JOC Article

Design of a Nonreductive Method for Chemoselective Cleavage of Hydrazines in the Presence of Unsaturations: Application to a Stereoconvergent Three-Component Synthesis of (−)-Methyl Palustramate

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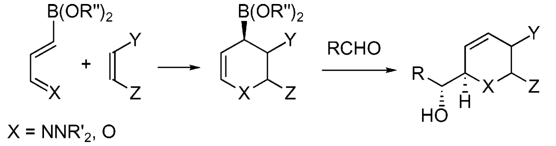
A chemoselective hydrazine (N−N) cleavage methodology that preserves the integrity of alkenes was developed based on a mild acid-promoted fragmentation of tetrasubstituted 1-(trimethylsilylmethyl)-1-benzylhydrazines. This strategy was applied to a concise asymmetric synthesis of (−)-methyl palustramate (**4**), which featured a convergent stereo- and regioselective sequential three-component aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene rearrangement between diene **1f**, dienophile **2b**, and propionaldehyde to afford *cis*-2-carboxy-6-hydroxyalkylpiperidine **25**. The acid-promoted hydrazinolysis of **25** cleanly afforded key intermediate **31**, and the latter led to target **4** in four steps after a series of functional group transformations.

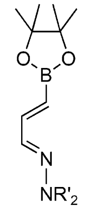
Introduction

In recent years, synthetic chemists have become increasingly aware of the power of multicomponent reactions[1] for the stereoselective construction of complex natural products.[2] By rapidly generating molecular complexity from readily available starting materials, these reactions represent attractive step-economical strategies in target-oriented synthesis. Inspired by the original carbocyclic variant of Vaultier and co-workers,[3] we have recently reported the tandem hetero[4+2]cycloaddition/allylboration three-component reaction for the preparation of α-hydroxyalkylated piperidines[4] and pyrans[5a] (eq 1).

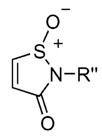


(1)

Ghosez and co-workers were first to demonstrate the use of hydrazines as electron releasing groups to reverse the polarity of 1-azadienes and access piperidine derivatives via [4+2] cycloaddition reactions.[6] Our design of a tandem aza[4+2]/allylboration strategy was based on this seminal work, and relied on the hybrid 1-dialkylamino-1-aza-4-boronobutadienes (**1**).



1



2

Thus, the one-pot three-component process shown in eq 1 is initiated by a hetero-Diels−Alder reaction between azadienes **1** and electron-poor dienophiles such as maleimides. The formation of the resulting cycloadduct unmasks an allylboronate that adds in situ onto aldehydes to provide polysubstituted α-hydroxyalkyl piperi-

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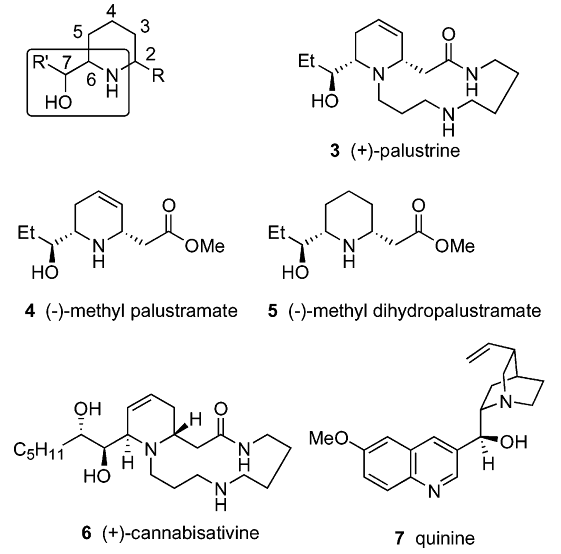

3 (+)-palustrine

4 (-)-methyl palustramate

5 (-)-methyl dihydropalustramate

6 (+)-cannabisativine

7 quinine

FIGURE 1. Selected α-hydroxyalkyl piperidine containing natural products.

dine products in a highly stereoselective fashion. This motif is encountered in the structure of a number of natural products such as the palustrine family exemplified by palustrine itself (**3**),[7] methyl palustramate (**4**) and its saturated degradation product methyl dihydropalustramate (**5**), and other alkaloids such as (+)-cannabisativine (**6**)[8] and quinine (**7**)[9] (Figure 1). Although a number of total syntheses of these natural products have appeared in the literature,[10] the stereocontrolled introduction of the 6-hydroxyalkyl side chain has often necessitated the recourse to a linear approach. Our one-pot three-component tandem aza[4+2]/allylboration delivers this key structural unit in a highly convergent and stereocontrolled fashion.[4a,b] Efforts to apply this reaction strategy in target-oriented synthesis have recently culminated in a concise asymmetric synthesis of methyl dihydropalustramate (**5**).[11] Waldner's sulfinimide dienophile,[12] a chiral derivative of **2**, played a key role in our successful synthesis of **5**. Unfortunately, a synthesis of **4** could not be envisaged at this time due to the lack of reliable methodology for the chemoselective cleavage of the tetraalkyl hydrazine remnant of diene **1**. Such a transformation is required to liberate the free piperidine while preserving the double bond, the only feature distinguishing **4** from **5**.

Current methodologies that preserve the integrity of the alkene functionality during the cleavage of an N−N bond first consist of activating the hydrazine in a regioselective manner via acylation, followed by reductive cleavage of the resulting hydrazide with sodium or lithium[13a−d] in liquid ammonia, samarium iodide,[14] or through an oxidative cleavage with magnesium monoperoxyphthalate (MMPP).[15] It should be noted that most of these preactivation strategies are not applicable to unsymmetrical alkylhydrazines such as those employed in our studies. Herein, we report the synthesis of a new class of hydrazines, namely the 1-(trimethylsilylmethyl)-1-benzylhydrazines, which can be cleaved nonreductively under mild acidic conditions in the presence of unsaturations. This unique methodology was successfully applied to a concise total synthesis of (−)-methyl palustramate (**4**). A mechanistic insight pertaining to this new N−N cleavage strategy is also discussed.

Results and Discussion

Scope of the Aza-Diels−Alder Reaction. Our three-component aza[4+2]cycloaddition/allylboration has shown a very broad substrate scope in terms of hydrazine and aldehyde components, which makes it particularly suited for applications in diversity-oriented synthesis (DOS).[4b] Unfortunately, in the normal electron-demand [4+2] cycloaddition manifold, the bulky electron-withdrawing pinacol boronate substituent exerts a strong deactivating effect on the diene. Thus, the thermal cycloaddition works well only with very electron-poor diactivated dienophiles such as *N*-substituted maleimides; monoactivated dienophiles such as acrylates and vinyl sulfones are unreactive.[4b] However, as targets **3**−**7** do not bear any substituent at the 3-position (Figure 1), their syntheses would require further fine-tuning of the dienes' reactivity or the

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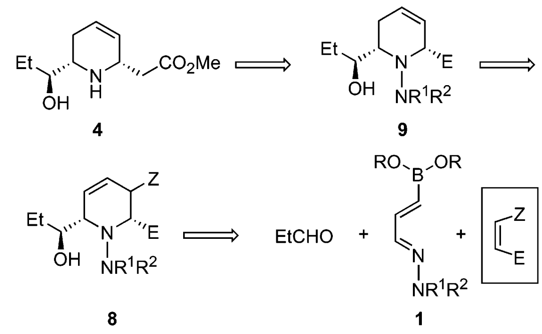
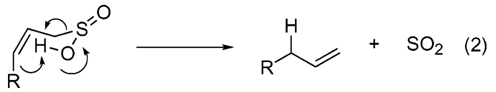
SCHEME 1. Retrosynthetic Analysis for (−)-Methyl Palustramate (4)

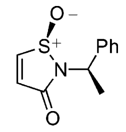


use of dienophiles bearing easily removable activating groups. Unfortunately, all our attempts to increase the reactivity of dienes **1** only met with failure. Accordingly, we next considered the use of suitable diactivated dienophiles to overcome the limitations of our methodology with respect to the mitigated reactivity of dienes **1**. However, any such dienophiles would have to meet the following requirements: (1) possess the requisite electronic characteristics to react with heterodienes **1**, (2) provide high enantiofacial selectivity, and (3) provide high regioselectivity and lead to a cycloadduct convertible to the C3−C4 dehydro unit of **4** via an allylic transposition (i.e., **8** to **9**) as depicted in the retrosynthetic analysis shown in Scheme 1.

With these criteria in mind, we turned our attention to the 4-isothiazolin-3-one 1-oxide dienophiles (**2**) first reported by Weiler and Brennan.[16] We anticipated that the hydrolysis of the MCR adducts of these compounds would provide allylic sulfinic acids capable of undergoing a retro-ene fragmentation[17] concomitant with the required alkene migration (eq 2).



Thus, sulfinimide dienophiles **2a**−**d** bearing a variety of substituents at the nitrogen were obtained in excellent yield, and in only three steps following some small modifications to the original procedure.[16] Gratifyingly, these dienophiles reacted smoothly with heterodienes **1** in the presence of aldehydes under our previously optimized reaction conditions (Table 1). This process afforded the three-component adducts **10** in moderate to good yield following aqueous sodium bicarbonate workup and flash chromatography purification. It is remarkable that only a single regioisomer and stereoisomer of adducts **10** was observed in the crude reaction mixture. Obviously, the endo pathway operates in the aza-Diels−Alder reaction, and the regiochemistry is controlled by the electron-donating 1-amino substituent of the diene along with the carbonyl of the dienophile, which overrides the effect of the sulfoxide group. Moreover, the use of Waldner's chiral dienophile **2b**, obtained from the inexpensive and commercially available optically active (*R*)-(+)-α-methylbenzylamine,[12] afforded products that were virtually optically pure. The stereochemical outcome is explained by the endo transition structure whereby the diene approaches the dienophile from the face opposite to the S−O bond.



2b

Optimization of the Retro-Sulfinyl-Ene Fragmentation. To the best of our knowledge, the retro-sulfinyl-ene rearrangement process (eq 2) has never been employed in target-oriented synthesis, and only one study examined cyclic substrates.[17c] Thus, our design strategy to 2,6-disubstituted piperidines and the palustrine alkaloids relied on the successful implementation of such a retro-sulfinyl-ene fragmentation[17] involving the cyclic adducts **10** from the aza[4+2]/allylboration reaction between dienes **1**, dienophiles **2**, and aldehydes (Table 1). In this scenario, SO_2 extrusion from **10** would be concomitant with a migration of the C4−C5 unsaturation to the C3−C4 position, which is necessary for accessing methyl palustramate (**4**). Toward this end, **10e** (entry 5, Table 1) was arbitrarily selected for early exploratory work. The latter was submitted to standard retro-ene reaction conditions consisting of a treatment with 5% aq NaOH, followed by acidification to generate in situ the sulfinic acid intermediate **11**. The desired retro-ene product **12e** was obtained, albeit in low yield. To our surprise, when the *tert*-butyl group of the dienophile was replaced with the *n*-propyl-substituted analogue **10c** (entry 3, Table 1), no retro-ene product was observed. Likewise, when the aldehyde side chain was replaced with a less sterically demanding group (e.g **10f**, entry 6, Table 1), no product formation was observed either. Longer stirring time in the acidic media or attempt to warm the solution to room temperature mainly resulted in decomposition. Clearly, an improved retro-ene procedure was required. This was achieved by carefully quenching the acidic solution with a weak base (aqueous $NaHCO_3$), followed by removal of the solvent. The sulfinic acid intermediate **11** was then dissolved in chloroform and heated. Only then was the desired product isolated in all cases, although the reaction time and temperature were still a function of the steric bulk of R^3 and R^4. In general, as the size of these groups increases, the reaction time and temperature can be decreased significantly.

Although the reasons for this reactivity trend remain speculative, conformational effects may be at play to explain the different behavior of **10a**−**10i**. To reach the six-membered transition state for a concerted retro-sulfinyl-ene fragmentation,[17d] the sulfinic acid substituent must occupy a pseudoaxial orientation (conformer B) (Figure 2). This reactive conformer also features two disfavored gauche interactions between the bulky hydrazine substituents (R^1 and R^2) and both the α-hydroxyalkyl chain and the carboxamide. To minimize this type

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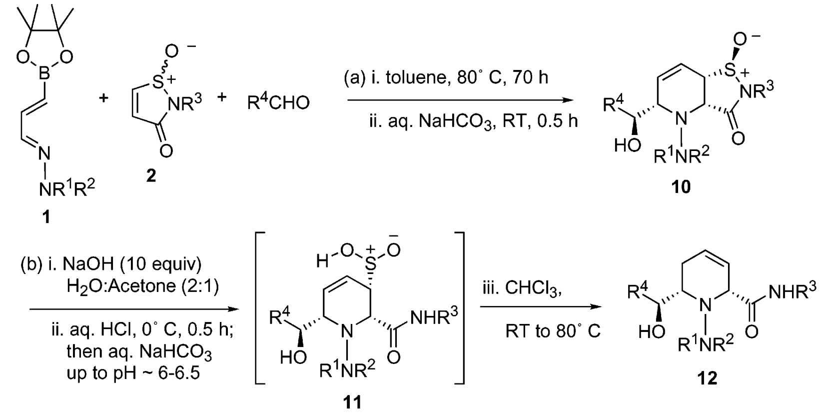
TABLE 1. Scope of the Three-component Aza[4+2]/Allyboration and the Retro-Sulfinyl-Ene Fragmentation Reaction Sequence[a]



entry	diene no.	diene R^1	diene R^2	dienophile no.	dienophile R^3	aldehyde R^4	product	yield[b] (%)	product	yield[c] (%)
1	**1a**	Me	Me	**2a**	*t*-Bu	Cy	**10a**	65	**12a**	55
2	**1a**	Me	Me	**2b**	PhCH(Me)	Ph	**10b**	50	**12b**	65
3	**1a**	Me	Me	**2c**	*n*-Pr	Ph	**10c**	51	**12c**	52
4	**1a**	Me	Me	**2d**	PhCH(Me)	*n*-Bu	**10d**	52	**12d**	65
5	**1a**	Me	Me	**2a**	*t*-Bu	Ph	**10e**	49	**12e**	69
6	**1a**	Me	Me	**2a**	*t*-Bu	Et	**10f**	41	**12f**[d]	
7	**1a**	Me	Me	**2b**	PhCH(Me)	Et	**10g**	44	**12g**	80
8	**1b**	Ph	Me	**2b**	PhCH(Me)	Et	**10h**	41	**12h**	80
9	**1c**	Bn	Bn	**2b**	PhCH(Me)	Et	**10i**	62	**12i**	78
10	**1d**	H	Boc	**2b**	PhCH(Me)	Et	**10j**	0	**12j**	
11	**1e**	H	Ac	**2b**	PhCH(Me)	Ph	**10k**	0	**12k**	
12	**1g**	*e*		**2b**	PhCH(Me)	Ph	**10l**	0	**12l**	

[a] All aza[4+2]/allylboration reactions were carried out by heating a 1:1:2 mixture of diene/dienophile/aldehyde, except for propionaldehyde where 5 equiv were used, in anhydrous toluene [0.2−0.3 M] at 80 °C for 72 h. Racemic **2b** was used throughout except for making **10b**, **10g**, **12g**, and **12i**, which were accessed from optically pure **2b** (*β*-sulfoxide diastereomer) derived from (*R*)-(+)-α-methylbenzylamine (see experimental details in the Supporting Information). [b] Yields of isolated products after flash chromatography purification. [c] The products were obtained after reflux for 12−48 h in $CHCl_3$ and flash chromatography purification (**12e** was simply stirred at room temperature). [d] Reaction not attempted. [e] Diene made from *O*-methylhydroxylamine, R^1NR^2 = OMe. For **1f**, see Scheme 3.

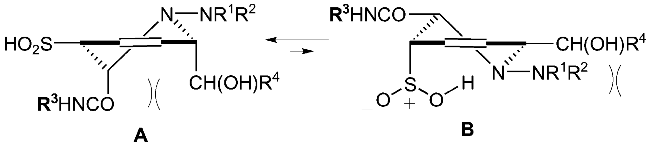


FIGURE 2. Suggested conformational equilibrium to explain the influence of the amide substituent (R^3) of intermediates **11** in the retro-sulfinyl-ene rearrangement.

of strain, closely related *cis*-2,6-disubstituted piperidines have been shown to adopt a "diaxial" conformation of type A.[18] In this nonreactive conformer A, the carboxamide group occupies a pseudoaxial orientation. Thus, we hypothesize that bulkier *N*-alkyl substituents on the amide may affect the conformational equilibrium and facilitate the retro-ene fragmentation by destabilizing conformer A to the benefit of reactive conformer B. Another possible explanation is epimerization of the sulfinic acid substituent in **11**, forcing a highly unfavorable reactive conformer with all-axial substituents.

Overall, this tandem aza[4+2]/allylboration/retro-ene sequence allowed the construction of the entire core with all the requisite stereocenters of the palustrine natural products (**3**−**5**) in only two synthetic operations (compounds **12**, Table 1). From there, the completion of the synthesis of **3** and **4** requires the chemoselective cleavage of the N−N bond followed by a one-carbon homologation of the amide side chain (Scheme 1). Strategically, we first decided to tackle what we perceived as the major challenge: the chemoselective cleavage of the N−N bond in the presence of the C3−C4 olefin.

Model Studies toward Methyl Palustramate (4): Examination of Traditional Methods for Hydrazine Cleavage. Our synthetic plan, from the outset, first stressed the need to cleave the N−N bond in a chemoselective manner that would preserve the C3−C4 double bond. We envisioned three main strategies to accomplish this task: (1) the use of hydrazides or *N*-alkoxyamines, which usually can be cleaved under mild reaction conditions to afford the desired amines, (2) activation of trialkylhydrazines after the retro-ene reaction step, or (3) exploring the feasibility of a direct cleavage of tetraalkylhydrazines by using either the oxidative or reduction cleavage methods mentioned above. To test the first hypothesis, we prepared the known dienes **1d**−**e** (entries 11 and 12, Table 1)[4b] and **1g**, and tested their ability to undergo the aza-Diels−Alder reaction with dienophile **2**. Despite significant efforts, no desired cycloaddition product was obtained probably due to the lower reactivity of these dienes, which are less electron

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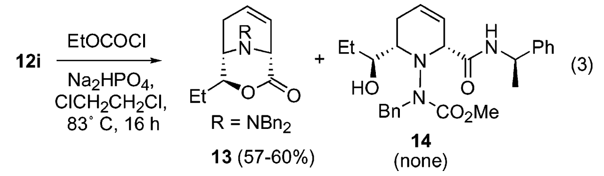
(18) For example, *N*-acylated *cis*-2,6-disubstituted piperidines exist in the "diaxial" conformation to escape $A^{1,3}$ strain between the planar exocyclic amide group and the neighboring substituents in the "diequatorial" conformation: Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442−3445 and references therein. In the case of compounds **11**, the planar hydrazine can be considered isosteric to an acyl group.

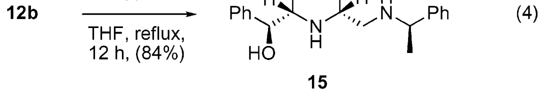
rich than **1a**−**c**. We next examined the activation of the hydrazine moiety following the MCR/retro-ene sequence. Toward this goal, we hoped to take advantage of the well-established *N*-debenzylation of tertiary amines using chloroformates, although this strategy had never been applied to hydrazines before.[19a,b] Accordingly, 1-dibenzylhydrazine was synthesized in two steps then condensed with 3-boronoacrolein,[4b] and the resulting diene **1c** was carried through our sequential tandem [4+2]/allylboration/retro-sulfinyl-ene reaction to afford **12i** (entry 9, Table 1). However, when the latter was treated with ethylchloroformate or α-chloro ethylchloroformate under known reaction conditions,[19c] none of the expected debenzylated product **14** was obtained (eq 3).

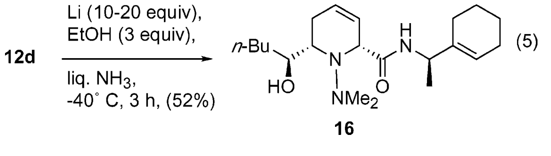


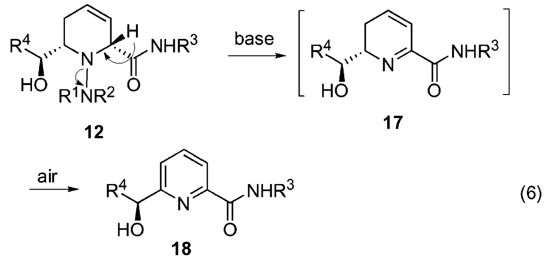
Instead, the intramolecular lactonization product **13** was observed. The latter most likely results from indirect amide activation through intramolecular acyl transfer between the first formed, quaternized acylated hydrazine and the secondary amide.

These failures prompted us to explore the use of more direct strategies. Our first attempt relied on the oxidative cleavage methodology.[15] On the basis of the proposed mechanism for this reaction, we reasoned that the oxidant would preferentially react with the least hindered exocyclic nitrogen, hence leading to a selective N−N fragmentation. In this approach, the high reactivity of the nitrogen toward electrophilic peroxide reagents should also preclude any competitive epoxidation of the C3−C4 olefin. However, when we put this hypothesis to the test with substrate **12g** under various reaction conditions (e.g. MMPP, mCPBA), only decomposition product was observed.

Likewise, treatment of **12g** with zinc, a reductive N−N cleavage method,[6] did not yield any of the desired N−N cleaved product. However, powerful reducing agents, typified by Red-Al, did yield the desired N−N cleavage product **15** albeit the carbonyl functionality could not be preserved during this operation, thereby rendering the one carbon homologation difficult (eq 4). Finally, an attempt to achieve the one-pot amide debenzylation/N−N cleavage under Bouveault-Blanc-type conditions, and variants thereof,[20] only resulted in the reduction of the aromatic moiety to afford **16**. The latter result is particularly telling of the difficult challenge that represents the cleavage of tetraalkylhydrazines (eq 5).







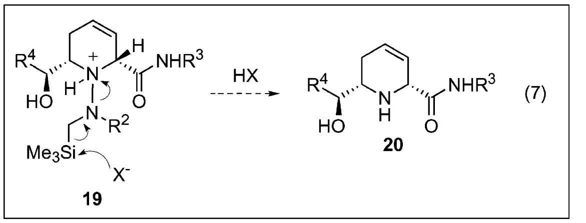


FIGURE 3. Design of a nonreductive hydrazine cleavage strategy.

Design of a Nonreductive Hydrazine Cleavage Strategy. The failures of traditional N−N cleavage methods with tetraalkylhydrazines **12** exposed an important methodological gap in organic synthesis. A potential solution to this problem arose from an understanding of the reactivity of compounds **12**. In the course of our studies, we had realized that these compounds are unstable to basic conditions, giving pyridines as products. Indeed, treatment of **12** with bases such as Et_3N or DBU results in the effective cleavage of the N−N bond to give **17**, presumably via deprotonation of the acidic C2 proton, followed by air oxidation to afford **18** (eq 6, Figure 3).

Along this line, we reasoned that compound **20** could be obtained if a suitable anion precursor could be introduced next to the exocylic nitrogen. After careful consideration, we chose to include a Me_3SiCH_2- substituent to the hydrazine **19**, and test the feasibility of a fragmentation process reminiscent of the removal of a [2-(trimethylsilyl)ethoxy]methyl (SEM) protective group[21a,b] (eq 7, Figure 3). This type of silylated hydrazine, however, was apparently unknown. The discovery of a convenient synthetic route to this class of reagent became the next focus of our efforts.

A New Acid-Cleavable Hydrazine. The commercially available ((trimethylsilyl)methyl)benzylamine was first nitrosated under standard reaction conditions in an aqueous acetic acid solution (Scheme 2). The unstable nitroso intermediate **21** undergoes slow decomposition at room temperature, which can be accelerated by heating. Consequently, it was rapidly reduced to the desired hydrazine **22** at low temperature. The latter was obtained in sufficiently high purity that it could be carried through the next step without the need for any purification. Alternatively, the hydrazine could be purified by simple acid−base extraction or bulb-to-bulb distillation.

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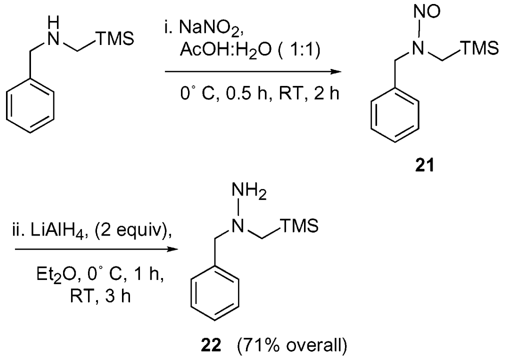
[19] (a) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567−1570. (b) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfoot, T. *J. Org. Chem.* **1984**, *49*, 2081−2082. (c) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195−196.

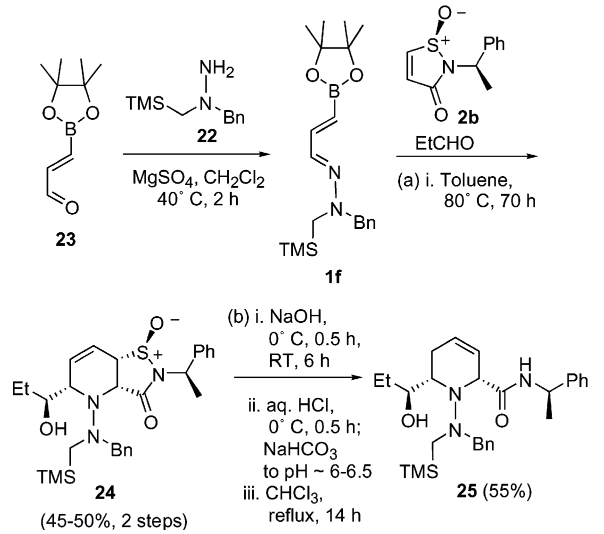
[20] See the Supporting Information for the preparation of compound **1** in: Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390.

[21] (a) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343−3346. (b) Whitten, J. P.; Matthews, D. P.; McCarthy J. R. *J. Org. Chem.* **1986**, *51*, 1891−1894.

SCHEME 2. Synthesis of 1-(Trimethylsilylmethyl)-1-benzylhydrazine



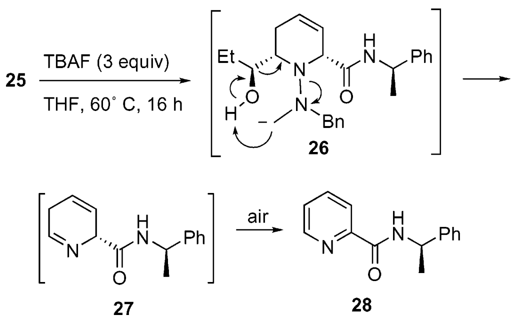
SCHEME 3. Sequential Aza[4+2]/Allylboration Route to the Key Hydrazine Cleavage Precursor 25



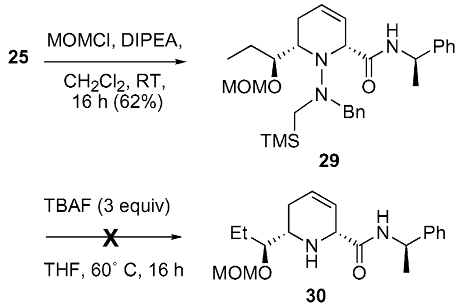
Synthesis of (−)-Methyl Palustramate (4): Construction of the [4+2]/Allylboration/Retro-Sulfinyl-Ene Adduct 25. Hydrazine **22** was first condensed with boronoacrolein **23** in refluxing dichloromethane under dehydrating reaction conditions to afford diene **1f** as a mixture of different geometrical isomers. The latter was carried through the three-component [4+2]/allylboration reaction involving dienophile **2b** and freshly distilled propionaldehyde (Scheme 3). The MCR-adduct **24** was obtained as a single stereoisomer, albeit, in moderate yield due to partial decomposition of the product under the conditions involving long reaction times. Compound **24** was then submitted to our optimal conditions for the retro-sulfinyl-ene reaction to afford key intermediate **25**. The latter was found to be slightly unstable on silica gel, and thus was best carried through the next step without any purification from **24**. The stage was now set for testing the hydrazine cleavage strategy.

Chemoselective N−N Fragmentation on Intermediate 25. We first explored the tetrabutylammonium fluoride (TBAF)-mediated desilylation reaction conditions.[21a,b] Compound **25** was heated in THF in the presence of 3 equiv of TBAF overnight. To our dismay, after workup, the ^{1}H NMR spectrum of the crude product revealed a clean conversion of the starting material to pyridine **28**, which is consistent with a C−C fragmentation via the proposed mechanism depicted in Scheme 4. To prevent the reaction from proceeding via this undesired pathway, the alcohol was protected as its methoxymethyl ether **29**. When the latter product was submitted to the above reaction conditions, however, none of the desired product **30** was obtained (Scheme 5).

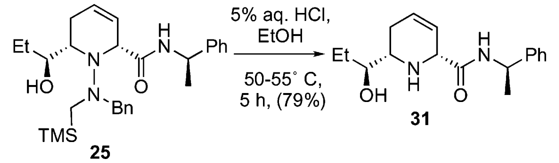
SCHEME 4. Undesired TBAF-Promoted C−C Cleavage



SCHEME 5. Attempted TBAF-Promoted N−N Cleavage with MOM-Protected Substrate 29



We then turned our attention to the acid-promoted desilylation conditions.[21b] Gratifyingly, when key intermediate **25** was stirred in ethanolic aqueous HCl solution, a very clean conversion of the starting hydrazine to the desired product **31** along with benzylamine coproduct were observed in the ^{1}H NMR of the crude reaction mixture (eq 8).



(8)

Completion of the Synthesis of Methyl Palustramate (4). With this key N−N cleaved product **31** in hand, we next addressed the one-carbon homologation issue that we hoped to accomplish via the previously described Arndt−Eistert reaction sequence.[11] For this purpose, the amino alcohol **31** was first converted in excellent yield to its carbamate derivative with use of carbonyl diimidazole (Table 2). Selective hydrolysis of the amide group could only be performed through formation of the *N*-nitroso derivative **32**.[22a] Unfortunately, epimerization occurred at C2 in this operation, and the desired 2,6-cis-configured acid product was only obtained as the minor

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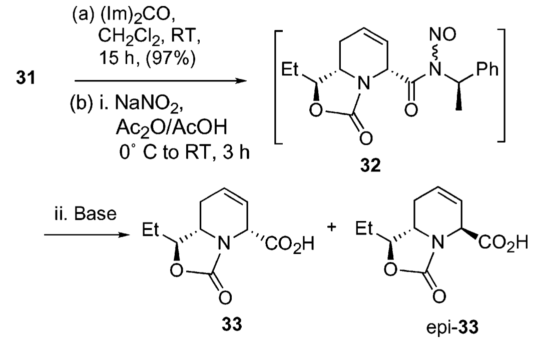
[22] (a) White, E. M. *J. Am. Chem. Soc.* **1955**, *77*, 6011−6014. (b) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535−4538.

TABLE 2. Optimization of the Hydrolysis of Amide 31



entry	base	temp (°C)	time (h)	ratio[b] **33**:*epi*-**33**
1	NaOH	23	16	1:7
2	KOH	23	16	1:4
3	LiOH	23	16	1:5
4	$Ba(OH)_2$	23	16	1:2.3
5	$Ba(OH)_2$	0	8	1:1.6
6	$Ba(OH)_2$	−10	16	1:1
7	LiOOH	0	8	1:1
8	LiOOH	−10	15	3.3:1

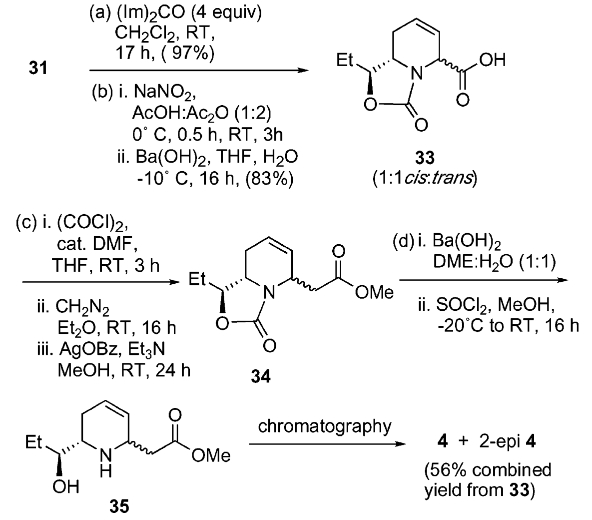
[a] The reaction was performed on a 10−15 mg sample of **32**. [b] The ratio of **33**:*epi*-**33** was determined by proton NMR of the crude reaction mixture after workup.

isomer in a 2:1 ratio. This result contrasted with our earlier observations with the saturated analogue, whereby the 2,6-*cis*-piperidine was always observed as the major product for a nitrosation time of 3 h or less.[11] It is interesting to note that the nitroso compound **32** is prone to epimerization even in the absence of any external base. Indeed, complete inversion of the C2 stereochemistry could be observed by simply maintaining a chloroform solution of **32** at room temperature overnight. Moreover, when the *N*-nitrosation was allowed to proceed at room temperature for longer reaction times, the undesired 2,6-trans-isomer *epi*-**33** was obtained almost exclusively.

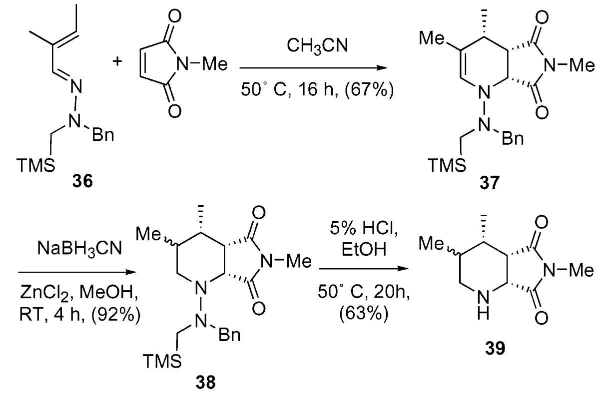
To reverse this trend, we thus set out to investigate the effect of base and temperature on the stereochemical outcome of this hydrolysis reaction. The results are summarized in Table 2.

The best result was obtained at low temperature, using the highly nucleophilic lithium hydrogen peroxide previously reported by Evans and co-workers (entry 8, Table 2).[22b] However, in this case, the product was always contaminated by an inseparable pyridine byproduct. Thus, for the completion of the synthesis, we opted for the barium hydroxide conditions, which provided a clean reaction with a 1:1 ratio of C2 epimers (entry 6, Table 2). The required homologation was performed on the 1:1 epimeric mixture of carboxylic acids **33**, using an Arndt−Eistert sequence (Scheme 6). The two epimers **34** were directly subjected to the final step of amino alcohol deprotection with the method of Weinreb and co-workers, using barium hydroxide.[23] Re-esterification of the resulting amino acid and effective chromatographic separation afforded (−)-methyl palustramate (**4**), which possessed spectral characteristics and an optical rotation value in agreement with reported literature data.[10f]

SCHEME 6. Synthesis of Methyl Palustramate (4)



SCHEME 7. Construction of Model Compound 38 for Investigation of the Scope and Mechanism of the Hydrazine Cleavage Methodology



Preliminary Study of the Scope and Mechanism of the Hydrazine Cleavage Method. The C−C fragmentation during the TBAF-promoted N−N cleavage (i.e. **25** to **28**) prompted us to investigate any possible implications of the proximal side chain alcohol under the hydrazinolysis conditions. Toward this end, bicyclic compound **37** was prepared via an aza-Diels−Ader reaction between diene **36** and *N*-methyl maleimide (Scheme 7). The sodium cyanoborohydride reduction of the enamine **37** resulted in a 2:1 diasteromeric mixture at the methyl stereocenter, which was inconsequential for our study. When the latter compound (**38**) was subjected to our N−N cleavage conditions, the desired reaction product **39** was obtained in a nonoptimized yield of 63%. The reaction time, however, was significantly longer. In light of this result, it seems plausible that the alcohol functionality in the α-hydroxyalkyl derivative **25** participates and accelerates the N−N cleavage via nucleophilic attack of the silicon atom. Considering the failure of the TBAF-promoted method, protonation of the endocyclic nitrogen seems essential for a successful N−N cleavage in this context. Despite the longer reaction time, the successful N−N cleavage of compound **38** suggests a wide scope of application for this novel class of acid-cleavable hydrazine.

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[23] Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240−3245.

Conclusion

In summary, we have described a three-component aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene sequential reaction approach to access *cis*-2,6-disubstituted piperidines in a highly regio-, diastereo-, and enantioselective fashion. Few multicomponent reaction strategies demonstrate such a high level of stereocontrol in the formation of complex, functionalized compounds. The utility of this powerful step-economical process was successfully demonstrated with a concise enantioselective synthesis of the palustrine relative (−)-methyl palustramate (**4**). The entire sequence to reach target **4** was accomplished with only two purification steps, and in only 10 linear synthetic operations from commercial 3,3′-diethoxypropyne.[4b] Along the way, we have developed the first class of hydrazines that can be cleaved nonreductively under mild acidic conditions in the presence of unsaturations. This new trimethylsilylmethyl-substituted hydrazine played a pivotal role in the completion of the synthesis of **4**. Further applications of this class of hydrazines including the development of a chiral variant are currently under investigation and will be reported in due course.

Acknowledgment. Financial support for this research by the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant to D.G.H.), AstraZeneca (Chemistry Award to D.G.H.), and the University of Alberta is gratefully acknowledged. B.B.T. thanks the Canadian Institutes for Health Research (CIHR) for a graduate scholarship. We are grateful to Prof. Steven R. Angle (University of California-Riverside) for a copy of the ^{13}C NMR spectrum of **4**. We thank Glen Bigam and Lai Kong for NMR analyses.

Supporting Information Available: Full experimental details with synthetic procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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