Formal Enantioselective Synthesis of (–)-Carbovir and (–)-Abacavir: An Application of the Rhodium(I)-Catalysed Tandem Hydrosilylation–Intramolecular Aldol Reaction

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Abstract: An efficient synthesis of the highly potent anti-HIV carbocyclic nucleosides (–)-carbovir and (–)-abacavir has been accomplished from D-(–)-ribose using a rhodium(I)-catalysed tandem hydrosilylation-intramolecular aldol strategy to access a key intermediate.

Key words: asymmetric synthesis, carbocyclic nucleosides, aldol reaction, hydrosilylation, rhodium

Development of efficient synthetic routes to carbocyclic nucleoside analogues has attracted considerable attention in recent years, not only as a consequence of their interesting biological activities but also because of the constant challenge associated with stereoselective construction of 5-membered ring carbocycles. Since the first racemic synthesis of the carbocyclic analogue of adenosine by Shealy and Clayton1 in 1966 and the subsequent isolation of its (–)-enantiomer, the antifungal antibiotic aristeromycin 2 (Figure 1) from Streptomyces citricolor, interest in this class of compounds has continued to grow rapidly. In particular, (–)-carbovir 2, which was first prepared by Vince’s group3 in 1988, was shown to efficiently combat acquired immunodeficiency syndrome (AIDS) by selectively inhibiting human immunodeficiency virus (HIV) reverse transcriptase. It was however removed from a clinical trial test due to its pharmacokinetic and toxicological deficiencies. More recently, a produg of (–)-carbovir, known as (–)-abacavir or Ziagen 3,4 with higher oral bioavailability and the capacity to penetrate the central nervous system, has been approved by the Food and Drug Administration (FDA) for treatment of AIDS (Figure 1).

As a consequence of their biological activity, a considerable number of synthetic approaches to (–)-carbovir and its related analogue (–)-abacavir have been developed,5 and such molecules have proven to be an excellent test bed in the search for alternative and perhaps more efficient stereoselective strategies for the preparation of carbocyclic nucleosides. A considerable majority of the above syntheses have relied on the use of cyclopentadiene as the preformed carbocyclic core. Although this starting material has the clear advantage of being very inexpensive, a major disadvantage is the subsequent necessity for introduction of chirality into the carbocyclic ring, often involving classical resolution, enzymatic resolution or desymmetrisation of a meso intermediate. Only very few syntheses have involved a stereoselective cyclisation method for generation of the cyclopentyl moiety and most of these rely on either a ring closing metathesis or alkylidene carbene insertion strategy and on the use of chiral auxiliaries to establish the absolute configuration of the pseudo-sugar. In this context, Crimmins6 has reported an efficient and general strategy based on an asymmetric aldol/ring closing metathesis sequence for the synthesis of (–)-carbovir and (–)-abacavir. Tanimori7 has described a different approach based on intramolecular cyclopropanation of a chiral α-diazo-β-ketoester which takes advantage once again of the asymmetry induced by a chiral auxiliary. More recently, Florent8 has used (S)-ethyl lactate from the chiral pool in an enantioselective formal total synthesis of (–)-carbovir. The two key steps of this route involved a Claissen [3,3]-sigmatropic rearrangement and a ruthenium-catalysed ring closing metathesis. Unfortunately, however, a 1:1 mixture of diastereomers was generated in the very last step of the synthesis. Since we have recently reported that the rhodium(I)-catalysed tandem hydrosilylation-intramolecular aldol reaction9 is a very promising approach for construction of functionalised carbocycles from the chiral pool, and in view of the ongoing interest in the synthesis of carbocyclic nucleosides, we therefore envisaged the application of this sequence to the syntheses of (–)-carbovir and its related analogue (–)-abacavir. Our strategy, as depicted in the retrosynthetic analysis of Scheme 1, utilises the stereoselective rhodium(I)-catal-
ysed tandem hydrosilylation–aldol cyclisation to form the pseudo-sugar ring with the appropriate relative stereochemistry for the Trost asymmetric allylic alkylation protocol (AAA).\textsuperscript{10} Furthermore, the absolute stereochemistry would be generated from the chiral pool, through selection of the cheap and readily available D-ribose (Scheme 1).

The key highly functionalised carbocyclic intermediate 4 required for our synthetic approach was obtained in four steps from commercially available D-(−)-ribose (Scheme 2).\textsuperscript{9}

Thus, protection of D-(−)-ribose as its isopropylidene derivative 5 using 2,2-dimethoxypropane and a catalytic quantity of p-toluenesulfonic acid proceeded in 76% yield. Subsequent Wittig olefination with Ph$_3$PCHCO$_2$Me.

Scheme 1  Retrosynthetic analysis

Scheme 2  Reagents and conditions: (a) 2,2-Dimethoxypropane, p-toluenesulfonic acid, acetone, 0 °C, 1 h; (b) Ph$_3$PCHCO$_2$Me, CH$_2$Cl$_2$, r.t., 5 h; (c) NaIO$_4$, CH$_2$Cl$_2$, H$_2$O, r.t., 5 h; (d) Et$_3$SiH, 1 mol% RhH(PPh$_3$)$_4$, toluene, 50 °C, 16 h

afforded diol 6 in 60% yield. Oxidative cleavage of diol 6 with NaIO₄ then furnished the aldehydic cyclisation precursor 7 in 68% yield. Finally, rhodium(I)-catalysed tandem hydrosilylation–intramolecular aldol reaction of a Z/E mixture of 6-oxo-2-hexenoate 7 using our preferred catalyst, RhH(PPh₃)$_2$, led to the highly substituted five-membered ring carbocycle 4 in 81% yield as a mixture of diastereomers in a 5.4:4.0:2.0:1.0 ratio, which were separated by column chromatography. The moderate yield obtained in the Wittig olefination of lactol 5 is due to the propensity of unsaturated ester 6 to participate in an intramolecular Michael addition to afford the corresponding tetrahydrofuran derivative. The Wittig reaction of sugar lactols with stabilised ylides such as alkoxycarbonylmethylene triphenylphosphoranes has been intensively investigated, and this behaviour has previously been noted. Further improvements in the yield of this transformation could presumably be achieved by replacement of the standard Wittig reagent with a more bulky phosphorane (tert-butyl or benzyl groups), as recently reported by Clive. With the appropriate carbocyclic precursor 4a in hand, preparation of the selectively protected syn-diol 8 was then achieved (Scheme 3).

Thus, deprotection of the triethylsilyl ether was accomplished with $n$-Bu₄NF in THF at room temperature, leading to the corresponding cyclopentanol 9 in 97% yield. Subsequent reduction of the methyl ester using LiAlH₄ afforded diol 10 in 86% yield, which was quantitatively converted to the diacetate 11. Selective deprotection of the relatively robust acetonide protecting group was then required. In the first instance, attempted deprotection by acidic hydrolysis with 2.0 M HCl led to removal of both acetate-protecting groups whereas the isopropylidene functionality remained intact. In the event, however, use of a mixture of TFA–H₂O (9:1) gave the desired syn-diol 8 in 92% yield.

With ready access to the syn-diol 8, several possible routes to the cyclopentene were investigated. Although a variety of methods are known to effect deoxygenation of the 2′-3′ vicinal diol to the corresponding alkene, this transformation proved to be problematic in the present case. The Garegg–Samuelsson procedure using I₂, PPh₃ and imidazole was attempted for the direct conversion of the syn-diol 8 to the olefin. Unfortunately, no reaction was observed. Since the direct conversion of the 1,2-diol into the corresponding alkene was unsuccessful, we therefore elected to convert it into the bistriflate derivative in order to attempt the Tipson–Cohen protocol. Although syn-diol 8 was readily converted to the corresponding bistrafilate by reaction with triflic anhydride, pyridine and DMAP, exposure to NaI and Na₂S₂O₃ in DMF at 85 °C led to a complex mixture of compounds with no evidence of the expected cyclopentene. In view of the fact that the most promising protocols failed with this

![Scheme 3](image)

**Scheme 3** Reagents and conditions: (a) $n$-Bu₄NF, THF, r.t., 1 h; (b) LiAlH₄, THF, 0 °C, 2 h; (c) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 0 °C, 2 h; (d) TFA, H₂O, 0 °C, 0.5 h; (e) pentafluorophenylchlorothionoformate, pyridine, DMAP, r.t., 5 h; (f) 1,3-dimethyl-2-phenyl-1,3-diazaphospholinedione, THF, 40 °C, 4 h
sensitive substrate, a milder method was therefore required. In the event, the Corey–Hopkins procedure was found to be the most effective. Thus, cyclic thionocarbonic acid 12 was readily accessed from diol 8 by exposure to pentfluoroanilinochlorothionofomate, pyridine and DMAP in toluene at room temperature in 78% yield. Subsequent treatment of 12 with 3 equivalents of 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine in anhydrous THF at 40 °C, afforded the desired cyclopentene 13 in 65% yield after column chromatography (Scheme 3).

As previously described by Crimmins, a palladium-catalysed tandem hydrosilylation–intramolecular aldol reaction was carried out in oven-dried glassware under a N2 atmosphere. The resulting oil was purified by column chromatography [petroleum ether (30–40 °C)–EtOAc, 9:1] to afford the silyl-protected cyclopentanol 4 (4.95 g, 81%) as four diastereomers [α]D20 = −20.7 [c = 0.50, CHCl3–MeOH (9:1)].

FTIR (film): 2936, 2878, 1733, 1439, 1376, 1262, 902 cm−1.

1H NMR (500 MHz, CDCl3): δ = 0.51 (q, J = 7.7 Hz, 6 H), 0.86 (t, J = 7.7 Hz, 9 H), 1.21 (s, 3 H), 1.35 (s, 3 H), 1.89 (dd, J = 6.3, 13.8 Hz, 1 H), 2.24 (ddd, J = 5.4, 10.7, 13.8 Hz, 1 H), 3.02 (ddd, J = 4.0, 6.3, 10.7 Hz, 1 H), 3.60 (s, 3 H), 4.20 (d, J = 5.4 Hz, 1 H), 4.28 (d, J = 4.0 Hz, 1 H), 4.67 (t, J = 5.4 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 37.5, 57.2, 22.8, 25.1, 30.8, 46.2, 50.4, 76.8, 78.2, 84.9, 108.9, 171.1.

HRMS (FAB): m/z = 331, 301, 241, 211, 187.

HRMS–FAB: m/z [M + H]+ calcd for C16H31O5Si: 331.19406; found: 331.19408.

Methyl (1S,2S,3S,4S)-2-Hydroxy-3,4-isopropylidenedioxycyclopentane Carboxylate (9)

To a solution of methyl (1S,2S,3S,4S)-2-triethylsilyloxy-3,4-isopropylidenedioxycyclopentane carboxylate 4a (300 mg, 0.9 mmol) in anhyd THF (3 mL), was added dropwise 1.0 M TBAF in THF (2 mL, 2.0 mmol) and the reaction mixture was stirred at r.t. for 1 h. After diluting with water (5 mL), the resulting solution was extracted with CHCl3 (2 × 5 mL). The combined organic extracts were dried over MgSO4, filtered and concentrated. Purification by flash column chromatography [petroleum ether (30–40 °C)–EtOAc, 8:2] afforded cyclopentanol 4 (190 mg, 97%) as a white solid.

Methyl (1S,2S,3S,4S)-2-Hydroxy-1-(hydroxymethyl)-3,4-isopropylidenedioxycyclopentane (10)

To a solution of cyclopentanol 9 (170 mg, 0.79 mmol) in anhyd THF (10 mL) was added 1.0 M LiAlH4 in Et2O (1.73 mL, 1.73 mmol) at 0 °C under a N2 atmosphere. After 2 h, the reaction was quenched with a 10% aq NaOH solution (3.5 mL). EtOAc (10 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organic extracts were dried over MgSO4, filtered and concentrated. Purification by flash column chromatography [petroleum ether (30–40 °C)–EtOAc, 1:1] afforded the desired product 10 (127 mg, 86%) as a clear oil. [α]D20 = −21.7 [c = 1.60, CHCl3–MeOH (9:1)].

FTIR (film): 3463, 2988, 2936, 1730, 1440, 1375, 1269, 1211, 1028 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.29 (s, 3 H), 1.43 (s, 3 H), 2.09–2.24 (2 m, 2 H), 3.08 (ddd, J = 4.0, 8.0, 12.0 Hz, 1 H), 3.74 (s, 3 H), 4.30 (d, J = 8.0 Hz, 1 H), 4.44 (d, J = 5.6 Hz, 1 H), 4.78 (t, J = 5.6 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 23.7, 26.1, 33.4, 44.9, 52.1, 76.1, 79.2, 84.9, 109.4, 174.9.

LRMS (ES): m/z = 239, 217.


(1R,2S,3S,4S)-2-Hydroxy-1-(hydroxymethyl)-3,4-isopropylidenedioxycyclopentane (10)

(1S,2S,3S,4S)-2-Hydroxy-1-(hydroxymethyl)-3,4-isopropylidenedioxycyclopentane (10)

To a solution of cyclopentanol 9 (170 mg, 0.79 mmol) in anhyd THF (10 mL) was added 1.0 M LiAlH4 in Et2O (1.73 mL, 1.73 mmol) at 0 °C under a N2 atmosphere. After 2 h, the reaction was quenched with a 10% aq NaOH solution (3.5 mL). EtOAc (10 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organic extracts were dried over MgSO4, filtered and concentrated. Purification by flash column chromatography [petroleum ether (30–40 °C)–EtOAc, 1:1] afforded the desired product 10 (127 mg, 86%) as a clear oil. [α]D20 = −21.7 [c = 1.60, CHCl3–MeOH (9:1)].

FTIR (film): 3417, 2987, 2935, 1376, 1265, 1210, 1029 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.30 (s, 3 H), 1.43 (s, 3 H), 1.77 (dd, J = 6.4, 13.6 Hz, 1 H), 2.02 (td, J = 5.2, 13.6 Hz, 1 H), 2.31–2.38 (m, 1 H), 2.52 (s, 1 H), 3.13 (s, 3 H), 3.83 (dd, J = 6.0, 11.0 Hz, 1 H), 4.03 (dd, J = 3.6, 11.0 Hz, 1 H), 4.22 (d, J = 5.2 Hz, 1 H), 4.37 (d, J = 5.6 Hz, 1 H), 4.78 (t, J = 5.6 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 23.8, 26.1, 31.6, 41.4, 61.8, 78.0, 79.7, 86.3, 109.7.

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(1R,2S,3S,4S)-2-Acetoxy-1-(acetoxymethyl)-3,4-isopro-pylidencyclopentane (11)
To a solution of diol 10 (280 mg, 1.49 mmol) in anhyd CH2Cl2 (10 mL) was added Et3N (0.45 mL, 3.28 mmol) at 0 °C under a N2 atmosphere. The aqueous phase was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with aq sat. NaHCO3 (10 mL), dried over MgSO4, filtered and concentrated. Purification by flash column chromatography [petroleum ether (30–40 °C)–EtOAc, 6:4] afforded the desired product 11 (400 mg, 99%) as a clear oil.

[α]D20 = −20.0 (c = 0.65, CH2Cl2).

FTIR (film): 2984, 2934, 1743, 1438, 1370, 1234 cm–1.

HRMS–ES: m/z = 295, 273, 213.


1H NMR (400 MHz, CDCl3): δ = 1.21 (s, 3 H), 1.39 (s, 3 H), 1.63 (td, J = 5.2, 13.6 Hz, 1 H), 1.90 (dd, J = 6.4, 13.6 Hz, 1 H), 1.98 (s, 6 H), 2.59–2.65 (m, 1 H), 4.01 (dd, J = 3.6, 11.0 Hz, 1 H), 4.08 (dd, J = 6.0, 11.0 Hz, 1 H), 4.33 (dd, J = 5.2, 11.2 Hz, 1 H), 4.67 (t, J = 5.2 Hz, 1 H), 5.05 (d, J = 5.6 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 20.9, 23.8, 26.0, 33.7, 38.6, 62.1, 77.4, 79.2, 84.2, 110.4, 170.0, 171.0.

LRMS (ES): m/z = 295, 273, 213.

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References

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