COMMUNICATION

Practical enantiodivergent syntheses of both enantiomers of carbovir, 1592U89 and six-membered ring analogues

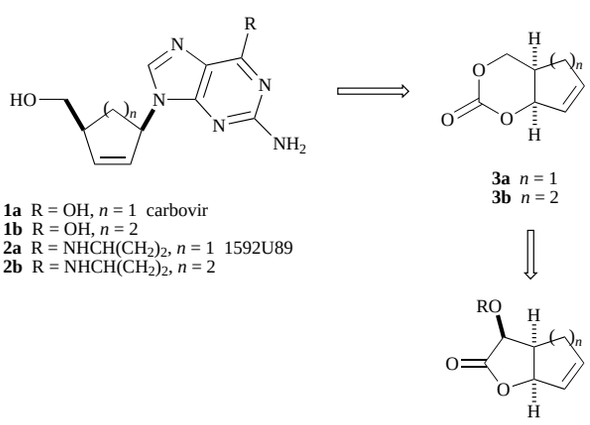
Horacio F. Olivo * and Jiaxin Yu

Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA

The hydroxylactones 4a–b (both available in optically pure form from biocatalytic processes) have been used in the preparation of carbovir, 1592U89, and their six-membered ring analogues.

Carbocyclic analogues of nucleosides display a wide range of biological activity and have attracted considerable attention as antitumor and antiviral agents.[1] In particular, carbonucleosides carbovir (**1a**)[2] and 1592U89 (**2a**)[3] have been shown to act as potent antiviral agents. Carbovir emerged as a potent and selective anti-HIV agent;[4] however, it was removed from clinical trials due to toxicity issues. More recently 1592U89, the cyclopropylamine derivative of carbovir, was reported to have excellent oral bioavailability and to penetrate the central nervous system as well as AZT.[5] A unique activation pathway enables 1592U89 to overcome the pharmacokinetic and toxicological deficiencies of carbovir while maintaining potent and selective anti-HIV activity.[6] Having demonstrated an excellent preclinical profile, 1592U89 is now in clinical evaluation in HIV-infected patients.

Considerable effort has been devoted to the practical synthesis of both enantiomers of these compounds and also to their six-membered ring analogues.[7] Interest in the cyclohexenyl analogues arose from the observation that pyranosyl-like nucleosides have also shown antiviral activity.[7] An efficient, convergent approach to the synthesis of carbonucleosides has proved to be Trost's palladium-catalyzed coupling[8] of carbonates or allylic acetates with heterocyclic bases.[9] Carbovir (**1a**) and 1592U89 (**2a**) have been prepared by Crimmins from bicyclic carbonate **3a**.[2e] Carbovir was also prepared by Roberts and Olivo from *endo*-hydroxylactone **4a**.[10] The cyclohexenyl nucleosides **1b** and **2b** have been recently prepared by Vince in racemic form.[7a] We report herein a practical synthesis of bicyclic carbonates **3a**–**b** from optically pure *endo*-hydroxylactones **4a**–**b**, and an extension of this methodology to the six-membered ring series. This new route to both enantiomers of carbovir and 1592U89 avoids the protection–deprotection steps used in our previous synthesis,[10] and also allows access to enantiomerically pure cyclohexenyl carbonucleosides represented by **1b** and **2b**.



1a R = OH, *n* = 1 carbovir
1b R = OH, *n* = 2
2a R = NHCH(CH$_2$)$_2$, *n* = 1 1592U89
2b R = NHCH(CH$_2$)$_2$, *n* = 2

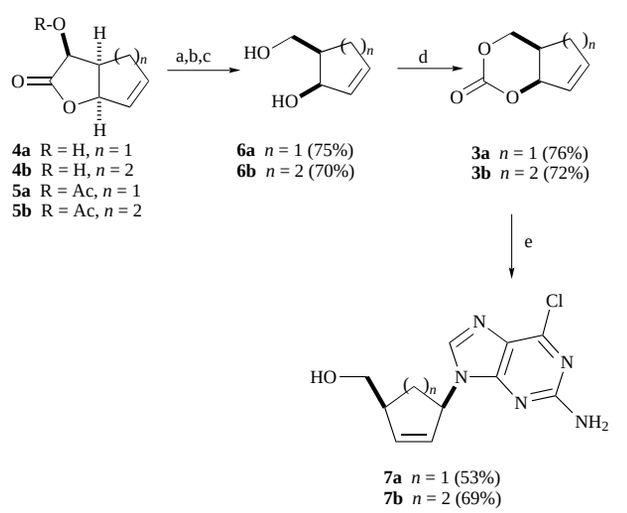
3a *n* = 1
3b *n* = 2

4a R = H, *n* = 1
4b R = H, *n* = 2
5a R = Ac, *n* = 1
5b R = Ac, *n* = 2

endo-Hydroxylactones **4a**–**b** were easily obtained by the water-promoted reaction of glyoxylic acid with cyclopentadiene and 1,3-cyclohexadiene, respectively.[11] The versatile hydroxylactone **4a** has been used previously in the synthesis of sesbanimide,[12] brefeldin A,[13] carbonucleosides,[10,14] and anti-hypercholesterolemic agents.[15]

Hydroxylactone (±)-**4a** has been kinetically resolved using *Pseudomonas fluorescens* lipase in both the hydrolysis and the esterification modes.[16] Optically pure hydroxylactone (+)-**4a** and its acetyl ester (−)-**5a** were obtained by enzymatic esterification of (±)-**4a** in vinyl acetate. Acetyl esters (±)-**5a**–**b** were also enzymatically hydrolyzed in a buffer solution (0.1 M phosphate, pH 7.0) to yield hydroxylactone (−)-**4a**–**b** {[*a*]$_D$ −104 (*c* 1.0, $CHCl_3$)[10] and [*a*]$_D$ −144 (*c* 1.0, $CHCl_3$),[17] respectively} † and acetyl ester (+)-**5a**–**b** {[*a*]$_D$ −6.6 (*c* 1.0, $CHCl_3$)[10] and [*a*]$_D$ −22.3 (*c* 1.0, $CHCl_3$),[17] respectively}. The resolved alcohols and esters were easily separated by flash column chromatography.

(−)-Hydroxylactones **4a**–**b** were converted in three steps to (−)-diols **6a**–**b** in 70–75% overall yield, Scheme 1. Diol **6a** has also been elegantly synthesized by Crimmins, in a combination of an asymmetric aldol condensation with a ring closure metathesis.[2e] (−)-Bicyclic carbonates **3a**–**b** were obtained by the addition of triphosgene to diols **6a**–**b** in 72 and 76% yield.[18]



4a R = H, *n* = 1
4b R = H, *n* = 2
5a R = Ac, *n* = 1
5b R = Ac, *n* = 2

6a *n* = 1 (75%)
6b *n* = 2 (70%)

3a *n* = 1 (76%)
3b *n* = 2 (72%)

7a *n* = 1 (53%)
7b *n* = 2 (69%)

Scheme 1 *Reagents and conditions*: a, $LiAlH_4$, THF, reflux; b, $NaIO_4$, Et_2O–H_2O; c, $NaBH_4$, EtOH; d, triphosgene, Et_3N, CH_2Cl_2; e, 2-amino-6-chloropurine, Pd(PPh$_3$)$_4$, DMSO–THF (1:1).

† [*a*]$_D$ Values are given in 10^{-1} deg cm^2 g^{-1}.

Palladium-catalyzed coupling of bicyclic allylic carbonate (−)-**3a** with 2-amino-6-chloropurine [$Pd(PPh_3)_4$, DMSO–THF] in the absence of base provided a separable mixture of N9–N7 coupling products in 53 and 24% yields respectively.[19] Coupling of carbonate (−)-**3b** under the same conditions furnished coupling product (−)-**7b** in 69% yield. In this case, we were not able to identify the N7 coupling product regioisomer.

Direct hydrolysis of the 2-chloro-4-aminopurine adduct (−)-**7a**[20] provided (−)-carbovir (**1a**) in 89% yield. Similarly, hydrolysis of adduct (−)-**7b** provided homocarbovir **1b** in 90% yield.[21] Treatment of the 2-chloro-4-aminopurine adduct (−)-**7a** with cyclopropylamine in refluxing ethanol provided (−)-1592U89 (**2a**) in 72% yield, and similarly the six-membered ring analogue **2b** was obtained in 69% yield.[21] The dextrorotatory carbonucleosides **1a**–**b** and **2a**–**b** were obtained when the acetyl esters (+)-**5a**–**b** were used as starting material and the same methodology was followed.

In summary, we have presented a simple preparation of either racemic or enantiomerically pure cyclic carbonates **3a**–**b**. Short syntheses of both enantiomers of carbonucleosides carbovir and 1592U89 were achieved by palladium coupling of the cyclic allylic carbonate prepared from enzymatically resolved hydroxylactones. This enantiodivergent methodology was successfully extended to the syntheses of optically pure six-membered ring analogues **2a**–**b**.

[4-(2′-Amino-6′-chloropurin-9′-yl)cyclohex-2-en-1-yl]methanol 7b

To a solution of carbonate **3b** (0.110 g, 0.714 mmol) in a 1:1 mixture of dimethylsulfoxide–tetrahydrofuran (4 cm^3) was added $Pd(PPh_3)_4$ (0.042 g, 0.036 mmol) and 2-amino-6-chloropurine (0.121 g, 0.714 mmol). The solution was stirred at 60 °C for 8 h. The solution was cooled to room temperature, poured into water (10 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined organic layers were washed with brine (15 cm^3), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Purification of the residue by silica gel column chromatography (dichloromethane–methanol, 19:1) furnished the title compound (137 mg, 69% yield) as a white solid.

R_f 0.35 (10% MeOH in $CHCl_3$); mp 167–169 °C; $[a]_{25}$ −53.1 (*c* 0.2, CH_3OH); δ_H(360 MHz; ^{2}[H_6]DMSO) 7.99 (1H, s), 6.92 (2H, s), 6.12 (1H, d, *J* 10),‡ 5.85 (1H, d, *J* 10), 4.97 (1H, m), 4.70 (1H, t, *J* 5.4), 3.46 (2H, m), 2.26 (1H, m), 1.92 (2H, m), 1.65 (1H, m) and 1.42 (1H, m); δ_C(90 MHz; [$^2H_6$]DMSO) 159.7 (C), 153.5 (C), 149.4 (C), 141.7 (CH), 135.9 (CH), 124.5 (CH), 123.7 (C), 63.9 (CH_2), 48.5 (CH), 37.7 (CH), 26.8 (CH_2) and 20.4 (CH_2); ν_{max}/cm^{-1} 3420, 3316, 3202, 1617, 1562, 1507, 1466, 1402 and 1363; *m*/*z* (FAB) 280 (M + H^+, 46%), 170 (36), 91 (100), 73 (38) (Found: M + H^+, 280.0969. $C_{12}H_{15}N_5OCl$ requires M + H^+, 280.0965).

‡ *J* Values are given in Hz.

References

1 (*a*) L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10 611; (*b*) A. D. Borthwick and K. Biggadicke, *Tetrahedron*, 1992, **48**, 571; (*c*) D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745.

2 For recent syntheses of carbovir: (*a*) N. Katagiri, M. Takebayashi, H. Kokufuda, C. Kaneko, K. Kanehira and M. Torihara, *J. Org. Chem.*, 1997, **62**, 1580; (*b*) S. Tanimori, M. Tsubota, M. He and M. Nakayama, *Synth. Commun.*, 1997, **27**, 2371; (*c*) L. E. Martinez, W. A. Nugent and E. N. Jacobsen, *J. Org. Chem.*, 1996, **61**, 7963; (*d*) B. M. Trost, R. Madsen, S. G. Guile and A. E. H. Elia, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1569; (*e*) M. T. Crimmins and B. W. King, *J. Org. Chem.*, 1996, **61**, 4192; (*f*) M. Tanaka, Y. Norimine, T. Fujita, H. Suemune and K. Sakai, *J. Org. Chem.*, 1996, **61**, 6952; (*g*) T. Berranger and Y. Langlois, *Tetrahedron Lett.*, 1995, **36**, 5523; (*h*) B. M. Trost, M. G. Organ and G. A. O'Doherty, *J. Am. Chem. Soc.*, 1995, **117**, 9662.

3 For syntheses of 1592U89: see S. M. Daluge, U.S. Patent, 5 034 394, 1991; also ref. 2*e*.

4 (*a*) R. Vince, M. Hua, J. Brownell, S. Daluge, F. Lee, W. M. Shannon, G. C. Lavelle, J. Qualls, O. S. Weislow, R. Kiser, P. G. Canonico, R. H. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Shomaker and M. R. Boyd, *Biochem. Biophys. Res. Commun.*, 1988, **156**, 1046; (*b*) R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17.

5 (*a*) S. M. Daluge, S. S. Good, M. B. Faletto, W. H. Miller, M. H. St. Clair, L. R. Boone, M. Tisdale, N. R. Parry, J. E. Reardon, R. E. Dornsife, D. R. Averett and T. A. Krenitsky, *Antimicrob. Agents Chemother.*, 1997, **41**, 1082; (*b*) S. S. Good, S. M. Daluge, S. V. Ching, K. M. Ayers, W. B. Mahoney, M. B. Faletto, B. A. Domin, B. S. Owens, R. E. Dornsife, J. A. McDowell, S. W. LaFon and W. T. Symonds, *Antiviral Res.*, 1995, **26**, A229.

6 M. B. Faletto, W. H. Miller, E. P. Garvey, M. H. St. Clair and S. M. Daluge, *Antimicrob. Agents Chemother.*, 1997, **41**, 1099.

7 (*a*) M. J. Konkel and R. Vince, *Tetrahedron*, 1996, **52**, 799; (*b*) M. J. Konkel and R. Vince, *Nucleosides and Nucleotides*, 1995, **14**, 2061.

8 (*a*) B. M. Trost, G.-H. Kuo and T. Benneche, *J. Am. Chem. Soc.*, 1988, **110**, 621; (*b*) L.-L. Gundersen, T. Benneche and K. Undheim, *Tetrahedron Lett.*, 1992, **33**, 1085.

9 (*a*) B. M. Trost and T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*, ed., G. Wilkinson, Pergamon Press, Oxford, 1982; vol. 8, ch. 57; (*b*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395.

10 R. A. MacKeith, R. McCague, H. F. Olivo, C. F. Palmer and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1993, 313.

11 A. Lubineau, J. Augé and N. Lubin, *Tetrahedron Lett.*, 1991, **32**, 7529.

12 P. A. Grieco, K. J. Henry, J. J. Nunes and J. E. Matt Jr., *J. Chem. Soc., Chem. Commun.*, 1992, 368.

13 (*a*) A. J. Carnell, G. Casy, G. Gorins, A. Kompany-Saeid, R. McCague, H. F. Olivo, S. M. Roberts and A. J. Willetts, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3431; (*b*) G. Casy, G. Gorins, R. McCague, H. F. Olivo and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1994, 1085.

14 (*a*) V. K. Aggarwal and N. Monteiro, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2531; (*b*) F. Burlina, A. Favre, J.-L. Fourrey and M. Thomas, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 247; (*c*) V. K. Aggarwal, N. Monteiro, G. J. Tarver and S. D. Lindell, *J. Org. Chem.*, 1996, **61**, 1192.

15 (*a*) R. McCague, H. F. Olivo and S. M. Roberts, *Tetrahedron Lett.*, 1993, **34**, 3785; (*b*) S. M. Roberts, H. F. Olivo and R. McCague, Patent Appl. WO 94 07 888.

16 R. A. MacKeith, R. McCague, H. F. Olivo, S. M. Roberts, S. J. C. Taylor and H. Xiong, *Bioorg. Med. Chem.*, 1994, **2**, 387.

17 D. E. Hibbs, M. B. Hursthouse, L. J. S. Knutsen, K. M. Abdul Malik, H. F. Olivo, S. M. Roberts, D. R. Varley and H. Xiong, *Acta Chem. Scand.*, 1995, **49**, 122.

18 S. Hildbrand, T. Troxler and R. Scheffold, *Helv. Chim. Acta*, 1994, **77**, 1236.

19 Crimmins reported similar ratio of regioisomeric coupling products, see ref. 2*e*.

20 R. Vince and M. Hua, U.S. Patent 4 931 559, 1990. Compound **7a** was also employed by Daluge, see ref. 3.

21 Carbovir[ref. 11] (**1a**): $[a]_D$ −62 (*c* 0.4, MeOH); 1592U89[ref. 2e] (**2a**): $[a]_D$ −31.8 (*c* 0.51, MeOH); homocarbovir (**1b**): $[a]_D$ −26.8 (*c* 0.53, MeOH); homo-1592U89 (**2b**): $[a]_D$ −37.3 (*c* 0.18, MeOH).

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