3-Aza-Cope Rearrangement of Quaternary *N*-Allyl Enammonium Salts. Stereospecific 1,3 Allyl Migration from Nitrogen to Carbon on a Tricyclic Template

David F. McComsey and Bruce E. Maryanoff*

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477

bmaryano@prius.jnj.com

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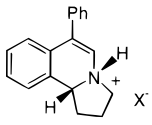
N-Allyl enamines can undergo a [3,3] sigmatropic rearrangement known as a 3-aza-Cope (or amino-Claisen) reaction. We explored a 3-aza-Cope reaction involving 1,3 allylic migration from nitrogen to carbon in *N*-allyl enammonium quaternary salts, exemplified by benzo[*a*]quinolizine **8** and pyrrolo-[2,1-*a*]isoquinoline **13**, with an interest in stereochemistry and mechanism. Salts **8** and **13** were accessed, respectively, through stereospecific allylation of hydroxy amines **4** and **11a**/**11b** to give **7** and **12a**/**12b**, which were dehydrated with trifluoroacetic acid. Allylic migration in these tricyclic tetrahydroisoquinolines occurred with high stereospecificity, with the major products **9** (from **8**) and **15a** (from **13**) apparently deriving from a concerted suprafacial [3,3] rearrangement. The rearrangement of **8** to **9** was facile at 23 °C ($t_{1/2}$ = ca. 5 h) and was >98% stereospecific, whereas the rearrangement of **13** to **15a**/**15b** required heating between 50 and 100 °C, with ca. 90−95% stereospecificity ($t_{1/2}$ = ca. 0.3 h at 100 °C). A deuterium-labeling experiment with **21** (^{2}H-**13**) confirmed that allylic inversion accompanies the 1,3 migration en route to major isomer **22a** (^{2}H-**15a**), supporting the predominance of a concerted [3,3] sigmatropic mechanism. However, the 5−10% loss of stereospecificity in the rearrangements of the pyrroloisoquinolines **13** and **21**, reflected by formation of minor isomers **15b** and **22b**, respectively, indicates a minor nonconcerted reaction pathway.

The 3-aza-Cope (or amino-Claisen) reaction, a member of the [3,3] class of sigmatropic rearrangements, occurs thermally in *N*-allyl enamine systems with varying degrees of facility depending on structural features.[1] Whereas neutral allylic enamines rearrange to δ-ene imines at rather elevated temperatures, 170−250 °C, the corresponding protonated, Lewis acid-coordinated, or quaternarized molecules tend to rearrange at considerably milder temperatures, 20−120 °C.[1] We developed an interest in the 3-aza-Cope reaction because of our studies on enammonium-iminium rearrangements with tricyclic tetrahydroisoquinoline derivatives.[2] For example, with **1** 1,3 proton migration from nitrogen to carbon yielded **2** stereospecifically, even in a reaction medium conducive to free proton exchange. We have explained this rearrangement process in terms of a "conducted-tour" mechanism involving tight ion-pairing and an inner sphere of trifluoroacetic acid that acts as a solvent cage.[2b,c] As an extension of these proton-migration studies, we decided to investigate the related 1,3 migration of an allyl group in this tricyclic system, which would provide a means of introducing a quaternary C-allyl center to obtain analogues in the pyrrolo[2,1-*a*]isoquinoline series of potent neuronal uptake inhibitors.[3] Since noteworthy biological activity for this class of inhibitor molecules was exclusive to the trans diastereomers (viz. **3**), we viewed the 3-aza-Cope process as a promising means for stereocontrolled synthesis via stereospecific allyl transfer from nitrogen to carbon. However, in reviewing the literature reports on 3-aza-Cope rearrangements of quaternary *N*-allyl enammonium salts,[4] we found that no one had ever addressed stereochemical aspects of allyl migration from the stereogenic nitrogen atom to a pro-stereogenic carbon



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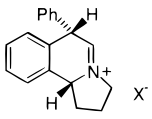

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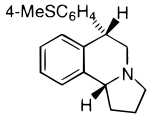

3 (McN-5652-Z)

(1) (a) For a useful overview of the 3-aza-Cope reaction, see: Walters, M. A. *J. Org. Chem.* **1996**, *61*, 978−983. (b) For a general review on aza-Cope reactions, see: Przheval'skii, N. M.; Grandberg, I. I. *Russ. Chem. Rev.* **1987**, *56*, 477−491. (c) For additional discussions, see: Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. Blechert, S. *Synthesis* **1989**, 71−82.

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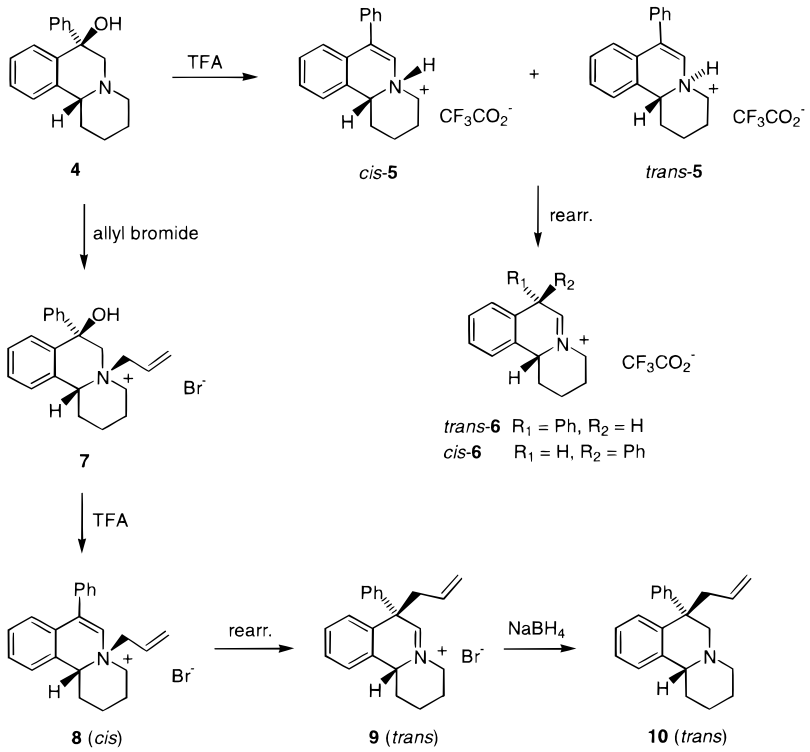
Scheme 1



atom.[5] In this context, we now describe the first 3-aza-Cope reaction associated with stereospecific 1,3 transfer of an *N*-allyl group, by using the tricyclic tetrahydroisoquinoline nucleus as a rearrangement template. Also, we report confirmation of the predominantly concerted sigmatropic nature of this [3,3] rearrangement by means of a deuterium-labeling study.

Results and Discussion

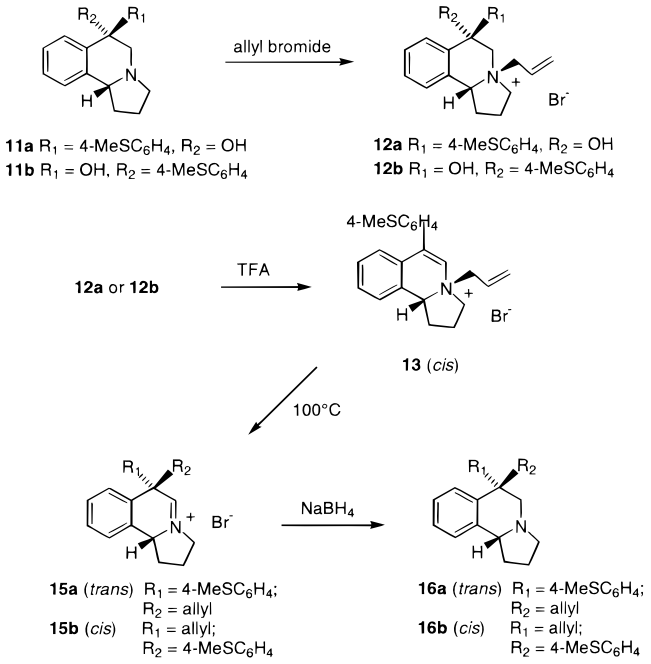
Rearrangement Reactions. Our first attempt to probe a 3-aza-Cope reaction with rearrangement of an *N*-allyl group involved the use of amino alcohol **4**, which previously[2c] was shown to undergo dehydration to enammonium salts trans-**5** and cis-**5** (25:75 ratio) followed by stereospecific 1,3 proton migration to iminium salts cis-**6** and trans-**6** (25:75 ratio) (Scheme 1). Reaction of **4** with excess allyl bromide at 23 °C occurred with essentially 100% stereoselectivity to yield a single quaternary salt, **7**, which possessed a cis-fused ring junction on the basis of ^{1}H NMR data. Of particular note were the vicinal coupling constants for H_{11b} (a doublet of doublets at δ 5.10) of 12.2 and 3.5 Hz, which are diagnostic of the so-called cis-B structural form.[6] The dehydration of **7** to **8** was effected efficiently at 23 °C with deuterated trifluoroacetic acid (TFA-*d*); after 10 min, the mixture was evaporated in vacuo to give oily **8**, which was immediately dissolved in $CDCl_3$. The cis-B stereochemistry of enammonium salt **8** was retained during the dehydration, as determined by a singlet at δ 5.99 for H_6, a doublet of doublets at δ 4.90 for H_{11b} with vicinal couplings of 12.1 and 1.0 Hz, and a multiplet at δ 3.83 for the H_4 protons.[2,6] At 23 °C, **8** rearranged slowly and cleanly to a single iminium salt, trans isomer **9**. The progress of the reaction was monitored conveniently by ^{1}H NMR and ca. 36 h were required for complete conversion, with a $t_{1/2}$ of ca. 5.0 h. The ^{1}H NMR spectrum of trans isomer **9** showed a singlet at δ 9.28 for the iminium proton H_6 (consistent with the significant downfield shift), a multiplet for H_{11b} at δ 5.25, and two H_4 protons at δ 4.70 (H_{4e}) and 4.00 (H_{4a}). Reduction of trans isomer **9** with $NaBH_4$ in ethanol occurred readily, as expected,[2] to yield a single amine product, trans isomer **10**, nicely confirming the structural assignment for trans isomer **9**. The ^{1}H NMR spectrum of the single isomer **10** showed the characteristic trans stereochemistry previously encountered,[2c,6] with a doublet of doublets at δ 2.90 and couplings of 1.2 and 7.6 Hz for the two H_6 protons and a broadened doublet at δ 2.70 for H_{4e} with a coupling of 11.3 Hz. It is significant that intramolecular rearrangement of the allylic group from N_5 to C_7 occurred from the same face to furnish *only* iminium salt **9**. This result indicates a lack of dissociation of the allyl group during the rearrangement, since dissociation would have led to a mixture of cis and trans iminium salts (and, ultimately, to a mixture of cis and trans amines (Scheme 1). Furthermore, the sole formation of trans isomer **9** strongly suggests a concerted suprafacial rearrangement.

We turned our attention to the pyrroloisoquinoline isomers **11a** and **11b** to test the effects of the five-membered ring (Scheme 2). Cis isomer **11a** was reacted with allyl bromide with essentially 100% stereoselectivity to give a single quaternary salt, **12a**, which was assigned a cis ring fusion on the basis of ^{1}H NMR data (dd for H_{10b} at δ 5.31, J = 7.9, 7.9 Hz). Dehydration with TFA gave one enammonium salt, **13**, which was nearly identi-

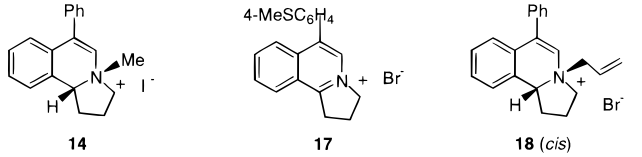
(5) Mariano and co-workers[4d–f] have reported intriguing, stereospecific 3-aza-Cope rearrangements of *N*-vinylisoquinuclidene ammonium salt, which involve the transfer of stereochemistry in allyl migration from a stereogenic nitrogen atom to a pro-stereogenic carbon atom (of an *E*-vinyl group). Unfortunately, the stereochemical information at the destination carbon atom was lost because of isomerization of the iminium species to an enamine under the reaction conditions.

(6) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. C.; Olofson, R. *J. Am. Chem. Soc.* **1989**, *111*, 2487−2496.

Scheme 2



cal by ^{1}H NMR (TFA-*d*) to the analogous, previously prepared cis-fused salt **14**.[2b] Interestingly, salt **13** rearranged much more slowly than did six-membered-ring analogue **8**, with little rearrangement being noted at 23 °C in DMSO-d_6, DMF-d_7, methanol-d_4, or chloroform-*d*; however, it did rearrange in DMSO-d_6 on heating between 50 and 100 °C. After about 2 h at 100 °C in DMSO-d_6, the rearrangement of **13** was complete and, by ^{1}H NMR, trans iminium salt **15a** was the predominant product ($t_{1/2}$ of ca. 20 min). There was also a small amount of cis isomer **15b** (ca. 5%), as suggested by a broad singlet at δ 9.55, and a minor impurity assigned as oxidized byproduct **17**, which we identified previously.[2b] The formation of these two minor components suggests some allylic dissociation, possibly caused by the higher temperature required in this less facile rearrangement. Again, the ^{1}H NMR spectrum of trans isomer **15a** was nearly identical to that of a trans iminium salt without an allyl group, which we obtained in earlier work.[2b] Reduction of the product mixture with $NaBH_4$ gave a mixture of amines **16a** and **16b** in a 91:9 ratio, which was purified for identification (see Experimental Section). This 9% level of minor isomer **16b**, the degree of loss of stereospecificity, reflects the proportion of a nonconcerted reaction pathway (vide infra). In a similar manner, trans isomer **11b** was converted to quaternary salt **12b**, and this salt was dehydrated with TFA to yield one enammonium salt, **13**, identical by ^{1}H NMR to the salt formed from **11a**/**12a**. Reduction of **15a**/**15b** from the dehydration of **12b** gave a 91:9 mixture of amines **16a** and **16b**, as witnessed above for **12a**. Therefore, independent of the original stereochemistry at C-6 in **11a** and **11b**, allyl quaternization at nitrogen exclusively favored the cis-ring fusion, as in **12a** and **12b**, and dehydration/rearrangement yielded **15a**/**15b**. Compared with the 1,3 allylic rearrangement in the benzoquinolizidine system, the rearrangement in the pyrroloisoquinoline system was less facile, yet highly stereospecific, although to a lesser extent of ca. 90−95%.



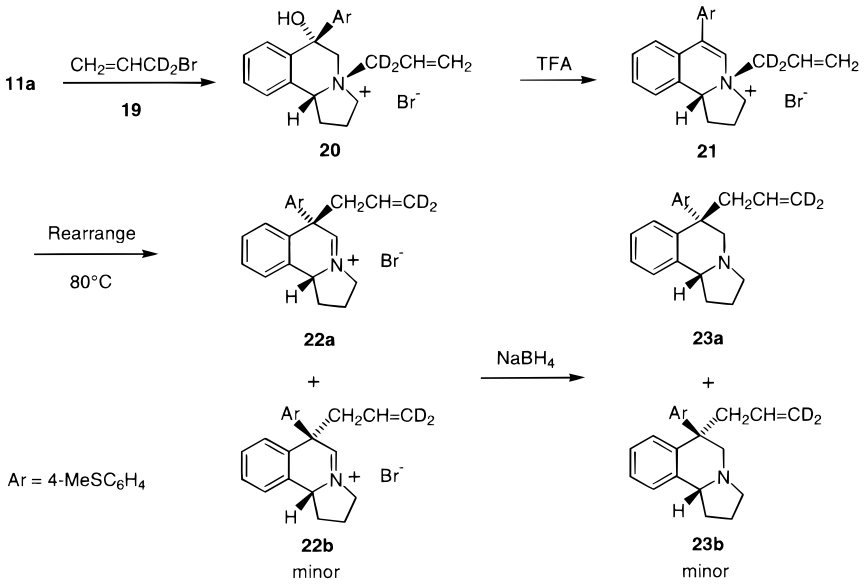
In comparing the rearrangements for the benzoquinolizidine (6−6−6) and pyrroloisoquinoline (6−6−5) ring systems, we wanted to ensure that the thiomethyl substituent was not affecting the reaction rate, i.e., impeding the rate for the 6−6−5 system. Thus, we prepared enammonium salt **18**[7] and subjected it to the same reaction conditions used for enammonium salt **13**. The rearrangement of **18** at 100 °C in DMSO-d_6 proceeded in the same manner (with a $t_{1/2}$ of ca. 15 min) to give the iminium salts corresponding to **15a** and **15b** (Scheme 2) in a ratio of ca. 95:5 (^{1}H NMR). (In a separate experiment, no rearrangement of **18** occurred at 23 °C over the course of 24 h.) Reduction with $NaBH_4$ provided the respective amines in a ratio of 85:15.

Deuterium-Labeling Study. To determine if the rearrangement proceeds by a concerted pericyclic [3,3] sigmatropic process, we tested for allylic group inversion during the reaction. An appropriate deuterium label was incorporated into the allylic substituent, as shown in Scheme 3. Amino alcohol **11a** was reacted with excess **19**[8] to afford solely the cis-fused quaternary salt **20**, which appeared by ^{1}H NMR to be the same as **12a** except for the absence of the allylic methylene protons at δ 4.18. Dissolution of **20** in TFA-*d* resulted in clean dehydration to cis enammonium salt **21**, which was caused to rearrange in DMSO-d_6 at 80 °C to give predominantly trans iminium salt **22a**, with ca. 5% of cis isomer **22b** present (^{1}H NMR). The ^{1}H NMR spectrum of **22a**/**b** clearly showed a preponderance of allylic inversion, ca. 90−95%, by the location of the deuterium atoms at the terminal vinyl position. There was a residual signal for the protio species of the terminal vinyl position at δ 5.10, which amounted to ca. 13% based on integrated area. Since 6% of this protio signal is attributable to the original isotopic purity of **19**, there is ca. 7% associated with leakage from the concerted, suprafacial [3,3] sigmatropic rearrangement. A nonconcerted or dissociative pathway would lead to some scrambling of the deuterium label between the vinyl and allyl positions. Reduction of **22a**/**b** with sodium borohydride gave a mixture of amines **23a** and **23b** in a ratio of 91:9, which possessed ca. 0.12 protio species as indicated by a multiplet at δ 5.05. Purification of the major isomer and examination of **23a** by ^{1}H NMR revealed that ca. 12% of the protio terminal vinyl was present as a doublet of doublets at δ 4.95, again indicative of ca. 6% originating from a nonconcerted pathway. Thus, our deuterium-labeling experiment confirms that the [3,3] allylic rearrangement in the pyrroloisoquinoline system has a high predominance, ca. 90−95%, of con-

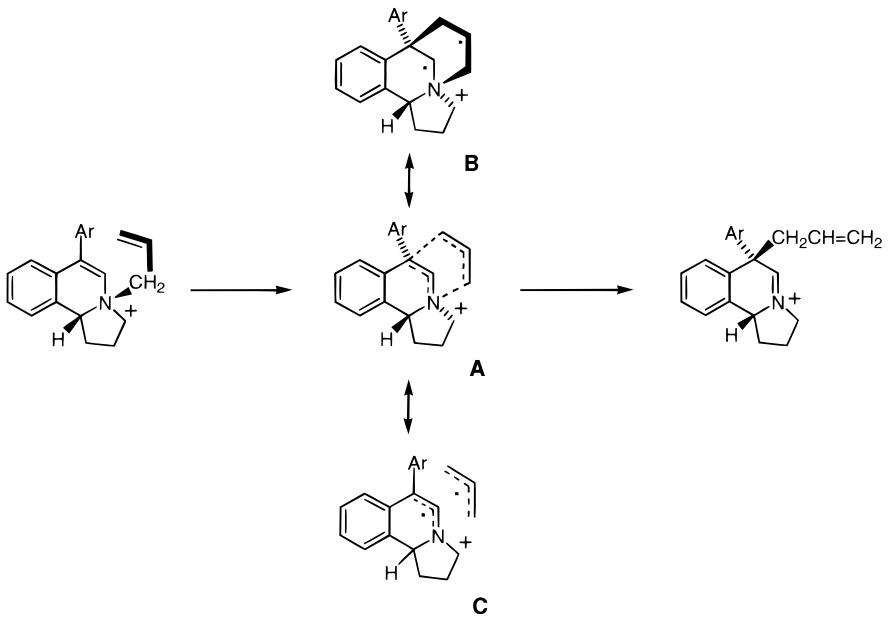
(7) Prepared from 1,2,3,5,6,10bα-hexahydro-6α-hydroxy-6β-phenylpyrrolo[2,1-*a*]isoquinoline[3a] by the procedure used for **13** (see Experimental Section). For **18**: ^{1}H NMR (DMSO-d_6) δ 2.02 (m, 2H, H_{2a}/H_{2e}), 2.26 (m, 1H, H_{1a}), 2.65 (m, 1H, H_{1e}), 3.90 (m, 1H, H_{3a}), 4.12 (d, 2H, CH_2CH=CH_2, J = 7.3 Hz), 4.18 (m, 1H, H_{3e}), 5.10 (dd, 1H, H_{10b}, J = 8.5, 9.3 Hz), 5.52 (d, 1H, CH_2CH=CH_2, J = 10.7 Hz), 5.57 (d, 1H, CH_2CH=CH_2, J = 16.9 Hz), 5.98 (m, 1H, CH_2CH=CH_2), 6.52 (s, 1H, H_5), 7.11 (d, 1H, H_7, J = 7.5 Hz), 7.42−7.56 (m, 8H, aromatic).

(8) (a) Kim, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1897−1904. (b) Schuetz, R. D.; Millard, F. W. *J. Org. Chem.* **1959**, *24*, 297−300. (c) Synder, J. *J. Org. Chem.* **1972**, *37*, 1466−1469. (d) The ^{1}H NMR spectrum of **19** showed a small doublet at δ 3.97 (J = 7.0 Hz) for ca. 6% protio species at the beginning of the rearrangement study.

Scheme 3



Scheme 4



certed sigmatropic character, with a minor (5−10%) dissociative (homolytic or heterolytic) pathway.

Mechanistic Considerations. The aza-Cope rearrangement under study herein could proceed by several mechanisms. The most reasonable one would seem to be concerted, suprafacial [3,3] allylic migration with 1,3 inversion of the allylic group, with or without diradicaloid character.[9] A concerted antarafacial migration to the opposite, concave face of the tricyclic template would be quite energetically disfavored. However, there could also be a dissociative process such as nonconcerted intramolecular migration within a solvent cage or, probably less likely, intermolecular allyl exchange.[9] A depiction of the possible rearrangement transition states and pathways for the aza-Cope rearrangement (by analogy to the standard Cope rearrangement) is presented in Scheme 4. Species **A** represents the transition structure for the generally low-energy, concerted, chairlike rearrangement, while species **B** and **C** represent higher-energy diradicaloid transition structures.[9] A pathway involving a discrete intermediate related to **C** could result in a loss of stereochemical integrity, which was observed in the rearrangement of the pyrroloisoquinoline system.

A rational structural basis can be invoked to explain the difference in reaction rate and stereochemical integrity for the concerted [3,3] rearrangement mechanism in the two systems studied. From an inspection of molecular models, benzo[*a*]quinolizine system **8** has a more favorable geometry, with a closer positioning of the allylic and enammonium termini, than does pyrrolo[2,1-*a*]isoquinoline system **13**/**21**, on account of torsional strain introduced by the fused five-membered ring in **13**/**21**. Thus, the rearrangement of **8**, probably via a chairlike transi-

(9) (a) Hrovat, D. A. Beno, B. R.; Lange, H.; Yoo, H.-Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **1999**, *121*, 10529−10537 and references therein. (b) Doering, W. v. E.; Wang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10112−10118. (c) Doering, W. v. E.; Birladeanu, L.; Sarma, K.; Blaschke, G.; Scheidemantel, U.; Boese, R.; Benet-Bucholz, J.; Klärner, F.-G.; Gehrke, J.-S.; Zimny, B. U.; Sustmann, R.; Korth, H.-G. *J. Am. Chem. Soc.* **2000**, *122*, 193−203. (d) Staroverov, V. N.; Davidson, E. R. *J. Am. Chem. Soc.* **2000**, *122*, 186−187.

tion state, might be expected to proceed in a more facile manner than the rearrangement of **13**/**21**, as we observed. Indeed, this process for **8** occurred at room temperature (23 °C) and yielded solely **9**, the product of a concerted [3,3] sigmatropic rearrangement. By contrast, the rearrangement of **13** or **21** required heating in the range of 50−100 °C and also resulted in some homolytic dissociation, as evidenced by the formation of oxidized byproduct **17** and nonconcerted rearrangement products **15b** or **22b**. This minor amount of nonconcerted mechanism (via pathway **C** in Scheme 4) might be facilitated by a combination of a nitrogen atom in the aza-Cope array, an aromatic substituent, and the aforementioned torsional strain.[10]

Conclusion

By employing a tricyclic tetrahydroisoquinoline template, we have observed highly stereospecific, suprafacial 1,3 migration of the allyl group from nitrogen to carbon in *N*-allyl enammonium quaternary salts. This enammonium−iminum rearrangement was accessed by a convenient dehydration route (i.e., **7** → **8** and **12a**/**b** → **13**) that was pioneered in our earlier work in this area.[2] Benzo[*a*]quinolizine **8** rearranged with >98% stereospecificity, reflecting an exclusive concerted [3,3] sigmatropic process, which is not surprising given the geometric features involved with migration on this tricyclic template. However, pyrrolo[2,1-*a*]isoquinoline **13** rearranged with 90−95% stereospecificity, thereby showing a degree of leakage from a pure concerted [3,3] mechanism. A deuterium-labeling experiment with pyrroloisoquinoline **21** indicated predominant allylic inversion, consistent with this 3-aza-Cope reaction proceeding largely via a concerted [3,3] sigmatropic rearrangement. However, there was a minor amount of leakage from the concerted mechanism with the pyrroloisoquinoline system, via a nonconcerted pathway, based on the 5−10% loss of stereospecificity in the rearrangement and some scrambling of the deuterium label in major isomer **23a**.

Experimental Section

General. All chemicals were reagent grade and were used as purchased without further purification; solvents were HPLC grade and stored over 3A molecular sieves. Reactions were performed under an inert argon atmosphere. ^{1}H NMR spectra were obtained at 300 or 400 MHz in $CDCl_3$ (unless otherwise noted) with Me_4Si as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broadened). In general, electrospray (ES) or fast-atom bombardment (FAB) mass spectra were obtained to characterize intermediates, while accurate mass measurements (HRMS) were obtained, in FAB mode, to characterize key compounds.

***trans*-1,3,4,6,7,11b-Hexahydro-7-phenyl-7-(2-propenyl)-2*H*-benzo[*a*]quinolizine (10).** Allyl bromide (72 mg, 0.60 mmol) was added to the amino alcohol **4**[2c] (5.0 mg, 0.018 mmol) in acetonitrile (1.0 mL) and stirred at 23 °C for 40 h. The solution was evaporated in vacuo to give quaternary salt **7** (7.5 mg, 100%): CI-MS (NH_3) *m*/*z* 320 (M^+); ^{1}H NMR δ 1.7−2.1 (m, 5H), 2.26 (br d, 1H, J = 13 Hz), 3.59 (br d, 1H, J = 13.3 Hz), 3.96 (d, 1H, J = 14.3 Hz), 4.00 (m, 1H), 4.60 (d, 1H, J = 14.3 Hz), 4.85 (m, 2H), 5.10 (dd, 1H, J = 12.2, 3.5 Hz), 5.19 (s, 1H, OH), 5.65 (m, 2H), 6.20 (m, 1H), 7.21−7.45 (m, 9H). The salt (7.5 mg) was dissolved in trifluoroacetic acid-*d* (TFA-*d*, 1.0 mL, 99.5% D), allowed to stand at 23 °C for 10 min, and evaporated in vacuo to enammonium salt **8** (7.5 mg, 100%), the cis isomer: ^{1}H NMR δ 1.75−2.20 (m, 6H), 3.83 (br m, 2H), 4.06 (dd, 1H, J = 8.2, 12.8 Hz), 4.18 (dd, 1H, J = 6.7, 12.8 Hz), 4.90 (d, 1H, J = 12.1, 1.0 Hz), 5.58 (d, 1H, J = 16.8 Hz), 5.75 (d, 1H, J = 10.0 Hz), 5.99 (s, H_6), 6.0 (m, 1H), 7.20−7.60 (m, 9H). Oily **8** (7.5 mg) was dissolved in $CDCl_3$, and rearrangement was monitored by ^{1}H NMR; after 36 h, reaction was complete to give trans iminium salt **9** (quantitative yield): CI-MS (NH_3) *m*/*z* 302 (M^+); ^{1}H NMR δ 1.70−2.25 (m, 5H), 2.56 (br d, 1H, J = 14.0 Hz), 3.18 (dd, 1H, J = 5.6, 14.0 Hz), 3.56 (dd, 1H, J = 7.3, 14.0 Hz), 3.99 (dt, 1H, J = 3.0, 13.0 Hz), 4.72 (dd, 1H, J = 2.0, 12.0 Hz), 4.97 (dd, 1H, J = 3.0, 12.2 Hz), 5.04 (dd, 1H, J = 2.0, 9.4 Hz), 5.2−5.3 (m, 2H), 7.10−7.45 (m, 9H), 9.31 (s, 1H). The sample was immediately evaporated in vacuo to an oil, which was dissolved in absolute ethanol (1 mL) and treated with sodium borohydride (4 mg). The reaction was stirred at 23 °C for 30 min, quenched with water, and extracted into methylene chloride. The solution was washed with brine, dried (K_2CO_3), and evaporated in vacuo to amine **10** (5.0 mg, 90%): ES-MS *m*/*z* 304 (MH^+); ^{1}H NMR δ 1.30−1.90 (m, 5H), 2.25 (m, 2H), 2.70 (br d, 1H, J = 11.3 Hz), 2.79 (pair of dd, 2H, J = 11.4, 11.7 Hz), 2.90 (dd, 2H, J = 1.2, 7.6 Hz), 3.15 (dd, 1H, J = 2.5, 10.4 Hz), 4.94 (dd, 1H, J = 1.9, 10.1 Hz), 5.06 (dd, 1H, J = 1.9, 17.1 Hz), 5.48 (m, 1H), 7.10−7.36 (m, 9H).

***trans*- and *cis*-1,2,3,5,6,10b-Hexahydro-6-[(4-methylthio)phenyl]-6-(2-propenyl)pyrrolo[2,1-*a*]isoquinolines (16a/16b).** Amino alcohol **11a**[2b] (15.0 mg, 0.048 mmol) was stirred in acetonitrile (1 mL) as allyl bromide (216 mg, 1.80 mmol) was added, and the reaction was stirred at 23 °C for 24 h. The solvent was evaporated in vacuo to quaternary salt **12a** (21.0 mg, 100%): ES-MS *m*/*z* 352 (M^+); ^{1}H NMR δ 2.26 (m, 2H), 2.47 (s, 3H), 2.70 (m, 2H), 3.82 (d, 1H, J = 13.6 Hz), 4.05 (m, 1H), 4.18 (m, 2H), 4.45 (m, 1H), 4.58 (d, 1H, J = 13.6 Hz), 5.31 (dd, 1H, J = 7.9, 7.9 Hz), 5.41 (d, 1H, J = 16.7 Hz), 5.50 (s, 1H, OH), 5.53 (d, 1H, J = 10.1 Hz), 5.69 (m, 1H), 7.13−7.40 (m, 8H). Salt **12a** (7.0 mg, 0.016 mmol) was dissolved in TFA-*d* (1.0 mL), stirred at 23 °C for 10 min, and evaporated in vacuo to cis enammonium salt **13** (100% yield): ES-MS *m*/*z* 334 (M^+); ^{1}H NMR δ 2.09 (m, 2H), 2.46 (m, 1H), 2.54 (s, 3H), 2.75 (m, 1H), 3.95 (m, 1H), 4.10−4.22 (m, 3H), 5.09 (dd, 1H, J = 8.7, 9.0 Hz), 5.61 (d, 1H, J = 16.9 Hz), 5.67 (d, 1H, J = 10.1 Hz), 5.91 (s, 1H), 5.97 (m, 1H), 7.24−7.50 (m, 8H); ^{1}H NMR (TFA-*d*) δ 2.15−2.25 (m, 2H), 2.45 (m, 1H), 2.52 (s, 3H), 2.8 (m, 1H), 3.80−4.05 (m, 3H), 4.15 (dd, 1H, J = 7.4, 12.6 Hz), 4.82 (dd, 1H, J = 8.7, 9.2 Hz), 5.61 (d, 1H, J = 16.8 Hz), 5.72 (d, 1H, J = 10.0 Hz), 5.97 (s, 1H), 6.04 (m, 1H), 7.28−7.50 (m, 8H). Salt **13** (7.0 mg) was dissolved in DMSO-d_6 and heated at 100 °C for 2 h to give predominantly trans isomer **15a** (7.0 mg, 100%): ^{1}H NMR (DMSO-d_6) δ 2.10−2.25 (m, 3H), 2.50 (s, 3H), 2.95−3.30 (m, 3H), 4.45 (m, 2H), 5.07 (dd, 1H, J = 10, 1.0 Hz), 5.14 (dd, 1H, J = 16.0, 1.0 Hz), 5.29 (m, 1H), 5.63 (m, 1H), 6.78 (d, 1H, J = 7.6 Hz), 7.25−7.45 (m, 7H), 9.20 (s, 1H). This material (7.0 mg) was dissolved in absolute ethanol (2 mL), and sodium borohydride (4 mg) was added. The reaction was stirred at 23 °C for 40 min, quenched with water, and worked-up as indicated above to give a mixture of amines **16a** and **16b** (4.0 mg, 73%; 91:9 ratio by ^{1}H NMR), which was subjected to flash-column chromatography with ethyl acetate/hexane (1:1) to give a purified mixture of **16a** and **16b**. For **16a**: FAB−HRMS calcd for $C_{22}H_{25}NS + H^+$ 336.1786, found 336.1787; ^{1}H NMR δ 1.70−1.90 (m, 2H, H_{2a}/H_{2e}), 2.34 (m, 2H, H_{1a}/H_{1e}), 2.44 (s, 3H, Me), 2.73 (d, 1H, H_{5a}, J = 11.3 Hz), 2.93 (m, 3H, H_{3e}/CH_2CH=CH_2), 3.04 (d, 1H, H_{5e}, J = 11.4 Hz), 3.24 (dd, 1H, H_{10b}, J = 9.5, 6.7 Hz), 4.98 (br d, 1H, CH_2CH=CH_2, J = 10.3 Hz), 5.07 (br d, 1H, CH_2CH=CH_2, J = 17.0 Hz), 5.53 (m, 1H, CH_2CH=CH_2), 6.96 (d, 1H, H_7, J = 7.6 Hz), 7.10−7.30 (m, 7H, aromatic). For **16b**: FAB−HRMS calcd for $C_{22}H_{25}NS + H^+$ 336.1786, found 336.1791; ^{1}H NMR δ 1.70−1.95 (m, 2H, H_{2a}/H_{2e}), 2.33 (m, 1H, H_{1a}), 2.45 (s, 3H, Me), 2.50 (m, 1H, H_{1e}), 2.73 (d, 1H, H_{5a}, J = 11.4 Hz), 2.96 (m, 2H, CH_2CH=CH_2), 3.11 (d, 1H, H_{5e}, J = 11.4 Hz), 3.41 (dd, 1H, H_{10b}), 4.95

(10) A two-step, diradical mechanism has been evoked for a Cope rearrangement in a strained polycyclic system, see: Roth, W. R.; Gleiter, R.; Paschmann, V.; Hackler, U. E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem*. **1998**, 961−967. Also, see ref 9c.

(br d, 1H, $CH_2CH{=}CH_2$, J = 9.8 Hz), 5.00 (br d, 1H, $CH_2CH{=}CH_2$, J = 17.0 Hz), 5.81 (m, 1H, $CH_2CH{=}CH_2$), 6.95 (d, 1H, H_7, J = 7.6 Hz), 7.10−7.30 (m, 7H, aromatic). In an identical manner, amino alcohol **11b** (15.0 mg, 0.048 mmol) was treated with allyl bromide to give quaternary salt **12b** (20.0 mg, 90%): ^{1}H NMR δ 2.03 (m, 2H), 2.46 (s, 3H), 2.50 (m, 1H), 2.95 (m, 1H), 3.36 (d, 1H, J = 14.0 Hz), 3.40 (m, 1H), 4.07 (d, 1H, J = 14.2 Hz), 4.36 (m, 1H), 4.55/4.72 (m, 2H), 5.30 (s, 1H, OH), 5.59 (br d, 1H, J = 9.9 Hz), 5.60 (m, 1H), 5.78 (br d, 1H, J = 16.8 Hz), 6.35 (m, 1H), 7.15−7.38 (m, 8H). Salt **12b** (20.0 mg) was dissolved in TFA-*d* (1.0 mL), stirred at 23 °C for 10 min, and evaporated in vacuo to give cis enammonium salt **13** (15.0 mg, 75%), which was identical by ^{1}H NMR to that prepared above from **12a**, and which rearranged in the same way to trans isomer **15a**. A portion of this material (**15a**; 8.0 mg, 0.018 mmol) was dissolved in absolute ethanol (2 mL) and treated with sodium borohydride (4 mg). The reaction was stirred at 23 °C for 40 min, quenched with water, and worked-up as above to give amines **16a** and **16b** (4.5 mg, 70%; 91:9 ratio by ^{1}H NMR).

***trans*-1,2,3,5,6,10b-Hexahydro-6-[(4-methylthio)phenyl]-6-(3,3-dideuterio-2-propenyl)pyrrolo-[2,1-*a*]isoquinolines (23).** Amino alcohol **11a**[2b] (10.0 mg, 0.032 mmol) was stirred in acetonitrile (1 mL) as allyl bromide **19**[8] (100 mg, 0.80 mmol) in acetonitrile (1 mL) was added, and the reaction was stirred at 23 °C for 24 h. The solution was evaporated in vacuo to afford the cis-quaternary salt **20** (14.0 mg, 100%): ^{1}H NMR δ 2.24 (m, 2H), 2.45 (s, 3H), 2.68 (m, 2H), 3.76 (d, 1H, J = 13.4 Hz), 4.05 (m, 1H), 4.16 (m, 1H), 4.53 (d, 1H, J = 13.5 Hz), 5.29 (d, 1H, J = 16.7 Hz), 5.30−5.60 (m, 3H), 5.80 (s, 1H, OH), 7.15−7.36 (m, 8H). Salt **20** (14.0 mg) was dissolved in TFA-*d* (1.0 mL), stirred at 23 °C for 15 min, and evaporated in vacuo to enammonium salt **21** (15.0 mg, quantitative yield): ES-MS m/z 336 (M^+); ^{1}H NMR δ 2.09 (m, 2H), 2.47 (m, 1H), 2.54 (s, 3H), 2.75 (m, 1H), 3.96 (m, 1H), 4.13 (m, 1H), 5.10 (dd, 1H, J = 9.0 Hz), 5.61 (d, 1H, J = 17.2 Hz), 5.66 (d, 1H, J = 11.1 Hz), 5.93 (s, 1H), 5.98 (dd, 1H, J = 10.1, 16.7 Hz), 7.24−7.54 (m, 6H). Salt **21** (7.0 mg) was dissolved in DMSO-d_6 (1 mL) and heated at 80 °C for 4 h to give iminium salts **22a** and **22b** (quantitative yield): ES-MS m/z 336 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.05−2.35 (m, 3H), 2.50 (s, 3H), 2.95−3.08 (m, 1H), 3.11 (dd, 1H, J = 7.4, 14.0 Hz), 3.27 (dd, 1H, J = 7.2, 14.0 Hz), 4.45 (m, 2H), 5.10 (dd, 0.13H), 5.29 (m, 1H), 5.62 (m, 1H), 6.77 (d, 1H, J = 7.6 Hz), 7.20−7.50 (m, 7H), 9.20 (br s, 1H). Reduction of **22** (ca. 7 mg) was immediately carried out with $NaBH_4$ as described above to yield a mixture of trans and cis amines **23a** and **23b** (5.0 mg, ca. 90%) in a 91:9 ratio by ^{1}H NMR: FAB−HRMS calcd for $C_{22}H_{23}D_2NS + H^+$ 338.1912, found 338.1913; ^{1}H NMR δ 1.70−2.00 (m, 3H), 2.35 (m, 2H), 2.48 (s, 3H), 2.72 (d, 1H, J = 11 Hz), 2.95 (m, 3H), 3.08 (d, 1H, J = 11 Hz), 3.24 (dd, 1H), 5.05 (m, 0.12H), 5.52 (m, 1H), 6.95 (d, 1H, J = 7.6 Hz), 7.10−7.30 (m, 7H).

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Supporting Information Available: Proton NMR spectral data for new compounds with suggested peak assignments and copies of proton NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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