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π-Face selective azaspirocyclization of ω-(methoxyphenyl)-*N*-methoxyalkylamides

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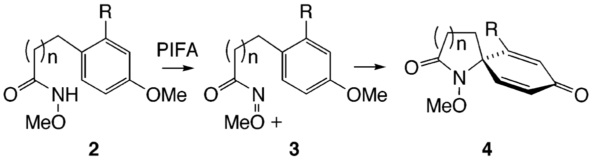
Abstract—A novel method for the stereoselective preparation of 1-azaspiranes is described. Treatment of α- and β-substituted 3-(methoxyphenyl)-*N*-methoxypropionamides **1** with phenyliodine(III) bis(trifluoroacetate) initiates efficient azaspirocyclization, via a putative *N*-acylnitrenium ion intermediate, to provide cyclohexa-2,5 and 2,4-dienone spirolactams **8** and **11** with good π-facial selectivity. Furthermore, a preliminary study indicates that this strategy is also amenable to the preparation of 1-azaspiro[5.5]undeca-2,5-dienones. © 2003 Elsevier Science Ltd. All rights reserved.

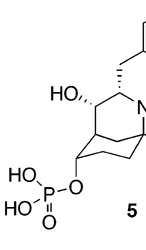
Spirocyclic cyclohexadienones are useful synthetic intermediates, which have been employed in the preparation of an extensive range of biologically active molecules. These molecules are most often prepared via the oxidative spirocyclization of phenols,[1] a process which formally involves generation of an aryloxenium ion and intramolecular capture of this intermediate by *O*-, *C*- and, less commonly, *N*-nucleophiles.[2]



Scheme 1. *N*-Acylnitrenium ion-promoted spirocyclization.

In contrast to the numerous applications of phenolic oxidation, dearomatizing spirocyclizations, which are triggered by an electrophilic center pendant to the aromatic ring, are not as routinely utilized in synthesis. Examples of this type of reaction include the Brønsted acid-catalyzed cyclization of α-diazo ketones,[3] the Lewis acid-catalyzed spirocyclization of phenethyl oximes[4] and allenyl ketones,[5] and the spiroannelation of phenolic tosylates.[6] Unfortunately, low yields, restrictive structural requirements and harsh reaction conditions are serious obstacles to these transformations, which, at times, have impeded their application.[7] In this context, the azaspirocyclization of *N*-acyl-*N*-alkoxynitrenium ions **3** (Scheme 1), which can be generated under mild conditions by the treatment of *N*-methoxyamides **2** with iodine(III) reagents, is attractive since it is both efficient and compatible with a range of substrates and functional groups.[8]

Furthermore, the potential of this underutilized chemistry is enhanced by the fact that the accessible 1-azaspiro[4.5]decane and -[5.5]undecane systems **4** form the substructure of a diverse range of natural products[9] and other bioactive molecules.[10] Significantly, the spirocenters of many of these targets, including FR901483 (**5**) and Fasicularin (**6**) are asymmetric (Fig. 1). As part of an ongoing program to realize the potential of *N*-acyl-*N*-alkoxynitrenium ions, we recently reported the synthesis of the 1-azaspiro[4.5]decane alkaloids TAN1251A[11a] and desmethylamino FR901483.[11b] Herein, we now disclose a strategy to effectively control the π-facial selectivity of this reaction which represents a novel approach to the stereocontrolled preparation of 1-azaspiranes.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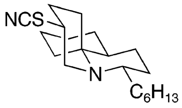
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Figure 1. Azaspirocyclic natural products.

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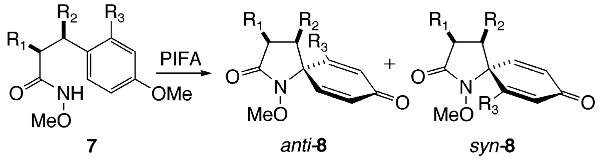
Table 1. Diastereoselective spirocyclization of α- and β-substituted 3-(4-methoxyphenyl)-*N*-methoxypropionamides **7**[18]



7 *anti*-**8** *syn*-**8**

Entry	7	R$_1$	R$_2$	R$_3$	Yield of **8** (%)[a]	dr (*anti*:*syn*)[b]
1	**7a**	H	Me	Me	75[c]	>98:2
2	**7b**	Me	H	Me	75	5.6:1
3	**7c**	H	*n*-Bu	Me	79[c]	>98:2
4	**7d**	*n*-Bu	H	Me	87[e]	5.3:1
5	**7e**	H	Me	*i*-Pr	81	>98:2
6	**7f**	Me	H	*i*-Pr	72	6:1
7	**7g**	H	Me	OMe	90	4:1
8	**7h**	Me	H	OMe	85[d]	12:1
9	**7i**	H	*n*-Bu	OMe	97	1.6:1
10	**7j**	*n*-Bu	H	OMe	68[d]	11:1
11	**7k**	CH$_2$Ph	H	OMe	98[e]	11:1
12	**7l**	OTIPS	H	OMe	88[e]	12:1

[a] Unless otherwise noted, yields reported for combined diastereomers, isolated after purification by chromatography and/or recrystallization.
[b] Ratio of *anti*-**8** and *syn*-**8** determined by NMR analysis of appropriate, characteristic proton signals in the unpurified product mixture.
[c] Single diastereomer observed in the ^{1}H NMR spectrum of the unpurified product.
[d] Chromatographically inseparable mixture of diastereomers; recrystallization from EtOAc and hexanes provided pure *anti*-**8**.
[e] Inseparable mixture of diastereomers.

Despite the current interest in asymmetric dearomatization,[12] the issue of π-facial selectivity in the context of oxidative spirocyclizations has received surprisingly little attention. A review of the literature reveals that in many of the substrates from which spirocyclic cyclohexa-2,5-dienones are generated, the arene has a longitudinal plane of symmetry and, as a result, dearomatization leads to the formation of a chirotopic nonstereogenic quaternary center,[13] e.g. **2**→**4** (R = H). However, if the aromatic ring is substituted in a way that breaks this symmetry, i.e. **2** (R ≠ H), then the π-faces become heterotopic and a new quaternary stereogenic center is formed upon spirocyclization. While a few reports indicate that induction at the *ipso* position during the oxidative spirocyclization of phenols is feasible,[14] examples involving pendant electrophile-triggered spirocyclizations have rarely been documented.[15]

Our first undertaking has been to examine the influence that stereogenic centers, present in the *N*-acyl side-chain of **2**, have upon π-facial selectivity. To this end, a series of 3-(4-methoxyphenyl)-*N*-methoxypropionamides **7a**–**l** (Table 1) bearing a variety of *o*-aryl and side-chain substituents were prepared from the corresponding carboxylic acids, through coupling with methoxyamine. These acids, in turn, were accessed from either the parent aryl bromides, cinnamic acid esters or dihydrocinnamic acids by well established synthetic methods.[16]

In our previous investigations the cyclization of *N*-methoxyamides was carried out at 0°C;[11] however, during the course of this study, we found that the efficiency of this process could be improved by carrying out the reactions at low temperature. Thus, treatment of **7** with phenyliodine(III) bis(trifluoroacetate) (PIFA) at −78°C followed by addition of water at −20°C (to ensure hydrolysis of the intermediate acetal)[11a] cleanly gave spirolactam **8** in good to excellent yield. After separation by chromatography and/or crystallization, the relative stereochemistry of the individual diastereomers was readily assigned on the basis of correlations observed in the 2D-NOESY spectra.

In the case of products **8d**, **8k** and **8l**, the diastereomers proved to be inseparable and, as a result, characterization was carried out on the purified mixtures. As indicated in Figure 2, the relative configuration of *anti*-**8e** was further confirmed by X-ray crystallographic analysis.[17]

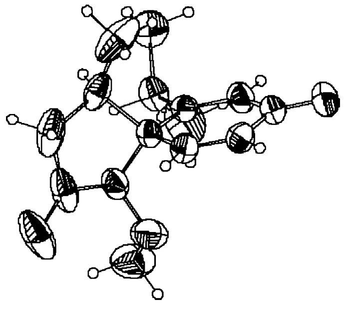
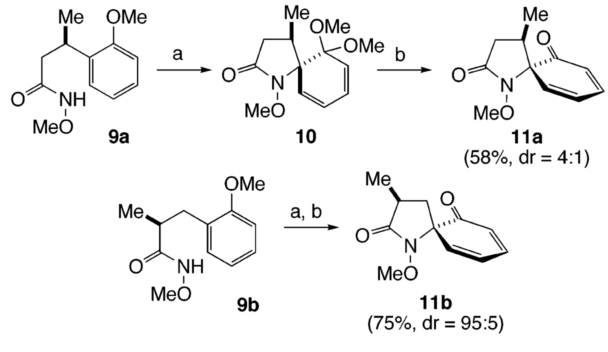


Figure 2. X-Ray crystal structure of compound *anti*-**8e**.

A priori, we anticipated that spirocyclization of the nitrenium ion generated from **7** would preferentially proceed via a transition state resembling **A**‡ to form *anti*-**8**. Conformer **B**‡, on the other hand, would be destabilized due to nonbonding interactions (benzylic strain)[19] between the substituents on the side-chain and the *ortho* position of the aromatic ring (Fig. 3).[20] Indeed, consistent with this model, in all cases studied, the *anti* isomers were found to be the predominant products with selectivities ranging from modest (entry 9) to excellent (entries 1, 3 and 5).

However, an examination of Table 1 does reveal some rather surprising trends. First, for substrates with *o*-methoxyl substituents, the level of 1,3-induction is significantly higher than 1,2-induction (**7g** versus **7h**). These results are contrary to our original expectation that benzylic 1,3-strain between R_2 and R_3 would be the predominant control element irrespective of the *ortho*-substituent. Conversely, in the case of **7a** and **7b** (entries 1 and 2), which have *o*-methyl groups, this trend is reversed and the level of 1,2-induction is substantially higher. Second, for substrates with *o*-methoxyl substituents, an increase in the size of the β-substituent (R_2) results in a decrease in stereoselectivity (**7g** versus **7i**), again contrary to expectation. Interestingly, this behavior is not replicated in the *o*-alkyl series, where the substitution of methyl (**7a**) for *n*-butyl (**7c**) at the β-position does not have a deleterious effect upon stereoselectivity.

Encouraged by these initial findings, we extended our study of the Ar_1-5 cyclization manifold to 3-(2-methoxyphenyl)propionamides **9**, which undergo spirocyclization to form 2,4-dienones **11** (Scheme 2). While there is much interest in the preparation and use of orthoquinone monoketals and their orthoquinol variants,[1,14d] known methods for the preparation of azaspirocyclic 2,4-dienones are limited,[8b] despite the potential value of these molecules as synthetic building blocks.



Scheme 2. Stereoselective preparation of cyclohexa-2,4-dienone spirolactams **11**: *Reagents and conditions*: (a) PIFA, CH_2Cl_2, MeOH, −78→−20°C, 1.5 h; (b) 1 M HCl, THF, H_2O, rt, 40 min.

Oxidation of **9a** provided dienone **11a** accompanied by varying amounts of dimethyl acetal **10**, which presumably arises from interception of the Wheland-type intermediate generated upon azaspirocyclization.[21] Since **10** and **11a** proved to be chromatographically inseparable, this mixture was hydrolyzed with aqueous HCl to provide **11a** as a 4:1 mixture of *anti* and *syn* diastereomers that were separated by column chromatography. Cyclization of **9b** and subsequent hydrolysis also proceeded smoothly to provide **11b** as a 95:5 mixture of diastereomers (by ^{1}H NMR), which upon purification by column chromatography yielded *anti*-**11b**.[22,23] The increased level of π-facial selectivity observed during the dearomatization of **9b**, in comparison with its 2,4-dimethoxyphenyl congener **7h** (Table 1, entry 8), is unexpected given the similarity between these substrates. Whether this observation is due to the differing reactivity of the *o*-methoxy- and *o*,*p*-dimethoxyarenes, or some other factor such as selective product decomposition, has yet to be established. That π-facial selectivity was observed during the reaction of **9b** is intriguing in itself given that the oxidative spirolactonization of a related α-methyl substituted 3-(2-hydroxyphenyl)propionic acid has recently been reported to proceed with negligible stereoinduction.[14d]

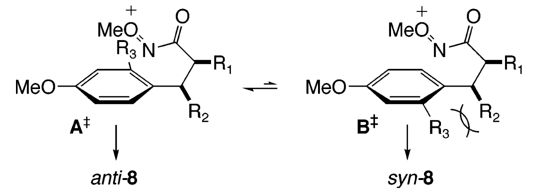
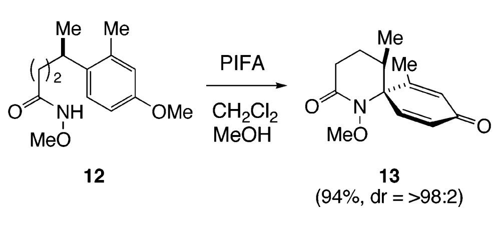


Figure 3. Stereochemical course for the spirocyclization 3-(4-methoxyphenyl)-*N*-methoxypropionamides **7**.

Methods for the expeditious synthesis of 1-azaspiro[5.5]undecanes are of considerable importance as this ring system is present in a number of bioactive natural products,[24] including the histrionicotoxins[25] and the cytotoxic marine alkaloid fasicularin (**6**).[26] A preliminary investigation of the Ar_1-6 cyclization pathway was therefore also undertaken in an effort to gauge the generality of our methodology (Scheme 3). Gratifyingly, upon treatment with PIFA under the conditions previously described for **7**, 4-arylbutanoamide **12** underwent cyclization to provide 1-azaspiro[5.5]-undecadienone **13** in excellent yield and with complete *anti* selectivity, as indicated by a 2D-NOESY experiment.



Scheme 3. Stereoselective preparation of 1-azaspiro[5.5]-undeca-2,5-dienone **13**.

In summary, we have developed a novel strategy for the stereocontrolled preparation of 1-azaspiranes based on the π-face selective spirocyclization of *N*-acylnitrenium ions. The products of this reaction represent potentially useful building blocks for the preparation of a range of biologically active target molecules. Further work to establish the scope and limitations of this methodology, through its application to the synthesis of azaspirocyclic natural products, is underway. Our progress will be reported in due course.

Acknowledgements

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16. The preparation of cyclization substrates **7a–l**, **9a**, **9b**, and **12** will be reported elsewhere.
17. Crystal data for compound *anti*-**8e**. $C_{14}H_{19}NO_3$, $M=249.30$; crystallized in the triclinic system with $Z=4$ and two molecules per asymmetric unit. The figure shows one of the two. Both had the same relative stereochemistry. Unit cell $P\bar{1}$ with $a=8.7808(7)$, $b=11.3943(9)$, $c=15.3131(13)$ Å, $\alpha=70.712(2)$, $\beta=88.155(2)$, $\gamma=79.707(2)°$, and $V=1422.2(2)$ Å^3. Refinement against F^2 with 6446 unique reflections (2375 with $I>2\sigma(I)$) gave $R=0.0676$ and $wR_2=0.1787$ for reflections with $I>2\sigma(I)$ and $R=0.1787$ and $wR_2=0.2398$ for all data. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 201039.
18. Representative procedure for the preparation of spirolactams (*anti*-**8a**): To a suspension of PIFA (108 mg, 0.25 mmol) in MeOH (1 mL), under an atmosphere of N_2 at −78°C, was added a cold (−78°C) solution of **7a** (50 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) via cannula. The reaction mixture was then allowed to warm to −20°C (bath temperature) over 1.5 h whereupon H_2O (4 mL) was added and the cooling bath removed. After stirring for 10 min, the biphasic mixture was concentrated under reduced pressure and the concentrate partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $KHCO_3$ (10 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts dried ($MgSO_4$), filtered, concentrated under reduced pressure, and the residue purified by radial chromatography on silica gel (2 mm, EtOAc/hexanes, 1:1) to provide *anti*-**8a** (35 mg, 75% yield) as white crystals.
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22. Notably, **11a** and **11b** are quite stable and can be stored for several weeks without apparent decomposition. In comparison, analogous cyclohexa-2,4-dienone spirolactones[14d] and isoxazolines,[23] rapidly undergo Diels–Alder dimerization and consequently cannot be isolated. In our case, this pathway may be less favorable since the *N*-methoxyl group effectively blocks the adjoining π-system from attack.
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