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Synthesis of neodysiherbaine

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Abstract—The stereocontrolled synthesis of neodysiherbaine from diacetyl-L-arabinal is described. Key steps in the synthesis include the use of an asymmetric phase-transfer catalyzed glycine imine alkylation to introduce the α-amino acid function, and the RuO_4-mediated oxidative cyclization of a 1,5-diene to generate the 2,7-dioxabicyclo[4.3.0]nonane ring system.

Neodysiherbaine **1**[1] and dysiherbaine **2**[2] are potent excitatory amino acids isolated from the Micronesian sponge *Dysidea herbacea*. Both compounds have been reported to induce epilepsy-like seizures in mice and appear to act as agonists at KA and AMPA glutamate receptors.[1,3] Their potent activity and unusual structure has attracted significant interest from synthetic chemists and this has resulted in successful syntheses of both dysiherbaine[4] and neodysiherbaine.[1] A number of synthetic approaches towards these targets have also been reported.[5]

Our interest in these natural products stems from recent investigations into the synthesis of *C*-glycopeptides. During the course of these studies, we were able to establish that carbon-Ferrier rearrangement involving a glucal (e.g., **4**, R = CH_2OAc) and allylsilane **5**, followed by asymmetric alkylation with glycine imine **6**, could form the basis of an efficient, stereoselective approach to structures such as **3**, R = CH_2OAc.[6] Here, we demonstrate that the same approach can be applied in the preparation of compound **3**, R = H, and that this can serve as an advanced intermediate for the synthesis of neodysiherbaine **1** (Fig. 1).

For this study, we employed diacetyl-L-arabinal **7** as the starting material. Crucially this glucal possesses a β-acetoxy group at C-4, which is required in order to establish the correct stereochemistry at C-1 during the carbon-Ferrier rearrangement.[7] Reaction with allylsilane **5** was achieved using $Yb(OTf)_3$ catalysis[6,8] and delivered the desired intermediate **8** in high yield and with good diastereoselectivity (16:1 dr by ^1H NMR).[9]

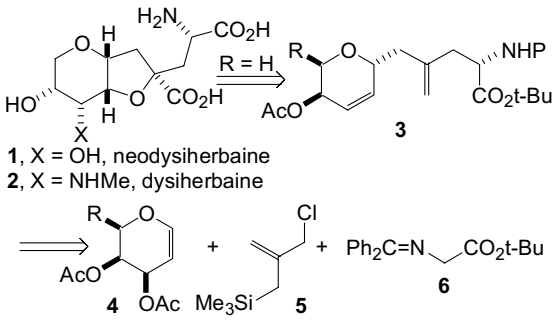

Figure 1.

Next we needed to introduce the amino acid functionality via reaction of allyl halide **8** with glycine imine **6**. It is now well established that alkylations of this type can be performed under phase-transfer conditions and that high levels of stereocontrol can be obtained via the use of chiral phase-transfer catalysts.[10] In this instance, we elected to use *O*-benzyl-*N*-(9-anthracenylmethyl)-dihydrocinchonidinium bromide as the phase-transfer catalyst.[11] This particular catalyst was chosen because our earlier studies on related substrates had demonstrated that it delivers high selectivity for the desired (*S*)-stereoisomer.[6] In order to minimize the chances of acetate hydrolysis in the alkylation, chloride **8** was first converted into the more reactive iodide, and this was then used directly in the asymmetric alkylation (Scheme 1). After imine hydrolysis and *N*-protection, the amino acid derivative **10**[9] was isolated in high overall yield.

Keywords: Neodysiherbaine; Amino acid; Oxidative cyclisation; Asymmetric alkylation.
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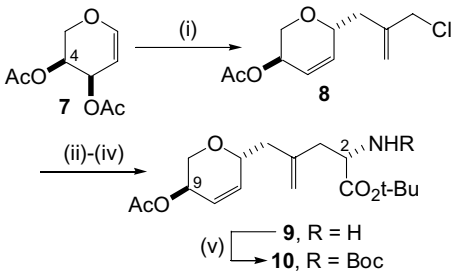
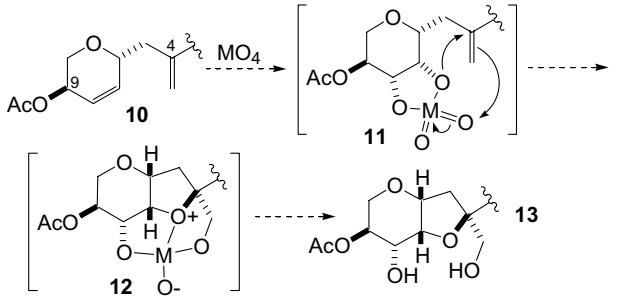


Scheme 1. Reagents and conditions: (i) **5** (1.2 equiv), $Yb(OTf)_3$ (10 mol %), CH_2Cl_2, −5 °C, 30 min (89%, 16:1 dr); (ii) NaI, acetone, rt, 15 h; (iii) **6**, *O*-benzyl-*N*-(9-anthracenylmethyl)-dihydrocinchonidinium bromide (10 mol %), 9 M aq KOH, PhMe, rt, 18 h; (iv) 15% aq citric acid, THF, rt, 8 h (93% from **8**); (v) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 18 h (95%).

This material appeared to be a single diastereoisomer (by ^1H NMR), but at this stage we were unable to unambiguously establish the nature of the stereochemistry at C-2.

Compound **10** contains the entire carbon skeleton of neodysiherbaine **1** but lacks the tetrahydrofuran ring. We envisaged that this functionality should be accessible via oxidative cyclization of the 1,5-diene moiety. Cyclizations of this type have been achieved using a variety of reagents (e.g., $KMnO_4$, OsO_4, RuO_4)[12] and this constitutes a powerful method for the stereocontrolled construction of tetrahydrofurans. That said, the range and complexity of the diene precursors studied to date has been limited, and we are not aware of any reports involving the substitution pattern found in compound **10**.

Scheme 2 outlines one possible pathway by which such an oxidative cyclization could proceed, but this transformation could proceed via a variety of related pathways.[13] In this scheme, the desired 2,7-dioxabicyclo-[4.3.0]nonane ring system **13** is generated via initial reaction of the metal oxide on the ring alkene in diene **10**. We envisaged that preferential reaction on the α-face of this alkene might be favoured on stereoelectronic grounds due to the presence of the β-C-9 acetate. Assuming the sequence shown, oxidative cyclization through intermediate **11** could then only generate the desired stereochemistry at C-4. Compound **13** could also be generated via a similar series of transformations involving initial reaction at the β-face of the 1,1-disubstituted alkene.



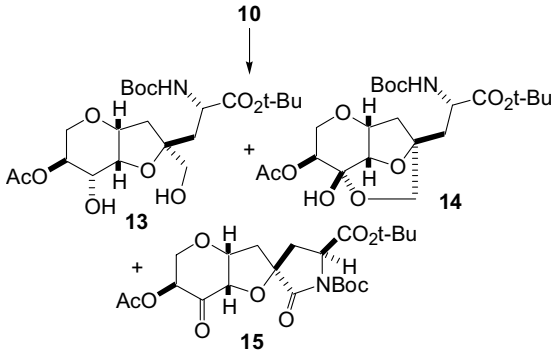
Scheme 2.

After screening a range of oxidants and conditions we were able to establish that RuO_4 was the reagent of choice for this transformation.[14] By varying the reaction conditions (e.g., Table 1) we were able to generate a number of different cyclized products **13**–**15**. All appeared to have the desired stereochemistry at the quaternary centre C-4, but they differed in the degree of oxidation that had occurred. The best conditions found employed $RuO_2/NaIO_4$ in an acetone/water/ethyl acetate mixture.[12d,15] This gave the desired diol **13** in ca. 61% yield after chromatography however, we were never able to completely separate this product from an unidentified contaminant.

We were able to overcome this problem by converting impure diol **13** into lactone **16**[9] by treatment with TsOH. Lactone **16** was readily purified by chromatography, and by linking the two steps together the lactone could be isolated in a significantly improved 81% overall yield (Scheme 3).

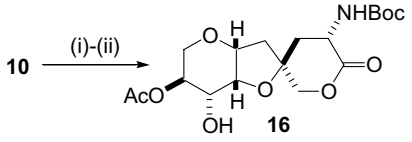
Conversion of lactone **16** into neodysiherbaine was then achieved via the sequence outlined in Scheme 4. This

Table 1

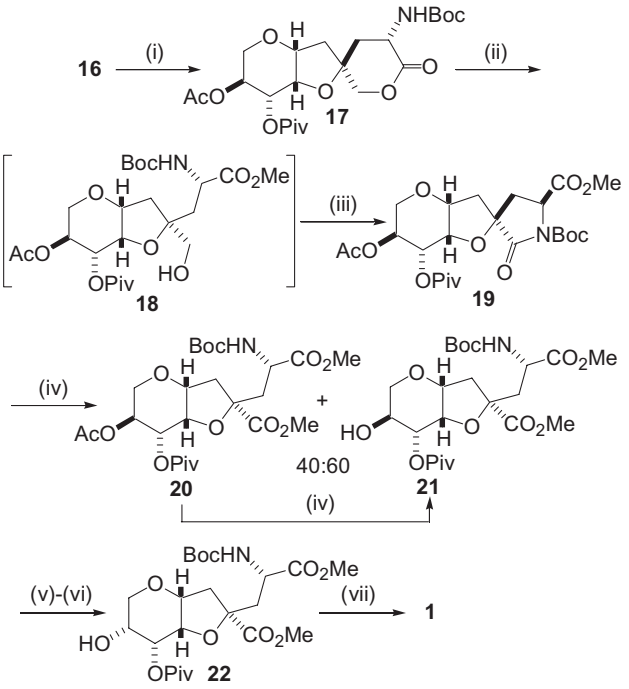


Entry	Oxidant (no. equiv)	Yield (%)[d]	Ratio **13**:**14**:**15**
1	$RuCl_3/NaIO_4$ (0.02/4.1)[a]	30	5:1:0
2	$RuCl_3/NaIO_4$ (0.4/4.1)[a]	43	7:1:1
3	$RuCl_3/NaIO_4$ (0.4/8.2)[a]	55	1:0:4.5
4	$RuO_2/NaIO_4$ (0.04/4.0)[b]	37	6:1:0
5	$RuO_2/NaIO_4$ (0.05/2.5)[c]	71	6:1:0

[a] rt, CCl_4/MeCN/H_2O.
[b] rt, EtOAc/MeCN/H_2O.
[c] rt, acetone/H_2O/EtOAc.
[d] Combined yield of cyclized products.



Scheme 3. Reagents and conditions: (i) RuO_2 (5 mol %), $NaIO_4$ (2.5 equiv), acetone/H_2O/EtOAc (1/1/2), rt, 30 min; (ii) TsOH (10 mol %), $CHCl_3$, rt, 48 h (81% overall).



Scheme 4. Reagents and conditions: (i) PivCl, Et_3N, DMAP, (10 mol %), CH_2Cl_2, rt, 2 h (90%); (ii) MeOH, reflux, 24 h; (iii) CrO_3·2py, CH_2Cl_2, rt, 30 min (50% overall+47% **17**); (iv) 0.004 M K_2CO_3 in MeOH, rt, 18 h (100%); (v) PCC, PhH, reflux, 18 h; (vi) $NaBH_4$, MeOH, 0 °C, 10 min (90% overall); (vii) 6 N HCl, 60 °C, 18 h (95%).

first involved conversion of the C-8 hydroxyl into the corresponding pivalate **17**. Ring opening of the lactone with methanol, followed by oxidation of the resulting alcohol then gave lactam **19**. Modified Collins' oxidation[16] was employed in this sequence in an effort to minimize re-cyclization of hydroxyester **18** to lactone **17**. Even with this precaution substantial amounts of lactone **17** were recovered from the two-step sequence. Fortunately the recovery was high and by recycling lactone **17** high overall yields of lactam **19** could be obtained.

At this point we were able to obtain a crystal structure of intermediate **19** (Fig. 2), confirming the structure of this intermediate and hence the stereochemical assignments at C-2 and C-4.

Next we required selective deprotection of the C-9 hydroxyl in order to invert the stereochemistry at this position. This was achieved by treating lactam **19** with 0.004 M K_2CO_3 in methanol. Deprotection under these conditions was accompanied by ring opening of the lactam. After 18 h at room temperature, a 40:60 mixture of diesters **20** and **21** could be isolated. Extended reaction times and/or increased concentration of base led to cleavage of the pivalyl ester, so it was preferable to stop the reaction at this point and to resubject **20** to the same reaction conditions. In this way, efficient conversion into the desired alcohol **21** was possible. Inversion of the C-9 hydroxyl group was effected via a straightforward oxidation/reduction sequence, the reduction occurring from

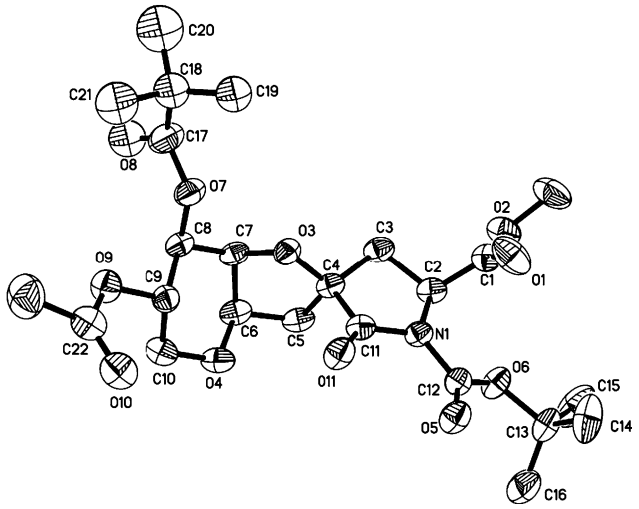


Figure 2. X-ray structure of **19**.[17]

the less hindered face of the substrate to give alcohol **22** with high diastereoselectivity (>95:5 by ^1H NMR). Global deprotection then provided neodysiherbaine **1**, isolated as its hydrochloride salt, in good overall yield. Material obtained via this sequence exhibited ^{13}C data[9] in good agreement with that reported previously.[1]

In conclusion, we have been able to develop a short stereocontrolled sequence to the natural product neodysiherbaine **1** starting from glucal **7**. This approach makes use of an asymmetric PTC alkylation to install the α-amino acid function, and a stereoselective RuO_4-mediated oxidative cyclization to generate the 2,7-dioxabicyclo[4.3.0]nonane ring system. The chemistry developed during the course of this study should allow access to a range of neodysiherbaine analogues and efforts towards this end are currently under investigation.

Acknowledgements

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9. Selected NMR data.
   Chloride **8**: δ_H (400 MHz, $CDCl_3$) 5.90 (1H, ddd, *J* 10.5, 2.0, 1.0), 5.85–5.81 (1H, m), 5.21–5.20 (1H, m), 5.20–5.16 (1H, m), 5.04–5.03 (1H, m), 4.33–4.29 (1H, m), 4.10–4.07 (2H, m), 4.06 (1H, dd, *J* 11.5, 5.0), 3.52 (1H, dd, *J* 11.5, 6.5), 2.42 (1H, ddd, *J* 15.0, 8.0, 1.0), 2.37 (1H, ddd, *J* 15.0, 5.5, 1.0), 2.03 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.6, 141.6, 133.7, 124.6, 117.4, 72.1, 64.9, 64.8, 48.4, 37.3, 21.1.
   Diene **10**: δ_H (400 MHz, $CDCl_3$) 5.93–5.89 (1H, m), 5.86–5.82 (1H, m), 5.25–5.19 (1H, m), 5.01 (1H, br d, *J* 7.5), 4.96 (1H, br s), 4.93 (1H, br s), 4.34–4.25 (2H, m), 4.10 (1H, dd, *J* 11.5, 5.0), 3.56 (1H, dd, *J* 11.5, 6.5), 2.55 (1H, dd, *J* 14.5, 6.5), 2.43–2.33 (2H, m), 2.25 (1H, dd, *J* 15.0, 5.0), 2.07 (3H, s), 1.46 (9H, s), 1.43 (9H, s); δ_C (100 MHz, $CDCl_3$) 171.7, 170.7, 155.3, 141.2, 134.1, 124.3, 116.3, 82.1, 79.8, 72.3, 65.0, 64.9, 52.7, 39.6 (2), 28.4, 28.1, 21.2.
   Lactone **16**: δ_H (500 MHz, $CDCl_3$) 5.39 (1H, br d, *J* 5.5), 5.01–4.96 (1H, m), 4.52–4.47 (1H, m), 4.41 (2H, app s), 4.28–4.27 (1H, m), 4.12–4.11 (1H, m), 3.94 (1H, dd, *J* 11.0, 5.0), 3.80 (1H, dd, *J* 9.5, 4.0), 3.12 (1H, app t, *J* 11.0), 3.22 (1H, dd, *J* 13.0, 6.0), 2.20 (1H, d, *J* 14.0), 2.09 (3H, s), 2.00 (1H, dd, *J* 14.0, 4.0), 1.96 (1H, app t, *J* 13.0), 1.44 (9H, s); δ_C (125 MHz, $CDCl_3$) 171.6, 170.9, 155.5, 80.6, 80.5, 79.5, 78.0, 75.4, 71.0, 70.0, 66.2, 48.4, 43.7, 39.8, 28.4, 21.1.
   Neodysiherbaine **1**: δ_H (400 MHz, D_2O) 4.07 (1H, br s), 3.99 (1H, br s), 3.75 (1H, app t, *J* 3.5), 3.66 (1H, dd, *J* 13.0, 2.5), 3.57 (1H, br s), 3.48 (1H, br d, *J* 11.0), 3.39 (1H, d, *J* 13.0), 2.55 (1H, br d, *J* 15.0), 2.40 (1H, d, *J* 14.0), 2.06 (1H, dd, *J* 14.0, 3.5), 1.86 (1H, dd, *J* 15.0, 12.0); δ_C (125 MHz, 50 μl CD_3OD in D_2O) 180.9, 174.5, 88.1, 81.0, 77.4, 70.3, 68.6, 67.9, 54.5, 45.2, 40.1.
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13. The cyclization shown in Scheme 2 is based on the mechanism proposed for OsO_4-promoted oxidative cyclization.[12g] For more detailed discussion on the different mechanisms that may operate with other oxidants, see Ref. 12 and Baldwin, J. E.; Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940–941; Crossley, M. J.; Lehtonen, E. M. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918–920.
14. We were only able to isolate dihydroxylation products from reactions involving OsO_4. $KMnO_4$-based oxidations did generate **13** but in significantly lower yield than RuO_4-based oxidations.
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17. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 274553. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].