Pergamon

Tetrahedron Letters 41 (2000) 1947–1950

TETRAHEDRON LETTERS

Total synthesis of (2*S*,3*S*,4*R*)-plakoridine A

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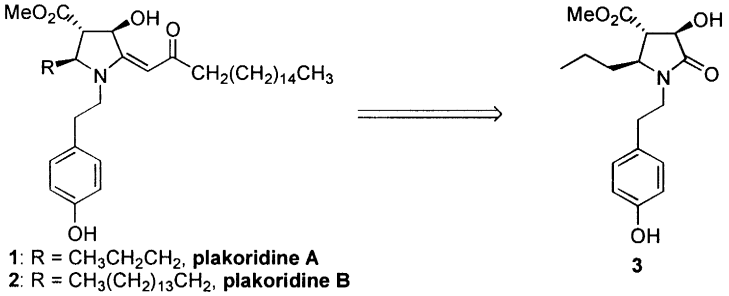
Received 25 August 1999; revised 5 January 2000; accepted 11 January 2000

Abstract

The β-amino ester **6** is synthesized via the diastereoselective Michael addition of the lithium amide derived from amine **5** to methyl (*E*)-2-hexenoate. This ester is converted to the pyrrolidinone **8** via an aldol condensation/deprotection/cyclization. Transformation of the lactam **8** into thiolactam **11** followed by Eschenmoser sulfide contraction provides (2*S*,3*S*,4*R*)-plakoridine A. © 2000 Elsevier Science Ltd. All rights reserved.

Plakoridine A (**1**)[1] and plakoridine B (**2**)[2] are two novel tyramine-containing pyrrolidine alkaloids that possess a fully substituted, functionally diverse pyrrolidine ring system. Both compounds were isolated from the extracts of an Okinawan sponge of the genus Plakortis. Preliminary studies showed that plakoridine A is cytotoxic against the murine lymphoma L1210 cell line. Their structures were established largely by extensive NMR studies and the absolute configurations of both compounds remained undetermined.[1,2] In order to verify further the length of the aliphatic chain of plakoridine A, Kobayashi and co-workers ozonolyzed this compound and obtained two fragments corresponding to lactam **3** and heptadecanoic acid.[1] Plakoridine A may be available from the lactam **3** through the Eschenmoser sulfide contraction.[3,7,8] In 1995, Stafford reported his studies on a racemic synthesis of **3** using nitrone cycloaddition chemistry.[4] Since then no reports concerning its synthesis have appeared. Herein we wish to report the first total synthesis of (2*S*,3*S*,4*R*)-plakoridine A.



1: R = $CH_3CH_2CH_2$, **plakoridine A**
2: R = $CH_3(CH_2)_{13}CH_2$, **plakoridine B**

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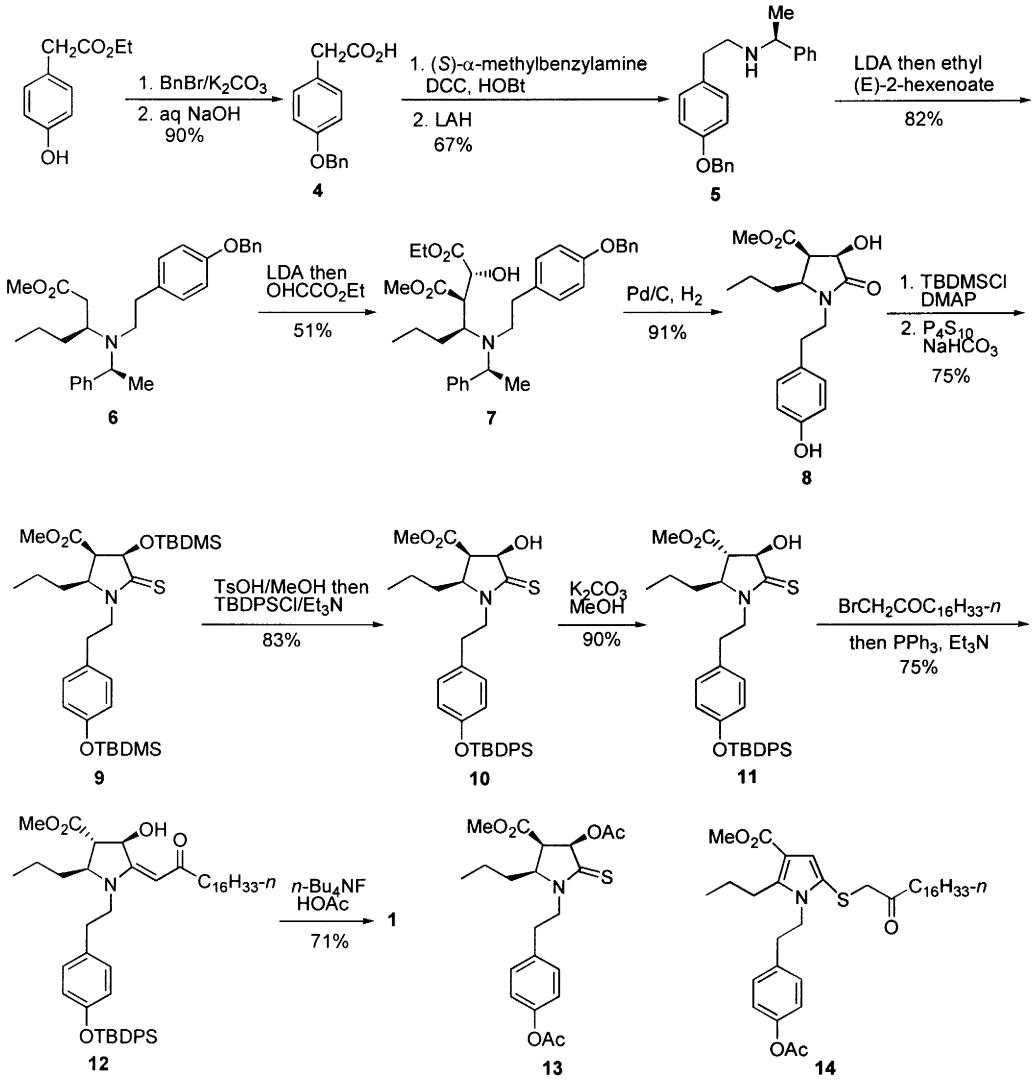
PII: S0040-4039(00)00096-4



Scheme 1.

As outlined in Scheme 1, the desired pyrrolidinone **8** was synthesized from ethyl 4-hydroxyphenylacetate. This ester was converted into 4-benzyloxyphenylacetic acid **4** by treatment with benzyl bromide and potassium carbonate in DMF followed by hydrolysis with 2N NaOH in methanol. After the chiral auxiliary was introduced by coupling **4** with (*S*)-α-methylbenzylamine, the amide was reduced with LAH to afford the secondary amine **5**. Next, treatment of this amine with *n*-BuLi followed by trapping the anion with methyl (*E*)-2-hexenoate provided the Michael addition product **6**. The diastereoselectivity of this step was higher than 97% because only one isomer was observed in its ^{1}H NMR spectrum. According to Davies' studies,[5] the configuration of the newly created chiral center should be *S*. With β-amino ester **6** in hand, we planned to condense it with ethyl glyoxalate to set up the polysubstituted pyrrolidinone ring system.[6] Accordingly, the ester **6** was treated with 3 equiv. of LDA and the anion was reacted with ethyl glyoxalate to give **7** in 51% yield together with other isomers. Attempts to improve the selectivity by using trimethyl borate as an additive failed. Finally, hydrogenation of **7** followed by heating the deprotected product in ethyl acetate at reflux afforded

(2*S*,3*R*,4*R*)-**8** in 91% yield. Its stereochemistry was confirmed by NOESY spectra in which significant NOEs were observed between 2-H and 3-H, 2-H and 4-H, and 3-H and 4-H.

Treatment of the pyrrolidinone **8** with *tert*-butyldimethylsilyl chloride followed by reaction with phosphorus pentasulfide produced the thiolactam **9** in 75% yield. At this time we decided to try to use the thiolactam **11** with a free hydroxyl group to carry out the Eschenmoser sulfide contraction. Accordingly, the silyl protecting groups were removed from **9** under the action of TsOH in methanol, and the phenol hydroxy group was reprotected with TBDPS to provide **10**. The compound **10** was isomerized to **11** by treatment with potassium carbonate in methanol for 30 min. It was observed that *S*-alkylation of **11** with 1-bromo-2-octadecanone in methylene chloride and subsequent Eschenmoser sulfide contraction mediated by triphenylphosphine and triethylamine worked well to afford the olefin **12** in 75% yield. Finally, deprotection of **12** with TBAF/HOAc in THF furnished (2*S*,3*S*,4*R*)-plakoridine A in 71% yield. Its spectral data were the same as those of the natural product except for its optical rotation (lit.[1] $[\alpha]_D^{20}=-0.4$ (*c* 0.5, $CHCl_3$), our observed: ($[\alpha]_D^{22}=-43.0$ (*c* 0.5, $CHCl_3$)).[9] Although the reason for this difference is not clear, one possible explanation is that the natural plakoridine A isolated by Kobayashi's group may be racemic.

Initially, an acetyl group was chosen for protecting the two hydroxy groups in **8** because of its small steric hindrance and easy deprotection. However, we found that *S*-alkylation[8] of the thiolactam **13** with 1-bromo-2-octadecanone in methylene chloride with the assistance of silver triflate followed by treatment with triphenylphosphine and triethylamine did not give the desired olefin but delivered a polysubstituted pyrrole **14**. This product might result from the elimination of the 4-OAc. When the thiolactam **10** was used for the Eschenmoser transformation, a similar elimination product (involving the 4-hydroxy as a leaving group) was obtained. No *S*-alkylation occurred when the thiolactam **9** reacted with 1-bromo-2-octadecanone, perhaps because of the larger steric hindrance of the silyloxy group. When the thiolactam **11** was used as a substrate in which the 4-OH is *cis* to 3-H, the elimination was depressed thereby giving the desired olefin.

In conclusion, we have developed a stereoselective route to (2*S*,3*S*,4*R*)-plakoridine A from the conveniently available β-amino ester **6**. The overall yield for the 14 steps is about 3%. It is notable that the present synthesis also provides an unusual example of an Eschenmoser sulfide contraction of a fully substituted thiolactam, which will be a guide for synthesizing other polysubstituted pyrrolidines or piperidines.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences and National Natural Science Foundation of China (grant 29725205) for their financial support. We thank Professor Kobayashi for providing NMR spectrum of natural plakoridine A.

References

1. Takeuchi, S.; Ishibashi, M.; Kobayashi, J. *J. Org. Chem*. **1994**, *59*, 3712.
2. Takeuchi, S.; Kikuchi, T.; Tsukamoto, S.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1995**, *51*, 5979.
3. (a) Roth, M.; Dubs, P.; Goschi, E.; Eschenmoser, A. *Helv. Chim. Acta*. **1971**, *54*, 710. (b) Tamaru, Y.; Harada, T.; Yoshida, I. *J. Am. Chem. Soc.* **1980**, *102*, 2392. (c) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc*. **1985**, *107*, 1255.
4. Stafford, J. A. *Tetrahedron Lett*. **1995**, *36*, 681.
5. (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. (b) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141. (c) Davies, S. G.; Smyth, G. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1001. (d) Davies,

S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387. (e) Davies, S. G.; Ichihara, O. *Tetrahedron Lett*. **1998**, *39*, 6045.
6. (a) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 575. (b) Ma, D.; Zhang, J. *Tetrahedron Lett*. **1998**, *39*, 9067.
7. (a) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654. (b) Campbell, J. A.; Rapoport, H. *J. Org. Chem*. **1996**, *61*, 6313. (c) Lin, R.; Castells, J. Rapoport, H. *J. Org. Chem*. **1998**, *63*, 4069.
8. (a) Shiosaki, K.; Fels, G.; Rapoport, H. *J. Org. Chem*. **1981**, *46*, 3230. (b) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc*. **1984**, *106*, 4539.
9. Selected data for **1**: IR (KBr) 3166, 2853, 1740, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.03 (d, *J*=8.5 Hz, 2H), 6.99 (br s, 1H), 6.81 (d, *J*=8.5 Hz, 2H), 5.40 (br s, 1H), 5.21 (d, *J*=5.5 Hz, 1H), 5.09 (s, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 3.44 (m, 1H), 3.28 (m, 1H), 2.90 (t, *J*=5.5 Hz, 1H), 2.83–2.71 (m, 2H), 2.37 (t, *J*=6.6 Hz, 2H), 1.69 (m, 1H), 1.54 (m, 1H), 1.50 (m, 30H), 0.93 (t, *J*=7.1 Hz, 3H), 0.88 (t, *J*=6.9 Hz, 3H); FABMS *m/z* 572 (M^++H^+); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 172.8, 165.8, 154.8, 129.9, 129.8, 115.7, 90.2, 75.9, 65.4, 52.6, 52.2, 46.2, 43.5, 35.3, 31.2, 29.7, 29.6, 29.4, 26.4, 22.7, 17.7, 14.1, 13.9.