Pergamon

Tetrahedron Letters, Vol. 37, No. 28, pp. 4987-4990, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00990-2

Efficient Synthesis of an Enantiomeric Pair of Pinidine: An Illustration of Organochemical Carving on the Rigid Bridged System as the Stereochemical Tactics

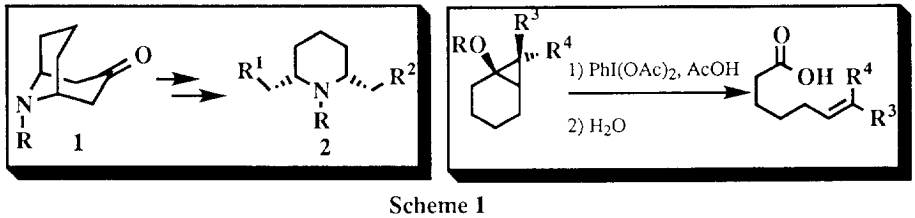
Takefumi Momose,* Takashi Nishio, and Masayuki Kirihara

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Abstract: Asymmetric synthesis of (-)-pinidine and its enantiomer was accomplished by starting from norgranatanone *via* the asymmetric enolization, stereoselective cyclopropanation, and oxidative ring cleavage of the resulting cyclopropanol system with a hypervalent iodoid as key steps.

The 9-azabicyclo[3.3.1]nonan-3-ones (norgranatanone derivatives) (**1**) act as an important synthon for the synthesis of the *cis*-2,6-disubstituted piperidine system (**2**). Among the procedures illustrating their utility is the asymmetric deprotonation of **1** and subsequent cleavage of the resulting chiral enol ether.[1] Moreover, the organochemical carving on a bridged bicyclic body often plays a promising role in the highly stereoselective synthesis of organic molecules since a rather simple principle operates on the stereochemical process.[2]

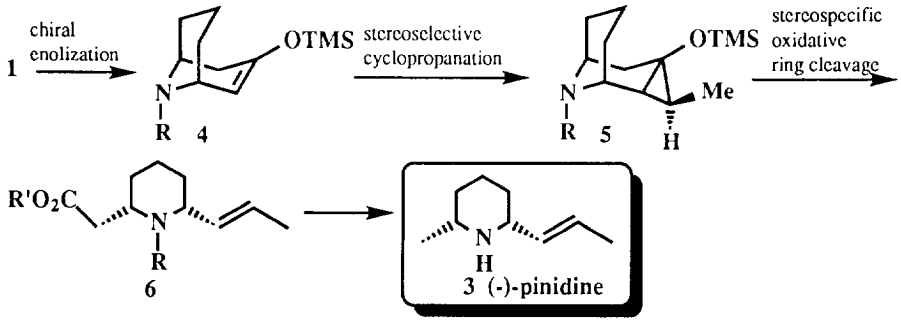
Recently, we found that the reaction of a 1-(trimethylsiloxy)bicyclo[n.1.0]alkene, available from the Simmons-Smith reaction of the enol silyl ether derived from a cycloalkanone, with phenyliodine(III) diacetate (PIDA) in acetic acid causes oxidative bond cleavage to afford an alkenoic acid in high yield.[3] We also found that an *exo* monoalkylated siloxycyclopropane with PIDA gives only an (*E*)-alkene while an *endo* compound gives only a (*Z*)-alkene.[3] We wish to report the efficient asymmetric synthesis of the piperidine alkaloid (-)-pinidine (**3**)[4,5] and its enantiomer (+)-**3** from **1**[6] by application of this oxidative fragmentation.



Scheme 1

Our synthetic plan for **3** involves the above mentioned homologative cleavage of the σ-symmetric ketone **1** (**Scheme 2**). Stereoselective cyclopropanation affording the *exo* methyl compound (**5**) is required since pinidine has an (*E*)-olefin moiety.

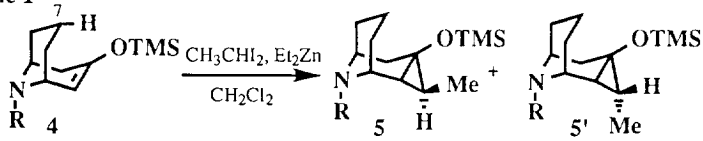
First, we examined the selectivity of *exo* orientation of the methyl in the cyclopropanation of racemic enol silyl ethers (**4**)[7] as a model study. Treatment of **4** with 1,1-diiodoethane and diethylzinc afforded the cyclopropyl silyl ethers **5** and **5'**.



Scheme 2

The cyclopropanation took place only on the β–face of the enol ethers in all cases because the 'fork head' axial proton (C7 ax.-H) blocked the α–face from an attack of the carbenoid. The results are shown in **Table 1**. As noted in runs 1-6, no stereoselectivity was acquired with an enol ether (**4**) bearing an alkoxycarbonyl or an acyl group on the bridged nitrogen. Fortunately, in the case of the substrate bearing an *N*-sulfonyl group, the cyclopropanation proceeded stereoselectively to give the desired *exo*-methyl compound **5** predominantly (runs 5 and 6).

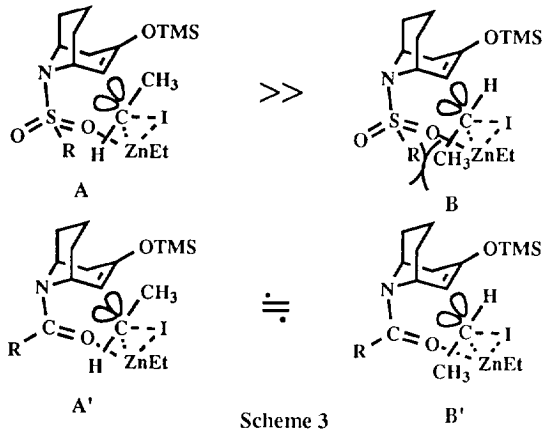
Table 1



Runs	4	R	Yields of 5 and 5' (%)	exo (5) : endo (5')*
1	**4a**	CO_2Me	83	1 : 1
2	**4b**	Cbz	78	1 : 1
3	**4c**	$COCF_3$	63	1 : 1
4	**4d**	Bz	43	1 : 1
5	**4e**	Ms	51	4 : 1
6	**4f**	Ts	99	10 : 1

* Determined by n.m.r.

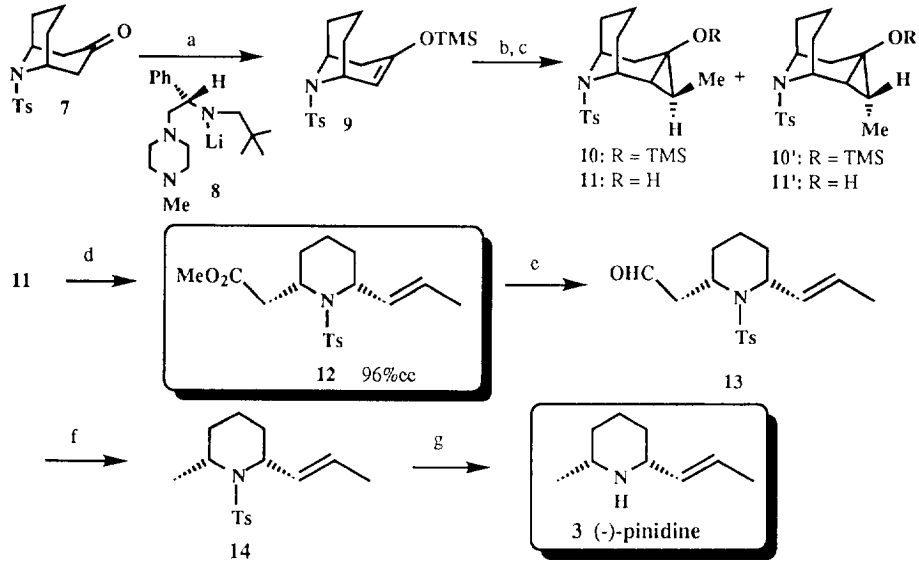
While details of the mechanism for the reactions of **4** with zinc/methyl-substituted carbenoid remain unknown, it is apparent that the sulfonamide moiety in **4** plays an important role in the stereoselectivity. We assume that the zinc on the carbenoid coordinates with the sulfonamide oxygen, and the carbenoid attacks the double bond in a less hindered fashion (**A**) as shown in **Scheme 3**. The fact that the tosylated compound **4f** (run 6) exhibits better stereoselectivity than does the mesylated one **4e** (run 5) strongly supports our postulate. On the other hand, in the case of **4a - 4d**, the coordination of zinc/carbenoid with the carbonyl oxygen causes no steric interaction between "R" and the methyl of the carbenoid.



Scheme 3

Next, we examined the asymmetric enolization of *N*-tosylated norgranatanone (**7**) and subsequent cyclopropanation. The treatment of **7** with a chiral lithium amide (**8**) and excess trimethylsilyl chloride (TMSCl) in tetrahydrofuran (THF) at -100°C according to the method of Koga[8] gave the corresponding enol silyl ether (**9**). After the cyclopropanation of **9**, the resulting mixture of *exo* and *endo* compounds (**10** and **10'**) was subjected to desilylation. The separation of an *exo* isomer (**11**) from an *endo* one (**11'**) was performed by using a column chromatography on silica gel. The PIDA oxidation of **11** in methanol gave the desired (*E*)-alkene (**12**) stereospecifically.[9]

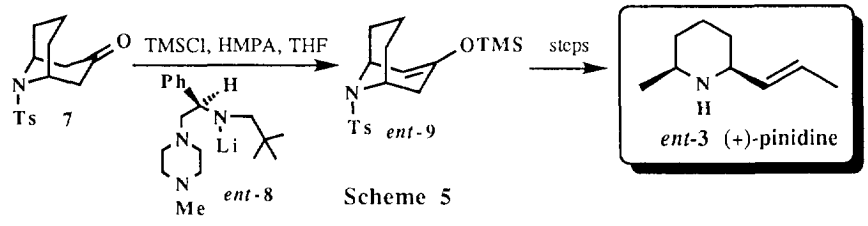
Scheme 4



Reagents and conditions: a) lithium amide (**8**), TMSCl, THF, HMPA, -100°C (51%); b) CH_3CHI_2, Et_2Zn, CH_2Cl_2, rt; c) nBu_4NF, THF (81% for **11**, 9% for **11'** in 2 steps); d) PIDA, MeOH, rt (53%); e) DIBAL, CH_2Cl_2, -78°C (91%); f) $RhCl(PPh_3)_3$, C_6H_6, reflux (89%); g) Na, liq. NH_3, EtOH, -78°C (81%).

At this stage, the optical purity of **12** was determined by HPLC and it turned out to be over 96% ee. The reduction of **12** with dibutylaluminum hydride afforded an aldehyde (**13**), and the decarbonylation of **13** with Wilkinson's catalyst gave *N*-tosylpinidine (**14**).[5] The spectral data and specific rotation of **14** were identical with those reported.[10] Deprotection of **14** according to Kibayashi's method[5] afforded (-)-pinidine (**3**). The synthetic product was proved to be identical with the natural one by comparison of their physical properties.[11]

(+)-Pinidine (***ent*-3**), the enantiomer of **3**, was also synthesized from **7** *via* the asymmetric enolization using the enantiomeric amide ***ent*-8** in the same manner as described above.[12]



Scheme 5

Acknowledgment. This work was supported in part by Grant-in-Aid (No.07772092) for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

REFERENCES AND NOTES

1. T. Momose, N. Toyooka, Y. Hirai, *Chem. Lett.* **1990**, 1319-1322; T. Momose, N. Toyooka, S. Seki, Y. Hirai, *Chem. Pharm. Bull.* **1990**, *38*, 2072-2074; T. Momose, K. Okumura, H. Tsujimori, K. Inokawa, G. Tanabe, O. Muraoka, *Heterocycles* **1993**, *36*, 7-11; O. Muraoka, K. Okumura, T. Maeda, G. Tanabe, T. Momose, *Tetrahedron: Asymmetry* **1994**, *5*, 317-320.
2. T. Masamune, H. Matsue, H. Murase, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127-134; R. S. Garigipati, D. M. Tschaen, S. M. Weinreb, *J. Am. Chem. Soc.* **1990**, *112*, 3475-3482; H. Nagaoka, K. Shibuya, Y. Yamada, *Tetrahedron Lett.* **1993**, *34*, 1501-1504.
3. M. Kirihara, S. Yokoyama, H. Kakuda, T. Momose, *Tetrahedron Lett.* **1995**, *36*, 6907-6910.
4. W. H. Tallent, V. L. Stromberg, E. C. Horning, *J. Am. Chem. Soc.* **1955**, *77*, 6361-6364; W. H. Tallent, E. C. Horning, *ibid.* **1956**, *78*, 4467-4469; R. K. Hill, T. H. Chan, J. A. Joule, *Tetrahedron* **1965**, *21*, 147-161.
5. The first asymmetric synthesis of (-)-pinidine and (+)-pinidine: N. Yamazaki, C. Kibayashi, *J. Am. Chem. Soc.* **1989**, *111*, 1396-1408.
6. K. Stach, O. Dold, *Arzneim. Forsch.* **1962**, *12*, 1022-1026.
7. Enol silyl ethers (**4**) were prepared in almost quantitative yields from *N*-protected norgranatanones by reaction with trimethylsilyl triflate in the presence of triethylamine.
8. R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc.* **1986**, *108*, 543-545; R. Shirai, K. Aoki, D. Sato, H.-D. Kim, M. Murakata, T. Yasukata, K. Koga, *Chem. Pharm. Bull.* **1994**, *42*, 690-693.
9. The PIDA oxidation in methanol was found to give the corresponding methyl ester: M. Kirihara, S. Yokoyama, T. Momose, *unpublished results.*
10. The specific rotation of **14**: $[\alpha]_D$= +35.1° (c 1.34 $CHCl_3$); lit.[5] $[\alpha]_D$= +35.7° (c 0.96 $CHCl_3$).
11. The specific rotation of **3**•HCl: $[\alpha]_D$= -9.5° (c 0.55 EtOH); lit.[4] $[\alpha]_D$= -9.5° (c 5.3 EtOH).
12. The specific rotation of ***ent*-3**•HCl: $[\alpha]_D$= +9.5° (c 0.13 EtOH); lit.[5] $[\alpha]_D$= +9.5° (c 0.20 EtOH).

(*Received in Japan* 12 *April* 1996; *revised* 22 *May* 1996; *accepted* 24 *May* 1996)