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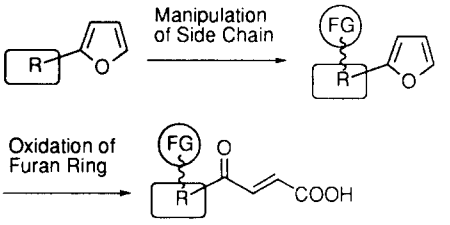
Chiral Synthesis of (+)-Aspicilin by using a Furyl Group as the Masked γ-Oxo-α,β-unsaturated Carboxylic Acid

Yuichi Kobayashi,* Miwa Nakano, and Hiroki Okui

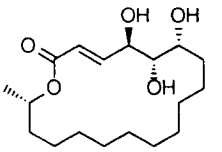
Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226, Japan

Abstract: *Synthesis of (+)-aspicilin is described. The decisive steps are the diastereoselective dihydroxylation of the key intermediate 2, the subsequent furan ring oxidation, and the chelation-controlled reduction of ketone 1.* © 1997 Elsevier Science Ltd.

Aspicilin is an 18-membered macrolide which was isolated from various lichens of the *Lecanoraceae* family.[1] Its unique structure has attracted much interest among synthetic chemists and consequently several total syntheses have been published.[2] Although the biological profile of aspicilin is not yet elucidated, it is desirable to develop a stereoselective route to aspicilin and its analogues as well. However, the scope of the previous methods was limited and did not extend to synthesis of the analogues of aspicilin. Recently, we have found the conditions for the efficient transformation of 2-substituted furans to γ-oxo-α,β-unsaturated carboxylic acids,[3] the basic idea of which was published by Hase.[4] Since the furan ring is chemically stable, this transformation is compatible with a wide range of the recent stereoselective and/or asymmetric reactions, thus allowing stereo- and/or enantioselective installation of functional groups (FG) onto the side chain (R) before the oxidative ring cleavage (Scheme 1). Keeping this idea in mind, we have succeeded in an asymmetric synthesis of (+)-aspicilin, which is described below.

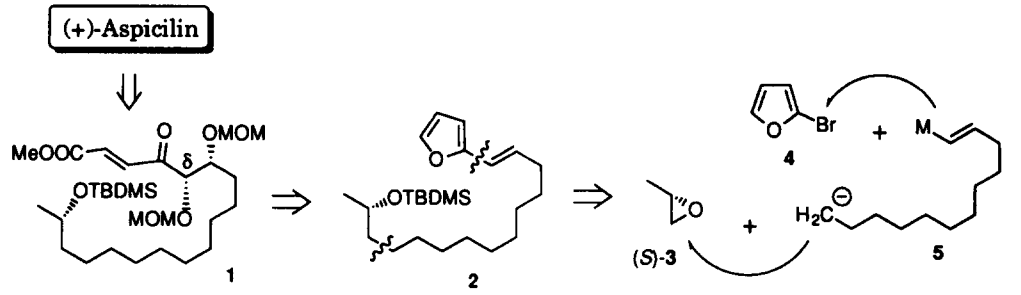


Scheme 1



(+)-Aspicilin

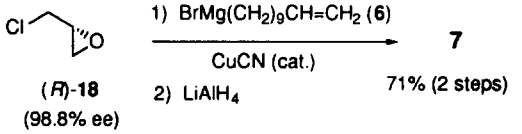
Our synthetic plan is illustrated in Scheme 2, where the key intermediate is the ketone **1**. To generate the hydroxyl group with the correct stereochemistry, *anti* Cram reduction should take place. In other words, selective chelation of a metal cation to the oxygen at the δ position of **1** is a crucial requirement for production of the desired isomer. As a precursor of **1**, we have deduced the alkenyl furan **2**. Asymmetric dihydroxylation (AD) of **2** according to the protocol of Sharpless[5] would furnish the diol and the oxidation of the furan ring would afford the ketone **1**. On the other hand, **2** was disconnected into the three components of epoxide (*S*)-**3**, 2-bromofuran (**4**)[6] and the conceptional anion **5**. Thus, success of the plan depended on the degree of the



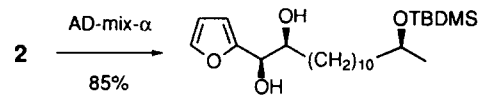
Scheme 2

stereoselectivity in the above conversions.

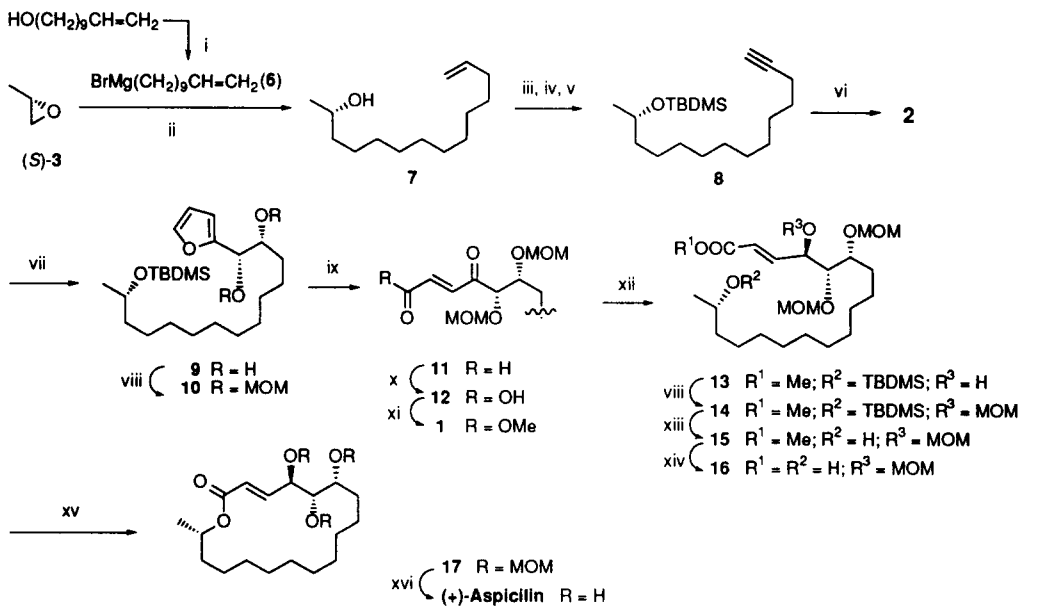
The results are summarized in Scheme 3. Chiral epoxide (*S*)-**3** ($[\alpha]_D^{20}$ −13~−14 (neat); (*R*)-isomer of >97% ee: $[\alpha]_D^{20}$ +12~+14) was purchased from a company (Merck) and was converted to alcohol **7** in 88% yield by the copper–catalysed reaction with the Grignard reagent **6**, which was derived from 10-undecen-1-ol. Since precise information on enantiomeric purity was not available for (*S*)-**3**, enantiomeric excess (ee) of **7** was determined by ^{1}H NMR spectroscopy of the derived MTPA ester to be >95%. The alcohol **7** was also obtained from (*R*)-**18** of 98.8% ee by the epoxide ring-opening with **6** followed by reductive dechlorination with $LiAlH_4$ in 71% yield. Olefin **7** was transformed into acetylene **8** in good yield by the classical method followed by protection of the hydroxyl group as *tert*-butyldimethylsilyl (TBDMS) ether. Stereoselective conversion of **8**



into **2** was achieved in 92% yield by hydroboration of **8** with disiamylborane followed by coupling with **4** in the presence of the palladium catalyst and NaOH (the Suzuki coupling).[7] The coupling constant between the olefinic protons of **2** indicates *trans* geometry (J = 16 Hz) and no *cis* isomer could be detected in the ^{1}H NMR (500 MHz) spectrum. Next, the Sharpless asymmetric dihydroxylation of **2** proceeded efficiently at room temperature overnight and the sole production of one diastereoisomer was confirmed by ^{1}H NMR (300 MHz) spectroscopy of the derived MTPA ester. Absolute stereochemistry of the diol was tentatively assigned as represented by **9** according to the well-established empirical rule and later, at the final stage, it was confirmed to be true. It is worth mentioning that the dihydroxylation using AD-mix-β proceeded with the high yield of 91%, while the classical osmium-catalyzed dihydroxylation afforded the diol only in moderate yield (50%), thus suggesting competitive oxidation of the furan ring under the latter conditions. Similarly, dihydroxylation of **2** using AD-mix-α resulted in the diastereoselective production of **19**. During our investigation, AD reaction of 2-(1-alkenyl)furans was reported by Ogasawara.[8] The alcohol **9** was converted into MOM ether **10** in high yield and the stage was set for the furan ring oxidation.



19



Scheme 3: i, CBr_4, PPh_3 (100%), then Mg, THF; ii, **6**, CuCN (0.05 equiv), THF (88%); iii, Br_2, $CHCl_3$; iv, $NaNH_2$, NH_3 (86% from **7**); v, TBDMSCl, imidazole, DMF (100%); vi, Sia_2BH (2 equiv), THF, -10 °C, 1 h, then **4** (3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), NaOH aq. (1.5 equiv), reflux, 5 h (92%); vii, AD-mix-β, 0 °C to room temp. (91%); viii, MOMCl, $^iPr_2NEt$, CH_2Cl_2, 30 °C (92% for **10**, 84% for **14**); ix, NBS (1.1 equiv), $NaHCO_3$ (2 equiv), acetone-H_2O (10 : 1), -15 °C, 15 min, then furan (3 equiv), 30 min and C_5H_5N (2 equiv), overnight (71%); x, $NaClO_2$ (5 equiv), Me_2C=CHMe (15 equiv) (88%); xi, [2-Cl-C_5H_4NMe]I (3 equiv), MeOH (1.2 equiv), NEt_3 (2.4 equiv) (65%); xii, $Zn(BH_4)_2$, Et_2O, -78 °C to -40 °C (90%); xiii, NBS (1.1 equiv), Me_2SO-H_2O (19 : 1) (79%); xiv, LiOH, MeOH-H_2O; xv, 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, then DMAP, toluene, 110 °C (53% from **15**); xvi, $HS(CH_2)_2SH$, BF_3•OEt (56%).

Oxidation of furan **10** was carried out with *N*-bromosuccinimide (NBS) in aqueous acetone to give a somewhat unstable keto aldehyde **11** which, upon further oxidation with $NaClO_2$, furnished the acid **12** in 62% yield from **10**. Esterification of **12** by using the Mukaiyama reagent[9] afforded the key intermediate **1** in 65% yield.

Chelation-controlled reduction of **1** was carried out using excess $Zn(BH_4)_2$ in Et_2O at −78 °C according to the procedure of Nakata[10a] and the desired *anti* alcohol **13** was obtained with >15 : 1 diastereoselectivity in 90% yield. The alcohol **13** was converted to MOM ether **14**, which was then transformed to the seco acid **16** by deprotection of TBDMS with NBS[11] followed by hydrolysis in good yield. Finally, lactonization by the Yamaguchi method[12] afforded **17** (FAB mass, M^+ + Na = 483) and deprotection of the three MOM groups furnished (+)-aspicilin in 30% yield after chromatography on silica gel. Physicochemical data of (+)-aspicilin thus obtained were consistent with the reported values[2e,f] (300 MHz ^1H NMR and optical rotation ($[\alpha]_D^{22}$ +37.5 (*c* 0.55, $CHCl_3$); lit.[2e] $[\alpha]_D^{23}$ +37.7 (*c* 0.22, $CHCl_3$), lit.[2f] $[\alpha]_D$ +38.5 (*c* 1.05, $CHCl_3$)).

In summary, we have developed a synthetic route to (+)-aspicilin. Our route is highly stereoselective and applicable to synthesis of its stereoisomers and analogues. For example, 17(*R*)-isomer of aspicilin would be prepared simply by switching the starting epoxide (*S*)-**3** to (*R*)-isomer, while the C(4)-C(6) diastereoisomers by preparation of *cis* isomer of **2** thereby producing *anti* diol upon the AD reaction, by dihydroxylation using AD-mix-α and/or by non-chelation controlled reduction of the γ-ketone producing *syn* alcohol.

We gratefully acknowledge Daiso Co. Ltd. for the generous supply of (*R*)-**18**. We also thank Prof. Tadashi Eguchi and Dr. Hiroshi Ikeda of this institute, for the mass spectrum of **17** and 500 MHz ^{1}H NMR spectrum of **2**, respectively.

REFERENCES AND NOTES

1. Feige, G. B.; Lumbsch, H. T.; Huneck, S.; Elix, J. A. *J. Chromatography* **1993**, *646*, 417-427 and references cited therein.
2. (a) Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhorn, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* **1988**, *71*, 1719-1794; (b) Quinkart, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Dürner, G. *Helv. Chim. Acta* **1989**, *72*, 1753-1786; (c) Quinkert, G.; Becker, H.; Dürner, G. *Tetrahedron Lett.* **1991**, *32*, 7397-7400; (d) Oppolzer, W.; Radinov, R. N.; De Brabander, J. *Tetrahedron Lett.* **1995**, *36*, 2607-2610; (e) Enders, D.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1185-1191; (f) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1997**, *62*, 377-386.
3. (a) Kobayashi, Y.; Kishihara, K.; Watatani, K. *Tetrahedron Lett.* **1996**, *37*, 4385-4388; (b) Kobayashi, Y.; Watatani, K.; Kikori, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 6125-6128.
4. Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, 2633-2636.
5. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
6. Keegstra, M. A.; Klomp, A. J. A.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3371-3374.
7. Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972-980; Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
8. Taniguchi, T.; Ohnishi, H.; Ogasawara, K. *Chem. Commun.* **1996**, 1477-1478; Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synlett* **1996**, 971-972; Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509-511.
9. Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863-1866.
10. (a) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411-1415; (b) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139-5142; (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069-1073; (d) Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc.* **1987**, *109*, 3981-3987; (e) Oishi, T.; Nakata T. *Acc. Chem. Res.* **1984**, *17*, 338-344. and references cited therein.
11. Batten, R. J.; Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *Synthesis* **1980**, 234-236.
12. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989-1993.

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