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Synthesis of (-)-Neplanocin A *via* C-H Insertion of Alkylidenecarbene

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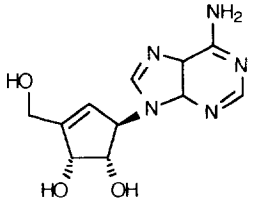
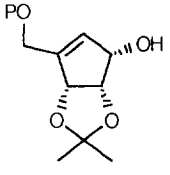
Abstract: (-)-Neplanocin A, a naturally occurring carbocyclic nucleoside was synthesized via C-H insertion reaction of the alkylidenecarbene, which was generated by the reaction of lithiotrimethylsilyldiazomethane and the ketone derived from D-ribose.

(-)-Neplanocin A (NPA, **1**), originally isolated from the culture filtrate of the soil fungus *Ampullariella regularis* [1], is one of the carbocyclic nucleosides recently proving attractive to synthetic chemists because of their potent biological activities.[2] Although NPA exhibits significant antitumor activity, it is not itself a sufficient drug for the clinical treatment of cancer,[3a] therefore, many analogues of (-)-**1** have been synthesized.[3] Protected tetrol (**2**) is an important synthetic precursor not only of NPA, but also its analogues and other cyclopentenoids.[4] The practical route to **2** is based on the Wittig-Horner type reaction with D-ribonolactone derivative,[5, 4b] although a loss of optical purity was observed in one case.[4c]

We describe here the short synthesis of (-)-**1** via the precursor (**2**) starting from D-ribose. The C-H insertion reaction of the alkylidenecarbene was used as the key reaction to construct the functionalized cyclopentene ring.[6]



1



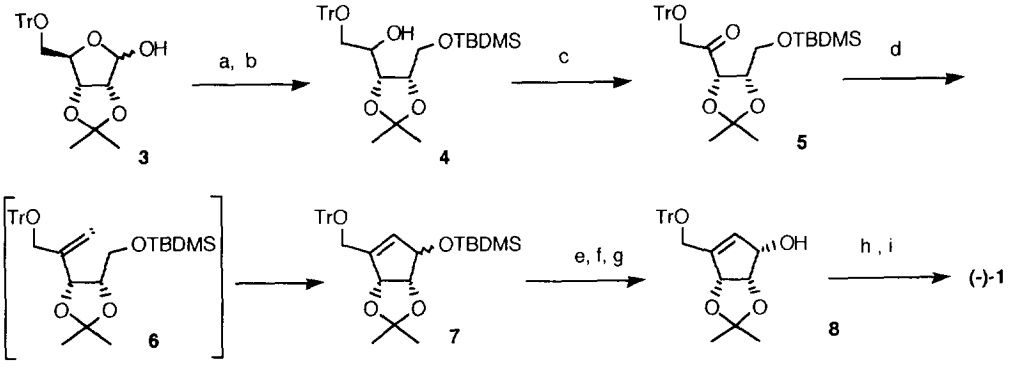
2

P=protecting group

Triphenylmethyl ether of 2,3-O-isopropylidene-D-ribose (**3**) was reduced with lithium aluminum hydride (LAH) to give the corresponding diol whose primary hydroxyl group was protected as t-butyldimethylsilyl ether (**4**).[7] Swern oxidation of the secondary alcohol furnished the corresponding ketone (**5**).[7] Ketone (**5**), which is not stable if allowed to stand a long time, was used immediately in the next key reaction after purification by silica-gel chromatography. Exposure of the ketone with 3 eq. of lithiotrimethylsilyldiazomethane[8] in tetrahydrofuran (THF) at 0°C for 1h generated the alkylidenecarbene (**6**), which was inserted to the C-H bond adjacent to the protected hydroxyl group. The cyclopentene derivative (**7**) was obtained in 55-65% yield as 2.7:1 epimeric mixture. It was realized at a later stage that the major product has undesired stereochemistry, owing to interaction between the bulky siloxy group and the acetonide group during the cyclization. Uses of dimethyl diazomethylphosphonate and potassium t-butoxide[9] for the same conversion resulted in much lower yield of **7** because of the lower reactivity of the reagent.

After removal of the t-butyldimethylsilyl group with tetrabutylammonium fluoride, oxidation of the epimers

with pyridinium dichromate followed by the reduction with LAH afforded the alcohol (**8**)[7] as a single stereoisomer. The ^{1}H-NMR spectrum of **8** was identical with the alcohol derived from the minor isomer of (**7**). The total yield of (**8**) from the compound (**3**) was 18% - 23%. According to Nokami's procedure,[10] **8** was treated with adenine under Mitsunobu's conditions, followed by removal of the protecting groups under the acidic condition to give the final product (-)-(**1**).[7] The physical and spectroscopic properties of the synthetic compound were essentially identical with those reported.[1a,5]



(a) $LiAlH_4$, Et_2O (85%); (b) TBDMSCl, imidazole, DMF (97%); (c) $(COCl)_2$, DMSO then Et_3N, CH_2Cl_2 (89%)
(d) TMSC(Li) N_2, THF, 0°C, 1h (55-65%); (e) Bu_4NF, THF (69%); (f) PDC, CH_2Cl_2 (80%); (g) $LiAlH_4$, THF (87%)
(h) adenine, DEAD, Ph_3P, THF (52%); (i) HCl, MeOH (quant.)

References and Notes

1. (a) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y. Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359-366. (b) Hayashi, M.; Yaginuma, S.; Yoshida, H.; Hakatsu, K. *J. Antibiot.* **1981**, *34*, 359-366.
2. Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623.
3. (a) Shuto, S.; Itoh, H.; Obata, T.; Nakagami, K.; Yaso, M.; Yaginuma, S.; Tsujino, M.; Saito, T.; Matsuda, A.; Ueda,T. *Nucleosides & Nucleotides* **1992**, *11*, 437-446. and references cited therein. (b) Bodenteich, M.; Marquez, V. E.; Barchi, J. J.; Hallows, W. H.; Goldstein, B. M.; Driscoll, J. S. *J. Org. Chem.* **1993**, *58*, 6009-6015. (c) Shudo, S.; Obara,T.; Toriya, M.; Hosoya, M.; Snoeckk, R.; Andrei,G.; Balzarini, J.; De Clercq, E.; *J. Med. Chem.* **1992**, *35*, 324-331. (d) Wolfe, M. S.; Lee, Y.; Bartlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782-1791. (e) Da Silva, A. D.; Coimbra, E. S.; Fourrey, J.-L.; Machado, A. S.; Robert-Gero, M. *Tetrahedron Lett.* **1993**, *34*, 6745-6748. (f) Kitade, Y.; Monguchi, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1993**, *34*, 6579-6580.
4. (a) Knapp, S.; Purandare, A.; Rupitz, K.; Withers, S. G. *J. Am. Chem. Soc.* **1994**, *116*, 7461-7462. (b) Shiozaki, M.; Arai, M.; Kobayashi, Y.; Kasuya, A.; Miyamoto, S. *J. Org. Chem.* **1994**, *59*, 4450-4460. (c) Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331-2334.
5. Bodenteich, M.; Marquez, V. E.; Hallows, W. H.; Goldstein, B. M. *J. Org. Chem.* **1992**, *57*, 2071-2076.
6. (a) Ohira, S.; Moritani, T.; Ida, T.; Yamato, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1299-1300. (b) Ohira, S.; Ishi, S. ; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039-1040.
7. **4**: $[\alpha]_D^{24}$ -1 ° (c 1.6, $CHCl_3$). **5**: $[\alpha]_D^{24}$ -15.9° (c 1.67, $CHCl_3$). **8**: mp 138-138.5 °C; $[\alpha]_D^{20}$ 29.4° (c 1.52, $CHCl_3$); IR($CHCl_3$) ν 3570, 1600, 1490, 1450cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$) δ 1.37 (3H, s), 1.38 (3H, s), 2.74 (1H, d, J=10.0Hz), 3.68 (1H, dt, J=14.3Hz, 1.8Hz), 3.89 (1H, d, J=14.3Hz), 4.60 (1H, bs), 4.75 (1H, t, J=5.5Hz), 4.89 (1H, d, J=5.5Hz), 5.99 (1H, bs), 7.22-7.32 (9H, m), 7.45-7.48 (6H, m); ^{13}C NMR(100MHz, $CDCl_3$) δ 26.7, 27.6, 60.8, 73.3, 77.7, 83.2, 86.9, 112.4, 127.0, 127.7, 128.5, 129.7, 143.3, 143.8. **1**: mp 216.0-216.5°C (lit.[1a] 220-222°C); $[\alpha]_D^{22}$ -167 ° (c 0.20, H_2O) (lit.[1a] $[\alpha]_D^{23}$ -157° (c 0.5, H_2O)).
8. Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721-722.
9. (a) Seyferth, D.; Marmor, R. M.; Hilbert, P. H. *J. Org. Chem.* **1971**, *36*, 1379-1386. (b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656-3663 and references cited therein. (c) Ohira, S. *Syn. Commun.* **1989**, *19*, 561-564.
10. Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. *Synlett* **1994**, 491-493. We are grateful to Prof. Nokami for information on the conditions.

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