

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

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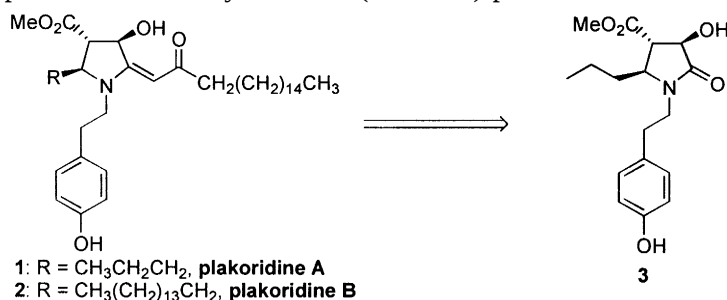
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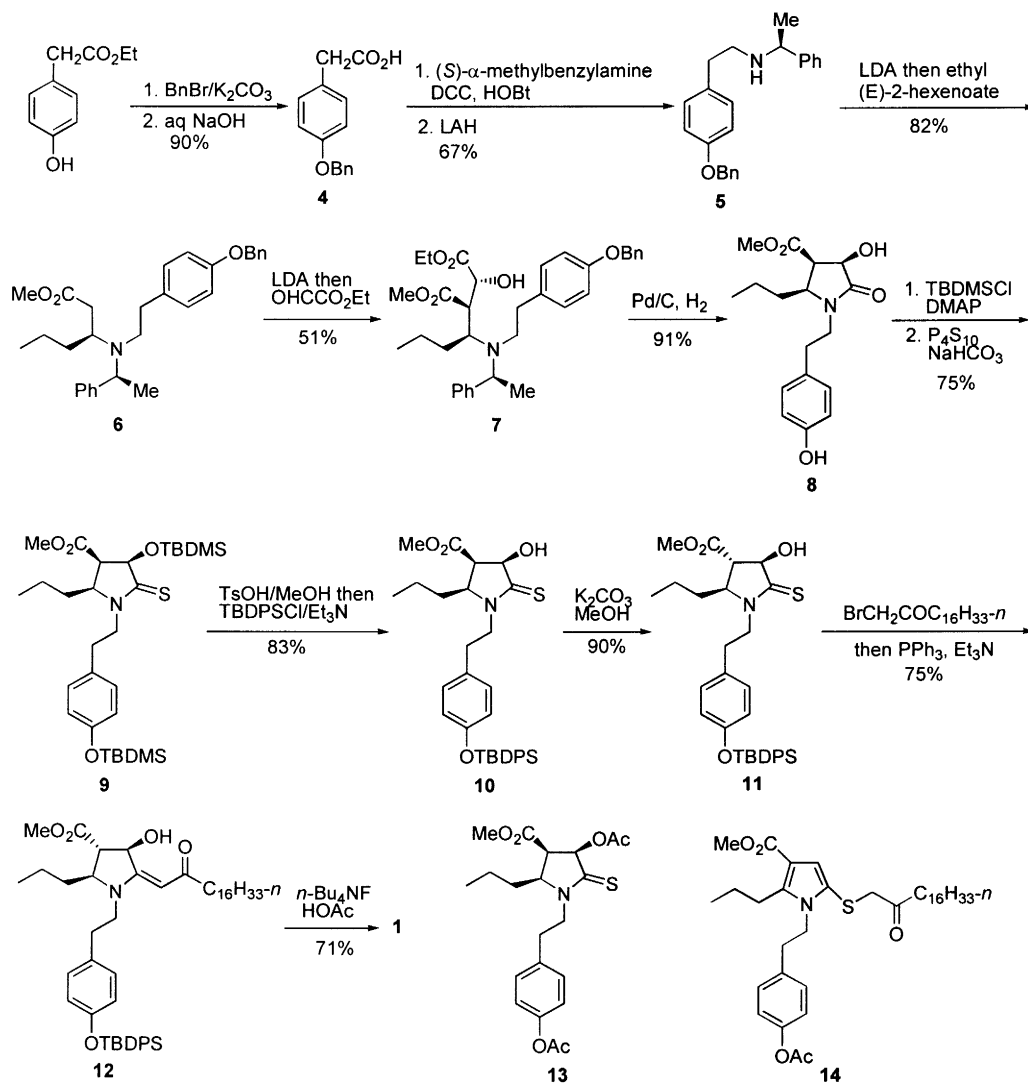
Abstract

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 nitron 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.



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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 ¹H 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 $[\alpha]_{\text{D}}^{20} = -0.4$ (*c* 0.5, CHCl₃), our observed: $([\alpha]_{\text{D}}^{22} = -43.0$ (*c* 0.5, CHCl₃)).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*-alkylation⁸ 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

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9. Selected data for **1**: IR (KBr) 3166, 2853, 1740, 1606 cm^{-1} ; ^1H 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 ($\text{M}^+ + \text{H}^+$); ^{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.