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A convenient route to the furopyran core of dysiherbaine

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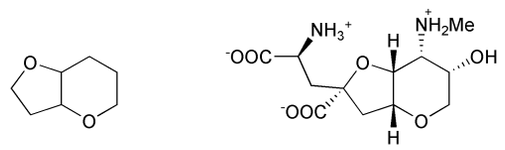
Received 21st December 2002, Accepted 30th January 2003
First published as an Advance Article on the web 10th February 2003

The bicyclic core, furo[3,2-*b*]pyran, of the dysiherbaines has been synthesized *via* two routes involving the imino 1,2-Wittig rearrangement of allyl furohydroximate and the asymmetric dihydroxylation of furylpropenol derivative.

Hexahydro-2*H*-furo[3,2-*b*]pyran nucleus **1** (Fig. 1) is an important element in many pharmacologically active compounds, such as nucleotide antibiotics[1] and carbohydrate derivatives.[2] Furthermore, dysiherbaine **2**[3a] and neodysiherbaine A,[3b] recently isolated from a Micronesian marine sponge *Dysidea herbacea*, also have the furopyran core. Dysiherbaine has received much attention not only from synthetic chemists but also medicinal chemists since it is a selective agonist of non-NMDA type glutamate receptors in the central nervous system. Dysiherbaine is also particularly interesting as a lead compound for the discovery of new drugs. Several groups[3b,4] already have accomplished the total synthesis of **2** and neodysiherbaine A.



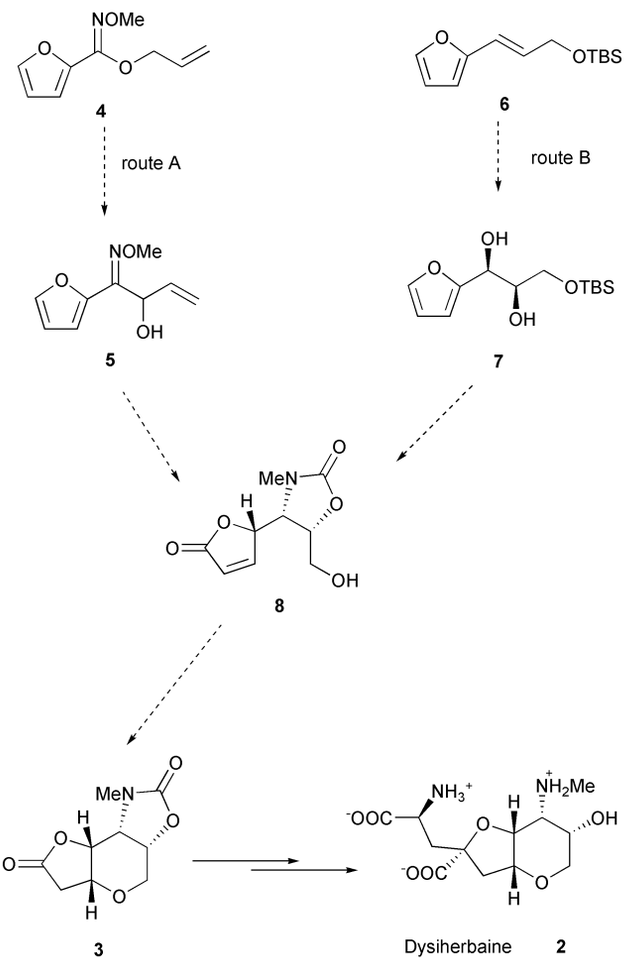
1 Dysiherbaine **2**

Fig. 1 Furo[3,2-*b*]pyran and dysiherbaine.

We focused our attention on developing a practical method for the synthesis of biologically active furopyrans and established the alternative synthesis of furopyran **3**, which is the key intermediate for dysiherbaine synthesis.[4d] Our synthetic approach consists of two different routes, that is, route A and route B as shown in Scheme 1. The common characteristic for both methods is as follows: (1) the furan ring is efficiently employed for the construction of tetrahydrofuranone moiety in **3**; (2) the amino alcohol moiety is introduced by either imino 1,2-Wittig rearrangement of hydroximate **4** (route A) or the dihydroxylation of allyl alcohol derivative **6** followed by selective conversion of one of two hydroxy groups into the amino group (route B); (3) intramolecular Michael addition of the hydroxy group to α,β-unsaturated furanone in **8**.

First route A to **3** (Scheme 2) was accomplished *via* 1,2-Wittig rearrangement of hydroximates as a key reaction. Previously, we found[5] that imino 1,2-Wittig rearrangement of benzyl and allyl hydroximates proceeded smoothly to give 2-hydroxy oxime ethers and this reaction was suitable for practical synthesis of amino alcohols which are important partial structures of biological active compounds.[5b]

The hydroximate **4** was prepared in 74% yield in three steps from 2-furoyl chloride according to the reported procedure.[5,6] The imino Wittig rearrangement of hydroximate **4** proceeded smoothly by the treatment with LDA at −40 °C to give the 2-hydroxy oxime ether **5** in 95% yield. After the silylation of the hydroxy group, attempted Lemieux–Johnson oxidation of **9** was not successful but dihydroxylation of the olefin in **9** with OsO_4–NMO followed by glycol cleavage with sodium periodate gave the corresponding aldehyde which was reduced

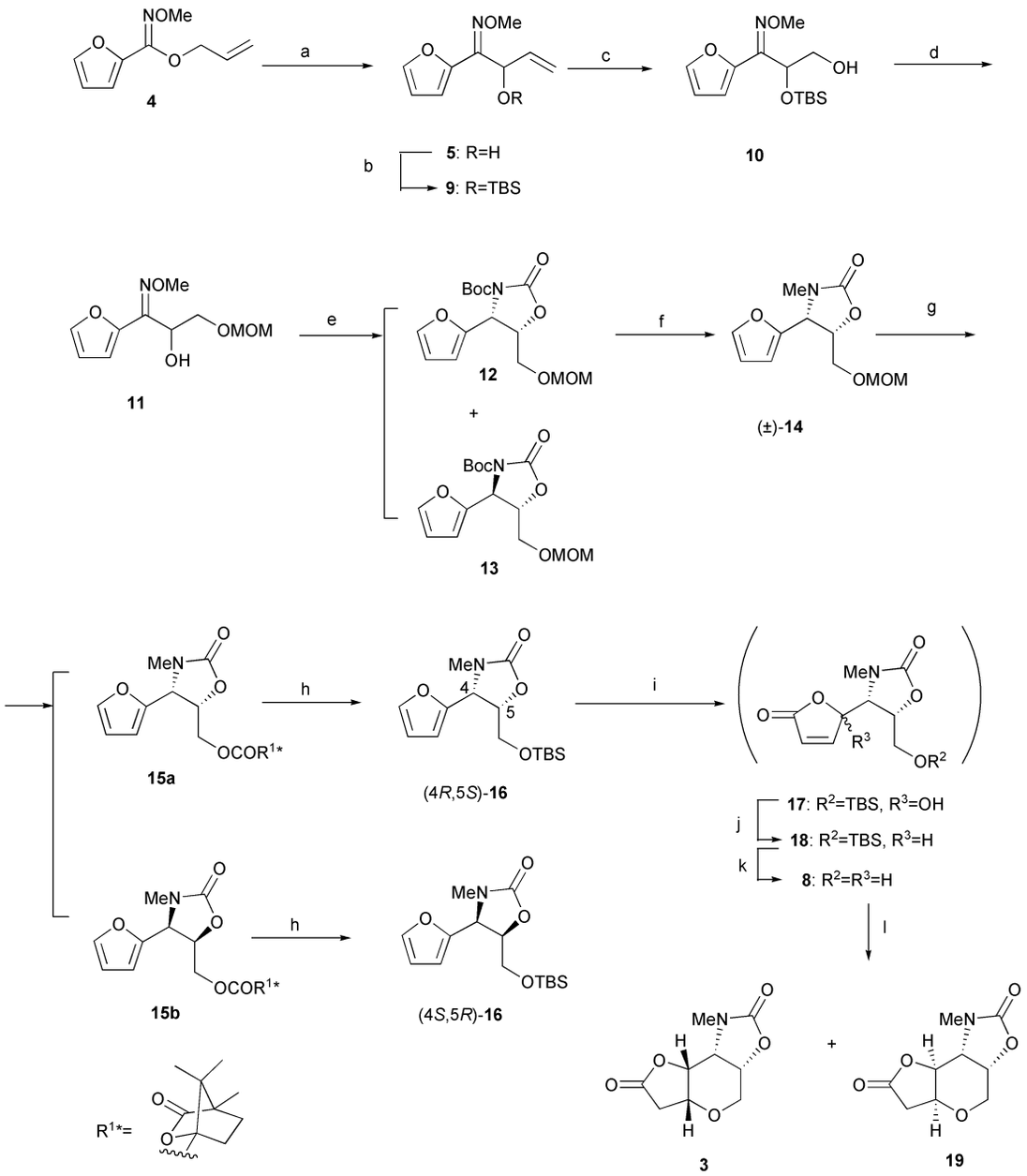


Scheme 1

with $NaBH_4$ to afford the alcohol **10**. The protection of the hydroxy group with MOMCl followed by desilylation gave the secondary alcohol **11**.

We next investigated the conversion of oxime ether into amino alcohol according to the reported procedure.[5,7] The reduction of **11** with $LiAlH_4$ followed by acylation of the resulting demethoxylated amino alcohol with 2.2 equiv. of Boc_2O afforded a *ca.* 1 : 1 mixture of two *N*-Boc-oxazolidinones, *cis*-**12** and *trans*-**13** in 78% yield. The reduction of **11** with either Red-Al or BH_3·Py followed by acylation with Boc_2O gave *trans*-**13** as a major product in both cases (Red-Al: 51%; *trans*-**13** : *cis*-**12** = 3 : 1. BH_3·Py: 21%; *trans*-**13** : *cis*-**12** = 7 : 1). Conventional deprotection of the Boc group of **12** followed by *N*-methylation gave the (±)-*N*-methyloxazolidinone **14**. The optical resolution of racemic **14** was readily accomplished *via* the conventional separation of the corresponding diastereoisomers. The acylation of unstable (±)-alcohol derived from **14** with (−)-camphanic chloride gave a mixture of two corresponding esters **15a** and **15b** which was easily separated into their diastereomers in high yield by column chromatography. Hydrolysis of each

DOI: 10.1039/b212556k

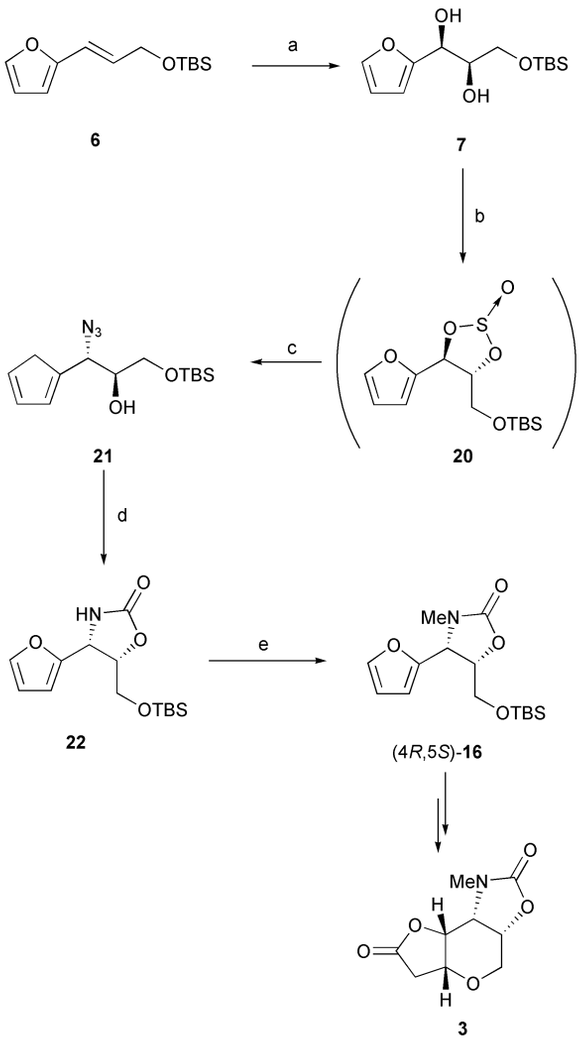


Scheme 2 *Reagents and conditions*: a, LDA, −40 °C, 95%; b, TBSOTf, 2,6-lutidine, 0 °C, 99%; c, i. OsO_4, NMO, rt, ii, $NaIO_4$, rt, iii. $NaBH_4$, 0 °C, 57% (from **9**); d, i. MOMCl, diisopropylethylamine, 0 °C, 83%, ii. TBAF, rt, 87%; e, i. $LiAlH_4$, 0 °C then 35 °C, ii. $(Boc)_2O$, DMAP, rt, 78% (from **11**); f, i. TFA, 0 °C, 72%, ii. MeI, NaH, rt, 78%; g, i. 6 M HCl, rt, ii. (−)-camphanic chloride, rt, 60% (from **14**); h, i. KOH, rt, ii. TBSCl, DMAP, 72% (from (4*R*,5*S*)-**15a**) 70% (from (4*S*,5*R*)-**15b**); i, MCPBA, 0 °C; j, $NaBH_4$, $CeCl_3$, 0 °C; k, 48% HF, 60 °C; l, $NaHCO_3$, rt, **3**: 10% (from (4*R*,5*S*)-**16** in 4 steps); **19**: 19% (from (4*R*,5*S*)-**16** in 4 steps).

ester **15a** and **15b** gave the corresponding enantiomeric alcohols which were subjected to silylation to give the desired (4*R*,5*S*)- and (4*S*,5*R*)-oxazolidinones **16**, respectively. Finally, we converted (4*R*,5*S*)-**16** into the desired furopyran **3** as follows. For the oxidation of furan ring, treatment of (4*R*,5*S*)-**16** with MCPBA followed by reduction of the resulting hydroxybutenolide **17** with $NaBH_4$ in the presence of $CeCl_3$ afforded the unstable butenolide **18** as a *ca*. 1 : 1 mixture of two stereoisomers. Careful deprotection of the silyl group of **18** with HF at 60 °C gave a mixture of two cyclized lactones **19** and **3** after treatment with $NaHCO_3$. Monitoring the reaction by TLC showed that upon treatment with HF, an isomer (R^3 = α-hydrogen) of intermediate **8** cyclized directly to **19** but another one (R^3 = β-hydrogen) underwent cyclization to form **3** when treated with $NaHCO_3$. The furopyran **3** is a key intermediate for the synthesis of dysiherbaine **2**. The physical and spectral data of **3** were identical with those reported in the literature[4d] and private communication.[4e]

We next investigated the most concise synthesis of furopyran **3** *via* route B (Scheme 3). The known[8] optically active glycol **7** (95.5% ee for dibenzoate)[9] was prepared by the asymmetric dihydroxylation of olefin **6**[8] and then converted into the oxazolidinone **22** by slightly modifying Nakata's and Mori's procedures involving the S_N2 reaction of the hydroxy group into the azido group.[10] The preparation of the unstable cyclic sulfite **20** followed by ring opening by treatment with sodium azide gave the azide **21** which was acylated with phenyl chloroformate followed by the treatment with Ph_3P to give the desired (4*R*,5*S*)-oxazolidinone **22** as the result of reduction of the azide group and subsequent cyclization. The methylation at the nitrogen atom gave the desired (4*R*,5*S*)-oxazolidinone **16**. According to the procedure in route A, (4*R*,5*S*)-**16** was also converted into the desired furopyran **3**.

In conclusion, we have now developed a new strategy for the synthesis of furopyran with an amino alcohol which is an intermediate in the dysiherbaine synthesis.



Scheme 3 *Reagents and conditions*: a, AD-mix-β, $MeSO_2NH_2$, 0 °C, 99%; b, $SOCl_2$, Et_3N, 0 °C 78%; c, NaN_3, 60 °C, 56%; d, i. PhOCOCl, Py, rt, 93%, ii. PPh_3, 0 °C then H_2O, 100 °C, 67%; e, MeI, NaH, 0 °C, then, rt, 92%.

Experimental

A representative general procedure: conversion of (4*R*,5*S*)-oxazolidinone 16 into furopyrans 3 and 19

To a solution of (4*R*,5*S*)-oxazolidinone **16** (123 mg, 0.4 mmol) in CH_2Cl_2 (10 ml) was added MCPBA (136 mg, 0.8 mmol) at 0 °C under a nitrogen atmosphere. After being stirred at the same temperature for 7 days, the reaction mixture was concentrated under reduced pressure. To a solution of residue (crude hydroxybutenolide **17**) in MeOH (5 ml) was added $CeCl_3$ (5 mg) and $NaBH_4$ (60 mg, 1.6 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was acidified by adding conc. HCl and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried with $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue (crude butenolide **18**) in MeCN (4.5 ml) was added 48% HF (0.2 ml) at room temperature under nitrogen atmosphere. After being stirred at 60 °C for 5 h, to the reaction mixture was added an excessive amount of saturated aqueous $NaHCO_3$ at 0 °C. After being vigorously stirred at room temperature for 16 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was washed with H_2O, dried with $MgSO_4$, and concentrated under reduced pressure. Purification of residue by short column chromatography (*n*-hexane–AcOEt 3 : 1, 1 : 2, then AcOEt, then AcOEt–MeOH 20 : 1) afforded the furopyran **3** (8 mg, 10%) and its isomer **19** (16 mg, 19%). The furopyran **3** was identical with the authentic sample upon direct comparisons of their spectral data.

3: colorless crystals, mp 192–193 °C (AcOEt); $[a]_D^{28}$ +131.8 (*c* 0.35, MeOH) (lit.[4e] $[a]_D^{30}$ +127.8 (*c* 0.41, MeOH)).

19: colorless crystals, mp 202–205°C (AcOEt); $[a]_D^{27}$ −40.7 (*c* 0.46, MeOH); ν_{max}/cm^{-1} 1772, 1745 (γ-lactone, oxazolidinone); δ_H (500 MHz; $CDCl_3$) 2.70 (1H, br d, *J*=18.5 Hz, 6-H), 2.87 (1H, dd, *J*=18.5, 6 Hz, 6-H), 2.96 (3H, s, NMe), 3.54 (1H, dd, *J*=13, 7 Hz, 4-H), 3.97 (1H, dd, *J*=13, 5 Hz, 4-H), 4.20 (1H, br dd, *J*=8.5, 1.5 Hz, 8b-H), 4.53 (1H, br dd, *J*=6, 4 Hz, 5a-H), 4.61 (1H, dd, *J*=4, 1.5 Hz, 8a-H), 4.72 (1H, ddd, *J*=8.5, 7, 5 Hz, 3a-H); HRMS (EI) $[M^+]$ calcd for $C_9H_{11}NO_3$: 213.0636, found: 213.0639.

Acknowledgements

We are grateful to Professor S. Hatakeyama (Faculty of Pharmaceutical Sciences, Nagasaki University, Japan) for providing us the authentic sample of furopyran **3** and the Ministry of Education, Culture, Sports, Science and Technology of Japan for Grant-in-Aid for Scientific Research on Priority Areas (A) and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

References and notes

1 (*a*) S. Knapp, *Chem. Rev.*, 1995, **95**, 1859–1876; (*b*) S. Knapp, C. Jaramillo and B. Freeman, *J. Org. Chem.*, 1994, **59**, 4800–4804.

2 (*a*) T. Gracza, T. Hasenöhrl, U. Stahl and V. Jäger, *Synthesis*, 1991, 1108–1112; (*b*) M. A. Leeuwenburgh, C. Kulker, H. I. Duynstee, H. S. Overkleeft, G. A. van der Marel and J. H. van Boom, *Tetrahedron*, 1999, **55**, 8253–8262; (*c*) O. Arjona, A. G. Csákÿ, M. C. Murcia and J. Plumet, *Tetrahedron Lett.*, 2000, **41**, 9777–9779.

3 (*a*) R. Sakai, H. Kamiya, M. Murata and K. Shimamoto, *J. Am. Chem. Soc.*, 1997, **119**, 4112–4116; (*b*) R. Sakai, T. Koike, M. Sasaki, K. Shimamoto, C. Oiwa, A. Yano, K. Suzuki, K. Tachibana and H. Kamiya, *Org. Lett.*, 2001, **3**, 1479–1482.

4 (*a*) M. Sasaki, T. Maruyama, R. Sakai and K. Tachibana, *Tetrahedron Lett.*, 1999, **40**, 3195–3198; (*b*) M. Sasaki, T. Koike, R. Sakai and K. Tachibana, *Tetrahedron Lett.*, 2000, **41**, 3923–3926; (*c*) B. B. Snider and N. A. Hawryluk, *Org. Lett.*, 2000, **2**, 635–638; (*d*) H. Masaki, J. Maeyama, K. Kamada, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *J. Am. Chem. Soc.*, 2000, **122**, 5216–5217; (*e*) Private communication from Professor Hatakeyama who revised $[a]_D$ value of **3** as shown in experimental procedure; (*f*) D. Phillips and A. R. Chamberlin, *J. Org. Chem.*, 2002, **67**, 3194–3201.

5 (*a*) O. Miyata, T. Koizumi, I. Ninomiya and T. Naito, *J. Org. Chem.*, 1996, **61**, 9078–9079; (*b*) O. Miyata, H. Asai and T. Naito, *Synlett*, 1999, 1915–1916.

6 O. Miyata, A. Nishiguchi, I. Ninomiya, K. Aoe, K. Okamura and T. Naito, *J. Org. Chem.*, 2000, **65**, 6922–6931.

7 (*a*) M. Shimizu, K. Tsukamoto and T. Fujisawa, *Tetrahedron Lett.*, 1997, **38**, 5193–5196; (*b*) D. R. Williams, M. H. Osterhout and J. P. Reddy, *Tetrahedron Lett.*, 1993, **34**, 3271–3274; (*c*) M. Masui and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 5195–5198; (*d*) S. Boukhris and A. Souizi, *Tetrahedron Lett.*, 1999, **40**, 1669–1672.

8 M. Takeuchi, T. Taniguchi and K. Ogasawara, *Synthesis*, 1999, 341–354.

9 The optical purity of **7** was determined by HPLC using a chiral column (CHIRALCEL OD, elution with i-PrOH–*n*-hexane, 1 : 500 v/v) after conversion into the benzoate.

10 (*a*) Y. Sakamoto, A. Shiraishi, J. Seonhee and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 4203–4206; (*b*) M. Seki and K. Mori, *Eur. J. Org. Chem.*, 1999, **64**, 2965–2967.