ORGANIC LETTERS

2004
Vol. 6, No. 26
4941−4944

Diastereoselective Synthesis of (2*S*,5*R*)-5-Hydroxypipecolic Acid and 6-Substituted Derivatives

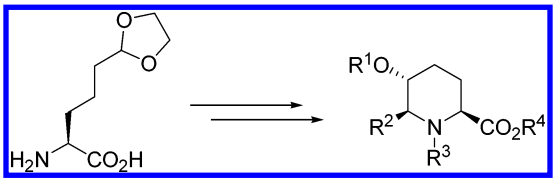
Peter N. M. Botman,[†] F. Jan Dommerholt,[‡] René de Gelder,[‡] Quirinus B. Broxterman,[§] Hans E. Schoemaker,[§] Floris P. J. T. Rutjes,[‡] and Richard H. Blaauw*,[†]

Chiralix B.V., P.O. Box 31070, 6503 CB Nijmegen, The Netherlands, Radboud University Nijmegen, IMM, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands, and DSM Research, Life Sciences—Advanced Synthesis, Catalysis and Development, P.O. Box 18, 6160 MD Geleen, The Netherlands

richard.blaauw@chiralix.com

Received October 29, 2004

ABSTRACT



Herein, we report a diastereoselective synthesis of the natural product (2*S*,5*R*)-5-hydroxypipecolic acid and 6-substituted derivatives thereof. The key step in the synthetic sequence is a novel highly diastereoselective epoxidation reaction of an enantiomerically pure cyclic enamide intermediate.

The amino acid 5-hydroxypipecolic acid (**1**) is a natural product that has been found in various plants and microorganisms.[1] Furthermore, the 5-hydroxypiperidine skeleton constitutes the core of numerous naturally occurring alkaloids (Figure 1) such as febrifugine (**2**) and pseudoconhydrin (**3**).

As part of a larger research program, we investigated the conversion of L-allysine ethylene acetal **4** into (2*S*,5*R*)-5-hydroxypipecolic acid (*trans*-**1**).[2] We now report a diastereoselective route that was developed leading to this natural product.[3] Additionally, one of the intermediates in the synthetic sequence allowed facile introduction of substituents at the 6-position involving *N*-acyliminium ion chemistry.[4]

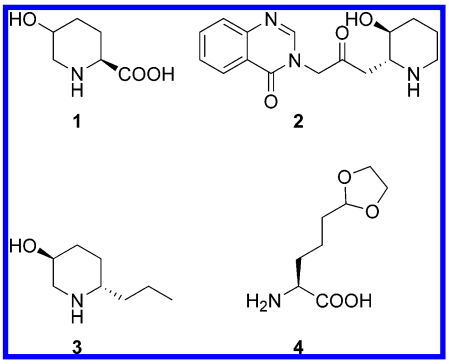


Figure 1.

[†] Chiralix B.V.
[‡] Radboud University Nijmegen.
[§] DSM Research.

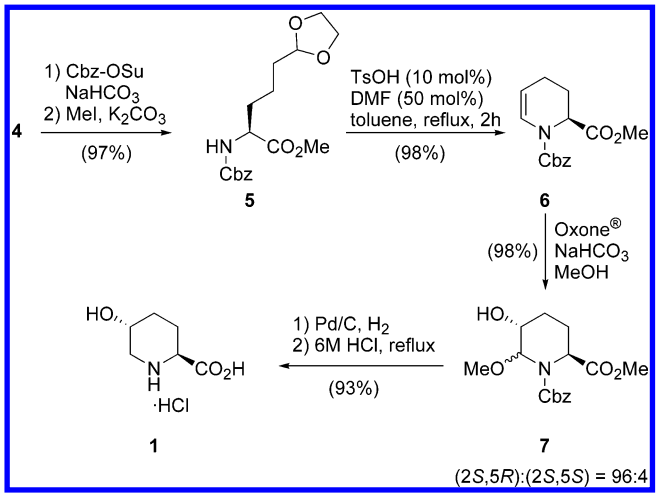
(1) (a) Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 192. (b) Kondo, Y. *J. Sericult. Sci. Japan* **1957**, *26*, 345. (c) Goas, G.; Larher, F.; Goas, M. *C. R. Acad. Sci. Paris* **1970**, *271*, 1368. (d) Fowden, L. In *Progress in Phytochemistry*; Reinhold, L., Liwischitz, Y., Eds.; Wiley: London, 1970; 2, 203. (e) Hatanaka, I. *Sci. Pap. Coll. Gen. Educ. Univ. Tokyo* **1972**, *22*, 117. (f) Despontin, J.; Marlier, M.; Dardenne, G. *Phytochemistry* **1977**, *16*, 387.

(2) (a) Rumbero, A.; Martín, F. C.; Lumbreras, M. A.; Liras, P.; Esmahan, C. *Bioorg. Med. Chem.* **1995**, *3*, 1237. (b) Boesten, W. H. J.; Broxterman, Q. B.; Plaum, M. J. M. EP0905257, **1999**; *Chem. Abstr.* **1999**, *130*, 251283.

10.1021/ol047774v CCC: $27.50
Published on Web 11/23/2004

The sequence to *trans*-**1** started with N-carbonylation of **4** with Cbz-OSu, followed by methylation of the carboxylic acid with MeI to obtain the protected amino acid **5** (Scheme 1).

Scheme 1. Synthesis of (2*S*,5*R*)-5-Hydroxypipecolic Acid

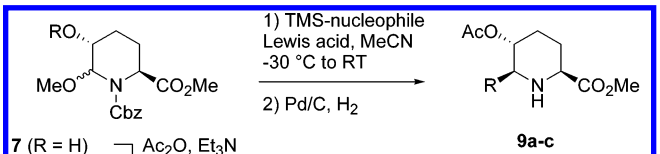


Upon treatment of **5** with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene, a smooth cyclization−elimination sequence occurred, providing tetrahydropyridine **6** in an excellent yield.[5,6]

The key step in our strategy was the epoxidation of enamide **6**, which was performed in MeOH to invoke immediate ring-opening of the unstable epoxide intermediate.[7] The use of oxone gave the best results, leading to the 5-hydroxypipecolic acid derivative **7** with a 96:4 diastereoselectivity for the (2*S*,5*R*)-configured product. Subsequent hydrogenation, followed by hydrolysis of the methyl ester and precipitation from aqueous acetone provided the diastereomerically pure target natural product *trans*-**1** as the corresponding HCl salt, with an overall yield of 87% starting from **4**.[8]

Since *N*,*O*-acetal **7** constitutes a suitable *N*-acyliminium ion precursor, we next turned our attention to its application in the synthesis of 6-substituted 5-hydroxypipecolic acid derivatives.[9] Indeed, in situ formation of the *N*-acyliminium ion intermediate by treatment of **7** with a catalytic amount of $Sn(OTf)_2$ in the presence of allyltrimethylsilane afforded the 6-allylated product. However, the isolation and purification of the desired compound was seriously hampered by the formation of significant amounts of the corresponding O-silylated product. To circumvent this undesired silyl transfer reaction, the hydroxyl function was converted into the corresponding acetate (**8**). This precursor could be reacted smoothly with various suitable π-nucleophiles (Table 1).

Table 1. *N*-Acyliminium Ion Chemistry



entry	nucleophile[a]	cond. 1)[b]	cond. 2)	R	% yield[c]
1	TMS	$Sn(OTf)_2$, 4 h	EtOAc, 1.5 h		82 (**9a**)
2	TMS	$BF_3{\cdot}OEt_2$, 5 h	MeOH, 4 h		90 (**9a**)
3	TMS−CN	$Sn(OTf)_2$, 18 h	EtOAc, 3 h	NC	89[d] (**9b**)
4[e]	TMSO, Ph	$Sn(OTf)_2$, 18 h	MeCN, 1 h	O, Ph	92[f] (**9c**)

[a] Performed with 5 equiv. [b] Performed with 10 mol % $Sn(OTf)_2$ or 2 equiv $BF_3{\cdot}OEt_2$. [c] Products isolated as a single diastereomer. [d] Isolated as a (5*R*,6*S*):(5*R*,6*R*) = 1.7:1 mixture. [e] Performed with 20 mol % $Sn(OTf)_2$. [f] Based on recovered starting material (10%) in hydrogenation.

The stereochemical assignment of the formed products by ^{1}H NMR proved to be difficult due to the presence of rotamers. Therefore, the obtained products were hydrogenated with Pd/C under an atmosphere of H_2, affording the 6-substituted 5-acetoxy pipecolic acid methyl esters **9a**−**c**. The preferred Lewis acid proved to be $Sn(OTf)_2$, although 2 equiv of $BF_3{\cdot}OEt_2$ were required to reach full conversion in the reaction with propargyltrimethylsilane (entry 2). Products **9a** and **9c** (entries 1, 2, and 4) were isolated as single diastereomers, which were shown to possess the (2*S*,5*R*,6*S*)- configuration. The observed cis relationship between the introduced alkyl group and the ester substituent was expected, since it is known that in similarly substituted piperidines, the incoming nucleophile preferably attacks the *N*-acyliminium ion intermediate in a pseudoaxial fashion.[10]

(3) For previous synthetic approaches to enantiomerically pure *trans*-**1**, see: (a) Herdeis, C.; Engel, W. *Tetrahedron: Asymmetry* **1991**, *2*, 945. (b) Herdeis, C.; Heller, E. *Tetrahedron: Asymmetry* **1993**, *4*, 2085. (c) Bailey, P. D.; Bryans, J. S. *Tetrahedron Lett.* **1988**, *29*, 2231. (d) Horeau, S.; Fauchère, J. L.; Pappalardo, L.; Roumestant, M. L.; Viallefont, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2585. (e) Shibasaki, T.; Sakurai, W.; Hasegawa A.; Uosaki, Y.; Mori, H.; Yoshida, M.; Ozaki, A. *Tetrahedron Lett.* **1999**, *40*, 5227.

(4) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082.

(5) Although the exact role still remains unclear, the addition of DMF (0.5 equiv) proved to be necessary to obtain a clean conversion of **5** to **6**.

(6) (a) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043. (b) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393. (c) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575. (d) Teoh, E.; Campi, E. M.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2002**, 978. (e) Clive, D. L. J.; Coltart, D. M.; Zhou, Y. *J. Org. Chem.* **1999**, *64*, 1447. (f) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 4073.

(7) For a related example, see: Rani, S.; Vankar, Y. D. *Tetrahedron Lett.* **2003**, *44*, 907.

(8) The whole sequence can be performed without any intermediate purification steps (making it convenient for scale-up) in which case the final product is obtained in 50% overall yield on multigram scale.

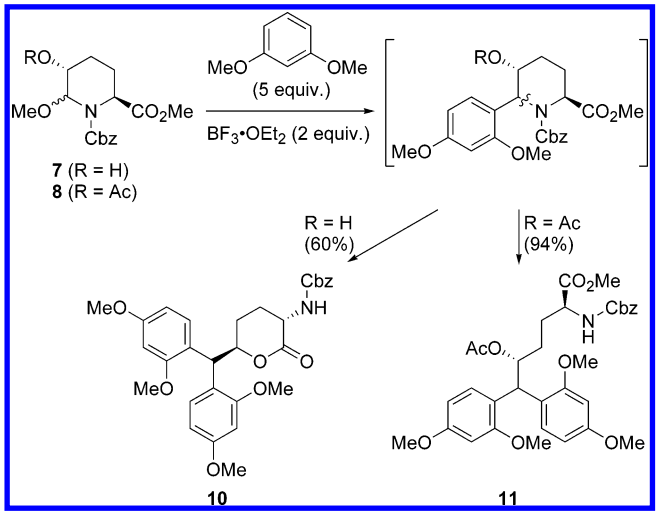
(9) For recent examples of *N*-acyliminium ion alkylations of piperidines, see: (a) Vink, M. K. S.; Schortinghuis, C. A.; Luten, J.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2002**, *67*, 7869. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (c) Mentink, G.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2002**, *4*, 3497. (d) Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87. (e) Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93.

Only the relatively small nucleophile TMS−CN gave rise to a mixture of diastereomers (**9b**), which was determined to be 1.7:1 in favor of the (2*S*,5*R*,6*S*)-isomer.[11]

For the hydrogenations, the choice of solvent proved to be crucial for the outcome of the reactions. The use of Pd/C in EtOAc effected a smooth reduction in the case of the allyl- and cyanide-substituted intermediates (entries 1 and 3), affording products **9a** and **9b**, respectively, in good yields over two steps. However, for the hydrogenation of the allenyl-substituted intermediate (entry 2), the solvent had to be changed to methanol. The use of methanol in the case of the cyanide (entry 3) caused reduction of the cyano group to the primary amine. Finally, the Cbz deprotection of the acetophenone-substituted intermediate (entry 4) in either methanol or EtOAc was accompanied by the reduction of the ketone function to the corresponding alcohol. This problem of overreduction could be circumvented by performing the hydrogenation in acetonitrile, affording the desired product **9c** in good yield.

In addition to the TMS-nucleophiles, we investigated the reaction of *N*-acyliminium ion precursors **7** and **8** with electron-rich aromatic nucleophiles. However, the reaction with 1,3-dimethoxybenzene in the presence of $BF_3{\cdot}OEt_2$ brought about an unexpected ring-opening of the intermediate piperidine product (Scheme 2). Apparently, the highly

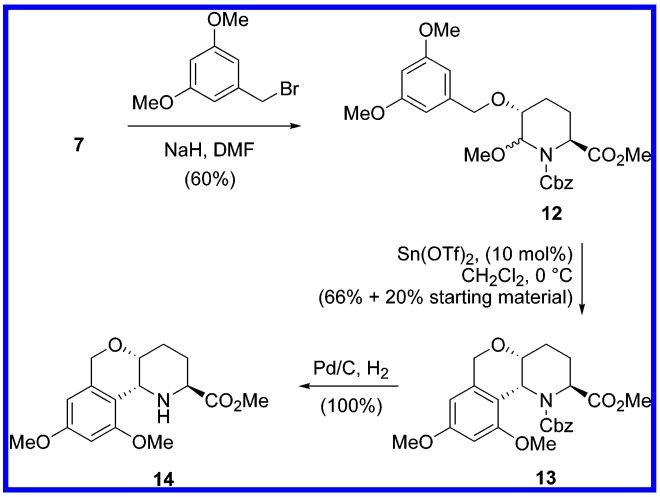
Scheme 2. Unexpected Opening of the Piperidine Ring



electron-rich aromate significantly weakens the C−N bond and subsequently stabilizes the formed cation, which is trapped by a second aromatic moiety producing diarylated products. In addition, in case of precursor **7**, the piperidine ring opening was followed by spontaneous lactonization affording product **10**.

Besides the intermolecular C−C bond formations, our attention was drawn toward intramolecular *N*-acyliminium ion reactions. To this end, the hydroxyl part of **7** was alkylated with 3,5-dimethoxybenzyl bromide (Scheme 3).

Scheme 3. Intramolecular C−C Bond Formation



Treatment of cyclization precursor **12** with a catalytic amount of $Sn(OTf)_2$ provided **13** in a reasonable yield of 66% along with 20% of starting material. Attempts to force the reaction to completion by applying longer reaction times or higher temperatures merely led to decomposition of **13**. Most probably, the origin of the instability of **13** resides in the ring-opening of the piperidine ring as was observed for the intermolecular coupling with 3,5-dimethoxybenzene (Scheme 2). After hydrogenation, amine **14** was obtained as a single diastereomer. X-ray structure analysis of the corresponding HCl salt unequivocally proved the product to possess the expected (2*S*,5*R*,6*R*)- configuration (Figure 2).[12]

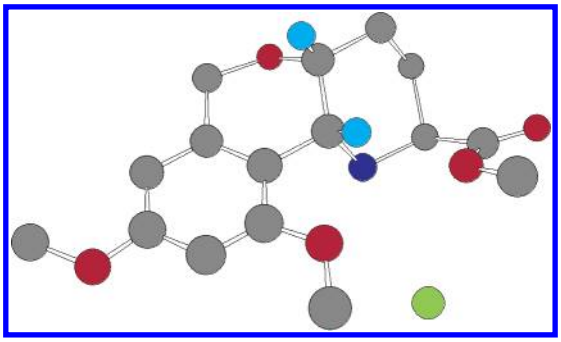


Figure 2. Chem3D representation of the crystal structure of **14**·HCl.

In conclusion, we have developed a straightforward, diastereoselective synthesis of the natural product (2*S*,5*R*)-5-hydroxypipecolic acid, involving a highly diastereoselective epoxidation of an enantiomerically pure cyclic enamide. One

(10) (a) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321. (b) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**, 699.

(11) Stereochemistry of products **9a** and **9b** was proven by ^{1}H NMR NOESY experiments. The assignment of **9c** was made by comparison of its ^{1}H NMR spectrum with those of **9a** and **9b**.

of the intermediates in this synthesis proved to be a versatile precursor to various 6-substituted derivatives by means of *N*-acyliminium ion chemistry. Currently, we are aiming to apply the developed methodology to the total synthesis of the natural products febrifugine (**2**) and pseudoconhydrin (**3**).

(12) Crystal structure data can be obtained free from charge via the Internet at www.ccdc.cam.ac.uk/conts/retreiving.html with the following deposition number: CCDC 253396.

Acknowledgment. Senter (Ministry of Economic Affairs, The Netherlands) is gratefully acknowledged for providing financial support.

Supporting Information Available: Full experimental procedures, characterization of all new products, X-ray data, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047774V