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TWO SYNTHETIC APPROACHES TO REBECCAMYCIN

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Summary: Two synthetic approaches to a new indolocarbazole antitumor antibiotic, rebeccamycin, were developed. The absolute configuration of rebeccamycin was determined by a total synthesis.

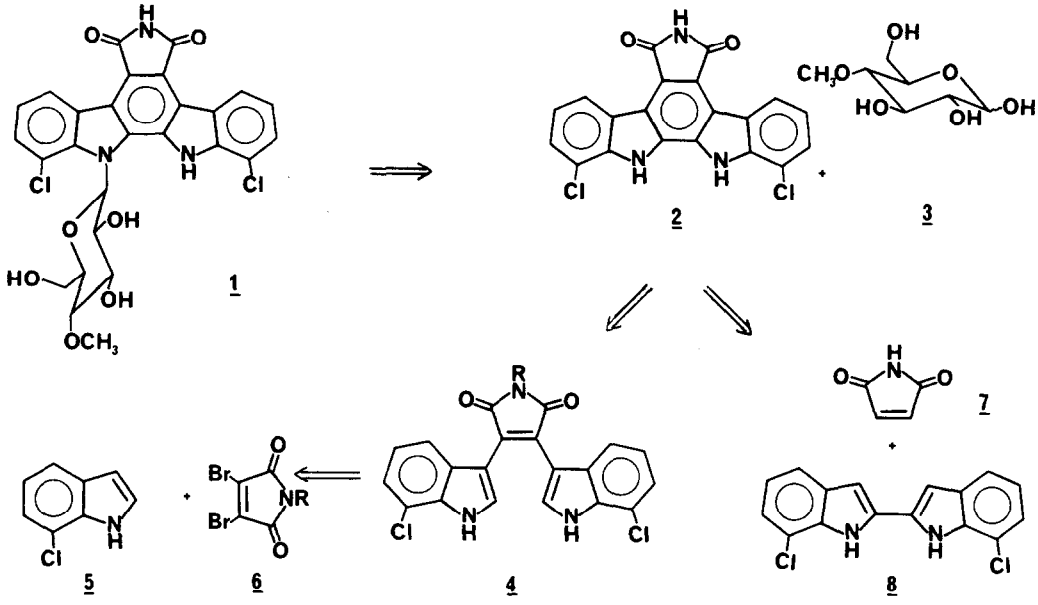
Rebeccamycin 1 is a new antitumor antibiotic produced by Nocardia aerocoligenes strain C38383. Its structure with the exception of absolute configuration was determined by spectroscopic means and x-ray crystallography as described in the preceding paper.[1] In this communication we report the total synthesis of rebeccamycin and the determination of its absolute configuration.

Rebeccamycin is an N-glycoside consisting of a unique indolocarbazole chromophore and 4-O-methylglucose. At present, only a few natural products possessing a similar chromophore are known. They include staurosporine,[2] an antibiotic, and arcyriaflavins,[3] pigments from a slime mold. Steglich et.al.[3] have reported the synthesis of compounds related to arcyriaflavins. More recently, syntheses of staurosporin have been described by several groups.[4-7]

In the retrosynthesis of rebeccamycin two routes were considered as shown in Scheme I. The first route involves the cleavage of the central bond connecting the 2 and 2' position of the indole units. The resulting compound could then be constructed applying the indole Grignard method developed by Steglich. The second route involves disconnection of the two bonds connecting the indole units to the imide moiety. This in synthetic terms means a Diels-Adler reaction between maleimide and 2,2'-bisindole.

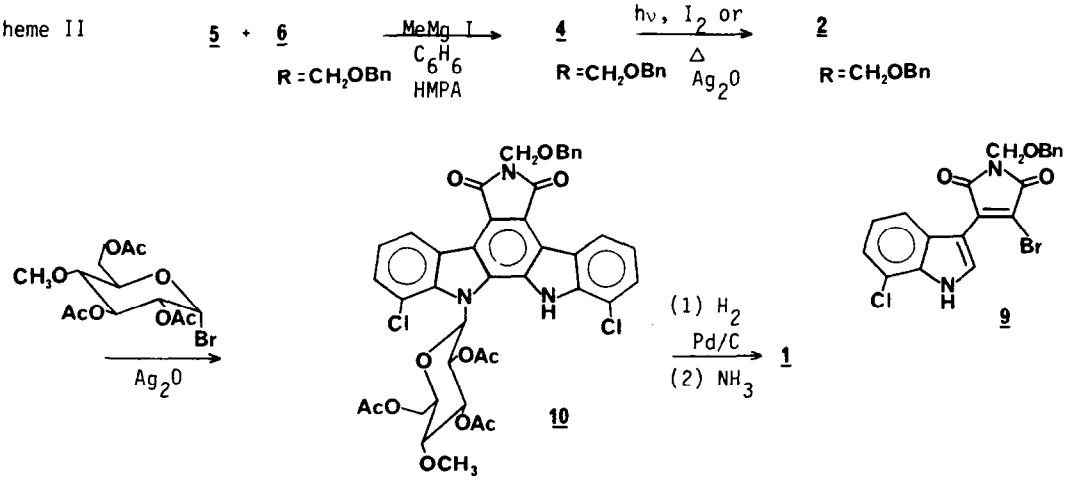
For the indole Grignard route, 7-chloroindole was prepared according to the method of Sugasawa et.al.[8] When 7-chloroindole was treated at room temperature with 4 eq of MeMgI and 1 eq of N-benzyloxymethyl-2,3-dibromomaleimide[9] in benzene containing a small amount of HMPA, the desired 2:1 adduct (4,R=CH_2OBn)[10] was obtained in 27% yield. The byproduct was

Scheme I



shown to be the 1:1 adduct (9, 4%). The 2:1 adduct could be photocyclized to 2 (R=CH_2OBn) by irradiating with mercury lamps at 3000 Å in the presence of I_2 and air[12]. A more convenient one-pot method, however, was developed effecting the cyclization and the glycosidation both in refluxing benzene in the presence of Ag_2O. In this case it is presumed that the triene system 4 is thermally cyclized and Ag_2O is acting as an oxidizing agent. The sugar moiety, 1-bromo-2,3,6-tri-O-acetyl-4-O-methylglucose, was prepared from D-glucose according to the method of Bouveng.[13] After addition of this bromosugar to the benzene solution and refluxing, the N-glycoside 10[14] was obtained in 32% yield. Removal of

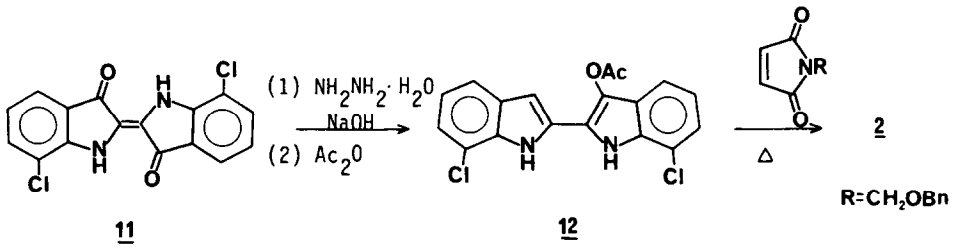
Scheme II



the benzyloxymethyl group by hydrogenation and the acetyl groups by ammonolysis gave rebeccamycin in 95% yield. The synthetic material was identical to the natural product by NMR, IR, TLC, and optical rotation. Since we prepared the sugar moiety from D-glucose, the absolute configuration of rebeccamycin was determined to be the same as D-glucose.

A conceptually shorter approach utilized a Diels-Adler reaction of maleimide and 2,2'-bisindole. The preparation of 7,7'-dichloro-2,2'-bisindole by the method of Bergman[15], however, turned out to be inefficient. This led to a modification of this route in which a readily available reduced indigo was substituted for the 2,2'-bisindole. Thus, 7,7'-dichloroindigo[16] was reduced under Wolff-Kishner conditions and acetylated[17] to give monoacetyl bisindole 12[18] in 95% yield. Heating of this material with N-benzyloxymethylmaleimide[19] in a sealed tube at 105°C for 8 days gave the chromophore 2 in 22% yield. Presumably the initial Diels-Adler reaction was followed by loss of acetic acid and dehydration. The material obtained was identical to the intermediate prepared by the first approach. Thus, two concise approaches to rebeccamycin were developed. The total synthesis also determined the absolute configuration of rebeccamycin.

Scheme III



11 12

References and Notes

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9. Prepared from dibromomaleimide and benzylchloromethyl ether using K_2CO_3 as a base in acetone.

10. Mp 220-223 °C; NMR ($CDCl_3$) δ 4.71(s, 2H), 5.21(s, 2H), 6.70(t, 2H, J = 7.9 Hz), 6.80(d, 2H, J = 8.1 Hz), 7.09(d, 2H, J = 7.4 Hz), 7.22-7.39(m, 5H), 7.84(d, 2H, J = 2.8 Hz), 8.76(bs, 2H); EIMS m/e 515 (M^+).

11. Mp > 300 °C; NMR (DMSO-d_6) δ 4.68(s, 2H), 5.22(s, 2H), 7.24(d, 1H, J = 7.0 Hz), 7.30(t, 2H, J = 7.2 Hz), 7.37(d, 2H, J = 7.0 Hz), 7.43(t, 2H, J = 7.8 Hz), 7.72(d, 2H, J = 7.9 Hz), 8.94(d, 2H, J = 7.9 Hz), 12.06(s, 1H); IR(KBr) 3390, 1760, 1700, 1400, 1340, 1070 cm^{-1}; EIMS m/e 513 (M^+).

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14. Mp 114-116 °C; NMR ($CDCl_3$ δ 1.15(s, 3H), 1.95(s, 3H), 2.14(s, 3H), 3.58(s, 3H), 3.88(t, 1H, J = 9.6 Hz), 4.26(dt, 1H, J = 7.7, 2.2 Hz), 4.74(dd, 1H, J = 12.4, 2.4 Hz), 4.78(s, 2H), 4.85(dd, 1H, J = 12.4, 7.7 Hz), 5.29(t, 1H, J = 9.2 Hz), 5.35(s, 2H), 5.42(t, 1H, J = 9.2 Hz), 7.23-7.45 (m, 8H), 7.62(t, 2H, J = 7.7 Hz), 9.18(d, 1H, J = 8.0 Hz), 9.33(d, 1H, J = 7.6 Hz), 10.36(s, 1H).

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18. NMR (DMSO-d_6) δ 2.53(s, 2H), 7.01(d, 1H, J = 2.0 Hz), 7.07(t, 1H, J = 7.8 Hz), 7.08(t, 1H, J = 7.8 Hz), 7.24(d, 1H, J = 7.5 Hz), 7.29(d, 1H, J = 7.5 Hz), 7.39(d, 1H, J = 7.9 Hz), 7.59(d, 1H, J = 7.8 Hz), 11.65(s, 2H); IR (KBr) 3380, 2920, 1730, 1330, 1230 cm^{-1}; EIMS 358 (M^+).

19. Prepared from maleimide and benzylchloromethyl ether using diisopropylethylamine as a base in tetrahydrofuran.

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