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Toward an Enantioselective Total Synthesis of Sarain A: Construction of an Advanced Intermediate and Rearrangement of the Sarain A Core under Mild Conditions

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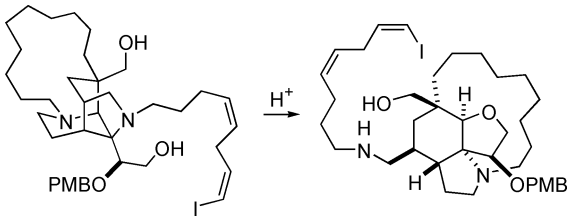
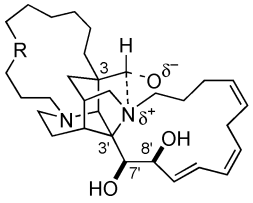
ABSTRACT



A high-yielding *N*-sulfonyliminium ion–enoxysilane cyclization and a ring-closing metathesis are key steps in the enantioselective synthesis of late-stage intermediates en route to sarain A. Also revealed is an unprecedented rearrangement of the tetracyclic sarain A core under mildly acidic conditions.

The structurally unique sarains A−C (**1**−**3**) were isolated originally by Cimino and co-workers from the sponge *Reniera sarai*, collected in the Bay of Naples.[1] A distinctive diazatricycloundecane core with a proximity interaction between the C2 aldehyde and the N1 tertiary amine defines these alkaloids. Surrounding this heterocyclic core are two macrocyclic rings, one saturated and one containing a vicinal diol and a skipped triene. Sarains A−C display antibacterial, insecticidal, and antitumor activities,[2] although interest in these molecules derives largely from their unprecedented structures. Syntheses of the diazatricycloundecane core of sarains A−C have been reported by the groups of Weinreb,[3] Heathcock,[4] Cha,[5] and our laboratory.[6]



sarain A (**1**) R = CH_2
sarain B (**2**) R = –(*Z*)-CH=CH–
sarain C (**3**) R = –(*Z*)-CH=$CHCH_2$–

In the most advanced progress disclosed to date, Weinreb and Cha described potential intermediates that contain the heterocyclic core, the C3 all-carbon quaternary stereocenter, and the saturated macrocyclic ring.[3a,b,5a,b]

(1) (a) Cimino, G.; De Stefano, S.; Scognamiglio, G.; Trivellone, E. *Bull. Soc. Chim. Belg.* **1986**, *95*, 783−800. (b) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863−3872. (c) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519−1525. (d) Guo, Y.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341−8348.

(2) Caprioli, B.; Cimino, G.; DeGuilio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol.* **1992**, *103B*, 293−296.

(3) (a) Hong, S.; Weinreb, S. M. Presented at the 226th National Meeting of the American Chemical Society, New York, Sept 2003; ORGN 202. (b) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587−595. (c) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945−4951. (d) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210−3211.

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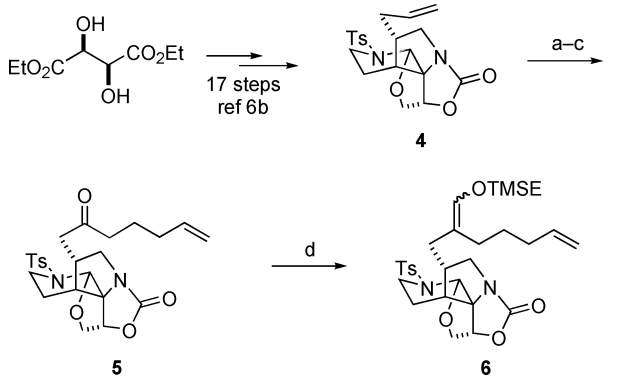
A distinctive feature of our approach to sarains A−C is generation of a highly functionalized diazatricycloundecane core that incorporates the C3 quaternary center and a C3′ side chain containing the C7′ alcohol stereocenter by an *N*-sulfonyliminium ion−enoxysilane cyclization.[6−8] Herein, we report construction of an enantiopure, advanced tetracyclic intermediate and an unanticipated late-stage rearrangement of the sarain core under mild conditions.

The present studies began by preparing multigram quantities of enantiopure tetracyclic aminal **4** in 17 steps from D-diethyl tartrate (Scheme 1).[9] A side chain, which eventually

Scheme 1 [a]

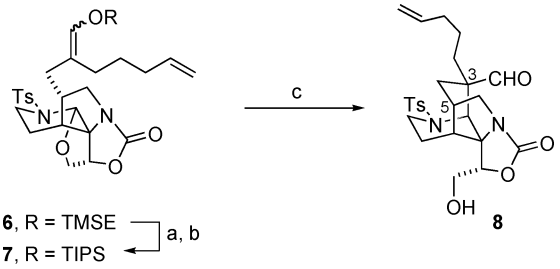


[a] Reaction conditions: (a) (i) O_3, $NaHCO_3$, CH_2Cl_2/MeOH, −78 °C; (ii) Me_2S, −78 °C to room temperature (90%). (b) $H_2C{=}CH(CH_2)_3MgBr$, THF/Et_2O, −78 to −10 °C. (c) Swern oxidation (81%, two steps). (d) KHMDS, $TMSEOCH_2PPh_3Cl$, THF, −78 to 0 °C (98%, 3:2 mixture of isomers); TMSE = 2-(trimethylsilyl)ethyl.

will be employed to form the saturated macrocyclic ring, was installed next. This four-step sequence began by ozonolysis of **4** to provide the corresponding aldehyde. Addition of 4-pentenylmagnesium bromide to this intermediate, followed by Swern oxidation of the resulting inconsequential mixture of epimeric alcohols, provided ketone **5** in 72% yield over the three steps. Wittig reaction of ketone **5** with the ylide derived from trimethylsilylethoxymethylene triphenylphosphonium chloride and potassium hexamethyldisilazane provided 2-trimethylsilylethyl (TMSE) enol ether **6** in 98% yield as a 3:2 mixture of double-bond stereoisomers.

With enol ether **6** in hand, we examined the pivotal intramolecular *N*-sulfonyliminium ion cyclization to forge the C3 all-carbon quaternary stereocenter and complete the diazatricycloundecane core of sarains A−C (Scheme 2). Following

Scheme 2 [a]



[a] Reaction conditions: (a) HF (aq), MeCN, rt; (b) TIPSOTf, Et_3N, CH_2Cl_2, −78 °C to room temperature (87%, two steps); (c) BCl_3 (4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine, 0 °C to room temperature (92%, R = TIPS; 55%, R = TMSE).

precedent from earlier studies,[6b,10,11] aminal enol ether **6** was exposed to a large excess of BCl_3 and 2,6-di-*tert*-butyl-4-methylpyridine at −78 °C in CH_2Cl_2. These conditions provided the desired product **8** in poor (<10%) yield, with the remainder of the recovered mass being an intractable mixture. Decreasing the amount of BCl_3 to 4 equiv and raising the reaction temperature first to 0 °C and then to room temperature increased the yield of the tetracyclic aldehyde product **8** to 55%. Of primary importance, this product was produced as a single stereoisomer having the required configuration at the all-carbon quaternary center C3.[12,13]

In an attempt to improve the yield of this pivotal cyclization, the enol ether nucleophile of cyclization precursor **6** was converted to a more reactive enoxysilane. This transformation was accomplished by reaction of **6** with 5% aqueous HF in MeCN, followed by treatment of the resulting mixture of epimeric aldehydes with triisopropylsilyl triflate and Et_3N to provide enoxysilane **7**, a 3:2 mixture of

(4) (a) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616−9617. (b) Griffith, D. A.; Heathcock, C. H. *Tetrahedron Lett.* **1995**, *36*, 2381−2384. (c) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. *Synlett* **1995**, 467−474. (d) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056−7066.

(5) (a) Lee, H. I.; Sung, M. J.; Lee, H. B.; Cha, J. K. *Heterocycles* **2004**, *62*, 407−422. (b) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *J. Org. Chem.* **2003**, *68*, 2205−2008. (c) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017−2019.

(6) (a) Jaroch, S.; Matsuoka, R. T.; Overman, L. E. *Tetrahedron Lett.* **1999**, *40*, 1273−1276. (b) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096−8097.

(7) Weinreb was the first to employ an *N*-sulfonyliminium ion cyclization to form the diazatricycloundecane core of the sarain alkaloid;[3d] in the Sisko−Weinreb cyclization, the C3 quaternary stereocenter is not formed.

(8) For a review of *N*-sulfonyliminium ion chemistry, see: Weinreb, S. M. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1997; Vol. 190, pp 131−184.

(9) A slight modification of our previously reported sequence was employed.[6b] Modifications include beginning the synthesis with D-diethyl tartrate rather than L-diethyl tartrate and substituting allyl bromide for 3-bromo-2-methylpropene in an early alkylation step. Compound **4** was prepared originally by Dr. Michael Becker.

(10) Cyclization of related intermediates in which the $(CH_2)_3CH{=}CH_2$ group of **7** was replaced with a $(CH_2)_7OBn$ group had shown that the correct stereochemistry at the C3 center could be obtained (dr = 6:1) under these conditions.[11]

(11) Dr. Peter Chua, unpublished studies, University of California−Irvine, Irvine, CA, 1999.

(12) Assigned by NOESY; see Supporting Information for details.

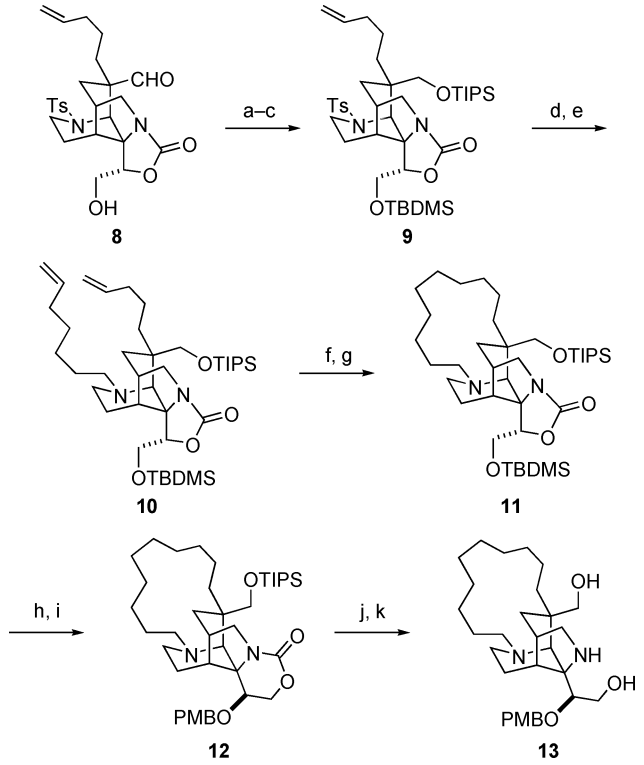
(13) Enol ether stereoisomers either interconvert under the reaction conditions or react similarly, as subjecting the minor isomer to identical cyclization conditions provided a product distribution identical to that obtained using the mixture of enol ether stereoisomers.

(14) (a) Stereoselection in forming the C3 stereocenter under these conditions is >20:1. Trace amounts of several side-products resulting from chloride-terminated Prins cyclization of the newly unmasked aldehyde with the tethered alkene accounted for the remainder of the mass balance. (b) In our earlier model study wherein the C3 substituent was a methyl group rather than a 4-pentenyl side chain, the major product had the undesired configuration at C3.[6b] High stereoselection in the present case is believed to be the result of thermodynamic equilibration prior to loss of the triisopropylsilyl group.

stereoisomers, in 87% yield for the two steps. To our delight, this TIPS enoxysilane cyclized to provide advanced intermediate **8** in 92% yield.[14]

As preliminary survey experiments had indicated that macrolactamization was not a viable strategy for closing the saturated macrocyclic ring,[11] we turned to ring-closing metathesis (RCM),[15] a tactic first verified in this context by the Weinreb group (Scheme 3).[3b] Elaboration of aldehyde **8** was initiated by protection of the primary alcohol as a *tert*-butyldimethylsilyl ether, reduction of the aldehyde with $NaBH_4$, and protection of the resulting alcohol to give TIPS ether **9** in 75% yield over the three steps. Removal of the tosyl group with sodium naphthalenide,[16] followed by reductive amination with 6-hepten-1-al and $NaBH_3CN$, provided diene **10** in 78% yield over the two steps.

Scheme 3[a]



[a] Reaction conditions: (a) TBDMSCl, imidazole, MeCN; (b) $NaBH_4$, MeOH; (c) TIPSOTf, Et_3N, CH_2Cl_2 (75%, three steps); (d) Na, naphthalene, DME/THF, −78 °C; (e) 6-hepten-1-al, $NaBH_3CN$, AcOH, 4 Å mol sieves, MeCN, rt (78%, two steps); (f) 5 mol % $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 0.25 mM (75−80%); (g) H_2, Pd/C, EtOAc, rt (95%); (h) HCl (aq), THF, rt, (83%); (i) PMBCl, NaHMDS, DMF, rt (89%); (j) TAS-F, DMA, 100 °C (85%); (k) KOH, EtOH, 90 °C (90%).

With tetracyclic diene **10** in hand, we examined closure of the macrocyclic ring. Heating **10** in CH_2Cl_2 (at 1 mM) at reflux using 15 mol % of the "second generation" Grubbs ruthenium catalyst[17] provided the desired 13-membered ring macrocycle as a mixture of (*E*)- and (*Z*)-isomers, albeit in only 17% yield. The major products produced under these conditions, which were isolated in 61% combined yield, incorporated two units of the starting material. These major "dimer products" resulted from thermodynamic control, as resubmitting them individually to the reaction conditions returned a 3:1 mixture of 13- and 26-membered ring products. To minimize secondary metathesis reactions that were converting the 13-membered RCM product to 26-membered ring macrocyclic dimers, the less active $(PCy_3)_2Cl_2Ru{=}CHPh$ catalyst[18,19] was employed. Cyclization of **10** under optimal conditions (5 mol % catalyst, 0.25 mM in refluxing CH_2Cl_2) produced the desired 13-membered ring metathesis product in 75−80% yield. Hydrogenation of this inconsequential 2:1 mixture of pentacyclic alkene stereoisomers provided the saturated macrocycle **11** in 95% yield.

We turned our attention to construction of the more complex macrocyclic ring containing the skipped triene unit. The TBDMS and oxazolidinone protecting groups of **11** could be removed under basic conditions to provide the corresponding amino diol; however, this intermediate could not be functionalized on nitrogen by either reductive amination or acylation. Hypothesizing that the lack of reactivity resulted from steric hindrance by the neighboring TIPS ether functionality, we adjusted the protecting groups of **11**. Exposure of **11** to aqueous HCl selectively cleaved the TBDMS group. Reaction of the resulting primary alcohol with sodium hexamethyldisilazane and *p*-methoxybenzyl chloride in DMF resulted in rearrangement of the 5-(hydroxymethyl)-[1,3]-oxazolidin-2-one fragment to generate the corresponding 5-hydroxy-[1,3]oxazinan-2-one with concurrent protection of the secondary hydroxyl group to provide **12** in 74% yield from **11**.[20] After some experimentation, it was found that the hindered TIPS group of **12** could be removed by reaction with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) in *N*,*N*-dimethylacetamide (DMA) at 100 °C to provide the corresponding neopentylic alcohol in 85% yield.[21] Cleavage of the oxazinanone functionality of this product with KOH in EtOH at 90 °C then provided amino diol **13** in 90% yield.

With amino alcohol **13** in hand, we reexamined functionalization of the pyrrolidine nitrogen (Scheme 4). Heating a

(15) For reviews of the use of RCM reactions in alkaloid synthesis, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959−968.

(16) Sungchul, J.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312.

(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

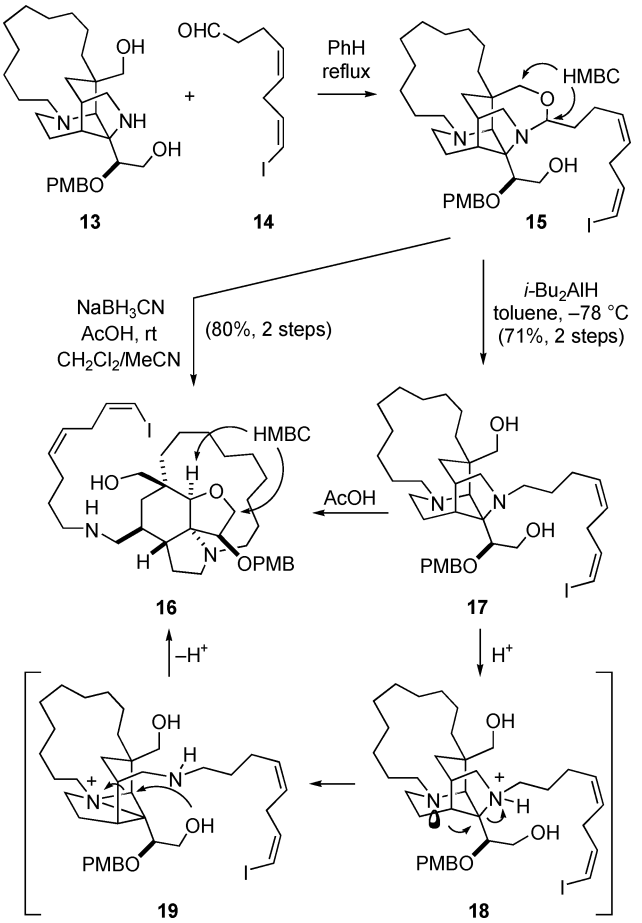
(18) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554. (b) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749−750.

(19) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(20) To our knowledge, base-promoted rearrangement of an *N*-alkyl-5-(hydroxymethyl)-[1,3]oxazolidin-2-one to *N*-alkyl-5-hydroxy-[1,3]oxazinan-2-one with concurrent protection of the secondary alcohol is unprecedented. Examples of this rearrangement with substrates in which nitrogen is substituted with a hydrogen, allowing the reaction to proceed through the corresponding isocyanate, are known; see, for example: (a) Tadanier, J.; Martin, J. R.; Hallas, R.; Rasmussen, R.; Grampovnik, D.; Rosenbrook, W., Jr.; Arnold, W.; Schuber, E. *Carbohydr. Res.* **1981**, *98*, 11−23. (b) Sadybakasov, B. K.; Ashirmatov, M. A.; Afanas'ev, V. A.; Struchkov, Y. T. *Zh. Strukt. Khim.* **1989**, *30*, 135−140.

(21) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.

Scheme 4



benzene solution of tetracyclic amino diol **13** and iododienal **14**, available in five steps from 4-pentynoic acid, resulted in dehydration to provide a pentacyclic product **15** as a single stereoisomer. To our surprise, the HMBC correlation depicted in Scheme 4 established that the pyrrolidine nitrogen and the neopentylic primary alcohol had combined with the aldehyde to generate a [1,3]oxazocane ring. A second surprise ensued when this eight-membered ring aminal was treated at room temperature with $NaBH_3CN$ and acetic acid in $MeCN/CH_2Cl_2$ to provided a tetracyclic reduction product **16** in 80% yield. Initially, this product appeared to have spectral characteristics (^1H NMR, ^{13}C NMR, IR, COSY, HMQC, ESI-MS) consistent with the desired reductive amination product. However, our inability to oxidize **16** to a dialdehyde led us to question the initial structural assignment. Finally, additional NMR studies established that **16** contained a $CH-O-CH_2$ fragment (HMBC correlation), leading us to conclude that extensive rearrangement of the sarain core structure had taken place to produce tetracyclic product **16**. Fortunately, the desired reductive amination product **17** was obtained in good overall yield when [1,3]-oxazocane **15** was reduced with $(i\text{-Bu})_2AlH$ at −78 °C in toluene.

Insight into how the structural reorganization to form **16** takes place was gained when we discovered that tetracyclic diol **17** was converted to tetracyclic amino ether **16** when exposed at room temperature to acetic acid in $MeCN/CH_2Cl_2$. As summarized in Scheme 4, we hypothesize that protonation of **17** triggers displacement of the pyrrolidine nitrogen by the piperdine nitrogen to form aziridinium ion intermediate **19**. Opening of this latter intermediate by attack of the primary alcohol on the aziridinium ion then provides **16**. To our knowledge, this is the first example of an aziridinium ion rearrangement in which the leaving group is a tertiary amine.[22]

In summary, an enantioselective synthesis of an advanced intermediate en route to sarain A has been developed. Our strategy employs a high-yielding and highly stereoselective intramolecular *N*-tosyliminium ion−enoxysilane condensation to generate the diazatricycloundecane core, install the C3 all-carbon quaternary stereocenter, and reveal a C3′ side chain containing the C7′ alcohol stereocenter. An efficient reductive amination/RCM sequence was used to install the saturated macrocycle. An unanticipated rearrangement of the sarain core structure under mild acidic conditions was discovered, which is believed to occur by an aziridinium ion rearrangement in which a tertiary amine serves as the leaving group. Efforts to construct the second macrocyclic ring from advanced intermediate **17** to complete an enantioselective total synthesis of sarain A are ongoing.

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Supporting Information Available: Experimental procedures for the preparation of **8**, **11**, and **15**−**17**; copies of ^1H and ^{13}C NMR spectra for all new compounds; copies of COSY, HMQC, and HMBC spectra of **15**−**17**; and a copy of the NOESY spectrum of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Fragmentation of protonated 1,2-ethylenediamine to an aziridinium ion has been observed in the gas phase; see: Bouchoux, G.; Choret, N.; Penaud-Berruyer, P.; Flammang, R. *J. Phys. Chem. A* **2001**, *105*, 9166−9177. (b) *N*,*N*′-Dimethyl-1,3-propanediamine exchanges methyl groups slowly in water in the presence of acid; see: Callahan, B. P.; Wolfenden, R. *J. Am. Chem. Soc.* **2003**, *125*, 310−311.