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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8141–8144

Formal synthesis of *ent*-dysiherbaine from sulfinyl dihydropyrans by sigmatropic rearrangement and tethered aminohydroxylation

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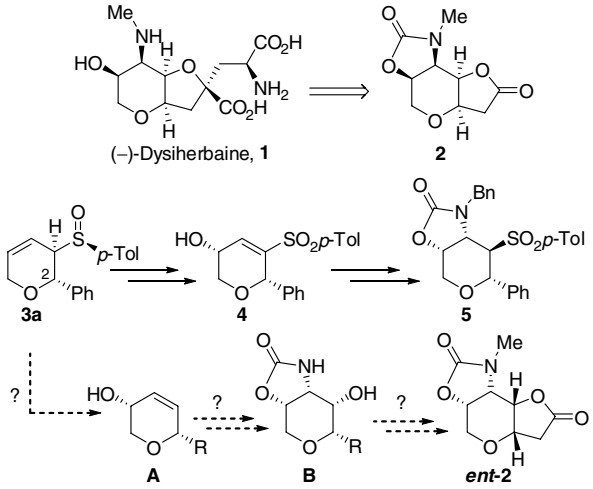
Received 13 August 2007; accepted 17 September 2007
Available online 21 September 2007

Abstract—A stereospecific [2,3]-sigmatropic rearrangement of a sulfinyl dihydropyran, followed by a tethered aminohydroxylation reaction, are the key steps of a formal synthesis of *ent*-dysiherbaine from an enantiopure sulfinyl dienol.

Tetrahydropyrans are key fragments of many natural and bioactive products, such as (−)-dysiherbaine **1** (Scheme 1). This neurotoxic aminoacid was first isolated in 1997 from the marine sponge *Dysidea herbacea* and presents very interesting biological activity as a potent agonist of non-NMDA type glutamate receptors in the central nervous system.[1] The structure of **1** was determined by extensive spectroscopic studies to be an unprecedented diamino dicarboxylic acid, which is characterized by a structurally novel cis-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamate substructure. The potent biological activity and structural novelty has led to many approaches towards the synthesis of dysiherbaine.[2] Recently, Chamberlin described the use of the Donohoe tethered aminohydroxylation reaction,[3a] to install the amino diol and create the four contiguous stereocenters in the tetrahydropyran ring and completed the synthesis of an advanced synthetic intermediate.[2j] In this Letter, we report a formal synthesis of *ent*-dysiherbaine that features a stereospecific [2,3]-sigmatropic rearrangement and a tethered aminohydroxylation as the key steps; this chemistry evolves from our desire to develop applications of our novel methodology to prepare dihydropyranyl allylic sulfoxides.[4]



Scheme 1. Structure of dysiherbaine and synthetic intermediate **2**. Previous approach and synthetic strategy.

A few years ago, we reported the selective base-promoted cyclization of enantiopure sulfinyl dienols to afford configurationally stable allylic sulfinyl dihydropyrans like **3a** (Scheme 1).[4] Within the context of the different studies of reactivity, this structure was subjected to dihydroxylation and elimination to obtain vinyl sulfone **4**. Formation of the benzyl carbamate and cyclization under basic conditions afforded oxazolidinone **5** in excellent yield.[4] This model substrate presented the relative stereochemistry enantiomeric to dysiherbaine aside from the sulfone-bearing center. A reasonable option to convert a structure related to **5** into the required functionality would imply the transformation of the sulfone moiety into a carbonyl group,[5] and a straightforward reduction to the desired α-hydroxyl.

Keywords: Allylic sulfoxides; Sigmatropic rearrangement; Tethered aminohydroxylation.
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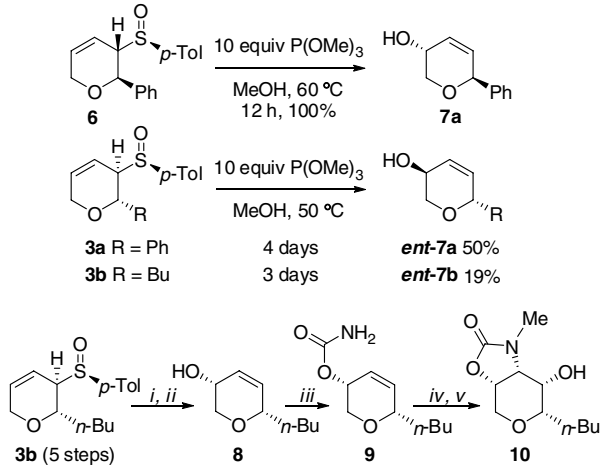
doi:10.1016/j.tetlet.2007.09.103

Typically, this transformation requires a metalation at the sulfone-bearing center and the capture of the anion with an oxygen-based electrophile. The precise structure of these intermediates, with two good leaving groups flanking the reactive metalated sulfone, suggested that competing β-eliminations could be important in this case. These considerations prevented us from pursuing this route further.

At this stage, we evaluated an alternate approach starting from an allylic sulfoxide related to **3a** with the appropriate functionalization at C-2 that could be transformed into alcohol **A** by a [2,3]-sigmatropic rearrangement in the presence of a thiophile and subsequently into **B** by a tethered aminohydroxylation protocol (Scheme 1). This structure, after the transformations of the side chain at C-2 could be converted into *ent*-**2**, enantiomer of the intermediate used in a total synthesis of dysiherbaine.[2c] The key step of the synthetic plan was the sigmatropic rearrangement of an allylic sulfoxide similar to **3a** to an allylic alcohol **A**.[6]

In the preliminary studies, we had found remarkable differences in the rate and the yield of the sigmatropic rearrangements of diastereomeric allylic sulfoxides (Scheme 2).[4] Thus, sulfoxide **6** with 2,3-*trans* relative configuration afforded alcohol **7a** in excellent yield, but in the case of the 2,3-*trans* diastereoisomers **3a** and **3b**, longer reaction times were required only to obtain poor yields of the corresponding products *ent*-**7a** and *ent*-**7b**. Since we planned to base our synthesis in a 2,3-*trans* allylic sulfoxide similar to **3a** and **3b** these results posed a major problem which had to be overcome to validate our synthetic approach. After considerable experimentation with different substrates, thiophilic agents, solvents and temperatures, we found that changing the reaction conditions from trimethyl phosphite in MeOH (the most common protocol for this type of reaction),[7] to DABCO



Scheme 2. Previous results on sigmatropic rearrangements. Synthesis of model oxazolidinone **10**. Reagent and conditions: (i) DABCO, toluene, 70 °C, 83%; (ii) (a) PPh_3, *p*-nitrobenzoic acid, DIAD, THF, rt. (b) K_2CO_3, MeOH, rt, 86%; (iii) (a) $Cl_3CCONCO$, CH_2Cl_2, 0 °C. (b) K_2CO_3 (aq), MeOH, 0 °C–rt, 92%; (iv) $K_2OsO_2(OH)_4$, ^{t}BuOCl, NaOH, DIPEA, PrOH, rt, 21–24%, 15–33% recovered starting material; (v) MeI, BaO, $Ba(OH)_2$, DMF, 0 °C, 66%.

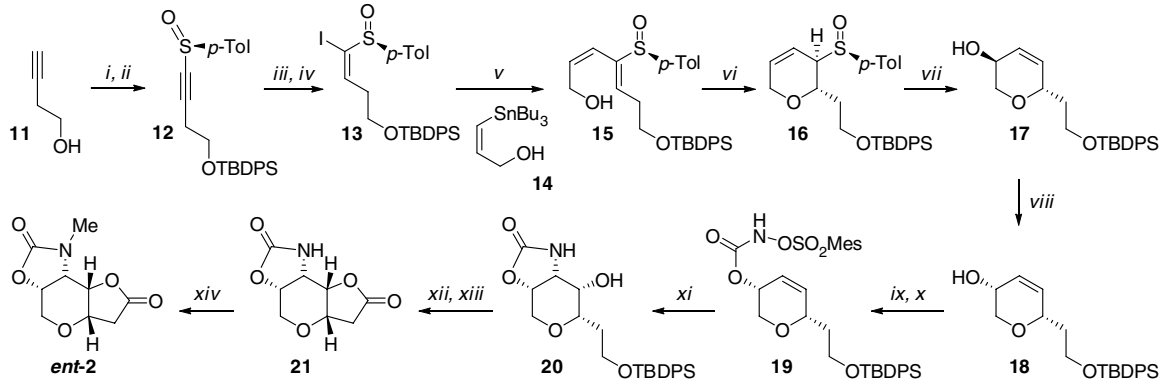
in toluene, solved the problem of the sigmatropic rearrangement step, leading to the desired allylic alcohol in good yields and as a single isomer.[8]

To test the viability of the initial part of the synthetic scheme, we then focused on the known and easily available substrate **3b** (Scheme 2), that underwent a smooth sigmatropic rearrangement to produce the corresponding *trans* allylic alcohol, which was converted into the cis isomer **8** by a Mitsunobu reaction.[9] The treatment of allylic alcohol **8** with trichloroacetylisocyanate followed by aqueous K_2CO_3 in MeOH afforded carbamate **9** in excellent yield. Aminohydroxylation of carbamate **9**, under the conditions originally described by Donohoe,[3a] gave the desired product in 21–24% yield, along with 15–33% recovered starting material.[10,11] All efforts to improve the yield of this transformation, including a change of ligand to $(DHQ)_2PHAL$, changes of the batches and the sources of the reagents, etc., proved to be fruitless. Nonetheless, this model study was completed by N-methylation to afford **10** in 66% yield.

At this stage, we decided to carry on with the formal synthesis of *ent*-dysiherbaine, with the expectation that the outcome of the aminohydroxylation could be improved for the precise substrate required and our efforts are gathered in Scheme 3. To install the appropriate side chain at C-2 that allowed for the formation of the butyrolactone in the final structure, we started the synthesis from 3-butyn-1-ol **11**. After the protection of hydroxyl group as a TBDPS ether, the alkynyl sulfoxide **12** was formed by the reaction with EtMgBr and (−)-menthyl *p*-toluenesulfinate. Hydrostannylation of **12** and tin–iodine exchange led to vinyl iodide **13**, which was subjected to a Stille coupling with hydroxy vinyl stannane **14** to give sulfinyl diene **15** in excellent yield. Base-promoted cyclization with LDA afforded sulfinyl dihydropyran **16** as a single isomer. The modified conditions for the [2,3]-sigmatropic rearrangement worked perfectly on allylic sulfoxide **16** to produce allylic alcohol **17**, which was inverted by a Mitsunobu protocol to give 3,6-*cis* alcohol **18**.[12]

Treatment of alcohol **18** with trichloroacetylisocyanate followed by aqueous K_2CO_3 as described above gave a carbamate in excellent yield (structure not shown); this carbamate was submitted to the original conditions for aminohydroxylation,[3a] to afford a disappointing 26% yield of oxazolidinone **20** along with 50% recovered starting material. In addition, **20** was often produced along with variable amounts of a regioisomeric oxazolidinone; related isomerizations have been described by Chamberlin and Handa.[2j,11] This isomerization, along with the poor yield obtained for the aminohydroxylation represented a major drawback for the success of the sequence.

At this time, Donohoe reported a modification on the original conditions for the tethered aminohydroxylation that entailed the use of *N*-sulfonyloxy derivatives.[3g] This new protocol allowed for the reaction to proceed without a chlorinating agent (*t*-BuOCl) or hydroxide base. Encouraged by this alternative, we decided to examine



Scheme 3. Formal synthesis of *ent*-dysiherbaine. Reagent and conditions: (i) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt, 100%; (ii) (a) EtMgBr, Et_2O. (b) (−)-Menthyl *p*-toluenesulfinate, toluene, −20 °C, 89%; (iii) Bu_3SnH, $Pd(PPh_3)_4$, toluene, −78 °C–rt, 83%; (iv) I_2, CH_2Cl_2, rt, 88%; (v) **14**, $AsPh_3$, BHT, $Pd_2(dba)_3{\cdot}CHCl_3$, THF, rt, 94%; (vi) LDA, THF, −78 °C–rt, 89%; (vii) DABCO, toluene, 70 °C, 93%; (viii) (a) PPh_3, *p*-nitrobenzoic acid, DIAD, THF, rt. (b) K_2CO_3, MeOH, rt, 81%; (ix) (a) CDI, MeCN, rt. (b) Imidazole, NH_2OH, 0 °C, 86%; (x) $MesSO_2Cl$, Et_3N, toluene–DMF, 0 °C, 88%; (xi) $K_2OsO_2(OH)_4$, DIPEA, PrOH-H_2O, rt, 77%; (xii) DOWEX, MeOH, rt, 100%; (xiii) TEMPO, (diacetoxyiodo)benzene, CH_2Cl_2, rt, 84%; (xiv) NaH, MeI, THF–DMF, −40 °C, 59%, 19% recovered starting material.

the modified procedure for the aminohydroxylation and the required *N*-sulfonyloxy carbamate was readily prepared by the sequential reaction of alcohol **18** with carbonyldiimidazole and hydroxylamine, followed by sulfonylation to afford **19** in good yield.[13] The tethered aminohydroxylation worked very well on this substrate leading to oxazolidinone **20**, containing the four contiguous cis stereocenters of the final structure in good yield. Cleavage of the silyl ether with Dowex resin and selective oxidation of the primary alcohol with TEMPO with concurrent cyclization led to butyrolactone **21**.[14] Finally, an N-methylation that required different conditions to those used for the model substrate (Scheme 2) completed the synthesis of tricyclic structure *ent*-**2** that had identical data to those described in the literature, except for the sign of the optical rotation.[2c]

In conclusion, we have described the synthesis of dysiherbaine intermediate *ent*-**2** based on an efficient [2,3]-sigmatropic rearrangement of an allylic sulfoxide, and a tethered aminohydroxylation step that allowed for the creation of the four contiguous stereocenters. A related approach to the malayamicin A core, with a trans-fused hexahydrofuro[3,2-*b*]pyran ring system, from 3,6-*trans* allylic alcohol **17** is currently under study.

Acknowledgements

This research was supported by DGI MEC (CTQ2006-04522/BQU) and CM (S-SAL-0249-2006). We thank JANSSEN-CILAG for generous additional support and MEC for a doctoral fellowship to N.L.

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12. Interestingly, the fully deprotected 3,6-*cis*-diol derived from **18** could be obtained in a single step from allylic sulfoxide **16** by the treatment with Na_2S with good yield and selectivity (90%, cis:trans, 91:9). Unfortunately, selective protection to generate **18** was not efficient. These results will be described in detail in due time.
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