]^+$; HRMS calcd for $C_{20}H_{21}NO_4$ 339.1471, found 339.1471.

(3*S*,1*S*′)-1-(2′-Acetoxy-1′-benzylethyl)-3-[*N*-(*tert*-butoxycarbonyl)amino]-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (55): 22% yield from (*S*)-4-benzyl-2-[(*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-(4-hydroxyphenyl)ethyl]-2-oxazoline; chromatography 1:1 EtOAc/hexane, $R_f = 0.40$; colorless crystals; mp 97−99 °C (Et_2O/hexane); $[\alpha]^{20}_D = -20.8°$ ($c = 1.48$); ^{1}H 1.46 (s, 9H), 1.79 (dd, 1H, $J = 11.2, 12.7$), 2.01 (s, 3H), 2.50 (dd, 1H, $J = 8.3, 12.7$), (dd, 1H, $J = 4.8, 13.2$), 3.12 (m, 1H), 3.41 (dd, 1H, $J = 10.9, 13.2$), 4.35 (dd, 1H, $J = 5.2, 11.4$), 4.36 (m, 1H), 4.52 (dd, 1H, $J = 8.8, 11.4$), 4.85 (br d, 1H, $J = 10.2$), 5.23 (d, 1H, $J = 4.8$, NH), 5.95 (dd, 1H, $J = 1.8, 10.2$), 6.19 (dd, 1H, $J = 1.8, 10.2$), 6.79 (dd, 1H, $J = 3.1, 10.2$), 7.12−7.36 (m, 5H); ^{13}C 20.9, 28.2, 34.8, 57.4, 60.3, 62.6, 80.6, 127.3, 128.6, 128.9, 129.8, 130.9, 137.5, 147.7, 148.3, 155.7, 170.2, 172.5, 184.0; IR 3335, 1740 1710, 1695, 1675; MS (CI) 455 $[M + H]^+$; HRMS calcd for $C_{25}H_{30}N_2O_6$ 454.2104, found 454.2092.

(3*S*,1*S*′)-1-(2′-Acetoxy-1′-benzylethyl)-3-[*N*-acetyl-*N*-(4-methylphenyl)sulfonylamino]-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (56): 41% yield from (*S*)-4-benzyl-2-[(*S*)-1-[*N*-(4-methylphenyl)sulfonylamino]-2-(4-hydroxyphenyl)ethyl]-2-oxazoline; chromatography 1:1 EtOAc/hexane; pale yellow foam; $[\alpha]^{20}_D = -22.4°$ ($c = 1.25$); ^{1}H 2.03 (s, 3H), 2.29 (s, 3H), 2.45 (dd, 1H, $J = 4.1, 13.2$), 2.47 (s, 3H), 2.53 (dd, 1H, $J = 9.9, 13.2$), 3.07 (dd, 1H, $J = 6.1, 12.4$), 3.15 (m, 1H), 3.25 (dd, 1H, $J = 7.0, 12.4$), 4.29 (dd, 1H, $J = 4.6, 11.2$), 4.57 (dd, 1H, $J = 8.3, 11.2$), 5.23 (m, 1H), 6.04 (dd, 1H, $J = 1.9, 9.9$), 6.12 (dd, 1H, $J = 2.8, 9.9$), 6.24 (dd, 1H, $J = 1.9, 10.2$), 6.83 (dd, 1H, $J = 2.8, 10.2$), 7.18−7.32 (m, 5H), 7.42 (d, 2H, $J = 7.9$), 8.04 (d, 2H, $J = 7.9$); ^{13}C: 20.9, 21.7, 25.1, 35.6, 57.3, 59.9, 62.5, 126.9, 127.6. 128.5, 128.9, 129.8, 130.1, 130.2, 136.1, 137.5, 145.5, 148.5, 148.8, 169.6, 169.8, 170.2, 184.1; IR 1745, 1705, 1675; MS 550 $[M]^+$; HRMS calcd for $C_{27}H_{28}N_2O_6S$, 550.1774, found 550.1769.

1-(2′-Acetoxyethyl)-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (54): 42% yield from 2-[2-(4-hydroxyphenyl)ethyl]-2-oxazoline; chromatography 100% EtOAc; $R_f = 0.27$; pale yellow oil; ^{1}H 1.96 (s, 3H), 2.14 (t, 2H, $J = 8.1$), 2.52 (t, 2H, $J = 8.1$), 3.23−3.27 (m, 2H), 4.03−4.07 (m, 2H), 6.27 (d, 2H, $J = 9.9$), 6.75 (d, 2H, $J = 9.9$); ^{13}C 20.7, 28.8, 30.0, 40.1, 61.6, 62.0, 129.9, 148.9, 170.4, 174.9, 183.9; IR 1745, 1700, 1675; MS 249 $[M]^+$; HRMS calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1000.

(2*S*,5*S*,10*R*)-2-Benzyl-1-aza-4-oxatricyclo[8.3.0.0^{5,10}]-tridec-8-ene-7,13-dione (42). A solution of 1-[(*S*)-2′-acetoxy-1′-benzyl-ethyl]-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (170.0 mg, 0.5 mmol) in MeOH (3 mL) containing K_2CO_3 (7 mg, 50 mmol) was stirred for 2 h at rt, and then it was filtered over silica gel (1 g; MeOH) and concentrated to yield 0.14 g (94%) of **42**: colorless oil; $[\alpha]^{20}_D = -104.6°$ ($c = 0.70$); ^{1}H 2.11−2.19 (m, 2H), 2.44−2.71 (m, 2H), 2.75−2.78 (m, 2H), 2.82 (ddd, 1H, $J = 1.1, 5.2, 13.1$), 2.92 (dd, 1H, $J = 10.3, 13.1$), 3.40 (ddd, 1H, $J = 1.1, 2.6, 11.8$), 3.75 (m, 1H), 3.81 (d, 1H, $J = 11.8$), 4.27 (ddd, 1H, $J = 2.6, 5.2, 10.3$), 6.11 (d, 1H, $J = 10.3$), 6.72 (dd, 1H, $J = 2.9, 10.3$), 7.20−7.33 (m, 5H); ^{13}C 29.3, 29.9, 37.5, 40.7, 49.8, 59.3, 67.1, 81.1, 126.7, 128.1, 128.6, 129.4, 137.4, 150.3, 173.2, 194.3; IR 1665; MS 297 $[M]^+$; HRMS calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1363.

Representative Procedure for Hydrogenation of Dienones: 1-[(*S*)-2′-Acetoxy-1′-benzylethyl]-1-azaspiro[4.5]-deca-2,8-dione (70). A solution of **48** (340 mg, 1 mmol) in EtOAc (10 mL) containing suspended 1% Pt on 60−100 mesh carbon (80 mg) was stirred at rt under H_2 (balloon). The reaction was followed by TLC to avoid reduction of the ketone, and it was complete after 20 min. The catalyst was filtered off and the solvent evaporated to yield 310 mg (90%) of **70**: colorless crystals; mp 119−121 °C; $[\alpha]^{20}_D = -21.7°$ ($c = 0.23$); ^{1}H 1.18−1.37 (m, 2H), 1.77−1.84 (m, 1H), 1.93−2.25 (m, 5H), 2.03 (s, 3H), 2.37−2.46 (m, 4H), 3.01 (dd, 1H, $J = 5.0, 12.9$), 3.32 (m, 1H), 3.49 (dd, 1H, $J = 9.7, 12.9$), 4.42 (dd, 1H, $J = 6.6, 11.2$), 4.56 (dd, 1H, $J = 6.8, 11.2$), 7.14−7.29 (m, 5H); ^{13}C 20.9, 28.4, 33.3, 34.5, 34.9, 37.6, 37.7, 54.7, 62.7, 64.1, 126.8, 128.5, 129.6, 138.5, 170.6, 175.1, 208.5; IR 1740, 1715, 1680; MS 343 $[M]^+$; HRMS calcd for $C_{20}H_{25}NO_4$ 343.1784, found 343.1784.

Amide Formation in the Indole Series. A cold (0 °C) solution of an indolic acid (3.0 mmol), BOP-Cl (0.8 g, 3.0 mmol), and Et_3N (0.3 g, 3.0 mmol) in CH_2Cl_2 (6 mL) was stirred for 30 min prior to addition of (*S*)-2-amino-3-phenyl-1-propanol (0.45 g, 3 mmol). A solution of Et_3N (0.3 g, 3.0 mmol) in CH_2Cl_2 (1.2 mL) was then introduced dropwise during 2 h, with continued stirring at 0 °C. The mixture was stirred an additional 2 h at 0 °C and 8 h at rt, and then it was quenched with H_2O and treated as follows. Reactions involving tryptophane derivatives were acidified to pH 6 with saturated NH_4Cl solution. Reactions involving other indolic acids were acidified to pH 1 with 4 M aqueous HCl. In all cases, the organic layer was separated and the water phase was extracted with more EtOAc. The combined extracts were washed (saturated aqueous $NaHCO_3$), dried ($MgSO_4$), and evaporated.

***N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-3-(indol-3′-yl)propionamide (77):** 95% yield from 3-(indol-3′-yl)propionic acid; colorless foam; $[\alpha]^{20}_D = -16.1°$ ($c = 4.98$); ^{1}H 2.46 (t, 2H, $J = 7.4$), 2.66 (dd, 1H, $J = 7.4, 13.5$), 2.72 (dd, 1H, $J = 6.6, 13.5$), 3.01 (t, 2H, $J = 7.4$), 3.39 (dd, 1H, $J = 5.1, 11.4$), 3.47 (dd, 1H, $J = 3.7, 11.4$), 4.09 (m, 1H), 6.03 (d, 1H, $J = 8.1$), 6.80 (d, 1H, $J = 2.2$), 7.04−7.21 (m, 7H), 7.30 (d, 1H, $J = 8.1$), 7.54 (d, 1H, $J = 7.4$), 8.54 (s, 1H, NH ind.); ^{13}C 21.2, 36.6, 37.1, 52.5, 63.4, 111.3, 114.1, 118.4, 119., 121.7, 121.8, 126.4, 126.9, 128.4,

129.1, 136.21, 137.5, 173.6; IR 3325, 1625; MS (CI) 323 (100) $[M + H]^+$; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1665.

(*S*)-*N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-3-(indol-3′-yl)-2-[*N*-(4-methylphenyl)sulfonylamino]propionamide (78): 51% yield from *N*-tosyl-L-tryptophan (chromatography 3:1 Et_2O/EtOAc, $R_f = 0.27$; recrd EtOAc/Et_2O); colorless crystals; mp 183−185 °C; $[\alpha]^{20}_D = -17.1°$ ($c = 0.86$, dioxane); ^1H (DMSO-d_6) 2.26 (s, 3H), 2.45 (dd, 1H, $J = 7.4, 14.7$), 2.66−2.75 (m, 2H), 2.89 (dd, 1H, $J = 5.5, 13.6$), 3.08 (dd, 1H, $J = 5.5, 10.3$), 3.17 (dd, 1H, $J = 4.8, 10.3$), 3.69 (m, 1H), 3.89 (m, 1H), 6.90 (m, 1H), 6.99−7.05 (m, 2H), 7.08 (d, 2H, $J = 7.4$), 7.16−7.20 (m, 3H), 7.24−7.28 (m, 3H), 7.33 (d, 1H, $J = 8.1$ NH), 7.41 (d, 2H, $J = 7.4$), 7.74 (d, 1H, $J = 8.1$, NH), 7.82 (d, 1H, $J = 8.1$), 10.71 (s, 1H, NH ind.); ^{13}C (DMSO-d_6) 21.1, 29.0, 36.4, 52.5, 57.3, 61.8, 109.4, 111.3, 118.2, 118.3, 120.8, 124.0, 126.1, 126.4, 127.3, 128.2, 129.1, 129.3, 136.1, 138.1, 139.1. 142.1, 170.4; IR 3330, 1650; MS 491 $[M]^+$; HRMS calcd for $C_{27}H_{29}N_3O_4S$ 491.1879, found 491.1865.

***N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-3-(2′-methyl-indol-3′-yl)propionamide (79).** 88% yield from 3-(2-methyl-indol-3′-yl)propionic acid; pale yellow oil; $[\alpha]^{20}_D = -16.9°$ ($c = 0.94$); ^1H 2.33 (s, 3H), 2.44 (t, 2H, $J = 7.0$), 2.56−2.68 (m, 2H), 3.01−3.04 (m, 2H), 3.34 (dd, 1H, $J = 5.5, 11.4$), 3.43 (dd, 1H, $J = 3.3, 11.4$), 3.99 (m, 1H), 5.48 (d, 1H, $J = 7.4$, NH), 6.98−7.27 (m, 8H), 7.47 (d, 1H, $J = 6.6$), 7.96 (s, 1H, NH ind.); ^{13}C 11.5, 20.4, 36.7, 37.5, 52.8, 63.9, 110.0, 110.4, 117.7, 119.2, 121.1, 126.5, 128.2, 128.5. 129.1, 131.6, 135.3 137.4, 173.6; IR 3290, 1650; MS (CI) 337 $[M + H]^+$, 336 $[M]^+$; HRMS $C_{21}H_{24}N_2O_2$ calcd 336.1838, found 336.1840.

Preparation of Indolic Oxazolines. A degassed (argon) solution of an indolic amide (1.5 mmol) and Burgess reagent (0.4 g, 1.7 mmol) in THF (10 mL) was heated at 70 °C in a pressure Pyrex tube for 2 h. The mixture was cooled to rt, diluted with Et_2O (precipitate of ammonium salts), and filtered through a short plug of silica gel (Et_2O). Concentration afforded material of sufficiently good quality that no further purification was required before oxidation.

(*S*)-4-Benzyl-2-[2-(indol-3′-yl)ethyl]-2-oxazoline (80): 64% yield from *N*-[(*S*)-1-benzyl-2-hydroxyethyl]-3-(indol-3′-yl)propionamide; colorless oil; $[\alpha]^{20}_D = -11.1°$ ($c = 1.16$); ^1H 2.60 (dd, 1H, $J = 8.1, 13.2$), 2.67−2.72 (m, 2H), 3.07 (dd, 1H, $J = 5.2, 13.2$), 3.10−3.15 (m, 2H), 3.97 (dd, 1H, $J = 7.1, 8.3$), 4.17 (dd, 1H, $J_1 = J_2 = 8.3$), 4.38 (m, 1H), 6.99 (d, 1H, $J = 2.2$), 7.11−7.37 (m, 8H), 7.63 (d, 1H, $J = 7.4$), 8.24 (s, 1H, NH); ^{13}C 21.7, 28.9, 41.7, 67.1, 71.5, 111.1, 115.0, 118.7, 119.2, 121.4 121.9, 126.4, 127.2, 128.4, 129.2, 136.2, 137.9, 167.8; IR 3415, 1660; MS (CI) 305 $[M + H]^+$; HRMS calcd for $C_{20}H_{20}N_2O$ 304.1576, found 304.1564.

(*S*)-4-Benzyl-2-[(*S*)-2-(indol-3′-yl)-1-[*N*-(4-methylphenyl)-sulfonylamino]ethyl]-2-oxazoline (81): 54% yield from (*S*)-*N*-[(*S*)-1-benzyl-2-hydroxyethyl]-3-(indol-3′-yl)-2-[*N*-(4-methylphenyl)sulfonylamino]propionamide; pale yellow foam; ^1H 2.06 (dd, 1H, $J = 7.4, 13.2$), 2.35 (s, 3H), 2.64 (dd, 1H, $J = 4.4, 13.2$), 3.18 (d, 2H $J = 5.9$), 3.76 (dd, 1H, $J = 5.9, 7.4$), 3.86 (dd, 1H, $J_1 = J_2 = 7.4$), 3.90 (m, 1H), 4.34 (m, 1H), 5.64 (d, 1H, $J = 8.8$), 6.97 (d, 1H, $J = 8.1$), 7.02−7.06 (m, 2H), 7.11−7.25 (m, 6H), 7.30 (d, 2H $J = 8.1$), 7.43 (d, 2H $J = 8.1$), 7.64 (d, 2H, $J = 8.1$), 8.57 (s, 1H, NH ind.); IR 3400, 1665; MS 473 $[M]^+$; HRMS calcd for $C_{27}H_{27}N_3O_3S$ 473.1773, found 473.1774.

(*S*)-4-Benzyl-2-[2-(2′-methyl-indol-3′-yl)ethyl]-2-oxazoline (82): 65% yield from *N*-[(*S*)-1-benzyl-2-hydroxyethyl]-3-(2′-methyl-indol-3′-yl)propionamide; colorless oil; $[\alpha]^{20}_D = -7.5°$ ($c = 0.95$); ^1H 2.36 (s, 3H), 2.50−2.61 (m, 3H), 3.01−3.06 (m, 3H), 3.95 (dd, 1H, $J = 6.6, 8.8$), 4.15 (dd, 1H, $J_1 = J_2 = 8.8$), 4.35 (m, 1H), 7.08−7.32 (m, 8H), 7.52 (dd, 1H, $J = 2.2, 5.9$), 7.91 (s, 1H, NH); ^{13}C 11.5, 20.8, 29.2, 41.6, 67.2, 71.5, 110.2, 110.3, 117.9, 119.1, 120.9, 126.4, 128.4, 128.4, 129.2, 131.2, 135.2, 137.9, 167.8; IR 3405, 1660; MS (CI) 319 $[M + H]^+$; HRMS calcd for $C_{21}H_{22}N_2O$ 318.1732, found 318.1731.

Oxidation of Indolic Oxazolines. A solution of DIB (370.0 mg, 1.1 mmol) in TFE (5 mL) was added dropwise over 5 min to a solution of indolic oxazoline (1.0 mmol) in TFE (5 mL), and the resulting mixture was stirred for 30 min at rt. Solid $NaHCO_3$ (0.25 g) was added, and the suspension was filtered over glass wool and evaporated. The crude product was purified by column chromatography as detailed below.

7,8-Benzo-2-benzyl-1,6-diaza-4-oxatricyclo[7.3.0.0^{5,9}]-dodec-7-en-12-one. Obtained in 48% overall yield from (*S*)-4-benzyl-2-[2-(indol-3′-yl)ethyl]-2-oxazoline as a 1:1 mixture (^1H NMR) of (2*S*,5*S*,9*S*) and (2*S*,5*R*,9*R*) diastereomers (separated by chromatography, 100% Et_2O). **(2*S*,5*S*,9*S*)-Isomer (84):** $R_f = 0.56$; 26% yield; colorless oil; $[\alpha]^{20}_D = -53.3°$ ($c = 1.61$); ^1H 2.16 (m, 1H), 2.30 (ddd, 1H, $J_1 = 9.6$, $J_2 = J_3 = 11.8$), 2.53 (m, 1H), 2.72−2.85 (m, 2H), 3.36−3.46 (m, 2H), 3.68 (m, 1H), 3.96 (dd, 1H, $J = 3.7, 13.2$), 4.53 (s, 1H, NH), 5.08 (s, 1H), 6.63 (d, 1H, $J = 8.1$), 6.74 (dd, 1H, $J_1 = J_2 = 7.4$ Hz), 7.06 (d, 1H, $J = 7.4$), 7.11 (dd, 1H, $J = 7.4, 8.1$), 7.15−7.28 (m, 5H); ^{13}C 29.7, 34.2, 35.0, 53.3, 60.9, 67.2, 93.3, 109.1, 119.4, 121.7, 126.3, 128.4, 129.6, 129.6, 130.2, 138.0, 147.7, 175.3; IR 3320, 1680; MS (CI) 321 $[M + H]^+$; HRMS calcd for $C_{20}H_{22}N_2O_2$ 320.1525, found 320.1516.

(2*S*,5*R*,9*R*)-Isomer (85): $R_f = 0.30$; 22% yield; colorless crystals; mp 209−211 °C (recrd Et_2O/hexane); $[\alpha]^{20}_D = +16.0°$ ($c = 0.78$); ^1H 2.05 (ddd, 1H, $J = 3.0, 8.9, 12.5$), 2.27 (ddd, 1H, $J = 9.6, 10.3, 12.5$), 2.41−2.51 (m, 2H), 2.68−2.81 (m, 2H), 3.40 (dd, 1H, $J = 4.0, 12.1$), 3.56 (dd, 1H, $J = 3.3, 12.1$), 4.28 (m, 1H), 4.56 (s, 1H, NH), 4.71 (s, 1H), 6.75 (d, 1H, $J = 8.1$), 6.83 (dd, 1H, $J_1 = J_2 = 7.4$), 7.11−7.26 (m, 7H); ^{13}C 29.2, 33.4, 36.9, 50.3, 62.0, 66.7, 93.6, 110.2, 119.9, 122.8, 126.4, 128.4, 129.4, 130.9, 137.7, 147.4, 174.7; IR ($CDCl_3$) 3300, 1680; MS (CI) 321 $[M + H]^+$; HRMS calcd for $C_{20}H_{22}N_2O_2$ 320.1525, found 320.1528.

7,8-Benzo-2-benzyl-11-[*N*-(4-methylphenyl)sulfonylamino]-1,6-diaza-4-oxatricyclo[7.3.0.0^{5,9}]dodec-7-en-12-one: 41% yield from (*S*)-4-benzyl-2-[(*S*)-2-(indol-3′-yl)-1-[*N*-(4-methylphenyl)sulfonylamino]ethyl]-2-oxazoline as a 1:1 ratio (NMR) of (2*S*,5*S*,9*S*,11*S*) and (2*S*,5*R*,9*R*,11*S*) diastereomers (separated by chromatography, 5:1 Et_2O/hexane).

(2*S*,5*S*,9*S*,11*S*)-Isomer (86): $R_f = 0.37$; 19% yield; colorless oil; $[\alpha]^{20}_D = -3.6°$ ($c = 1.49$); ^1H 2.25 (dd, 1H, $J = 7.4, 14.0$), 2.43 (s, 3H), 2.70 (dd, 1H, $J = 9.0, 14.0$), 2.81 (dd, 1H, $J = 9.2, 13.8$), 3.40 (dd, 1H, $J = 6.3, 11.3$), 3.54 (d, 1H, $J = 11.3$), 3.65 (dd, 1H, $J = 7.2, 9.2$), 3.82−3.91 (m, 2H), 4.42 (s, 1H, NH), 4.95 (s, 1H), 5.23 (d, 1H, $J = 1.8$, NHTs), 6.64 (d, 1H, $J = 8.1$), 6.83 (ddd, 1H, $J_1 = 0.8$, $J_2 = J_3 = 7.4$), 7.06 (d, 1H, $J = 7.4$), 7.11−7.34 (m, 8H), 7.77 (d, 2H, $J = 8.5$); ^{13}C 21.6, 34.3, 39.0, 53.5, 54.9, 62.7, 68.5, 90.7, 109.8, 120.4, 123.1, 126.5, 127.4, 128.4, 128.5, 129.0, 129.1, 129.9, 134.8, 135.7, 144.0, 148.3, 171.9; IR 3385, 1695; MS 489 $[M]^+$; HRMS calcd for $C_{27}H_{27}N_3O_4S$ 489.1722, found 489.1720.

(2*S*,5*R*,9*R*,11*S*)-Isomer (87): $R_f = 0.18$; 22% yield; colorless foam; $[\alpha]^{20}_D = +4.2°$ ($c = 2.11$); ^1H 2.26 (dd, 1H, $J = 10.8, 12.5$), 2.43 (s, 3H), 2.47 (dd, 1H, $J = 11.0, 13.4$), 2.56 (dd, 1H, $J = 7.7, 12.5$), 2.68 (dd, 1H, $J = 4.6, 13.4$), 3.43 (dd, 1H, $J = 3.7, 12.4$), 3.56 (dd, 1H, $J = 2.8, 12.4$), 4.11 (m, 1H), 4.22 (m, 1H), 4.64 (s, 1H, NH), 4.68 (s, 1H), 5.60 (s, 1H, NHTs), 6.74−6.82 (m, 2H), 6.98 (d, 1H, $J = 7.0$), 7.05−7.32 (m, 8H), 7.76 (d, 2H, $J = 8.1$); ^{13}C 21.5, 36.6, 43.1, 50.2, 52.2, 62.0, 68.5, 93.6, 110.5, 120.0, 122.5, 126.6, 127.2, 128.5, 129.1, 129.3, 129.7, 129.9, 136.1, 137.0, 143.9, 147.6, 170.5; IR 3380, 1695; MS 489 $[M]^+$; HRMS calcd for $C_{27}H_{27}N_3O_4S$ 489.1722, found 489.1726.

2-Benzyl-10-bis(2,2,2-trifluoroethoxy)-5-methyl-1,6-diaza-4-oxatetracyclo[11.3.0.0^{5,13}0^{7,12}]hexadec-6,8,11-trien-16-one. Obtained in 23% overall yield from (*S*)-4-benzyl-2-[2-(2′-methyl-indol-3′-yl)ethyl]-2-oxazoline as a 1.2:1 mixture (^1H NMR) of (2*S*,5*S*,9*S*) and (2*S*,5*R*,9*R*) diastereomers (separated by chromatography with 100% Et_2O).

(2*S*,5*S*,13*S*)-Isomer (89): $R_f = 0.46$; minor product, 9% yield as a brownish oil; $[\alpha]^{20}_D = -19.3°$ ($c = 0.40$); ^1H 1.66 (s, 3H), 1.91 (dd, 1H, $J = 8.1, 11.8$), 2.33 (m, 1H), 2.52−2.83 (m, 2H), 2.76 (dd, 1H, $J = 11.0, 13.2$), 2.97 (dd, 1H, $J = 2.2, 13.2$), 3.51 (d, 1H, $J = 13.2$), 3.63−3.71 (m, 2H) 3.83−4.04 (m, 4H), 6.03 (d, 1H, $J = 2.4$), 6.48 (dd, 1H, $J = 2.4, 10.2$), 6.85 (d, 1H, $J = 10.2$), 7.19−7.30 (m, 5H); ^{13}C 14.1, 31.3, 31.9, 35.8, 52.4, 58.5, 60.5 ($J_{CF} = 36.2$), 64.9, 96.2, 104.1, 119.4, 123.2 ($J_{CF} = 278.1$), 125.9, 126.6, 128.5, 129.9, 136.9, 137.5, 147.1, 161.7, 174.7; ^{19}F (188.31 MHz, $CDCl_3$) −74.48 (br s); IR 1685; MS (CI) 531 $[M + H]^+$; HRMS (CI) calcd for $C_{25}H_{25}F_6N_2O_4$ $[M + H]^+$ 531.1719, found 531.1724.

(2*S*,5*S*,13*S*)-Isomer (90): R_f = 0.21; major product, 14% yield as a brownish oil; $[\alpha]^{20}_D$ = +13.3° (*c* = 0.67); ^{1}H 1.64 (s, 3H), 1.95 (m, 1H), 2.29 (dd, 1H, *J* = 10.3, 13.2), 2.34−2.55 (m, 2H), 2.67 (m, 1H), 2.90 (dd, 1H, *J* = 10.3, 13.2), 3.25 (dd, 1H, *J* = 4.4, 13.2), 3.52 (dd, 1H, *J* = 6.6, 13.2), 3.94−4.11 (m, 4H), 4.29 (m, 1H), 6.19 (d, 1H, *J* = 2.7), 6.61 (dd, 1H, *J* = 2.7, 10.3), 6.93 (d, 1H, *J* = 10.3), 7.12−7.29 (m, 5H). ^{13}C: 14.1, 31.3, 31.9, 38.8, 51.2, 60.5, 60.6 (J_{CF} = 36.2), 60.7, 64.8, 96.2, 103.8, 122.2, 123.2 (J_{CF} = 278.1), 125.9, 126.8, 128.6, 128.8, 136.4, 137.2, 147.8, 162.8, 175.2; ^{19}F (188.31 MHz, $CDCl_3$) −74.40, −74.47; IR 1695; MS (CI) 531 $[M + H]^+$; CI-HRMS (CI) calcd for $C_{25}H_{25}F_6N_2O_4$ $[M + H]^+$ 531.1719, found 531.1716.

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Supporting Information Available: Procedures for the preparation of several intermediates not included in the above Experimental Section and full physical data for these. This material is available free of charge via the Internet at http://pubs.acs.org.

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