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An Improved Approach to Chiral Cyclopentenone Building Blocks. Total Synthesis of Pentenomycin I and Neplanocin A†

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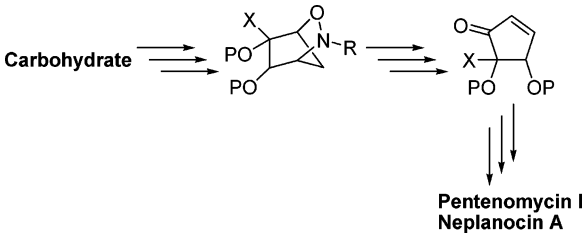

An improved approach to enantiomerically pure hydroxylated cyclopentenones is reported here, which involves intramolecular nitrone cycloaddition of sugar-derived chiral pent-4-enals and hex-5-en-ones-2 followed by N−O bond cleavage, quaternization of the amine thus produced, and finally oxidative elimination of the amino group. Synthesis of pentenomycin I and neplanocin A is described following this methodology.

Introduction

Cyclopentenones (+)-**1** and (−)-**1** are very important chiral building blocks, widely used in organic synthesis.[1] Indeed, a plethora of natural and nonnatural products, such as carbocyclic nucleosides,[2] azasugars,[3] and prostaglandins,[4] have been prepared from these key intermediates. Therefore, work toward their enantioselective syntheses has been published, including both asymmetric[5] and chiral pool[6] approaches. Additionally, pentenomycin I (**2**), a hydroxymethylated cyclopentenone isolated from culture broths of *Streptomyces eurythermus*, is a member of the well-studied family of pentenomycin antibiotics which show combined activity against Gram-positive and Gram-negative bacteria.[7] This branched analogue of deprotected (+)-**1** has been targeted by several groups, and several of its syntheses[8] have been released during the past decades. On the other hand, (−)-neplanocin A (**3**), isolated from *Ampullariella regularis*,[9] and (−)-carbovir (**4**) are two of the most popular carbocyclic nucleosides. They heavily caught the attention of synthetic chemists[10−12] because of their remarkable antiviral and anticancer activity.[13]

† Respectfully dedicated to Prof. G. Karabatsos.

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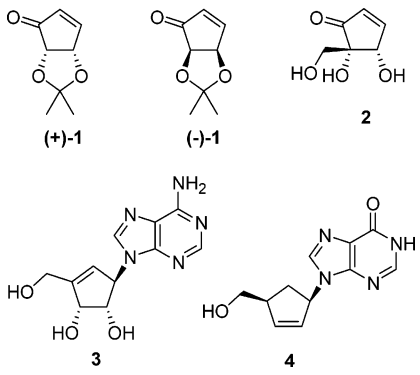
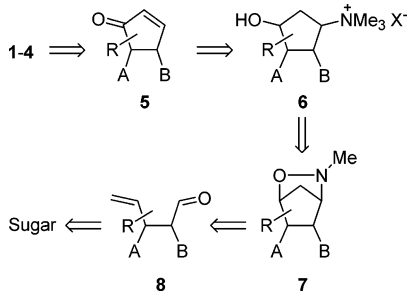


Recently, we have reported a short and efficient total synthesis of **2** from L-arabinose.[14] On the basis of the methodology described in that earlier communication, we now wish to report a new simple method for the preparation of both parent (+)-**1** and (−)-**1** through key nitrone cycloaddition intermediates using again naturally abundant carbohydrates as starting materials. Full details for the preparation of **2** according to optimized procedures as well as elaborate description for the synthesis of the required nitrone adducts[15] are also given. Moreover, the same approach was evaluated in the direct construction of the carbocyclic core of **3** and **4**.

SCHEME 1. Retrosynthetic Plan



Results and Discussion

We envisioned that a common and versatile retrosynthetic plan (Scheme 1) could easily lead to our proposed targets. This plan involves three key steps: (i) cyclopentenone derivative **5** could be accessible from quaternized ammonium salt **6** upon oxidative elimination, (ii) hydroxyamine needed for the preparation of **6** could be obtained from bicyclic isoxazolidine **7** upon reductive rupture of N−O bond, and (iii) carbocycle **7** could be the intramolecular cycloaddition adduct derived from the suitable functionalized sugar derivative **8**. Cyclopentenones **5** are considered to be either simple protected derivatives of **1**−**2** or advanced precursors of nucleosides mimics **3** and **4**.

This concept was originally tested by our group in the synthesis of pentenomycin I[14] and proved to be very successful. Thus, the acetonide of L-erythrose (**9**)[16] was used as the starting point for the preparation of the required pent-4-enal **13** (Scheme 2). The quaternary chiral center was constructed according to a well-established approach,[17,18] namely, the aldol condensation of our sugar substrate with formaldehyde. The resulting alcohol **10** after tritylation[18] was subjected to a Wittig olefination to yield **12**, almost quantitatively. Oxidation of the latter under normal Swern reaction conditions afforded the rather unstable aldehyde **13** which was directly used in a two-step procedure involving formation of the intermediate nitrone and intramolecular cycloaddition upon heating. This sequence produced in a good overall yield the two possible diastereoisomeric adducts

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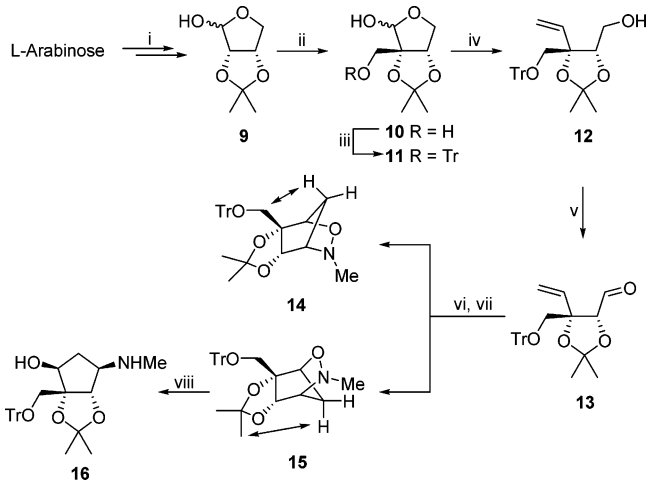
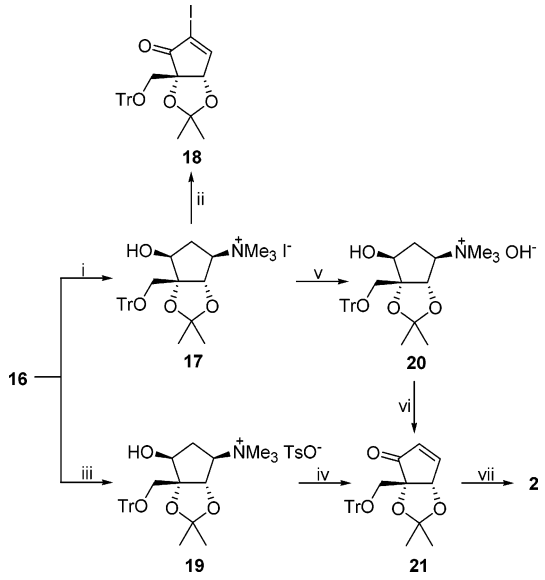
SCHEME 2. Synthesis of Pentenomycin I Precursors[a]



[a] Reagents and conditions: (i) ref 16; (ii) HCHO, K_2CO_3, MeOH, 65 °C, 82%; (iii) TrCl, pyridine, 60 °C, 87%; (iv) $Ph_3P^+CH_3Br^-$, *n*-BuLi, 12-crown-4-ether, −60 to 20 °C, 98%; (v) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, −60 to 20 °C; (vi) MeNHOH·HCl, Na_2CO_3, EtOH, 20 °C; (vii) PhCl, 135 °C, 6% of **14** and 50% of **15** overall from **12**; (viii) Zn, AcOH, Et_2O, 20 °C, 90%.

SCHEME 3. Synthesis of Pentenomycin I[a]



[a] Reagents and conditions: (i) MeI, K_2CO_3, THF, 20 °C; (ii) PDC, CH_2Cl_2, 20 °C; 98% overall from **16**; (iii) MeOTs, K_2CO_3, THF, 65 °C; (iv) as in ii, 66% overall from **16**; (v) Ag_2O, H_2O, 20 °C; (vi) as in ii, 70% overall from **16**; (vii) HCl, Et_2O, 20 °C, 90%.

14 and **15** in a ratio of ca. 1:8, showing that steric hindrance induced by the acetonide is significantly greater than the one trityloxymethyl substituent imposes. The minor diastereoisomer **14** could not be obtained pure; however, its structure was easily deduced from the ^{1}H NMR spectra of its mixture with **15**. The structural assignment of both diastereoisomers was based on NOE studies which revealed the indicated crucial effects (see Scheme 2). The major one was smoothly taken forward in the synthetic scheme giving initially the corresponding amino alcohol **16** upon reductive cleavage of the N−O bond with Zn in the presence of acetic acid. These reaction conditions highly improved the yields of the isolated product in comparison with heterogeneous Pd-$(OH)_2$/C hydrogenolysis performed initially by us.[14] This is possibly explained by accepting a nonreversible absorption of the substrates on the surface of catalyst. Having in place the right carbocyclic core, the next manipulation to deal with was the formation of the enone system. However, this was proved quite tricky since simple quaternization of **16** with methyl iodide (preparation of iodide **17**) and subsequent oxidative cleavage[19] with PDC yielded exclusively the iodinated analogue of pentenomycin I **18** (Scheme 3). It was obvious that iodide is also oxidized to iodine and that the latter simply iodinates the protected pentenomycin derivative **21** formed initially.[20] To overcome this unpleasant result, we sought to examine the oxidative elimination of quaternary ammonium salts with different counteranions. *p*-Toluenesulfonate **19**, formed directly from the corresponding amine, and hydroxide **20**, derived from iodide **17** with anion exchange upon treatment with aqueous silver oxide,[21] led after oxidation to the desired intermediate **21**. It was found, however, that whereas the tosylate path works better in small-scale runs, reproducibility of the reactions is more consistent via the corresponding hydroxides even in larger quantities. Moreover, tosylate reaction mixtures demand tedious purifications since methyl tosylate has a similar R_f with the desired product. The same sequence (e.g., reductive cleavage, quaternization with MeI, exchange with hydroxide and oxidation) was also applied to the mixture of diastereoisomers **14** and **15** furnishing **21** in a similar overall yield (68%). Cyclopentenone **21**, produced either from **14** or **15**, was then deprotected in a straightforward way upon acidic hydrolysis to yield pentenomycin I (**2**).[22]

It was apparent that the synthetic scheme described above is also applicable to the synthesis of the parent cyclopentenones (+)-**1** and (−)-**1**, using the appropriate aminocyclopentitols. These intermediates (**26a** and **31**) could be shortly approached starting from carbohydrates as well. We have reported some time ago[15] a facile entry to chiral aminocyclopentitols in high yield and with excellent stereoselectivity starting from D-ribose (Scheme 4). Application of Vasella's reaction conditions[23] to iodo-derivative **22** led to the required volatile aldehyde **23**. This enal, which could also be derived from L-arabinose,[24]

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(22) Target compounds **(+)-1**, **(−)-1**, **2**, and **3** have physical and spectroscopic properties identical to those reported in the literature. All new compounds gave spectroscopic and analytical data consistent with the proposed structures. These data and detailed experimental procedures are given either in the Experimental Section or in the Supporting Information.

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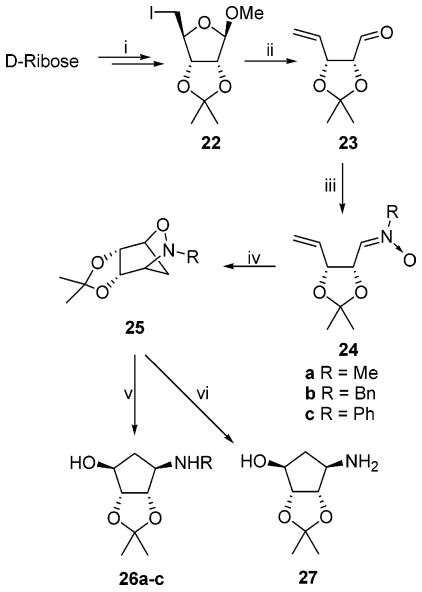
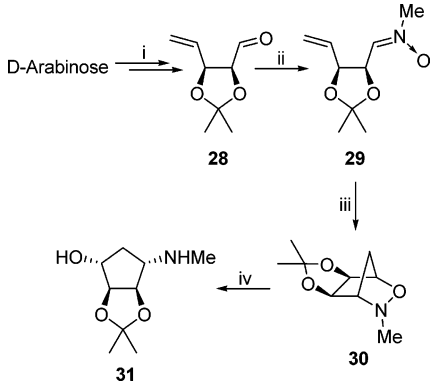
SCHEME 4. Synthesis of Aminocyclopentitols 26−27[a]



[a] Reagents and conditions: (i) ref 24; (ii) Zn, EtOH, 80 °C; (iii) RNHOH·HCl, Na_2CO_3, EtOH, 20 °C; (iv) PhCl, 135 °C, 70% of **25a**, 62% of **25b**, 53% of **25c** overall from **22**; (v) Zn, AcOH, Et_2O, 0−20 °C, 99% for **26a**, 91% for **26b**, 78% for **26c**; (vi) H_2, Pd/C, HCO_2NH_4, MeOH, 20 °C, 98% from **25b**.

SCHEME 5. Synthesis of Aminocyclopentitol 31[a]



[a] Reagents and conditions: (i) ref 25; (ii) MeNHOH·HCl, Na_2CO_3, EtOH, 20 °C; (iii) PhCl, 135 °C, 72% overall from **28**; (iii) Zn, AcOH, Et_2O, 0−20 °C, 95%.

gave with a range of N-substituted hydroxylamines the corresponding nitrones **24**. These dipoles underwent thermal cycloadditions producing **25** as the single products. The N−O bond in bicyclic isoxazolidines **25** was then cleaved to prepare either parent aminocyclopentitol **27** (precursor of noraristeromycin) or N-substituted derivatives **26**, depending on the conditions and substrates involved. Following the same general pathway, *N*-methyl-aminocyclopentitol **31** was synthesized using the enantiomeric pentenal **28** (derives from D-arabinose[25]) as the key intermediate (Scheme 5). Both enantiomeric carbocyclic amines **26a** and **31** were then quaternized with MeI (Scheme 6). To avoid iodination in the next step,

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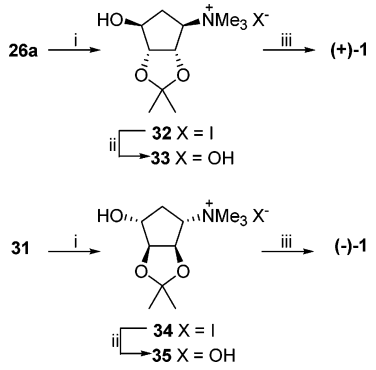
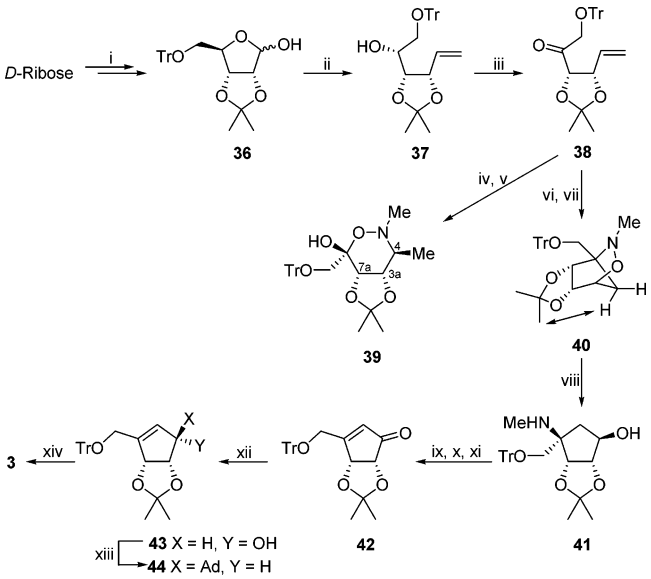
SCHEME 6. Synthesis of Cyclopentenones (+)-1 and (−)-1[a]



[a] Reagents and conditions: (i) MeI, K_2CO_3, THF, 20 °C; (ii) Ag_2O, H_2O, 20 °C; (iii) PDC, CH_2Cl_2, 20 °C, (+)-**1**: 45% overall from **26a**, (−)-**1**: 42% overall from **31**.

SCHEME 7. Synthesis of Neplanocin A[a]



[a] Reagents and conditions: (i) ref 26; (ii) NaH, $Ph_3P^+CH_3Br^-$, THF, DMSO, −10 °C to 60 °C, 93%; (iii) DMSO, DCC, TFA, py, benzene, 0−20 °C, 84%; (iv) MeNHOH·HCl, Na_2CO_3, EtOH, 20 °C; (v) PhCl, 135 °C 84% overall from **38**; (vi) MeNHOH·HCl, pyridine, 20 °C; (vii) as in v, 75% overall from **38**; (viii) Zn, AcOH, Et_2O, 20 °C, 98%; (ix) MeI, K_2CO_3, THF, 20 °C; (x) Ag_2O, H_2O, 20 °C; (xi) PDC, CH_2Cl_2, 20 °C, 60% overall from **41**; (xii) LAH, THF, 0 °C, 100%; (xiii) Ph_3P, DIAD, adenine, THF, 0−20 °C, 63%; (xiv) TFA, 20 °C, 89%.

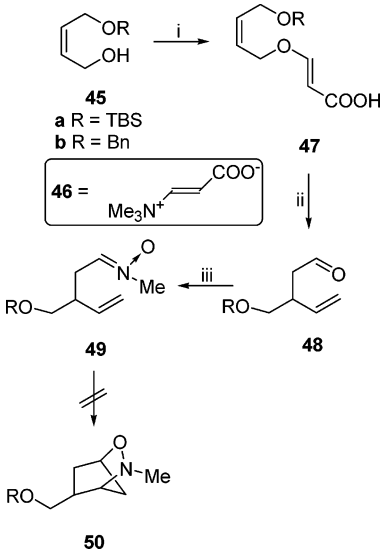
where the enone functionality is formed, the iodide anion was replaced by hydroxide on treatment with Ag_2O to obtain **33** and **35** from **32** and **34**, respectively. Furthermore, oxidation of the secondary hydroxyl groups with PDC gave directly the protected enantiomerically pure cyclopentenones (+)-**1** and (−)-**1** in very good overall yields.[22]

Being acquainted with this methodology, we speculated that enone **38** (Scheme 7) could result in the branched cyclopentenone **42**, which is the direct precursor of neplanocin A and related carbocyclic nucleosides.[11h] This goal was realized using D-ribose as starting material through its suitably protected[26] derivative **36**. Thus, Wittig olefination of lactol **36** gave alkene **37**, which upon

Moffatt oxidation afforded **38**. Marginal C-2 epimerisation (sugar numbering) was observed during the Wittig reaction. It seemed that template **38** would smoothly enter the next steps, for example, nitrone formation and cycloaddition to produce **40**. Surprisingly, previously applied conditions, where nitrone was formed in the presence of sodium carbonate, led almost exclusively to the reverse Cope rearrangement[27] product **39** whereas the desired adduct **40** was formed only in traces.[28] The structure of the unexpected oxazine **39** was undoubtly confirmed from its spectral data.[29] To increase the yield of the desired adduct **40**, we thoroughly investigated different bases and reaction temperatures. We were delighted to discover that treatment of **38** with MeNHOH in pyridine at 25 °C affords the desired intermediate nitrone, which without isolation is converted to isoxazolidine **40** by refluxing in chlorobenzene for 1 h in 75% overall yield. This event is not fully rationalized and further exploration of the specific role of the base is currently underway. The structural assignment of **40** was based again on NOE studies (see Scheme 7). Uneventfully, **40** was easily converted to **42** in high overall yield, according to the general procedure, namely, N−O bond cleavage by Zn in AcOH to produce **41**, quaternization of the amine produced with excess of MeI, and replacement of iodide by hydroxide on treatment with Ag_2O, followed by standard PDC oxidation of the secondary hydroxyl group. Cyclopentenone **42** is known to give neplanocin A in three steps.[11h] Indeed, highly stereoselective $LiAlH_4$ reduction of keto group led to the formation of **43**, as the single diastereoisomer isolated. Then, introduction of the adenine moiety under Mitsunobu conditions (preparation of nucleoside **44**) and full deprotection by neat trifluoroacetic acid afforded **3**.[22]

Next, we were keen to explore the possibility of synthesizing carbovir (**4**) according to the general scheme. The initial plan involved the preparation of enals **48** and subsequently the investigation of cycloaddition reactions (Scheme 8). The results of this model scheme could be transferred to a chiral approach leading finally to the required enantiopure cyclopentenone[30] ready for the introduction of the purine base and the completion of the synthesis. Therefore, two different monoprotected derivatives[31,32] of *cis*-butene-1,4-diol (**45**) were selected as the readily available substrates of choice to check the role of the bulkiness of the protecting groups in the following reactions. Condensation of alcohols **45** with betaine **46**[33] yielded the acrylic acid derivatives **47** which in turn served as substrates for Claisen rearrangements.[34,35] Pentenals **48** were isolated in good overall yields[36] through this two-step sequence, whereas a direct acid-catalyzed Johnson-Claisen rearrangement[37] of *cis*-butene-1,4-diol in the presence of ortho esters produced the corresponding enoates in disappointing yields. Formation of the nitrones **49** was followed by a direct attempt to reach adducts **50** upon heating, but only slow decomposition of the dipoles was observed. Considering that using crude nitrones in the cycloaddition reactions was the issue, we purified them and reexamined their reactivity. Unexpectedly, we were unable to detect the formation of the desired isoxazolidines although several reaction conditions were examined for both entries. It seems quite intriguing that these 3-substituted pentenals failed to undergo cycloaddition taking into account that more hindered systems, like enone **38** derived nitrone, react smoothly under similar conditions. The most plausible explanation we can adopt is that these systems prefer to keep apart the two reacting sites (e.g., nitrone and double bond) and only in cases where the dipole and dipolarphile are locked into close proximity does the intramolecular addition take place.[38] We are currently engaged in further investigation of this unexpected observation.

SCHEME 8. A Model Approach toward Carbovir[a]



[a] Reagents and conditions: (i) for **47a**: NaH, **46**, THF, 60 °C, 91%, for **47b** see ref 34; (ii) for **48a**: 155 °C, 15 mmHg, 80%, for **48b** see ref 34; (iii) MeNHOH·HCl, Na_2CO_3, EtOH, 20 °C, 76% for **49a**, 78% for **49b**.

In conclusion, the work described in this article presents a short, efficient, and general synthetic approach for the preparation of enantiomeric cyclopentenones.

(26) Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A.; Shin, D. H.; Jeong, L. S. *J. Org. Chem.* **2004**, *69*, 2634−2636.
(27) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243−269.
(28) Very slow formation of oxazine **39** was detected during the preparation of the corresponding nitrone whereas heating in chlorobenzene substantially accelerated this event.
(29) Crucial for the determination of stereochemistry of C-4 was the observation of a J_{ax-ax} coupling constant between H-3a and H-4 (9.2 Hz) whereas H-3a and H-7a have a smaller coupling constant of 5.5 Hz (J_{ax-eq}).
(30) The same cyclopentenone moiety could also serve as the direct precursor for the synthesis of other carbocyclic nucleosides, e.g., Abacavir.
(31) Monosilylated derivative **45a** was prepared according to Kozlowski, M. C.; Bartlett, P. A. *J. Org. Chem.* **1996**, *61*, 7681−7696.
(32) Monobenzylated derivative **45b** is commercially available.
(33) (a) Büchi, G.; Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406−5408. (b) Vogel, D. E.; Büchi, G. *Org. Synth.* **1988**, *66*, 29−36.
(34) Benzylated derivative **47b** was lately prepared according to this method, see: Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145−4148.
(35) For recent reviews on Claisen rearrangements, see: (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 7.2, pp 827−873. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882, (c) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50.
(36) Pentenal **48a** was found to easily decompose upon column chromatography purification. Therefore, it was used crude in the nitrone formation.
(37) Rico, R.; Zapico, J.; Bermejo, F.; Bamidele Sanni, S.; Garcia-Granda, S. *Tetrahedron: Asymmetry* **1998**, *9*, 293−303.
(38) Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.* **1994**, *59*, 4375−4377.

Thus, synthesis of the parent ones, (+)-**1** and (−)-**1**, two widely used key intermediates in organic synthesis, was accomplished in a straightforward manner. Moreover, branched analogues such as pentenomycin I (**2**) and the pseudo-sugar moiety of neplanocin A (**3**) are easily approached according to the same methodology.

Experimental Section

General Procedure (A): Preparation of Nitrones in the Presence of Na_2CO_3. The crude aldehyde obtained as described in each case was dissolved in EtOH 95% (10 mL/mmol), and RNHOH·HCl (1.2−2.4 equiv) along with Na_2CO_3 (2−3 equiv) was added. The mixture was stirred at RT for 1−4 h, while the reaction progress was monitored with TLC. Then, the solids were removed by filtration, and the filtrate was concentrated. The resulting nitrone was used in the cycloaddition reaction as it was unless otherwise mentioned.

General Procedure (B): Cycloaddition Reactions. The residue, which contained the intermediate nitrone, was dissolved in chlorobenzene (10 mL/mmol), and the solution was heated at reflux for 1−2 h, while the reaction progress was monitored with TLC. Then, the solvent was evaporated and the residue was purified by column chromatography.

General Procedure (C): Reductive Cleavage of Isoxazolidines with Zn. To a solution of isoxazolidine in Et_2O (20 mL/mmol) kept in an icebath were added glacial acetic acid (2.2 mL/mmol) and activated[39] Zn dust (15 equiv). The suspension was allowed to reach RT and was stirred vigorously for 24 h. Then, the solids were filtered off and the filtrate was neutralized with 2 M NaOH under cooling. The organic layer was washed with H_2O (150 mL), and the aqueous one was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried and concentrated in a vacuum and the residue was purified by column chromatography.[40]

General Procedure (D): Preparation of Ammonium Iodides. Amino alcohol was dissolved in dry THF (20 mL/mmol), and K_2CO_3 (2.5 equiv) was added. Subsequently, MeI (20 equiv) was added portionly under an inert atmosphere. The mixture was stirred at RT for 20 h and after evaporating off the volatiles the resulting solid (ammonium iodide derivative) was used in the next reaction without any further purification.

General Procedure (E): Preparation of Ammonium Hydroxides. Crude iodide was dissolved in water (20 mL/mmol). Ag_2O (1.5 equiv) was added under vigorous stirring and the mixture was allowed to react for 48 h at RT. After filtration, the solvent was evaporated giving a crude solid, which was used in the next reaction without any further purification.

General Procedure (F): Oxidative Elimination with PDC. Crude iodide or tosylate or hydroxide prepared as described in each case was suspended in dry CH_2Cl_2 (20 mL/mmol) in the presence of PDC (1.3 equiv) at RT. After 4 h, the solution was washed with water (20 mL) and dried, and the organic solvent was removed in a vacuum at RT. The residue was purified by column chromatography.

(1*R*)-1-[(4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]-2-trityloxy-1-ethanol (37). NaH (95%) (593 mg, 23.5 mmol) was suspended in dry THF (15 mL), and DMSO (3.35 mL, 47.0 mmol) was added at 0 °C. The mixture was stirred under an argon atmosphere for 30 min, and then it was transferred to a suspension of methyl triphenylphosphonium bromide (8.45 g, 23.7 mmol) in dry THF (25 mL) at −5 °C. Stirring was continued for 90 min while the temperature was kept between −5 to 0 °C. Then, the mixture was recooled to −10 °C and a solution of **36** (3.25 g, 7.5 mmol) in dry THF (25 mL) was added dropwise. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm to RT, was left for 1 h, and warmed to reflux for 2 h. The reaction after cooling was quenched by the addition of saturated aqueous NH_4Cl (5 mL). CH_2Cl_2 (50 mL) was added, and the mixture was washed with water (100 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL), the combined organic phases were dried, and the solvent was evaporated. The residue was purified by column chromatography (EtOAc/hexanes = 1/12) to give alcohol **37** (2.98 g, 93%) as a white solid: mp 78−80 °C (lit.[26] 78.2−79.5 °C); $[\alpha]_D^{25}$ −5.2° (*c* 2.3, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ −5.0° (*c* 2.2, $CHCl_3$)]; FTIR (neat film) 3468, 3058, 2986, 2933, 2878, 1595, 1491, 1449, 1381, 1217, 1059, 1032, 874 cm^{-1}; ^1H NMR and ^{13}C NMR spectra are identical with those reported in the literature;[26] HRMS *m/e* calcd for $C_{28}H_{30}O_4Na$: [(M + Na)$^+$]: 453.2036; found: 453.2036.

1-[(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]-2-trityloxy1-ethanone (38). To a solution of pyridine (1.2 mL, 7.0 mmol) in dry benzene (25 mL), TFA (0.6 mL, 7.0 mmol) and DMSO (2 mL, 28 mmol) were added. This was added to a solution of **37** (2.96 g, 6.9 mmol) in dry benzene (30 mL), and the mixture was cooled to 0 °C. Then, DCC (3.6 g, 17.5 mmol) was added under an inert atmosphere and the resulting solution was allowed to warm to RT. After 20 h of stirring, ether (30 mL) was added, and dicyclohexylurea precipitated as a white solid. The clear solution obtained by filtration was washed with water (50 mL) and the aqueous phase was extracted with dicloromethane (2 × 100 mL). The combined organic phases were dried and the solvent was evaporated off. The residue was purified by column chromatography (EtOAc/hexanes = 1/15) to give ketone **38** (2.47 g, 84%) as a white solid: mp 105−107 °C (lit.[26] mp 106.8−107.6 °C); $[\alpha]_D^{25}$ −18.9° (*c* 1.6, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ −19.1° (*c* 1.73, $CHCl_3$)]; FTIR (neat film) 3059, 3031, 2988, 2927, 2915, 2861, 1733, 1597, 1490, 1450, 1378, 1260, 1213, 1158, 1108, 1001, 938, 871 cm^{-1}; ^1H NMR and ^{13}C NMR spectra are identical with those reported in the literature;[26] HRMS *m/e* calcd for $C_{28}H_{28}O_4Na$: [(M + Na)$^+$]: 451.1880, found: 451.1881.

(3a*S*,4*S*,7*R*,7a*S*)-2,2,4,5-Tetramethyl-7-trityloxymethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (39). Prepared from **38** (925 mg, 2.2 mmol) following successively general procedures A and B. Elution with EtOAc/hexanes = 1:7 to obtain **39** (880 mg, 84%, overall from **38**) as a foam: $[\alpha]_D^{25}$ +29.7° (*c* 1.1, $CHCl_3$); FTIR (neat film) 3445, 3088, 3061, 3023, 2979, 2934, 2878, 1598, 1489, 1463, 1447, 1417, 1372, 1219, 1073, 941, 780, 747, 702, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 7.9 Hz, 6H), 7−32−7.20 (m, 9H), 4.27 (bs, 1H), 4.16 (d, J = 5.5 Hz, 1H), 3.94 (dd, J = 9.2, 5.5 Hz, 1H), 3.26 (s, 2H), 2.60 (s, 3H), 2.56−2.48 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.10 (d, J = 6.1 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 128.8, 127.7, 127.0, 109.4, 97.4, 86.7, 77.1, 74.3, 65.2, 62.6, 42.4, 28.0, 26.2, 14.9; HRMS *m/e* calcd for $C_{29}H_{33}NO_5$-Na: [(M + Na)$^+$]: 498.2251, found: 498.2251.

(1*R*,2*R*,6*R*,7*S*)-4,4,9-Trimethyl-1-trityloxymethyl-3,5,8-trioxa-9-aza-tricyclo [5.2.1.0^{2,6}]decane (40). Ketone **38** (2.4 g, 5.6 mmol) was dissolved in dry pyridine (60 mL) and MeNHOH·HCl (1.64 g, 19.6 mmol) was added at RT. The resulting solution was stirred under an inert atmosphere for 24 h until complete consumption of the starting material. Then, the solvent was evaporated and the crude nitrone was dissolved in chlorobenzene (50 mL). The resulting solution was heated to reflux for 1 h. Evaporation of the solvent afforded a residue which was purified by (EtOAc/hexanes = 1/10) to give adduct **40** (1.92 g, 75%) as an amorphous solid: $[\alpha]_D^{25}$ −33.7° (*c* 0.8, $CHCl_3$); FTIR (neat film) 3058, 2986, 2929, 2885, 1634, 1491, 1449, 1375, 1208, 1072, 864, 768, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.47 (m, 6H), 7.33−7.21 (m, 9H), 4.39−4.29 (m, 3H), 3.60 (d, J = 10.4 Hz, 1H), 3.34 (d, J = 10.4 Hz, 1H), 2.41 (s, 3H), 1.91−1.81 (m, 2H), 1.42 (s, 3H), 1.33 (s,

(39) Casey, M.; Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*; Blackie and Son: Glasgow, U.K., 1991; p 49.

(40) Optical rotation value for **27** was mistakenly assigned in our original comunication paper. The correct value is given here and it is in accordance with the one given in the literature, see: Marco-Contelles, J.; Rodríguez-Fernández, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2249−2256.

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 128.8, 127.8, 127.1, 111.1, 86.8, 80.1, 79.6, 71.9, 58.4, 41.6, 29.7, 29.5, 25.8, 24.6; HRMS *m/e* calcd for $C_{29}H_{31}NO_4Na$: [(M + Na)$^+$]: 480.2145, found: 480.2144.

(3a*S*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-methylamino-6-trityloxymethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (41). Prepared from **40** (915 mg, 2 mmol) following general procedure C. Elution with EtOAc/hexanes = 2:1 to obtain amino alcohol **41** (900 mg, 98%) as an oil: $[\alpha]_D^{25}$ −8.2° (*c* 2.6, $CHCl_3$); FTIR (neat film) 3325, 3022, 3058, 2933, 1597, 1491, 1449, 1381, 1210, 1122, 1059, 889 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.49 (m, 6H), 7.32−7.20 (m, 9H), 4.68 (d, *J* = 5.5 Hz, 1H), 4.46 (d, *J* = 5.5 Hz, 1H), 3.97 (d, *J* = 4.3 Hz, 1H), 3.38 (d, *J* = 9.5 Hz, 1H), 3.37 (bs, 2H), 3.02 (d, *J* = 9.5 Hz, 1H), 1.88 (s, 3H), 1.71 (bd, *J* = 14.0 Hz, 1H), 1.56 (dd, *J* = 14.0, 4.3 Hz, 1H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 128.6, 127.6, 126.9, 110.0, 87.0, 86.4, 83.9, 75.9, 68.8, 58.8, 34.7, 25.4, 26.2, 24.0; HRMS *m/e* calcd for $C_{29}H_{33}NO_4Na$: [(M + Na)$^+$]: 460.2482, found: 460.2481.

(3a*R*,6a*R*)-2,2-Dimethyl-6-trityloxymethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one (42). Prepared from **41** (355 mg, 0.77 mmol) following successively general procedures D−F). Elution with EtOAc/hexanes = 1:8 to obtain cyclopentenone **42** (198 mg, 60%, overall from **41**) as a white solid: mp 160−162 °C (lit.[26] 161.2−163.2 °C); $[\alpha]_D^{25}$ +10.8° (*c* 2.0, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ +10.56° (*c* 1.8, $CHCl_3$)]; FTIR (neat film) 3058, 3034, 2990, 2935, 1724, 1626, 1491, 1448, 1373, 1209, 1152, 1080, 871, 766, 703 cm^{-1}; ^{1}H NMR, and ^{13}C NMR spectra are identical with those reported in the literature;[26] HRMS *m/e* calcd for $C_{28}H_{26}O_4Na$: [(M + Na)$^+$]: 449.1723, found: 449.1721.

(3a*S*,4*S*,6a*R*)-2,2-Dimethyl-6-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta [*d*][1,3]dioxol-4-ol (43). To a solution of enone **42** (292 mg, 0.69 mmol) in dry THF (10 mL) was added $LiAlH_4$ (40 mg, 1 mmol) at −5 °C. The mixture was stirred at this temperature for 2 h under an inert atmosphere. At this point, the reaction was quenched by the addition of EtOAc (5 mL). Then, the solids were filtered off and the solvent was removed by evaporation. The residue was purified by column chromatography (EtOAc/hexanes = 1/6) to give alcohol **43** (293 mg, 100%) as a white solid: mp 137−139 °C (lit.[11h] 138−138.5 °C); $[\alpha]_D^{25}$ +29.9° (*c* 1.5, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ +29.4° (*c* 1.52, $CHCl_3$)]; IR, ^{1}H NMR and ^{13}C NMR spectra are identical with those reported in the literature;[11h] HRMS *m/e* calcd for $C_{28}H_{28}O_4Na$: [(M + Na)$^+$]: 451.1880, found: 451.1877.

9-((3aS,4R,6aR)-4,6a-Dihydro-6-(trityloxymethyl)-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-4-yl)-9H-purin-6-amine (44). A solution of alcohol **43** (198 mg, 0.46 mmol), Ph_3P (243 mg, 0.93 mmol), and adenine (75 mg, 0.56 mmol) in dry THF (6 mL) was kept at 0 °C. DIAD (0.11 mL, 0.56 mmol) was added dropwise under an argon atmosphere, and the resulting mixture was allowed to reach room temperature under stirring for 3 h. The mixture was filtered to remove the resulting solids and then was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexanes = 1/1) to give protected neplanocin A **44** (157 mg, 63%) as a thick oil: $[\alpha]_D^{25}$ −25.2° (*c* 1.7, $CHCl_3$); FTIR (neat film) 3439, 3055, 2974, 2923, 2856, 1580, 1554, 1448, 1356, 1111, 1078, 717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.65 (s, 1H), 7.47−7.44 (m, 9H), 7.29 (t, *J* = 7.0 Hz, 6H), 6.04 (bs, 1H), 5.61 (bs, 1H), 5.24 (d, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 6.0 Hz, 1H), 4.00 (d, *J* = 15.0 Hz, 1H), 3.85 (d, *J* = 15.0 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 149.8, 149.4, 143.7, 132.1, 132.0, 129.3, 128.5, 127.9, 127.1, 122.3, 112.4, 87.2, 84.7, 84.2, 64.3, 61.4, 27.5, 26.1; HRMS *m/e* calcd for $C_{33}H_{31}N_5O_3Na$: [(M + Na)$^+$]: 568.2319, found: 568.2322.

(−)-Neplanocin A (3). Protected neplanocin A (**44**, 130 mg, 0.24 mmol) was dissolved in TFA (6 mL) under an inert atmosphere at room temperature and was left stirring for 4 h. Then, volatiles were evaporated off at 20 °C, and the residue was refluxed with ether. The supernatant ethereal face was discarded and the same procedure was repeated twice giving a semicrystalline material which was then dissolved in boiling methanol. This cloudy solution was filtered through a short pad of Celite, and the filtrate was alkalized with the addition of 15% aqueous NH_4OH to pH 11−12. The resulting solution was evaporated to dryness at 35 °C to give a gummy residue. The latter was crystallized upon trituration with 70% aqueous EtOH (56 mg, 89%): mp 211−213 °C (lit.[11b] 212−213 °C); $[\alpha]_D^{25}$ −153.5° (*c* 0.3, H_2O) [lit.[11b] $[\alpha]_D^{25}$ −153.8° (*c* 0.3, H_2O)]; ^{1}H NMR, and ^{13}C NMR spectra are identical with those reported in the literature;[11b] HRMS *m/e* calcd for $C_{11}H_{13}N_5O_3Na$ [(M + Na)$^+$]: 286.2424, found: 286.2425.

Acknowledgment. A fellowship to C. I. S. from the Hellenic Ministry of Education is gratefully acknowledged.

Supporting Information Available: Experimental and spectral data of the compounds in Schemes 2−6 and 8. ^{1}H and ^{13}C NMR spectra of isolated intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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