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TOTAL SYNTHESIS OF (±)-NEPLANOCIN F

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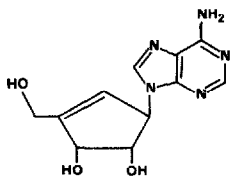
Abstract: (±)-Neplanocin F was synthesized in 12 steps from the racemate (3/4), which was available from D-ribonolactone.

Of the natural fermentation products isolated from ampullariella regularis A11079,[1] (-)-neplanocin A (1) has received the most attention because of its novel carbocyclic structure and its potent antiviral and antitumor properties.[2] Among the other naturally occurring neplanocins, (-)-neplanocin F (2), the allylic rearranged isomer of (-)-neplanocin A,[3,4] attracted our attention as both a synthetic target and as a molecule of potential biological interest. In addition, it was felt that a total synthesis of neplanocin F would firmly establish the chemical structure of this compound and resolve a discrepancy between three published communications[2-4] and the patent literature,[5] regarding the stereochemistry of the 2'-hydroxyl group.

An undesired side product, obtained from the scale-up synthesis of (-)-neplanocin A, was the racemate (3/4) of a pivotal cyclopentenone intermediate 3.[6] For the synthesis of neplanocin F, however, it is the opposite enantiomer in this racemic mixture (compound 4), which is the critical precursor.

As reported earlier for compound 3, the racemic cyclopentenone mixture (3/4) was reduced regioselectively and stereoselectively to the α-allylic alcohol 5 (only one enantiomeric form is shown in Scheme 1).[6] Protection of the newly formed alcohol as a benzyl ether, followed by the acid-catalyzed removal of the isopropylidine moiety, gave



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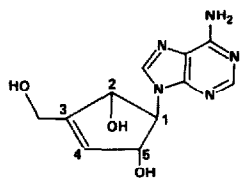

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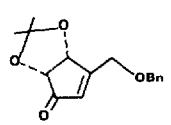

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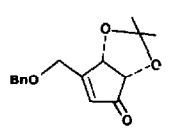

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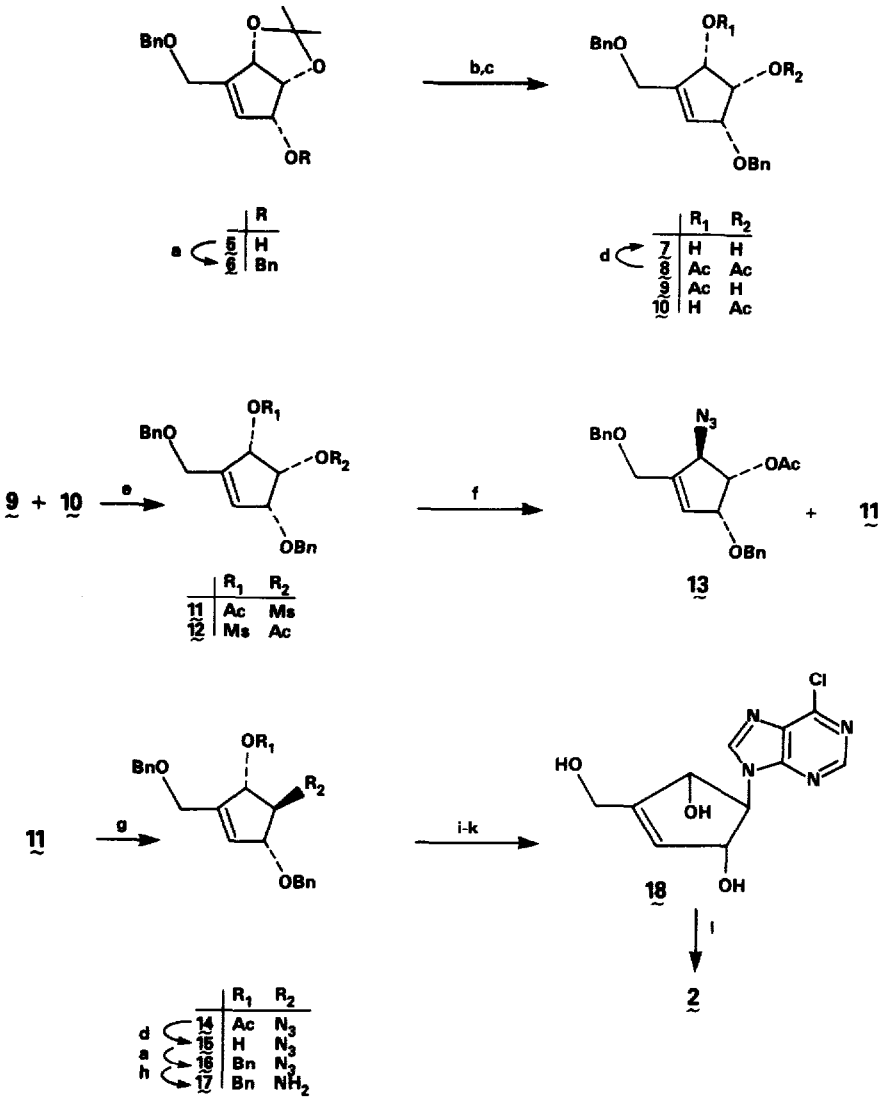
Scheme 1



a. *(i)* **NaH, DMF, rt, 30 min. *(ii)*** $PhCH_2Br$ **(BnBr), DMF, rt, 1 h; b. TFA (aq), rt, 15 min; c.** Ac_2O **(1.2 equiv.),** Et_3N**, DMAP,** CH_2Cl_2**, rt, 30 min; d. NaOMe/MeOH, rt, 30 min; e.** $MeOSO_2Cl$ **(MsCl, 1.2 equiv.),** Et_3N**,** CH_2Cl_2**, rt, 30 min; f.** LiN_3**, DMSO, rt, 30 min; g.** LiN_3**, DMSO, 110°C, 3 days; h. Lindlar cat. [**H_2**], MeOH, rt, 1 h; i. 2,6-diamino-5-chloropyrimidine (2 equiv.),** Et_3N**, n-BuOH, Δ, 3 days; j.** $(EtO)_3CH$**, HCl, rt, 8 h; k.** BCl_3**,** CH_2Cl_2**, −78°C, 2.5 h; l.** NH_3**/MeOH, 110°C, 3 days.**

the diol intermediate 7 [85%, mp 54-55°C, ^{1}H NMR ($CDCl_3$) δ 2.80 (d, J = 8.4 Hz, 1 H, OH), 3.11 (d, J = 6.2 Hz, 1 H, OH), 4.20 (s, 2 H, CH_2OBn), 4.24-4.68 (m, 7 H, 2 x CH_2Ar, H-1, H-2, H-5), 5.89 (s, 1 H, H-4), 7.30-7.38 (m, 10 H, ArH)]. Treatment of this diol with 1.2 equivalents of Ac_2O gave a quantitative yield of a mixture of three compounds: the diacetate 8 and the monoacetates 9 and 10 in a 4:4.5:1.5 ratio, respectively. Although the diacetate 8 was easily separated from the reaction mixture by column chromatography, the monoacetates 9 and 10 resisted all attempts toward separation. The mixture of monoacetates reached an equilibrium point favoring the allylic monoacetate 9 over its isomer 10 by a 3:1 ratio, as ascertained by ^{1}H NMR spectroscopy. This difference was further exploited to accomplish the desired separation of isomers by reacting the mixture of monoacetates with methanesulfonyl chloride. The resulting mixture of mesylates 11 and 12 was subsequently reacted at room temperature with LiN_3. Under these conditions, only the allylic mesylate (isomer 12) reacted to give the corresponding azide 13, which was then easily separated from the unreactive mesylate 11 by column chromatography. As shown in Scheme 1, the diacetate 8 could be hydrolyzed back to the diol 7 and recycled again through the same sequence of steps. With the least reactive mesylate now in hand, the desired azide 14, with the expected inversion of configuration, was obtained after prolonged heating with LiN_3 [26% yield after three steps from 7, colorless oil, ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H, $OCOCH_3$), 3.97-4.02 (m, 3 H, CH_2OBn, H-1), 4.32-4.34 (m, 1 H, H-5), 4.48-4.51 (AB quartet, 2 H, CH_2Ar), 4.60-4.71 (AB quartet, 2 H, CH_2Ar), 5.61 (d, J = 4.4 Hz, 1 H, H-2), 6.00 (s, 1 H, H-4), 7.29-7.41 (m, 10 H, ArH); IR (film) 2100 cm^{-1} (N_3)]. Purine ring building reactions later showed that the acetate protecting group in compound 14, as well as the free hydroxyl group in 15, interfered with this process.[7] Consequently, protection of this alcohol function with the stable benzyl group was performed to give the tri-O-benzyl compound 16 (86%, oil). Hydrogenation of the azide 16, over Lindlar catalyst, proceeded in good yield to give the carbocyclic amine 17 [86%, oil, ^{1}H NMR ($CDCl_3$) δ 1.12 (br s, 2 H, NH_2), 3.43 (br s, 1 H, H-1), 4.00-4.13 (m, 4 H, CH_2OBn, H-2, H-5), 4.40-4.70 (m, 6 H, 3 x CH_2Ar), 5.92 (s, 1 H, H-4), 7.32 (s, 15 H, 3 x ArH)]. Formation of the required purine moiety was performed by the classical sequence: (1) condensation of 17 with 2 equiv of 5-amino-4,6-dichloropyrimidine in refluxing butanol in the presence of Et_3N and (2) ring closure of the resulting compound with triethyl orthoformate and HCl to give the corresponding protected chloropurine intermediate.[8,9]

Following the removal of the three benzyl protective groups with boron trichloride in dichloromethane, the chloropurine carbocyclic nucleoside 18 was obtained [33% yield (three steps), mp > 225°C dec]. This compound was finally converted into (±)-neplanocin F (2) by treatment with saturated methanolic ammonia at 110° C under pressure. Recrystallization from water afforded (±)-neplanocin F as colorless crystals [95%, mp

256-7°C dec, ^{1}H NMR (Me_2SO-d_6) δ 3.90-4.19 (m, 2 H, CH_2OH), 4.30 (t, J = 6.6 Hz, 1 H, H-1′), 4.82 (t, J = 5.5 Hz, 1 H, CH_2OH), 4.55-5.01 (m, 2 H, H-2′, H-5′), 5.40-5.50 (overlapping doublets, 2 H, 2 x OH), 5.65 (s, 1 H, H-4′), 7.21 (s, 2 H, NH_2), 8.09 (s, 1 H, H-8), 8.18 (s, 1 H, H-2); high resolution FAB MS, m/z 264.1097 (MH^+, calcd. 264.1099)].[10] The proton NMR of synthetic (±)-neplanocin F was identical to the one from a sample of natural (-)-neplanocin F kindly provided to us by Dr. Satoshi Yaginuma, from the Toyo Jozo Co., in Japan.

In summary, the synthesis of (±)-neplanocin F, achieved in this work, represents another example of the utility of our previously developed cyclopentenone synthon (3/4) toward the synthesis of novel carbocyclic nucleosides, particularly those belonging to the neplanocin family. Evaluation of the biological potential of neplanocin F is under investigation together with efforts toward the preparation of optically pure material.

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7. When the carbocyclic amine obtained from compound 14 was used in the condensation reaction with 2,4-dichloro-5-aminopyrimidine, acyl group migration from the ester to the amine interfered with the reaction. On the other hand, use of the carbocyclic amine generated from compound 15, gave the desired condensation product in acceptable yields. However, the final cyclization step did not go to completion due to the ease with which the free allylic alcohol reacted with triethyl orthoformate.
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10. Combustion analyses for C, H, and N, performed on the final product (±)-neplanocin F, as well as in the intermediate compounds, were within ± 0.4% of the calculated values.

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