CHEMISTRY LETTERS, pp. 2157 - 2158, 1984.

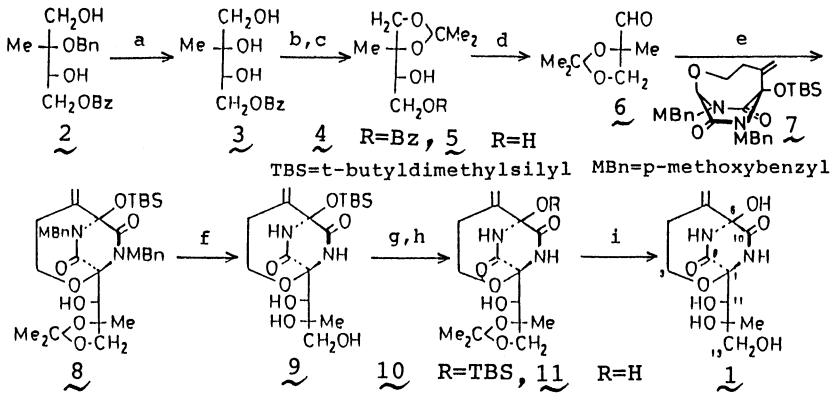
THE CHIRAL SYNTHESIS OF BICYCLOMYCIN

Juji YOSHIMURA,* Masanori YAMAURA, Tsuneji SUZUKI,
and Hironobu HASHIMOTO
Laboratory of Chemistry for Natural Products,
Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

The optically active bicyclomycin was successfully synthesized in 17 steps from *N,N'*-diacetyl-anhydroglycine.

On bicyclomycin[1] (1) syntheses of racemic compound[2] and *N,N'*-dimethyl-4-desmethylene derivative[3] have been reported, but no synthesis of optically active one has appeared in literature. For that purpose, we have reported that *p*-methoxybenzyl group is suitable as *N*-protecting group, removable with ceric ammonium nitrate (CAN) under mild conditions[4] and that the bicyclic key intermediate[5] (7) could be obtained in 12 steps from *N,N'*-diacetyl-anhydroglycine. This paper communicates the chiral synthesis of 1 through the condensation of racemic 7 and 2,3-*O*-isopropylidene-2-*C*-methyl-L-glyceraldehyde (6).

For the synthesis of 6, 4-*O*-benzoyl-2-*O*-benzyl-2-*C*-methyl-D-erythritol[6] (2) was hydrogenolyzed to give the corresponding *O*-debenzylated product [3: mp 116-117 °C, $[\alpha]_D$ +26.5° (*c* 1.0, MeOH)] which was converted into the corresponding 1,2-*O*-isopropylidene derivative [4: mp 65-67 °C, $[\alpha]_D$ -4.1° (*c* 1.1, $CHCl_3$)]. Treatment of 4 with catalytic sodium methoxide in methanol gave *O*-debenzoylated product (5), which was oxidized with sodium metaperiodate to give 6 [bp 50-53 °C/32 Torr, $[\alpha]_D$ -7.0° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr}: 1725 cm^{-1} (CHO); ^1H NMR ($CDCl_3$); δ 9.64 (s, 1 H, CHO), 4.27 and 3.75 (ABq, 2 H, J=9.0 Hz, CH_2), 1.47 (s, 6 H, Ip), 1.36 (s, 3 H, CMe)]. Condensation of the carbanion of 7 with 6 gave three diastereomers, among which the main product was 7,9-di-(*p*-methoxybenzyl)-7,9-diaza-1-[(1*S*,2*S*)-2,3-*O*-isopropylidene-2-methyl-1,2,3-trihydroxypropyl]-5-methylene-6-(*t*-butyldimethylsilyl)-oxy-(1*S*,6*R*)-2-oxabicyclo[4,2,2]decane-8,10-dione. [8: mp 61-63 °C (amorphous solid); $[\alpha]_D$ +135° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.49, 7.28, 6.68 and 6.67 (each d, 8 H, J=7.0 Hz, aromatic), 6.36 (d, 1 H, OH), 5.43 and 4.87 (each bs, 2 H, methylene), 5.08 and 4.56, 4.71 and 4.37 (each ABq, J=15.0 and 14.0 Hz, 2 x CH_2 in MBn), 4.63 (d, 1 H, J=9.5 Hz, H-11), 4.05 and 3.76 (ABq, 2 H, J=8.5 Hz, H-13), 3.79 (s, 6 H, 2 x OMe), 3.6-3.25 and 3.05-2.80 (m, 2 H, H-3), 1.85-1.65 (m, 2 H, H-4), 1.41 and 1.36 (each s, 6 H, Ip), 1.27 (s, 3 H, CMe), 0.96 (s, 9 H, *t*-Bu), 0.46 and 0.28 (each s, 6 H, 2 x Me in TBS), ^{13}C NMR: ppm 168.5 and 167.3 (each s, C-8 and C-10), 159.2, 158.9, 128.3 and 127.1 (each s, 4 x quarternary in MBn) 132.8, 130.6, 113.4 and 113.2 (each d, 4 x tertiary in MBn), 149.3 (s, C-5), 117.4 (t, methylene) 110.4 (s, quarternary in Ip), 87.5 and 86.9 (each s, C-1 and C-6), 82.7 (s, C-12), 79.7 (d, C-11), 75.4 (t, C-13), 65.4 (t, C-3), 55.2 (q, 2 x OMe), 47.2 and 44.8 (each t, 2 x CH_2 in MBn), 34.2 (t, C-4), 28.1 and 26.1 (each q, 2 x



TBS=t-butyldimethylsilyl MBn=p-methoxybenzyl

Reagents and conditions: a) 10% Pd-C/H_2, MeOH, 1 day (96 %); b) 6.0 equiv. 2-methoxypropene/cat. PPTS (pyridinium *p*-toluenesulfonate)/acetone, -30 °C →r.t., 7 h (82%); c) cat. 1 M NaOMe/MeOH, r.t., 30 min (93%); d) 1.2 equiv. $NaIO_4$/MeOH-H_2O, r.t., 30 min (72%); e) 2.0 equiv. *n*-BuLi/4.0 equiv. 6/THF, -100 °C →0 °C, 6 h (32%); f) 4.0 equiv. 0.2 M CAN/CH_3CN-H_2O (4:1), r.t., 25 min (49%); g) 6.0 equiv. 2-methoxypropene/cat. PPTS/acetone, r.t., 12 h (99%); h) 1.5 equiv. Bu_4NF/CH_2Cl_2, 0 °C, 1.5 h (95%); i) 80% AcOH, r.t., 8 h (92%).

Me in Ip), 27.0 (q, *t*-Bu), 21.1 (q, CMe), 19.8 (s, quarternary in TBS, -2.3 (q, 2 x MeSi)]. Treatment of 8 with CAN was accompanied with *o*-deisopropylidenation to give 9 [mp 99-100 °C (amorphous solid); $[\alpha]_D$ +37.8 (*c* 0.9, $CHCl_3$)]. For prevention of rearrangement of the bicyclic skeleton[7], 9 was again *o*-isopropylidenated to give 10 [mp 81-82 °C (amorphous solid); $[\alpha]_D$ +58.2° (*c* 1.0, $CHCl_3$)], and then TBS group was removed to afford 11 [mp 204 °C (decomp.); $[\alpha]_D$ +71.6° (*c* 1.0, MeOH)]. *o*-Deisopropylidenation of 11 gave 1 [^{13}C NMR: ppm 170.4 and 167.2 (each s, C-8 and C-10), 149.9 (s, C-5), 116.1 (t, methylene), 88.7 and 82.4 (each s, C-1 and C-6), 78.0 (s, C-12), 71.4 (d, C-11), 67.6 (t, C-13), 64.2 (t, C-3), 36.3 (t, C-4), 24.8 (q, CMe)], whose physical data (mp, IR, ^1H NMR, and $[\alpha]_D$) were identical with those of reported.[1] During the preparation of the manuscript, another total synthesis was reported [R. M. Williams, R. W. Armstrong, and J.-S. Dung, J. Am. Chem. Soc., 106, 5749 (1984)]. The authors are grateful to Fujisawa pharmaceutical Co. for the gift of natural product.

References

1) T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sakai, and H. Imanaka, J. Antibiot., 25, 569 (1972); T. Kamiya, S. Maeno, M. Hashimoto, and Y. Mine, *ibid.*, 25, 576 (1972); S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, H. Ochiai, K. Abe, K. Koizumi, K. Asao, K. Mitsuki, and T. Hoshino, *ibid.*, 25, 610 (1972).

2) S. Nakatsuka, K. Yamada, K. Yoshida, O. Asano, Y. Murakami, and T. Goto, Tetrahedron Lett., 24, 5627 (1983), and references cited therin.

3) R. M. Williams, O. P. Anderson, R. W. Armstrong, J. Joey, H. Meyers, and C. Erikson, J. Am. Chem. Soc., 104, 6092 (1982); R. M. Williams, J.-S. Dung, J. Joey, R. W. Armstrong, and H. Meyers, ibid., 105, 3214 (1983), and references cited therin.

4) J. Yoshimura, M. Yamaura, T. Suzuki, and H. Hashimoto, Chem. Lett., 1983, 1001.

5) M. Yamaura, T. Suzuki, H. Hashimoto, J. Yoshimura, and C. Shin, Chem. Lett., 1984, 1547.

6) J. Yoshimura, K. Hara, M. Yamaura, K. Mikami, and H. Hashimoto, Bull. Chem. Soc. Jpn., 55, 933 (1982).

7) O. Wacker, W. Kump, and B. W. Müller, Tetrahedron Lett., 24, 5607 (1983).

(Received October 19, 1984)