ORGANIC
LETTERS

2002
Vol. 4, No. 8
1367−1370

trans-6-Aminocyclohept-3-enols, a New Designed Polyfunctionalized Chiral Building Block for the Asymmetric Synthesis of 2-Substituted-4-hydroxypiperidines

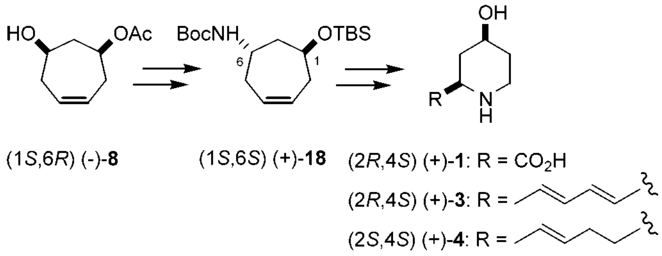
Paolo Celestini, Bruno Danieli, Giordano Lesma,* Alessandro Sacchetti, Alessandra Silvani, Daniele Passarella, and Andrea Virdis

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano,
via Venezian 21, 20133 Milano, Italy

giordano.lesma@unimi.it

Received February 7, 2002

ABSTRACT



***trans*-6-Aminocyclohept-3-enols 18 and *ent*-18 are new designed polyfunctionalized chiral building blocks for piperidine alkaloids synthesis and are prepared in high yields from the enzymatically derived cyclohept-3-ene-1,6-diol monoacetate (–)-8. Efficient highly enantioselective syntheses of *cis*-4-hydroxypipecolic acid (1) and piperidines 3 and 4, in both enantiomeric forms, are described.**

Piperidine subunits constitute an integral feature of many chiral natural compounds and synthetic derivatives which exhibit interesting biological activities and in many cases have proved to be useful chemotherapeutic agents.

These reasons have prompted an exceptional growth of research resulting in the development of synthetic strategies[1] for the preparation of these compounds, and a wide range of methodologies have been reported in the past decade.

In this regard, several enantiopure naturally occuring *cis*- and *trans*-2-substituted-4-hydroxy-piperidines, for example, *cis*- and *trans*-4-hydroxy-2-pipecolic acids (**1** and **2**), were utilized as chiral building blocks of biologically active molecules,[2] and in particular, (2*S*,4*R*)-*ent*-**1** was employed in a recent synthesis of the potent antiviral agent palinavir.[2b]

In addition, the biologically active 2-alkyl-4-hydroxy-piperidines **3** and **4** were isolated as cometabolites of a piperidine-producing organism[3] and are proposed as intermediates in the biosynthesis of the potent antimicrobial agent streptazolin.[3a,4] However, to the best of our knowledge, only

---

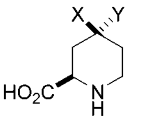
(1) For reviews on the synthesis of substituted piperidines, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (c) Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proc. Int.* **1996**, *28*, 499. (d) Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Proc. Int.* **1992**, *24*, 585.

(2) (a) Bellier, B.; Da Nascimento, S.; Meudal, H.; Gincel, E.; Roques, B. P.; Garbay, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1419. (b) Gillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallee, P. *J. Org. Chem.* **1996**, *61*, 2226.

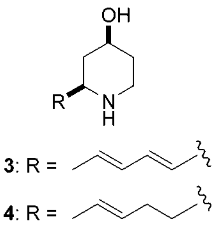
(3) (a) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeek, A. *J. Antibiot.* **1991**, *44*, 797. (b) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335. (c) Keller-Schierlein, W.; Wuthier, D.; Drautz, H. *Helv. Chim. Acta* **1983**, *66*, 1253. (d) Arnone, A.; Cardillo, R.; Nasini, G.; Vajna de Pava, O.; Quaroni, S. *Phytochemistry* **1988**, *27*, 3611. (e) Komoto, T.; Yano, K.; Ono, J.; Okawa, J.; Nakajima, T. Jpn. Kokai 35788, Feb 2, 1986; *Chem. Abstr.* **1986**, *105*, 132137w.

10.1021/ol025683x CCC: $22.00

two syntheses of the above-mentioned piperidinols in optically active form have been reported to date. In the first one,[5] the 2-pentadienylpiperidin-4-ol (**3**) was prepared, in both enantiomeric forms, by a diastereoselective intramolecular Mannich reaction using planar chiral iron dienal complexes. More recently, a biomimetic synthesis[6] of the 2-pent-3-enylpiperidin-4-ol (**4**) has been accomplished via the successful cyclization of an aminostreptenol precursor.



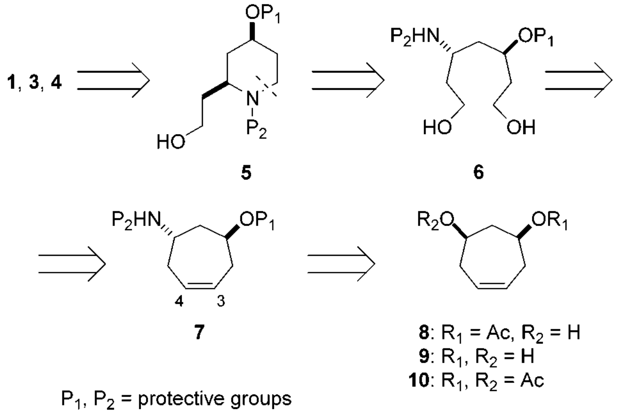
1: X = OH, Y = H
2: X = H, Y = OH



As part of a program aimed at the design and preparation of polyfunctionalized chiral building blocks useful for the enantiosynthesis of alkaloids, by a chemoenzymatic approach,[7] we introduce here optically pure, protected, *trans*-6-aminocyclohept-3-enols for the asymmetric synthesis of 2-alkyl-4-hydroxypiperidines. The utility of these new synthons is well illustrated in the concise, high -yielding enantioselective syntheses of both enantiomers of *cis*-4-hydroxy-2-pipecolic acid (**1**)[8] and *cis*-2-alkyl-4-hydroxypiperidines **3** and **4**.

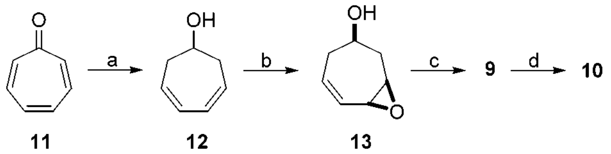
Our retrosynthetic analysis was guided by the retrosynthetic symmetrization concept (Scheme 1). The C-2 appendages in **1**, **3**, and **4** can be derived by appropriate elaboration of the 2-hydroxyethyl side chain of a piperidine **5**, accessible by regioselective intramolecular *N*-alkylation of a suitable protected aminotriol **6**, which can be prepared by oxidative cleavage of the C3/C4 bond of a *trans*-6-aminocyclohept-3-enol derivative **7**. This in turn can be fashioned by selective functional group modification of the cyclohept-3-ene-1,6-diol monoacetate **8** with C_1-symmetry, which can be prepared in both enantiomeric forms from the corresponding *meso*-diol **9** and *meso*-diacetate **10** by employing lipase-mediated transesterification[9] or hydrolysis,[10] respectively.

Scheme 1. Retrosynthetic Symmetrization of **1**, **3**, and **4**



The *meso*-substrates **9** and **10** were prepared, in line with established literature precedents,[10,11] from commercially available tropone (**11**) (Scheme 2).

Scheme 2. Synthesis of *meso*-Precursors **9** and **10**[a]



[a] Reagent and conditions: (a) $NaBH_4$, $MeOH/H_2O$, rt, 88%; (b) MCPBA, $CH_2Cl_2/H_2O-NaHCO_3$, 0 °C, 94%; (c) $LiAlH_4$, THF, rt, 80%; (d) Ac_2O, pyridine, rt, 99%.

Thus, controlled reduction of **11** with $NaBH_4$ in MeOH afforded 3,5-cycloheptadienol (**12**) (88%). Selective monoepoxidation of **12** with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature, as described earlier,[10] was found to be unexpectedly low-yielding in our hands (<33%). Fortunately, we found that epoxidation of **12**, as described above, but in the presence of 1.2 equiv of aqueous $NaHCO_3$, provided predominantly the *cis*-epoxyalcohol **13** in very high yield (94%). Reduction of **13** with $LiAlH_4$ in THF afforded diol **9** (80%), which by further acetylation gave the corresponding diacetate **10** (99%). Using this procedure, the overall yield of diol **9** (and diacetate **10**) was 64−66%, and multigram amounts may be prepared with minimal purification.

To obtain first the (1*R*,6*S*)-*ent*-**8**, we attempted the lipase-catalyzed transesterification of diol **9**, as described by Lautens.[9] Surprisingly, at variance with this report, we found that acetylation of **9**, in isopropenyl acetate in the presence of *Candida cylindracea* lipase, afforded selectively the (1*S*,6*R*)-**8** enantiomer with high ee[12] (>96%), but moderate yield (58%). Moreover, *C. rugosa* lipase produced the same enantiomer with 99% ee, but in very low yield (<30%), whereas porcine pancreatic lipase (PPL) and *Pseudomonas*

---

(4) Mayer, M.; Thiericke, R. *J. Org. Chem.* **1993**, *58*, 3486.

(5) Ripoche, I.; Canet, J.-L.; Aboab, B.; Gelas, J.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3485.

(6) Dollt, H.; Hammann, P.; Blechert, S. *Helv. Chim. Acta* **1999**, *82*, 1111.

(7) See, for example: (a) Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. Chiral Synthons via Enzyme-Mediated Asymmetrization of Meso-Compounds. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; 1993; Vol. 1, pp 143−219. (b) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231 and references therein.

(8) For recent syntheses of **1**, see: (a) Sabat, M.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1209. (b) Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551. (c) Di Nardo, C.; Varela, O. *J. Org. Chem.* **1999**, *64*, 6119. (d) Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4231.

(9) Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, *36*, 4185.

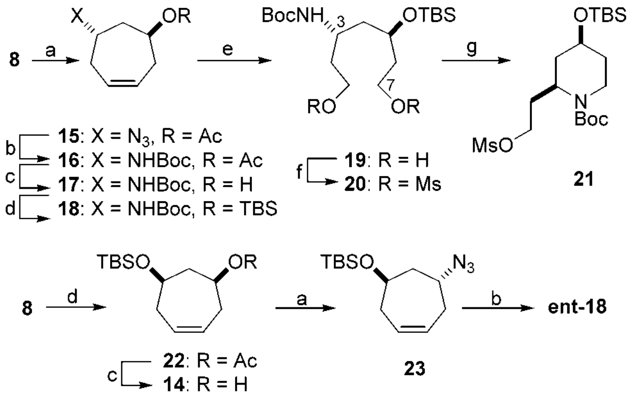
(10) Kaku, H.; Tanaka, M.; Norimine, Y.; Miyashita, Y.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1997**, *8*, 195.

(11) Chapman, O. L.; Pasto, D. J.; Griswold, A. A. *J. Am. Chem. Soc.* **1962**, *84*, 1213.

(12) Optical purities of the diol monoacetate **8** and of the diol monosililated **14** were determined by ^1H NMR spectra after transformation into the (*R*)- and (*S*)-MTPA esters (see refs 10 and 9, respectively).

fluorescens lipase (PFL) were completely ineffective. Although the *meso*-diol **9** could not be desymmetrized satisfactorily, the *meso*-diacetate **10** was desymmetrized in clear-cut manner under hydrolysis conditions in the presence of Lipase PS (from *P. cepacea*) to give the enantiopure monoacetate **8**,[12] (>97% ee), $[\alpha]^{24}_{D}$ −50.9 (*c* 2.0, $CHCl_3$), in 95% yield. By a sequential functional group protection and deprotection, starting from **8**, a formal enantiomeric conversion was performed, affording enantiopure monosilylated diol **14**[12] $[\alpha]^{24}_{D}$ +6.1 (*c* 1.3, $CHCl_3$); the sequence[9] involved reaction with TBSCl and imidazole in DMF and hydrolysis of acetate group with NaOH in MeOH (Scheme 3).

Scheme 3[a]



[a] Reagent and conditions: (a) $(PhO)_2P(O)N_3$, DEAD, TPP, THF, rt, (77% for **15**; 72% for **23**); (b) $SnCl_2$, MeOH, rt, 4 h; then TEA, Boc_2O, rt, (64% for **16**; 66% for *ent*-**18**); (c) NaOH, MeOH/H_2O, 45 °C, (98% for **17**; 95% for **14**); (d) TBSCl, DMF, imidazole, 40 °C, (99% for **18**; 92% for **22**); (e) O_3, CH_2Cl_2−MeOH (1:1), −78 °C; then Me_2S, $NaBH_4$, −78 → 25 °C, 72%; (f) TsCl, TEA, CH_2Cl_2, rt, 98%; (g) NaH, DMF, rt, 59%.

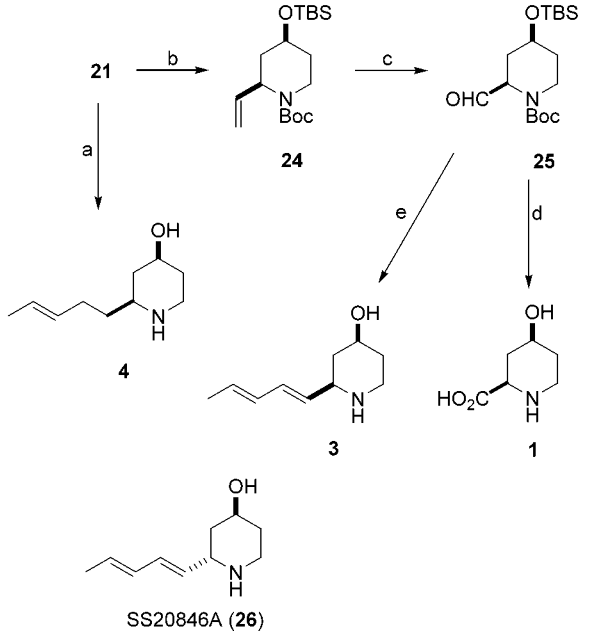
As the first step in our synthetic plan, we devised the synthesis of the protected *trans*-6-aminocyclohept-3-enol intermediates **18** and *ent*-**18**.

Enantiopure diol monoacetate **8** was treated under Mitsunobu conditions[13] with diphenylphosphoryl azide[14] to give cleanly the *trans*-azidoacetate **15** which furnished the protected *trans*-aminoacetate **16**, in 64% yield, by a straightforward one-pot, two-step reduction ($SnCl_2$/MeOH) and carbamoylation sequence. For the synthesis of the target **21**, which is the synthetic equivalent of **5**, the conversion of the acetate function of **16** into *tert*-butyldimethylsilyl (TBS) ether was required. After hydrolysis of the acetate of **16** under conventional conditions (98%), the resulting protected amino alcohol **17** was then silylated with TBSCl to afford (1*S*,6*S*)-**18**, $[\alpha]^{24}_{D}$ +3.4 (*c* 1.0, $CHCl_3$), in quantitative yield. By a similar sequence, the enantiomer (1*R*,6*R*)-*ent*-**18**, $[\alpha]^{24}_{D}$ −3.2 (*c* 1.0, $CHCl_3$), was obtained from **14** by Mitsunobu azidation and sequential reduction−carbamoylation of the resulting *trans*-azidoacetate **23**, both in satisfactory yields. Having in hand the key intermediates **18** and *ent*-**18** possessing the requisite *N*- and *O*-protected groups with the correct stereochemistry, our next efforts were devoted to the elaboration of the *cis*-2,4-disubstituted piperidine moiety.

Toward this end, cleavage of the cycloheptene ring in **18** by ozonolysis in MeOH/CH_2Cl_2 at −78 °C followed by in situ reduction, with $NaBH_4$,[15] of the intermediate dialdehyde (not isolated) provided the dihydroxy derivative **19** in 72% yield. The following step involves the critical piperidine ring formation, utilizing the nitrogen and oxygen functionalities present at C-3 and C-7 in **19**, via a favored 6-*exo-tet* intramolecular cyclization. Mesylation of **19** gave the rather unstable dimesylate **20** (98%) which was not isolated but directly subjected to cyclization by reaction with NaH (1.3 equiv) in DMF at 0 °C, affording the *cis*-2,4-disubstituted piperidine **21** in 59% yield from **19**.

With the piperidine ring formation now solved, the synthesis of hydroxypiperidines **1**, **3**, and **4** was addressed (Scheme 4).

Scheme 4[a]



[a] Reagent and conditions: (a) (*E*)-propenylmagnesium bromide, CuI, THF, −78 → 25 °C, 5h; then 3 N HCl−MeOH, rt, (55%); (b) (i) 2-nitrophenyl selenocyanate, $NaBH_4$, EtOH, 0 → 24 °C; (ii) H_2O_2, THF, 76%; (c) O_3, CH_2Cl_2−MeOH (1:1), −78 °C; then Me_2S, −78 → 25 °C, 88%; (d) $KMnO_4$, NaH_2PO_4, *t*BuOH/H_2O; then 3 N HCl, MeOH, 50 °C, 79%; (e) (i) Me-CH═CH−CH═PPh_3, THF; (ii) I_2, benzene, *hν*, 40 min; (iii) 3 N HCl, MeOH, rt, 64%.

Treatment of the intermediate **21** with (*E*)-propenylmagnesium bromide/CuI[16] in THF, followed by acidic workup, afforded the (2*S*,4*S*)-(+)-2-pent-3-enylpiperidin-4-ol (**4**), in 55% yield, possessing spectral properties in accordance with

---

(13) Mitsunobu, O. *Synthesis* **1981**, 1.

(14) Using the Weinreb amide as amination reagent, product formation required 2−3 days and resulted in 21% yield.

(15) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *58*, 7185.

the literature[6] {$[\alpha]^{24}_D$ +6.9 (*c* 2.0, MeOH); lit.[6] $[\alpha]^{24}_D$ +7.3 (*c* 2.5, MeOH)}.

The aldehyde **25** was considered as a common attractive intermediate for the synthesis of *cis*-4-hydroxy-2-pipecolic acid (**1**), and 2-pentadienylpiperidin-4-ol (**3**), by oxidation and Wittig olefination, respectively.[17] Conversion of **21** to vinylpiperidine **24** was performed (according to Sharpless procedure[18]) by reaction wit 2-nitrophenyl selenocyanate followed by an oxidation−elimination reaction in 76% combined yield for the two steps.

Ozonolysis of **24** gave smoothly the aldehyde **25** which was not purified but used directly in the next stage to avoid compromising the stereochemical integrity at the C-2 carbon atom.

Finally, treatment of **25** with $KMnO_4$ in aqueous *tert*-BuOH in the presence of NaH_2PO_4[19] followed by full deprotection with 3 N HCl in methanol provided (2*R*,4*S*)-**1** as a single stereoisomer (as shown by ^{1}H NMR spectroscopy), in 79% yield, possessing spectral properties in accordance with the literature[8c,d] {$[\alpha]^{24}_D$ +21.3 (*c* 0.5, H_2O); lit.[2b] $[\alpha]^{24}_D$ −23.5 (*c* 1, H_2O) for the enantiomer}.

Aldehyde **25** was also subjected to Wittig olefination with *n*-but-2-enylidenetriphenyl-λ^5-phosphane,[20] olefin isomerization[21] (I_2/benzene, $h\nu$), and deprotection (HCl/MeOH). After recrystallization from diethyl ether, (2*R*,4*S*)-(+)-**3** was obtained in 64% yield, as colorless needles {$[\alpha]^{24}_D$ +37.8 (*c* 1.0, $CHCl_3$); lit.[5] $[\alpha]^{25}_D$ +39.0 (*c* 1.0, $CHCl_3$), mp 67 °C (lit.,[5] for the enantiomer, 67−68 °C)}, whose ^{1}H NMR, ^{13}C NMR, and MS spectral data were identical in all respects to those reported in the literature.[5]

Repetition of the entire reaction sequence described in Schemes 3 and 4, starting from *ent*-**18**, afforded first *ent*-**21** and then the enantiomers *ent*-**4** {$[\alpha]^{24}_D$ −6.1 (*c* 2.0, MeOH)}, *ent*-**1** {$[\alpha]^{24}_D$ −19.1 (*c* 1.0, H_2O)}, and *ent*-**3** {$[\alpha]^{24}_D$ −36 (*c* 1.0, $CHCl_3$)} in comparable yields. It is also interesting to note that the naturaly occurring relevant antibacterial and anticonvulsant agent (−)-SS20846A (**26**)[3a,e] is potentially available from *ent*-**3** by inversion of the C-4 hydroxy group by Mitsunobu reaction.

In conclusion, a concise asymmetric enzyme-mediated preparation of protected *trans*-6-aminocyclohept-3-enols (**18** and *ent*-**18**), designed polyfunctionalized chiral building blocks for the asymmetric synthesis of *cis*-2-alkyl-4-hydroxypiperines, is reported. The utility of these building blocks was illustrated in efficient enantioselective syntheses of *cis*-4-hydroxy-2-pipecolic acid (**1**) and *cis*-2-alkyl-4-hydroxypiperidines **3** and **4**, in both enantiomeric forms. Since the key intermediates **21** and *ent*-**21** allow the introduction of various functionalities at the C-2 side chain, the sequence may be widely applicable to the stereoselective preparation of a variety of natural and nonnatural *cis*-2-alkyl-4-hydroxypiperidines useful for biologic evaluation.

Acknowledgment. This research was supported by CNR, Centro di Studio per le Sostanze Organiche Naturali.

Supporting Information Available: Experimental procedure and spectroscopic data for all new compounds. This material is available free of charge via the Internet at htpp://pubs.acs.org.

OL025683X

---

[16] (a) Bartmann, E.; Bogdanovic, B,; Janke, N.; Liao, S.; Schlichte, K.; Spliethoff, B.; Treber, J.; Westeppe, U.; Wilczok, U. *Chem. Ber.* **1990**, *123*, 1517. (b) Harmange, J.-C.; Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 6819.

[17] A similar strategy, describing the use of a related aldehyde for the synthesis of *trans*-4-hydroxy-2-pipecolic acid **2** and the antibacterial (−)-SS20846A (**26**), has been recently reported, see: Johonson, C. R.; Sabat, M. *Tetrahedron Lett.* **2001**, *42*, 1209.

[18] Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

[19] Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

[20] (a) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839. (b) Chen, X.; Millar, J. G. *Synthesis* **2000**, 113.

[21] Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358.