Tetrahedron Letters,Vol.24,No.50,pp 5559-5562,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain ©1983 Pergamon Press Ltd.

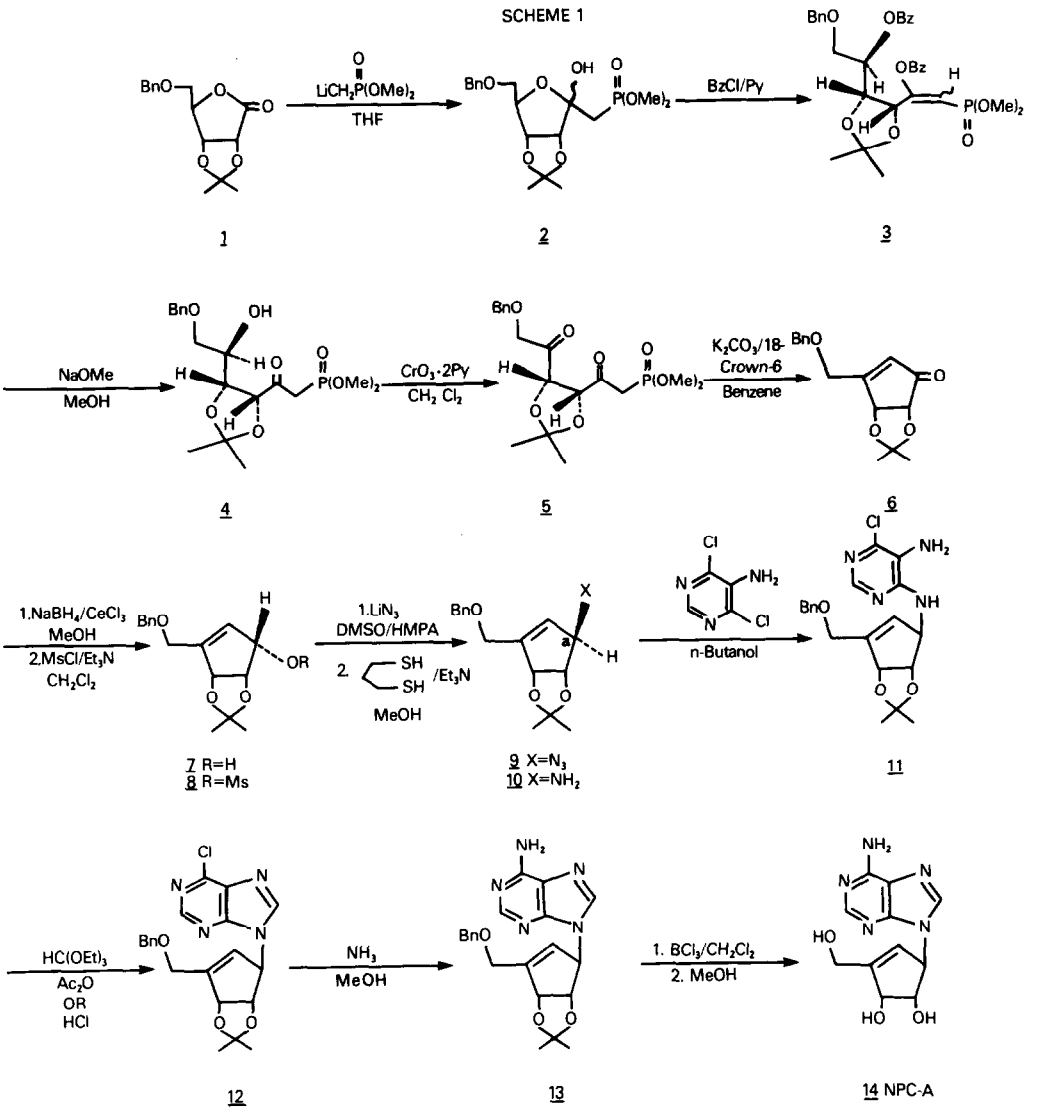
TOTAL SYNTHESIS OF (-)-NEPLANOCIN A[1]

Mu-Ill Lim* and Victor E. Marquez
Drug Design and Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

Abstract: A total synthesis of (-)-neplanocin A has been accomplished in 15 steps starting from the readily available D-(+)-ribonic acid γ-lactone.

The neplanocin antibiotics (NPC-A, B, C, D, and F) were isolated in 1979 from the culture filtrate of ampullariella regularis A11079.[2] Of all the active neplanocins, NPC-A (14), demonstrated to have a superior antitumor activity producing a 120% increase of life span (ILS) in mice bearing L1210 leukemia.[3] In view of its chemotherapeutic potential and good therapeutic ratio, we sought to develop a synthetic approach to this important antibiotic. In addition to achieving our main objective, it was important that the synthetic approach would be versatile enough to permit the elaboration of other purine and pyrimidine congeners bearing the unusual cyclopentene ring structure. During the course of this work, Ohno's group disclosed an enantioselective synthesis of NPC-A by a chemoenzymatic approach starting from the Diels-Alder adduct of cyclopentadiene and dimethyl acetylenedicarboxylate.[4] Our strategy, conceptually different from that of Ohno et al., hinged upon an efficient synthesis of the key 2-cyclopentenone derivative 6 from which the cyclopentenylamine 10 was to be stereoselectively generated. The conversion of this amine to the adenine base is known and was also used in the total synthesis of neplanocin A.[4,5] We have recently reported a synthesis of the cyclopentenone intermediate 6 from D-(-)-ribose by a twelve-step sequence.[6] However, in connection with this total synthesis of NPC-A, we wish to describe a significant improvement in the expedience and yield of obtaining 6 by a synthetic sequence five steps shorter than the previous one. The synthesis started with (-)-5-O-benzyl-2,3-O-isopropylidene-D-ribolactone 1[7] which was coupled with 2.5 equiv of lithium dimethyl methylphosphonate[8] in THF (-78° → 0°C, 2h) to afford the hemiketal 2 in quantitative yield (Scheme 1). Benzoylation of 2 with 5 equiv of benzoyl chloride in pyridine (24°C, 16h) gave the acyclic dibenzoate 3 (60% yield) as a mixture of E and Z isomers. No separation of these geometric isomers was attempted because as seen in the next step it was of no consequence to the chirality of 4. Treatment of 3 with 2.5 equiv of methanolic sodium methoxide (24°C, 18h) resulted in complete debenzoylation to give the β-ketophosphonate 4 (68%). Oxidation of 4 with 6 equiv of the modified Collins reagent[9] ($CrO_3 \cdot 2Py$) in dichloromethane (24°C, 1h) produced the important diketophosphonate 5 (75%). The critical intramolecular cyclization was effected by the modified procedure of Aristoff.[10] Thus, reaction of 5 with 1.2 equiv of powdered anhydrous potassium

SCHEME 1



1 2 3 4 5 6

7 R=H
8 R=Ms

9 X=N3
10 X=NH2

11 12 13 14 NPC-A

carbonate and 0.5 equiv of 18-crown-6 ether in benzene under high dilution (60°C, 5h) gave the desired 2-cyclopentenone 6 [50%, $[\alpha]_D^{24}$ -5.6° (c 1.0, $CHCl_3$), ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.39 (s, 6H), 4.32 and 4.48 (2dd, J_{gem} = 17.5, J = 1.5 Hz, 1H each), 4.48 (d, J = 5.5 Hz, 1H), 4.61 (s, 2H), 5.08 (d, J = 5.5 Hz, 1H), 6.18 (t, J = 1.5 Hz, 1H), 7.34 (m, 5H)]. The necessary β-stereochemistry of the amino group attached to the cyclopentene moiety, as demanded by the structure of NPC-A, required the reduction of the prochiral enone carbonyl of 6 to be regioselective (1,2 reduction rather than 1,4 reduction) and stereoselective in generating solely the allylic alcohol with the α-configuration. The concave-convex nature of the bicyclic [3,3,0] system in 6 imposed the necessary restrictions on the incoming reducing hydride, allowing it to approach the molecule exclusively from the less congested convex α-face. Indeed, reduction of 6 with 1.2 equiv of sodium borohydride in a 0.4M $CeCl_3 \cdot 7H_2O$ methanol solution[11] (2.5 ml/mmole of 6, 0°C, 5 min) afforded a single allylic alcohol 7 (85%). This alcohol was readily mesylated to give 8 (1.5 equiv of MsCl and 3 equiv of Et_3N, CH_2Cl_2, 0°C, 10 min) and the mesyl group on 8 was nucleophilically displaced by lithium azide (1.5 equiv in DMSO-HMPA, 24°C, 16h) with the expected inversion of configuration to afford the β-azide 9 [84%, IR ($CHCl_3$) 2120 cm^{-1}, ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.34 and 1.38 (2s, 3H each), 4.16 (s, 2H), 4.35 (s, 1H), 4.57 (m, 3H), 5.11 (d, J = 5.5 Hz, 1H), 5.75 (s, 1H), 7.21 (m, 5H)]. Reduction of 9 with 5 equiv of 1,3-propanedithiol and 5 equiv of triethylamine in absolute methanol[12] (24°C, 16h) gave the 2-cyclopentenylamine 10 [85%, ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.34 and 1.39 (2s, 3H each), 1.57 (s, 2H), 3.93 (s, 1H), 4.14 (s, 2H), 4.38 (d, J = 5.5 Hz, 1H), 4.57 (s, 2H), 5.18 (d, J = 5.5 Hz, 1H), 5.73 (s, 1H), 7.34 (m, 5H)]. In the ^{1}HNMR spectra of both 9 and 10 the anomeric proton (Ha) at δ 4.35 and 3.93, respectively, appeared as a sharp singlet confirming the β-configuration of amino and azido groups. Completion of the remaining adenine moiety was performed by a known three-step sequence[4,5]: (1) condensation of 10 with 2.5 equiv of 5-amino-4,6-dichloropyrimidine in the presence of triethylamine (n-BuOH, reflux, 48h) to give 11 (52%); (2) ring closure with triethyl orthoformate and Ac_2O or HCl to give 12; and (3) treatment with methanolic ammonia (65°C, 24h) to generate 13 [overall yield 58%, $[\alpha]_D^{24}$ -26.1° (c 1.16, $CHCl_3$), ^{1}HNMR ($CDCl_3$, 220 MHz) δ 1.36 and 1.48 (2s, 3H each), 4.28 (s, 2H), 4.63 (s, 2H), 4.74 (d, J = 5.5 Hz, 1H), 5.39 (d, J = 5.5 Hz, 1H), 5.58 (s, 1H), 5.83 (s, 1H), 6.61 (s, 2H), 7.34 (m, 5H), 7.68 (s, 1H), 8.35 (s, 1H)]. Finally, debenzylation of 13 with 5 equiv of boron trichloride in dichloromethane (-78°C, 2h), which was accompanied by removal of the isopropylidene group during work-up, afforded neplanocin A (NPC-A, 14) in 61% yield. Synthetic NPC-A was found to be identical in all respects to natural NPC-A[13] (^{1}HNMR, IR, UV, TLC mobility, and specific rotation). Likewise, the mass spectrum confirmed the molecular weight and showed all the expected diagnostic fragments.[14] When synthetic NPC-A was tested, it displayed potent antitumor activity (ID_{50} 6.5 μM) against P388 cells in culture.

In summary, the synthesis of neplanocin A achieved in this work has permitted (1) the ready utilization of a carbohydrate chiral pool and (2) the facile and efficient generation of cyclopentenone 6 which represents an attractive intermediate for the generation of other purine and pyrimidine neolanocin analogs. Investigations of this nature are currently being undertaken in our laboratory.

Acknowledgement. We thank Dr. James A. Kelley from this laboratory for measuring the mass spectrum and Miss Joanne K. Linevsky for exemplary technical assistance during the summer of 1983.

References and Notes

1. Presented at the 186th ACS Annual Meeting, Washington, D.C., on Aug. 28-Sept. 2, 1983, Abstr. Carb. 19.
2. S. Yaginuma, M. Tsujino, N. Muto, M. Otani, M. Hayashi, F. Ishimura, T. Fuji, S. Watanabe, T. Matsuda, T. Watanabe, and J. Abe, "Current Chemotherapy of Infectious Disease," Proc. 11th Intl. Congr. Chemotherap., 2, 1558 (1979).
3. M. Tsujino, S. Yaginuma, T. Fuji, K. Hayano, T. Matsuda, T. Watanabe, and J. Abe, ibid., 2, 1559 (1979).
4. M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, J. Am. Chem. Soc., 105, 4049 (1983).
5. Y. F. Shealy and J. D. Clayton, J. Am. Chem. Soc., 91, 3075 (1969).
6. M.-I. Lim and V. E. Marquez, Tetrahedron Lett., in press.
7. P. Camps, J. Cardellach, J. Font, R. M. Ortuno, and O. Ponsati, Tetrahedron, 38, 2395 (1982).
8. E. J. Corey and G. T. Kwiatkowski, J. Am. Chem. Soc., 88, 5654 (1966).
9. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
10. P. A. Aristoff, Syn. Commun., 13, 145 (1983).
11. J. L. Luche, J. Am. Chem. Soc., 100, 2226 (1978). For the stereoselective reduction of a similar bicyclic concave-convex system with $NaBH_4$-Ce^{3+}, see: A. B. Smith, III, and R. E. Richmond, J. Am. Chem. Soc., 105, 575 (1983).
12. H. Bayley, D. N. Standring, and J. R. Knowles, Tetrahedron Lett., 3633 (1978).
13. (a) S. Yaginuma, N. Muto, M. Tsujino, Y. Sudate, M. Hayashi, and M. Otani, J. Antibiot., 34, 359 (1981). (b) M. Hayashi, S. Yaginuma, H. Yoshioka, and K. Nakatsu, ibid., 34, 675 (1981). (c) Synthetic NPC-A, $[\alpha]_D^{24}$ -155°(c 0.3, H_2O): Natural NPC-A, $[\alpha]_D^{23}$ -157° (c 0.5, H_2O).
14. The mass spectrum was obtained by fast atom bombardment (FAB) in the positive mode: M/Z 264 $(MH)^+$, 136 $(b + 2H)^+$.

(Received in USA 29 September 1983)