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# STEREOCHEMISTRY OF THE PROPOSED INTERMEDIATES IN THE BIOSYNTHESIS OF MYCINAMICINS

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*Summary*: Stereochemistry of the proposed intermediates in the biosynthesis of mycinamicins isolated from the culture filtrate of *Micromonospora griseorubida* sp. has been established.

Recently, Kinoshita et al.[1] reported the isolation of three compounds **2** ~ **4** considered to be biosynthetic intermediates of the macrolactone protomycinolide IV (**1**) and the related macrolide antibiotics from the culture filtrate of *Micromonospora griseorubida* sp. without showing their stereochemistry. If these are true biosynthetic intermediates of the macrolides, the isolation of these compounds may be particularly interesting since it strongly supports the "processive" mechanism postulated to the biosynthesis of macrolide antibiotics.[2] We report herewith the enantio-controlled synthesis of these compounds which revealed their relative and absolute structures.

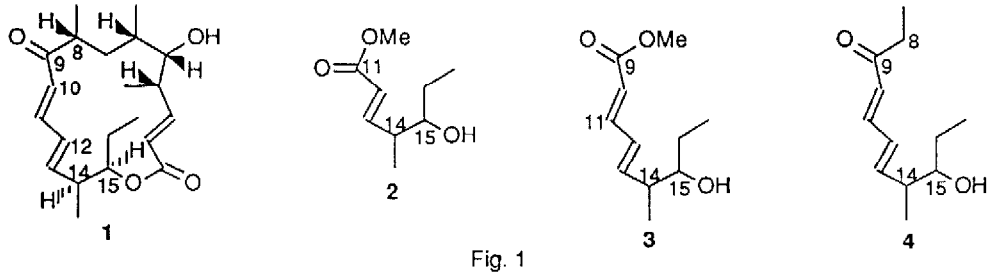
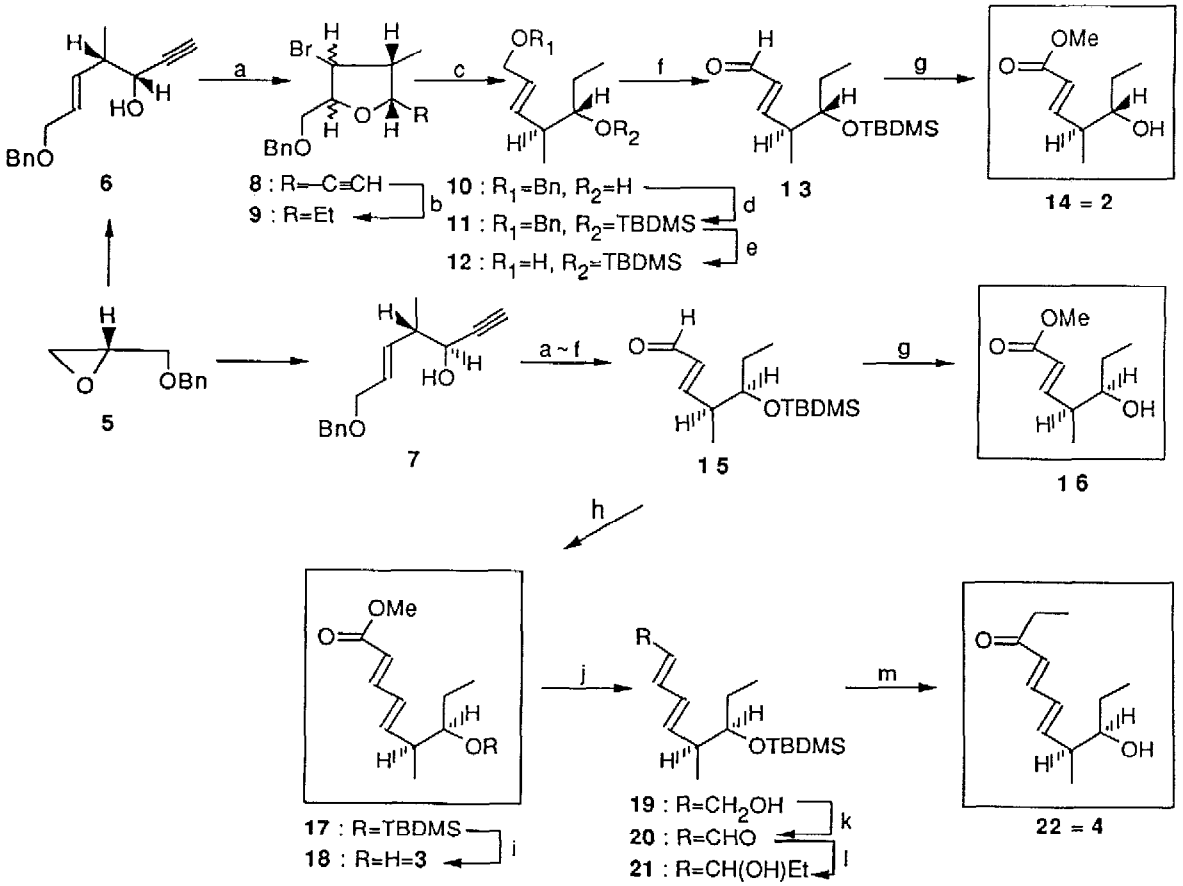



Fig. 1

Since we already established[3] efficient synthesis of the erythro-(**6**) and the threo-(**7**) acetylenic alcohols from (*S*)-*O*-benzylglycidol (**5**), we used these as starting materials. Treatment of **6** with NBS followed by sequential hydrogenation and reductive elimination of the resulting bromo-ether **8** afforded the enol **10** (52% overall). **10** was then transformed into the aldehyde **13** (79% overall) in a three-step sequence of reactions. Similarly, **7** was converted into the epimeric aldehyde **15** (44% overall). On oxidative esterification[4] both aldehydes gave the corresponding esters **14** (78%) and **16**[5] (73%), respectively. Of these the former was identical[6] with the natural product (**2**) in all respects. On the contrary, the ester **18** (77%) from the latter aldehyde **15** *via* **17** was found to be identical[6] with the natural product **3**. Furthermore, the dienone **22** (56% overall) from **17** was identical[6] with the natural dienone **4**. These results unambiguously clarified the stereochemistry of three natural products, namely, **2** should have *S,S*-configuration, while both **3** and **4** should have *S,R*-configuration which correspond to the 14,15-centers of the macrolide **1**. The present synthesis may be worthwhile

not only determining their structures, but also for the preparation of the labelled compounds for the biosynthetic study of mycinamicins.




**Conditions:** a, NBS, aq. THF; b, $H_2$, $PtO_2$, hexane; c, Zn, MeOH, HCl (cat.); d, TBDMS-Cl, imidazole, DMF; e, Li, liq. $NH_3$-THF; f, $MnO_2$, $CH_2Cl_2$; g, (i) $MnO_2$, NaCN, AcOH, MeOH, (ii) c. HCl (cat.), MeOH; h, $(iPrO)_2P(O)CH_2CO_2Me$, $^tBuOK$, THF, i, c. HCl (cat.), MeOH; j, DIBAL, THF; k, $MnO_2$, $CH_2Cl_2$; l, EtMgBr, THF; m, (i) $MnO_2$, $CH_2Cl_2$, (ii) c. HCl (cat.), MeOH.

## References and Notes


1. K. Kinoshita, S. Takenaka, and M. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1988, 943.
2. S. Yue, J. S. Duncan, Y. Yamamoto, and C. R. Hutchinson, *J. Am. Chem. Soc.*, 1987, **109**, 1253.
3. S. Takano, Y. Sekiguchi, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1987, 555.
4. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616.
5. Recently, **16** was isolated from the same culture filtrate which produces the macrolide **1**: Private communication from Dr. K. Kinoshita, Development Division of Fermentation Technology, Toyo Jozo Co. Ltd..
6. Direct and spectral comparison were kindly carried out by Dr. K. Kinoshita.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