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Remarkable Stereoselectivity in Intramolecular Borono-Mannich Reactions: Synthesis of Conduramines

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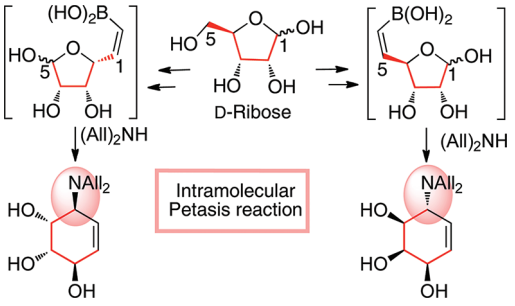
ABSTRACT



An unprecedented intramolecular Petasis condensation provides a novel approach to biologically important conduramines. The compounds are produced with an exclusive *anti* stereoselectivity for the newly created β-amino alcohol motif. The stereochemical outcome of the reaction is opposite to the one usually observed in the intermolecular reaction.

The Petasis multicomponent reaction of aryl- or vinylboronic acids with amines and carbonyl compounds, such as α-hydroxy aldehydes, α-keto acids, and salicylaldehydes, has recently been the subject of considerable attention.[1] In a single process, with minimum protecting group manipulation and in mild reaction conditions, amino acids, β-amino alcohols, or aminophenol derivatives are produced. When the carbonyl partner is an optically pure α-hydroxyaldehyde, the reaction remarkably leads to the corresponding amino alcohol with a high degree of diastereocontrol, forming exclusively the *anti* adduct as a single enantiomer.[2,3] The reaction is believed to proceed through a transient iminium species followed by an intramolecular transfer of the organyl ligand from the activated 'ate' complex of organoboronic acid.[4] Using this methodology, the syntheses of elaborated compounds such as polyfunctionalized pyrrolidines,[5] iminosugars,[6] *N*-acetylneuraminic acid,[7] or new constructs such as

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(3) Very recently, *syn* β-amino alcohols were produced for the first time using a catalytic diastereoselective Petasis reaction of boronates, α-hydroxy aldehydes, and amines: Muncipinto, G.; Moquist, P. N.; Schreiber, S. L.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8172–8175.

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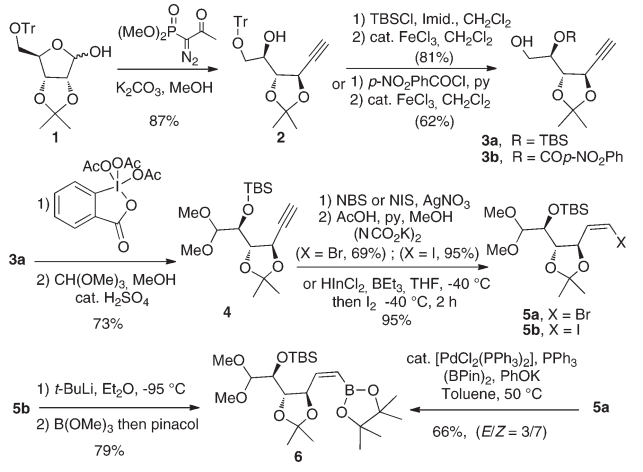
anti-neuraminidases and anti-influenza agents were achieved.[8] Here we report a novel approach to biologically important conduramines[9,10] that exploits an unprecedented intramolecular Petasis-type condensation.

The synthesis of the highly fonctionnalized intermediate **6**, having at the same time the α-hydroxyaldehyde function and a (*Z*) vinylic boronic acid, was first considered (Scheme 1). From the known 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose **1**,[11] an alkyne function, which will be the precursor of the boronic acid, was introduced with dimethyl(1-diazo-2-oxopropyl) phosphonate[12] under Demailly's conditions[13] (K_2CO_3, MeOH, 55 °C, 8 h) leading to **2** in a 87% yield.

Scheme 1. Conditions for the Preparation of Boronic Ester **6**

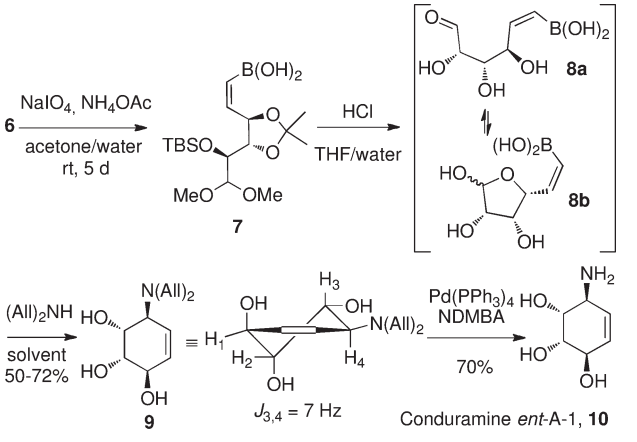


During this reaction, complete inversion of the center alpha to the alkyne occurred, resulting in the exclusive formation of the *trans* acetonide. There is some precedence for such an epimerization that could be attributed to the greater thermodynamic stability of the *trans*- over the *cis*-structure.[14,15] After protection of the resulting alcohol with a TBS group and deprotection of the trityl group in the presence of iron trichloride,[16] the primary alcohol **3a** was oxidized with the Dess Martin periodinane. The resulting aldehyde was then treated in the presence of trimethylorthoformate and a catalytic amount of sulfuric acid providing acetal **4** in a good 73% yield.

Direct hydroboration methods tested at this stage to obtain the vinylic boronic acid with a (*Z*) configuration,[17] which is required for the following cyclization,[18] provided disappointing results. The syntheses of the alkenyl bromide or iodide were thus considered. From **4**, vinyliodide **5b** was directly obtained using triethyl borane induced hydrometalation followed by iodolysis of the corresponding *Z*-alkenylindium species to furnish the desired adduct in a good 95% yield.[19] Bromide **5a** and iodide **5b** were also synthesized in two steps by halogenation of the alkyne with NBS or NIS in the presence of silver nitrate[20] followed by diimide *cis*-hydrogenation.[21]

The alkenylbromide **5a** was then submitted to a cross-coupling reaction of bis(pinacolato)diboron catalyzed by palladium in the presence of potassium phenolate.[22] However, the retention of the configuration of the double bond was not complete, and the reaction led to the alkenylboronic acid pinacol ester **6** in a 66% yield and a (*Z*)/(*E*) mixture of 70:30. Alternatively, halogen–metal exchange was carried out followed by treatment with trimethylborate and pinacol.[23] A large excess of trimethyl borate (20 equiv) was required to obtain the boronic ester **6** in a good yield. The latter was treated with sodium metaperiodate to lead to the corresponding boronic acid **7** in 73% yield over two steps (Scheme 2).

Scheme 2. Synthesis of Conduramine *ent*-A1



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(15) This was further proven by X-ray diffraction of **3b** obtained by *p*-nitrobenzoylation of **2** and deprotection of the trityl group in the presence of iron trichloride (see Scheme 1 and SI). CCDC 819082 contains the supplementary crystallographic data (www.ccdc.cam.ac.uk/data_request/cif).

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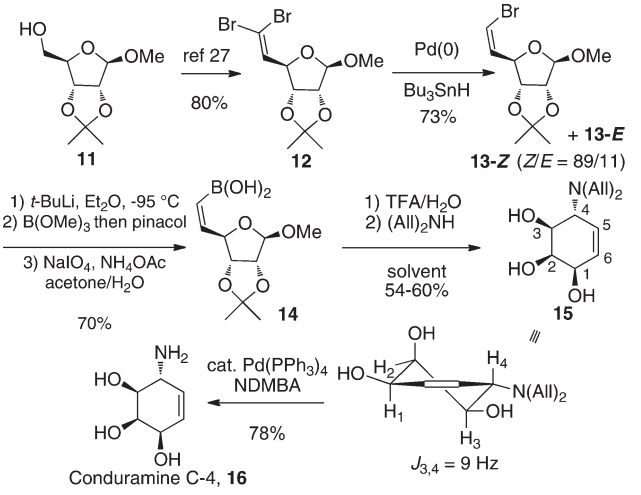
After fruitless attempts to selectively deprotect the α-hydroxyaldehyde, we opted for the removal of all the protecting groups by treatment with 6 N hydrochloric acid in THF. The reaction mixture was then concentrated and used directly in the intramolecular Petasis reaction. After optimization, the best results were obtained with an excess of diallylamine in a 4:1 mixture of ethanol/water at 80 °C for 192 h. The cyclization product **9** was obtained as a unique diastereomer in 72% yield. Using a 4:1 mixture of CH_2Cl_2/HFIP at 50 °C, the reaction time could be reduced to 96 h leading to the same cyclization adduct **9** in a 50% yield. For this compound, the coupling constant $^3J_{3,4}$ = 7.0 Hz points to a *trans* diaxial orientation between H-3 and H-4. In order to confirm this selectivity, **9** was deallylated using Guibe's conditions[24] to furnish conduramine *ent*-A-1 **10**, $[\alpha]_D^{25}$ +19.0 (*c* 0.1, MeOH).[10e] This compound, having an *anti* relationship between the amine and the α-hydroxyl group, is not the expected diastereoisomer according to the previous studies on intermolecular borono-Mannich condensation.[2,3,25]

Using the same strategy, conduramine C-4 was also prepared in a short six-step sequence from commercially available 2,3-*O*-isopropylidene-β-D-ribofuranoside **11** (Scheme 3).[26] Oxidation of the primary alcohol and elongation of the resulting aldehyde with PPh_3, CBr_4 in the presence of activated zinc afforded dibromoolefin **12**.[27] Pd-catalyzed hydrogenolysis of **12** with *n*-Bu_3SnH provided **13** as a 90:10 mixture of (*Z*):(*E*) stereoisomers that could be easily separated by flash chromatography.[28] Boronic acid **14** was obtained in a 70% yield after halogen−lithium exchange, intermediate trapping with trimethylborate, formation of the pinacol ester, and deprotection with sodium metaperiodate.

Complete deprotection of **14** was carried out with TFA for 2 h, and treatment of the crude reaction mixture with diallylamine in EtOH/water (80 °C, 192 h) or in CH_2Cl_2/HFIP (50 °C, 64 h) afforded **15** as a unique diastereoisomer in 54% and 60% yields respectively. The relative stereochemistry can be deduced unambiguously at this stage from the analysis of the ^{1}H NMR spectrum, showing a coupling constant $^3J_{3,4}$ = 9.0 Hz. This indicates a *trans* diaxial orientation between H-3 and H-4 that again implies an *anti* relationship between the C−N bond at C4 and the C−O bond at C3 of a new amino alcohol motif in **15**. Palladium-catalyzed removal of the allyl protecting group then provided conduramine C-4, $[\alpha]_D^{25}$ −170.0 (*c* 0.3, MeOH), in 78% yield (Scheme 3).[10a]

Scheme 3. Synthesis of Conduramine C-4



To rationalize the observed stereoselectivity of this intramolecular reaction leading to the formation of β-amino alcohols **9** and **15**, transition states (TSs) modeling was undertaken using dimethylamine. Transition structures based on all possible intramolecular coordinations at the boron atom by the α-, β-, or γ-oxygen relative to the aldehyde were built by blocking the C(boron)−C[N−(Me)$_2$] distance, forming a tetracoordinated borate intermediate in a seven-, six-, or five-membered ring.[29] For both compounds, 1000 conformations of each possible transition structure were generated by the Monte Carlo random search method[30] and optimized by PRCG molecular mechanics minimization[31] using the Macromodel (Version 5.5) program[32] with the MM2* force field.[33,29]Ab initio gradient optimizations of these structures using the B3LYP/6-31G(d,p) basis set were, then, performed with the Gaussian 03 program.[29]

The analysis of the energies and the geometries of these transition structures (see experimental section, Tables 1−6 in the Supporting Information) revealed that the most stable TSs were obtained with the six-membered rings having the B-atom coordinated with the β-oxygen (Scheme 4, Figure 1).

(18) Treatment of (*E*)-configurated vinylic boronic acid **14-*E*** (obtained from **13-*E***) with TFA and then with diallylamine in EtOH/water (4:1) failed to yield any cyclization product.

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(25) The *anti*-selectivity reported here in a cyclic system obviously corresponds to a *syn*-selectivity in an acyclic system.

(26) 2,3-*O*-Isopropylidene-β-D-ribofuranoside was also easily synthesized in one step from D-ribose: Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849–7856.

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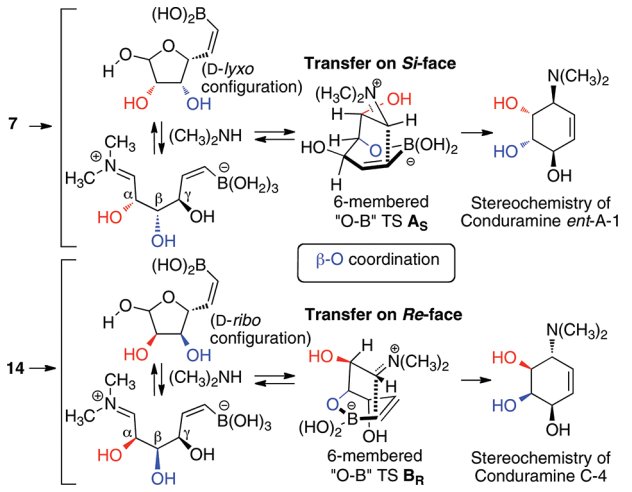
(33) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

Scheme 4. Rationalization of the Selectivity via a Six-Membered Ring TS



In these TSs, the $N(Me)_2$ group is in a *trans* position to both the α-OH and the $B(OH)_2$ groups, with the vinyl group transfer on the *Si*-face in $\mathbf{A_S}$ and the *Re*-face in $\mathbf{B_R}$ of the iminium ion (Scheme 4). This clearly explains the experimental formation of conduramine *ent*-A-1 from **7** and conduramine C-4 from **14**. The transition structures with the $N(Me)_2$ group in a *cis* position to the α-OH would lead to the other diastereoisomer, as in TS $\mathbf{B_S}$ (Figure 1). However, as the $N(Me)_2$ is also *cis* to the $B(OH)_2$, the steric interaction between a methyl group of the iminium ion and the hydroxyl group of the boronic acid strongly destabilizes the system by 8.91 kcal/mol.[34]

We have developed a novel approach to biologically important conduramines *ent*-A-1 and C-4 that exploits an unprecedented intramolecular Petasis-type condensation with high stereocontrol. The exclusive *anti* stereoselectivity for the newly created β-amino alcohol motif is opposite to the anticipated one found in previous *intermolecular* borono-Mannich condensations. According to our calculations on the key tetracoordinated borate intermediates, the reaction most likely proceeds through a six-membered TS involving the β-hydroxyl group of the aldehyde, with the α-OH and the $N(allyl)_2$ groups in *trans* positions. Further investigations are ongoing to clarify the precise mechanism and to extend the scope of this reaction.

(34) This rationalization may be hidden by the *anti*-relationship of the α-OH in both examples. *β-O*-Coordination was also suggested by the reaction of the α-OBn derivative of **8** which provided the cyclic amine with the same stereoselectivity.

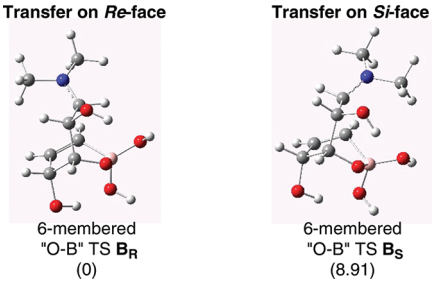


Figure 1. Comparison of the optimized geometries of the *β-O*-coordinated transition states for the formation of conduramine C-4 (ΔE in kcal/mol).

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Supporting Information Available. Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for all new compounds, crystallographic data for compound **3b**, results of the molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.