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Efficient Functionalization of Acylnitroso Cycloadducts: Application to the Syntheses of Carbocyclic Nucleoside Precursors

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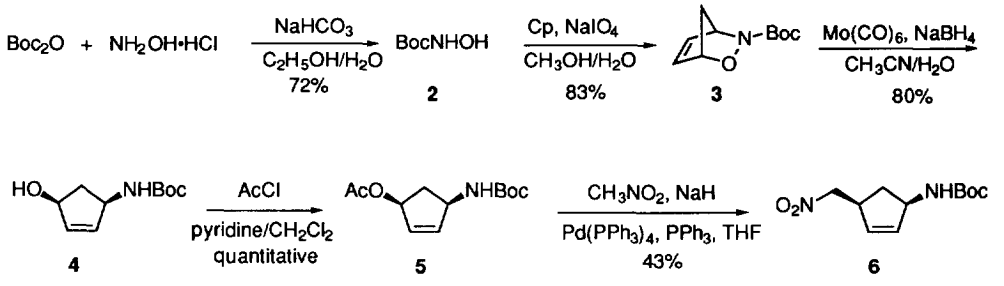
Abstract: 1,4-*cis*-disubstituted cyclopentene precursors of carbocyclic nucleosides were readily prepared utilizing acylnitroso hetero Diels-Alder reactions and Pd(0)-catalyzed alkylation reactions as the key steps. The chemistry was explored in both racemic and asymmetric fashion. The hydroxymethyl components of the carbocyclic nucleoside precursors were obtained from nitromethyl groups under oxidative Nef conditions and may be further elaborated into a variety of compounds of potential biological interest.

We recently developed an asymmetric hetero Diels-Alder approach involving amino acid-derived acylnitroso dienophiles for the synthesis of novel carbocyclic nucleosides.[1] As part of the ongoing project, we are interested in synthesizing 1-amino-4-hydroxymethyl-2-cyclopentenes (e.g., **1**) as versatile precursors to natural and unnatural carbocyclic nucleosides.[2] Herein, we describe a simple, direct synthesis of racemic **1**, related dihydroxylated derivatives, and an asymmetric route to these versatile intermediates.

Acylation of hydroxylamine with Boc_2O afforded hydroxamic acid **2**. Oxidation of **2** to the corresponding nitroso compound in the presence of cyclopentadiene (Cp) induced a hetero Diels-Alder reaction to produce bicyclic compound **3** in 83% yield (Scheme 1). Allylic alcohol **4** was obtained by reductive cleavage of the N-O bond using $Mo(CO)_6$ and $NaBH_4$. Reaction of **4** with acetyl chloride provided allylic acetate **5** suitable for planned introduction of a hydroxymethyl synthon by Pd(0) chemistry. Trost and coworkers first utilized Pd(0) reactions of a nitromethylsulfonate to introduce the related hydroxymethyl equivalents.[3] In our synthesis of racemic **1**, we chose nitromethane as the hydroxymethyl synthon and found that a Pd(0)-mediated reaction of nitromethane with **5** produced **6** directly.[4] A modified Nef reaction was then anticipated to convert **6** to desired hydroxymethyl derivative **1**.[5] However, this conversion became the most challenging aspect of the synthesis.

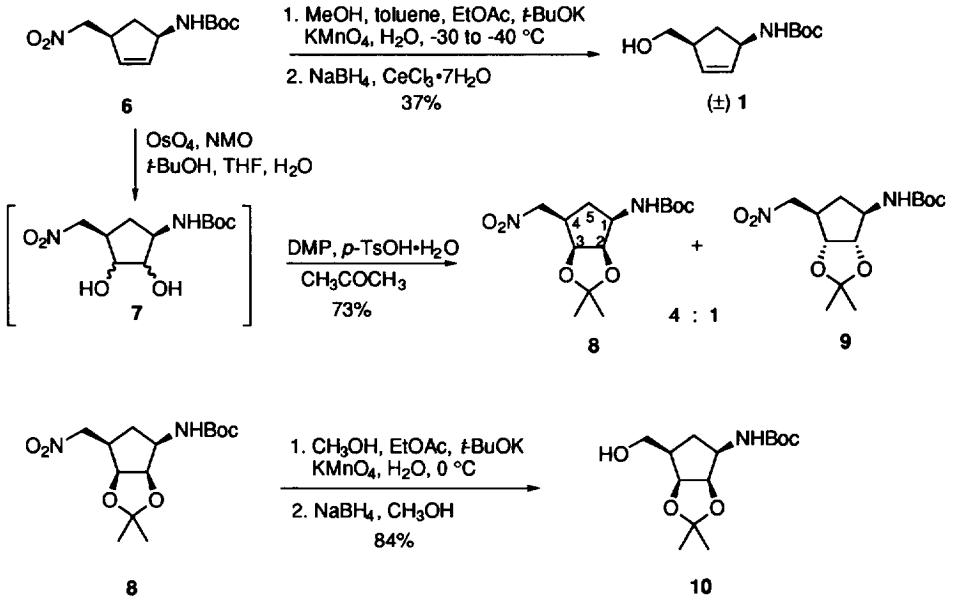
Scheme 1



Several versions of the Nef reaction have been reported to effect the transformation of nitromethyl groups to carbonyl groups.[5] Here, use of buffered Ti(III) initially seemed to be an appropriate choice since reduction of the N-O bond and subsequent hydrolysis of the intermediate imine were anticipated to be compatible with the isolated double bond and acid sensitive Boc group.[6] However, when **6** was subjected to an NH_4OAc buffered (pH 5-6) $TiCl_3$ solution, no desired aldehyde was obtained. Variation of the pH and buffer (L-tartaric acid at pH 5-6) also failed to effect the desired transformation.

Oxidative Nef reactions also effect the conversion of nitromethyl groups to carbonyl groups, but we initially had concerns about the compatibility of oxidative conditions with the C=C bond in the cyclopentene core of **6**. However, with the precedent of a few examples in which oxidative Nef transformation products were obtained in the presence of a C=C bond,[7] we attempted related processes. A controlled ozonolysis[7c] produced only mixtures of recovered starting material and uncharacterizable by-products. Studies related to the use of potassium permanganate as the oxidizing agent were more productive (Scheme 2).

Scheme 2

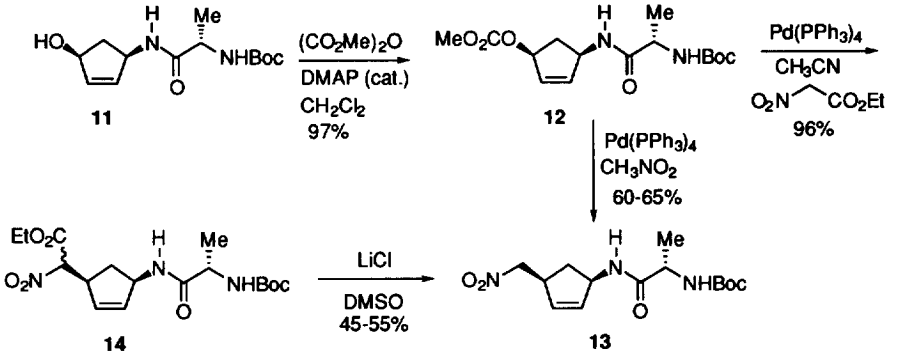


Thus, treatment of the potassium nitronate of **6** with aqueous potassium permanganate at 0 °C followed by immediate reduction with $NaBH_4/CeCl_3$[8] gave desired alcohol **1** in 15-18% yield together with 15-20% of recovered starting material. Encouraged by these results, we modified the conditions by adding the potassium permanganate solution to a precooled (-30 to -40 °C) solution of the potassium nitronate of **6** in MeOH/EtOAc/toluene. After workup, the residue was subjected to the reduction conditions ($NaBH_4/CeCl_3$) to give desired alcohol **1** in 37% yield together with 5% recovered starting material. Even under carefully controlled conditions possible C=C bond oxidation and overoxidation of the intermediate aldehyde to an acid might account for the still moderate yield obtained. To further test this assumption, we converted **6** to acetonides **8** and **9** by transformation to diols **7** with OsO_4/NMO and protection of the diols

with dimethoxypropane (DMP) in the presence of a catalytic amount of *p*-TsOH. The all *cis* stereochemistry of **8**, separated from a 4:1 mixture of **8** and **9**, was determined by use of a NOESY experiment, and is consistent with the unusual directive effect noted by Trost.[3a] The NOESY spectrum of **8** showed significant NOE between H_1 and H_2, H_2 and H_3, H_3 and H_4, H_4 and $H_{5\alpha}$, $H_{5\alpha}$ and H_1 which indicated that all these hydrogens are *cis* to each other. However, the NOESY spectrum of **9** showed only significant NOE between H_2 and H_3, H_4 and $H_{5\alpha}$. With alkene-free nitromethyl compound **8** in hand, we initiated the oxidative Nef reaction using $KMnO_4$ as an oxidant at 0 °C. The resulting intermediate aldehyde was immediately reduced to give alcohol **10** in 84% overall yield. Thus, removal of the alkene significantly improved the yield of the oxidative Nef transformation and culminated an efficient, racemic synthesis of **10**. Related products derived from the directed dihydroxylation are valuable precursors of Mannostatin.[9] Similar subjection of **9** to the same sequence would produce an attractive, selectively protected precursor of a number of carbocyclic nucleosides with the correct relative stereochemistry. Studies on the reversal of the directive effect during the dihydroxylation reaction (**6** to **9** selectively rather than **8**) are in progress.

Combination of this method with our asymmetric Diels-Alder reaction would extend the chemistry to the asymmetric syntheses of forms of **1** and **10**. Carbonate **12** was obtained in 97% yield from alcohol **11**.[10] Direct introduction of the nitromethyl group by the use of nitromethane in the Pd(0)-mediated alkylation furnished **13**. Alternatively, we also chose a nitroacetate for the Pd chemistry because: 1) the moderate acidity of nitroacetates (ethyl nitroacetate, pKa 5.75)[11] makes them ideal substrates for Pd chemistry,[12] 2) decarboalkoxylation can be done under virtually neutral conditions, and 3) after reduction of the nitro group, the resulting amino acid derivatives can be further elaborated toward carbocyclic nikkomycins and analogs.[13]

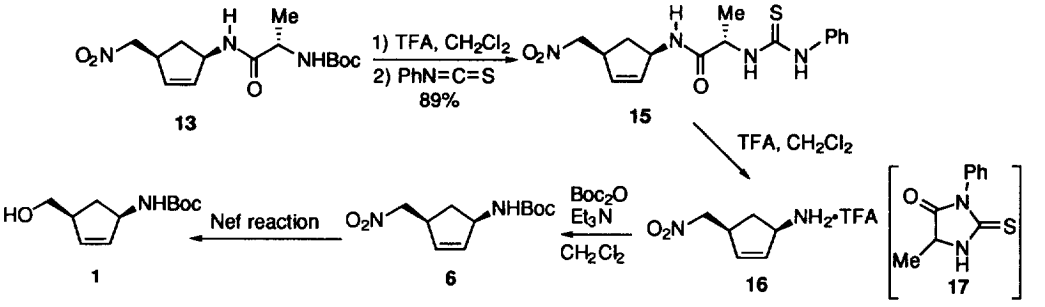
Scheme 3



Thus, **14** was obtained in 96% yield through Pd(0)-catalyzed alkylation reaction of **12** with ethyl nitroacetate (Scheme 3). Decarboethoxylation of **14** under Krapcho's conditions[14] provided nitromethyl derivative **13**. Removal of the L-alanine side chain also was challenging. All of our attempts to hydrolyze the amide linkage were unsuccessful. However, classical Edman degradation conditions were considered to be a feasible alternative (Scheme 4).[15] Thus, the free amine obtained after removal of the Boc group from **13** was treated with phenylisothiocyanate. The resulting crystalline thiourea, **15**, was treated with TFA to produce the TFA salt of amine **16** along with thiohydantoin by-product **17**. Although all these intermediates

were isolated and characterized, this four step transformation, starting from **13** and including the Boc protection of the free amine of **16**, subsequently was performed in one pot to give optically active **6** directly. This synthetic sequence was repeated using (1*R*,4*S*)-isomer **11**.[10] With **6** in hand, the methods utilized in our earlier racemic synthesis will provide optically pure forms of **1**, a versatile intermediate for the preparation of carbovir, aristeromycin, and related analogs which show potent and selective anti-HIV activity.[2]

Scheme 4



Studies related to conversion of these functionally rich synthetic intermediates to novel, optically pure carbocyclic nucleosides and analogs and their biological evaluation will be reported in due course.

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References:

1. a) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602. b) Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 5808.
2. Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394 and references cited.
3. a) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621. b) Trost, B. M.; Stenkamp, D.; Pulley, S. R. *Chem. Eur. J.* **1995**, *1*, 568. c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
4. For early examples of the use of nitroalkanes in Pd(0)-mediated reactions of allylic acetates, see: Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365.
5. For a comprehensive review of the Nef reaction, see: Pinnick, H. W. In Organic Reactions; John Wiley; New York, 1990; Vol. 38, pp 655.
6. a) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1979**, *45*, 410. b) Also see: Hoffman, C.; Tanke, R. S.; Miller, M. J. *J. Org. Chem.* **1989**, *54*, 3750.
7. a) Kornblum, N.; Erickson, A. S.; Kelly, W. J.; Henggeler, B. *J. Org. Chem.* **1982**, *47*, 4534. b) Steliou, K.; Poupart, M.-A. *J. Org. Chem.* **1985**, *50*, 4971. c) Peel, M. R.; Sternbach, D. D.; Johnson, M. R. *J. Org. Chem.* **1991**, *56*, 4990.
8. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
9. King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089.
10. Ghosh, A.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 6399.
11. Adolph, H. G.; Kamlet, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 4761.
12. For a discussion on the relation of pKa and nucleophilicity pertaining to π-allyl Pd complexes, see: Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426.
13. For an approach to a carbocyclic nikkomycin analog, see: Baumgartner, H.; Marschner, C.; Pucher, R.; Singer, M.; Griengl, H. *Tetrahedron Lett.* **1992**, *33*, 6443.
14. For a review see, Krapcho, A. P. *Synthesis*, **1982**, 805, 893.
15. Edman, P. *Acta. Chem. Scanda.* **1950**, *4*, 283.

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