Controlling Stereoselection in Aza-Cope–Mannich Reactions

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Abstract. The synthesis of 2-substituted *cis*-octahydroindolones from the reaction of *cis*-2-amino-1-alkenylcyclopentanols with aldehydes was studied to examine whether stereoselection in the aza-Cope–Mannich reaction could be controlled by the nature of the nitrogen substituent. 2-Alkylamino-1-(1- phenylethenyl)cyclopentanols **7** and **8**, which contain nitrogen substituents of widely differing size (Me and $CHPh_2$), were condensed with four aldehydes to give oxazolidines **9a–d** and **10a–c**. Rearrangement of these intermediates at 23–60 °C, in the presence of 0.9 equiv of (±)-10-camphorsulfonic acid in acetonitrile, gave *cis*-octahydroindolones **11a–d** and **12a–c** in yields of 77–95%. Using a combination of single-crystal X-ray crystallography, ^{1}H nOe measurements, and comparisons with known materials it was established that the *N*-methyl oxazolidines **9a–d** provided exclusively *cis*-octahydroindolones having the 2-substituent trans to the angular substituents, while *N*-benzhydryl analogs **10a–c** provided exclusively the all-cis products **12a–c**. These results are interpreted to mean: (1) When the nitrogen substituent is small (Me), the stereochemistry-determining [3,3]-sigmatropic rearrangement occurs preferentially through a transition-state topography having the R^2 substituent oriented quasi-equatorially (**14** → **15** → **16**); (2) When this substituent is large ($CHPh_2$), destabilizing steric interactions between the vicinal R^1 and R^2 substituents causes the rearrangement to occur preferentially through the alternate iminium ion stereoisomer (**17** → **18** → **19**).

INTRODUCTION

The aza-Cope–Mannich reaction is a powerful reaction for assembling nitrogen heterocycles.[1] Key features of this transformation can be illustrated by the reactions depicted in Fig. 1. Acid-promoted condensation of an acyclic homoallylic amine containing an allylic hydroxyl (or alkoxyl) group with an aldehyde or ketone forms a 3-acylpyrrolidine (e.g., **1** → **2**).[2] When the amine and alcohol substituents are vicinally positioned on a ring, the aza-Cope–Mannich reaction affords a product in which pyrrolidine annulation is coupled with a one-carbon ring-expansion (e.g., **3** → **4**).[3] The mild conditions of the aza-Cope–Mannich transformation have allowed this reaction to be extended to more functionalized substrates, as illustrated in the conversion of bicyclononylamine **5** to **6**, which was the penultimate step in a short synthesis of the *Aspidosperma* alkaloid (±)-16-methoxytabersonine.[4] The constructions of *cis*-octahydroindolone **4** and pentacycle **6** also illustrate the high stereoselectivity that is typically realized in the synthesis of nitrogen heterocycles by the aza-Cope–Mannich reaction. We have employed this versatile reaction as the central strategic element in total syntheses of more than 15 alkaloids, most recently (–)-strychnine.[5]

The stereochemical outcome of aza-Cope–Mannich reactions typically can be rationalized, and more importantly, readily predicted from the preference for the sigmatropic reorganization to occur through a chair topography, and, in the case of aldehyde-derived iminium ions, from preferential rearrangement of *E* iminium ion stereoisomers.[1,3] These features are illustrated in Fig. 2 for the formation of *cis*-octahydroindolone **4** from aminocyclopentanol **3**.

During the recent development of our asymmetric synthesis of opium alkaloids,[6] we demonstrated that the stereochemical outcome of iminium ion–vinylsilane cyclizations could be controlled by the size of the nitrogen substituent.[7] If similar control could be realized in aza-Cope–Mannich reactions, the scope of this latter reaction would be expanded. The synthesis of 2-substituted

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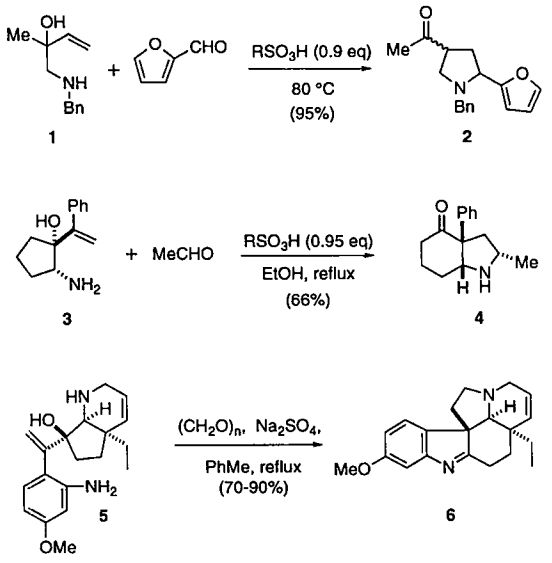


Fig. 1. Representative aza-Cope–Mannich reactions.

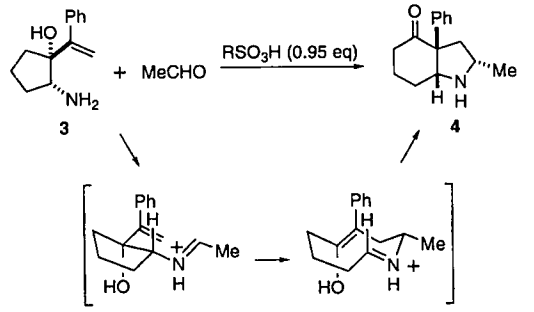
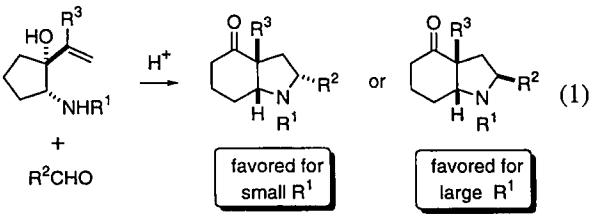


Fig. 2. Stereochemical analysis of the formation of **4**.

cis-octahydroindolones from condensation of *cis*-2-amino-1-alkenylcyclopentanols with aldehydes was chosen as an appropriate arena for examining this possibility. We report herein that either stereoisomer of a 2-substituted *cis*-octahydroindolone can be obtained depending on the size of the nitrogen substituent (eq 1).



(1)

RESULTS

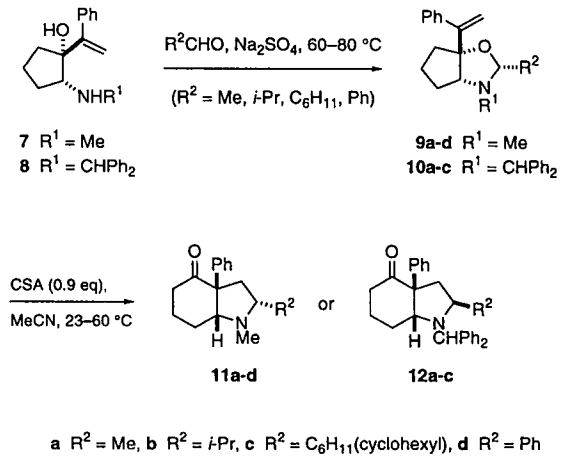
Aza-Cope–Mannich Rearrangement of Oxazolidines 9 and 10 in Acetonitrile

2-Alkylamino-1-(1-phenylethenyl)cyclopentanols **7** and **8**, which contain nitrogen substituents of widely differing size, were prepared from cyclopentene using a slight modification of our previously reported procedures.[3] These intermediates were condensed with four representative aldehydes (acetaldehyde, isobutyraldehyde, cyclohexanecarboxaldehyde, and benzaldehyde) at 60–80 °C in the presence of Na_2SO_4 to form the corresponding oxazolidines **9** or **10** (Scheme 1). Yields were excellent with all four aldehydes when the amino alcohol component was **7** (Table 1). An acid scavenger (K_2CO_3) was employed in the preparation of **9a**, since in its absence aza-Cope–Mannich rearrangement of this oxazolidine occurred at a rate competitive with its formation. In contrast, oxazolidines derived from amino alcohol **8** containing the bulky benzhydryl nitrogen protecting group were much more difficult to form. Cyclohexanecarboxaldehyde and isobutyraldehyde re-

Table 1. Formation of oxazolidines **9a–d** and **10a–c**

Amino alcohol	R^2CHO	Rxn. conds.	Oxazolidine	Yield
7	MeCHO	60 °C, 30 min[a]	**9a**	94%
7	*i*-PrCHO	80 °C, 36 h[b]	**9b**	92%
7	$C_6H_{11}CHO$	80 °C, 5 d[c]	**9c**	87%
7	PhCHO	80 °C, 48 h[c]	**9d**	95%
8	MeCHO	80 °C, 24 h[b]	**10a**[d]	92%
8	*i*-PrCHO	80 °C, 9 d[b]	**10b**	83%
8	$C_6H_{11}CHO$	80 °C, 10 d[c]	**10c**	23%[e]
8	PhCHO	no reaction[f]		

[a]Na_2SO_4 (1.5 equiv), K_2CO_3 (0.02 equiv), MeCHO (100 equiv). [b]Na_2SO_4 (1.5 equiv), RCHO (100 equiv). [c]Na_2SO_4 (1.5 equiv), PhMe (0.1M), RCHO (5 equiv). [d]Isolated as an inseparable mixture of diastereomers. [e]51% based on consumed **8**. [f]No reaction with benzaldehyde, benzaldehyde dimethyl acetal, or *N*-benzylidenemethylamine.

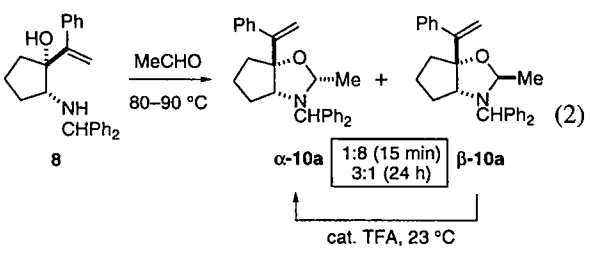


a R^2 = Me, b R^2 = *i*-Pr, c R^2 = C_6H_{11}(cyclohexyl), d R^2 = Ph

Scheme 1

acted only sluggishly with **8,** while benzaldehyde failed to condense with this amino alcohol under any of the conditions examined.

Oxazolidines **9** and **10** were produced as largely one stereoisomer (>90% by ^{1}H NMR analysis). In the case of **10a**, where the reaction of **8** and acetaldehyde occurred readily, both stereoisomeric oxazolidines could be detected. When the condensation of **8** with acetaldehyde was terminated after 15 min at 90 °C, stereoisomers **α-10a** and **β-10a** were produced in a ratio of 1:8 α:β (eq 2). Allowing this reaction to take place for 24 h at 80 °C provided **α-10a** as the predominant stereoisomer (3:1 α:β). That the α stereoisomer was the thermodynamic product was confirmed by the nearly complete isomerization of **β-10a** → **α-10a** when **β-10a** was exposed to a catalytic amount of trifluoroacetic acid at room temperature.[8] The stereochemical assignments for **α-10a** and **β-10a** followed from ^{1}H nOe measurements, which are summarized in Fig. 3. Other oxazolidines for which only a single stereoisomer was detected at long reaction times are accordingly assigned the α stereochemistry.



Aza-Cope–Mannich rearrangements of oxazolidines **9a–d** and **10a–c** were carried out under identical conditions in the presence of 0.9 equiv of (±)-10-camphorsulfonic acid (CSA) in acetonitrile (Scheme 1). After purification on silica gel, *cis*-octahydroindolones **11a–d** and **12a–c** were isolated in yields of 77–95% (Table 2). In each case, only a single stereoisomeric product could be detected by 500 MHz ^{1}H NMR analysis of the crude cyclization reaction mixture. We were able to establish by HPLC analysis that stereoselection in the formation of **12a** from benzhydryl precursor **10a** was extremely high (104:1), since the methyl epimer of this product was also available (*vide infra*). Aza-Cope–Mannich rearrangements of **10b** and **10c** were best conducted at room temperature since products **12b** and **12c**

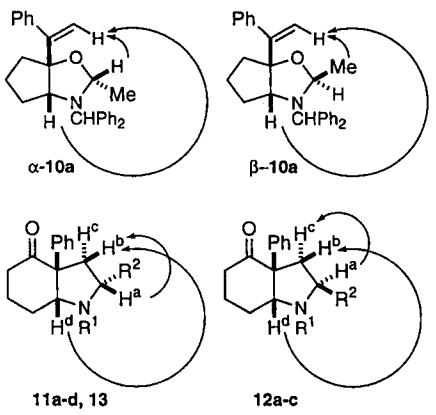


Fig. 3. Representative ^{1}H nOe enhancements.

Table 2. Formation of *cis*-octahydroindolones **11a–d** and **12a–c**

Amino alcohol	R^2	Rxn. Conds.[a]	Octahydroindolone	Yield
9a	Me	60 °C, 24 h	**11a**	92%
9b	*i*-Pr	60 °C, 24 h	**11b**	91%
9c	C_6H_{11}	60 °C, 36 h	**11c**	91%
9d	Ph	60 °C, 40 h	**11d**	95%
10a	Me	60 °C, 40 h	**12a**	92%
10b	*i*-Pr	23 °C, 3 d	**12b**	77%[b]
10c	C_6H_{11}	23 °C, 12 d	**12c**	87%

[a]MeCN (0.035 M), CSA (0.9 equiv). [b]97% based on consumed **10b**.

Table 3. Diagnostic ^{1}H NMR data for *cis*-octahydroindolone products[a]

compd	R^1	R^2	H^a	H^b	H^c	H^d	R^1
11a	Me	Me	[b]	2.77 (dd; 5.4, 12.8)	[b]	3.18 (s)	2.20 (s)
11b	Me	*i*-Pr	2.20 (m)	2.95 (dd; 6.7, 13.3)	1.45 (dd; 10.1, 13.3)	3.14 (s)	2.15 (s)
11c	Me	C_6H_{11}	2.35 (m)	2.99 (dd; 6.6, 13.2)	1.46 (dd; 10.4, 13.2)	3.12 (s)	2.15 (s)
11d	Me	Ph	3.28 (dd; 6.4, 10.3)	3.13 (dd; 6.4, 13.2)	1.99 (dd; 10.4, 13.1)	3.33 (m)	2.08 (s)
12a	$CHPh_2$	Me	3.36 (m)	3.05 (dd; 8.1, 13.0)	1.54 (dd; 6.0, 13.0)	4.13 (dd; 3.4, 6.6)	5.05 (s)
12b	$CHPh_2$	*i*-Pr	3.16 (ddd; 3.3, 6.9, 9.0)	2.74 (dd; 9.0, 13.3)	1.70 (dd; 6.9, 13.3)	4.28 (dd; 2.7, 7.4)	5.13 (s)
12c	$CHPh_2$	C_6H_{11}	3.07 (m)	2.71 (dd; 9.4, 13.4)	[b]	4.22 (m)	5.06 (s)
13	$CHPh_2$	Me	2.93 (m)	2.65 (dd; 4.7, 12.8)	1.76 (dd; 9.9, 12.8)	3.77 (m)	5.13 (s)

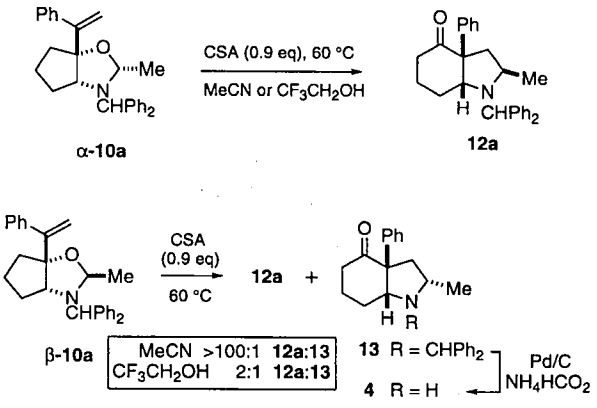
[a]Hydrogen assignments are shown in Fig. 3; data are presented in the following format: δ ppm (multiplicity; *J* values in Hz). [b]Signals for these hydrogens were obscured by other signals.

suffered partial loss of the benzhydryl group when these reactions were carried out at 60 °C.

It was readily established that rearrangement of *N*-methyl oxazolidines **9a–d** provided *cis*-octahydroindolones **11a–d** having the 2-substituent trans to the angular substituents, while *N*-benzhydryl analogs **10a–c** provided the all-cis products **12a–c**. Octahydroindolone **11a** had been prepared before and shown to have a trans relationship of the methyl and angular substituents.[3] Single crystal X-ray analysis confirmed the all-cis stereochemistry of octahydroindolone **12b**. The stereostructure of the remaining *cis*-octahydroindolones was established by ^{1}H nOe measurements, after ^{1}H-^{1}H COSY experiments were employed to fully assign the ^{1}H NMR spectra.[9] Representative nOe data are presented in Fig. 3, while ^{1}H NMR assignments are summarized in Table 3.

Independent Rearrangement of Oxazolidines α-10a and β-10a

Since oxazolidine **10a** could be obtained enriched in either methyl epimer, we had the opportunity to explore whether or not oxazolidine stereochemistry influences the stereochemical outcome of the aza-Cope–Mannich rearrangement. When acetonitrile was employed as solvent, samples of **10a** enriched in either the α (3:1 α:β) or β epimer (1:8 α:β) provided exclusively (>100:1) *cis*-octahydroindolone **12a** (Scheme 2). That this outcome arose from the α and β oxazolidine epimers interconverting more rapidly than they rearranged to **12a** was suggested when the rearrangement of **β-10a** (1:3.6 α:β) was terminated after 2 h to give 50% of **12a** and 46% of **α-10a** (>19:1 α:β). In contrast, when aza-Cope–Mannich rearrangements of **10a** were carried out at 60 °C in trifluoroethanol, **β-10a** (1:3.5 α:β) provided **12a** and its methyl epimer **13** in a 1.5:1 ratio, while **α-10a** (10:1 α:β) provided **12a** exclusively. Analysis of these results, and results of rearrangements of three additional epimeric mixtures (see Experimental Section), suggests that: (a) aza-Cope–Mannich rearrangements of **α-10a** and **β-10a** in trifluoroethanol at 60 °C occur faster than oxazolidine equilibration, (b) epimer **β-10a** rearranges to **12a** at twice the rate it is converted to **13**, and (c) epimer **α-10a** rearranges to **12a** exclusively.

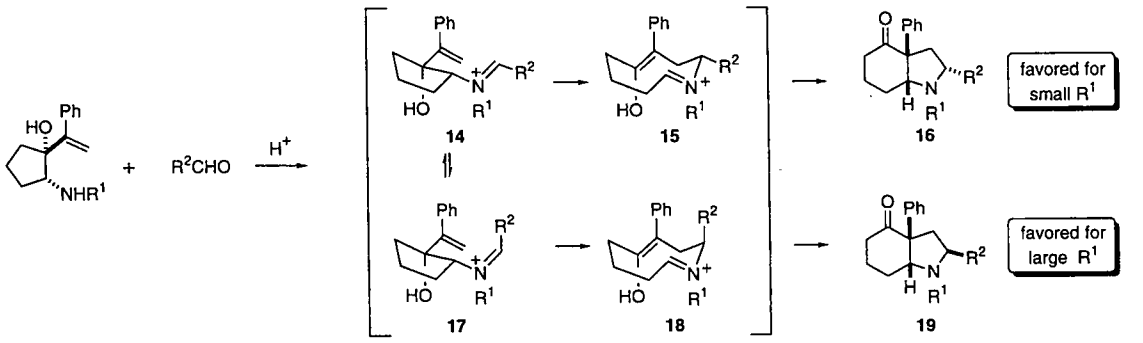


Scheme 2

DISCUSSION

This study demonstrates that the stereochemical outcome of aza-Cope–Mannich rearrangements of aldehyde-derived iminium ions can be controlled by the size of the substituent on nitrogen. As summarized in Scheme 3, when the nitrogen substituent is small (Me), the stereochemistry-determining [3,3]-sigmatropic rearrangement occurs preferentially through a transition-state topography having the R^2 substituent oriented quasi-equatorially.[3] However, when this substituent is large ($CHPh_2$), destabilizing steric interactions between the vicinal R^1 and R^2 substituents are sufficient to raise the energy of the **14** → **15** transition state such that rearrangement occurs preferentially through the alternate iminium ion stereoisomer: **17** → **18** → **19**.[10]

The disparate stereochemical outcome observed in aza-Cope–Mannich rearrangements of the epimers of



Scheme 3

oxazolidine **10a** in trifluoroethanol requires brief comment. Apparently in this non-nucleophilic protic solvent, [3,3]-sigmatropic rearrangement occurs at a rate comparable to the rate of interconversion of iminium ion stereoisomers. This being the case, a stereoelectronic preference for forming a specific iminium stereoisomer from an oxazolidine precursor would affect the stereochemical outcome of the aza-Cope–Mannich process. Fragmentation of an oxazolidine to an iminium cation requires an antiperiplanar orientation of the nitrogen non-bonded electron pair and the C–O σ-bond.[10] We evaluated the relative energies of conformers of α- and β-**10a** that would have the proper orientation for fragmentation by molecular mechanics calculations using the MM2* force field and fixing the dihedral angle between the nitrogen non-bonded electron pair and the C–O σ bond at 180 ± 5°.[11,12] These calculations reveal that for oxazolidine α-**10a**, conformer **A** depicted in Fig. 4 (which would fragment to iminium ion **17**, R^1 = $CHPh_2$, R^2 = Me) is favored by 6 kcal/mol over the lowest energy conformers having the correct orientation for fragmentation to the alternate iminium ion stereoisomer.[13] Thus, rearrangement of this oxazolidine stereoisomer proceeds directly as observed along the **17** → **18** → **19** pathway. On the other hand, the minimum energy conformations of oxazolidine β-**10a** that would lead to stereoisomeric iminium ions (Fig. 4, **B** and **C**) are close in energy. We propose that this oxazolidine epimer fragments to form both iminium ion stereoisomers, and in trifluoroethanol the rate of [3,3]-sigmatropic rearrangement is competitive with iminium ion interconversion, which results in the formation of both **12a** and **13**.

EXPERIMENTAL

rel-(2R,3aR,6aR)-Hexahydro-2,3-dimethyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole (9a)

A mixture of acetaldehyde (7.8 mL, 140 mmol), **7** (302 mg, 1.39 mmol), Na_2SO_4 (300 mg, 2.1 mmol), and K_2CO_3 (38 mg, 0.28 mmol) was placed in a sealed tube and heated to 60 °C for 30 min. Upon cooling to rt, the mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel chromatography (sgc, 5% MeOH–CH_2Cl_2) to yield 317 mg (94%) of **9a** as a light yellow oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 5.43 (d, J = 1.3 Hz, 1 H), 5.09 (d, J = 1.3

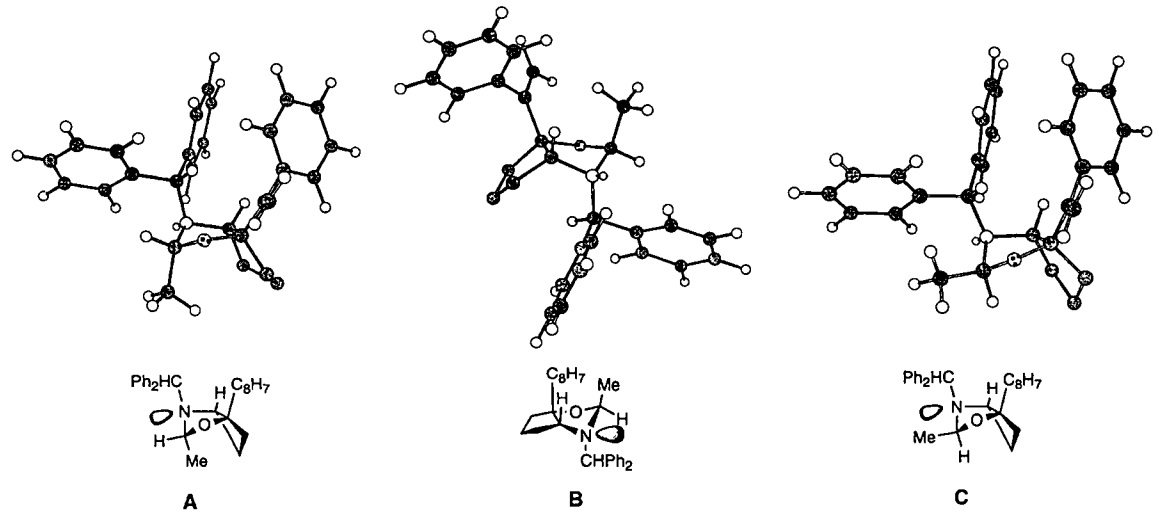


Fig. 4. Conformations for iminium ion formation.

Hz, 1 H), 3.91 (q, J = 5.1 Hz, 1 H), 3.15 (d, J = 5.6 Hz, 1 H), 2.30 (s, 3 H), 2.00–1.80 (m, 2 H), 1.80–1.50 (m, 3 H), 1.45–1.25 (m, 1 H), 1.2 (d, J = 5.1 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 152.2, 141.4, 128.5, 127.8, 127.0, 113.3, 92.7, 91.6, 74.1, 39.9, 37.6, 33.3, 24.0, 18.7; IR (film) 1626 cm^{-1}; HRMS (CI, isobutane) *m/z* 244.1708 (244.1701 calcd for $C_{16}H_{22}NO$, MH).

rel-*(2R,3aR,6aR)-Hexahydro-2-isopropyl-3-methyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole* ***(9b)***.

General Procedure A

A mixture of amine **7** (75 mg, 0.35 mmol), isobutyraldehyde (2.0 mL, 22 mmol) and Na_2SO_4 (75 mg, 0.53 mmol) was maintained at 80 °C for 36 h in a sealed tube. The resulting mixture was cooled to rt, filtered through a cotton plug, and the filtrate was concentrated. Purification of the residue by sgc (9:1:0.1 hexane–EtOAc–Et_3N) gave 87 mg (92%) of **9b** as a light yellow oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5 H), 5.41 (d, J = 1.7 Hz, 1 H), 5.05 (d, J = 1.7 Hz, 1 H), 3.67 (d, J = 2.1 Hz, 1 H), 3.12 (d, J = 5.5 Hz, 1 H), 2.23 (s, 3 H), 2.00–1.20 (m, 7 H), 0.97 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 152.6, 141.6, 128.7, 127.7, 126.9, 113.0, 99.0, 92.0, 74.2, 39.5, 37.6, 33.5, 29.4, 24.2, 19.0, 14.2; IR (film) 1626 cm^{-1}; HRMS (CI, isobutane) *m/z* 272.2012 (272.2014 calcd for $C_{18}H_{26}NO$, MH).

rel-*(2R,3aR,6aR)-Hexahydro-2-cyclohexyl-3-methyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole* ***(9c)***.

General Procedure B

A mixture of amine **7** (350 mg, 1.61 mmol), cyclohexanecarboxaldehyde, 980 μL, 8.0 mmol, 5.0 equiv), Na_2SO_4 (350 mg, 2.4 mmol, 1.5 equiv), and PhMe (8 mL) was heated at 80 °C for 5 d. After cooling to rt, the mixture was filtered through a cotton plug and the filtrate was concentrated to yield a light yellow oil. Purification of this residue by sgc (19:1:0.1 hexane–EtOAc–Et_3N) gave 434 mg (87%) of **9c** as a pale yellow oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 5.40 (d, J = 1.7 Hz, 1 H), 5.04 (d, J = 1.8 Hz, 1 H), 3.65 (d, J = 2.0 Hz, 1 H), 3.11 (d, J = 5.5 Hz, 1 H), 2.24 (s, 3 H), 1.95–1.15 (m, 17 H); ^{13}C (75 MHz, $CDCl_3$) δ 152.5, 141.6, 128.7, 127.7, 126.9, 113.0, 98.9, 92.2, 74.1, 39.7, 39.4, 37.9, 33.6, 29.8, 26.9, 26.8, 26.3, 25.0, 24.1; IR (film) 1626 cm^{-1}; HRMS (CI, isobutane) *m/z* 312.2329 (312.2327 calcd for $C_{21}H_{30}NO$, MH).

Other oxazolidines were prepared by either procedure A or B using reaction conditions described in Table 1.

rel-*(2R,3aR,6aR)-Hexahydro-3-methyl-2-phenyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole* ***(9d)***

95% (procedure A), a light yellow oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.60–7.20 (m, 10 H), 5.5 (d, J = 1.3 Hz, 1 H), 5.14 (d, J = 1.2 Hz, 1 H), 4.64 (s, 1 H), 3.29 (d, J = 5.1 Hz, 1 H), 2.2–2.0 (m, 2 H), 2.19 (s, 3 H), 1.85–1.6 (m, 3 H), 1.5–1.3 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 151.8, 141.2, 138.4, 129.0, 128.5, 128.1, 127.9, 127.6, 126.9, 113.4, 96.7, 93.5, 73.3, 39.6, 36.6, 33.2, 24.2; IR (film) 1626 cm^{-1}; HRMS (CI, isobutane) *m/z* 306.1861 (306.1858 calcd for $C_{21}H_{24}NO$, MH). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.35; H, 7.67; N, 4.56.

rel-*(2R,3aR,6aR)-Hexahydro-3-diphenylmethyl-2-isopropyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole* ***(10b)***

83% (procedure A, unconsumed **8** was recovered in 10%), a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.40–7.10 (m, 15 H), 5.38 (s, 1 H), 5.15 (s, 1 H), 4.87 (s, 1 H), 4.30 (d, J = 1.4 Hz, 1 H), 3.65 (dd, J = 3.1, 8.0 Hz, 1 H), 2.10–0.85 (m, 7 H), 0.95 (d, J = 5.9 Hz, 3 H), 0.69 (d, J = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 152.2, 143.8, 143.1, 141.3, 128.7, 128.6, 128.5, 128.3, 128.0, 127.7, 127.1, 126.9, 126.8, 113.8, 99.9, 92.8, 73.0, 69.7, 39.4, 35.1, 31.1, 24.1, 19.1, 14.5; IR (film) 1599 cm^{-1}; HRMS (CI, isobutane) *m/z* 424.2622 (424.2640 calcd for $C_{30}H_{34}NO$, MH).

rel-*(2R,3aR,6aR)-Hexahydro-2-cyclohexyl-3-diphenyl-methyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole* ***(10c)***

23% (procedure B, unconsumed **8** was recovered in 55%); colorless crystals (an analytical sample was obtained by recrystalization from hexanes–EtOAc, mp 108–110 °C): ^{1}H (300 MHz, $CDCl_3$) δ 7.50–7.00 (m, 15 H), 5.35 (d, J = 1.5 Hz, 1 H), 5.14 (d, J = 1.5 Hz, 1 H), 4.84 (s, 1 H), 4.26 (d, J = 3.0 Hz, 1 H), 3.63 (dd, J = 3.5, 8.1 Hz, 1 H), 3.30–0.50 (m, 17 H); ^{13}C (75 MHz, $CDCl_3$) δ 152.2, 143.8, 143.2, 141.4, 128.7, 128.5, 128.4, 128.3, 128.0, 127.7, 127.1, 126.9, 126.7, 113.8, 99.6, 92.9, 73.2, 69.5, 41.3, 39.4, 35.1, 29.7, 26.7, 26.3, 25.2, 24.1; IR (film) 1598 cm^{-1}; HRMS (CI, isobutane) *m/z* 464.2955 (464.2953 calcd for $C_{33}H_{38}NO$, MH). Anal. Calcd for $C_{33}H_{37}NO$: C, 85.49; H, 8.04; N, 3.02. Found: C, 85.37; H, 8.07; N, 3.00.

rel-*(2R,3aR,6aR)-Hexahydro-3-diphenylmethyl-2-methyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole (α-10a) and* rel-*(2S,3aR,6aR)-Hexahydro-3-diphenylmethyl-2-methyl-6a-(1-phenylethenyl)-2H-cyclopentoxazole (β-**10a**)*

Following procedure A, a mixture of **8** (187 mg, 0.50 mmol), acetaldehyde (1.0 mL, 18 mmol), and Na_2SO_4 (110 mg, 0.75 mmol) was allowed to react at 80 °C for 1 d in a sealed tube to give 182 mg (92%) of a colorless oil, which ^{1}H NMR analysis showed was a 3:1 ratio of the inseparable oxazolidines **α-10a and β-10a**.

Heating a mixture of **8** (249 mg, 0.670 mmol), acetaldehyde (1.5 mL, 27 mmol) and Na_2SO_4 (150 mg, 1 mmol) at 90 °C for 15 min in a sealed tube gave, after sgc (19:1:0.1 hexane–EtOAc–Et_3N), a light yellow oil that ^{1}H NMR analysis showed to be a 1:8 mixture of oxazolidines **α-10a** and **β-10a**. NMR signals for the major isomer **β-10a** could be readily discerned from this mixture: ^{1}H (300 MHz, C_6D_6) δ 7.60–7.00 (m, 15 H), 5.69 (d, J = 2.0 Hz, 1 H), 5.17 (d, J = 2.0 Hz, 1 H), 4.69 (q, J = 5.4 Hz, 1 H), 4.55 (s, 1 H), 3.87 (dd, J = 4.5, 7.9 Hz, 1 H), 2.10–1.95 (m, 1 H), 1.80–1.70 (m, 1 H), 1.65–1.55 (m, 2 H), 1.20–1.05 (m, 1 H), 1.00–0.90 (m, 1 H), 0.87 (d, J = 5.4 Hz, 3 H); ^{13}C (75 MHz, C_6D_6) δ 154.0, 144.4, 144.2, 142.6, 129.2, 129.0, 128.8, 128.6, 128.5, 127.4, 127.2, 127.0, 113.9, 91.9, 91.7, 69.7, 69.2, 39.2, 30.2, 27.1, 24.7, 21.9; IR (film) 1599 cm^{-1}; HRMS (CI, isobutane) *m/z* 396.2324 (396.2327 calcd for $C_{28}H_{30}NO$, MH).

Treatment of this 1:8 mixture of **α-10a** and **β-10a** (950 mg, 2.4 mmol) with a catalytic amount of trifluoroacetic acid (~5 μL) in $CHCl_3$ (90 mL) at rt for 24 h yielded 943 mg of a

>19:1 mixture of α-**10a** and β-**10a**, respectively, as a colorless oil: ^{1}H (500 MHz, C_6D_6) δ 7.40–6.90 (m, 15 H), 5.46 (d, *J* = 2.0 Hz, 1 H), 5.14 (d, *J* = 1.6 Hz, 1 H), 4.87 (s, 1 H), 4.71 (q, *J* = 5.2 Hz, 1 H), 3.71 (dd, *J* = 3.4, 8.2 Hz, 1 H), 2.15–2.05 (m, 1 H), 2.05–1.95 (m, 1 H), 1.85–1.75 (m, 1 H), 1.65–1.55 (m, 1 H), 1.45–1.35 (m, 1 H), 1.35–1.25 (m, 1 H), 1.10 (d, *J* = 5.2 Hz, 3 H) ^{13}C (75 MHz, $CDCl_3$) δ 152.4, 143.8, 143.1, 128.6, 128.5, 128.3, 128.2, 127.8, 127.1, 127.0, 126.8, 113.9, 93.5, 93.0, 72.7, 69.8, 39.1, 35.4, 23.8, 23.1.

rel-*(2S,3aS,7aR)-Octahydro-1,2-dimethyl-3a-phenyl-4H-indol-4-one (**11a**). General Procedure for Aza-Cope–Mannich Rearrangements*

A solution of oxazolidine **9a** (63 mg, 0.26 mmol, 1.0 equiv), (±)-10-camphorsulphonic acid (CSA, 54 mg, 0.23 mmol, 0.9 equiv), and MeCN (7.4 mL, 0.035M) was maintained at 60 °C for 24 h. After cooling to rt, CH_2Cl_2 and aqueous 1 M NaOH (20 mL each) were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (K_2CO_3), concentrated and the residue was purified by sgc (9:1:0.1, hexane–EtOAc–Et_3N) to give 58 mg (92%) of **11a** as a colorless oil. This sample showed ^{1}H and ^{13}C NMR spectra that were indistinguishable from an authentic sample.[4]

rel-*(2S,3aS,7aR)-Octahydro-2-isopropyl-1-methyl-3a-phenyl-4H-indol-4-one (**11b**)*

90% as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 5 H), 3.14 (s, 1 H), 2.95 (dd, *J* = 6.7, 13.3 Hz, 2 H), 2.4–1.6 (m, 7 H), 2.15 (s, 3 H), 1.45 (dd, *J* = 10.1, 13.3 Hz, 1 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 209.8 141.5, 128.7, 126.5, 70.5, 69.5, 61.0, 40.0, 37.7, 34.9, 28.3, 23.6, 20.9, 19.9, 15.3; IR (film) 1705 cm^{-1}; HRMS (CI, isobutane) *m/z* 272.2018 (272.2014 calcd for $C_{18}H_{26}NO$, MH).

rel-*(2S,3aS,7aR)-Octahydro-2-cyclohexyl-1-methyl-3a-phenyl-4H-indol-4-one (**11c**)*

91% as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5 H), 3.11 (s, 1 H), 2.97 (dd, *J* = 6.6, 13.2 Hz, 1 H), 2.35 (m, 1 H), 2.25–1.95 (m, 5 H), 2.15 (s, 3 H), 1.80–1.40 (m, 7H), 1.46 (dd, *J* = 10.4, 13.2 Hz, 1 H), 1.30–0.90 (m, 5 H); ^{13}C (75 MHz, $CDCl_3$) δ 209.9, 141.5, 128.7, 126.5, 70.3, 69.0, 61.2, 40.0, 39.2, 37.8, 36.0, 30.7, 26.9, 26.3, 25.7, 23.5, 21.0; IR (film) 1705 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.38; N, 4.50. Found: C, 80.73; H, 9.51; N, 4.34.

rel-*(2S,3aS,7aR)-Octahydro-1-methyl-2,3a-diphenyl-4H-indol-4-one (**11d**)*

95% as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.40–7.15 (m, 10 H), 3.33 (s, 1 H), 3.28 (dd, *J* = 6.4, 10.3 Hz, 1 H), 3.13 (dd, *J* = 6.4, 13.2 Hz, 1 H), 2.50–2.05 (m, 5 H), 2.08 (s, 3 H), 1.99 (dd, *J* = 10.4, 13.1 Hz, 1 H), 1.85–1.75 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 209.8, 143.5, 140.9, 128.8, 128.2, 127.8, 126.9, 126.7, 126.4, 70.0, 69.3, 62.1, 43.1, 39.8, 37.4, 23.5, 21.5; IR (film) 1707 cm^{-1}; HRMS (CI, isobutane) *m/z* 306.1864 (306.1858 calcd for $C_{21}H_{24}NO$, MH).

rel-*(2R,3aS,7aR)-Octahydro-1-diphenylmethyl-2-methyl-3a-phenyl-4H-indol-4-one (**12a**)*

92% as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.50–7.10 (m, 15 H), 5.05 (s, 1 H), 4.13 (dd, *J* = 3.4, 6.6 Hz, 1 H), 3.36 (m, 1H), 3.05 (dd, *J* = 8.1, 13.0 Hz, 1 H), 2.35–2.20 (m, 2 H), 2.00–1.85 (m, 1 H), 1.80–1.65 (m, 1 H), 1.54 (dd, *J* = 6.0, 13.0 Hz, 1 H), 1.5–1.35 (m, 1 H), 1.25–1.10 (m, 1 H), 0.68 (d, *J* = 6.4 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 211.9, 143.3, 142.9, 141.8, 129.3, 128.5, 128.3, 128.0, 127.8, 127.1, 126.8, 126.6, 126.5, 68.0, 66.0, 62.7, 53.9, 43.8, 38.3, 23.6, 21.3, 21.1; IR (film) 1706 cm^{-1}; HRMS (CI, isobutane) *m/z* 395.2251 (395.2249 calcd for $C_{28}H_{29}NO$, M).

rel-*(2R,3aS,7aR)-Octahydro-1-diphenylmethyl-2-isopropyl-3a-phenyl-4H-indol-4-one (**12b**)*

77% as colorless crystals (an analytical sample was obtained by recrystalization from hexanes–EtOAc, mp 147–148 °C) and 30 mg (21%) of recovered **10b**; **12b**: ^{1}H (300 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2 H), 7.40–7.15 (m, 13 H), 5.13 (s, 1 H), 4.28 (dd, *J* = 2.7, 7.4 Hz, 1 H), 3.16 (ddd, *J* = 3.3, 6.9, 9.0 Hz, 1 H), 2.74 (dd, *J* = 9.0, 13.3 Hz, 1 H), 2.27 (m, 2 H), 2.00–1.85 (m, 1 H), 1.82–1.70 (m, 1 H), 1.70 (dd, *J* = 6.9, 13.3 Hz, 1 H), 1.40–1.25 (m, 2 H), 0.93–0.80 (m, 1 H), 0.57 (d, *J* = 6.6 Hz, 3 H), 0.52 (d, *J* = 6.9 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 212.5, 143.5, 142.8, 141.3, 129.5, 128.5, 128.4, 128.0, 127.8, 127.3, 127.0, 126.7, 126.6, 68.0, 65.8, 63.5, 62.4, 37.7, 35.3, 27.7, 22.4, 20.8, 20.3, 15.5; IR (film) 1706 cm^{-1}; HRMS (CI) *m/z* 424.2645 (424.2640 calcd for $C_{30}H_{34}NO$, MH). Anal. Calcd for $C_{30}H_{33}NO$: C, 85.06; H, 7.85; N, 3.31. Found: C, 84.86; H, 7.88; N, 3.25.

rel-*(2R,3aS,7aR)-Octahydro-2-cyclohexyl-1-diphenylmethyl-3a-phenyl-4H-indol-4-one (**12c**)*

56% as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.50–7.10 (m, 15 H), 5.06 (s, 1 H), 4.22 (m, 1 H), 3.07 (m, 1 H), 2.71 (dd, *J* = 9.4, 13.4 Hz, 1 H), 2.30–2.20 (m, 2 H), 2.00–0.50 (m, 16 H); ^{13}C (75 MHz, $CDCl_3$) δ 212.6, 143.6, 143.1, 141.5, 132.4, 130.1, 129.3, 128.4, 128.3, 128.1, 127.9, 127.2, 127.1, 126.7, 126.6, 68.7, 65.9, 63.7, 62.5, 39.1, 37.4, 36.6, 30.8, 26.8, 26.7, 26.0, 25.8, 21.8, 20.6; IR (film) 1706 cm^{-1}; HRMS (CI, isobutane) *m/z* 464.2972 (464.2953 calcd for $C_{33}H_{38}NO$, MH).

*Aza-Cope–Mannich Rearrangement of Mixtures of Oxazolidines α-**10a** and β-**10a** in Trifluoroethanol. Isolation of* rel-*(2R,3aS,7aR)-Octahydro-1-diphenylmethyl-2-methyl-3a-phenyl-4H-indol-4-one (**13**)*

A solution of oxazolidines α-**10a** and β-**10a** (1:8 ratio, 49 mg, 0.12 mmol), CSA (26 mg, 0.111 mmol) and trifluoroethanol (1.9 mL, 0.07 M) was maintained at 60 °C for 2 h, cooled to rt, and concentrated. The residue was taken up in CH_2Cl_2 (20 mL), extracted with aqueous 1 M NaOH (20 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (K_2CO_3), concentrated, and the residue was purified by sgc (9:1:0.1 hexane–EtOAc–Et_3N) to give 43 mg (88%) of a 1:2.5 mixture of **12a** and **13** as a colorless oil. Isomer **13** could be isolated in pure form by repeated sgc (19:1:0.1,

hexane–EtOAc–Et_3N): ^1H (300 MHz, $CDCl_3$) δ 7.50–7.10 (m, 15 H), 5.13 (s, 1 H), 3.77 (m, 1 H), 3.00–2.85 (m, 1H), 2.65 (dd, J = 4.7, 12.8 Hz, 1 H), 2.50–2.00 (m, 5 H), 1.76 (dd, J = 9.9, 12.8 Hz, 1 H), 1.70–1.60 (m, 1 H), 0.89 (d, J = 6.3 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 211.4, 142.2, 141.2, 139.0, 129.8, 128.8, 128.7, 128.0, 127.8, 127.1, 126.7, 126.6, 67.5, 66.0, 61.7, 53.1, 42.0, 39.3, 25.2, 22.9, 21.6; HRMS (CI) *m/z* 396.2315 (396.2327 calcd for $C_{28}H_{30}NO$, MH).

Using identical conditions, a series of mixtures of oxazolidines α-**10a** and β-**10a** were submitted to cyclization in trifluoroethanol. It was found that cyclization of 1:3, 1:1, and 3.6:1 ratios of α-**10a** and β-**10a** gave **12a** and **13** in 3:1, 6:1, and 12.5:1 ratios, respectively.

Hydrogenolysis of **13** (NH_4HCO_2, Pd/C, DMF at 60 °C) gave **4** as a pale yellow oil that showed ^1H spectra indistinguishable from an authentic sample.[4]

CONCLUSION

The stereochemical outcome of aza-Cope–Mannich rearrangements of aldehyde-derived iminium ions can be controlled by the size of the substituent on nitrogen, a demonstration that expands the range of heterocycles that can be prepared in this way. These examples further confirm that the stereochemical outcome of iminium ion transformations can be modulated by proper tuning of the geometry of the iminium ion component.[7] This strategy should find many other applications in stereocontrolled synthesis of nitrogen heterocycles.

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