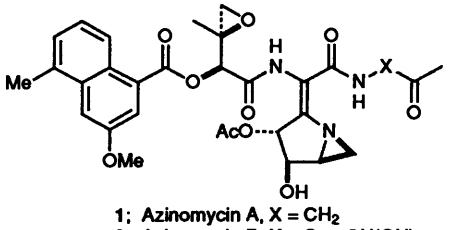
Simple and Efficient Access to the Left-hand Segment of Azinomycins

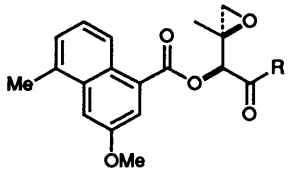
Kozo Shishido,* Tomoki Omodani and Masayuki Shibuya
Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

A practical synthesis of the epoxy carboxylic acid **4**, the left-hand segment of azinomycins, and its conversion into the naturally occurring amide **3** have been achieved enantioselectively.

Azinomycin A **1** and B **2**, antitumour antibiotics, were isolated from the culture broth of strain *Streptomyces griseofuscus* S42227 by Nagaoka *et al.*[1] along with the biologically inactive amide **3**, which is the common structural unit of azinomycins. Although the synthesis of the left-hand segment of these antibiotics, such as the amide **3**[2] or the carboxylic acid **4**,[3] has already been established, no concise route has so far been reported. Therefore, we embarked upon the development of a practical synthetic route to **3** and **4**, which would serve as key components in the total synthesis, and now report a simple and efficient synthesis of these compounds starting from the Schreiber's epoxy alcohol **6**.



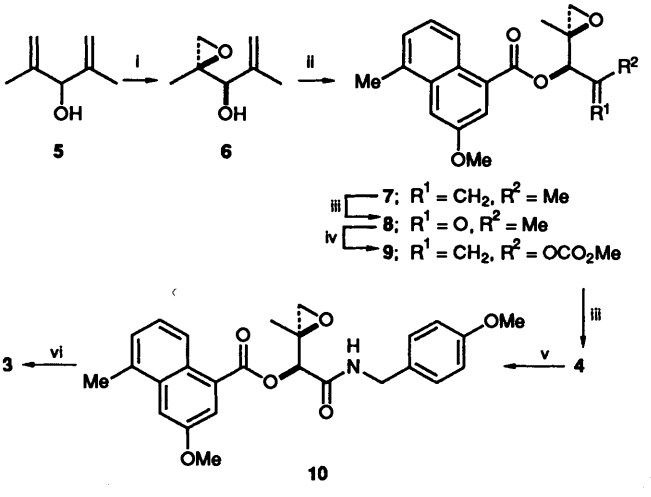
1; Azinomycin A, X = CH_2
2; Azinomcyin B, X = C=CH(OH)



3; R = NH_2
4; R = OH

Fig. 1

According to the protocol of Schreiber,[4] the Sharpless asymmetric epoxidation of diisopropenyl carbinol **5** using D-(−)-diisopropyl tartrate provided the epoxy alcohol **6** in 69% yield. Esterification with 3-methoxy-5-methylnaphthalene-1-carboxylic acid[5] with the aid of DCC provided the ester **7**,†‡ which was treated with a catalytic amount of osmium tetroxide and sodium metaperiodate to give the methyl ketone **8** in 86% overall yield from **6**. Since attempted haloform reaction for the requisite conversion of the methyl ketone moiety in **8** into the carboxyl group was unsuccessful, we chose the following two-step sequence. Thus, treatment of **8** with lithium hexamethyldisilazide in the presence of HMPA followed by the addition of methyl chloroformate afforded quantitatively the enol carbonate **9**, which was then exposed to the conditions of Lemieux–Johnson oxidation to provide the required carboxylic acid **4**,§ identical with the sample[3e] prepared previously, in 62% yield. It should be noted that the conversion of **9** into **4** took a prolonged reaction time (255 h) because of steric hindrance. With a key compound in hand, we next explored both the conditions for coupling of **4** with an appropriate amine and the conversion of the amide thus prepared into **3**, since mild and practical methods for these transformations have not been established so far. For these objectives, we chose *p*-methoxybenzylamine as an amine component. The amide formation was best carried out using benzotriazolyloxytri(pyrrolidinyl)phosphonium hexafluorophosphate (PyBOP®)[6] and 1-hydroxybenzotriazole (HOBT) in the presence of triethylamine to give the *p*-methoxybenzylamide **10** in 69% yield. Finally, treatment of **10** with DDQ[7] afforded the amide **3** (81% yield) {m.p. 153–154 °C, lit.[2] m.p. 153–154 °C; $[\alpha]_D$ +45.2¶ (*c* 0.31, MeOH), lit.[1b]; $[\alpha]_D$ +48.0 (*c* 0.33, MeOH), lit.[2]; $[\alpha]_D$ +47.5° (*c* 0.32, MeOH)}, the characteristics of which were identical with those of authentic material[2]



Scheme 1 *Reagents and Conditions:* i, D-(−)-diisopropyl tartrate, Bu^{t}OOH, Ti(OPr^i)$_4$, CH_2Cl_2, −20 °C, 16 h, 69%; ii, 3-methoxy-5-methylnaphthalene-1-carboxylic acid, DCC, 4-DMAP, CH_2Cl_2, room temp., 5 h, 94%; iii, $NaIO_4$, OsO_4, Et_2O-H_2O (1:1), for **7**, room temp., 42 h, 92%, for **9**, room temp., 255 h, 62%; iv, LiHMDS, HMPA, $ClCO_2Me$, THF, −78 °C–room temp., 1 h, 100%; v, *p*-methoxybenzylamine, PyBOP®, HOBT, Et_3N, DMF, room temp., 0.5 h, 69%; vi, DDQ, CH_2Cl_2–H_2O (18:1), 0 °C, 4 h, 81%.

In summary, we have described a simple and efficient synthesis of the epoxy carboxylic acid **4** and its conversion into the naturally occurring amide **3** in an enantiomerically pure form.

† All new compounds gave spectral data (IR, NMR, MS) in accord with their assigned structures, and satisfactory combustion analyses or an accurate mass measurement.

‡ *Selected spectral data.* For **7**: $[\alpha]_D$ +31.1 (*c* 0.39, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1719; δ_H(270 MHz, $CDCl_3$) 1.41 (3 H, s), 1.89 (3 H, br s), 2.60–2.73 (4 H, m), 2.97 (1 H, d, *J* 4.9), 3.97 (3 H, s), 5.10 (1 H, br s), 5.20 (1 H, br s), 5.42 (1 H, s), 7.35 (2 H, m), 7.45 (1 H, d, *J* 2.6), 7.81 (1 H, d, *J* 2.6) and 8.61 (1 H, m); *m/z* 326 (M^+) (Found: M^+, 326.1506. $C_{20}H_{22}O_4$ requires *M*, 326.1517).

§ $[\alpha]_D$ +2.76 (*c* 1.08, EtOH). We correct the value of the optical rotation reported in ref. 3*a*.

¶ $[\alpha]_D$ Values in units of 10^{-1} deg cm^2 g^{-1}.

The synthetic route developed here will be of significant value for the convergent total synthesis of azinomycins.

Experimental

Preparation of the Amide **10**.—To a stirred solution of a mixture of the carboxylic acid **4** (80 mg, 0.24 mmol) and *p*-methoxybenzylamine (37 mg, 0.27 mmol) in dimethylformamide (2.0 ml) was successively added PyBOP® (141 mg, 0.27 mmol), HOBT (41 mg, 0.27 mmol) and triethylamine (54 mg, 0.53 mmol) at 0 °C. After the mixture had been stirred at room temperature for 0.5 h, benzene (10 cm^3) and ethyl acetate (20 cm^3) were added and the resulting diluted solution was successively washed with 5% aqueous (aq.) hydrochloric acid, water, saturated aq. sodium hydrogen carbonate and saturated brine. The organic phase was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed on silica gel with hexane–ethyl acetate (7:3, v/v) as eluent to afford the amide **10** (75 mg, 69%) as colourless prisms, m.p. 115–117 °C; $[\alpha]_D$ +30.6 (*c* 0.56, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3434, 1729 and 1692; δ_H(270 MHz, $CDCl_3$) 1.53 (3 H, s), 2.67 (3 H, s), 2.76 (1 H, d, *J* 4.5 *), 2.99 (1 H, d, *J* 4.5), 3.77 (3 H, s), 3.96 (3 H, s), 4.45 (2 H, t, *J* 5.1), 5.26 (1 H, s), 6.43 (1 H, br t, *J* 4.3), 6.83 (2 H, d, *J* 8.7) and 7.21 (2 H, d, *J* 8.7); *m/z* 449 (M^+) (Found: M^+, 449.1810. $C_{26}H_{27}NO_6$ requires *M*, 449.1838).

* *J* Values in Hz.

References

1 K. Nagaoka, M. Matsumoto, J. Oono. K. Yokoi, S. Ishizaki and T. Nakashima, *J. Antibiot.*, 1986, **39**, 1527; K. Yokoi, K. Nagaoka and T. Nakashima, *Chem. Pharm. Bull.*, 1986, **34**, 4554.
2 M. Shibuya and H. Terauchi, *Tetrahedron Lett.*, 1987, **28**, 2619.
3 (*a*) K. Ando, T. Yamada and M. Shibuya, *Heterocycles*, 1989, **29**, 2209; (*b*) P. England, K-H. Chun, E. J. Moran and R. W. Armstrong, *Tetrahedron Lett.*, 1990, **31**, 2669.
4 S. L. Schreiber, T. S. Schreiber and D. B. Smith, *J. Am. Chem. Soc.*, 1987, **109**, 1525.
5 M. Shibuya, *Tetrahedron Lett.*, 1983, **24**, 1175.
6 J. Coste, D. Le-Nguyen and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 205.
7 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.

Paper 2/03076D
Received 10*th June* 1992
Accepted 23*rd June* 1992