Tetrahedron 74 (2018) 1533–1539

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of myxol and deoxymyxol stereoisomers and their application to determining the absolute configurations of the natural products

Yumiko Yamano [a, *], Miki Masumoto [a], Shinichi Takaichi [b], Akimori Wada [a]

[a] Department of Organic Chemistry for Life Science, Kobe Pharmaceutical University, 4-19-1 Motoyamakita-machi, Higashinada-ku, Kobe 658-8558, Japan
[b] Department of Molecular Microbiology, Faculty of Life Science, Tokyo University of Agriculture, Sakuragaoka, Setagaya-ku, Tokyo 156-8502, Japan

ARTICLE INFO

Article history:
Received 17 January 2018
Received in revised form
5 February 2018
Accepted 6 February 2018
Available online 7 February 2018

Keywords:
Carotenoids
Myxol
Deoxymyxol
Total synthesis
HPLC separation

ABSTRACT

The total synthesis of myxol stereoisomers **1a,b** and deoxymyxol (plectaniaxanthin) stereoisomers **2a,b** was accomplished by Wittig reaction of (*S*)- and (*R*)-C_{10}-phosphonium salts **8a,b** bearing a silyl-protected 1,2-dihydroxy-ψ end group with C_{30}-apocarotenals **6** and **7**. The phosphonium salts **8a,b** were derived from aldehydes **11a,b** possessing a cyclopentylidene ketal moiety, prepared via Sharpless asymmetric epoxidation of allylic alcohol **12** followed by regioselective cleavage of the oxirane ring. We established an analytical HPLC method using a chiral column to separate stereoisomers **1a,b** and **2a,b** and thus determined the absolute configurations of the natural products. The HPLC analyses established that both myxol and deoxymyxol isolated from bacteria have the 2′*S*-configuration.

1. Introduction

Carotenoids having a 1,2-dihydroxy-ψ end group, such as myxol (**1**) and deoxymyxol (also called plectaniaxanthin) (**2**), have been isolated from several microorganisms and are typically glycosides or fatty acid esters.[1–9] The absolute configurations of such carotenoids have been postulated by comparing their CD spectra with those of the fungal carotenoid plectaniaxanthin, whose chirality was determined as 2′*R* using a synthetic approach. Specifically, the shape of the CD spectrum of natural plectaniaxanthin acetonide was almost the opposite that of (2′*S*)-16′,17′-dinor-plectaniaxanthin acetonide synthesized from D-mannitol.[2] However, it was demonstrated that the CD spectrum of plectaniaxanthin is not conserved, has a weak Cotton effect, and is strongly temperature dependent.[2,10,11].

Our aim was to accurately determine the absolute configuration of naturally occurring myxol and deoxymyxol, and thus we synthesized stereoisomers of these carotenoids (**1a,b** and **2a,b**) and established an analytical HPLC method for their separation using a chiral column. Application of this method allowed us to investigate the absolute configurations of these carotenoids isolated from bacteria. Here, we present the results (see Fig. 1).

2. Results and discussion

(2′*S*)-Plectaniaxanthin (**2a**) was synthesized by Pfander's group[11] using (*S*)-C_{10}-phosphonium salt **5**, which was derived from L-serine (**3**) (Scheme 1). The phosphonium salt **5**, possessing a 1,2-dihydroxy moiety, was generated by acid hydrolysis of the acetonide **4,** but the possibility of racemization at the allylic hydroxyl group of compound **5** could not be excluded.

Scheme 2 shows our retrosynthetic analyses. We previously reported[12,13] that the polyene system of carotenoids can be constructed stereoselectively by the Wittig condensation of aldehydes with tri-*n*-butylphosphonium salts instead of triphenylphosphonium salts. We therefore planned to synthesize the myxols **1a,b** and deoxymyxols **2a,b** by Wittig condensation of the known C_{30}-apocarotenals **6**[14] and **7**[15] with C_{10}-tri-*n*-butylphosphonium salt **8** bearing a silyl-protected 1,2-dihydroxy-ψ end group. The phosphonium salt **8** would be prepared from the dienal **9**, whose chirogenic center is expected not to undergo racemization even under acidic conditions due to the electron-withdrawing nature of the formyl group. The dienal **9** would be derived from the C_5-aldehyde

* Corresponding author.
E-mail address: y-yamano@kobepharma-u.ac.jp (Y. Yamano).

https://doi.org/10.1016/j.tet.2018.02.018
0040-4020/

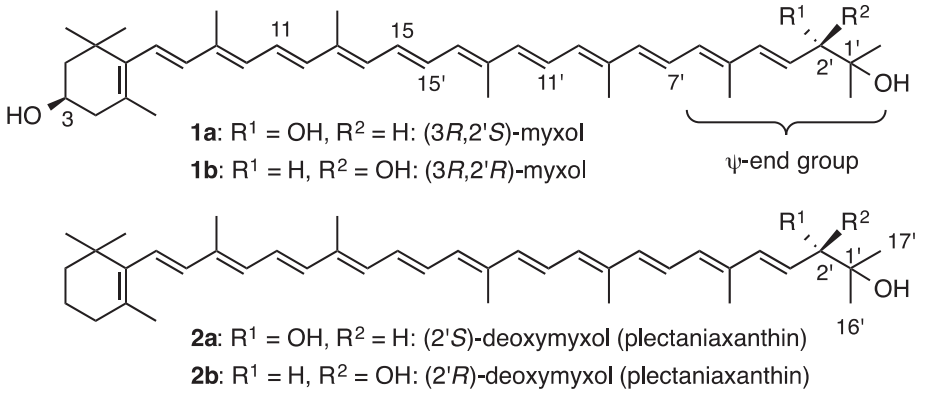
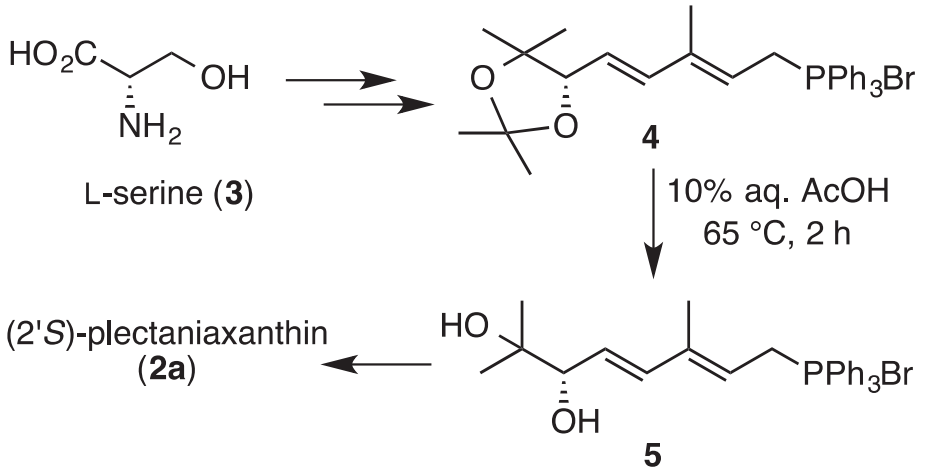
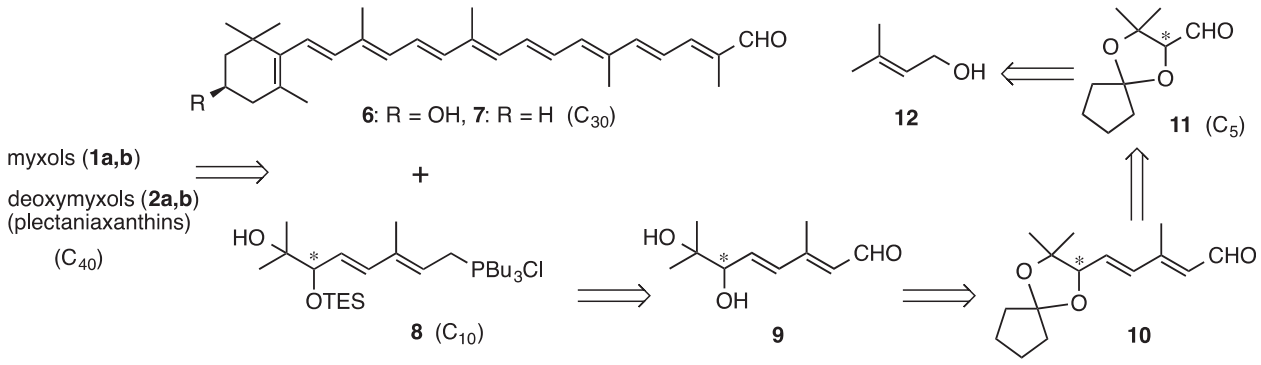


Fig. 1. Chemical structures of myxol and deoxymyxol (plectaniaxanthin).



Scheme 1. Previous synthetic method for (2′*S*)-plectaniaxanthin (**2a**).[11]



Scheme 2. Retrosynthetic analyses.

11, whose (*S*)-enantiomer has been prepared via Sharpless asymmetric epoxidation of the allylic alcohol **12**.[16]

Synthetic routes to these carotenoid stereoisomers are shown in Scheme 3. First, (*S*)-C_5-aldehyde **11a** was prepared by modifying a method previously reported by Smith's group.[16] According to this method,[16] 3-methyl-2-butenal (**12**) was oxidized by using (+)-diisopropyl tartrate (DIPT), Ti(O^iPr)$_4$, and cumene hydroperoxide to provide (*S*)-epoxide **13a**. Compound **13a** was then subjected to 3,5-dinitrobenzoylation and subsequent recrystallization from methanol to give benzoate **14a** as needles with 98% ee. Acid-mediated oxirane-ring opening of **14a** with cyclopentanone generated cyclopentanonide **15a**, which was deacylated using a methanolic solution of diethylamine,[17] and the resulting alcohol **16a** was oxidized with Dess-Martin periodinane to give the known aldehyde **11a**.[16] The aldehyde **11a** was then condensed with phosphonate **17** and the resulting dienoate **18a** was subjected to $LiAlH_4$ reduction, followed by MnO_2 oxidation and subsequent ketal-hydrolysis, to afford an isomeric mixture (*E*/*Z* ~2/1) of dihydroxy aldehyde **9a**. After protecting the secondary hydroxyl group in **9a** with a triethylsilyl (TES) group and subsequent reduction with $NaBH_4$, the resulting allylic alcohol **19a** was transformed into the desired (*S*)-tri-*n*-butylphosphonium salt **8a** via the corresponding chloride. The