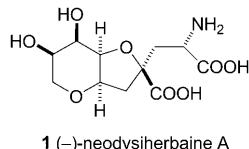


A Short and Efficient Synthesis of Neodysiherbaine A by Using Catalytic Oxidative Cyclization**

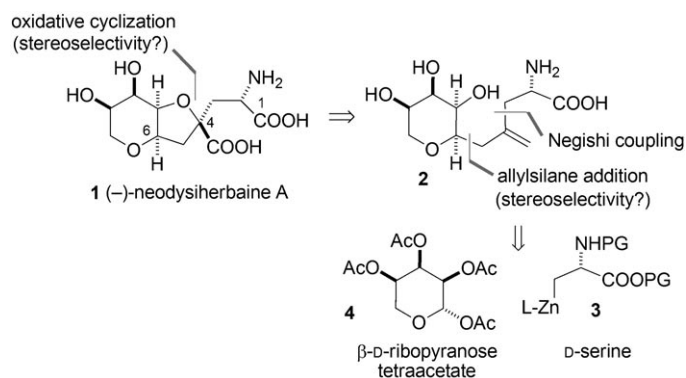
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Neodysiherbaine A is an excitatory amino acid isolated from the *Dysidea herbacea* Micronesian sponge by Sakai et al.^[1] Biological studies have shown that (–)-neodysiherbaine A



(1) is a potent convulsant and a highly selective agonist for kainate (KA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors.^[2] Considering its size, 1 has proven to be a challenging synthetic target and was first synthesized by Sakai et al. in 26 steps.^[1] Since the original report, 1 has also been synthesized by Sasaki and co-workers (23 steps)^[3] and Hatakeyama and co-workers (21 steps).^[4] The most efficient synthesis reported to date was completed by Lygo et al. in 15 steps starting from diacetyl-L-arabinal.^[5] However, all of these syntheses are lengthy and involve an oxidation/reduction sequence in order to accomplish hydroxy inversion on the sugar moiety.

As part of a program of research aimed at developing new catalytic methods for the formation of heterocycles, we chose 1 as a target upon which to test some recently developed methodology. Our retrosynthesis of this molecule began with the disconnection of the central tetrahydrofuran (THF) ring back to the hydroxy alkene 2 as shown in Scheme 1. We suspected that 2 would be an interesting precursor for our recently developed transition-metal-catalyzed oxidative cyclization.^[6] This reaction would enable the direct formation of



Scheme 1. Retrosynthetic analysis of (–)-neodysiherbaine A. PG = protecting group, L = ligand.

the heterocyclic ring and also set the correct stereochemistry at the quaternary C-4 center. Further disconnection of 2 reveals that the amino acid side chain could be installed by the Negishi coupling of a serine-derived organozinc reagent 3 with a vinyl halide that is attached to the sugar portion. Finally, we envisaged that the vinyl halide precursor for the Negishi coupling could be installed by the addition of an allyl-derived nucleophile to the anomeric center of the ribose sugar system 4 (note that the stereoselectivity of this addition would need to be *syn* to the existing stereogenic centers on the ribose to give the desired natural product stereochemistry at C-6). We anticipated that Woerpel and co-workers' recent work relating to the stereoselective addition of nucleophiles to oxocarbenium ions derived from pyranose sugar systems, could be usefully employed here.^[7]

Our synthesis began with commercially available β -D-ribose tetraacetate 4 (which can also be readily prepared in one step from D-ribose in 58% yield, if desired^[8]). This compound was treated with a Lewis acid (presumably forming an intermediate oxocarbenium ion) and the commercially available bromoallylsilane nucleophile 5 (Scheme 2). This reaction resulted in the installation of the bromoallyl group at the C-1 position of the sugar with *syn* selectivity; under the optimized conditions (Scheme 2, entry 5) we could isolate diastereoisomer 6 in 53% yield.

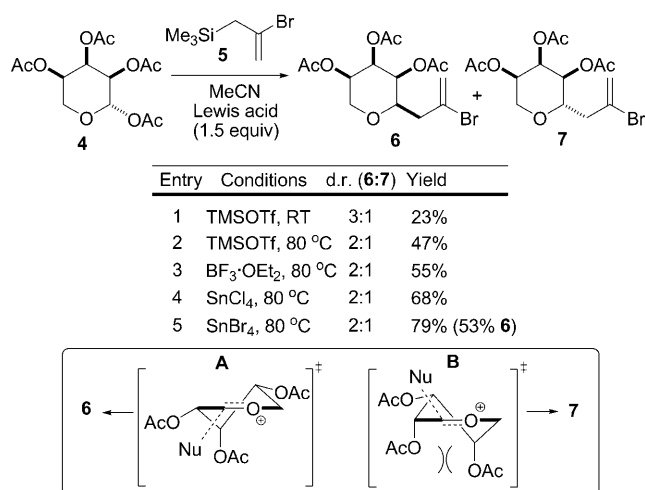
This selectivity may be rationalized by using a model proposed by Lucero and Woerpel.^[7a] Assuming an S_N1 mechanism, nucleophilic addition of the bromoallyl group can occur (axially) onto two conformers of an oxocarbenium ion, such that the product is formed via a chairlike transition structure. In this case, it is likely that transition structure B is destabilized by 1,3-diaxial interactions of the acetate groups, resulting in transition structure A being favored (Scheme 2).

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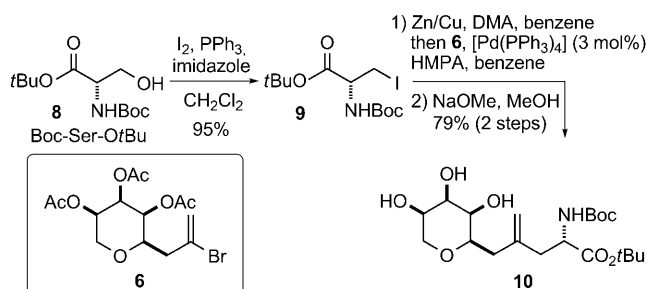
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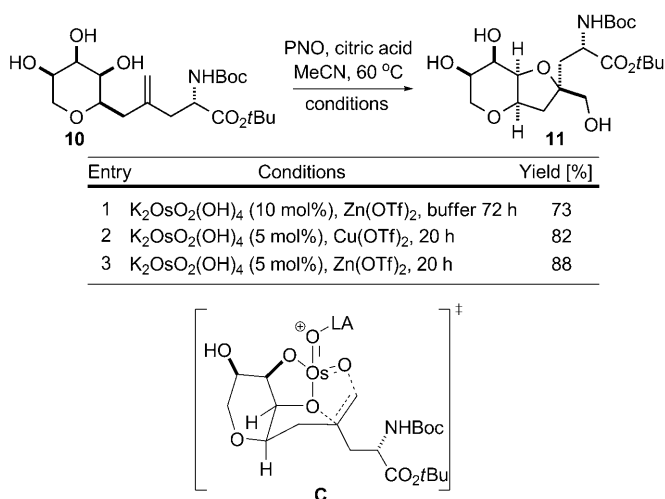
Scheme 2. Facial selectivity during nucleophilic attack.

The amino acid side chain was prepared from the commercially available Boc-Ser-OTfBu (**8**). Compound **8** was subjected to a halogenation reaction in order to furnish the iodinated serine derivative **9**, which was subsequently transformed into the corresponding organozinc reagent and coupled with vinyl bromide **6** under the action of catalytic palladium(0) (Scheme 3).^[1,4,9] The resulting product was treated with a catalytic amount of sodium methoxide in methanol in order to remove the acetate protecting groups and generate triol **10** in 79% yield over these two steps.



Scheme 3. Negishi coupling for the construction of the carbon skeleton. Boc = *tert*-butoxycarbonyl, DMA = *N,N*-dimethylacetamide, HMPA = hexamethylphosphoramide, Ser = D-serine.

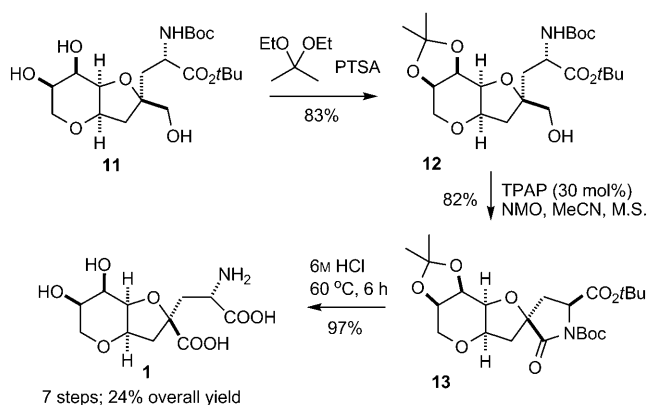
After just three linear steps, we arrived at the key intermediate for the oxidative cyclization, which we proposed would form the desired THF ring with complete stereochemical control. Compound **10** represents a severe test for the cyclization methodology because it contains acid-sensitive functional groups, forms a bicyclic ring system during cyclization and has a triol unit, rather than a diol, that is capable of binding to osmium. Consequently, **10** was subjected to the recently reported oxidative cyclization conditions that employ the use of a Lewis acid in the presence of a catalytic amount of K₂OsO₂(OH)₄ to promote cyclization (Scheme 4).^[6b] This reaction also uses PNO as a mild reoxidant capable of oxidizing osmium(IV) to osmium(VI), but not to unwanted osmium(VIII), which is not only toxic



Scheme 4. Oxidative cyclization for stereoselective THF formation. LA = Lewis acid, PNO = pyridine-*N*-oxide, Tf = triflate.

but would result in the dihydroxylation of the 1,1-disubstituted alkene.^[10] Scheme 4 (entry 1) shows that the combination of an aqueous buffer with a Lewis acid allows the cyclization to proceed at pH 6.5. Use of mildly acidic conditions is crucial if the integrity of the Boc and *tert*-butyl esters is to be maintained. Interestingly, it was discovered that replacing the buffer with water did not have a detrimental effect on these acid-sensitive groups, as the pH value of the reaction was only slightly lower at approximately 5. Crucially, the lower pH value of the reaction without buffer combined with the improved solubility of the reagents meant that the rate was greatly increased. Scheme 4 (entries 2 and 3) shows that high conversion and shorter reaction times could be attained by using zinc or copper triflates whilst reducing the amount of the osmium catalyst. As expected, cyclization occurred via a chelated osmate ester intermediate (**C**) to selectively form the *cis*-THF ring required for the target.

Subsequently, cyclized product **11** was protected as an isopropylidene acetal **12** and subsequently oxidized with catalytic TPAP and NMO to form lactam **13** (via the intermediacy of a hemiaminal, Scheme 5).^[11] Pleasingly, it



Scheme 5. Completion of the synthesis of neodysiherbaine A. M.S. = 4 Å molecular sieves, NMO = *N*-methylmorpholine-*N*-oxide, PTSA = toluene-*p*-sulfonic acid, TPAP = tetrapropylammonium per-ruthenate.

was possible to obtain a crystal structure of compound **13** by X-ray crystallographic analysis (Figure 1), which proved unambiguously that the relative stereochemistry is correct.^[12] Finally, the synthesis was completed by the addition of 6 M HCl which removed the acetal, ester and carbamate protecting groups, thus furnishing natural product **1** in 97% yield. The NMR spectra (¹H/¹³C) of our synthetic material were an excellent match with those reported in the literature.

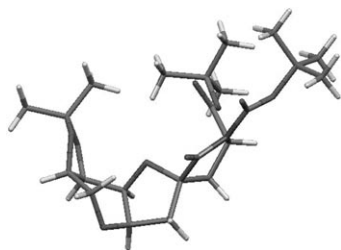


Figure 1. Crystal structure of compound **13**.

To conclude, we have accomplished a short and high-yielding synthesis of (–)-neodysiherbaine **A** by utilizing a *syn*-selective addition onto a ribopyranose-derived oxocarbenium ion and an oxidative cyclization under Lewis acidic conditions as the key stereochemistry-determining steps. The advantages of our approach are evident in the short synthetic sequence (seven linear steps; eight reactions in total) and high overall yield (24%) which compares well to that previously reported.

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