Acknowledgment. Technical assistance from A. Guerrini and financial support by the "Progetto Finalizzato Chimica Fine, CNR, Rome" are gratefully acknowledged.

Registry No. **1a**, 75-36-5; **1b**, 3350-78-5; **1c**, 98-88-4; **1d**, 1711-06-4; **1e**, 938-18-1; **1f**, 100-07-2; **1g**, 527-69-5; **1h**, 5271-67-0; **1i**, 111-50-2; **1l**, 88-95-9; **1m**, 99-63-8; **1n**, 100-20-9; **2a**, 13411-48-8; **2b**, 73452-05-8; **2c**, 5908-41-8; **2d**, 68185-95-5; **2e**, 114885-74-4; **2f**, 75748-09-3; **2g**, 80671-28-9; **2h**, 88372-95-6; **2i**, 114885-75-5; **2l**, 114907-34-5; **2m**, 107325-83-7; **2n**, 107325-82-6; **3**, 114885-76-6; Me_3SiLi, 18000-27-6; $(Me_3Si)_2CuLi$, 94140-66-6.

Studies on the Synthesis of (-)-Neplanocin A. Homochiral Preparation of a Key Cyclopentanoid Intermediate†

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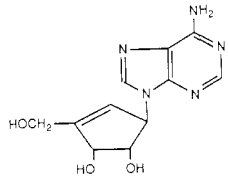
Received July 8, 1987

Certain carbocyclic analogues of purine and pyrimidine nucleosides are known to exhibit a variety of therapeutically promising properties[1] which include antitumor, antibacterial, and antiviral activities. Their presumed mechanism of action is that of biological mimicry. However, unlike furanosyl-derived nucleosides which are rapidly disabled by phosphorylase and hydrolase enzymes, carbocyclic analogues appear resistant to most nucleoside metabolases.[2] Appealing traits such as these have made carbocyclic nucleosides attractive synthetic targets.[3,4]

Our ongoing investigation into the total synthesis[3c,4] of neplanocin A (**1**), a novel cyclopentene-derived nucleoside,[5]



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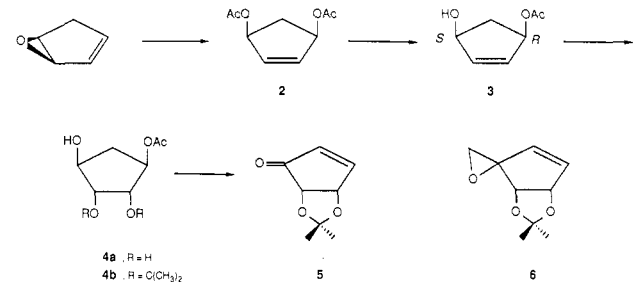
prompted our sojourn into cyclopentanoid chemistry.[6,7] Retrosynthetic analysis on neplanocin A had suggested to us that cyclopentenone **5** would make the ideal synthetic precursor since it could be easily homologated to epoxide **6**—a compound we perceive to be an effective 1,4-addition substrate. Herein, we describe the homochiral preparation[8,9] of enone **5** from optically inactive starting material. Interest in this elaborated cyclopentanoid appears to be widespread as evidenced by the fact that it has been the centerpiece of other synthetic ventures.[10]

The synthesis of optically pure **5** is diagrammed in Scheme I. The desired antipodal form of our retrosynthetic starting material, 3(*R*)-acetoxy-5(*S*)-hydroxycyclopent-1-ene (**3**),[7] is accessible via a stereoselective hydrolysis of its parent diester (**2**).[6] Compound **3** is prepared[7] in high optical (>99% ee; $[\alpha]^{26}_D$ +69.6°) and chemical (94%) yields by using the commercially available acetyl cholinesterase (from electric eel) in buffered media. Treatment of **3** with *N*-methylmorpholine *N*-oxide (NMO)[11] and catalytic OsO_4 gave triol **4a** as predicted from guidelines developed by Kishi.[12] Spectral evidence indicated the presence of only this isomer. Conversion of **4a** to hydroxy acetonide **4b** was

Scheme I



effected under standard conditions (acetone and *p*-TSA) in a 74% overall yield based on **3**. Pyridinium chlorochromate oxidation of **4b** proceeded with the fortuitous β-elimination of acetic acid to afford the conjugated enone **5** in 80% yield. Recrystallization of **5** from pentane/ether produced colorless crystals of high optical purity ($[\alpha]^{26}_D$ +70.0°).[13]

Experimental Section

^{1}H NMR spectra were obtained on a Varian EM 360A (60 MHz) or IBM AF 200 (200 MHz) spectrometer with $CDCl_3$ as solvent

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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and Me_4Si (δ = 0.00) as internal standard. Infrared spectra were recorded on a Perkin-Elmer 397 or a Beckman FT 2100 spectrometer. Optical rotations were measured on a JASCO DIP-369 polarimeter using a 1-mL capacity cell. Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt apparatus and are uncorrected. Elemental analyses were carried out by Desert Analytics, Tucson, AZ.

Osmium tetraoxide was purchased from Aldrich and used without further purification. Tetrahydrofuran (THF) was distilled under nitrogen from a deep blue solution of sodium/benzophenone ketyl. Acetone and methylene chloride were distilled from K_2CO_3 and CaH_2, respectively. Baker silica gel (60–200 mesh) was used for plugs and column chromatography. TLC was performed on Baker Si 250F (0.25 mm) TLC plates. All reactions were carried out under anhydrous conditions with an inert blanket of nitrogen or argon.

Preparation of 1(*R*)-Acetoxy-2,3(*R*,*R*),4(*S*)-trihydroxycyclopentane (4a). To a solution of 300 mg (2.11 mmol) of optically pure (>99% ee) **3**[7] in 3.5 mL of an 8:1 mixture of acetone/water was added 567 mg (4.8 mmol) of *N*-methylmorpholine *N*-oxide (NMO) followed by a small crystal of OsO_4 (approximately 15 mg, 0.06 mmol; reaction time is dependent upon the amount of OsO_4 present, however, under these conditions conversion is generally complete in 2–4 h). After complete consumption of the starting material (as deduced by TLC analysis), the solution was washed through a plug of silica gel (3 g) with 9:1 ethyl acetate/methanol. The filtrate was then concentrated under reduced pressure to give 638 mg of a crude brown oil. This residue was chromatographed over 36 g of silica gel to yield 350 mg (94%) of a clear oil; $[\alpha]^{25}_D$ −44.3° (*c* 1.30, MeOH), R_f 0.38 in 9:1 ethyl acetate/methanol. Due to the instability of this material it must be used immediately in the next step.

Preparation of Acetonide 4b. Triol **4a** (1.2 g, 6.8 mmol) and a small crystal of *p*-toluenesulfonic acid (*p*-TSA) were dissolved in 15.0 mL of dry acetone and 2 mL of 2,2-dimethoxypropane. The reaction was judged complete (as deduced by TLC) after being stirred overnight at room temperature. The mixture was passed through a plug of silica gel (5 g) with reagent grade acetone and concentrated in vacuo to give 1.49 g of a brown oil. This residue was chromatographed over 60 g of silica gel (1:1, hexane/ethyl acetate) to afford 1.168 g (79%) of the corresponding acetonide: $[\alpha]^{23}_D$ −10.3° (*c* 2.62, $CHCl_3$); ^1H NMR (60 MHz) δ 1.26 (s, 3 H, CCH_3), 1.40 (s, 3 H, CCH_3), 1.85 (dt, J = 1 Hz and 15 Hz, 1 H, β CH_2), 2.10 (s, 3 H, OAc), 2.30 (dt, J = 5 Hz and 15 Hz, 1 H, α CH_2), 2.7 (br s, 1 H, OH), 4.20 (br s, 1 H, HOCH), 4.60 (m, 2 H, COCH), 5.10 (d, J = 5 Hz, 1 H, AcOCH); IR (neat) 3295 (br, OH), 1730 (s, CO), 1370, 865 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.50; H, 7.46; O, 36.99. Found: C, 55.53; H, 7.66.

Preparation of Enone 5. To a stirred suspension of 2.4 g of diatomaceous earth and 1.75 g (8.2 mmol) of pyridinium chlorochromate in 20 mL of dry CH_2Cl_2 was added dropwise over 3 min a solution of 1.065 g (4.93 mmol) of **4b** in 4 mL of CH_2Cl_2. The reaction was complete after stirring 48 h at room temperature as indicated by TLC analysis. The suspension was filtered through an 8-g plug of silica gel with 150 mL of CH_2Cl_2 and the resulting filtrate was washed sequentially with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The clear solution was concentrated at atmospheric pressure by boiling off the solvent through a 15-cm Vigreux column to afford 0.610 g (80%) of a colorless crystalline solid, mp 65–67 °C: $[\alpha]^{25}_D$ +68.0° (*c* 0.93, $CHCl_3$). Recrystallization from pentane/ether (8:1) provided pure crystals of **5**, mp 68–69 °C: $[\alpha]^{26}_D$ +70.0° (*c* 0.92, $CHCl_3$); R_f 0.50 (1:1, hexane/ethyl acetate); ^1H NMR (200 MHz) δ 1.39 (br s, 6 H, 2 CH_3), 4.43 (d, J = 5.5 Hz, 1 H, OCH), 5.24 (dd, J = 2.2 Hz and 5.5 Hz, 1 H, OCH), 6.19 (d, J = 5.9 Hz, 1 H, α HC=C), 7.58 (dd, J = 2.2 Hz and 5.9 Hz, 1 H, β C=CH); IR ($CHCl_3$) 2937, 1729 (s, CO), 1097 cm^{-1}.

Acknowledgment. This investigation was generously supported through a Penta Corporation grant of Research Corporation to whom we are most grateful. Funds for the purchase of the IBM AF 200-MHz NMR spectrometer were provided by the National Science Foundation (RUI Grant Number CHE-8513187) and the Jones Foundation. We also thank Beckman Instruments, Inc. for the donation of a Fourier transform infrared spectrometer and the University of California, Irvine, for the use of their polarimeter.

Registry No. 1, 72877-50-0; 3, 60410-16-4; 4a, 114739-33-2; 4b, 113565-13-2; 5, 104010-72-2.

Application of Episelenonium Ion Chemistry to Heterocyclic Ring Closure

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Received December 23, 1987

Organoselenium derivatives have found numerous applications in organic synthesis,[1] and their use in either hetero- or carbocyclic ring formation is well documented.[2] Subsequent functional transformations through oxidative or reductive removal of the introduced seleno group have reinforced the interest of this approach. Furthermore, a number of easy to handle reagents such as *N*-(phenylseleno)phthalimide (NPSP) or -succinimide (NPSS) have been recently introduced.[3]

In connection with a synthetic program, we were interested in the formation of tetrahydroisoquinoline type ring systems. Several recent reports of Edstrom and Livinghouse[4] on the successful synthesis of tetrahydronaphthalenes prompted us to investigate the possibility of a selenium-mediated olefin–arene intramolecular bond formation according to Scheme I (path a).

Our investigation began with unsaturated amides **1–4**, which were of interest in our planned synthesis of alkaloids. Under the conditions described by Livinghouse[4] (see Table I, method A), amide **1** was transformed into **8** in 65% yield. Spectroscopic data of compound **8** did not support the expected tetrahydroisoquinoline structure. Disappearance of the amide absorption in IR spectroscopy led to the conclusion that **1** was cyclized into an oxazoline ring. Structural proof was obtained by reductive cleavage of the phenylseleno group with tributyltin hydride[5] and comparison of the resulting oxazoline **17** with an authentic sample prepared by standard procedures. Several amides were transformed into oxazolines under the same conditions.

The stoichiometry of the Lewis acid in analogous reactions seems to be of crucial importance as demonstrated by Ley et al.[5] Thus we varied reaction conditions in order to circumvent this undesired cyclization without success. Oxazoline formation[6] obviously proceeds via episelenonium ion opening by the amide oxygen atom. A related formation of imino lactones from unsaturated amides in the

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