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Synthesis of the dysiherbaine tetrahydropyran core employing a tethered aminohydroxylation reaction

Jamie L. Cohen and A. Richard Chamberlin*

Department of Chemistry, University of California, Irvine, Irvine, CA 92697, USA

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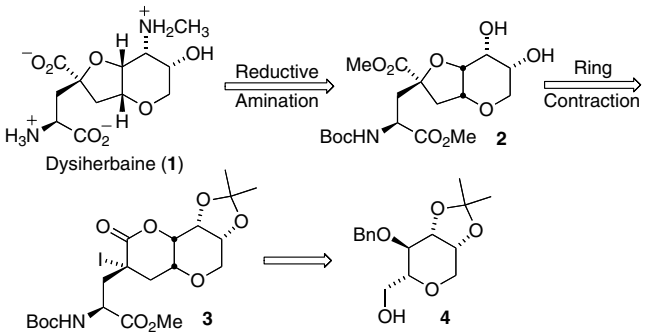
Abstract—A stereocontrolled and scalable synthesis of an advanced intermediate of the dysiherbaine tetrahydropyran core has been achieved in 11 steps and 27% overall yield. The key feature of this synthetic approach is the application of the Donohoe tethered aminohydroxylation reaction to install the amino diol and establish the four contiguous *syn* stereocenters on the tetrahydropyran ring.

Since its isolation in 1997, (−)-dysiherbaine (1) has attracted attention in the chemical and biological communities due to its interesting structure and unique biological activity.[1] The molecular architecture of dysiherbaine (DH), characterized by a cis fused hexahydrofuro[3,2-*b*]pyran ring system displaying a glutamic acid appendage, has generated a great deal of interest as a synthetic target.[2,3] Our own synthetic efforts were motivated by dysiherbaine's impressive biological profile.[4] Radioligand binding assays of DH activity at ionotropic glutamate receptors have demonstrated that DH is a potent agonist of non-NMDA type glutamate receptors, with a particularly high affinity for the KA receptor: IC50 = 33 and 230 nM for KA and AMPA, respectively.[1] Furthermore, DH induces epilepsy-like seizures in mice and has been shown to be the most potent epileptogenic excitatory amino acid yet identified. Both the kainate receptor selectivity and potency of DH make it a valuable pharmacological tool for investigating the physiological roles of the various glutamate receptors in the CNS.[4e] Furthermore, as a neurotoxin and potent convulsant, DH may also provide insight as to targets for therapeutic intervention in the treatment of seizures. The low natural abundance of DH, however, has limited its availability, thereby impeding further studies on its mode of action. As a consequence, total synthesis of DH is required for further physiological studies.

Since the initial elucidation of the dysiherbaine structure, several research groups, including our own, have independently accomplished the total synthesis of DH. The synthesis of DH previously developed in our laboratory featured a Fleet-inspired ring contraction of δ-lactone **3** to construct the bicyclic ring system and establish the stereochemistry at the tetrasubstituted γ-carbon of the glutamate side chain (Scheme 1).[2d]

Overall, the synthetic route was highly convergent and it provided sufficient quantities of DH for biological evaluation; however, the final stages of the synthesis were plagued by difficulties encountered with an oxidation and reductive amination sequence that ultimately produced the *N*-Me amino alcohol of **1** in poor yield. To circumvent this low yielding amination step, we have



Scheme 1. Retrosynthetic strategy for previous dysiherbaine synthesis.

* Corresponding author. Tel./fax: +1 949 824 7089; e-mail: archambe@uci.edu

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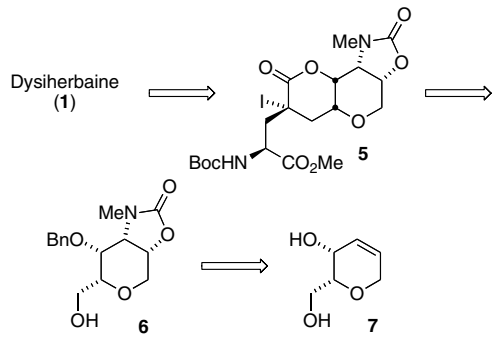


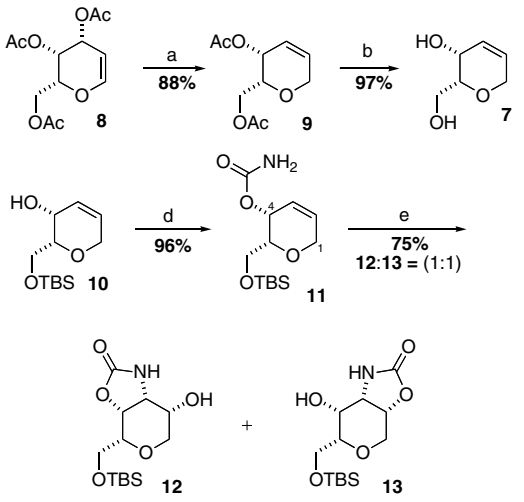
Scheme 2. Revised retrosynthetic strategy for dysiherbaine featuring early installation of amino alcohol.

explored an alternative approach to DH in which an analogous but more highly functionalized tetrahydropyran derivative, **6**, would be carried through a similar sequence in place of intermediate **4** (Scheme 2), with the critical installation of the *N*-Me amino alcohol moiety occurring prior to the lactone ring contraction. Moreover, we believe that the route we have developed to tetrahydropyran **6** has considerable merit in its own right-independent of its potential as a DH intermediate-as one of the few examples of a tethered amino hydroxylation reaction applied to natural product structures, and more importantly, as a caveat in the application of this exceptionally selective and high-yielding reaction to construct vicinal amino alcohols. We thus describe herein an efficient and scalable synthesis of the highly functionalized intermediate **6** that embodies the tetrahydropyran (THP) core of dysiherbaine.

Previous syntheses of advanced DH intermediates identified the four contiguous *syn* stereocenters and amino diol functionality of the tetrahydropyran core as a significant synthetic challenge.[2,3] The strategy reported herein was motivated by the view that a new synthetic approach to the DH pyran core would need to provide greater efficiency and implement high yielding processes in strategic roles. With this in mind, we recognized that the hydroxyamination of an unsaturated pyran derivative (**7**) might be ideally suited for this application. While the Sharpless asymmetric aminohydroxylation reaction of olefins has emerged as a powerful method to construct vicinal amino alcohols in the context of natural product synthesis,[5] it has not been employed to introduce the amino alcohol of dysiherbaine—possibly because of concerns regarding the regioselectivity of this transformation, which may detract from its potential synthetic utility. In 2002, Donohoe and co-workers introduced an innovative method of controlling aminohydroxylation regioselectivity, in which the nitrogen source is tethered to the olefin substrate. This tethered aminohydroxylation of olefins was reported to proceed with complete control of regioselectivity and was highly diastereoselective in cyclic substrates.[6,7] These characteristics, in conjunction with a substitution pattern in dysiherbaine ideally suited for this process, suggested that the Donohoe aminohydroxylation reaction might be an ideal means of achieving the desired levels of regio- and stereoselectivity in the synthesis of **6**. Thus, the tethered aminohydroxylation reaction figured prominently in our synthetic planning.

Our approach to **6** thus began with the preparation of the tethered aminohydroxylation substrate, allylic carbamate **11** (Scheme 3). The microwave accelerated indium catalyzed Ferrier rearrangement[8] of tri-*O*-acetyl-D-galactal (**8**) in the presence of triethylsilane consistently provided good yields (85%) of olefin **9**[9] on scales ranging from 100 mg to 20 g. Deacetylation of **9** was accomplished using NaOMe in MeOH to afford diol **7**, which was selectively protected at the primary alcohol as TBS silyl ether **10**. Sequential treatment of allylic alcohol **10** with trichloroacetylisocyanate and K_2CO_3/MeOH afforded multi-gram quantities of carbamate **11**, the substrate for the key tethered aminohydroxylation reaction, in 96% yield after purification.

Following the successful synthesis of carbamate **11**, the key tethered aminohydroxylation reaction was investigated. We first examined the tethered aminohydroxylation conditions reported by Donohoe, which were modeled after the traditional Sharpless asymmetric aminohydroxylation procedures. Satisfyingly, exposure of carbamate **11** to the standard tethered aminohydroxylation conditions (*t*-BuOCl, NaOH, $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, *n*PrOH/H_2O) cleanly installed the *syn* amino diol motif on the DH tetrahydropyran core in 75% yield. The remainder of the mass balance for this transformation consisted of recovered starting material that could be easily recycled through the hydroxyamination sequence. To our surprise, however, the aminohydroxylation product was not isolated as the single anticipated hydroxy oxazolidinone isomer **12**. On the contrary, a 1:1 mixture of hydroxy oxazolidinone isomers **12** and **13** was observed in the crude reaction mixture. Following careful chromatography to separate the two isomers, **12** and **13** were independently resubjected to the tethered aminohydroxylation reaction conditions.



Scheme 3. Reagents and conditions: (a) Et_3SiH, $InCl_3$, CH_3CN, μwave; (b) NaOMe, MeOH; (c) TBSCl, imidazole, DMF; (d) (i) $Cl_3CCONCO$, CH_2Cl_2; (ii) K_2CO_3, MeOH/H_2O; (e) *t*-BuOCl, NaOH, $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, *n*PrOH/H_2O.

Both reactions afforded identical 1:1 product mixtures regardless of the starting isomer, confirming that equilibration is quite facile and has reached thermodynamic equilibrium under the reaction conditions. The hydroxy oxazolidinone isomers **12** and **13** also undergo equilibration upon exposure to NaOMe/MeOH or NaH/THF.

The few reports in the literature of tethered aminohydroxylation reactions of allylic carbamates do not include any examples of related equilibrations, which clearly might diminish the synthetic utility of the reaction to some extent. We believe, however, that this side reaction is substrate dependent, and in this specific instance occurs because of the overwhelmingly axial disposition of the secondary alcohols in both the initially formed product (**12**) and in the migration product (**13**). Both alcohols are ideally positioned for direct acyl transfer; thus a plausible mechanism for equilibration in the specific case of **11**→**12** + **13** is the direct attack of the axial alkoxide on the urethane carbonyl group followed by a regioselectively arbitrary collapse of the tetrahedral intermediate and facile equilibration of the two urethanes. Significantly, carbamate migrations were not observed during the tethered aminohydroxylation reaction on an analogous cyclic substrate (C4-*epi*-**11**→**14**, Fig. 1) in which the allylic alcohol occupies an equatorial position.[6]

Indeed, molecular modeling[10] indicates that the equatorial alkoxide of **14** is poorly aligned for addition to $\pi^*C{=}O$, while the axial alkoxide of **12** is well positioned for attack at the Burgi–Dunitz angle. An alternative equilibration pathway might involve deprotonation of the carbamate N–H to form an isocyanate that is attacked indiscriminately by the flanking hydroxyl groups. This pathway, however, does not account for the difference in the migratory propensity of **12** and **14** under the reaction conditions, because one would not expect a significant difference in the rates of isocyanate formation from diastereomers **12** and **14**. This analysis suggests more generally that carbamate equilibration in the tethered aminohydroxylation reaction is a consequence of relative stereochemistry, and may be facile if the participating groups are favorably positioned for acyl transfer in energetically preferred conformers of the initially formed product. A related example describing oxazolidinone migration during the tethered aminohydroxylation reaction of a homoallylic carbamate[11] has recently appeared, supporting this contention.

Despite a considerable effort, conditions for preventing the equilibration of **12** could not be found; however, the problem was circumvented by processing both oxazolidinone isomers into a single advanced intermediate (**17**) by sequential treatment with Boc_2O, TBAF, and Cs_2CO_3 in MeOH.[12] Employing this optimized three-step protocol, the conversion of **12** and **13** into THP **17** was realized on an 11 g scale in 81% overall yield (Scheme 4). In order to strategically differentiate between the two secondary axial alcohols on pseudo-symmetric **17**, the DH tetrahydropyran core was selectively functionalized using benzaldehyde dimethylacetal and CSA (cat.) at 0 °C to exclusively provide the six-membered ring benzylidene acetal **18** in 78% yield. Sequential treatment of **18** with KO^{t}Bu and MeI then afforded *N*-Me oxazolidinone **19** as a crystalline solid in 95% yield. X-ray crystallographic analysis of **19** verified the structure and unambiguously established the all *syn* stereochemistry of the substituents on the THP ring (Fig. 2).[13] Finally, regioselective reductive cleavage of the benzylidene acetal[14] was best accomplished using $PhBCl_2$ and Et_3SiH at −78 °C to furnish multi-gram quantities of tetrahydropyran (**6**).

In summary, we have developed an efficient, stereocontrolled, and scalable synthesis of a highly functionalized amino hydroxy tetrahydropyran derivative in 11 steps and 27% overall yield. The key feature of this approach is the application of the Donohoe tethered aminohydroxylation reaction to install the *syn* amino diol motif found in dysiherbaine. We also observed, consistent with a recent literature report, that the initially formed product of this reaction can undergo facile acyl transfer to give a thermodynamic mixture of cyclic urethanes, although this process appears to be highly substrate

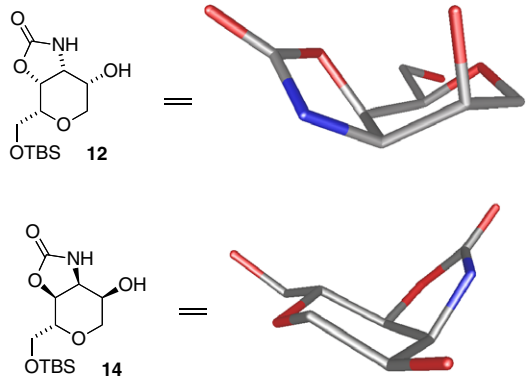
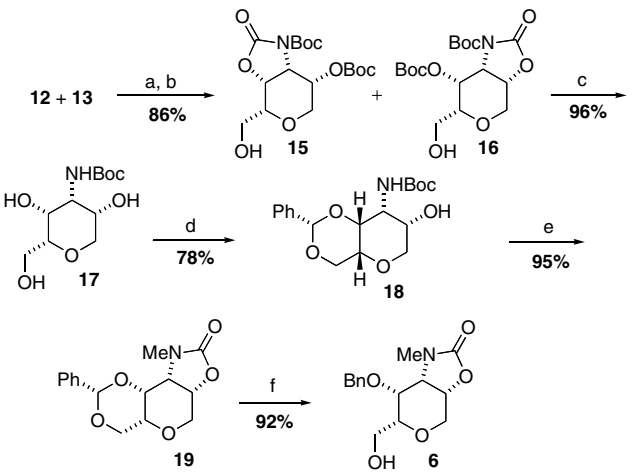


Figure 1. Comparison of oxazolidinone equilibration substrates (TBS group omitted for clarity).



Scheme 4. Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, THF; (b) TBAF, AcOH, DMF; (c) Cs_2CO_3, MeOH; (d) $PhCH(OMe)_2$, CSA, CH_2Cl_2; (e) KO^{t}Bu, MeI, THF; (f) $PhBCl_2$, Et_3SiH, 4 Å, CH_2Cl_2.

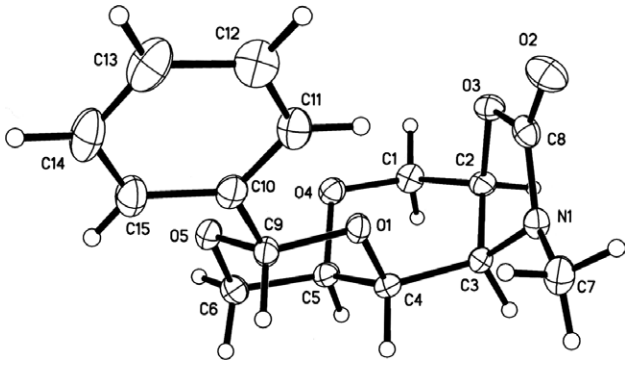


Figure 2. Single crystal X-ray structure of **19**.

dependent and in the case reported here, easily circumvented.

Acknowledgments

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Supplementary data

Complete experimental procedures, product characterization, and spectral data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.016.

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