Tetrahedron Letters, Vol.31, No.23, pp 3279-3282, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF (2*R*, 6*R*)-(-)-2,6-LUPETIDINE: 2,6-DISUBSTITUTED PIPERIDINES AS POTENTIALLY USEFUL "C_2-SYMMETRIC" CHIRAL REAGENTS.

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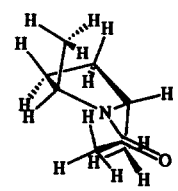
Abstract: *(2R, 6R)-(-)-2,6-Lupetidine has been synthesized from (S)-1,2-epoxypropane and (2S, 6S)-(-)-2,6-bis(benzyloxymethyl)piperidine has been synthesized from (S)-benzyloxymethyl oxirane.*

When compared to chiral auxiliary reagents with no symmetry, the presence of a C_2 symmetry axis within the auxiliary often offers unique advantage in achieving asymmetric induction for a given chemical transformation. Indeed the primary benefit of a C_2-symmetric auxiliary is that the number of competing diastereomeric transition-states is greatly reduced, making system and protocol design more rational.[2] Given the impressive asymmetric induction applications[3] found for *trans*-2,5-dimethylpyrrolidine (and analogs), we became intrigued with the chiral auxiliary possibilities for its 6-membered ring homolog *trans*-2,6-dimethylpiperidine. The dynamics of auxiliary-mediated transformations are such that subtle differences in non-bonding interactions spell the difference between excellent and unacceptable levels of asymmetric induction. In that vein, it is interesting to note the conformational differences between amides **1** and **2** which are displayed as computer generated stereoscopic views of MM2 minimized structures;[4] C_2 symmetry in the pyrrolidine auxiliary is obvious, while the piperidine auxiliary manifests functional C_2 symmetry as a consequence of rapid chair interconversions.



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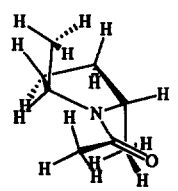

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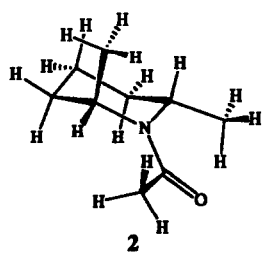

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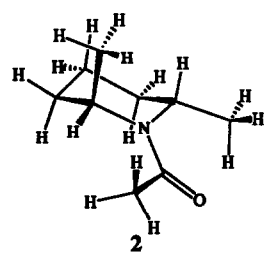

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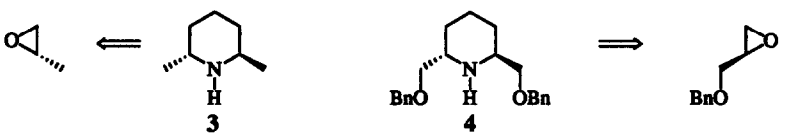
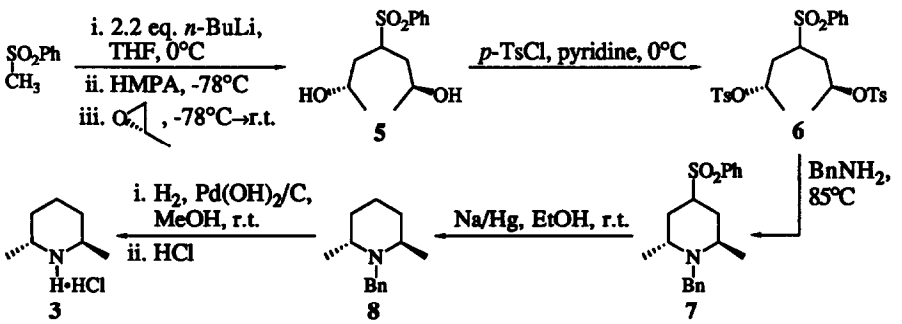
As briefly reviewed by Wasserman in his report of a (±)-teneraic acid synthesis, *trans*-2,6-disubstituted piperidine alkaloids exhibit notable biological activity but there are few general stereoselective methods for their synthesis.[5] We report here a synthesis of the natural product (2*R*, 6*R*)-(-)-2,6-lupetidine (**3**; to our knowledge, the first stereoselective synthesis of this alkaloid produced by *Nanophyton erinaceum*)[6] and its 2,6-bis(benzyloxymethyl) analog **4**.



3 4

A THF solution of readily available, enantiomerically pure (*S*)-1,2-epoxypropane[7] was added dropwise to a THF/HMPA solution of methyl phenyl sulfone dianion (from methyl phenyl sulfone and 2 eq. *n*-BuLi)[8] giving 4-(benzenesulfonyl)-(2*S*, 6*S*)-heptanediol (**5**) as a viscous oil after purification by chromatography on silica gel (96%; $[\alpha]_D$ +50.0°, *c* = 1.190 in $CHCl_3$). Treating a pyridine solution of **5** with *p*-toluenesulfonyl chloride (2.2 eq.) delivered bis(tosylate) **6** in 78% chromatographed yield ($[\alpha]_D$ -43.7°, *c* = 1.095 in $CHCl_3$) and set the stage for heterocycle formation. Thus, a neat solution of **6** in excess benzylamine (≈25 eq.) was heated at 85°C for 1 h.[9] Vacuum evaporation of the excess benzylamine followed by chromatography on silica gel produced piperidine **7** (90%). Both tosylate displacements proceeded with inversion as *trans*-**7** was the only product; none of the corresponding *cis*-dimethyl isomer was detected. The bis(mesylate) analog of **6** was not a useful precursor to piperidine **7** as it proved insoluble in neat benzylamine and a benzene/benzylamine co-solvent system which dissolved the bis(mesylate) gave no product after 24 hours at reflux.

In acyclic sulfones **5** and **6**, the carbon bearing the phenyl sulfone moiety is a chirotopic, nonstereogenic center.[10] Interestingly, even though the phenyl sulfone moiety in piperidine **7** is locked *cis* to one methyl substituent and *trans* to the other methyl substituent, this carbon remains chirotopic but nonstereogenic due to pyramidal inversion of the 3°-nitrogen. As a consequence, **7** has a "C_2 symmetry axis"[11] and this 1,2,4,6-tetrasubstituted piperidine derivative is obtained isomerically pure as a white solid (m.p. 134-5°C from hexane/ether; $[\alpha]_D$ -18.6°, *c* = 1.704 in $CHCl_3$).

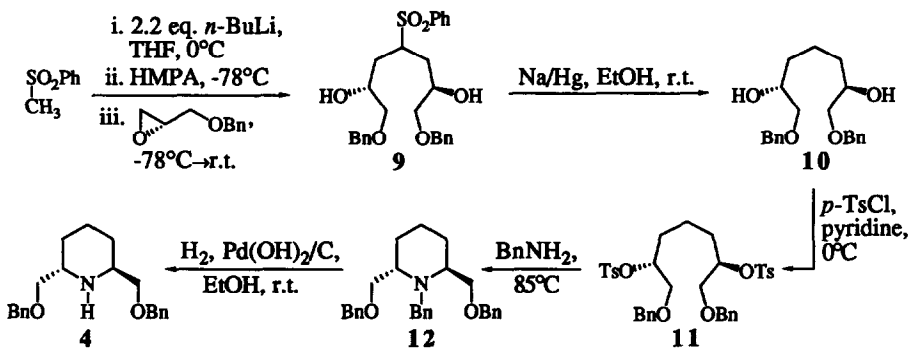


All that remained in the preparation of **3** was reductive removal of the benzyl and phenyl sulfone moieties; unfortunately, attempts at the one-pot conversion of **7** to **3** proved inadequate. For example, sodium in liquid ammonia reduction of **7** gave none of **3** and only a low yield of **8**. Therefore, a two-pot conversion was developed which consisted of 40% sodium amalgam desulfonylation to **8** (93%; $[\alpha]_D$ -72.2°, *c* = 3.18 in $CHCl_3$) followed by hydrogenolysis of the benzyl-

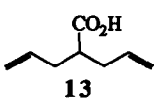
nitrogen moiety with Pearlman's catalyst. (-)-2,6-Lupetidine was conveniently isolated as its hydrochloride in 89% yield from **8** (**3**•HCl[12]: mp 247-9°C; $[\alpha]_D$ +12.8°, *c* = 3.06 in EtOH).

In similar fashion, the 2,6-bis(benzyloxymethyl) analog of **3**, piperidine **4**, was prepared starting from (*S*)-benzyloxymethyl oxirane.[13] Condensation of this electrophile with the methyl phenyl sulfone dianion produced 1,7-bis(benzyloxy)-4-benzenesulfonyl-(2*R*, 6*R*)-heptanediol (**9**) in 91% yield ($[\alpha]_D$ +19.1°, *c* = 1.04 in $CHCl_3$). To our surprise, the bis(tosylate) derived from this diol reacted only sluggishly with benzylamine whereas desulfonylated bis(tosylate) **11** reacted nicely. Thus, **9** was subjected to 40% sodium amalgam desulfonylation to give diol **10** ($[\alpha]_D$ -4.8°, *c* = 1.19 in $CHCl_3$) as a viscous oil in 91% yield after chromatography on silica gel. Bis(tosylation) with *p*-toluenesulfonyl chloride (2.2 eq.) in pyridine furnished **11** (86%; $[\alpha]_D$ +3.9°, *c* = 1.35 in $CHCl_3$) and set the stage for piperidine formation.

In the event, a neat solution of **11** in excess benzylamine (≈25 eq.) at 85°C for 3 h followed by vacuum evaporation of the excess benzylamine and chromatography on silica gel produced piperidine **12** in 88% yield ($[\alpha]_D$ -29.1°, *c* = 1.12 in $CHCl_3$). Selective *N*-debenzylation[14] was effected by stirring a dry ethanol solution of **12** for 1 h with Pearlman's catalyst under one atmosphere of hydrogen giving (2*S*, 6*S*)-(-)-2,6-bis(benzyloxymethyl)piperidine[15] (**4**; 96%; $[\alpha]_D$ -1.9°, *c* = 1.82 in $CHCl_3$).



This strategy for the preparation of "*C*2 symmetric" amines like **3** and **4** can be easily generalized to include a wide variety of 2,6-disubstituted piperidines. The synthetic potential of these substrates as chiral auxiliaries, for example in directing double diastereoselective (i.e., group and face selective) iodolactonization of dienamides derived from **3** or **4** and dienoic acid **13**, will be reported in due course.



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Acknowledgment: We are pleased to acknowledge support of this work by the National Science Foundation through grant CHE-8704836 and the National Institutes of Health through grant ES04699.

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1 Sloan Fondation Fellow (1987-1991) and NIH RCDA recipient (1989-1994; ES00182)

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11 A strict application of the *C*2 symmetry element does not apply in the ground-state arrangement of **3/4/7/8/12**. However, these substrates possess functional *C*2 symmetry since atoms lying on the pseudo-*C*2 axis are chirotopic but nonstereogenic.

12 Data for **3**•HCl: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 6 H), 1.67 (m, 4 H), 1.98 (m, 2 H), 3.54 (m, 2 H), 9.40 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.87 (2 C), 17.27 (1 C), 28.80 (2 C), 47.32 (2 C); HRMS (FB+) for $C_7H_{16}N$ (M - Cl), calcd *m/e* 114.1282, found 114.1274.

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15 Data for **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 2 H), 1.52 (quintet, J = 6.3 Hz, 2 H), 1.56 (m, 2 H), 2.62 (br s, 1 H), 3.20 (m, 2 H), 3.41, (dd, J = 4.3 & 9.0 Hz, 2 H), 3.56 (dd, J = 9.0 & 9.0 Hz, 2 H), 4.56 (s, 4 H), 7.33 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.87 (1 C), 27.25 (2 C), 49.91 (2 C), 72.40 (2 C), 73.15 (2 C), 127.44 (2 C), 127.53 (4 C), 128.29 (4 C), 138.38 (2 C); HRMS (FB+) for $C_{21}H_{28}NO_2$ (M + H), calcd *m/e* 326.2120, found 326.2106.

(Received in USA 19 March 1990; accepted 18 April 1990)