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Synthesis of Solenopsin B via Stereoselective Reduction of Bicyclic N,O-Ketals

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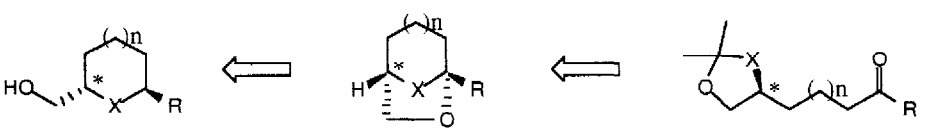
Key Words. Enantioselective synthesis; Solenopsin B. Stereoselective reduction; Bicyclic N,O-ketals, DIBALH

Abstract: A new enantionselective total synthesis of (-)-solenopsin B was described starting from L-glutamic acid as an optically active natural source, in which stereoselective reduction of bicyclic N,O-ketals with DIBALH was used as the key reaction step

Recently, we have developed an efficient procedure for the synthesis of 6-8 membered cyclic ether derivatives via stereoselective reduction of bicyclic ketals (Scheme 1; X=O, n=1-3).[1] The usefulness of this type of transformation has been gradually recognized by several groups.[2] Since the precursors of ω-keto-acetonides are readily accessible from conventional chiral pools,[3] the procedure is extremely useful for preparing enantiomerically pure cyclic ethers.

As an extension of our study in this field, we were particularly interested in the application of the method to the reduction of bicyclic N,O-ketals owing to the scarcity of similar reports [2d-f] Thus, replacing one of the two oxygen atoms by nitrogen as illustrated in Scheme 1 (X=NH), that is, passing through bicyclic N,O-ketal intermediates, the process will consitute an efficient entry to cyclic amino derivatives with well defined relative and absolute stereochemistry.

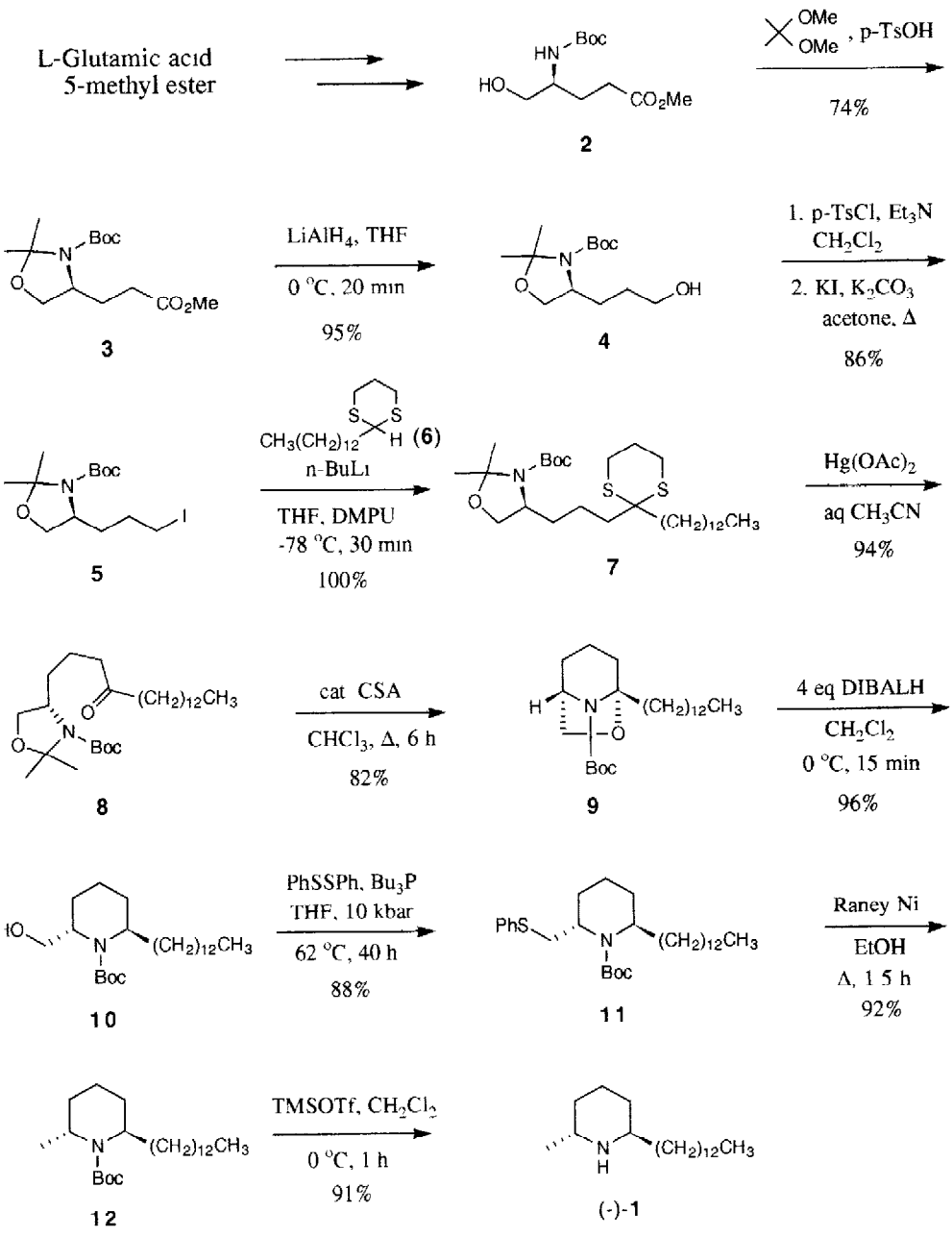


X = O or NH

Scheme 1

In order to demonstrate the feasibility of this strategy, an enantioselective synthesis of (-)-solenopsin B (**1**), a piperidine alkaloid isolated from the fire ant,[4] was undertaken. During this study a similar work was disclosed by Wasserman et al. but is only limited to racemic compounds.[2e] In this Letter we wish to describe our elegant approach to the target molecule starting from L-glutamic acid as a convenient chiral source[5] as outlined in Scheme 2.[6]

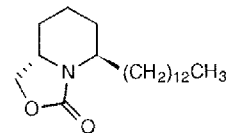
Commercially available L-glutamic acid 5-methyl ester[7] was converted into 4-amino-5-hydroxypentanoic acid (**2**) according to the method developed by Shimamoto and Ohfune.[8] Then a versatile chiral building block of iodide **5**, $[\alpha]^{18}_{D}$ +19.8° (*c* 1.00, $CHCl_3$), was prepared from **3** by the conventional 3-step procedure in 81.7% overall yield. Alkylation of **5** with a lithium anion of the 1,3-dithiane derivative **6** using a THF/dimethyl-


L-Glutamic acid
5-methyl ester
2
74%
3
LiAlH4, THF
0 °C, 20 min
95%
4
1. p-TsCl, Et3N
CH2Cl2
2. KI, K2CO3
acetone, Δ
86%
5
(6)
n-BuLi
THF, DMPU
-78 °C, 30 min
100%
7
Hg(OAc)2
aq CH3CN
94%
8
cat CSA
CHCl3, Δ, 6 h
82%
9
4 eq DIBALH
CH2Cl2
0 °C, 15 min
96%
10
PhSSPh, Bu3P
THF, 10 kbar
62 °C, 40 h
88%
11
Raney Ni
EtOH
Δ, 1.5 h
92%
12
TMSOTf, CH2Cl2
0 °C, 1 h
91%
(-)-1

Scheme 2

propyleneurea (DMPU) mixture as solvent proceeded cleanly to afford **7**, followed by removal of the dithiane functionality by treatment with $Hg(OAc)_2$ in aqueous CH_3CN furnished ketone **8** in high yield (gram scale). After examination of the several reaction conditions to obtain the optimum yield in the next transketalization step, we found that the carefully controlled reaction of **8** in the presence of a catalytic amount of (+)-*S*-camphor-10-sulfonic acid (CSA) in refluxing $CHCl_3$ was the best[9] and the desired key intermediate of bicyclic N,O-ketal **9**, $[\alpha]^{23}_D$ +21.0° (*c* 1.0, $CHCl_3$), was isolated in 82% yield. Similarly as described in our previous papers,[1] **9** was subsequently reduced with 4 equiv of DIBALH in CH_2Cl_2 at 0 °C to provide trans-alcohol **10**, $[\alpha]^{23}_D$ -21.1° (*c* 1.26, $CHCl_3$), in almost quantitative yield. The stereoselectivity of this reduction was found to be excellent (>99%) judging from the TLC and ^1H NMR evidence of the crude mixture in accord with the result reported by Wasserman et al.[2e] Unambiguous confirmation of this stereochemical assignment was achieved by comparing directly with the corresponding cis isomer derived from **10**.[10]

With the desired alcohol **10** in hand, we then proceeded with the final stage. In order to complete our synthetic scheme, deprotection of the Boc group and removal of the hydroxyl function from **10** are necessary. Unfortunately, we found that all attempts to realize these subjects under a variety of conditions (conc HCl in AcOEt; p-TsCl in pyridine) were unsuccessful due to the formation of the cyclic carbamate derivative **13** (IR, 1740 cm^{-1})[5] as the major byproduct. This unexpected reactivity of **10** to produce **13** would be due to attack of proximal hydroxyl to the Boc group.



13

After numerous trials with alternative procedures, we found that the Hata's reagent system, Bu_3P-PhSSPh,[11] to be most satisfactory for our purpose. Initially, according to the literature procedure, the reaction of **10** with 3 equiv of PhSSPh and 4 equiv of Bu_3P was carried out in refluxing THF. However, the reaction was very slow and even after refluxing for 85 h only 28% of **11** was produced along with 55% of recovery. As described in the preceding paper, we were delighted to find that this difficulty could be overcome by utilizing high pressure technique. Thus, when the same reaction was conducted at 10 kbar pressure and 62 °C for 40 h, phenylsulfide **11** was obtained in 88% yield. Desulfurization of **11** with Raney Ni followed by deprotection of the Boc group with 3 equiv of TMSOTf[12] in CH_2Cl_2 afforded (-)-solenopsin B (**1**), $[\alpha]^{22}_D$ -2.6° (*c* 1.00, EtOH) {lit.[13] $[\alpha]^{23}_D$ -0.51° (*c* 1.97, EtOH)}, in 83.7% yield. The spectral data including IR, ^1H and ^{13}C NMR, and MS/HRMS of this synthetic material were in good agreement with the literature data.[13]

In summary, a new enantioselective synthesis of solenopsin B (**1**) was accomplished by using stereoselective reducion of bicyclic N,O-ketals as the key reaction step, in which L-glutamic acid was employed as a versatile chiral source. The overall yield of **1** from iodide **5** was 54.5% for 7-step sequence.

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6. Satisfactory spectral and analytical data were obtained for all new compounds.

7. Purchased from Peptide Institute, Inc., Osaka.

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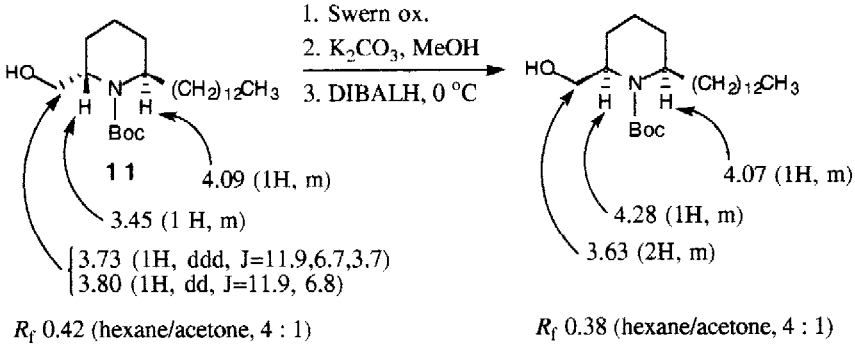
9. The reaction was highly dependent on solvents, added acid catalysts, and reaction period. For example, the use of CH_2Cl_2 as solvent or p-TsOH as acid catalyst caused a considerable decrease of product yield. Prolonged heating was also fruitless due to the decomposition of the product.

10. The corresponding cis-isomer was obtained from **10** by the following 3-step procedure: (1) Swern oxidation to the corresponding aldehyde, (2) base-catalyzed isomerization of the resulting aldehyde, (3) DIBALH reduction. And we found that each isomer can be clearly identified by TLC and ^1H NMR (400 MHz) as noted in the following Scheme. The full details of these results will be reported elsewhere.



R_f 0.42 (hexane/acetone, 4 : 1)

R_f 0.38 (hexane/acetone, 4 : 1)

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