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Rapid syntheses of either enantiomer of important carbocyclic nucleoside precursors†

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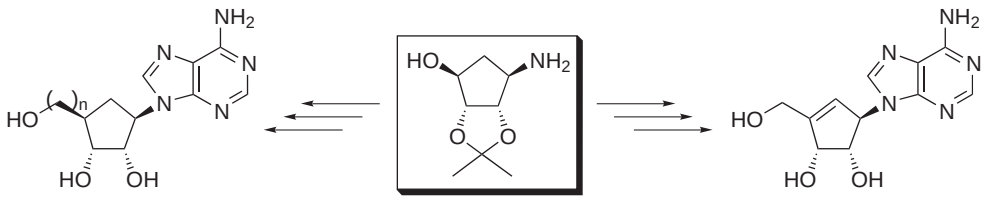
Abstract

The syntheses of both enantiomers of aminocyclopentanetriol **1**, a versatile carbocyclic nucleoside precursor, is reported utilizing an amino acid-derived acylnitroso Diels–Alder cycloaddition. The sequence is practical and proceeds in an overall yield of 36% from the D-alanine-derived hydroxamic acid.

The design and syntheses of carbocyclic nucleosides has led to the discovery of potent medicinal agents that resist metabolism due to the replacement of an oxygen atom of the parent furanose with a methylene unit.[1] Amino alcohol **1** has been reported as a key intermediate in the synthesis of the antiviral carbocyclic nucleoside 5′-noraristeromycin (**2**),[2] albeit in racemic form. 5′-Noraristeromycin (**2**) was developed[2,3] by Schneller as a non-toxic analog to the potent antiviral agent aristeromycin (**3**).[4,5] The synthesis of racemic neplanocin A (**4**) by Jung also utilized **1** as a key intermediate.[6] Neplanocin A (**4**), is an antitumor compound isolated from *Ampullariella regularis*.[7]



2, n=0 (-)-5'-noraristeromycin
3, n=1 aristeromycin

1

4, neplanocin A

In both of the above cases, racemic **1** was generated utilizing the acylnitroso Diels–Alder cycloaddition[8] as a method to aminohydroxylate a 1,3-diene. Other nitroso Diels–Alder reac-

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† This paper is dedicated to Professor Harry H. Wasserman on the occasion of his 80th birthday.

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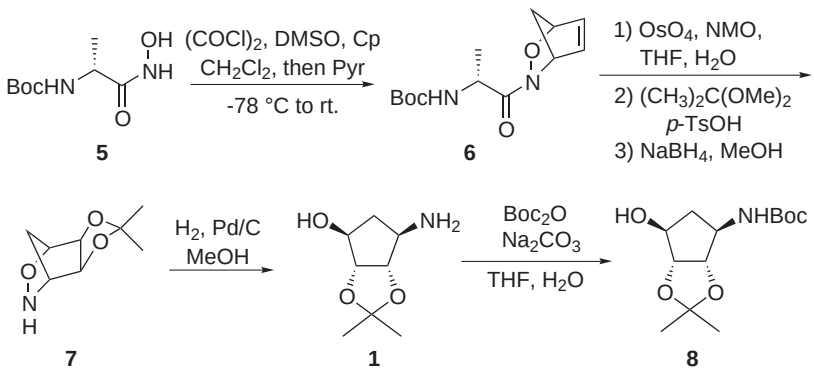
tions have also been reported for the preparation of (±)-**1**.[9,10] A synthesis of enantiomerically pure **1** was reported utilizing a camphor-derived hydroxamic acid as a chiral auxiliary in an acylnitroso Diels–Alder cycloaddition.[9a] We report here the syntheses of **1** and *ent*-**1** utilizing common methodology derived from D- or L-amino acids as chiral auxiliaries in the amino acid-derived acylnitroso Diels–Alder cycloaddition refined in our group.[11] The synthesis reported here complements earlier syntheses due to the ease of removal of the amino acid chiral auxiliary and the ability to utilize either enantiomer of the amino acid delivering either of the desired enantiomers, **1** or *ent*-**1**. In addition, a diastereospecific dihydroxylation provided the desired relative stereochemistry of the aminocyclopentanetriol.

The synthesis of **1** began with readily available hydroxamic acid **5**, derived from D-Ala. Trapping of the transient acylnitroso intermediate, generated from the oxidation of **5** under Swern conditions,[12] with cyclopentadiene generated cycloadduct **6** as a 5.9:1 mixture of readily separable diastereomers in a 78% combined yield (50% yield of the single diastereomer shown). Dihydroxylation of **6** provided a single diastereomer[11b,13] that was protected as the corresponding acetonide in 95% yield for the two steps. Reductive removal of the amino acid auxiliary occurred under mild conditions, mediated by $NaBH_4$ in MeOH, to provide enantiomerically pure **7** in 76% yield. It is instructive to point out that **7** was isolated from **6** without any chromatographic separation of the intermediates. In addition, **7** could be purified by standard extractive methods. Hydrogenation of **7** utilizing Pd/C in MeOH under an atmosphere of H_2 provided the desired amino alcohol, **1**, in quantitative yield. An analogous sequence of steps was carried out utilizing the enantiomer of **5**, L-Ala-NHOH, providing *ent*-**1**. The free amines of **1** or *ent*-**1** were then treated separately with Boc_2O in the presence of Na_2CO_3 in THF/H_2O to provide Boc-protected amine **8** or *ent*-**8** in 83 and 84% yields, respectively. The enantiomeric purity of **8** and *ent*-**8** was confirmed by conversion to the corresponding Mosher's esters. Each were demonstrated to be of >98% ee by comparison of their respective ^{19}F NMR spectra.



In conclusion, we have demonstrated the ability to synthesize both enantiomeric precursors **1** and *ent*-**1** to the carbocyclic nucleosides 5′-noraristeromycin (**2**) and neplanocin A (**4**). Each enantiomer is considered a valuable intermediate for the syntheses of 5′-norcarbocyclic nucleosides. The ability to synthesize **1** or *ent*-**1** rests in the choice of the configuration of the amino acid chiral auxiliary. The overall yield of **1** from D-Ala-NHOH (**5**) was 36%. The methodology is not only efficient and practical, but utilized a limited amount of chromatography.

Acknowledgements

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References

1. (a) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev*. **1986**, *6*, 1. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Chailand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (d) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.
2. Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem*. **1992**, *35*, 3372.
3. (a) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267. (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem*. **1994**, *37*, 1382. (c) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerq, E. *J. Med. Chem*. **1994**, *37*, 551. (d) Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095. (e) Seley, K. L.; Schneller, S. W.; Korba, B. *J. Med. Chem*. **1998**, *41*, 2168.
4. Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc*. **1966**, *88*, 3885.
5. For alternative routes to 5′-noraristeromycin or neplanocin A see: (a) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc*. **2000**, *122*, 5947. (b) Trost, B. M.; Kuo, G.-H., Benneche, T. *J. Am. Chem. Soc*. **1988**, *110*, 621. (c) Merlo, V.; Reece, F. J.; Roberts, S. M.; Gregson, M.; Storer, R. *J. Chem. Soc*., *Perkin Trans. 1* **1993**, 1717.
6. Jung, M.; Offenbacher, G.; Retey, J. *Helv. Chim. Acta* **1983**, *66*, 1915.
7. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot*. **1981**, *34*, 359.
8. Kirby, G. W. *Chem. Soc. Rev*. **1977**, *6*, 1–24.
9. (a) Lin, C.-C.; Wang, Y.-C.; Hsu, J.-L.; Chiang, C.-C.; Su, D.-W.; Yan, T.-H. *J. Org. Chem*. **1997**, *62* 3806. (b) Cowart, M.; Bennett, M. J.; Kerwin, J. F. *J. Org. Chem*. **1999**, *64*, 2240. (c) Ranganathan, S.; George, K. S. *Tetrahedron* **1997**, *53*, 3347.
10. For non-acylnitroso Diels–Alder approaches see: (a) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc*., *Perkin Trans. 1* **1994**, 613. (b) Marco-Contelles, J.; Rodriguez-Fernandez, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2249. (c) Farkas, F.; Sequin, U.; Bur, D.; Zehnder, M. *Tetrahedron* **1992**, *48*, 103. (d) Ref. 6a.
11. (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (b) Ritter, A. R.; Miller, M. J. *J. Org. Chem*. **1994**, *59*, 4602. (c) Ritter, A. R.; Miller, M. J. *Tetrahedron Lett*. **1994**, *35*, 9379. (d) Vogt, P. F.; Miller, M. J.; Mulvihill, M. J.; Ramurthy, S.; Savela, G. C.; Ritter, A. R. *Enantiomer* **1997**, *2*, 367. (e) Vogt, P. F.; Hansel, J.-G.; Miller, M. J. *Tetrahedron Lett*. **1997**, *38*, 2803. (f) Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R.; Miller, M. J. *Tetrahedron Lett*. **1995**, *36*, 2913. (g) Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem*. **1995**, *60*, 5808.
12. Martin, S. F.; Hartmann, M.; Josey, J. A. *Tetrahedron Lett*. **1992**, *33*, 3583.
13. **(1*S*,4*R*,5*S*,6*R*)-2,3-Oxazabicyclo[2.2.1]heptane-5,6-dioxy-isopropylidene (7)**. To **6**[11b] (0.647 g, 2.41 mmol) in THF/H_2O (5:1, 30 mL) was added *N*-methyl-morpholine-*N*-oxide (0.594 g, 5.07 mmol) followed by OsO_4 (0.3 mol%). After 30 min, EtOAc and 5% $Na_2S_2O_5$ (aq.) were added. The layers were separated and the aqueous layer was saturated with NaCl then extracted with EtOAc. The combined organics were washed with saturated $NaHCO_3$ and brine, then dried (Mg_2SO_4), filtered and concentrated to give a yellow oil that was dissolved in 2,2-dimethoxypropane (15.0 mL), and *p*-TsOH·H_2O (0.047 g, 0.156 mmol) was added. After 20 min, the reaction was partitioned between Et_2O and saturated $NaHCO_3$. The layers were separated and the aqueous was extracted with Et_2O. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford 0.783 g (95%) of a white solid.
    To the white solid (0.610 g, 1.78 mmol) from above in MeOH (10.0 mL) was added $NaBH_4$ (0.269 g, 7.12 mmol). After 30 min, the reaction mixture was partitioned between Et_2O and 1N HCl. The layers were separated and the

organic layer was washed with 1N HCl. The combined acidic aqueous layers were extracted with Et_2O then brought to pH 10 with saturated $NaHCO_3$ followed by 2.5 M NaOH under a blanket of EtOAc. The basic aqueous layer was saturated with NaCl and extracted with EtOAc (3×). The combined EtOAc extracts were washed with brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light yellow solid that could be further purified with silica gel chromatography utilizing 70% EtOAc/hexanes to give 0.232 g (76%) of **7** as a white solid. $R_f = 0.40$ (60% EtOAc/hexanes); $[\alpha]_D^{20} = +54.9$ (*c* 1.03, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (m, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.77 (m, 1H), 2.28 (m, 1H), 1.64 (m, 1H), 1.45 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.7, 78.9, 78.8, 75.3, 58.6, 33.6, 25.7, 24.2; MS *m*/*z* (MH^+) calcd for $C_8H_{14}NO_3$ 172.0974, found 172.0979.

Representative procedure for the preparation of bicycle **8** or *ent*-**8**. **(1*S*,2*R*,3*S*,4*R*)-2,3-Dioxy-isopropylidene-4-amino-(*tert*-butyloxycarbonyl)-1,2,3-cyclopentane-triol (1)**. Bicycle **7** (0.102 g, 0.596 mmol) in MeOH (3.0 mL) was reduced under an atmosphere of H_2 in the presence 10% Pd/C for 30 min. Then the reaction was purged with Ar and filtered through a short pad of Celite. After washing the Celite pad with MeOH until the washings were no longer ninhydrin positive, the washes were concentrated to give amine **1** as a white solid. Mp = 125.5–127°C (Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (dd, $J = 5.5$, 1.5 Hz, 1H), 4.41 (dd, $J = 5.0$, 1.5 Hz, 1H), 4.10 (m, 1H), 3.61 (dd, $J = 2.4$, 1.0 Hz, 1H), 2.09 (ddd, $J = 13.5$, 9.0, 4.5 Hz, 2H), 1.82 (bs, 3H), 1.65 (d, $J = 14.5$ Hz, 2H), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.7, 86.9, 85.7, 77.6, 57.6, 40.0, 26.1, 23.7.

The solid was partitioned between THF/H_2O (1:1, 3.0 mL) and treated sequentially with Na_2CO_3 (0.070 g, 0.660 mmol) and Boc_2O (0.142 g, 0.651 mmol). After 2 h, the reaction was extracted with EtOAc (2×). The combined organic layers were washed with brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid that was purified on silica gel utilizing 50% EtOAc/hexanes to give 0.136 g (84%) of **8** as a white solid. Mp = 99.5–101°C (EtOAc/hexanes), $[\alpha]_D^{20} = +22.2$ (*c* 0.78, CH_2Cl_2), $[\alpha]_D^{20} = -20.2$ (*c* 0.95, CH_2Cl_2) for *ent*-**8**, $R_f = 0.27$ (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, $J = 8.5$ Hz, 1H), 5.35 (d, $J = 3.0$ Hz, 1H), 4.34 (m, 2H), 4.0 (m, 1H), 3.75 (m, 1H), 2.02 (ddd, $J = 5.0$, 6.2, 13.3 Hz, 1H), 1.50 (d, $J = 14.0$ Hz, 1H) 1.39 (s, 9H), 1.31 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.1, 110.2, 86.2, 77.6, 56.8, 35.5, 28.4, 26.2, 23.8; MS *m*/*z* (MH^+) calcd for $C_{13}H_{24}NO_5$ 274.1654, found 274.1637.