Homocarboxylase (C) has been reported by several research groups. We have observed (6) homocarboxylase (C) as an effective compound. The synthesis of biologically active substances such as nucodazole nucleosides can be based on the synthesis of nucleosides. A recently discovered point of interest is the potent (7) untreated (c) homocarboxylase (C) and the use of less effective drugs. The major target is to explore (8) homocarboxylase (C), which has been reported to be in vivo effective in inhibition of HIV-1 replication. Nucodazole nucleosides are of great interest as potent anti-HIV and antiviral agents. The recently discovered nucodazole nucleosides, e.g., are effective analogs of normal nucleosides.

INTRODUCTION

Recombinant nucodazole was fully purified from N. crassa by a carboxylase-catalyzed coupling.

ABSTRACT: The synthesis of a carboxylase (C) homocarboxylate (C) was achieved from

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FROM THE ATOMIC TRANSDISTANCE SUBSTRATE
(6) HOMOCARBOXYLASE VIA AN ATTRACTIONAL COMPLEX FORMATION
EFFECTIVE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

The addition of nucleophiles to π-allylpalladium complexes has been investigated by many research groups, foremost among them those of Trost and Taiji. Trost and his co-workers have initially studied the synthesis of carbocyclic nucleosides by the direct introduction of purine moieties to cyclopentene derivatives via π-allylpalladium complex formation. Several other groups have also applied this method to the synthesis of carbocyclic nucleosides. The substrates in these reactions are allylic acetate, carbonates, and epoxides. Recently, we and other group have utilized 3-(N,N-ditosylimido)cyclopentene derivatives with Pd(0) for the synthesis of (±)-carbovir. We have also demonstrated the utility of Pd(0)-catalyzed coupling reactions of allyl N,N-ditosylimide with C, N, O nucleophiles. In this paper, we wish to report an efficient synthesis of the carbocyclic nucleoside, (±)-homocarbovir (3), via nucleophilic attack on a π-allylpalladium complex formed from a 3-(N,N-ditosylimido) cyclopentene derivative.

RESULTS AND DISCUSSION

The N-tosyl bicyclic enamine 5 (Scheme 1) was prepared via Meinwald-type rearrangement from the reaction of norbornadiene (4) with p-toluenesulfonyl azide in 76% yield. Hydrolysis of tosyl
examine 5 afforded quantitatively a ring opening product, N-tosylamido aldehyde 6. We believe that this reaction proceeds presumably via the formation of iminium intermediate I and subsequent rapid attack of water on the iminium ion.

The N-tosyl amido alcohol 7 was obtained by the reduction of the aldehyde 6 with NaBH₄ in excellent yield. Selective acetylation of the alcohol afforded quantitatively the acetate 8, which was then N-tosylated by treatment with sodium hydride and tosyl chloride to give 9 (Scheme 2).

The key coupling was then effected by treatment of 9 with the sodium salt of 2-amino-6-chloropurine in 1:1 THF:DMSO in the presence of 5 % Pd[P(OPr)₃]₄, which furnished the desired coupling adduct 10 and its isomer 11 as a 10:1 mixture in 71% isolated yield (Scheme 3).²²

The 3-(N,N-tosylamido)cyclopentene 9 served as a much better substrate than others for the formation of π-allylpalladium complex and the reaction was complete within 10 min, as we have
Scheme 3.  a) Pd(OAc)$_2$ (i-PrO)$_2$P, THF, rt  
ii) n-BuLi, rt  
iii) 9 in THF, 2-amino-6-chloropurine, NaH, DMSO, rt, 10 min (10:11 = 10:1, 71%)  
b) 1.0 M NaOH, reflux, 2h (89%)

seen previously.\textsuperscript{10} The attack of the anion of the purine base on the π-allylpalladium complex proceeds via 1,4-addition rather than 1,2-addition presumably because of steric hindrance to 1,2-addition due to the non-bonded interaction from the substituent in the cyclopentene ring. Hydrolysis of this mixture with aqueous sodium hydroxide gave (±)-homocarbocvir (3) in 89% yield. In summary, the synthesis of a carbocvir analogue, (±)-homocarbocvir (3), was achieved from norbornadiene (4) in seven steps and 27% overall yield.

(±)-Homocarbocvir (3) was evaluated for cytotoxicity against Vero (african green monkey kidney cell) and MT-4 (HTLV-1-infected human T lymphocyte) and for antiviral activity with herpes simplex virus (HSV) and human immunodeficiency virus (HIV). Unfortunately, antiviral screening revealed that (±)-homocarbocvir (3) did not exhibit any anti-HSV and anti-HIV activity. We are currently investigating the synthesis of phosphorylated homocarbocvir and other carbocyclic nucleosides.

**EXPERIMENTAL**

Proton (H) NMR spectra were obtained using a Bruker ARX-360 spectrometer (360 MHz) instrument operating in Fourier transform mode. Carbon-13 (13C) NMR spectra were recorded using a
909, 816, 750, 705, 666 cm⁻¹; ¹H NMR (CDCl₃) δ 9.67 (s, J = 1.0 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 0.7 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 5.71 (dt, J = 5.6, 1.9 Hz, 1H), 5.43 (dt, J = 5.6, 2.2 Hz, 1H), 5.28 (d, J = 8.9 Hz, 1H), 4.31 (m, 1H), 2.92 (m, 1H), 2.47 (m, 3H), 2.40 (s, 3H), 1.28 (dt, J = 13.7, 6.2 Hz, 1H); ¹³C NMR (CDCl₃) δ 201.27, 143.37, 137.72, 136.79, 131.28, 129.67, 125.95, 59.12, 49.60, 38.06, 37.92, 21.43; MS (EI) 279 (M⁺), 278 (M⁺-1), 235, 172, 155, 124, 106, 91, 80, 65.

cis-N-[4'-(Hydroxyethyl)cyclopetent-2'-enyl]-4-methylphenylsulfonamide (7). To a solution of the aldehyde 6 (1.13 g, 4.03 mmol) in THF (15 mL) was added sodium borohydride (0.187 g, 4.84 mmol). After being stirred for 1 h at ambient temperature, the reaction solution was treated with a saturated NH₄Cl, then extracted with diethyl ether (5 mL x 10). The extracts were dried with anhydrous MgSO₄ and concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2:1, v/v, Rf = 0.10) to afford a white solid 7 (1.02 g, 90%): mp 62-64 °C; IR (thin film) 3502, 3275, 3060, 2929, 2876, 1438, 1325, 1159, 1091, 1059, 912, 816, 743, 705, 666 cm⁻¹; ¹H NMR (CDCl₃) δ 7.76 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.76 (m, 1H), 5.41 (m, 1H), 5.18 (d, J = 9.1 Hz, 1H), 4.3 (m, 1H), 3.62 (m, 2H), 2.61 (m, 1H), 2.42 (s, 3H), 2.34 (dt, J = 13.6, 8.2 Hz, 1H), 1.88 (s, 1H), 1.68 (m, 1H), 1.51 (m, 1H), 1.19 (dt, J = 13.6, 5.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 143.31, 138.21, 137.93, 130.49, 129.68, 127.03, 60.96, 59.26, 40.97, 38.31, 38.09, 21.50; MS (EI) 281 (M⁺), 280 (M⁺-1), 236, 172, 155, 126, 110, 91, 80, 65.

cis-N-[4'-(Acetyloxyethyl)cyclopetent-2'-enyl]-4-methylphenylsulfonamide (8). To a solution of the alcohol 7 (0.820 g, 2.92 mmol) in pyridine (6 mL) was added acetic anhydride (1.48 g, 14.6 mmol). After being stirred for 10 h at ambient temperature, the reaction solution was diluted with diethyl ether, then washed with 1 N HCl. The organic phase was dried with anhydrous MgSO₄ and concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2:1, v/v, Rf = 0.10) to afford a gummy solid 8 (0.939 g, 99%): IR (thin film) 3237, 2957, 2932, 2863, 1738, 1437, 1367, 1381, 1246, 1161, 1094, 1042, 909, 816, 666 cm⁻¹; ¹H NMR (CDCl₃) δ 7.74 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 7.3 Hz, 2H), 5.71 (m, 1H), 5.39 (m, 1H), 5.16 (d, J = 9.0 Hz, 1H), 4.29 (m, 1H), 3.99 (m, 2H), 2.51 (m, 1H), 2.40 (s, 3H), 2.33 (dt, J = 13.5, 7.8 Hz, 1H), 1.97 (s, 3H), 1.69 (dq, J = 13.7, 6.5 Hz, 1H), 1.53 (dq, J = 15.0, 6.6 Hz, 1H), 1.11 (dt, J = 13.4,
6.7 Hz, 1H); $^1$C NMR (CDCl$_3$) $\delta$ 171.02, 143.21, 137.86, 137.48, 130.73, 129.58, 126.94, 62.72, 59.12, 40.99, 38.23, 34.51, 21.38, 20.84; MS (EI) 322 (M$^+$ -1), 280, 236, 168, 155, 108, 92, 91, 80, 65.

cis-$N$-[4'-(Acetoxyethyl) cyclopent-2'-enyl], $N$-(4-methylphenylsulfonyl)-4-methylphenyl sulfonamide (9). To a solution of compound 8 (0.128 g, 0.390 mmol) in anhydrous THF (5 mL) and HMPA (5 mL) was added sodium hydride (80% dispersion in mineral oil, 0.013 g, 0.43 mmol) under argon at 0 °C. Then, a solution of p-toluenesulfonyl chloride (0.083 g, 0.43 mmol) in anhydrous THF (2 mL) was added to the solution. After being stirred for 1 h at ambient temperature, the reaction solution was diluted with diethyl ether (5 mL), then washed with saturated brine solution. The organic phase was dried with anhydrous MgSO$_4$ and concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2/1, v/v) to afford a white solid 9 (R$_f$ = 0.40; 0.0864 g, 64%) with starting material 8 (R$_f$ = 0.35; 0.0364 g, 29%); IR(thin film) 2955, 1738, 1597, 1367, 1242, 1167, 1086, 1041, 870, 814, 663 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.91 (d, $J$ = 8.4 Hz, 4H), 7.33 (d, $J$ = 8.2 Hz, 4H), 5.77 (dt, $J$ = 5.5, 2.4 Hz, 1H), 5.54 (dt, $J$ = 9.1, 2.2 Hz, 1H), 5.33 (m, 1H), 4.08 (dt, $J$ = 9.1, 6.0 Hz, 1H), 4.03 (dt, $J$ = 11.6, 6.1 Hz, 1H), 2.63 (m, 1H), 2.44 (s, 6H), 2.35 (dt, $J$ = 13.0, 8.7 Hz, 1H), 2.01 (s, 3H), 1.84 (m, 2H), 1.70 (dq, $J$ = 14.2, 6.5 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$ 171.04, 144.65, 137.80, 135.86, 129.53, 128.73, 128.16, 67.52, 63.00, 41.23, 35.73, 33.90, 21.59, 20.90; MS (EI) 322 (M$^+$-Ts), 310, 261, 182, 171, 155, 139, 108, 92, 91, 77, 65, 64.

cis-2-Amino-6-chloro-9-[4'-acetoxyethyl)cyclopent-2'-enyl]purine (10). Triisopropyl phosphite (95%, 0.0601 mL, 0.239 mmol) was added at 25 °C to a solution of Pd(OAc)$_2$ (98%, 0.0068 g, 0.033 mmol) in dry THF (1.0 mL) under argon. After being stirred for 15 min, n-BuLi (2.0 M in hexane, 0.03 mL, 0.06 mmol) was added at 25 °C. The resulting mixture was stirred for 15 min to obtain tetrakis(triisopropylphosphite)palladium(0) catalyst. The in situ prepared Pd(0) catalyst was added to a solution of 2-amino-6-chloropurine (0.136 g, 0.794 mmol) and sodium hydride (60% dispersion in mineral oil, 0.0318 g, 0.794 mmol) in anhydrous DMSO (5 mL) via cannula at 25 °C. Then, a solution of the ditosylimide 9 (0.316 g, 0.662 mmol) in dry THF (4.0 mL) was added to the reaction mixture. After being stirred for 10 min, the reaction mixture was diluted with ethyl acetate (5.0 mL) and washed with saturated brine solution (10 mL). The aqueous phase was extracted with
ethyl acetate (5.0 mL x 5). The organic phase was dried with anhydrous MgSO₄ and concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography (diethyl ether only) to afford a yellow gummy solid mixture, 10 and 11 (Rᵣ = 0.29; 10/11 = 10/1, 0.152 g, 71%). Compound 10; IR (thin film) 3323, 3206, 1735, 1611, 1561, 1510, 1463, 1403, 1244, 1140, 1043, 1001, 905, 785, 643 cm⁻¹; ¹H NMR (CDCl₃) δ 7.76 (s, 1H), 6.15 (m, 1H), 5.81 (m, 1H), 5.49 (m, 1H), 5.39 (s, 2H), 4.13 (m, 2H), 2.89 (m, 1H), 2.83 (dt, J = 12.9, 8.1 Hz, 1H), 2.02 (s, 3H), 1.90 (dq, J = 13.7, 6.6 Hz, 1H), 1.73 (dq, J = 13.8, 6.9 Hz, 1H), 1.58 (dt, J = 12.9, 6.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 171.07, 158.97, 153.45, 151.11, 140.48, 140.43, 128.31, 125.513 62.70, 59.75, 41.88, 38.10, 34.14, 20.91; MS (EI) 321 (M⁺), 262, 235, 170, 169, 134, 93, 77, 66, 65.

cis-9-[4'-(Hydroxyethyl)cyclopent-2'-enyl]guanine, cis-homocarbovir (3). To a mixture 10/11 (0.199 g, 0.619 mmol) was added 1 N NaOH (18.5 mL, 18.5 mmol). The reaction mixture was heated at reflux temperature. After being stirred for 2 h, the reaction mixture was neutralized to pH 7-8 with 4.0 N HCl. After removal of water by evaporation, the residue was diluted with methanol (40 mL). To this solution, silica gel (1.5 g) was added, and then the resulting suspension was dried under reduced pressure. By the pre-loaded silica gel column chromatography with CHCl₃/MeOH (5/1, v/v, Rᵣ = 0.29), a white solid 3 was obtained (0.145 g, 89%): mp 216 °C (decomp.), mp (lit)° 220 °C (decomp.); IR (thin film) 3284, 1650, 1325, 1159, 1093, 1065, 993, 924, 815 cm⁻¹; ¹H NMR (CDCl₃) δ 10.7 (s, 1H), 7.56 (s, 1H), 6.44 (s, 2H), 6.16 (m, 1H), 5.85 (m, 1H), 5.31 (m, 1H), 4.44 (t, J = 4.9 Hz, 1H), 3.47 (m, 2H), 2.82 (m, 1H), 2.67 (dt, J = 13.2, 8.2 Hz, 1H), 1.69 (dq, J = 13.3, 6.6 Hz, 1H), 1.48 (m, 2H); ¹³C NMR (DMSO-d₆) δ 157.22, 153.82, 151.22, 140.75, 135.16, 128.76, 117.21, 59.66, 59.00, 41.76, 38.92, 38.59; MS (EI) 261 (M⁺), 151, 110, 91, 79, 77, 66.

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REFERENCES AND NOTES
(±)-HOMOCARBOVIR


12. The integration of the two H-8 proton chemical shifts of the 2-amino-6-chloropurine (δ 7.76 and
were compared for the determination of the ratio of diastereomers; Compound 11 could be
confirmed by the checking allylic protons at C-4' in 'H NMR spectrum (Two allylic protons at C-
4' show up at 2.66 ppm).


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