Piperidine Synthesis

Three-Component Sequential Aza[4+2] Cycloaddition/Allylboration/Retro-Sulfinyl-Ene Reaction: A New Stereocontrolled Entry to Palustrine Alkaloids and Other 2,6-Disubstituted Piperidines**

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Multicomponent reactions[1] that generate complex, functionalized structures from simple substrates are very attractive step-economical strategies in target-oriented synthesis.[2] We have recently reported on the three-component hetero[4+2] cycloaddition/allylboration reaction[3] for the preparation of α-hydroxyalkylated piperidines[4] and furans[5a] (Scheme 1). In the case of piperidines, this one-pot process is initiated by a hetero-Diels–Alder reaction between boronate-substituted hydrozonobutadienes (**1**) and electron-poor dienophiles. The formation of the resulting cycloadduct unmasks an allylboronate that adds in situ onto aldehydes to provide polysubstituted piperidine products in a highly stereoselective fashion.

We were interested in the challenge of adapting this process to access 2,6-disubstituted piperidine units[6] such as those featured in the palustrine class of alkaloids exemplified

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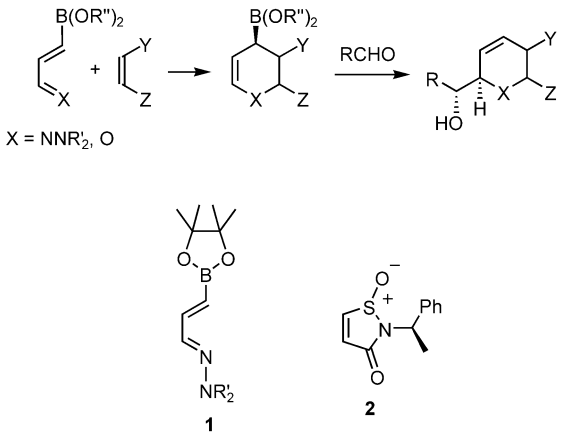
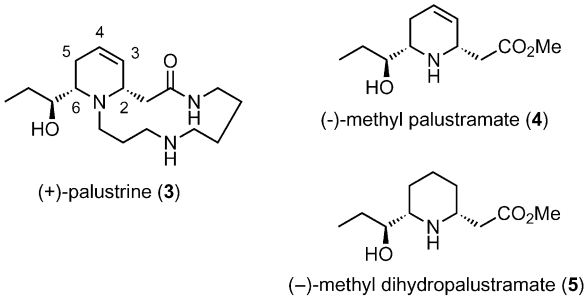


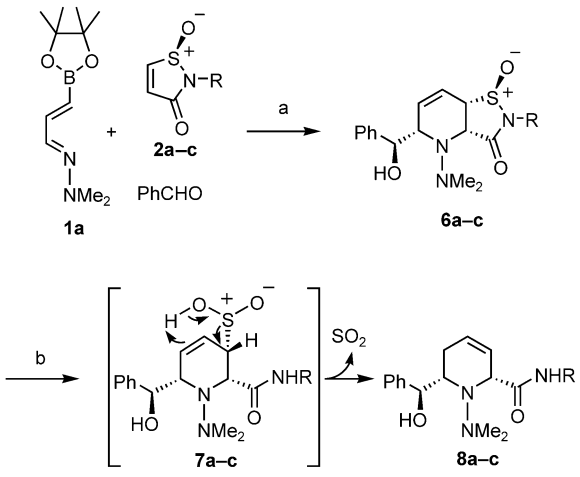
Scheme 1. Top: the three-component hetero[4+2] cycloaddition/allylboration reaction strategy to access α-hydroxyalkyl-substituted six-membered heterocycles. Bottom: the key components boronate-substituted hydrazonobutadiene **1** and the chiral sulfinimide dienophile **2** used in this study.

by palustrine itself (**3**), methyl palustramate (**4**), and the saturated degradation product methyl dihydropalustramate (**5**).[7,8] Unfortunately, in the normal electron-demand [4+2]



manifold, the bulky electron-withdrawing 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. Acrylates are unreactive,[9] and since targets **3**–**5** are unsubstituted in the 3-position, a new diactivated dienophile was needed that would meet the following requirements: 1) possess the requisite electronic characteristics to react with heterodienes **1**; 2) provide high enantiofacial selectivity; and 3) lead to a cycloadduct that can be converted to both C3–C4 dehydro compounds and the corresponding saturated series. Here, we describe how Waldner's chiral sulfinimide dienophiles[10] (**2**, Scheme 1) satisfy all these requirements in the way of a novel three-component sequential aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene reaction. This approach was then applied to the enantioselective synthesis of (−)-methyl dihydropalustramate (**5**).

Our design strategy to 2,6-disubstituted piperidines and the palustrine alkaloids relied on the successful optimization of a model retro-sulfinyl-ene reaction[11] involving the products **6** from the aza[4+2] cycloaddition/allylboration of diene **1a**, dienophiles **2**, and benzaldehyde (Scheme 2). To the best



	T [°C]	t [h]	Product	Yield [%]
a R = *n*Pr	60	16	**8a**	52
b R = *t*Bu	RT	12	**8b**	69
c R = 	60	12	**8c**	65

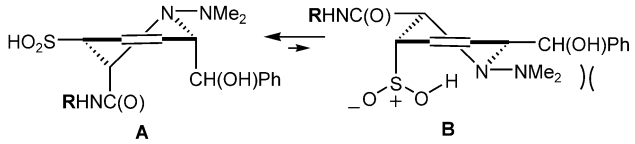
Scheme 2. Optimization of the aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene sequential reaction. a) 1. Toluene, 80°C, 70 h, 2. aq $NaHCO_3$, RT, 0.5 h; b) 1. NaOH (10 equiv), H_2O/acetone (3:1), 0°C, 0.5 h then RT, 6 h, 2. 10% aq HCl, 0°C, 0.5 h then aq $NaHCO_3$ up to pH 6–6.5, 3. $CHCl_3$. See table for reaction temperature and time. RT = room temperature.

of our knowledge, this interesting fragmentation process has never been employed in target-oriented synthesis, and only one study examined cyclic substrates.[11c] In the case of substrates **6**, SO_2 extrusion would be concomitant with a migration of the C4–C5 double bond to the C3–C4 position, which is necessary for accessing methyl palustramate (**4**) in addition to the saturated analogue **5** following hydrogenation. Model studies focused on the reaction of heterodiene **1a** with dienophiles **2a**, **2b**, and the chiral one **2c** developed by Waldner.[10]

To our satisfaction, with the same reaction conditions as those employed with maleimides,[4] the corresponding cycloadducts **6a**–**c** were isolated in good yields as single regio- and diastereomers.[12] Although the high diastereofacial selectivity of Diels–Alder reactions with dienophile **2c** had been demonstrated,[10] the use of its cycloadducts in retro-sulfinyl-ene reactions is unprecedented. Here, intermediates **6a**–**c** were subjected to hydrolytic conditions optimized to generate the corresponding sulfinic acids. First, the intermediates were treated with aqueous base, then the solution containing the sulfinate salt was carefully acidified[13] to pH 6.0–6.5 and concentrated to give the resulting sulfinic acids **7a**–**c**, which were stirred in chloroform.

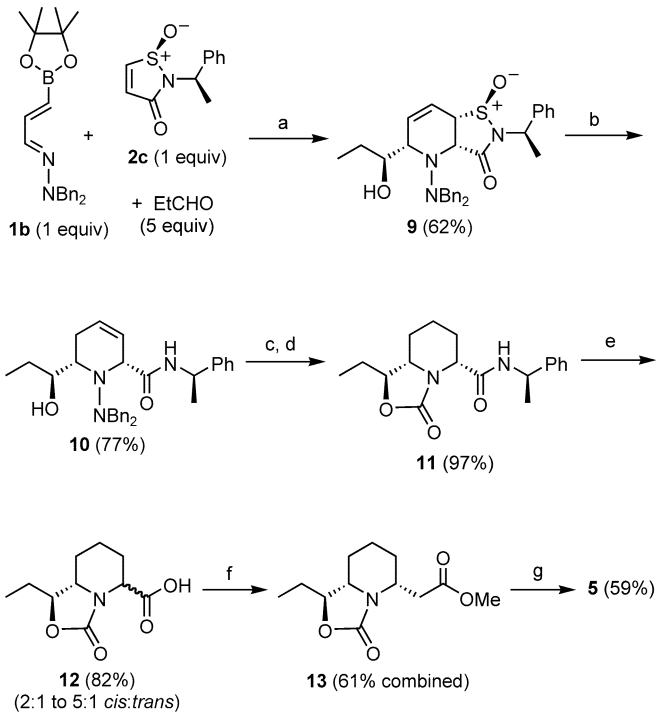
To our surprise, we found that the fragmentation propensity of **7a**–**7c** was highly dependent on the nature of the amide's N-alkyl substituent. Thus, while the *N-tert*-butyl derivative **7b** fragmented at room temperature, the *N*-propyl analogue **7a** required high temperatures and resulted in a lower yield of product. The chiral derivative **7c** required for a stereoselective synthesis of the palustrine alkaloids was found

to possess intermediate reactivity and provided an acceptable yield of *cis*-2-carbamoyl-6-hydroxyalkyl piperidine product **8c**.[12] Although the reasons for this reactivity trend remain speculative, conformational effects may be evoked to explain the different behavior of **7a**–**7c** (Scheme 3). To reach the six-membered transition state for a concerted retro-sulfinyl-ene fragmentation,[11d] the sulfinic acid substituent must assume a pseudoaxial orientation (conformer **B**). This reactive conformer also features two disfavored gauche interactions between the bulky NMe_2 hydrazine group, and the α-hydroxyalkyl chain and the carboxamide. To minimize this type of strain, closely related *cis*-2,6-disubstituted piperidines have been shown to adopt a "diaxial" conformation of type **A**.[14] In this nonreactive conformer **A**, the carboxamoyl group occupies a pseudo-axial position. 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**.



Scheme 3. Suggested conformational equilibrium to explain the influence of the amide substituent (R) of intermediates **7** in the retro-sulfinyl-ene rearrangement.

We tested the applicability of the sequential aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene reaction to the test by first targeting (−)-methyl dihydroplustramate (**5**) (Scheme 4). To this end, we employed butadiene **1b**, which was easily made from the known 3-boronoacrolein pinacolate[15] through simple dehydrative hydrazone formation with 1,1-dibenzylhydrazine.[12] The key one-pot three-component reaction between equimolar amounts of **1b** and **2c** in the presence of excess propanaldehyde furnished the heterobicyclic adduct **9** as a single regio- and diastereomer in 62% yield. To effect the retro-sulfinyl-ene fragmentation, **9** was hydrolyzed and heated as described above for compounds **6a**–**c**. The desired amide product **10** was isolated in 77%. Ra-Ni-promoted hydrogenolysis of the hydrazine and concomitant reduction of the double bond was followed by protection of the aminoalcohol to afford the carbamate intermediate **11** in high overall yield. Selective hydrolysis of the amide group of **11** was performed through formation of the *N*-nitroso derivative.[16] Unfortunately, in all conditions attempted, epimerization occurred in this operation, and the major 2,6-*cis*-configured acid product was always accompanied with variable amounts of the *trans* isomer. The required homologation was performed on the epimeric mixture of carboxylic acids **12** using an Arndt–Eistert sequence. The two isomers were readily separable at that stage, and the *cis* isomer **13** was subjected to the final step of aminoalcohol deprotection. This transformation proved difficult with a known hydrolysis procedure,[8d] but we eventually succeeded with the method of Weinreb and co-workers using barium hydroxide.[17]



Scheme 4. Total synthesis of (−)-methyl dihydropalustramate (**5**). a) 1. Toluene, 80°C, 70 h, 2. aq $NaHCO_3$, RT, 0.5 h; b) 1. NaOH, H_2O/acetone (3:1), 0°C, 0.5 h then RT, 6 h, 2. aq HCl, 0°C, 0.5 h then aq $NaHCO_3$ up to pH 6.5, removal of solvents; 3. $CHCl_3$, reflux, 16 h; c) Ra-Ni, EtOH, 60°C, 450 psi, 24–48 h, 85%; d) Im_2CO (4 equiv), CH_2Cl_2, RT, 17 h; e) 1. $NaNO_2$, AcOH/Ac_2O (1:2), 2. LiOH, THF, H_2O, 0°C to RT, 16 h; f) 1. $(COCl)_2$, cat DMF, THF, RT, 3 h, 2. CH_2N_2, Et_2O, RT, 16 h, 3. AgOBz, Et_3N, MeOH, RT, 24 h; g) 1. $Ba(OH)_2$, DME/H_2O, 2. $SOCl_2$, MeOH, 60°C, 16 h. DME = 1,2-dimethoxyethane, DMF = dimethylformamide, Im = imidazole.

Reesterification of the resulting amino acid afforded (−)-methyl dihydropalustramate (**5**), the spectroscopic characteristics and optical rotation value of which are in agreement with reported literature data.[12,18] The entire sequence to reach target **5** was accomplished with very few purification steps, and in only 10 linear synthetic operations from commercial 3,3′-diethoxypropyne.[12] Further adaptations of this strategy to include chemoselective cleavage of the N–N bond for preserving the C3–C4 unsaturation is expected to allow access to **3** and **4**.

In summary, we have described a novel three-component sequential aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene reaction to access *cis*-2,6-disubstituted piperidines in a highly regio- and diastereoselective fashion. The utility of this powerful and step-economical process was successfully demonstrated with a concise enantioselective synthesis of the palustrine degradation product (−)-methyl dihydropalustramate (**5**). Few multicomponent reaction strategies demonstrate such a high level of stereocontrol in the formation of complex, functionalized compounds.

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Keywords: allylation · asymmetric synthesis · cycloaddition · multicomponent reactions · nitrogen heterocycles · piperidines

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[18] We are grateful to Prof. Osamu Muraoka (Kinki University, Japan) for copies of the ^{1}H and ^{13}C NMR spectra of **5**.

