Highly Diastereoselective Intramolecular [1,2]-Stevens Rearrangements—Asymmetric Syntheses of Functionalized Isopavines as Morphinomimetics**

Stephen Hanessian* and Marc Mauduit

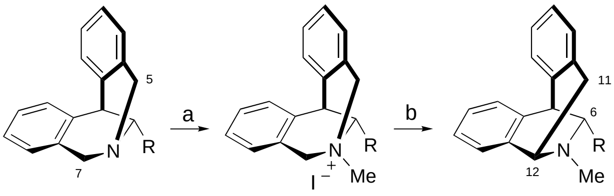
This paper is dedicated to Professor A. I. Meyers in recognition of his seminal contributions to organic synthesis

The isopavine alkaloids of the Papaveraceae family were first recognized as a novel heterocyclic framework following intensive studies on their isolation and structure elucidation four decades ago.[1] Isopavines and pavines have been associated with varying pharmacological properties[2, 3] pertaining to Alzheimer's disease, Parkinson's disease, and Down's syndrome. The traditional syntheses of the isopavines[4] have relied on intramolecular cyclizations of α-aryl-α-benzylamino acetaldehydes, proceeding first to 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines, followed by a second cyclization. Syntheses of enantiomerically pure or enriched isopavine alkaloids have traditionally resorted to optical resolution, or starting with naturally occurring compounds.[5] Other syntheses of racemic isopavines are also known.[6] Natural *O*-methylthalisopavine was first prepared by Meyers and co-workers,[7] by utilizing chiral nonracemic formamidines as substrates in an asymmetric synthesis. Dominguez and co-workers[8] relied on β-amino alcohols as chiral auxiliaries in their synthesis of the same alkaloid.

In view of the pharmacological importance of the isopavines, and the paucity of methods to access enantiopure analogues that would be useful to study selective interactions with designated receptors, we investigated various routes to their stereocontrolled synthesis. We report herein examples of highly stereocontrolled, diastereoselective [1,2]-Stevens rearrangements[9, 10] of 13-substituted dihydro methanodiarylazocines, which are readily available from α-amino acids,[11] to give 6-substituted enantiopure isopavines.

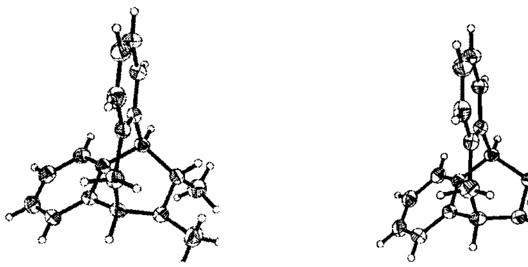
Scheme 1 illustrates the sequence and the generality of the [1,2]-Stevens rearrangement. Methylation of the individual azocine analogues **1a–h** afforded the corresponding quaternary ammonium salts **2a–h**. Treatment with a solution of potassium *tert*-butoxide in 1,4-dioxane[2b] at 80 °C for 1 h, and chromatographic purification gave the corresponding 6-substituted isopavines **3a–h** in excellent yields. The structures of **3a** and **3e** were ascertained by means of single-crystal X-ray analysis (Figure 1)

The facile construction of the 6*R*-methyl-*O*-methylthalisopavine **6** skeleton from the *N,N*-dibenzylamino alcohol **4** via the azocine **5** is shown in Scheme 2.



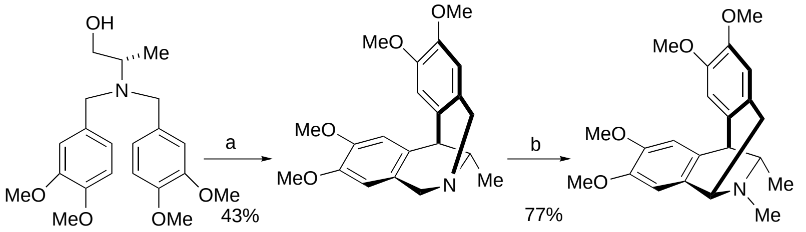
"azocine" **1a-h** **2a-h** "isopavine" **3a-h**

Scheme 1. Reagents and conditions: a) MeI, acetone, reflux; b) *t*BuOK, 1,4-dioxane, 80 °C, 1 h; **a**: R = Me, 85 %; **b**: R = *i*Pr, 88%; **c**: $CH_2CH(CH_3)_2$, 78 %; **d**: R = benzyl, 75 %; **e**: R = CH_2OH, 55 %; **f**: R = CH_2CH_2OH, 57 %; **g**: R = $CH_2CH_2CH_2OH$, 65 %; **h**: R = 3-indolyl, 28 % (yields over two steps).



3a **3e**

Figure 1. X-ray crystal structure of isopavines **3a** and **3e**.



4 **5** **6**

Scheme 2. Reagents and conditions: a) 1. Swern oxidation; 2. $AlCl_3$ (3 equiv.), CH_2Cl_2, 0 °C, 30 min; b) 1. MeI, acetone, reflux; 2. *t*BuOK (1.5 equiv.), 1,4-dioxane, 80 °C, 1 h. **6**: $[\alpha]_D^{23} = -98.2$ ($c = 1$, $CHCl_3$); (−)-*O*-methylthalisopavine: $[\alpha]_D^{23} = -103$ ($c = 1$, EtOH).[8]

The highly stereoselective [1,2]-Stevens rearrangement in this series is unprecedented[12, 13] and can be rationalized by considering two reaction pathways (Scheme 3). Abstraction of a C-7 benzylic proton in the azocinium ion intermediate (pathway a) leads to ylide A, which fragments to the iminium anion A or its diradical equivalent.[10] This is in a favorable alignment for an intramolecular attack (recombination), which leads to the observed isopavine **3a**. On the other hand, abstraction of the C-5 benzylic proton generates ylide B, which upon fragmentation results in an anion or diradical that is destabilized by allylic 1,2-strain in the incipient iminium ion B. These highly diastereoselective [1,2]-Stevens rearrangements are general throughout the series of 13-substituted azocines **1a–h**, and none of the isomeric isopavines of type B were detected.

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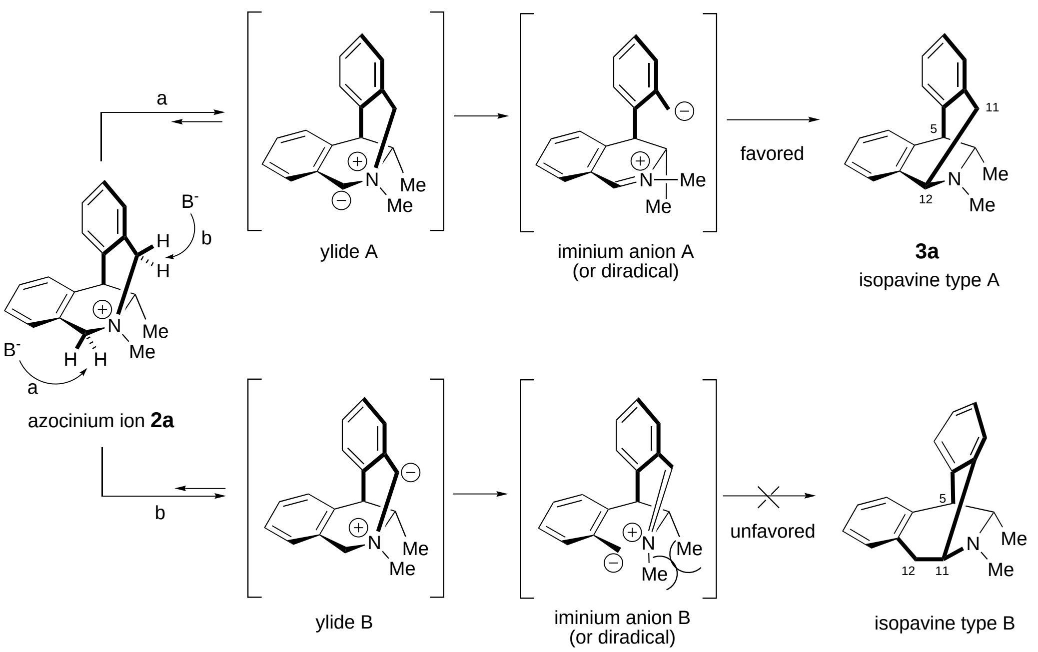
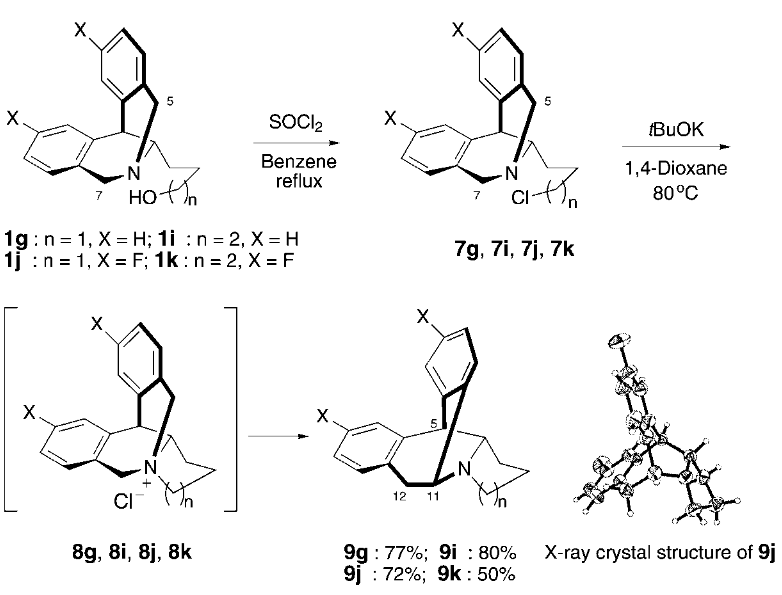


Scheme 3. [1,2]-Stevens rearrangement, which leads to isopavine type A via dianion (or diradical) intermediates.

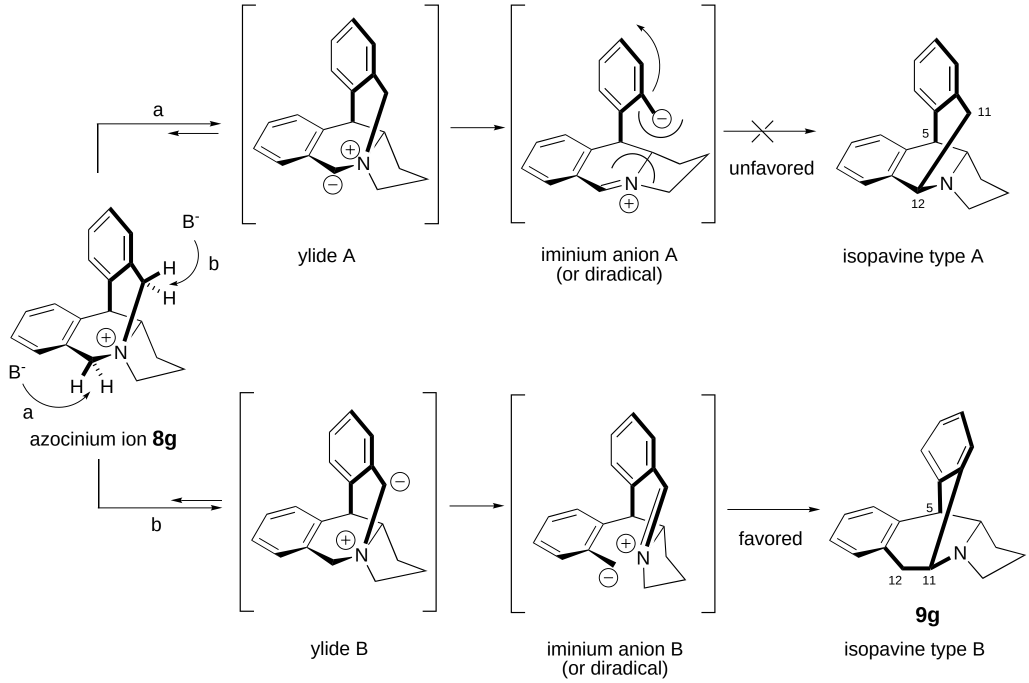
The isopavines A and B have interesting topologies, particularly when viewed in the context of constrained piperidine analogues. As such, they are closely related to morphine,[14] with a quasi-ideal convergence of their carbon skeleton and the strategic location of the tertiary nitrogen atom. The prospects of developing a morphinomimetic[15] would hinge, among other factors, on the proper orientation of the lone pair of electrons on the nitrogen atom.[16] Inspection of the X-ray crystal structure of 6-alkyl isopavines **3a** and **3e**[17] clearly shows that the orientation of the lone pair of electrons on the nitrogen atom is opposite to that found in morphine.[18] It became evident that the desired stereoelectronic effects could occur in a tetracyclic analogue related to the isopavine B skeleton (Scheme 4). Thus, chlorination of **1g** afforded the primary chloride **7g**, which upon treatment with *t*BuOK in refluxing dioxane gave the tetracyclic isopavine **9g** by means of a highly diastereoselective [1,2]-Stevens rearrangement of the azocinium ion **8g**.

The X-ray crystal structure[19] of the corresponding 3,8-difluoro analogue **9j** confirmed the expected course of the [1,2]-Stevens rearrangement and the correct "morphine-like" orientation of the lone pair of electrons on the nitrogen atom. The corresponding six-membered analogues **9i** and **9k** were also prepared. Contrary to the results observed with the 13-alkyl azocines (**1a**–**h**), the rearrangement of the tetracyclic analogues **1g**–**k** afforded only the products that correspond to the isopavine B skeleton (Scheme 5). In these cases, the most favorable trajectory for recombination involves the C-5 benzylic anion or radical following pathway b, rather than the C-7 counterpart (pathway a).

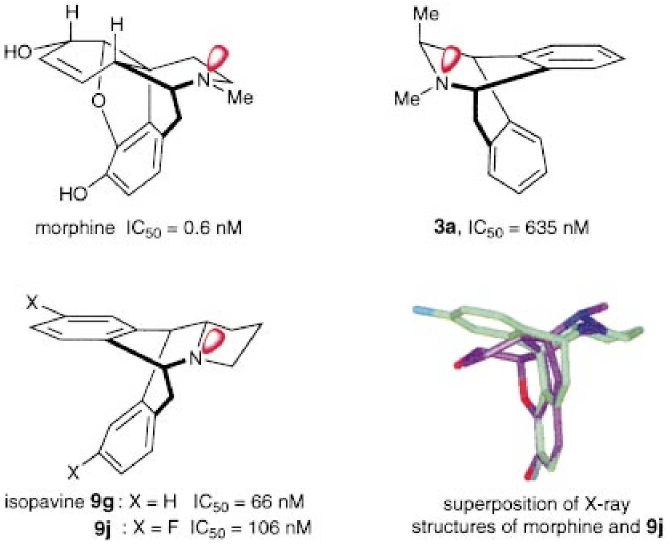
Our optimism in the quest towards a novel morphinomimetic was rewarded by the realization that the prototypical analogue **9g** showed an IC_{50} value of 60–66 nM against the human μ-opioid receptor (morphine, $IC_{50} = 0.6–1$ nM), with interesting selectivity ($IC_{50} = 6113$ nM for κ and 8226 nM for δ, compared to morphine, $IC_{50} = 169$ and 146 nM, respectively).[20] Figure 2 illustrates the spatial relationship between morphine and the tetracyclic type B isopavines **9g** and **9j**, including the orientation of the lone pair of electrons on the nitrogen atom. The piperidine analogue **9i** (Scheme 4) showed an IC_{50} value of 264 (μ receptor). The type A isopavine **3a** ($IC_{50} = 635$ nM) is, in fact, spatially related to the enantiomer of morphine ($IC_{50} = >100$ nM). Clearly, further elaboration of the type B isopavine struc-



Scheme 4. Synthesis of tetracyclic isopavine analogues of type B.



Scheme 5. [1,2]-Stevens rearrangement, which leads to isopavine type B via dianion (or diradical) intermediates.



morphine IC$_{50}$ = 0.6 nM

3a, IC$_{50}$ = 635 nM

isopavine **9g**: X = H IC$_{50}$ = 66 nM
9j : X = F IC$_{50}$ = 106 nM

superposition of X-ray structures of morphine and **9j**

Figure 2. Relationship of isopavine **9g**, **9j**, and **3a** to morphine, and IC$_{50}$ values for the human μ-opioid receptor.

ture by introducing anionic sites of interaction as in morphine, augurs well for increased morphinomimetic activity and selectivity.

The highly diastereoselective [1,2]-Stevens rearrangements outlined in this paper represent rare examples of applications of this venerable reaction to the synthesis of pharmacologically interesting compounds.[13] The discovery of promising morphine-like activity against the opioid receptor was achieved through an appreciation of the unique topologies of isopavines A and B, and the consequences of structure-based chemical design.

Experimental Section

Iodomethane (0.280 mL, 4.5 mmol, 15 equiv) was added to a solution of azocine **1a** (70.5 mg, 0.3 mmol, 1 equiv) in dry acetone (2 mL) at room temperature. The mixture was stirred at reflux for 1 h. Evaporation of solvent and excess iodomethane gave the desired azocinium salt. The crude azocinium salt was diluted in dry 1,4-dioxane (7 mL) and potassium *tert*-butoxide (101 mg, 0.9 mmol, 3 equiv) was added. The mixture was heated at 80 °C for 1 h. After diluting with water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography to give the desired isopavine **3a** in 85 % yield. M.p. 103–104 °C (ethyl acetate); $[\alpha]_D^{20} = -119$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.15$ (d, ^3J(H,H) = 6.3 Hz, 3H; CH_3), 2.68 (s, 3H; CH_3), 2.94 (dd, ^3J(H,H) = 3.3 and 18.1 Hz, 1H; CH), 3.21 (q, ^3J(H,H) = 6.3 Hz, 1H; CH), 3.59 (s, 1H; CH), 3.80 (dd, ^3J(H,H) = 3.3 and 18.1 Hz, 1H; CH), 4.10 (t, ^3J(H,H) = 3.3 Hz, 1H; CH), 7.05–7.25 (m, 8H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 22.6$, 31.7, 40.1, 54.0, 61.6, 62.7, 124.7, 125.6, 126.2, 126.3, 126.4, 127.1, 127.4, 131.0, 134.8, 138.8, 140.2, 143.7; HR-MS (peak matching, MAB (metastable atom bombardment)), calcd for [M^+]: 249.15175, found: 249.15059.

Thionyl chloride (0.073 mL, 1 mmol, 2 equiv) was added to a solution of the azocine **1g** (139.5 mg, 0.5 mmol, 1 equiv) in dry benzene (5 mL), and the mixture was heated at reflux for 1 h. Evaporation of the solvent gave the corresponding chloride in quantitative yield as an amorphous solid. The chloride was dissolved in dry 1,4-dioxane (10 mL), potassium *tert*-butoxide (168 mg, 1.5 mmol, 3 equiv) was added, and the mixture was heated at 80 °C for 1 h. Water was then added, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (chloroform/methanol 85:15) to give the desired isopavine **9g** in 77 % yield. $[\alpha]_D^{20} = +180$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): $\delta = 1.22$ (m, 1H; CH), 1.50 (m, 1H; CH), 1.62 (m, 1H; CH), 1.73 (m, 1H; CH), 2.64 (d, ^3J(H,H) = 17.8 Hz, 1H; CH), 2.70 (ddd, ^3J(H,H) = 5.5; 8.1 and 10.6 Hz, 1H; CH), 2.82 (dd, ^3J(H,H) = 7.2 and 11.2 Hz, 1H; CH), 3.47 (dd, ^3J(H,H) = 4.6 and 17.8 Hz, 1H; CH), 3.52 (d, ^3J(H,H) = 3 Hz, 1H; CH), 3.72 (ddd, ^3J(H,H) = 3.0; 6.3 and 9.5 Hz, 1H; CH), 4.20 (dd, ^3J(H,H) = 1.7 and 4.6 Hz, 1H; CH), 6.80 (m, 1H; CH), 6.82–7.05 (m, 7H; CH); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 24.1$, 26.8, 33.3, 46.2, 50.5, 55.4, 61.7, 122.7, 122.7, 123.1, 124.0, 124.1, 124.3, 127.6, 128.7, 132.9, 136.9, 138.7, 140.1; HR-MS (peak matching, MAB), calcd for [M^+]: 261.15175, found: 261.15216.

Experimental details for the synthesis of **1a**, **1g**, **3b**–**h**, **6**, **9j**, **9i**, and **9k** are found in the Supporting Information.

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A New Screen for Combinatorial Catalysis; On-Bead Testing in Agarose Gel[**]

Michael Müller, Trevor W. Mathers, and
Anthony P. Davis[*]

Catalyst discovery through combinatorial chemistry is under study in many laboratories.[1] Much of this work involves small- to medium-sized libraries, synthesized in parallel and tested in compartmentalized apparatus.[2] There are still rather few methods for screening the very large, bead-bound libraries accessible through "split-and-mix" synthesis.[3] Realistically, such libraries must be screened visually under conditions that allow picking of active beads. Visual screening for catalysis is nontrivial, given that starting materials and products can diffuse freely between beads. Published solutions rely on a) thermographic screening,[4] b) test reactions that give insoluble, colored products,[5] c) bead-bound indicators,[6] or d) screening for reactivity, as an indicator of potential catalytic properties.[7] A very recent method developed by Miller et al. employs a gel, covalently bonded to a fluorescent indicator, formed by polymerization around the library beads.[8]

Herein we report an alternative gel-based protocol for screening for bead-bound catalytic activity in aqueous media.

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