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A SYNTHETIC APPROACH TOWARDS NEPLANOCIN A: PREPARATION OF THE OPTICALLY ACTIVE CYCLOPENTENE MOIETY FROM D-RIBOSE

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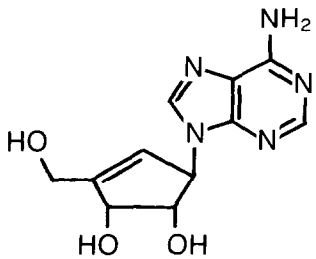
Abstract: D (-)-ribose has been converted to the chiral 2-cyclopenten-1-one derivative 13 which has the correct stereochemistry and appropriate functionalities for the construction of neplanocin A.

Among the neplanocin antibiotics (NPC-A, B, C, D, and F) recently isolated and identified by Yaginuma et al.[1] from a soil-derived strain of ampullariella regularis A11079, neplanocin A (NPC-A, 1), exhibited the most potent in vivo antitumor activity against L1210 murine leukemia (ILS 120% at 5 mg/kg qd 1-5).[2] A unique structural feature of this antibiotic constitutes the presence of a cyclopentene ring in place of the ribose sugar of adenosine. Another structurally related carbocyclic adenosine, aristeromycin 2, which contains a cyclopentane ring, is on the contrary devoid of antitumor activity against L1210 leukemia,[3] suggesting that presence of a double bond in the structure of NPC-A might be critical for activity.



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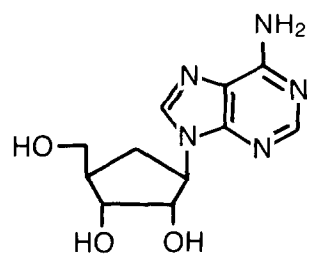

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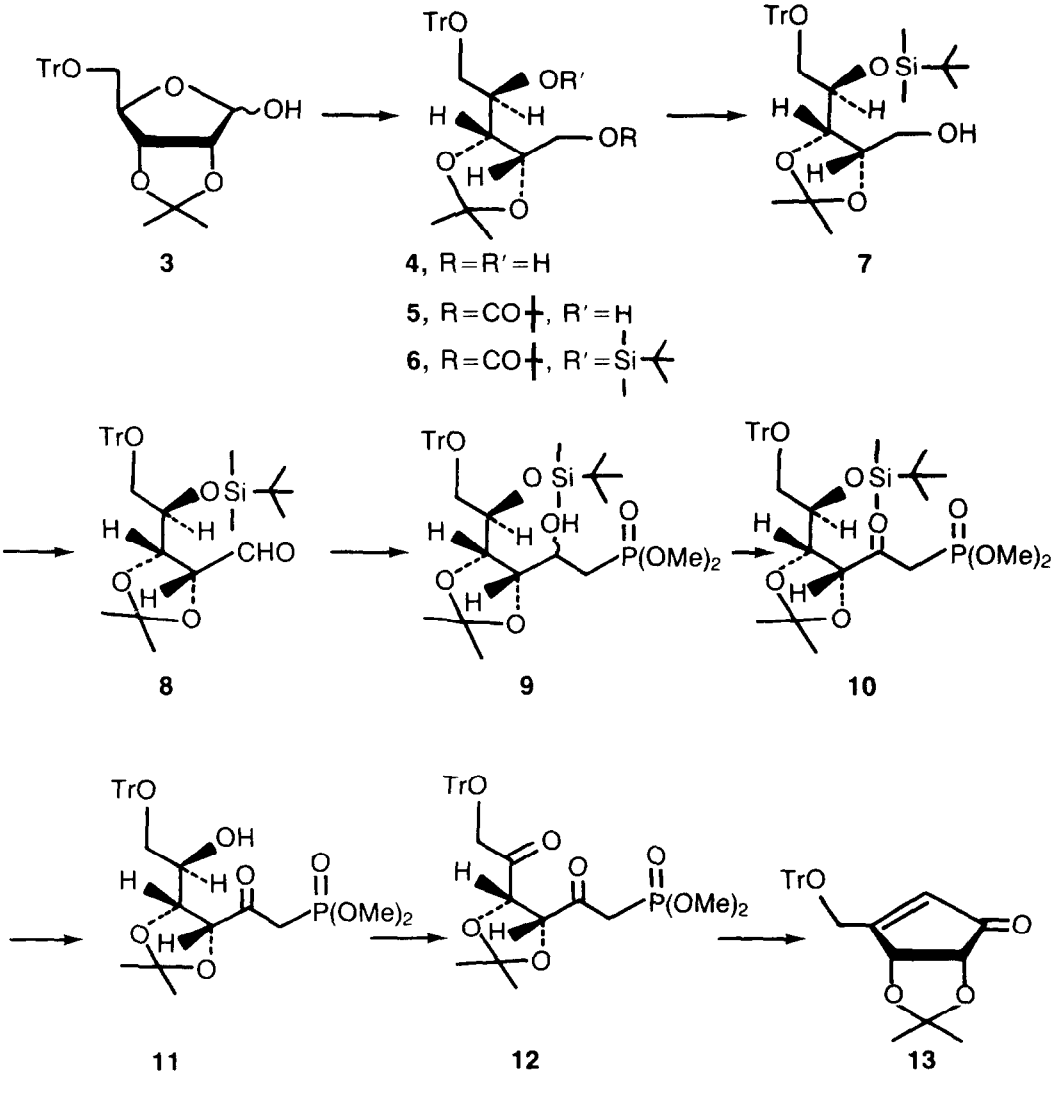
As part of a program directed towards the total synthesis of NPC-A and its congeners, the 2-cyclopentenone derivative 13 (Scheme I) was visualized as a key intermediate. The keto functionality in 13 was to provide a handle for further synthetic elaboration (i.e., functional transformation into halogen, amino, ester, etc.) and the subsequent construction of the nucleoside base by well established methods (i.e., stepwise building of the purine ring[3] or condensation with a persilylated base[4]). A recent communication dealing with the chemoenzymatic total synthesis of NPC-A,[5] starting from the Diels-Alder product formed from cyclopentadiene and dimethyl acetylenedicarboxylate, prompted us to disclose our preliminary results for the synthesis of the cyclopentene component of NPC-A containing the correct stereochemical configuration. Our synthetic strategy was based on the use of a suitably protected chiral carbohydrate,[6] such as D-ribose, which was to be converted to a 2,5-diketophosphonate derivative capable of undergoing an intramolecular Wittig-Horner reaction[7] to the desired

SCHEME I



cyclopentenone target. The synthesis started with the readily available 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose 3[8] which was converted to the ribitol 4[9] (72% yield) after reduction with sodium borohydride in ethanol (0°C, 1h). Selective protection of the primary hydroxyl group of 4 was accomplished with 1.1 equiv of trimethylacetyl chloride in pyridine (25°C, 1h) to afford compound 5 [87% yield, $[\alpha]_D^{25}$ -9.1° (c 1.15, $CHCL_3$)]. The remaining secondary hydroxyl group of 5 was protected after treatment with 1.2 equiv of t-butyldimethylsilyl triflate[10] and 2.5 equiv of 2,6-lutidine in dichloromethane (0°C, 1h) to give the corresponding t-butyldimethylsilyl ether 6 [84% yield, $[\alpha]_D^{25}$ -26.0° (c 0.82, $CHCL_3$)]. These synthetic manipulations produced a structure in which the three hydroxyl groups were chemically differentiated by the distinctive nature of their protective groups. Such strategy permitted the individual generation of every hydroxyl group as it was required during the synthesis. Treatment of 6 with 2.5 equiv of n-butyllithium in THF (0°C, 1h) removed the pivaloyl group producing the alcohol 7 [83% yield, $[\alpha]_D^{25}$ -27.70° (c 0.26, $CHCL_3$)]. Oxidation of 7 with 2 equiv of pyridinium chlorochromate[11] in dichloromethane (25°C, 18h) in the presence of powdered 4A molecular sieves afforded the aldehyde 8 [67% yield, $[\alpha]_D^{25}$ -43.57° (c 0.14, $CHCL_3$), IR ($CHCL_3$) 1730 cm^{-1}, NMR ($CDCL_3$, 220 MHz) δ -0.07 (s, 3H), 0.02 (s, 3H), 0.81 (s, 9H), 1.38 (s, 3H), 1.56 (s, 3H), 3.23 (m, 2H), 4.19 (m, 2H), 4.53 (dd, J = 2.2, J′ = 7.7 Hz, 1H), 7.18-7.48 (m, 15H), 9.58 (d, J = 2.2 Hz, 1H)]. The coupling of lithium dimethyl methylphosphonate[12] (2.5 equiv) with 8 in THF (-78°C, 0.5h) gave a mixture of diastereomeric alcohols 9 (64% yield) which was oxidized as such with Swern's reagent[13] (3 equiv of DMSO, 2 equiv of $(CF_3CO)_2O$, and excess of Et_3N) in dichloromethane (-78°C, 1h and 0°C, 0.5h) to give the ketophosphonate 10 [81% yield, $[\alpha]_D^{25}$ -3.6° (c 0.53, $CHCL_3$), IR ($CHCL_3$) 1720 cm^{-1}, NMR ($CDCL_3$, 220 MHz) δ -0.07 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.36 (s, 3H), 1.55 (s, 3H), 2.75 (dd, J_{gem} = 14.0, J_{HP} = 20.0 Hz, 1H), 3.27 (m, 2H), 3.51 (dd, J_{gem} = 14.0, J_{HP} = 20.0 Hz, 1H), 3.68 (d, J = 11.5 Hz, 3H), 3.72 (d, J = 11.5 Hz, 3H), 4.14 (m, 1H), 4.32 (d, J = 7.0 Hz, 1H), 4.56 (dd, J = 7.0, J′ = 2.0 Hz, 1H), 7.14-7.55 (m, 15H)]. Removal of the t-butyldimethylsilyl group of 10 with 1.5 equiv of tetra-butylammonium fluoride[14] in THF (54°C, 5h) resulted in the formation of ketophosphonate alcohol 11 [75% yield, $[\alpha]_D^{25}$ -10.50° (c 0.38, $CHCL_3$)] which after exposure to Swern's reagent, under the same conditions as described previously for compound 9, produced the diketophosphonate 12 [87% yield, $[\alpha]_D^{25}$ -12.80° (c 0.25, $CHCL_3$), IR ($CHCL_3$) 1730 cm^{-1}, NMR ($CDCL_3$, 220 MHz) δ 1.25 (s, 3H), 1.35 (s, 3H), 3.23 (dd, J_{gem} = 14.0, J_{HP} = 22.5 Hz, 1H), 3.48 (dd, J_{gem} = 14.0, J_{HP} = 22.5 Hz, 1H), 3.78 (d, J = 12.5 Hz, 6H), 4.16 (s, 2H), 4.72 (A2 system, 2H), 7.18-7.61 (m, 15H)]. After a number of futile attempts to cyclize 12 under standard conditions (NaH in glyme, THF, or toluene; n-butyl lithium in THF; benzyltriethylammonium chloride/NaOH in CH_2CL_2; etc.) the reagents of choice were found to be potassium carbonate and 18-crown-6 ether.[15] Hence, the intramolecular base-catalyzed cyclization of 12 with 1.2 equiv of powdered anhydrous potassium carbonate and 2 equiv of 18-crown-6 in toluene (65°C, 2h) rendered the desired 2-cyclopentenone 13 [30% yield, mp 152-154°C, $[\alpha]_D^{25}$ +5.0° (c 0.38, $CHCL_3$), IR ($CHCL_3$) 1718, 1620 cm^{-1}, NMR ($CDCL_3$, 220 MHz) δ 1.34 (s, 6H), 3.95 (d, J_{gem} = 17.5 Hz, 1H), 4.25 (d, J_{gem} = 17.5 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.98 (d, J = 5.0 Hz, 1H), 6.43 (s, 1H), 7.20-7.50 (m, 15H)]. Anal. Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.15. Found: C, 78.89; H, 6.25. The synthesis reported here will afford a convenient

entry into the neplanocin-type nucleosides via the 2-cyclopentenone intermediate 13 which has the potential versatility of being useful in the synthesis of other purine and pyrimidine derivatives carrying this novel carbocyclic moiety. Efforts to convert 13 to neplanocin and other related analogs are currently under study in our laboratories.

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